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The Aversive Stimulus Properties
of Self-Administered Drugs as Evidenced in
the Conditioned Taste Aversion Paradigm

Tony Hunt

A Thesis

in

The Department

of

Psychology

Presented in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy at
Concordia University
Montréal, Québec, Canada

August 1985

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ABSTRACT

The Aversive Stimulus Properties of Self-Administered Drugs as Evidenced in the Conditioned Taste Aversion Paradigm

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It was proposed that a qualitative distinction can be made between conditioned taste aversion (CTA) induced by noxious, primarily emetic agents and CTA induced by psychoactive drugs such as morphine, known to be self-administered by animals. Furthermore, it was hypothesized that a functional relationship may exist between the CTA-inducing stimulus properties of these drugs, and their positive reinforcing stimulus properties. In the first experiment, pre-exposure to low doses of morphine, not CTA-inducing, but known to be within the dose range self-administered by rats, was found to be as effective as pre-exposure to higher, CTA-inducing morphine doses in ~~serving to disrupt~~ a subsequent morphine CTA. These data both contrast with a previous report of dose-related pre-exposure effects involving an emetic agent, and also suggest that an important similarity may exist between the positive reinforcing and CTA-inducing stimulus properties of morphine. Experiment 2 demonstrated that a low, non-aversive dose of morphine was capable of maintaining a previously established morphine CTA. In Experiment 3, the disruption of morphine CTA by pre-exposure to morphine was found to be attenuated by pre-exposure administration of naloxone, an

opiate receptor antagonist. In Experiment 4, pre-exposure to intracerebroventricularly administered morphine resulted in a subsequent increase of saccharin consumption in both saline conditioned and morphine conditioned animals. Such a finding suggests that the route of drug administration is an important consideration in evaluating such effects of morphine treatment. Finally, in Experiment 5 the potential involvement of central cholinergic mechanisms in mediating the CTA-inducing properties of morphine and amphetamine was examined. The data were found to suggest such an involvement in a manner parallel to that previously reported for positive reinforcing effects of these drugs. In addition, the CTA-inducing properties of lithium chloride, an emetic agent, were not found to be altered by similar cholinergic manipulations.

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In the standard Conditioned Taste Aversion (CTA) paradigm, the presentation of a distinctive (often novel) tasting substance is initially paired with either a drug administration or exposure to some physiological manipulation (usually noxious) of the organism. Subsequently, following full recovery from the physiological effects of the particular treatment under investigation, the taste is again presented. An avoidance of the taste stimulus, as evidenced by reduced consumption of the distinctively flavoured substance, is taken to indicate formation of a CTA. Over the years, this phenomenon has been the subject of a vast number of published articles (see Riley & Clarke, 1977) and reviews (Ashe & Nachman, 1980; Gaston, 1978; Goudie, 1979; Logue, 1979; Rondeau, 1981; Rozin & Kalat, 1971; see also Milgram, Krames & Alloway, 1977; Barker, Best & Domjan, 1977). Perhaps one of the most striking attributes of CTA is the wide spectrum of various agents which may induce a CTA (see Riley & Clarke 1977; Goudie, 1979). The list of pharmacological agents capable of inducing CTA is continually expanding and covers drugs of every classification, from predominantly centrally-acting (e.g., atropine) to predominantly peripherally-acting (e.g., methylatropine), from pharmacological agonist (e.g., morphine) to antagonist (e.g., naloxone), from emetic agents (e.g., lithium chloride) to euphorogens (e.g., cocaine). Close examination of the literature in this area readily reveals that all attempts to organize this array of data

into meaningful physiological, pharmacological, or behavioral subcategories have met with failure. In the present thesis such a concept is proposed by which two distinct forms of CTA may be deduced. It will be argued that a clear distinction should be maintained between CTAs induced by agents which are predominantly emetic (such as lithium chloride and X-irradiation) and CTAs induced by psychoactive drugs which are known to act as positive reinforcers (such as morphine, amphetamine, ethanol, and barbituates). These latter drugs have generally been found to induce CTAs within a dose range similar to that self-administered by laboratory animals (Berger, 1972; Gappell & LeBlanc, 1973; Gappell, LeBlanc & Endrenyi, 1973; Vogel & Nathan, 1976). Such findings have been aptly described as presenting an 'apparent paradox' (Gappell et al., 1973; Goudie, 1979; White, Sklar, & Amit, 1977). The significance of reaching a clear understanding of the apparent capacity of these discriminatively complex drugs to be both 'rewarding' and 'aversive' would seem self-evident, particularly within the field of psychopharmacology. Accordingly, this issue will form a major focus of this thesis. It will be proposed that CTAs induced by self-administered (positive reinforcing) drugs can be categorically and qualitatively differentiated from CTAs induced by agents which are predominantly emetic within this paradigm. This distinction is suggested both by behavioral and neurochemical evidence. Furthermore, the accumulated evidence would suggest that rather than consider

the capacities of these drugs to be both positive reinforcing and CTA-inducing, as being necessarily dichotomous, the possibility is that both of these potential stimulus properties are, under certain environmental conditions, simultaneously induced by the same pharmacological event.

Optimally, the study of the CTA-inducing capacity of SA drugs in laboratory animals should provide important data for the investigation of the complex motivational properties of these drugs in general, and not simply be related to their potential to act as illness-provoking, toxic agents. In the present introduction, a brief, historical overview of the CTA phenomenon will first be provided. ~~More~~ detailed

accounts have previously appeared in the literature, (Garcia & Hankins, 1977; Logue, 1979) and therefore the major focus here will be an examination of the early attempts to account for the apparently unique 'primitive nature' of CTA within traditional learning theory. The theoretical framework constituted in these attempts will be shown to, perhaps unintentionally, reinforce the view that CTA is exclusively a measure of drug toxicity. Specific discussions of taste neophobia, the nature of the conditioned taste aversion response, and drug preexposure effects will also be provided.

A second section will examine the accumulating evidence that such a view of CTA as an index of toxicity is incorrect.

Following this, further sections will provide reviews of physiological and neurochemical mechanisms implicated in the mediation of CTA. Again, several comprehensive reviews have

already appeared concerning these aspects of CTA (Ashe & Nachman, 1980; Gaston, 1978; Rondeau, 1981), and therefore the discussion will primarily be intended to illustrate the need for classification of different types of CTA. An apparent functional relationship between neurochemical mechanisms mediating the positive reinforcing and CTA-inducing properties of self-administered (SA) drugs will be examined. In a fourth section, consideration will be given to the behavioral evidence which would seem to provide further support for maintaining a qualitative distinction between CTAs induced by primarily emetic agents and those induced by drugs which are also self-administered by laboratory animals.

CTA As a Learning Phenomenon

The behavioral efficiency with which animals appear to select nutritionally beneficial foods and conversely, to generally avoid toxic substances has been the subject of written reports since at least the early 1800s (see Garcia & Hankins, 1977). It is against this background of a learning model of 'nutritional wisdom' of animals (Richter, 1943) that the origins of the CTA literature may be traced (Rozin & Kalat, 1971; Zahorik, 1977). Two early papers described the adaptive ability of wild rats, surviving an initial exposure to poisonous bait, to subsequently avoid ingestion of that substance (Richter, 1953; Rzoska, 1953). The term 'bait shyness' was

introduced to describe this behavior. As described by Rzoska (1953) the "...rats turned their heads away when the bait was brought near them, some pushed it aside with their forepaws or grasped it fiercely, dropped it, or buried it in the litter." Numerous additional observations of 'bait shy behavior' confirm this early description (Barnett, 1963).

In 1955, Garcia, Kimeldorf and Koelling conducted an experimental analysis of this behavior, involving the separation of exposure to the gustatory cue from administration of the illness-inducing agent.

> Presentation of a novel-tasting substance

(saccharin-flavoured water) to laboratory rats was followed by exposure of these animals to X-irradiation. Subsequently, these rats displayed an aversion for the saccharin solution which persisted over weeks of preference testing. Control animals, not exposed to an explicit pairing of ingestional cue with X-irradiation, failed to show such an aversion. A classical conditioning terminology was later adopted to describe this CTA procedure, with a gustatory, conditioned stimulus (CS) being associated with exposure to a toxic agent, an unconditioned stimulus (UCS), inducing illness, an unconditioned response (UCR) (Garcia, McGowan & Green, 1972). A later study (Garcia, Kimeldorf & Hunt, 1957) demonstrated that, in contrast to the rapid acquisition (one conditioning trial) of CTA, it was more difficult to

train animals to learn a spatial avoidance response to a distinctive environment paired with X-irradiation exposure. Although more recent evidence has appeared showing one-trial place avoidance acquisition (e.g., Krane, 1980), the early findings of Garcia and colleagues (1955; 1957) are consistent with field observations of bait shyness behavior. While persistently avoiding ingestion of the illness-associated taste substance, animals failed to successfully avoid the place associated with the poisoning exposure (Barnett, 1963). Indeed, a pre-requisite in many field studies, demonstrating bait shyness acquisition across a variety of species, is that animals continue to approach environmental locales associated with presentation of the poisoned bait (see Gustavson, 1977). The initial observations of the apparent primacy of taste cues over other, non-gustatory cues, in that they are more readily associated with 'malaise' or 'gastrointestinal distress' in rats (Garcia, Hankins & Rusiniak, 1974), led to further experimental investigation of this particular aspect of taste aversion learning. A key study conducted by Garcia and Koelling (1966) involved simultaneous presentation to water-deprived rats of audio-visual and gustatory (taste) cues made contingent upon a drinking response, which was then associated with either exposure to painful electric shock or consequent illness induced by lithium chloride or X-irradiation administration. The results clearly

demonstrated that rats punished with foot-shock quickly learned to inhibit their drinking of water accompanied by audio-visual stimuli, while this inhibition was not observed upon presentation of saccharin-adulterated fluid. Conversely, rats punished by illness rapidly learned to avoid the saccharin fluid, but did not show avoidance of the water presented together with audio-visual stimuli. This basic finding has since been replicated using a longer CS-UCS delay (15 min) (Garcia, Ervin & Koelling, 1966); modified shock and illness parameters (Garcia, McGowan Ervin, & Koelling, 1968; Green, Bouzas & Rachlin, 1972), and independent pairings of audio-visual and taste cues with the distinctive UCSs (Domjan & Wilson, 1972). These data helped to contribute to the considerable interest shown at this time in CTA as a relatively unique form of learning (e.g., Garcia & Ervin, 1968; Garcia, Hankins & Rusiniak, 1974; Mackintosh, 1973; Rozin & Kalat, 1971; Seligman, 1971). This interest was generated based both on the relatively rapid rate of acquisition and apparent selective associability of gustatory cues with toxic consequences exhibited in these investigations of CTA learning. A third factor contributing to this interest involved the demonstration of CTA formation over CS-UCS delays which were considerably longer than those generally observed within other traditional learning paradigms (Revusky & Garcia, 1970; Mackintosh, 1974).

It is well established that taste aversion conditioning can occur despite long delays (extending to hours) between presentation of the CS and of the UCS (e.g., Etscorn & Stephens, 1973; Revusky & Parker, 1976; see Revusky & Garcia, 1970). This feature of CTA allows potential memory-disruptive agents to be administered during the CS-UCS interval, and thus, provides a promising strategy for the study of memory processes involved in the formation of such associations (e.g., Buresova & Bures, 1977). CTA learning in this context has been shown to be remarkably resistant to disruption in comparison to other learning paradigms (Bures & Buresova, 1977; Gaston, 1978; Rondeau, Jolicoeur, Mertcel, & Wayner, 1981). For instance, Nachman (1970) reported that electroconvulsive shock (ECS) introduced during the CS-UCS interval had only limited amnesiac effect in disrupting CTA formation. Although reports of such disruption have been reported using ECS (Kral & Beggerly, 1973, or the analeptic drug, pentylenetetrazol (metraxol) (Ahlers & Best, 1972; Shaw and Webster, 1979), an important qualification of these reports may be that the disruption of learning is only seen if the disruptive agent is administered in close temporal proximity to UCS administration (Shaw & Webster, 1982). Administration of cortical spreading depression (CSD) has been used to examine the role of the cerebral cortex in CTA formation in rats (see Bures & Buresova, 1977). Bilateral CSD

introduced before or immediately following UCS administration failed to prevent CTA acquisition or consolidation (Buresova & Bures, 1973). These investigators concluded that the association of the gustatory CS with the aversive UCS can proceed without cortical participation. Other studies report CTA formation despite the UCS being administered to curarized animals (Domjan & Wilson, 1972) or to animals under general anaesthesia (Roll & Smith, 1972; Buresova & Bures, 1977). Prolonged anaesthesia administered during an extended CS-UCS interval also was reported not to alter CTA acquisition (Rozin & Ree, 1972). The potency or 'primitive adaptive capacity' (Seligman, 1971) of taste aversion conditioning is further reflected in the ability of CTAs to suppress schedule-induced polydipsia (Bond & Corfield-Sumner, 1978; Riley, Lotter, & Kulkosky, 1979) and eating induced by lateral-hypothalamic stimulation (Wise & Albin, 1973). CTA learning has been reported in preweanling rats as young as five days post-partum (Gemberling, Domjan, & Amsel, 1980). As mentioned above, taste aversion learning is reported across a wide variety of animal species (Gustavson, 1977).

CTA formation is also reported in humans (e.g., Bernstein & Webster, 1980; Logue, Ophir, & Strauss, 1981). According to early anecdotal evidence (Rozin & Kalat, 1971; Seligman, 1970; Seligman & Hagar, 1972) food related aversions often persist despite post hoc

recognition that the cause of the illness was unrelated to the ingestion of the aversive food. More systematic evidence of the apparently noncerebral nature of CTA in humans is found in a survey of 517 undergraduate students (Logue et al., 1981). In the case of twenty-one percent of reported aversions, subjects were cognizant that some cause other than the food was responsible for their illness. These data are clearly suggestive of a 'specialized' nature of CTA perhaps reflecting the involvement of phylogenetically older neurological structures in formation of taste aversion associations. Early reviews of CTA in the animal learning literature emphasized the 'unique status' of CTA within traditional general process learning theory (Garcia & Ervin, 1968; Garcia, Hankins & Rusiniak, 1974; Rozin & Kalt, 1971; Seligman, 1971). Rozin and Kalat (1971) emphasized CTA and other feeding-related learning as 'adaptive specializations' incorporating 'two new principles of learning' which were 'belongingness and 'long-delay learning'. Seligman (1971) and Seligman and Hagar (1972) introduced an evolutionary notion of 'preparedness' by which to account for the relative ease of CTA acquisition in contrast to other forms of learning. Capretta (1961) focused on an hypothetical principle of 'stimulus relevance' in order to account for these particular characteristics of CTA learning. This notion predicts that associations are more readily learned if

both events are of the same class than if each event is from a different class. Garcia and his colleagues (Garcia & Ervin, 1968; Garcia et al., 1972; Garcia et al., 1974) proposed a theoretical distinction between behavioral adaptation in the 'milieu interne (gustatory-visceral) and behavioral adaptation in the 'milieu externe' (telereceptor-cutaneous). An early version of this position (Garcia et al., 1974) suggested that the former coping behavior reflects a more basic function involving shifts in internal incentive motivation associated with gustatory stimuli. This particular emphasis on the role of 'hedonic shifts' in the mediation of CTA will be discussed in more detail below. Discussion of the proposal that distinct neural mechanisms subserve the apparently dichotomous nature of these internal and external adaptive learning responses (Garcia et al., 1974) will be presented in the section of this introduction addressing the physiological mechanisms implicated in CTA learning. In contrast to this premise of a 'dichotomous environment', some investigators sought to account for the special qualities of CTA from within a more traditional classical conditioning framework (Krane & Wagner, 1975; Testa & Ternes, 1977). Others have proposed incorporation of CTA learning into modified laws of learning which acknowledge the selective influence of 'adaptive-evolutionary' or biological constraints on learning (Revusky, 1977; Revusky & Garcia, 1970; Rozin,

1977; Mackintosh, 1974). As Rozin (1977) has suggested "... the issue is not 'convergence' versus 'divergence' but striking a balanced view between general processes and specific adaptations". In a more recent review of this question, Logue (1979) cites evidence supportive of the view that differences observed between CTA and more conventional learning may be considered more quantitative (sharing common principles) than qualitative (requiring different learning principles). Sullivan (1984) has proposed that the apparent uniqueness of CTA learning may be attributable to the fact that both the conditioning exposure to the gustatory CS and the measure of the conditioned behavior (reduced consumption of the CS substance) involve the same consummatory response repertoire. Insofar as both initial conditioning and subsequent testing of this conditioning necessarily require behavior directed toward the same target stimulus, such learning may be more readily integrated.

From the above discussion, it is clear that close consideration of issues raised by the study of CTA has particular importance for achieving an integrated understanding of associative learning processes in animals (see Rescorla & Holland, 1982). Such a special theoretical stature is, perhaps, not surprising given the attention traditionally accorded to appetitive responses in the classical conditioning and motivation literatures. A closer examination of the gustatory nature

of the CS in CTA learning is therefore presented below.

The response to the CS: Neophobia and Taste Aversion

A wide variety of taste stimuli have served as conditioned stimuli in CTA studies, although sodium saccharin would appear the most widely used of these (see Riley & Clarke, 1977). An important similarity of CTA to other learning is evident in that CS generalization gradients can be found using a CTA paradigm (e.g., Nowlis, 1974; Nowlis, Frank, & Pfaffman, 1980; Parker & Revusky, 1982; Richardson, Williams & Riccio, 1984). Quantitative CS variables such as the amount consumed, duration of CS exposure (Barker, 1976; Bond & DiGuisto, 1975; but see Kalat, 1976) and concentration of CS solution (Barker, 1976; Nowlis, 1974; but see Steinert, Infurra, Jardula & Spear, 1979) have been reported to influence CTA learning. Food CS test substances are also reported to be more potent than fluid stimuli in taste aversion conditioning (e.g., Bernstein, Vitiello & Sigmundi, 1980), perhaps due to additional textural cues (Martin & Lawrence, 1979). However, formation of illness-induced CTAs are known to be induced using small oral infusions (e.g., Domjan & Wilson, 1972; Buresova & Bures, 1977) indicating both that neither voluntary ingestion nor consumption of large amounts of the taste substance are necessary for CTA learning to occur.

Indeed, Bradley and Mistretta (1971) demonstrated a CTA to saccharin administered by the intravascular route. Also, Baum, Foidart and Lapointe (1974) reported more rapid CTA extinction following noncontingent ip injections of the CS fluid.

The term 'saliency' was introduced by Kalat and Rozin (1970) to describe the finding that taste aversions are more readily formed with certain tastes than others. In a later study (Kalat, 1974) it was reported that the relative novelty of the taste stimulus appeared to be the most critical factor contributing to this saliency effect. Similarly, other investigators (Ahlers & Best, 1971; Revusky & Bedarf, 1967) found that when novel and familiar solutions are presented to rats in a CTA paradigm, a stronger aversion is shown to the novel solution. The phenomenon of 'neophobia', the suppression in consumption of novel fluids and foods, has been the subject of number of reviews (Barker et al., 1977, see also Logue, 1979). Enhanced neophobia is reported in animals previously exposed to non-contingent illness (e.g., Domjan, 1977). However such factors as the short-lived nature of this effect suggest that the enhancement of neophobia in these animals is unrelated to taste aversion conditioning (Domjan, 1977; Revusky, 1979).

Prior CS exposure has been widely reported to reduce the associability of the taste CS within a CTA paradigm (e.g., Best & Gemberling, 1977; Kalat & Rozin, 1973;

Revusky & Bedarf, 1967). This CS pre-exposure disruption of CTA has been shown to increase both with the number of prior exposures (e.g. Elkins, 1973; Best, 1975; Fenwick, Mikulka & Klein, 1975) and with the amount consumed during CS pre-exposure (e.g., Bond & Westbrook, 1982) and would appear comparable to latent inhibition in classical conditioning (Logue, 1979). CS pre-exposure has also been shown to disrupt a CTA induced by amphetamine, a psychoactive, self-administered drug (Pickens & Harris, 1968) in a manner similar to that observed in an emetic-induced CTA (Wellman, 1982). A 'learned safety' (Kalat & Rozin, 1973) or 'learned noncorrelation' (Kalat, 1977) has been proposed to explain this phenomenon (see Best & Barker, 1977; Kalat, 1977). The degree of neophobic response to a variety of taste stimuli was shown by Nachman and coworkers (1977) to be a good predictor of the relative CTA formed to these different tastes. It was suggested that the different levels of arousal or attention produced by presentation of these solutions may account for the observed CTA differences. Taste neophobia has been characterized by some investigators as a form of 'emotional reactivity' (Braveman, 1978) similar to exploratory open field behavior (Braveman, 1978; Weinberg, Smotherman & Levine, 1978, but see Pfister, Golus & McGee, 1981). Using a plasma corticosterone measure of pituitary-adrenal activation as an index of arousal, Smotherman, Margolis &

Levine (1980) reported both a 'coupling' of neophobic and pituitary-adrenal activation and a dissociation of these responses to presentation of a distinctive flavor dependent upon the number of CS pre-exposures (within a range of 5 to 10 pre-exposures). These authors suggested that changes in pituitary-adrenal activity may reflect the degree of conflict induced in water-deprived animals under 'forced-choice' (but not free-choice) conditions. Such an observation is consistent with the observation that, compared to a choice paradigm, a single stimulus CTA procedure is potentially less sensitive to the influence of neophobia in modulating CS fluid consumption in control animals over repeated trials, as these animals would presumably be motivated to some degree, to avoid increased fluid deprivation (see Domjan, 1977). This aspect of the forced choice CTA paradigm has potentially important theoretical significance with regard to a strict empirical definition of CTA. A CTA under these conditions is most often measured as a reduction in consumption of the test substance (Goudie, 1979). Evidence of such a reduction may be determined either by comparison of test day intake levels with within-group baseline intake levels, or by a between-group comparison of test day intake levels of a given treatment group with that of a control group. In the latter case, simply a failure to exhibit an increase in consumption of the test substance over repeated presentations relative to that

observed in the control group may be taken to indicate a CTA. However, this pattern of consumption may alternatively be explained in terms of a relative maintenance of initial neophobia to the test substance. Therefore, the more parsimonious, ~~to~~ within-group definition of CTA would appear to be the more appropriate criterion here, incorporating more unambiguously, an implicit avoidance response to the conditioned gustatory stimulus.

Although the relative novelty of the test substance within a CTA paradigm may contribute significantly to the saliency of the CS (Nachman, et al., 1977; Kalat & Rozin, 1974), neophobic reactivity and taste aversion learning would appear to be independent phenomena. Such a conclusion is based on the findings of Braveman and Jarvis (1978). In this study, rats exposed to a variety of distinctly flavoured solutions prior to taste aversion conditioning in which a different taste solution was used, exhibited reduced neophobia to this substance on the initial conditioning day. However, this manipulation was not found to alter the magnitude of the CTA subsequently observed in these animals relative to the CTA observed in animals not exposed to prior distinctive tastes. These findings were replicated by Miller and Holzman (1981) who additionally reported that pre-exposure to three of four distinctive flavours (salty, bitter, sweet, and sour) were effective in disrupting neophobia to novel salty and sour, but not to novel bitter or sweet test solutions.

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A further dissociation between neophobic and taste aversion response may be based on a greater potency of odor cues than taste cues in determining neophobic behaviors (Hankins, Garcia & Rusiniak, 1973) while a reversed potency is evident for taste aversion learning (e.g. Palmerino, Rusiniak & Garcia, 1980). Odor may also be more effective than taste as a CS in shock avoidance learning (Rusiniak, Palmerino, Rice, Forthman & Garcia, 1982). Additionally, while the presence of a taste stimulus is found to potentiate odor aversion, no such potentiation is observed in shock avoidance (Rusiniak et al., 1982; see also Westbrook, Homewood, Horn & Clarke, 1983).

The nature of the conditioned response in CTA

An early proposal by Garcia and his colleagues (Garcia & Hankins, 1977; Garcia, Hankins & Rusiniak, 1974) was that illness-induced CTA reflected a shift in hedonic valence of the conditioned gustatory stimulus. Thus, CTA was interpreted to reflect a 'conditioned nausea' response (Coil, Hankins, Jendin, & Garcia, 1978). Evidence for this was apparent in early observations of the pattern of response of animals encountering taste cues previously associated with illness (Garcia & Hankins, 1977; Gustavson, 1977; Rzoska, 1953). 'Conditioned disgust' responses (such as urinating on or burying the food) were observed in coyotes re-exposed to gustatory cues

associated with poisoning (Garcia & Hankins, 1977; Gustavson, 1977). Rats were reported to actively push away poisoned bait (Rzoska, 1953) or to scatter saccharin-adulterated food previously paired with illness (Garcia et al., 1974). Such spillage of illness-paired food closely resembled a similar response pattern directed toward aversive, quinine-adulterated food (Rozin, 1967). Conditioned 'pica' (consumption of non-nutritive substances) was also taken to indicate a similar change of incentive properties of the conditioned gustatory stimulus (Mitchell, Winter, & Marisaki, 1977). Based on observations of distinctive response topographies associated with exposure to positively valenced (Pfaffman, 1960) sucrose, as opposed to aversive quinine taste stimuli, Berridge, Grill, and Norgren (1981) examined the pattern of ingestive, consummatory responses of rats to sucrose previously paired with lithium chloride (LiCl) illness. Whereas control animals given sucrose showed no apparent aversive reactions to the taste stimulus, the response pattern of the LiCl CTA rats to the sucrose CS (mouth gaping, chin rubs, increased locomotion, and fluid ejection) unequivocally resembled quinine reactivity. Such observations are consistent with earlier reports (Garcia et al., 1974; Mitchell et al., 1977; Rozin, 1967). In addition, Berridge et al. (1981) found that the taste aversion conditioning served to abolish preabsorptive insulin release normally observed in

animals exposed to sucrose taste stimuli, clearly suggesting a CTA-related shift in taste palatability.

The evidence cited above, then, supports the view that the nature of the CR induced by at least some emetic agents reflects a definite shift in the hedonic value of the conditioned taste stimulus. However, a relatively recent study indicates that CTAs induced by self-administered drugs may not be mediated by such a hedonic shift (Parker, 1982). A comparison was made between the patterns of consummatory response of rats to saccharin taste stimuli previously paired with administration of either LiCl or amphetamine. Amphetamine is a psychoactive drug, well known to possess positive reinforcing properties (e.g., Pickens & Harris, 1968). Both drug treatments induced CTAs of equal magnitude. While both LiCl and amphetamine supported patterns of nonconsummatory, 'increased agitation-related' CRs (increased locomotor activity, rearing, stretching and limb flicking) only the LiCl-paired taste exposure elicited chin rub CRs, a pattern of consummatory response thought to be reflective of aversive behavior (Garcia, Hankins, & Rusiniak, 1974; Berridge et al., 1981). The question of what factors serve to determine the nature of a CR within a classical conditioning paradigm is complex and presently unresolved (see Rescorla & Holland, 1982). Within the CTA literature, physiological CRs have been reported which are both similar to the UCR (e.g.,

associated with recovery from thiamine deficiency; Zahorik, 1972) and opposite to the direction of the unconditioned physiological response (e.g., hypoglycemic response to saccharin previously associated with an injection of insulin; Deutsch, 1974). Additionally, Ader and Cohen (1975) have reported a conditioned immunosuppressive response to a taste previously paired with the immunosuppressive (and emetic) drug cyclophosphamide, after only one conditioning trial. Of potential interest in this regard is the recent observation of Blalock (1984), that the immune system appears to process and encode information in a manner in some ways similar to that of a sensory system. While such a comparison may be considered controversial, the appearance of such a suggestion exemplifies the current need to integrate theoretical formulations concerning general process learning and adaptive, defensive response capabilities of the organism, an issue also apparent in investigations of CTA. Despite the need for further elucidation of the physiological factors underlying conditioned responses of CTAs induced by various agents, the behavioral indications suggest that a categorical distinction can be made between those CTAs induced by some aversive agents and those induced by a self-administered drug such as amphetamine. Further investigation is required, for instance, to establish whether CTAs induced by particular toxic agents, in which

no behavioral signs of illness are visible during conditioning. (Berger, 1972) may also involve no shift in hedonic properties of the gustatory CS.

Alternative models of CTA learning have been proposed which emphasize similarities to UCS-UCS conditioning (Solomon, 1977) or a conditioned emotional response model (Spiker, 1977). Indeed it has been suggested (D'Mello & Stolerman, 1978) that CTA induced by positive reinforcing drugs may reflect a form of 'positive conditioned suppression' (Azrin & Hake, 1969). Although such analyses may initially seem appealing, these models fail to account for the considerable body of data demonstrating CTAs using a two-bottle choice paradigm. In these studies of CTA induced both by emetic (e.g., Kalat & Rozin, 1971) and positive reinforcing agents (Carey & Goodall, 1974; D'Mello & Stolerman, 1978), post-conditioning reductions in consumption were observed only for the specific conditioned taste fluid while no such reduction was found for simultaneously presented water or non-conditioned taste. These data are clearly inconsistent with an interpretation of CTA based upon these models (Spiker, 1977; Solomon, 1977; D'Mello & Stolerman, 1978) which would necessarily predict generalized suppression of consummatory behavior under these conditions.

Disruptive Effects of UCS Pre-exposure on CTA

Another aspect of the CTA phenomenon of special significance to learning theorists involves the investigation of the potentially disruptive effects of UCS pre-exposure upon subsequent taste aversion conditioning (see Braveman, 1977; Cappell & LeBlanc, 1975; Gamzu, 1977). Explanations of this phenomenon have variously emphasized the importance of drug tolerance (Berman & Cannon, 1974; Cappell & LeBlanc, 1975; 1977; Goudie, Taylor & Atherton, 1975), associative interference (Bateson & Best, 1979; Braveman, 1979; Rudy Iwens, & Best, 1977), or habituation to the novelty of the drug state (Amit & Baum, 1970; Gamzu, 1977; Vogel & Nathan, 1976). More recent interpretations, however, appear to support the view suggested by Cappell and LeBlanc (1975) that "very likely, no single hypothesis will be able to embrace all of the data in this general area." For instance, a tolerance hypothesis fails to explain how animals given prior, non-contingent exposure to lithium chloride (LiCl) subsequently exhibit a disruption of taste aversion conditioning with either LiCl or ethanol (Cannon, Baker & Berman, 1977).

Here again, a qualitative distinction is apparent between effects of positive reinforcing and emetic agents within this paradigm. Specifically, it has been reliably

demonstrated that the disruptive effect of LiCl pre-exposure upon a subsequent LiCl-induced CTA is dependent upon the distinctive environmental cues present during drug pre-exposure and conditioning trials (Bateson & Best, 1979; Dacanay & Riley, 1982). These studies showed that when drug pre-exposure and conditioning trials took place in distinctive environments, no disruption of the LiCl CTA was evident. Such a phenomenon is consistent with an associative 'blocking' explanation (Kamin, 1969) in which prior pairings of environmental cues with the drug UCS during pre-exposure trials serve to attenuate subsequent attempts to condition a taste-drug association in the presence of the same environmental cues. In contrast, in the case of morphine, a drug known to be self-administered by animals (e.g., Davis & Smith, 1975), the disruptive effect of the drug pre-exposure upon a subsequent morphine CTA is found to be independent of the particular pre-exposure and conditioning environments (Dacanay & Riley, 1982; Stewart & Eikelboom, 1978). Thus it would appear that an associative blocking explanation is insufficient to account for the disruptive effects of morphine pre-exposure upon a morphine CTA. Also, as indicated in a recent investigation by Ford and Riley (1984), it would appear that, in contrast to the environment-dependent nature of LiCl pre-exposure effects upon a CTA induced by LiCl, the disruptive effect of LiCl pre-exposure upon a CTA induced by amphetamine is

independent of the environmental stimuli present during pre-exposure and conditioning. Thus it would appear that CTAs induced by positive reinforcing drugs such as morphine and amphetamine are subject, to some degree, to learning factors which are qualitatively distinct from those implicated in CTAs induced by emetic drugs such as LiCl.

An intriguing finding within the drug pre-exposure CTA literature concerns the reports of asymmetrical, between-drug pre-exposure effects (e.g., Cappell, LeBlanc & Herling, 1975; Goudie & Thornton, 1975; Switzman et al., 1981; Vogel & Nathan, 1976). For instance, Cappell and colleagues (1975) reported that while amphetamine pre-exposure served to attenuate a morphine-induced CTA, pre-exposure to morphine did not serve to similarly attenuate a CTA induced by amphetamine. In the case of such asymmetrical findings involving a SA drug and an emetic drug, it has been proposed (Switzman et al., 1981) that, in contrast to poorly self-administered drugs (such as valium), SA drugs (such as morphine) may be relatively less effective as disruptive pre-exposure agents and conversely, may be more susceptible to pre-exposure disruption as CTA-inducing agents. In this case, pre-exposure to morphine may not be expected to disrupt a valium CTA, while valium pre-exposure may more readily disrupt a CTA induced by SA drugs such as morphine. The interpretation of such asymmetrical drug

pre-exposure effects involving two SA drugs, as in the study by Cappell et al. (1975) mentioned above involving morphine and amphetamine, would seem less clear (see Gamzu, 1977). It may be proposed that such findings reflect the intrinsic discriminative complexity of SA drugs such as morphine and amphetamine. Within the animal drug discrimination literature, there is at least one example of a similarly asymmetrical drug effect (Colpaert, Niemegeers & Janssen, 1976). In this study, animals were trained to discriminate between injections of fentanyl (a potent narcotic) and saline using a standard, two lever drug discrimination paradigm. Subsequently, the fentanyl discrimination was found to generalize to apomorphine in that, when this latter drug was injected in place of fentanyl, the animals responded on the drug-appropriate lever. In contrast, animals initially trained to form an apomorphine/saline discrimination failed to generalize the apomorphine discrimination when an injection of fentanyl was administered in place of the apomorphine. These data serve to underscore the need to gain further understanding of drug pre-exposure effects involving discriminatively complex psychoactive drugs such as opiates and psychomotor stimulants. In this context, it would seem evident that complex discriminative processes are involved in determining the relative saliency of various stimulus components of these drugs.

Taste Aversion Conditioning as an Index of Toxicity

Terms such as 'gastrointestinal illness', 'poison', 'nausea' and 'malaise' continue to be commonly used in the description of CTA effects (Barker, Best & Domjan, 1977; Milgram et al., 1977). Indeed, early reports tended to point to the CTA paradigm as a particularly sensitive behavioral indicator of sickness or toxicity (e.g., Garcia, Kimeldorf & Koelling, 1955; Nachman & Ashe, 1973; Smith, 1971) especially because CTA could be induced by exposure to agents which were accompanied by little or no overt signs of illness. However, the adequacy of such a model of CTA, as an index of toxicity (e.g., Riley & Zellner, 1978), or 'conditioned illness' (Garcia, Hankins & Rusiniak, 1974), has increasingly come into question (see reviews Ashe & Nachman, 1980; Gamzu, 1977; Goudie, 1979; Rondeau et al., 1981). The evidence for rejecting this 'toxiphobia' model, which carried as an underlying assumption that some form of gastrointestinal distress constituted the major aversive component of all CTA-inducing agents, is summarized below.

Berger (1972) first reported that CTAs could be established with the psychoactive drugs amphetamine, scopolamine and chlorpromazine at dosages not producing obvious signs of sickness, suggesting that such effects were not necessary for CTA to occur. Similarly, as mentioned earlier, CTAs induced by LiCl (Nachman & Ashe,

1973) or X-irradiation (Smith, 1971) were found at dose levels below the threshold for production of gastrointestinal distress. An examination of the relationship between overt signs of sickness and CTAs induced by LiCl, X-irradiation or cyclophosphamide failed to reveal any meaningful correlation as would be predicted by a conditioned illness model (Barker, Smith, & Suarez, 1977). In a study comparing the potency to induce CTA of a number of clearly toxic agents, Nachman and Hartley (1975) reported that several substances (e.g., cyanide and strychnine), known to be highly toxic, induced very weak or no aversion to a saccharin flavour paired with their administration. Failure to induce CTA by severe poisoning using such agents as melonate, cyanide and gallamine was also reported by Ionescu and Buresova (1977). Furthermore, CTAs may be induced by positive reinforcing drugs such as amphetamine, morphine, alcohol (Cappell and LeBlanc, 1973; Cappell, LeBlanc & Endrenyi, 1973) and barbituates (Vogel & Nathan, 1975) within a (presumably non-toxic) dose range actively self-administered by rats. Anti-emetic drugs such as scopolamine, which are used therapeutically to treat gastrointestinal illness (Wang, 1965) are capable of inducing robust CTA (e.g., Berger, 1972). In addition, the active constituent of marihuana, delta-9-tetrahyrocannabinol (delta-9-THC), despite being known to possess CTA-inducing properties in rats (e.g.,

Corcoran, Bolotow, Amit, & McCaughran, 1974; Switzman, Fishman & Amit, 1981) has also recently been proposed as a beneficial adjunct in the pharmacological treatment of illness due to cancer chemotherapy (Ballster, 19xx). Although an earlier study (Coil, Hankins Jendin & Garcia, 1978) reported that CTA induced by LiCl could be attenuated by treatment with various anti-emetic agents, a more recent study has failed to find such attenuative effects of these drugs on CTAs induced by LiCl, amphetamine or morphine, (Goudie, Stolerman, Demelweek & D'Mello, 1982).

Taken together, such data indicate that an explanation of CTA based on a notion of toxicity or illness cannot adequately account for the CTA-inducing capacity of certain agents (Berger, 1972; Nachman & Ashe, 1973; Smith, 1971) nor is it a sufficient condition (Cappell & LeBlanc, 1973; Nachman & Hartley, 1975; Ioneso & Buresova, 1977; Vogel & Nathan, 1972) for CTA formation to occur.

Physiological Mechanisms of CTA

The 'anatomical hypothesis' proposed by Garcia and Ervin (1968) has constituted a major theoretical framework for investigations of the neural and physiological mechanisms of taste aversion learning (Ashe & Nachman, 1980; Buresova & Bures, 1977; Gaston, 1978).

Earlier evidence of an anatomical convergence of such gustatory and visceral input at the nucleus of the solitary tract (NTS; Herrick, 1948) was taken to suggest an 'intimate relationship' between gustatory and visceral systems reflected in the selective nature of taste aversion learning (Garcia & Ervin, 1968). The proximity to the NTS of the area postrema, a structure implicated in emesis (see Wang, 1965), was taken to support the notion that the CTAs induced by such stimuli as X-irradiation and LiCl directly reflected the emetic properties of these agents. (Garcia & Ervin, 1968). Stimulation of gustatory receptors followed by eventual activation, by visceral illness, of the 'emetic centre', located in the lateral reticular formation and caudal nucleus of the solitary tract (Borison & Wang, 1953), was accordingly viewed as the sole requirement for acquisition of CTA (Garcia et al., 1974). This anatomical hypothesis was originally introduced in order to account for the apparently selective associability of gustatory and visceral stimuli in rats (as versus exteroceptive and cutaneous stimuli) as evidenced in a learned avoidance paradigm (Garcia & Koelling, 1966). In this view, gustatory stimuli were primarily constituted by taste 'cues', while visceral 'consequences' were seen to be primarily reflective of a gastrointestinal malaise, nausea, or sickness induced by such noxious agents as X-irradiation, LiCl or apomorphine (see Garcia, Hankins &

Rusiniak, 1974).

However, as pointed out by Ashe and Nachman (1980) in a review of this issue, the significance of anatomical convergence of gustatory and visceral afferents per se would not appear sufficient to account for all aspects of CTA learning (i.e., long CS-UCS intervals). Indeed, Garcia et al. (1974), while emphasizing the importance of the NTS as a locus of central neural integration in CTA learning, also acknowledged the potential relevance of gustatory projections to the cortex and the hypothalamus in mediating CTA learning (Norgren, 1976). Gustatory projections to the amygdala (via thalamic taste nuclei) have also been reported (Norgren, 1976) and by implication linked to CTA. It should be noted that in support of the idea of minimal involvement of phylogenetically more recent neural structures were several early studies demonstrating CTA acquisition in anaesthetized or curarized animals (e.g., Domjan & Wilson, 1972; Roll & Smith, 1972). Clearly, these data indicate the not so easily disruptible nature of at least some forms of CTA learning, as discussed in an earlier section of the present review. Other studies have demonstrated, however, that input from phylogenetically more recent structures (e.g., cortex) would often appear critical in CTA acquisition. For instance, Grill and Norgren (1978) reported that decerebrate rats failed to learn a CTA despite repeated CS-UCS pairings. Cortical

spreading depression induced just prior to CS presentation (but not after UCS exposure) was similarly found to disrupt CTA learning (see Buresova & Bures, 1977). Also, electrophysiological changes in lateral (decreased) and ventromedial (increased) hypothalamic reactivity to taste stimuli have been reported due to taste aversion conditioning (Aleksanyan, Buresova & Bures, 1976). Further evidence for the involvement in CTA of brain areas other than just the brainstem (i.e., hypothalamus, amygdala) has recently appeared in an elegant, electrophysiological study conducted by Chang and Scott (1984). These investigators demonstrated clear modifications in single neuron responses from the NTS to a range of taste stimuli following taste aversion conditioning. These neurophysiological changes reflected apparent modification of the hedonic properties (e.g., sweet or non-sweet) of the taste CS in a manner consistent with earlier descriptions of emetic CTA (Berridge, Grill and Norgren, 1981; Garcia et al., 1974). It was suggested by Chang and Scott (1984) that the latency (900msec) of the increased NTS activity observed following taste aversion conditioning may well reflect input from higher brain centres such as the hypothalamus and amygdala. Thus, it would seem that while the activation of brainstem regions (NTS) are a necessary component of CTA learning, participation of more rostral, limbic system regions may also play an important role in

CTA. Further evidence in this regard will be presented below (see also, reviews Ashe & Nachman, 1980; Gaston, 1978; Buresova & Bures, 1977).

As pointed out above, the predominant focus of early investigations was on CTAs induced by toxic agents with well-known emetic properties (Wang, 1965). Peripheral toxicosis, as evidenced by overt symptoms of gastrointestinal malaise (sedation, diarrhea, retching) was thought to constitute the aversive stimulus properties necessary for most CTA learning to occur (Nachman & Hartley, 1975). A paper by Borison and Wang (1953), frequently cited within the early CTA literature, identified both vagal afferents from the stomach and an area postrema, chemoreceptive region, sensitive to blood-borne toxins, as being two prominent afferent pathways both involved in eliciting emesis induced by copper sulphate, a prototype of peripherally-acting emetics (Wang, 1965). In parallel to these findings, subdiaphragmatic vagotomy is known to block CTA induced by copper sulphate administered via intragastric (ig) or intraperitoneal (ip), but not intravenous (iv) injections (Coil, Rogers, Garcia, & Novin, 1978). Conversely, ablation of the area postrema is reported to attenuate CTA induced by iv but not ig injections (Coil & Norgren, 1981). Accordingly, the aversive stimulus properties of copper sulphate, as evidenced within a CTA paradigm, may be related in a straight-forward fashion to this agent's

emetic effects. Interestingly, Martin, Cheng and Novin (1978) reported that vagotomy failed to attenuate a CTA induced by LiCl (administered ip), a drug widely known for its effectiveness in producing strong taste aversions (Nachman & Ashb, 1974; Ionescu & Buresova, 1977).

However, lesion of the area postrema has more recently been shown to successfully block CTA induced by ip LiCl administration (Ritter, Mcglone & Kelly, 1980). Area postrema lesions are also known to attenuate CTAs induced by scopolamine (Berger, Wise & Stein, 1973; Ritter et al., 1980), histamine (Rabin, Hunt, & Lee, 1983) and X-irradiation (Ossenkopp, 1983; Rabin et al., 1983). In a recent study (Rabin, Hunt & Lee, 1984), it was found that area postrema lesions performed after taste aversion conditioning by LiCl or X-irradiation did not disrupt CTAs induced by these agents. These latter data indicate that this region does not play a significant role in the retention of such CTAs. In contrast to the above evidence, it has been demonstrated that lesions of the area postrema fail to disrupt CTAs induced by apomorphine (Van Der Kooy, Swerdlow & Koob, 1983), morphine (Van Der Kooy, 1984) and amphetamine (Berger, Wise & Stein, 1973; Ritter et al., 1980). A common feature of all of these psychoactive drugs is their capacity to act as positive reinforcers, evidenced in operant paradigms by their being reliably self-administered by rats (e.g., Davis & Smith, 1975; Pickens & Harris, 1968; Wise, Yokel, & DeWit,

1976). Failures of vagotomy to disrupt CTAs induced by ip apomorphine (Kiefer, Rusiniak, Garcia & Coil, 1981) both ip and ig ethanol (Kiefer, Cabral, Rusiniak & Garcia, 1980) have also been reported. Again, ethanol is a drug self-administered by rats (e.g., Werner, Smith & Davis, 1976). It should be noted that vagotomy performed after taste aversion conditioning with either apomorphine or copper sulphate is reported to facilitate extinction of CTAs induced by these agents, (Kiefer et al., 1981), a finding which is perhaps suggestive of a role in these CTAs of vagal sensory and motor fibers in the mediation of the conditioned response to the previously conditioned taste stimulus. If participation of vagal afferents and/or the area postrema in mediating acquisition of CTA may be taken as a model of peripheral toxicosis and malaise involvement in taste aversion conditioning, then the weight of evidence would indicate that, in contrast to CTA induced by toxic agents such as copper sulphate or LiCl, CTAs induced by self-administered drugs are not due to such peripheral toxicosis.

A number of studies have also demonstrated that CTA may be induced by centrally-acting agents (such as centrally administered delta-9-THC and carbachol) thought not to involve peripherally-activated emetic pathways (e.g., Amit, Levitan, Brown, & Rogan, 1977; Buresova & Bures, 1984; Green & Rachlin, 1976; Greenshaw & Buresova, 1982; Myers & deCastro, 1977). The association of

gustatory stimuli with vestibular stimulation induced by body rotation has also been shown to establish a robust CTA (e.g., Braun & McIntosh, 1973; Green & Rachlin, 1976). Buresova, Semenov and Bures (1982), as reported in a recent paper by Buresova and Bures (1984), found that electrical stimulation of vestibular nuclei or specific administration of potassium chloride to these nuclei were similarly capable of inducing CTA, in a manner hypothesized to by-pass peripheral emetic afferents. Indeed, in support of such an interpretation, Ossenkopp (1983) recently reported that area postrema lesions in rats actually enhanced the magnitude of CTA induced by acute body rotation. Some further evidence of the central mediation of CTA induced by some agents is to be found in reports of CTA induced by intracerebral injections of carbachol (Myers & deCastro, 1977) and of harmaline (a serotonergic compound, Buresova & Bures, 1984). In perhaps the clearest demonstration of a centrally-mediated CTA, Amit et al. (1976) reported a CTA induced by intracerebral administration of delta-9-THC into the dorsal hippocampus, while no CTA was observed by a similar injection of this drug into the caudate nucleus. A CTA induced by intraventricular (icv) administration of amphetamine has also been reported (Greenshaw & Buresova, 1982). Interpretation of this latter finding as evidence of a centrally mediated CTA must remain tentative, however, due to the relatively high drug dose used in

this study. It has recently been demonstrated that a CTA may be induced by intracerebral administration of amphetamine into the area postrema of the rat (N. White, personal communication). At present, it would seem difficult to reconcile this finding with earlier data showing that lesions of the area postrema serve to block amphetamine CTA (Berger et al., 1972; McGlone et al., 1980). It may be that other, non-emetic effects of area postrema activation (i.e., catecholaminergic or serotonergic) could account for this finding (see Borison, 1984; Pickel & Armstrong, 1984). In a study conducted in our own laboratory (Hunt, Amit, Switzman, & Sinyor, 1981), we have found that while no CTA was induced by icv morphine administration, a CTA was observed when such a drug injection was accompanied by peripheral (ip) injection of naloxone, an opiate antagonist. In this study, exposure to peripheral naloxone alone did not result in a significant CTA. On the surface of things, naloxone, in addition to its central effects, may be hypothesized to contribute peripheral stimulus effects which may perhaps facilitate discrimination of the morphine-naloxone drug cue. It may be, therefore, that some peripheral stimulus effect of psychoactive drugs such as amphetamine and morphine may potentially enhance the aversive stimulus properties of these drugs in an as yet unspecified manner. However, it would seem equally clear from the accumulated evidence

cited above, that peripheral effects of such drugs alone are not sufficient to fully account for their CTA-inducing properties.

The important role of central neural mechanisms in CTA has been the subject of several comprehensive reviews (Ashe & Nachman, 1980; Gaston, 1978) and so will not be extensively addressed here. The gustatory neocortex has recently been implicated in the mediation of both LiCl (Kiefer, Rusiniak & Garcia, 1982, but see Lassiter & Glanzman, 1982) and ethanol CTA (Kiefer, Melzler & Lawrence, 1985). This region is hypothesized to play an important role in the recognition of the behavioral significance of tastes (see Kiefer, Leach & Braun, 1984) and thus may be critically involved in the processing of the CS in taste aversion conditioning. Specific nuclei of the amygdala have now been strongly implicated in the mediation of CTA (Aggelton, Petrides & Iverson, 1981; Fitzgerald & Burton, 1983; Lassiter, 1982). Grupp, Linseman and Cappell (1976) reported that relatively extensive lesions of the amygdala attenuate the acquisition of CTA induced both by LiCl or amphetamine. Low intensity electrical stimulation of the amygdala, but not of caudate-putamen or substantia nigra, disrupted a CTA induced by LiCl (LePiane & Phillips, 1978). Interestingly, these authors have more recently presented evidence indicating that such amygdaloid stimulation may itself act as a conditioning stimulus in a taste aversion

paradigm. (Phillips & LePiane, 1980). In this study, amygdaloid stimulation, given concurrently with presentation of water to water-deprived rats, was associated with a subsequent LiCl exposure. When the amygdaloid stimulation was again presented along with water presentation during a later test session, a reduction of fluid intake was observed in the LiCl-conditioned animals but not in control animals similarly treated but not previously exposed to LiCl. Accordingly, the capacity of such amygdaloid stimulation to act as a CS should be taken into consideration when evaluating the potential disruptive effects of such brain stimulation on acquisition and retention of CTA.

In the context of the findings presented above, it is of interest to note that anatomical studies reveal a potentially complex feedback system between the various neural regions presently implicated in the mediation of CTA. For instance, there is evidence to suggest the presence of projections from the hypothalamus to the area postrema (Hosoya & Matsushita, 1981); efferent connections from the area postrema to the solitary nucleus (Leslie & Gynn, 1984; Wang, 1965); projections from the solitary nucleus to the hypothalamus and amygdala (Ricardo & Koh, 1978), and amygdaloid connections with the gustatory neocortex (e.g., Lasiter, Glanzman & Mensah, 1982) and temporal cortex and thalamus

(Krettek & Price, 1978). In addition, gustatory input has been reported to reach the thalamus, amygdala and hypothalamus via the pontine taste area (Norgren, 1976). As previously pointed out by Ashe & Nachman (1980), the solitary nucleus is also critically involved in a general arousal system (Koella, 1974), and such a function may conceivably be important for acquisition of taste aversions. Additionally, in a recent review of brain reward circuitry (Phillips, 1984), it was suggested that amygdaloid-prefrontal cortex (Llambas, Avendeno & Reinosua-Suarez, 1977) and prefrontal cortex-solitary nucleus (Van Der Kooy, McGinty, Koda, Gerfen & Bloom, 1982) connections "...may form the basis of a complete circuit by which chemosensory and visceral information are integrated in the control of appetitive behavior." Further evaluation and extensions of such a schema within both CTA and brain reward areas of investigation promise to lead to a clearer elucidation of potential qualitative differences between CTAs induced by positive reinforcing drugs and agents which are primarily emetic in nature.

Neurochemical Systems Involved in CTA

As previously argued, studies of the physiological mechanisms subserving CTA suggest that the nature of the CTA-inducing properties of psychoactive drugs such as morphine, ethanol and apomorphine cannot be explained on the basis of peripherally-induced toxicosis or malaise.

Furthermore, it was suggested that, based on the accumulation of evidence in this regard, a categorical distinction can be made between CTAs induced by such psychoactive drugs which possess positive reinforcing properties and CTAs induced by other aversive agents not known to possess these properties. As will be described below, evidence derived from investigations of the neurochemical mechanisms subserving CTA formation would seem, in general, to even more firmly consolidate such a notion. Moreover, a growing number of these studies strongly implicate in the CTA-inducing properties of these drugs, specific neurochemical systems also known to be crucially involved in the mediation of their positive reinforcing properties.

Catecholamine depletion produced by ip injections of alpha-methyl-para-tyrosine (AMPT: an inhibitor of tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of catecholamines) has been demonstrated to block the formation of CTAs induced by amphetamine (Goudie, Thornton, & Wheatley, 1975; Lorden, Calahan & Dawson, 1980); fenfluramine (Lorden et al., 1980); morphine, and ethanol (Sklar & Amit, 1977) while not altering CTAs induced by LiCl (Goudie et al., 1975; Sklar & Amit, 1977) or delta-9-THC (Sklar & Amit, 1977). Pretreatment with AMPT has also recently been shown to block a CTA induced by acetaldehyde, the primary metabolite of ethanol hypothesized to be involved in mediating the positive

reinforcing properties of ethanol (Aragon & Amit, 1985). Catecholamine depletions induced by icv administration of the neurotoxin 6-hydroxydopamine (6-OHDA) are also reported to disrupt an amphetamine but not a LiCl-induced CTA (Roberts & Fibiger, 1975; Stricker & Zigmond, 1974). Selective dopamine depletion produced by icv 6-OHDA administration accompanied by pretreatment with desmethylimipramine (a noradrenergic uptake blocker) has been shown to similarly attenuate a CTA induced by methylamphetamine but not LiCl (Wagner, Foltin, Seiden, & Schuster, 1981). In this latter study, significant inverse correlations were observed between brain dopamine levels in the caudate or cortex of rats and the magnitude of the CTA induced by methylamphetamine in these animals. No such correlation was observed in animals conditioned with LiCl. In addition, depletion of brain norepinephrine by FLA-57, a dopamine beta-hydroxylase inhibitor, was found by Sklar and Amit (1977) to disrupt the CTA-inducing capacity of morphine while not affecting CTAs induced by LiCl or delta-9-THC. While some attenuation of ethanol CTA was observable due to the FLA-57 pretreatment, this effect did not reach levels of statistical significance. Noradrenergic involvement in the aversive stimulus properties of morphine was also investigated in a study conducted by Roberts & Fibiger (1977) in which 6-OHDA injection into the dorsal noradrenergic bundle was found to block the formation of a CTA induced by morphine (but

not amphetamine).

In partial contrast to the above findings, a recent study by Borsini and Rolls (1984) indicated that depletion of noradrenaline produced by injection of 6-OHDA into the basolateral region of the amygdala may serve to slightly attenuate a LiCl-induced taste aversion. Such a finding would appear consistent with the report by Grupp et al. (1976) that gross electrolytic lesions of the amygdala result in the failure of rats to exhibit strong CTAs induced either by LiCl or amphetamine (see previous section of this review). Specific connections of the amygdala may therefore be important for the mediation of CTAs induced by amphetamine or LiCl.

Despite some inconsistencies in the literature, the majority of the evidence cited above clearly supports the notion that distinct neurochemical mechanisms are involved in CTAs induced by self-administered drugs such as amphetamine, ethanol or morphine, in contrast to those CTAs induced by drugs which are not self-administered by animals. Moreover, the catecholamine systems implicated in the mediation of CTA induced by self-administered drugs are elsewhere strongly implicated in the mediation of these drugs' positive reinforcing properties (e.g., Fibiger, 1978; Phillips, 1984; Wise, 1980). For instance, treatments with AMPT or 6-OHDA have been shown to disrupt the positive reinforcing properties of morphine in rats (e.g., Davis & Smith, 1972) and the euphorogenic

properties of ethanol (Ahlenius, Carlsson, Engel, Svensson, & Soderstein, 1973) and of amphetamine in humans (Jonsson, Anggard, & Gunne, 1971). Administration of dopamine beta-hydroxylase inhibitors is also known to disrupt the positive reinforcing properties of ethanol and morphine in rats (Amit, Meade, & Corcoran, 1975, Davis & Smith, 1974; Davis, Smith & Khalsa, 1975).

Further evidence supporting the notion of a functional relationship between the positive reinforcing and CTA-inducing properties of self-administered drugs is provided by several studies investigating the potential role of particular neurochemical receptor populations in the mediation of CTA. Pimozide, a dopamine receptor blocker, has been found to attenuate CTAs induced by self-administered drugs (Grupp, 1977; Hunt, Switzman, & Amit, 1985; Sklar & Amit, 1977). Sklar and Amit (1977) demonstrated that pretreatment with pimozide served to attenuate CTAs induced by morphine or ethanol but did not alter CTAs induced by LiCl or delta-9-THC. Pimozide pretreatment has also been shown to attenuate CTAs induced by amphetamine (Grupp, 1977) and cocaine (Hunt, Switzman & Amit, 1985). In direct parallel to these findings, pimozide is also known to block self-administration both of amphetamine (Yokel & Wise, 1976) and cocaine (DeWit & Wise, 1977) in rats.

In a similar fashion, pretreatment with naloxone (ip), an opiate antagonist, acts to block both morphine

CTA (LeBlanc & Cappell, 1975; Van Der Kooy & Phillips, 1978) and to alter opiate self-administration (Weeks & Collins, 1976). Although naloxone pretreatment was found, in a study by Miceli, Marfaing-Jaillet and LeMagen (1979) to enhance both LiCl and ethanol CTAs, a more recent study, conducted in our own laboratory, indicated that pretreatment with naloxazone (a longer acting opiate antagonist) served to attenuate an ethanol-induced CTA (Ng Cheong Ton & Amit, 1984). Failure of naloxone to attenuate an amphetamine-induced taste aversion has also been reported (Goudie & Demellweek, 1980), a finding consistent with failure of naloxone to disrupt amphetamine self-administration (REF?).

In general, although seemingly 'paradoxical' (Cappell & LeBlanc, 1976; Goudie, 1979; Sklar & Amit, 1977), the most parsimonious account of the neurochemical evidence presented above would appear to indicate a strong functional relationship or perhaps a commonality between neurochemical systems mediating the positive reinforcing and the CTA-inducing properties of drugs which are self-administered by animals.

While brain catecholaminergic systems would appear to be particularly implicated in the mediation of CTA induced by positive reinforcing drugs, the role of central serotonergic mechanisms in CTA induced by various agents has not been as extensively explored. The data at present may be suggestive of a role for serotonin in

modulating the aversive stimulus properties of both emetic (LiCl) and SA (ethanol) drugs. In 1977, Lorden and Margules reported that both electrolytic and neurotoxicological lesions (by 5,7-dihydroxytryptamine) of dorsal and median raphe nuclei, which resulted in depletion of hypothalamic and telencephalic serotonin levels, served to produce a significant enhancement of a LiCl-induced CTA. Conversely, Lorden & Oltmans, (1978) reported that pretreatment with a low dose of the serotonin precursor dl-5-hydroxytryptophan (5-HTP) acted to prevent a LiCl CTA in raphe-lesioned rats while attenuating this CTA in normal rats. Interestingly, Zabik and Roache (1983) more recently reported that administration of 5-HTP immediately following novel exposure of rats to ethanol as a drinking fluid apparently resulted in a powerful CTA which was extremely resistant to extinction. These investigators reported that less powerful CTAs were produced by similar 5-HTP administration following exposure to saccharin or tartaric acid taste stimuli. Zimeldine, a selective serotonin uptake inhibitor, has also recently been demonstrated to induce a reliable CTA in rats (Gill & Amit, 1985). While central serotonergic neurons have been implicated in a range of aversive learning processes, the nature of their role in, for instance, altering subjective intensity of aversive stimuli or attentional and memory processes presently remains uncertain (Lorden & Oltman, 1978;

Ogren, Johansson, Johansson & Archer, 1982). There is also some recent evidence to suggest that a CTA induced by 5-HTP may be correlated with peripheral, but not central elevation of serotonin (Ervin, Carter, Webster, Moore, & Cooper, 1984). Overall, the CTA studies just described suggest that increased serotonergic activity may act to block a CTA induced by LiCl (Lorden & Oltmans, 1978) on the one hand and on the other, may serve to induce a CTA (Zabik & Roache, 1983; Gill & Amit, 1985). The resolution of these seemingly paradoxical findings must await further investigation.

However there is some indication that central serotonin does not play a significant role in taste neophobia (Borsini & Rolls, 1984; Royet, Gervais & Araneda, 1983). Depletion of norepinephrine but not of serotonin in the rat olfactory bulb was found to enhance consumption of a novel tasting fluid (reduce taste neophobia; Royet et al. 1983): Neither depletions of norepinephrine nor of serotonin in the basolateral region of the rat amygdala were found to alter taste neophobia, although depletion of norepinephrine did impair a LiCl CTA (Borsini & Rolls, 1984).

In this context, it should also be noted that these neurochemical data would seem to strongly support the point, presented in an earlier section of this introduction that taste neophobia and taste aversion conditioning are distinct phenomena. This is elegantly

illustrated in a study conducted by Ellis and Kesner (1981) who investigated the effects of injection into the rat amygdala of either physostigmine (an anticholinesterase) or of norepinephrine on taste associations. While, in a taste aversion paradigm, physostigmine administered soon after an ip injection of apomorphine served to attenuate the CTA induced by this drug, a similar norepinephrine injection did not alter this CTA. Conversely, identical norepinephrine injections served to prolong a taste neophobia when administered following exposure of animals to a novel taste, while similarly administered physostigmine injections had no effect on this measure.

Finally, it has been hypothesized that mechanisms involved in organismic responses to stress (Hennessy & Levine, 1979) may account for the CTA-inducing properties of a variety of agents (Braveman, 1977; Hennessey, Smotherman, & Levine, 1976; Riley, Jacobs & Lolordo, 1976; Riley, Zellner & Duncan, 1980). For instance, a strong correlation was found between plasma corticosterone levels, taken as an index of pituitary-adrenal activity, and the magnitude of a LiCl-induced CTA in rats re-exposed to a taste stimulus previously associated with administration of LiCl (Hennessy et al., 1976). It has also been suggested that different magnitudes of CTA observed across drugs (such as morphine and LiCl) may be explained on the basis of

differences in these drugs' unconditioned activation of the pituitary-adrenal system (see Braveman, 1977). Early handling of rats, a manipulation which was demonstrated to reduce pituitary-adrenal responsiveness to potentially stressful situations (i.e. neophobia), was also found to reduce the initial magnitude of a taste aversion induced by LiCl (Weinberg, Smotherman & Levine, 1978). In addition, the attenuation of CTA by prior exposure to the conditioned taste stimulus has also been hypothesized to be mediated by altered pituitary-adrenal activity (Riley et al., 1976; Weinberg et al., 1978). However, a more recent study using a multiple CS pre-exposure paradigm demonstrated a dissociation of behavioral (CTA) and pituitary-adrenal responses (Smotherman, Margolis & Levine, 1980). Moreover, Smotherman and Levine (1978) reported that the elevation in plasma corticosterone observed in animals re-exposed to a taste previously associated with LiCl would appear to be due to the apparent conflict inherent in a forced-choice CTA — paradigm. These authors have reported that when water-deprived rats are given a free choice to consume either water or the novel tasting fluid previously associated with LiCl, although a CTA is evidenced by reduced preference for the conditioned taste, no accompanying elevations in plasma corticosterone were observable.

Some support for a role of pituitary-adrenal

activation in mediating some forms of CTA is provided by a recent paper which demonstrated that pretreatment with dexamethasone, which inhibits pituitary release of adrenocorticotrophic hormone (ACTH) served to attenuate a CTA induced by X-irradiation (Cairnie & Leach, 1982). A CTA induced by epinephrine has also recently been reported (Caza, Brown, & Speir, 1982). Earlier studies have demonstrated that dexamethasone pretreatment disrupts the formation of a LiCl-induced CTA (Smotherman et al., 1976) while administration of ACTH or ACTH 4-10 prior to test presentations of the conditioned taste stimulus may retard the extinction of this CTA (Smotherman & Levine, 1978). There are also reports of the potentiation by ACTH 4-10 of a LiCl-induced CTA (Dray & Taylor, 1979) and of the potentiation of a morphine-induced CTA by simultaneous administration of ACTH (Sinyor, Switzman, & Amit, 1980). However, the efficacy of ACTH 4-10, a peptide devoid of apparent adrenocorticotrophic activity (deWeid, 1974) in mediating some of these effects mentioned above suggests that adrenal corticosterone release is not a necessary factor on these ACTH effects on CTA. Indeed, failure of adrenalectomy to disrupt a CTA induced by cyclophosphamide has been demonstrated (Ader, 1970). Also, no disruption of CTA was observed in hippocampal-lesioned rats despite the failure of these animals to exhibit elevations in plasma corticosterone seen in non-lesioned animals

exposed to taste aversion conditioning with LiCl (Smotherman, Burt, Kimble, Stickrod, BreMiller & Levine, 1980). As postulated in a paper by Hennessy, Smotherman and Levine (1980), the nature of dexamethasone and ACTH effects on CTA may be attributable to the influence of these agents on attentional or memory processes important in aversive conditioning. Consistent with such a notion is, for example, the finding that ACTH4-10 interferes with the discrimination of fentanyl, a potent narcotic, by rats (Colpaert, Nimegeers, Janssen, Van Ree, & DeWeid, 1978), an effect presumably mediated centrally.

In the context of the above discussion, it is interesting to note that an inverse relationship between the capacity of various opiates to elevate corticosteroid levels and their liability to be self-administered has recently been postulated (Lahti & Collins, 1982). These authors suggested that elevations in corticosteroid levels induced by different opiates may directly reflect these drugs' dysphoric properties. Seemingly contrary to this premise are the findings that hypophysectomy (but not adrenalectomy), served to interfere with the oral consumption of morphine in rats, while this consummatory behavior was reinstated following treatment with ACTH (Amit, Ziskind, Gelfand, & Hebert, 1977). Viable theoretical integration of the data discussed above, appears to require the necessary consideration of both attentional (e.g., see Hennessy et al., 1980) and

motivational factors (e.g., see Lahti & Collins, 1982) which together would appear to contribute to the positive reinforcing and/or aversive (CTA-inducing) stimulus properties of self-administered drugs such as opiates.

The Distinction between CTA induced by Emetic and Self-administered Drugs: Further Behavioral Evidence

In the preceding sections of this introduction the argument has been advanced that a categorical distinction can be made between CTAs induced by SA drugs and CTAs induced by various other, emetic agents not known to be self-administered by animals. Neurophysiological and neurochemical evidence has been cited which strongly substantiate this view. Also, it was suggested earlier that, based on certain behavioral observations (Parker, 1984; Switzman, 1985), the topographical patterns of response to the taste CS exhibited in these two hypothetical classes of CTA may possibly reflect corresponding differences in how the hedonic properties might be modulated within these CTA phenomena (see first section). There are, in addition, a number of specific behavioral findings reported within the CTA literature which serve to further establish CTA induced by SA drugs as a categorically distinct phenomenon. These data will be reviewed in the present section. It is

proposed that when considered as a whole, this behavioral evidence promises to provide a firm basis for the development of a comprehensive strategy by which CTAs induced by reinforcing drugs may be reliably differentiated from other forms of CTA. Furthermore, some of these data may also serve to provide additional support for the previously articulated hypothesis that a functional relationship exists between the positive reinforcing and CTA-inducing properties of drugs which are self-administered by animals.

First, there would appear to be an important difference in the dose-response characteristics of CTAs induced by self-administered drugs and CTAs induced by a variety of other agents. For example, a linear dose-response relationship has been demonstrated for LiCl-induced CTA (Nachman & Ashe, 1973) in which increasing doses of LiCl induce increasing magnitudes of CTA after a single conditioning trial. Similar linear dose-response functions are reported for CTAs induced by X-irradiation (Revusky, 1968) or delta-9-THC (Elsmore & Fletcher, 1972). In contrast, curvilinear dose-response functions are observable in CTAs induced by SA drugs such as morphine (Farber, Gorman & Reid, 1976; Riley, Jacobs & Lolordo, 1976; Switzman, Hunt & Amit, 1977); Leu-enkephalin (Switzman, Hammer, Shizgal & Amit, 1977); amphetamine (Cappell & LeBlanc, 1971) or methylphenidate (Riley & Zellner, 1978). This inverted-U pattern of dose

response, in which drug doses higher than some optimal intermediate dose either fail to induce a greater CTA, or indeed may induce weaker CTA, is consistent with the view, articulated earlier, that these CTAs cannot be considered to primarily reflect drug toxicity per se.

A notable exception to this characteristic curvilinear dose-response pattern in CTAs induced by self-administered drugs would seem to be found in the case of ethanol-induced CTA (Kulkosky, Sickel, & Riley, 1980; Lester, Nachman, & LeMagen, 1970). The absence of an inverted-U dose function in ethanol CTA, however, is consistent with the notion that the aversive effects of high doses of ethanol may primarily be mediated by peripheral toxicosis induced by elevated blood levels of acetaldehyde, the primary metabolite of ethanol (Brown, Amit, Smith, & Rockman, 1978). Further evidence in this regard has recently been provided (C.M.G. Aragon, personal communication). In this study, pretreatment with AMPT, at a dose (75 mg/kg) presumed to be maximally effective in depleting brain catecholamine levels, served to block a CTA induced by a low dose (.2g/kg) of acetaldehyde. However, an identical AMPT pretreatment failed to alter a CTA induced by a higher (.3g/kg) acetaldehyde dose, although a faster recovery over repeated extinction trials was observed due to this pretreatment. Accordingly, while the CTA induced by the lower dose of acetaldehyde would appear to have been

mediated centrally, the higher acetaldehyde dose CTA appeared to reflect non-catecholaminergic (and perhaps peripheral) effects of this drug. It should be noted that while the toxic effects of elevated peripheral acetaldehyde levels are well-known (Sellers, Naranjo, & Peachey, 1981), centrally delivered (icv) acetaldehyde is known to be self-administered by rats (Amit, Brown & Rockman, 1977). In a related study (C.M.G. Aragon, personal communication) pharmacological depletion of brain (but not peripheral) acetaldehyde levels, using a catalase enzyme inhibitor (3-amino 2,4-triazole) was found to block a CTA induced by a standard dose of ethanol (1.2g/kg), while not altering CTAs induced by morphine or LiCl. Thus, it may be suggested that CTA induced by ethanol reflects both centrally-mediated effects potentially related to ethanol's positive reinforcing properties (observed at lower doses) and peripherally-mediated toxic effects (observed at higher doses). This apparently unique, dichotomous nature of ethanol as a CTA-inducing agent may, then, underlie the failure to observe the curvilinear dose-response pattern found in CTAs induced by other SA drugs.

A second distinctive feature of CTAs induced by SA drugs is the greater variability across subjects observed in such CTAs induced by morphine (Gorman et al., 1978; Riley, Jacobs & Lolordo, 1976) Leu-Enkephalin (Switzman et al., 1977); methylphenidate (Riley & Zellner, 1978)

and cocaine (Goudie, 1981) relative to that seen in CTAs induced by emetic agents such as LiCl (Gorman et al., 1978; Nachman & Ashe, 1973). A related phenomenon is the relatively greater magnitude of CTAs induced by emetic agents as compared to CTAs induced by positive reinforcing drugs (Farber et al., 1976; Gorman et al., 1978; Nachman & Ashe, 1973). While it is rare to find water-deprived rats exhibiting a total avoidance of the conditioned taste fluid in a standard, forced-choice CTA paradigm involving a self-administered drug such as morphine (Farber et al., 1976; Gorman et al., 1978), such behavior is found to occur more reliably in CTAs induced by emetic agents (Gorman et al., 1978; Kulkosky et al., 1980; Nachman & Ashe, 1973; Revusky, 1968). Again, while animals have been reported to exhibit such complete avoidance behavior in an ethanol-induced CTA (Kulkosky et al., 1980), this may be due to peripheral, toxic effects of high ethanol doses as described earlier.

A third distinctive feature characterizing CTAs induced by SA drugs in contrast to emetic CTAs, is derived from drug pre-exposure CTA experiments. In general, pre-exposure to a particular CTA-inducing agent over several days prior to taste aversion conditioning with this agent serves to subsequently disrupt the CTA otherwise observed in drug naive animals (see Braveman, 1979; Cappell & LeBlanc, 1975; Gámzu, 1977). An explanation of this phenomenon based on development of

drug tolerance would not seem sufficient to account for all the data associated with this effect (Cannon, Baker, & Berman, 1977; Cappell & LeBlanc, 1975; Hunt, Spivak, & Amit, 1985). An alternative hypothesis emphasized an associative interference effect of the drug pre-exposures due to formation of associations between the pre-exposure environment and drug stimulus effects prior to taste aversion conditioning (in the same environment). Support for this hypothesis came from the finding that, for example, the disruption of a LiCl-induced CTA by LiCl pre-exposure is found to be dependent on the presence of similar pre-exposure and conditioning environments (Battson & Best, 1979; Dacanay & Riley, 1982). However, the disruptive effects of morphine pre-exposure upon morphine-induced CTA are found to be independent of similar environmental cue factors (Dacanay & Riley, 1982; Stewart & Eikelboom, 1978). Moreover, the attenuation of an amphetamine CTA by LiCl pre-exposure also has been found to be similarly environment-independent (Ford & Riley, 1984). These data, then, may be interpreted to suggest that CTAs induced by SA drugs can be distinguished on the basis of the apparent independence of these CTAs from the environmental associative interference effects implicated in drug pre-exposure effects involving emetic agents.

A fourth distinctive feature of CTAs induced by positive reinforcing drugs is suggested by the results of

a study by Switzman, Fishman and Amit (1981) which investigated drug pre-exposure effects on CTAs involving both a drug (morphine) known to be readily self-administered by animals (e.g., Weeks and Collins, 1964) and drugs (diazepam and delta-9-THC) which are not known to be readily self-administered by rats (Schuster & Johansson, 19xx). The potential disruptive effects of pre-exposure to either morphine, diazepam, or delta-9-THC, were examined in relation to CTAs induced by each of these drugs. The dose level for each drug was chosen so that the different drug treatments were equal in their potency to induce CTA. Despite being equipotent as CTA-inducing agents, a clear asymmetry of the pre-exposure effects of these three distinct pharmacological agents was observed. As pre-exposure agents, serving to disrupt subsequent taste aversion conditioning, morphine was found to be the least effective of these three drugs, acting to alter only a CTA induced by itself. In contrast, pre-exposure to delta-9-THC blocked CTAs induced by morphine, diazepam, and delta-9-THC, and diazepam pre-exposure blocked the CTAs induced by morphine and diazepam, while only attenuating the delta-9-THC CTA. Of the CTAs induced by these three drugs, the morphine-induced CTA was found to be the most easily disruptable, being blocked by pre-exposures to either morphine, diazepam, or delta-9-THC. It was proposed that this asymmetry may be

related to the known positive reinforcing properties of these drugs or their absence. The aversive stimulus properties of positive reinforcing drugs such as morphine may be distinguished from those of drugs not having this positive reinforcing capacity, in that they appear relatively less effective as pre-exposure agents, and would seem also to be more vulnerable as CTA-inducing agents to disruption by drug pre-exposure.

As indicated above, certain distinctive features of CTAs induced by SA drugs may be used to differentiate these CTAs from taste aversions induced by emetic agents. Important differences in patterns of dose-response, between-subject variability, and optimal magnitudes of these CTAs were described in this regard. Support for separate categorization of these CTAs was indicated in that, while the disruptive effects on CTA of drug pre-exposure involving emetic agents would appear environment-dependent, similar pre-exposure effects involving positive reinforcing drugs were found to be independent of the pre-exposure and conditioning environmental cues. Furthermore, it was suggested that in the context of pre-exposure effects involving drugs differentiated in terms of their capacity to act as positive reinforcers, the positive reinforcing drugs may be relatively less effective as pre-exposure agents, and conversely may be relatively more susceptible to disruption by drug pre-exposure in general. It is

conceivable that no one of these distinctive features, summarized above, may always be sufficient as a means to differentiate CTAs in the manner proscribed. However, when taken as a whole, we suggest that these behavioral data do promise a firm basis for realistically applying the hypothesized distinction between the CTAs induced by SA drugs versus the more traditionally accepted form of CTA induced by agents considered to be primarily emetic in nature.

In the experiments to be presented below, further investigation into this hypothesized distinction is undertaken. As previously described, CTAs induced by emetic agents and SA drugs may potentially be differentiated on the basis of behavioral differences observed within a drug pre-exposure CTA paradigm. In Experiment 1, a potential extension of this phenomenon is examined. A dose-response relationship of LiCl pre-exposure disruption of LiCl CTA has been demonstrated (Cannon et al., 1975) in which pre-exposure to a higher LiCl dose resulted in stronger disruption of a subsequent LiCl CTA than was observed with pre-exposure to a lower LiCl dose. However there has been no parallel investigation of such a manipulation of pre-exposure drug dose involving a SA drug such as morphine. It has been demonstrated that the positive reinforcing properties of these drugs may be functionally related to their CTA-inducing properties (e.g., Sklar & Amit, 1977;

Switzman et al., 1978). Therefore it would follow that pre-exposure to a low dose of morphine, known to be self-administered by animals, may be equally as effective as pre-exposure to a higher drug dose in serving to disrupt a subsequent morphine CTA, despite any disparity in the aversive CTA-inducing stimulus properties of these drug doses. This hypothesis is the focus of the first experiment. Experiment 2 provides a further testing of this notion that the positive reinforcing properties of SA drugs such as morphine may be integrally related to these drugs' CTA-inducing properties. In this experiment, the capacity of a low, (non CTA-inducing) dose of morphine to maintain a previously established morphine CTA is examined. If the differential capacity of these distinct morphine doses to induce CTA reflects a simple dichotomy involving the presence of aversive stimulus effects at higher but not lower doses, then the lower morphine dose should not be expected to maintain a previously established CTA. Instead, such a procedure should result in a rapid extinction of this CTA. However, if, as previously postulated, the stimulus properties of these different morphine doses reflect a continuum of positive reinforcing effects functionally related to their CTA-inducing properties, then the lower, non CTA-inducing, dose of morphine should serve to maintain the morphine CTA. In Experiment 3, the capacity of naloxone, an opiate receptor antagonist, to block the

Disruptive effect of morphine pre-exposure on a subsequent morphine CTA is examined. Naloxone administration has been shown to disrupt both opiate self-administration (e.g., Weeks & Collins, 1976) and morphine CTA (Van Der Kooy & Phillips, 1978). As well, naloxone administration has been found to interfere with the discrimination of opiates within an animal drug discrimination paradigm (Shannon & Holtzman, 1976). The results of this third experiment, therefore, are expected to provide a confirmation that the pre-exposure effects of morphine on a morphine CTA are similarly mediated by opiate receptor activation. In Experiment 4, the capacity of pre-exposure to centrally (icv) administered morphine to disrupt a CTA induced by peripherally administered morphine is investigated. While centrally infused morphine is known to be self-administered by animals (Amit, Brown & Sklar, 1976), centrally-administered morphine does not appear to induce a reliable CTA (Hunt et al., 1983). Successful disruption of a subsequent morphine CTA by such pre-exposure, then, might serve to add support to the notion that an important commonality exists between the positive reinforcing and aversive stimulus properties of SA drugs such as morphine. In Experiment 5, a potential involvement of central cholinergic systems in the mediation of CTAs induced by the SA drugs morphine and amphetamine is investigated. This experiment is based on a previous report indicating

a cholinergic involvement in these drugs' positive reinforcing properties (Davis & Smith, 1975). In this latter study, pretreatment with atropine (a centrally-acting cholinergic receptor antagonist) was found to attenuate self-administration of morphine but to enhance amphetamine self-administration in rats. In the context of an hypothesized functional relationship between these drugs' positive reinforcing and CTA-inducing properties, a similar pattern of atropine pretreatment effects to alter CTAs induced by these SA drugs is, therefore, anticipated.

Experiment 1

The disruptive effect of prior drug experience upon the subsequent learning of a drug-induced conditioned taste aversion (CTA) in rats is a well established phenomenon (see reviews Braveman, 1977; Gamzu, 1977). While the development of drug tolerance has been proposed to account for this effect (Berman & Cannon, 1974; Cappell & LeBlanc, 1975, 1977; Goudie, Taylor, & Atherton, 1975); such a hypothesis fails to explain how animals given prior, non-contingent exposure to LiCl subsequently exhibit a disruption of taste aversion conditioning with either LiCl or ethanol (Cannon et al., 1977).

An associative interference explanation of the drug pre-exposure phenomenon (Batson & Best, 1979; Braveman, 1979; Rudy, Iwens & Best, 1977) emphasizes the importance of the association formed between environmental cues and the drug effect during drug pre-exposure. Such an association would be expected to interfere with subsequent efforts to form an association between exposure to a second (novel taste) cue and the same drug treatment. This interpretation predicts that if different environmental cues are present during pre-exposure and conditioning drug treatments, then the disruptive effect of drug pre-exposure should be attenuated. Just such a finding has been reported by Batson and Best (1979) and, more recently by Dacanay and Riley (1982), using LiCl as both pre-exposure and conditioning agent. In contrast, such a manipulation of environmental

cues fails to alter morphine pre-exposure effects on a morphine CTA (Dacanay & Riley, 1982; Stewart & Eikelboom, 1978). It would seem, therefore, that while an associative 'blocking' explanation is sufficient to account for disruption of LiCl CTA by pre-exposure to this drug, this explanation cannot account for morphine pre-exposure disruption of a morphine CTA. Interestingly, it would also appear that this explanation cannot be applied to LiCl pre-exposure blockade of a CTA induced by another drug. In a recent paper, Ford and Riley (1984) reported that attenuation of an amphetamine CTA by pre-exposure to LiCl is also environment independent.

The present study investigates the potentially disruptive effects of morphine pre-exposure upon the subsequent capacity of morphine to induce a CTA. This phenomenon is examined across a range of morphine doses, using a 4 x 4 factorial design, so that the effect of the drug pre-exposure at each dose level can be evaluated in terms of its impact upon the pairing of a novel taste with a variety of morphine doses. While the effect of manipulating the number of pre-exposures has been examined by several investigators (Braveman, 1975; Cannon, Berman, Baker & Atkinson, 1975; Elkins, 1974), there are few reports within this literature concerning manipulation of pre-exposure drug dose. Cannon et al. (1975) have reported a dose effect with LiCl pre-exposure. A lower drug dose used during the pre-exposure appears to be less effective than a higher dose in

attenuating a LiCl-induced CTA. It would be interesting, then, to see if such a relationship, between pre-exposure dose and disruption of CTA, might also be obtained with a self-administered drug such as morphine. Of particular interest in this context is the finding that morphine can simultaneously have both positive reinforcing and aversive effects (Switzman, Amit, White, & Fishman, 1978; White, Sklar, & Amit, 1977). It is conceivable, therefore, that pre-exposure to morphine at a dose range known to be self-administered by rats (but at which little or no aversive effects have been demonstrated) may yet potentially have disruptive effects upon the subsequent capacity of morphine to induce a CTA. This hypothesis is the focus of the present investigation.

Experiment 1a.

Method

Subjects

Subjects were 119 male Sprague Dawley rats weighing 350-400 g at the start of the experiment. The animals were individually housed in stainless steel cages with free access to laboratory chow and tap water prior to the onset of the experiment, and maintained on a 12:12 h light:dark cycle with lights on at 08:00 h.

Drugs

Morphine hydrochloride (Merck, Sharp, and Dohme Canada Ltd.) was dissolved in injectable Ringer's solution (Abbott Laboratories Ltd.).

Procedure

After two weeks adaptation to laboratory housing conditions, the animals were placed on a 23 h 40 min water deprivation schedule. For the following 7 consecutive days, tap water was available to the rats for a 20-min period at the same time each day in the home cage. The water was presented in stoppered plastic test tubes fitted with stainless steel ball-bearing spouts inserted through the wire mesh in the front of the cage. The pre-exposure injections were administered following the 20-min drinking period on Days 2, 4, and 6 of the experiment. Animals received intraperitoneal (ip) injections of either one of three doses of morphine (2.5, 5.0, 15.0 mg/kg) or saline in a volume of 1 ml/kg body weight.

On Day 8 (conditioning day), the animals were presented with a 0.1% saccharin solution for a 20-min period. Within a minute after termination of the drinking period, each pretreated group received ip injections of one of the three doses of morphine (2.5, 5.0, 15.0 mg/kg) or Ringer's. A total of 16 independent groups of rats were run (7-8 animals per group, see Table 1).

For the following 5 consecutive days, tap water continued to be available for 20-min drinking periods. On Day 14 (conditioning day 2) the saccharin solution was again presented for 20 min followed by the appropriate drug treatment. The cycle of conditioning trial followed by 5 intervening water days was repeated until all subjects

underwent 5 complete cycles. On Day 38 (test day), animals were presented with the saccharin solution for a 20-min period. Table 1 presents the factorial design of this experiment with all combinations of Pre-exposure (four levels) and Conditioning (four levels) treatments.

Table 1. Summary of Treatment Groups

Saccharin presentation Days 8, 14, 20, 32, 37	Pre-exposure Days 2, 4, 6	
Ringer's	Ringer's	n=7
	Morphine 2.5 mg/kg	n=8
	Morphine 5.0 mg/kg	n=7
	Morphine 15 mg/kg	n=7
Morphine 2.5 mg/kg	Ringer's	n=7
	Morphine 2.5 mg/kg	n=8
	Morphine 5.0 mg/kg	n=7
	Morphine 15 mg/kg	n=7
Morphine 5.0 mg/kg	Ringer's	n=7
	Morphine 2.5 mg/kg	n=8
	Morphine 5.0 mg/kg	n=8
	Morphine 15 mg/kg	n=7
Morphine 15 mg/kg	Ringer's	n=8
	Morphine 2.5 mg/kg	n=8
	Morphine 5.0 mg/kg	n=7
	Morphine 15 mg/kg	n=8

Results and Discussion

Prior to considering the saccharin intake data for each pre-exposure by conditioning group (see Table 1), the effect of the pre-exposure treatment upon water intake, and upon initial saccharin intake was examined. A one way ANOVA on the water intake of each preexposure group on day 7 (the day just preceding the first saccharin presentation), yielded a significant group effect ($F(3,115) = 7.58, p < .05$).

Orthogonal analyses were conducted to compare group means.

This analysis revealed that animals pre-exposed to morphine drank significantly less water than did animals given

Ringer's ($F(1,115) = 8.42, p < .025$). In addition, animals pre-exposed to 15 mg/kg morphine consumed significantly less water than did rats pre-exposed to 2.5 mg/kg morphine. A

similar one way ANOVA conducted on initial saccharin intake of the animals in the four pre-exposure groups yielded a significant group effect. ($F(3,115) = 6.61, p < .05$).

Orthogonal comparisons of group means revealed that animals pre-exposed to morphine drank significantly less saccharin than did animals given Ringer's ($F(1,115) = 11.3, p < .025$).

This suppressant effect of the morphine pre-exposure on water and saccharin intake in water-deprived rats has been previously reported (Sanger & McCarthy, 1980).

A three-way ($4 \times 4 \times 6$) ANOVA, with repeated measures, performed on the saccharin intake data revealed a significant three-way interaction ($F(45, 515) = 1.5, p < .03$). Subsequently, two-way (4×6) ANOVAs (repeated measures)

were performed for each conditioning group (see separate panels, Fig. 1). Post-hoc Tukey tests were conducted, when appropriate, using harmonic means when applied to group comparisons involving unequal sample sizes (Kirk, 1968).

For the Ringer's solution conditioning group (see panel A, Fig. 1), a significant increase in saccharin intake was observed primarily to the non-associative, suppressive effect of morphine pre-exposure on initial saccharin consumption mentioned previously. Post-hoc Tukey tests did not reveal any significant differences among the mean saccharin intake levels of individual pre-exposure groups (collapsed across days).

A significant Pre-exposure x Days interaction ($F(15,125)=4.25, p<.01$) was found for animals conditioned with the 2.5 mg/kg morphine dose (see panel B, Fig. 1). A simple main effects test showed no change in saccharin intake for the Ringer's pre-exposed group ($F(5,150) = 1, p<.05$). Thus, the 2.5 mg/kg conditioning dose did not induce a CTA. Post-hoc Tukey tests indicated no difference among morphine pre-exposed group means over saccharin days 2 to 6. The saccharin intake of the Ringer's pre-exposed animals was significantly less than that of the morphine 15 mg/kg pre-exposed group over these same days. In addition, on the second pairing day (P2), there was a significant difference between the Ringer's and the morphine 5 mg/kg group means.

For animals conditioned with 5 mg/kg morphine (see panel C, Fig. 1), a significant Days x Pre-exposure

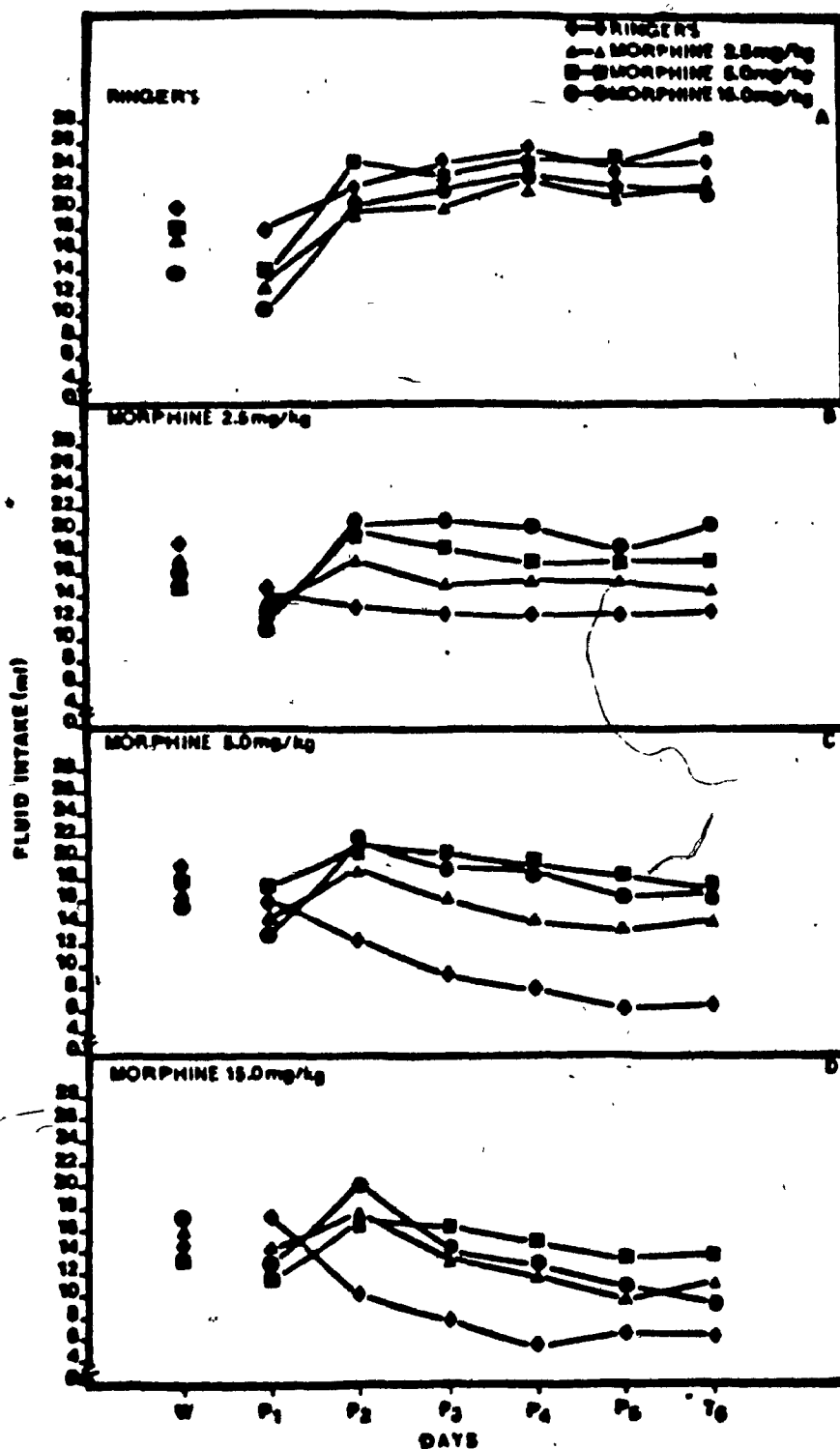


Figure 1. Saccharin fluid consumption (ml) of animals conditioned with either Ringer's vehicle or one of three morphine doses (2.5, 5.0 or 15.0 mg/kg) over six saccharin presentations (P1 to T6). Water consumption on the day preceding initial saccharin exposure (W) is also presented for each pre-exposure group within the different conditioning groups (panels A to D).

interaction was evident ($F(15,130)=39.59, p<.01$). A simple main effects test showed a significant reduction in saccharin intake for the Ringer's pre-exposed group ($F(5,156)=33.41, p<.01$). A significant CTA, then, was induced by the 5 mg/kg morphine conditioning dose. Post-hoc Tukey tests indicated that there was no significant difference in saccharin intake among the three morphine pre-exposed groups over saccharin days. Saccharin intake of the Ringer's group was significantly less than that of each morphine group over pairing days 2 to 6. As can be seen in Figure 1 (panel C), none of these morphine pre-exposed groups showed a reduction in saccharin intake. It therefore is apparent that pre-exposure to morphine at all three doses used was equally efficient in blocking the CTA induced by 5 mg/kg morphine.

Analysis of the saccharin intake data for rats conditioned with the 15 mg/kg morphine (see panel D, Fig. 1) revealed a significant Days x Pre-exposure interaction ($F(15,135)=20.71, p<.01$). A simple main effects test indicated a reduction of saccharin intake over days for the Ringer's pre-exposure group ($F(5,162)=14.5, p<.01$). The 15 mg/kg morphine conditioning therefore induced a robust CTA. Tukey tests showed there to be no difference between mean saccharin intake for the morphine pre-exposed groups (at all three doses) over saccharin days 2 to 4. On each of these pairing days, the Ringer's pre-exposed group mean was significantly less than that observed on days 2 to 4. On

each of these pairing days, the Ringer's pre-exposed group mean was significantly less than that observed for each of the morphine pre-exposure groups. The three pre-exposure doses of morphine, therefore were equally effective in blocking the 15 mg/kg morphine-induced CTA. On the fifth and sixth saccharin days (P5 and T6), only the 5 mg/kg pre-exposure showed greater mean intake of saccharin than was observed for the Ringer's pre-exposed group. In addition, on the sixth day (T6), the mean score for the 15 mg/kg pre-exposure group was significantly less than that of the 5 mg/kg dose. It is not presently clear why, over the last two saccharin days, the 5 mg/kg pre-exposure appeared to be more effective than the other morphine pre-exposure doses in attenuating the CTA induced by 15 mg/kg morphine. Such an effect was not observed with the 5 mg/kg morphine conditioning. All three pre-exposure doses, however, were equal in their capacity to attenuate the 15 mg/kg conditioning over the first four saccharin pairing days.

Experiment 1b

This study was subdivided into two separate sub-experiments, Part 1, and Part 2.

In Part 1, two low morphine doses (0.3 and 1.25 mg/kg) were tested for their capacity to induce CTA in animals given pre-exposure injections of Ringer's vehicle.

In Part 2, animals pre-exposed to one or the other of two morphine doses (0.3 and 1.25 mg/kg) were given taste aversion conditioning trials using doses of 5.0 or 15 mg/kg

morphine. These doses were shown in Experiment 1 to induce reliable CTAs.

Method

Subjects

Subjects were 51 male Sprague Dawley rats weighing 300-350 g at the start of the experiment. Housing conditions were the same as in Experiment 1.

Procedure

The procedure was the same as that used in Experiment 1. In the first sub-experiment (Part 1), rats were given pre-exposure injections of Ringer's vehicle (1 ml/kg) on days 2, 4, and 6 of a 23 h 40 min water deprivation schedule. Subsequently, on day 8, a novel 0.1% saccharin solution was presented in place of drinking water. Immediately following the drinking period, rats were injected ip with either Ringer's (n=8), 0.3 mg/kg morphine (n=7), or 1.25 mg/kg morphine (n=7). Over the next five days, the water deprivation schedule was continued. On day 14, saccharin presentation and drug administration were again conducted as on day 8. This cycle was repeated until six saccharin presentations had been given.

In a similar manner, in the second sub-experiment (Part 2), on days 2, 4, and 6 of a 23 h 40 min water deprivation schedule, animals were given pre-exposure injections of either 0.3 or 1.25 mg/kg morphine. On day 8, the 0.3 mg/kg morphine pre-exposed animals were presented with saccharin and subsequently injected (ip) with either 5.0 (n=7), or 15

mg/kg morphine. (n=8). Similarly, animals pre-exposed to 1.25 mg/kg morphine were given injections of either 2.5 (n=8), 5.0 (n=7) or 15 mg/kg morphine (n=7) following the saccharin drinking period. As in Part 1, this procedure of saccharin-drug pairing was repeated at 5 day intervals with the water deprivation schedule being continued on these intervening days.

Results and Discussion

Part 1. A two-way (Pre-exposure x Days) ANOVA, with repeated measures, was performed on the data (see panel A, Fig. 2). No significant difference was observed between the Ringer's pre-exposed animals conditioned either with Ringer's, 0.3, or 1.25 mg/kg morphine ($p > .764$). These data confirm that these low morphine doses are not effective when used as conditioning agents to reduce saccharin intake in a CTA paradigm.

Part 2. A two-way (Pre-exposure x Days, repeated measures) ANOVA revealed significant Days x Conditioning ($F(5,125)=7.29$, $p < .01$) and Days x Pre-exposure ($F(5,125)=4.65$, $p < .01$) interactions.

Post-hoc Tukey tests comparing the two pre-exposure groups collapsed across morphine conditioning doses (5 and 15 mg/kg) indicated that animals pre-exposed to the 0.3 mg/kg morphine dose drank significantly less saccharin than did animals pre-exposed to the 1.25 mg/kg on saccharin days 2, 3, 4, and 6. As can be seen in Figure 2, for animals conditioned with 5 mg/kg morphine that had been pre-exposed

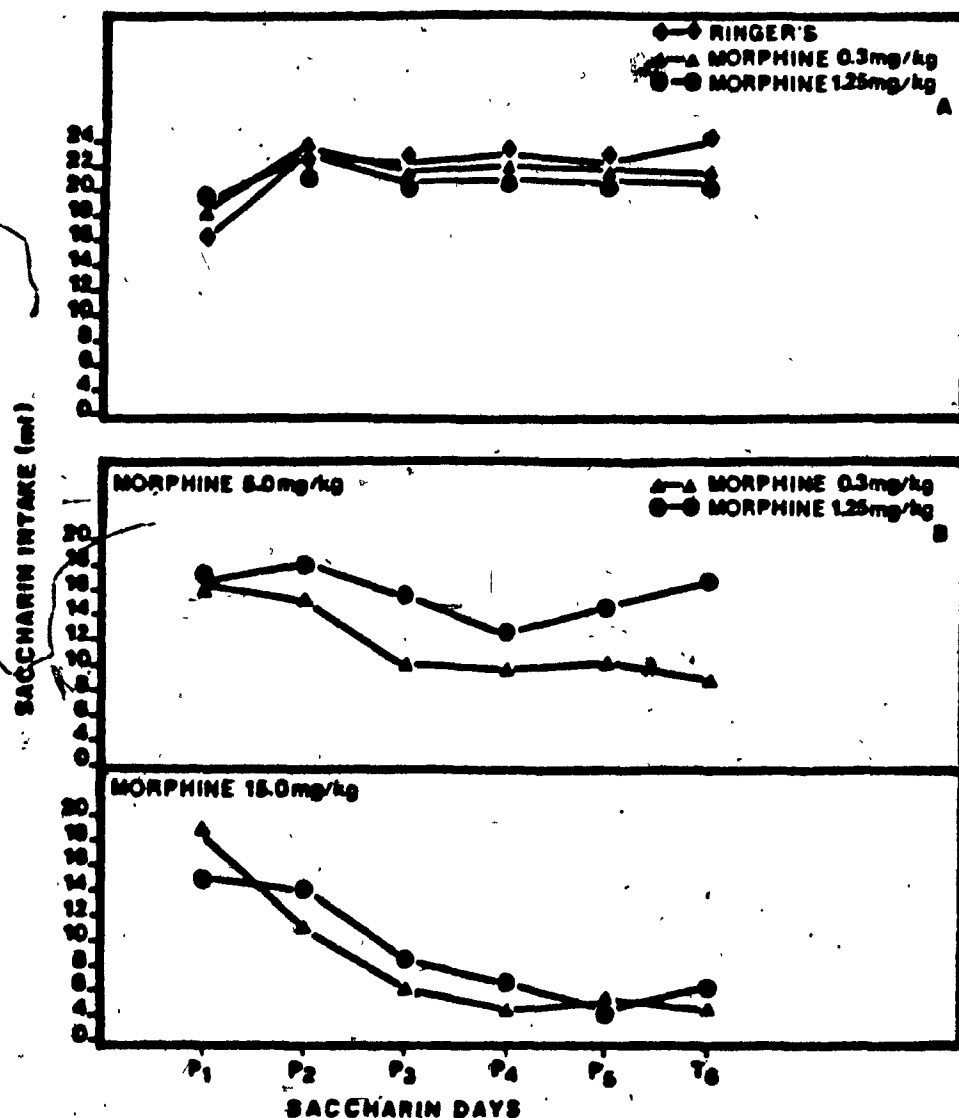


Figure 2. Panel A indicates saccharin consumption (ml) of drug-naive animals conditioned with either Ringer's or one of two morphine doses (0.3 or 1.25 mg/kg). In panel B, data are presented for animals conditioned with one of two morphine doses (5.0 or 15 mg/kg), given pre-exposure injections of either 0.3 or 1.25 mg/kg morphine.

to the 0.3 mg/kg dose, decreased saccharin intake was clearly observable over saccharin days. Thus, the 5 mg/kg morphine dose would appear to have induced a CTA in these animals, in a manner like that seen in Ringer's pre-exposed rats in Experiment 1a, (panel C, Fig. 1). In contrast, rats pre-exposed to the 1.25 mg/kg dose and then given conditioning trials with this 5 mg/kg dose failed to decrease their intake of saccharin (see Fig 2). Pre-exposure to a dose as low as 1.25 mg/kg morphine, then, would seem to be sufficient to block a morphine CTA induced by a moderate, 5 mg/kg dose. Examination of the data for rats given saccharin-morphine pairings using the higher 15 mg /kg dose (see Fig 2) suggests that the 1.25 mg/kg pre-exposure served to initially block the reduction in saccharin intake otherwise observed on the second saccharin day (P2) in the 0.3 mg/kg pre-exposed rats. However, this pre-exposure attenuation appeared to dissipate over subsequent saccharin days. These data indicate that a minimal effective dose in order to observe some disruptive effect of morphine pre-exposure upon morphine CTA is in the range of between 0.3 and 1.25 mg/kg.

General Discussion

The findings of the present study provide important new information concerning the discrimination of the motivational properties of morphine. In particular, these data suggest additional insights into what discriminative factors may be critically involved in determining morphine's

aversive (CTA-inducing) effects.

In Experiment 1a, three morphine doses, clearly distinguishable as differentially potent CTA-inducing agents, were found to be equipotent when evaluated as pre-exposure agents. These results demonstrate that providing the rat with prior experience with morphine's aversive (CTA-inducing) properties is not a necessary condition in order to observe the disruptive effect of non-contingent morphine pre-exposure on morphine CTA. In Experiment 1b, it was established that the minimal effective dose range to observe morphine pre-exposure disruption of morphine CTA is between 0.3 and 1.25 mg/kg, a dose range at which no CTA-inducing effects are observed. Such findings have significant implications in the context of the attempts within the CTA literature to identify the critical discriminative factors involved in the mediation of aversive effects of self-administered drugs such as morphine.

First, the equivalence of pre-exposure effect across morphine doses with different CTA-inducing properties reported in the present paper contrasts with a previous report concerning LiCl pre-exposure CTA effects. Cannon and colleagues (1975) suggested that an inverse relationship existed between dose of LiCl pre-exposure and the strength of a subsequent LiCl CTA. The higher of two pre-exposure doses appeared to be more effective than the lower dose in serving to attenuate CTAs induced by these two LiCl doses. The discrepancy between these findings and the present data may be interpreted in the context of other behavioral evidence indicating distinctive differences in CTAs

induced by SA and emetic drugs.

A second perspective from which possible insights into the present findings may be attained concerns the fact that while morphine is a drug known to be self-administered by rats (e.g., Weeks & Collins, 1964), LiCl is an emetic drug with no established properties of positive reinforcement. Parametric differences in CTAs induced by these two drugs, described previously, may well be directly related to this most important distinction between morphine and LiCl, based on hedonic valence. The distinctive characteristics of morphine CTA, then, can be seen to reflect the intrinsic complexity of morphine as an aversive stimulus. A critical finding is that morphine can have simultaneously both positive reinforcing and aversive properties (White et al., 1977; Switzman et al., 1978). The implications of this finding for the pattern of morphine pre-exposure effects reported in the present study are intriguing. The three doses of morphine investigated were found to be differentially effective in inducing CTA. While animals conditioned with the 2.5 mg/kg dose exhibited no significant reduction in saccharin intake over days, animals given .5 mg/kg demonstrated such a reduction only on the third conditioning day, and animals in the 15 mg/kg group exhibited an immediate CTA evidenced on the second saccharin day. In contrast to these differences observed in the potential aversive properties of the three morphine doses, the CTA-attenuating effects of pre-exposure at these doses was remarkably effective at all three doses. Thus, the 2.5mg/Kg dose, despite being ineffective as an aversive (CTA-inducing) agent, was very

effective when presented during pre-exposure in blocking the taste aversion conditioning impact of the two higher doses. Despite the considerable dissimilarity in the apparent aversive properties of these doses, pre-exposure to the low morphine dose was as effective as was pre-exposure to the high dose in blocking a strong morphine CTA. This would seem to be in conflict with the notion, implicit in an associative interference hypothesis, that the strength of the disruptive effects of drug pre-exposure is determined by the similarity of the psychopharmacological impact of the two agents involved in pre-exposure and conditioning treatments (Cannon et al., 1977). In order to account for the low dose pre-exposure effect within the context of this concept of stimulus similarity, it would be necessary to reconsider the nature of the discriminative and reinforcing properties of morphine within the CTA paradigm. Low doses of morphine, in the range used in the present study, have been shown to be self-administered by rats (e.g. Weeks & Collins, 1964). In that the capacity of morphine to induce a CTA has been demonstrated to be related to morphine's positive reinforcing properties (White et al., 1977; Switzman et al., 1977), the similarity of the low (2.5 mg/kg) and high (15 mg/kg) doses in terms of their respective positive reinforcing properties may over-ride any dissimilarity in respect to their capacity to induce a CTA. Consequently, it can be argued that a critical factor in determining morphine's ability to induce a CTA may not involve simply a discrimination of this drug's potentially 'aversive' effects, but rather may involve a discrimination of the more general stimulus properties

of morphine. A further evaluation of this hypothesis is presented in Experiment 2. In this study, the capacity of a low, non-aversive morphine dose to maintain a previously established morphine CTA is examined.

Experiment 2

In the previous experiment, pre-exposure to a low (2.5 mg/kg) morphine dose was found to block a morphine CTA. This dose was shown to have no aversive (CTA-inducing) properties, but has been demonstrated elsewhere to be within a dose range self-administered by rats (Weeks & Collins, 1964). The present study was designed to evaluate the capacity of this low dose of morphine to maintain a CTA initially induced by exposure to a higher morphine dose. It was hypothesized that if no important similarity were to exist between the positive reinforcing and CTA-inducing stimulus properties of morphine, then an attempt to maintain a previously established morphine CTA by continued taste-contingent exposure to a non-aversive morphine dose should lead to the eventual extinction of the CTA. Alternatively, if such a similarity were to exist, then such a strategy might serve to maintain the CTA in a manner similar to that observed in animals continuing to receive taste-contingent exposure to a higher morphine dose capable of inducing CTA.

Method

Subjects

Thirty-five male Sprague-Dawley rats, weighing 300-350 g, were housed in standard stainless steel cages for a week prior to the start of the experiment, with food and water available ad libitum. The animals were maintained on a standard 12:12 h light:dark cycle, with lights on at 08:00.

h.

Drugs

Morphine hydrochloride (May & Baker Ltd.) was dissolved in physiological saline. An injection volume of 1 ml/kg body weight was used.

Procedure

Animals were placed on a 23 h 40 min water deprivation schedule. Tap water was presented to each rat for 20 min daily in stoppered plastic tubes fitted with stainless steel ball-bearing spouts put through the front of the home cage. On day 8 of the water deprivation schedule, a novel 0.1% w/v saccharin solution was presented in place of the normal drinking water. Immediately following the saccharin presentation, animals were given intraperitoneal (ip) injections of either morphine or saline solution. On subsequent days the water deprivation schedule once again was presented as before. On day 14, the animals were given saccharin and drugs in a manner identical to that described for day 8. This procedure of saccharin-drug pairing followed by five intervening water days was repeated until ten such pairing days had been given. A final saccharin presentation without drug administration (test day) was given after a similar five day period following the last pairing day.

Five experimental groups (n=7) were run. In the first group (M0), the rats were given an injection of 15 mg/kg morphine on each of the first three pairing days (P1, P2, and P3). On subsequent pairing days (P4 to P10), these rats

received saline injections following the saccharin presentation. A second group (M1) similarly received injections of 15 mg/kg morphine over the first three pairing days. On subsequent days, these rats received injections of 2.5 mg/kg morphine. A third group (M2) received injections of 15 mg/kg on each pairing day (P1 to P10). A fourth group (M3) received an injection of 15 mg/kg on the first, a 10 mg/kg dose on the second, and a 5 mg/kg dose of morphine on the third pairing day. On subsequent pairings, these rats received injections of 2.5 mg/kg following each saccharin presentation. A final group (M4) received a 15 mg/kg injection of morphine on the first pairing day, and subsequently received morphine injections of 2.5 mg/kg over the remaining pairing days.

Results and Discussion

The results showed no significant differences among treatment groups in initial saccharin intake. Consequently, saccharin intake data (ml) for each animal were expressed as percent change from baseline intake as observed on the first saccharin-drug pairing day (P1). A two-way (5 x 10) ANOVA, with repeated measures, conducted on these data revealed a significant Days x Drug group interaction ($F(36, 270)=4.5$, $p<.01$). Post-hoc Tukey tests were performed comparing mean scores of the drug groups for each saccharin drug pairing day (see Fig. 3).

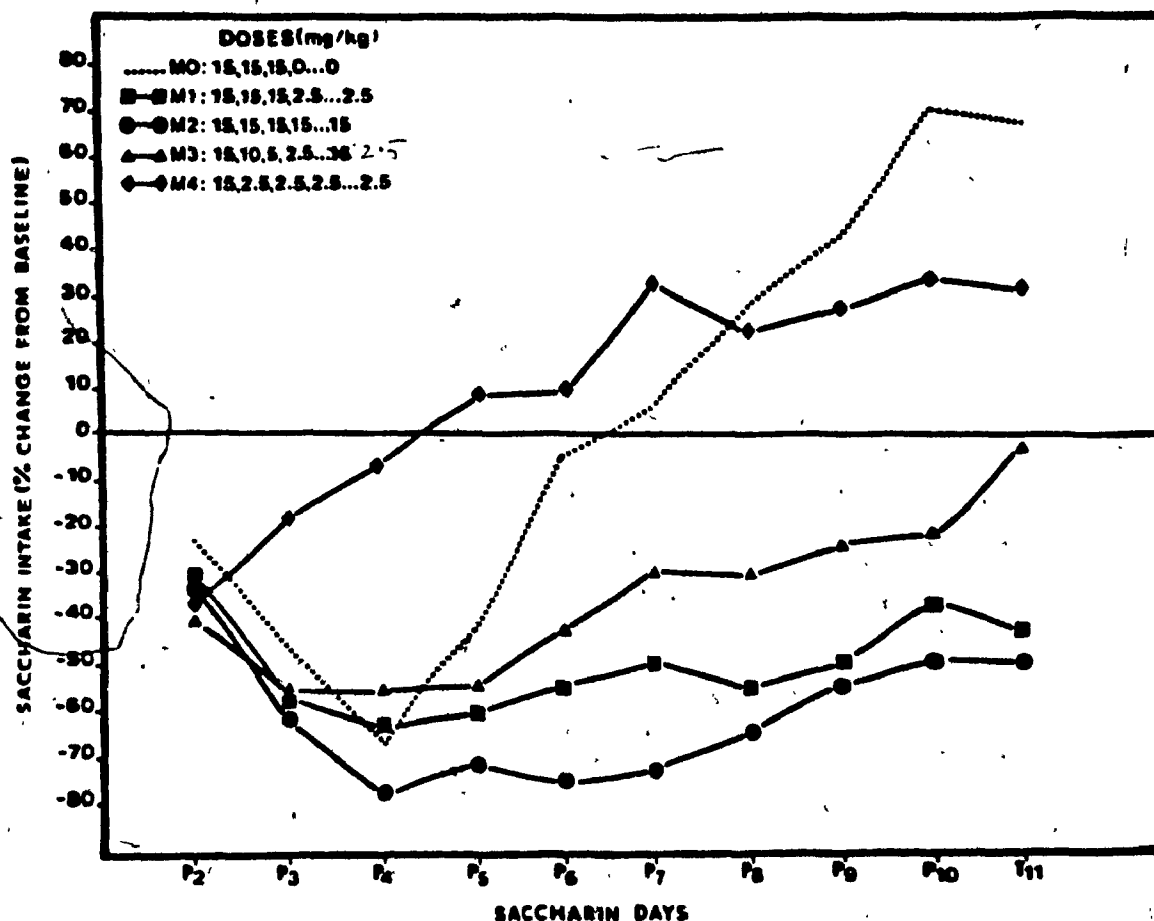


Figure 3. Percentage change from baseline saccharin intake over 9 subsequent pairing days and a final test day saccharin presentation. Three treatment groups were initially given saccharin paired with a 15 mg/kg morphine dose over pairing days P1 to P3, followed on subsequent conditioning days by saccharin-paired exposure to saline (Group M0), 2.5 mg/kg morphine (Group M1), or 15 mg/kg (Group M2). A fourth group (M3), received decreasing doses of morphine (15, 10 and 5 mg/kg) over the initial 3 pairing days, followed on subsequent days by 2.5 mg/kg morphine conditioning. A final group (M4) received a 15 mg/kg dose on P1, followed on subsequent pairing days by treatment with the 2.5 mg/kg morphine dose.

No significant differences were found among the M1, M2, and M3 drug groups over pairing days P2 to P10. On the final saccharin day (T11), the mean score for the M3 group was significantly different from that for group M2 ($p < .05$).

From the sixth pairing onward (P6 to T11), no significant difference was evident between the M0 and M4 groups. Significant differences were observed between these groups on pairing days P4 and P5, ($p < .05$).

The mean scores for the M4 group were significantly different from those of the M1, M2, and M3 groups from the fourth pairing day onward (P4 to T11). The mean scores of the M0 group were significantly different from the M1 and M2 groups on P6 and P7, ($p < .05$), and significantly different from M1, M2, and M3 on all subsequent days (P8 to T11, $p < .05$).

Thus a morphine CTA, established over three saccharin-drug pairings using a 15 mg/kg dose, was maintained over eight subsequent pairing days using a low, 2.5 mg/kg morphine dose. No difference was found between the scores of this group (M1), and a group which continued to receive 15 mg/kg of morphine on each pairing day (group M2). This low dose was shown in the previous experiment to be non CTA-inducing, as treatment with this dose did not result in any significant reduction in saccharin intake from baseline levels. However, several studies have demonstrated that this dose is self-administered by rats e.g., Weeks & Collins, 1964; 1979). It would therefore appear that exposure to the

predominantly positive reinforcing stimulus properties of morphine is alone sufficient to maintain a previously established morphine CTA.

Repeated pairings of a saccharin solution with the 2.5 mg/kg morphine dose following only a single saccharin-15 mg/kg morphine pairing (group M4) failed to maintain the initially observed reduction in saccharin intake over subsequent saccharin days (P4 to T11). Indeed, saccharin intake for these animals increased to 30% above their initial baseline level. Such a phenomenon would seem to be consistent with an evaluation of this 2.5 mg/kg morphine dose as non-aversive. However, repeated conditioning using the 2.5 mg/kg dose after pairing using decreasing morphine doses of 15, 10, and 5 mg/kg (group M3) was sufficient to maintain the morphine CTA. Thus it seems that in order for the 2.5 mg/kg dose to be effective in maintaining CTA behavior, at least two to three pairings of the novel saccharin taste with a CTA-inducing morphine dose must have occurred.

The present findings, then, add to the evidence suggesting an important similarity between the discriminative properties of low, non CTA-inducing doses and higher, CTA-inducing doses of morphine. Previous reports, based on behavioral and neurochemical data, has suggested that the discriminative stimulus properties of opiates are intrinsically complex (Colpaert, 1978). The results of the present study are consistent with this notion and would

appear to extend the consideration of such discriminative complexity to necessarily include distinct (positive reinforcing and aversive) motivational effects of these drugs. In the next experiment, the capacity of naloxone, an opiate receptor antagonist, to block the pre-exposure stimulus effects of morphine which serve to disrupt subsequent formation of a morphine CTA, will be examined.

Experiment 3

In the first experiment of this thesis, an investigation of the dose-response relationship involved in the disruptive effects of pre-exposure to morphine on a subsequent morphine CTA was conducted. In contrast to the disruptive effects of LiCl on a LiCl CTA, which were shown to be dose-dependent (Cannon et al., 1975), no such dose-relationship was observed in morphine CTA pre-exposure effects. Such a contrast in pre-exposure drug effects involving an emetic drug (LiCl) and a drug self-administered by animals (morphine) strengthens the notion that a qualitative distinction can be maintained between CTAs induced by emetic and SA drugs. In order to further explore the neurochemical mechanisms underlying the disruption of a morphine CTA by pre-exposure to this drug, the following experiment was performed.

Administration of naloxone, an opiate antagonist, has been demonstrated both to block a morphine-induced CTA (LeBlanc & Cappell, 1975; Van Der Kooy & Phillips, 1978) and to alter opiate self-administration (Weeks & Collins, 1976). The discriminative stimulus properties of opiates have also been shown to be disrupted by concomitant naloxone administration within an animal drug discrimination paradigm (Shannon & Holtzman, 1976). Accordingly, in the present experiment, the capacity of a similar naloxone administration to interfere with the disruptive effects of morphine pre-exposure on a morphine-induced CTA was

investigated. It was hypothesized that animals given pre-exposure injections of morphine accompanied by a concomitant injection of naloxone should subsequently exhibit a morphine-induced CTA similar in magnitude to that of saline pre-exposed (drug naive) animals. In contrast, animals given pre-exposure injections of morphine are expected to fail to exhibit a subsequent morphine CTA, in a manner similar to that observed in Experiment 1 of this thesis.

In order to evaluate any potential aversive (CTA-inducing) properties of naloxone at the dose used in this experiment during pre-exposure, an additional group was run in which drug-naive animals (given saline injections over pre-exposure days) were subsequently given injections of naloxone associated with the novel-tasting saccharin presented on repeated conditioning days.

Method

Subjects

Subjects were 43 male Sprague Dawley rats weighing 300-350 g at the start of the experiment. The animals were individually housed in stainless steel cages with free access to laboratory chow and tap water prior to the onset of the experiment. The animals were maintained on a 12:12 h light:dark cycle as in previous experiments.

Drugs

Morphine hydrochloride (Merck, Sharp & Dohme Canada Ltd.) and naloxone hydrochloride (Endo Laboratories, Inc.),

were each dissolved in physiological saline. An injection volume of 1 mg/kg body weight was used.

Procedure

A procedure was used here which was similar to that used in Experiment 1. Following adaptation to laboratory housing conditions, the animals were placed on a 23 h 40 min water deprivation schedule. The pre-exposure injections were administered following the 20 min drinking period on Days 2, 4, and 6 of the experiment. Animals received two ip injections, administered at the same time on either side of the midline of the abdomen, of either saline - saline; saline - morphine (15 mg/kg); naloxone (10 mg/kg) - saline, or naloxone (10 mg/kg) - morphine (15 mg/kg). Consequently, the animals were assigned to various conditioning treatment groups. In the saline - saline pre-exposure group, animals received conditioning injections of either saline (SS/S, n=5), or 10 mg/kg of naloxone (SS/N, n=7). Half of the naloxone - saline pre-exposed animals received injections of saline during conditioning (NS/S, n=7), while the remaining animals in this pre-exposure group were assigned to receive a conditioning injection of 15 mg/kg of morphine (NS/M, n=7). Both the naloxone - morphine (NM/M, n=7) and saline - morphine (SM/M, n=5) pre-exposed animals received injections of 15 mg/kg morphine during subsequent taste aversion conditioning trials.

On Day 8 (conditioning day), the animals were presented with a 0.1% saccharin solution for a 20 min period. Within a

minute after termination of the drinking period, each pre-exposure - conditioning group received ip injections of either morphine (15 mg/kg), saline, or naloxone (10 mg/kg) as previously described.

For the following 5 consecutive days, tap water continued to be available for 20 min drinking periods. On Day 14 (conditioning day 2), the saccharin solution was again presented for 20 min followed by the appropriate drug treatment. The cycle of conditioning trial followed by 5 intervening water days was repeated until all subjects underwent 5 complete cycles. On Day 38 (test day), animals were presented with the saccharin solution for a 20 min period.

Results and Discussion

A preliminary, one-way ANOVA showed no significant differences in water intake between the various treatment groups on the day prior to the first conditioning day ($F(6,42) = 0.97, p > 0.5$; see Fig 4). A two-way (3×6) ANOVA with repeated measures was initially performed on the data of the two saline-conditioned control groups (SS/S and NS/S) and the saline pre-exposed group subsequently conditioned with naloxone (SS/N) over the five saccharin pairing days and final test day (see Fig 4, panel A). This analysis revealed significant main effects of Treatment ($F(2,16) = 6.30, p < .01$) and of Days ($F(5,80) = 11.28, p < .01$), and a significant Treatment \times Days interaction ($F(10, 80) = 3.92, p < .01$). Post-hoc Tukey tests (using harmonic means when

required, see Kirk, 1968) indicated that the naloxone conditioning group (SS/N) consumed significantly less saccharin in comparison to that of the SS/S group on the last three saccharin days (P4 to T6) and less than that of the NS/S group on the last saccharin presentation (T6). Within-group Tukey comparisons showed no change in levels of saccharin intake of the SS/N animals over days, while an increase was observed for both SS/S and NS/S groups over days. The pattern of saccharin intake of the SS/N group indicated that naloxone, at the dose used in this study did not have CTA-inducing properties. However, as discussed in Experiment 1, the failure to increase saccharin consumption, observed in the naloxone-conditioned animals may be interpreted as evidence of a maintenance of taste neophobia.

Of potential interest is the finding that naloxone pre-exposed animals in the NS/S group exhibited a reduced level of saccharin consumption (greater neophobia) on the initial saccharin presentation (P1) relative to that observed in the SS/S group. No parallel difference was found however between the NS/S and SS/N groups on this measure. Such data, then, may be taken only as weak evidence of a reduction in initial saccharin intake induced by naloxone pre-exposure, a finding previously reported by Sanger and McCarthy (1980).

A second two-way (6 x 6) ANOVA with repeated measures was conducted for the data of all treatment groups excluding only the naloxone-conditioned, SS/N animals (see Fig 4,

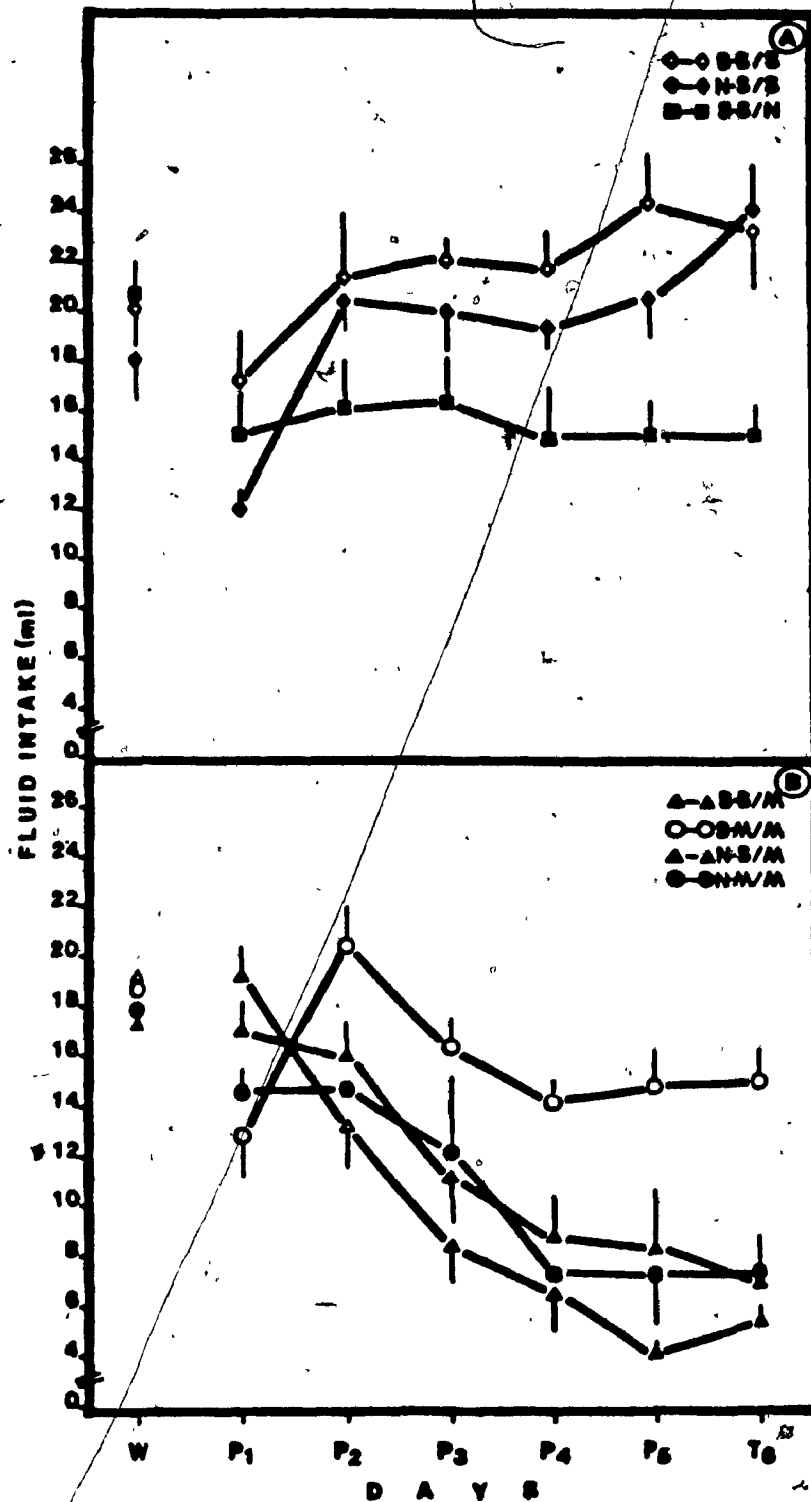


Figure 4. Panel (A). Saccharin consumption (ml) of animals given pre-exposure injections of either saline (S-S), or naloxone (N-S), and conditioned with either saline (S) or naloxone (N). In Panel (B) data are presented for morphine-conditioned animals pre-exposed to either saline (S-S), morphine (S-M), naloxone (N-S) or naloxone-morphine (N-M). Water intake (W) on the day prior to P1 is also shown.

panel B). While the data of the saline control groups, SS/S and NS/S, were included in this analysis, for reasons of visual clarity, these data are depicted only in panel A of Figure 4. Significant main effects of Treatment ($F(5, 30) = 14.24, p < .01$) and of Days ($F(5, 150) = 15.74, p < .01$) and a significant Treatment x Days interaction ($F(25, 150) = 12.73, p < .01$) were revealed by this analysis. Post-hoc Tukey tests were subsequently performed. On the initial saccharin day (P1), while a significantly lower level of saccharin intake was found for the NS/S group relative to that of the SS/M group, no other differences were observed. It should be noted here that the other treatment group (NS/M) pre-exposed to naloxone in a manner identical to that of the NS/S group, did not exhibit any similar reduction of initial saccharin consumption. Thus, it would appear that any such reduction in initial saccharin intake (increased neophobia) which might be attribute to naloxone pre-exposure must be considered cautiously as an essentially unreliable phenomenon.

Relative to the saline-conditioned control groups, NS/S and SS/S, animals conditioned with morphine (SS/M) exhibited reduced intake of saccharin from the second pairing day onward (P2 to T6). Within-group comparisons revealed that this SS/M group exhibited a significant reduction from its own baseline level of saccharin intake (P1) beginning from the third pairing day (P3), therefore indicating formation of a morphine-induced CTA. In contrast, no such reduction

was observed for the morphine-conditioned group pre-exposed to morphine (SM/M). Indeed, this group was found to show an increased level of saccharin consumption relative to that of the SS/M group from the second saccharin day (P2 to T6). The level of saccharin consumption for this morphine pre-exposed group was also higher in comparison to that of the NM/M group on days P5 and T6, and to that of the NS/M group on day T6. While an increase in saccharin intake was evident for the SM/M group on day P2, relative to this group's own baseline intake level, no further difference from this baseline value was found over remaining saccharin days P3 to T6. This failure of the SM/M group to exhibit an increase in consumption over saccharin days, as was observed in the NS/S and SS/S groups, is consistent with that pattern seen in morphine pre-exposed animals in Experiment 1. These data clearly indicate a blockade of the morphine-induced CTA by morphine pre-exposure.

Also noteworthy was the finding that the naloxone administered during morphine pre-exposure (in the NM/M group) would appear to have interfered with the morphine pre-exposure blockade of a morphine CTA. The NM/M group exhibited a significant CTA beginning from the fourth saccharin day (P4 to T6). Taken together, the data presented above clearly demonstrates that administration of naloxone serves to attenuate the disruptive effects of morphine pre-exposure on subsequent formation of a morphine-induced CTA. This finding therefore confirms that such effects of

morphine pre-exposure are mediated via naloxone-sensitive opiate receptors, in a manner consistent with previously published reports of similar opiate receptor involvement in both morphine self-administration (Weeks & Collins, 1976) and morphine CTA (Van Der Kooy & Phillips, 1977).

In Experiment 4, a further study is conducted investigating the role of central actions of morphine in mediating the disruptive effects of morphine pre-exposure on morphine CTA.

Experiment 4

The present study investigated the potential disruptive effects of pre-exposure to centrally (icv) administered morphine on a subsequent CTA induced by peripherally (ip) administered morphine. While animals are reported to self-administer morphine delivered centrally (icv; Amit, Brown & Sklar, 1976), morphine administered icv was reported to fail to induce a reliable CTA in rats (Hunt et al., 1983). However, the combination of central morphine plus peripherally (ip) administered naloxone did induce a significant CTA (Hunt et al., 1983). Aside from any specific interpretation of this aversive naloxone-morphine interaction, the above data would appear to suggest that morphine, when delivered via the intraventricular route, possesses positive reinforcing properties, but does not readily induce a CTA. In an earlier study, conducted by Greenshaw and Buresova (1982), it was found that another SA drug, amphetamine, when administered via the icv route, served to induce a CTA only at relatively high drug doses. The relative inefficiency of these SA drugs to induce a CTA when administered centrally suggests that some peripheral component of these drugs' actions may be important in mediating their CTA-inducing properties. In the present experiment a drug pre-exposure strategy similar to that used in Experiment 1 was used to test the hypothesis that pre-exposure to centrally administered morphine would serve to disrupt a subsequent morphine CTA induced by ip.

administered morphine. If a functional relationship exists between the positive reinforcing and CTA-inducing properties of SA drugs such as morphine, then CTA induced by peripheral morphine should be attenuated by pre-exposure to centrally administered morphine, although centrally administered morphine does not itself induce CTA.

Method

The present investigation was divided into two sub-experiments. In Part 1, a preliminary study was conducted in order to confirm the earlier finding that icv morphine does not induce a CTA (Hunt et al., 1983). In Part 2, animals pre-exposed to the same dose as was used in Part 1, subsequently underwent morphine taste aversion conditioning in a manner identical to that used in Experiment 1.

Subjects

Subjects were 67 male Sprague Dawley rats weighing 300-350 g at the start of the experiment. Housing conditions were the same as in Experiment 1.

Drugs

Morphine hydrochloride (Merck, Sharp & Dohme, Canada Ltd.) was dissolved in physiological saline. An injection volume of 1 ml/kg body weight was used for ip injections. Infusions of icv morphine or saline were given in a volume of 4 ul.

Procedure

Following adaptation to laboratory housing conditions, the animals were anesthetized with sodium pentobarbital (60 mg/kg). An intramuscular injection of 0.06mg atropine sulphate (Glaxo Laboratories, Canada) was also administered at this time. A stainless steel (22 gauge) cannula (Plastic Products Inc.) was implanted in each animal, stereotaxically aimed at the left lateral cerebral ventricle (co-ordinates AP -0.8 mm, L + 1.5 mm, V 3.5 mm, Incisor = 0.0). The cannula was secured in place by cranioplast cement anchored by 4 stainless steel screws. Nine animals randomly assigned to the first sub-experiment (Part 1) did not undergo this surgical procedure.

After a week to allow for post-operative recovery, the rats were placed on a 23 h 40 min water deprivation schedule as described in previous Experiments. For the purposes of the first sub-experiment (Part 1), the nine rats assigned to this study were otherwise left undisturbed over the initial seven days of the water deprivation schedule. The remaining rats received pre-exposure infusions (icv) of either morphine (10 ug/4ul) or an equivalent volume of saline on Days 2, 4, and 6, administered on each day following the 20 min drinking period. These infusions were administered, using a hand-held micro-syringe, over a 30 sec period, with an additional minute elapsing before removal of the infusion cannula.

On Day 8 (Conditioning day), the animals were presented with a novel 0.1% saccharin solution in place of their

drinking water. Immediately following the drinking period, animals assigned to Part 1 were either given ip injections of 15 mg/kg morphine ($n=5$), or were given icv morphine infusions (10 μ g/4 μ l) in a manner identical to that described above. Animals assigned to Part 2, that were given icv saline pre-exposure infusions, received either ip injections of 15 mg/kg morphine (group SM, $n=13$) or of saline (group SS, $n=14$). The rats given icv morphine pre-exposure received ip injections of 15 mg/kg morphine (group MM, $n=16$) or of saline (group MS, $n=15$).

For the following 5 consecutive days, tap water continued to be available for 20 min drinking periods. On Day 14, saccharin was again presented and appropriate drug treatments were administered as before. The cycle of conditioning trial followed by 5 intervening water days was repeated until all subjects underwent 4 complete cycles. On Day 32, a final saccharin presentation was given (Test day).

Results and Discussion

Part 1. A two way (2×5) ANOVA with repeated measures was performed on the data of animals given taste conditioning with either ip or icv morphine (see Fig 5). This analysis revealed a significant main effect of Treatment ($F(1,7) = 22.61, p < .01$), and a significant Treatment \times Days interaction ($F(5,35) = 6.71, p < .01$). Post-hoc Tukey tests indicated that while animals given ip injections exhibited reduced saccharin consumption both on days P4 and T5, animals receiving icv infusions of morphine

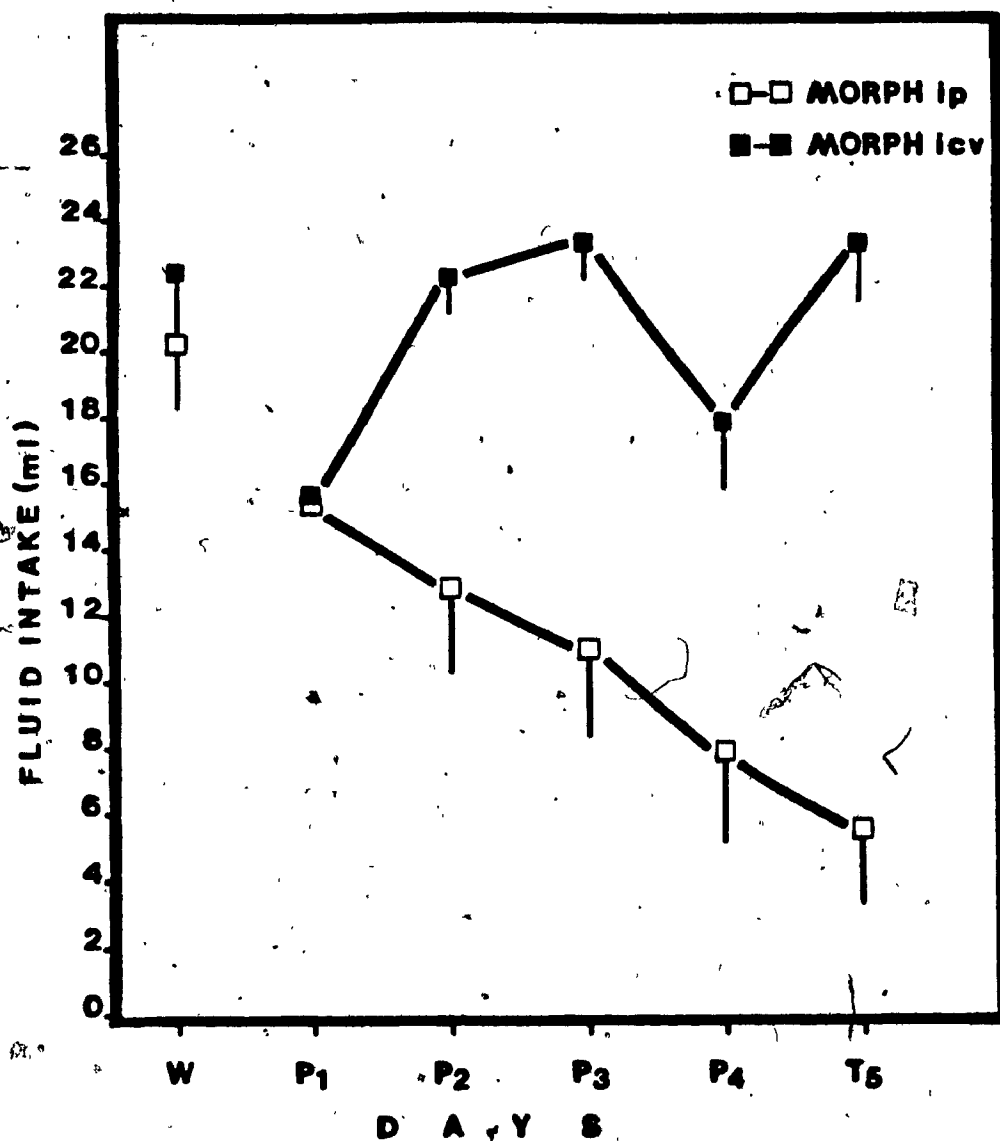


Figure 5. Saccharin consumption (ml) of animals conditioned with morphine administered intraperitoneally (Morph ip) or intracerebroventricularly (Morph icv). Water intake (W) for each group on the day preceding initial saccharin presentation is also shown.

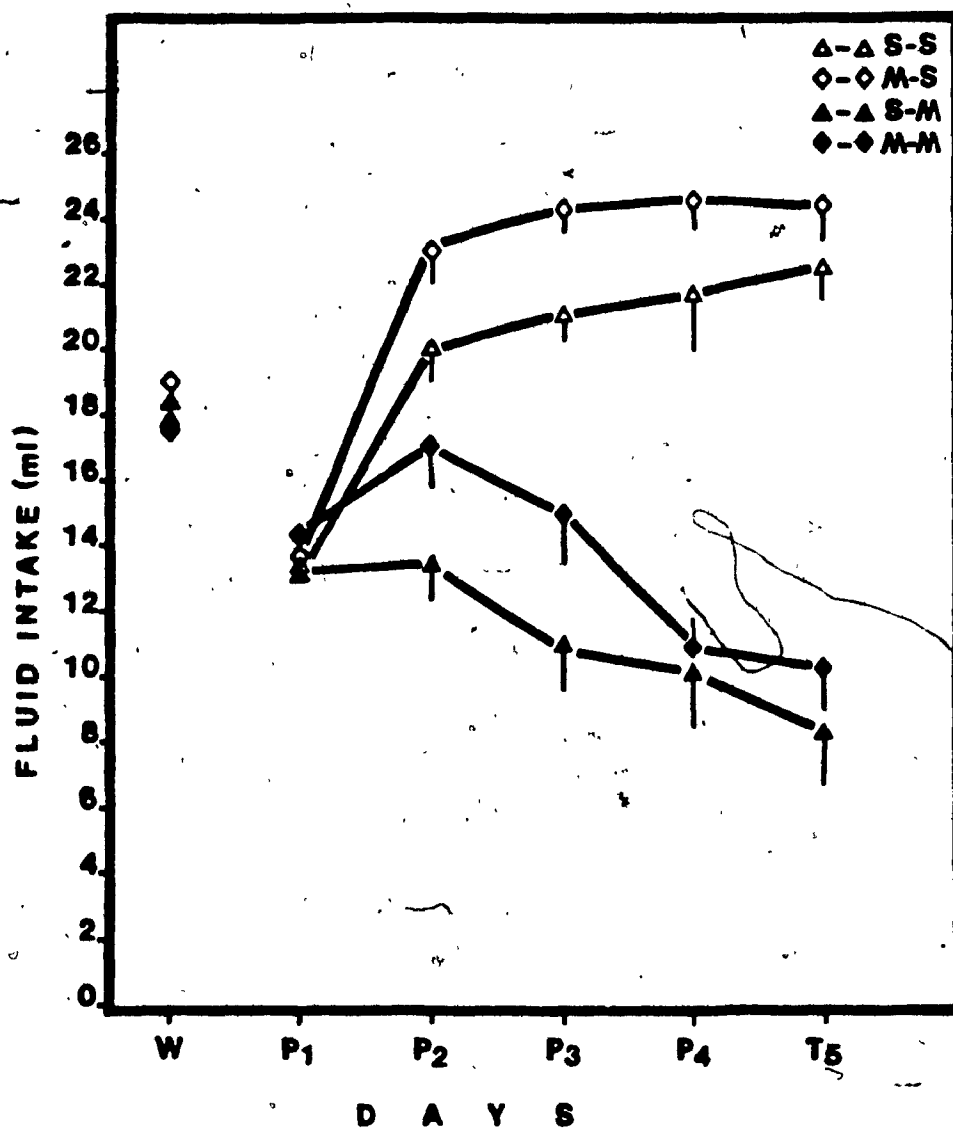


Figure 6. Saccharin consumption (mls) of animals pre-exposed to icv infusions of either saline (S) or morphine (M) and conditioned with ip injections of either saline (S) or morphine (M). Water intake on the day preceding initial saccharin exposure is also shown.

did not significantly alter their saccharin intake over conditioning days. These preliminary data would appear to confirm the previous report (Hunt et al., 1983) indicating failure of icv morphine to induce a reliable CTA.

Part 2. A three way ($2 \times 2 \times 5$) ANOVA with repeated measures revealed significant main effects of Pre-exposure ($F(1,55) = 5.39, p < .05$), of Conditioning ($F(1,55) = 95.77, p < .01$), and of Days ($F(4,22) = 13.87, p < .01$). A significant interaction of Conditioning \times Days ($F(4,22) = 36.1, p < .01$) was also observed (see Fig 6). Post-hoc Tukey tests indicated that animals conditioned with morphine exhibited a significant decrease in saccharin consumption on Days P4 and T5. Thus, a significant CTA was observed. As can be seen from Figure 6, the main effect of Pre-exposure would appear to reflect a greater level of saccharin intake for morphine pre-exposed animals both in the morphine conditioned (MM) and saline conditioned (MS) groups.

Two issues arise from consideration of these data. First, the pattern of effects observed due to icv morphine pre-exposure would seem in striking contrast to that observed following pre-exposure to ip morphine seen in Experiment 1. In this latter experiment, morphine pre-exposed animals were found to exhibit reduced intake both of water, on the day preceding the first saccharin presentation, and of saccharin, observed on the first conditioning day. In comparison, no such differences were apparent in either water intake or initial saccharin intake

for the icv morphine pre-exposed animals in the present investigation. Moreover these animals did show increased saccharin intake over subsequent saccharin days, an effect not observed in ip morphine pre-exposed animals in Experiment 1. Such differences in saccharin intake due to differing routes of administration of morphine pre-exposure would not appear, at present, to be readily interpretable. Whereas food and fluid intake are generally reported to be decreased by administration of opiate agonists (Sanger & McCarthy, 1980), administration of small doses of opiates and opioids appear to increase such consumption (see Sanger, 1983). In a finding of potential relevance to the present findings, icv administration of beta-endorphin is reported to increase food intake in rats (McKay, Kenney, Edens, Williams & Woods, 1981). Also, in a study comparing the capacity of naloxone administered peripherally and naloxone administered intraventricularly, to suppress food and water intake in deprived rats, a suppressive effect was observed with peripheral but not central naloxone administration (Hynes, Gallagher & Yaws, 1981). Such evidence is suggestive of the potential importance of route of administration (central versus peripheral) in drug exposure studies determining the effect of opiates on food and water intake. However, in comparison to the findings of Experiment 1, the data from the present study would seem problematic for any proposed interpretation based either on differential effects of dose or route of administration. Specifically, while in

Experiment 1, a decrease in both water and initial saccharin intake was observed following ip morphine pre-exposure, the increase in saccharin intake of icv morphine pre-exposed animals seen in the present study, was only observed on the second saccharin presentation (Day 14, P2), eight days after the last icv morphine pre-exposure (Day 6).

A second issue introduced by the present findings is more pertinent to the major focus of the experiment. Clearly, the observed increase of saccharin intake in saline conditioned animals pre-exposed to icv morphine, precludes the interpretation of any potential disruptive effects of this morphine pre-exposure on the development of a CTA in the morphine conditioned animals. The hypothesis that pre-exposure to the positive reinforcing stimulus properties of centrally administered morphine may result in a subsequent disruption of a morphine-induced CTA must, accordingly, remains presently unresolved.

The following experiment provides an investigation of the potential involvement of a specific neurochemical (cholinergic) system, previously implicated in the mediation of some of the positive reinforcing properties of morphine and amphetamine, in the mediation of these drugs' CTA-inducing properties.

Experiment 5

As previously discussed, a functional relationship has been proposed to exist between the positive reinforcing and CTA-inducing properties of SA drugs. Catecholaminergic systems involved in the mediation of the positive reinforcing properties of SA drugs such as morphine and amphetamine have also been implicated in the mediation of their capacity to induce CTA (e.g., Goudie et al., 1975; Sklar & Amit, 1977). In the present study, the potential involvement of central cholinergic systems in mediating the CTA-inducing properties of morphine and of amphetamine was investigated. In a previous study, Davis and Smith (1975) reported that pretreatment with atropine, a centrally acting muscarinic receptor antagonist, served both to attenuate self-administration of morphine, and to enhance amphetamine self-administration in rats. Additionally, these investigators found that administration of the peripherally-acting cholinergic antagonist, methylatropine, did not serve to alter the self-administration of these drugs. Thus it would appear that central, but not peripheral cholinergic systems are involved in the neurochemical mediation of morphine and amphetamine positive reinforcement. In that common neurochemical systems were hypothesized to be involved in both the positive reinforcing and CTA-inducing properties of these drugs, the present investigation examined the potential involvement of central cholinergic systems in the mediation of morphine and

amphetamine CTA. It was predicted that if such a functional relationship were to exist, then a similar pattern of effects of atropine and methylatropine pretreatment on morphine and amphetamine induced CTA should be observed as was observed in the study by Davis and Smith (1975).

Accordingly, in Experiment 1a, it was hypothesized that atropine pretreatment should serve to block a morphine induced CTA, in a manner similar to the previously reported blockade of morphine positive reinforcement (Davis & Smith, 1975). Moreover, methylatropine pretreatment should not attenuate the morphine CTA. In parallel, in Experiment 1b, it was hypothesized that atropine pretreatment should serve to enhance an amphetamine induced CTA, while pretreatment with methylatropine should not have any significant modulating effect. In order to evaluate any potential disruptive effects of these particular atropine and methyl-atropine pretreatments on the acquisition of a CTA induced by an emetic agent (Deutsch, 1978), an additional group of animals in this second experiment underwent LiCl taste conditioning following pretreatment with these cholinergic antagonists.

Experiment 5a

In this first experiment, the potential effects of atropine and methylatropine pretreatment on a CTA induced by morphine were examined.

Method

Subjects

Subjects were 42 male Sprague Dawley rats weighing 300-350 g at the start of the experiment. Housing conditions were the same as in the previous experiments.

Drugs

Morphine hydrochloride was dissolved in saline as before. Atropine sulphate and atropine methyl bromide (Sigma Chemical Company) were similarly dissolved in physiological saline. An injection volume of 1 ml/kg body weight was used.

Procedure

A standard CTA procedure similar to that used in Experiment 1 of this thesis was adopted here. Following a period of adaptation to laboratory housing conditions, animals were placed on a 23 h 40 min water deprivation schedule. On Day 8 (Conditioning Day) animals were given ip injections of either atropine (0.6 mg/kg), methylatropine (0.6 mg/kg) or saline, 40 min prior to presentation of a novel 0.1% saccharin solution given in place of their normal drinking water. Immediately following termination of the 20 min drinking period, animals were given ip injections of either morphine (15 mg/kg) or saline. A 3 x 3 factorial design was used here such that 5 animals in each pretreatment (saline, atropine or methyl-atropine) group received conditioning injections of saline (groups SAL-SAL, AT-SAL, and MA-SAL, n=5 respectively). The remaining 9 animals in each pretreatment group received injections of

morphine on each saccharin conditioning day (groups SAL-MORPH, AT-MORPH, and MA-MORPH, $n=9$ respectively). On Day 14, (Conditioning Day) drug treatments and saccharin presentation were given as on the first conditioning day. This cycle of conditioning trial followed by five intervening water days was repeated until three conditioning trials had been performed. On the sixth day following the third conditioning day, a final saccharin presentation was given (Test Day).

Results and Discussion

A one way ANOVA performed on levels of initial saccharin intake of the various treatment groups on the first conditioning day showed no significant differences in baseline saccharin consumption ($F(5,41) = 0.93, p < .5$). Accordingly, the saccharin intake data of each animal were expressed as percentage change from baseline consumption level. A three way ($3 \times 2 \times 3$) ANOVA, with repeated measures was subsequently performed on the transformed data (see Fig 7). This analysis revealed significant main effects of Conditioning ($F(1,36) = 28.02, p < .01$), and of Days ($F(2,72) = 8.42, p < .01$) and significant interactions of Pre-exposure \times Conditioning ($F(2,36) = 5.95, p < .01$) and of Conditioning \times Days ($F(2,72) = 4.62, p < .05$). Dunnett's tests ($p < .05$; see Kirk, 1968) indicated that whereas both saline and methylatropine pretreated groups in the saline conditioned animals (SAL-SAL and MA-SAL) exhibited an overall increase in saccharin intake over days, no change in

saccharin intake was found in atropine pretreated animals conditioned with saline (AT-SAL). Although atropine is known to suppress drinking (Stein, 1963), this cannot account for the present data, in which no suppressive effect of atropine on drinking was found on initial saccharin presentation. As well, the saccharin intake of the AT-SAL, saline-conditioned animals remained near baseline levels even on the final (Test Day) saccharin presentation, when no atropine pretreatment was given. It may be speculated that the failure to observe an increase (maintenance of neophobia) in saccharin intake in the atropine pretreated animals (AT-SAL) is consistent with reports within classical conditioning paradigms that atropine but not methylatropine, may interfere with habituation to the conditioning stimuli (e.g., Downs et al., 1972).

In animals conditioned with morphine, Dunnett's tests revealed that whereas both saline and methylatropine pretreated animals (SAL-MORPH and MA-MORPH) exhibited a significant decrease in saccharin intake (indicating a morphine-induced CTA) no significant change from baseline saccharin intake levels was observed in animals pretreated with atropine prior to morphine conditioning (AT-MORPH). Thus, pretreatment with atropine, but not methylatropine served to block the formation of a morphine-induced CTA. This effect was consistent with the findings of Davis and Smith (1975) where atropine, but not methylatropine, was found to block morphine self-administration. These data,

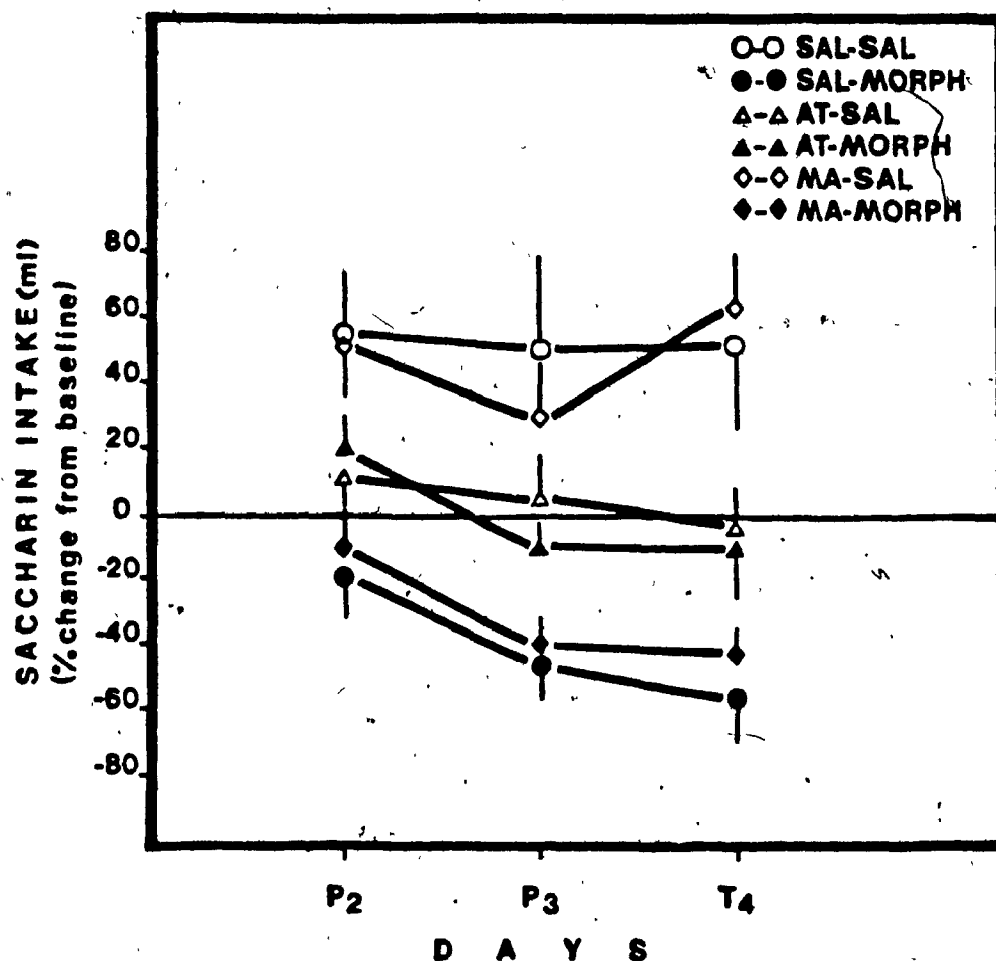


Figure 7. Saccharin fluid intake (ml), expressed as percent change from initial baseline level of consumption (on P1), of animals pretreated with either saline (SAL), atropine (AT) or methyl-atropine (MA), and conditioned with either saline (SAL) or morphine (MORPH).

therefore, support the hypothesis that a functional relationship exists between the CTA-inducing and positive reinforcing properties of morphine.

Experiment 5b

This second experiment examined the potential effects of atropine or methylatropine pretreatment on CTAs induced by either amphetamine or LiCl.

Method

Subjects

Subjects were 74 male Sprague Dawley rats weighing 300-350 g at the start of the experiment. Housing conditions were identical to those used previously.

Drugs

D-amphetamine sulphate (Smith, Kline & French, Canada, Ltd) was dissolved in physiological saline, as were atropine sulphate and atropine methyl bromide (Sigma Chemical Company). The injection volume of these drugs was 1 ml/kg body weight. LiCl was dissolved in distilled water to make a final 0.15 Molar solution and was injected in a volume of 3 ml/kg body weight.

Procedure

An identical procedure to that used in the preceding experiment was followed here. On Day 8 (conditioning day) of a 23 h 40 min water deprivation schedule, animals were pretreated with ip injections of atropine or methylatropine (0.6 mg/kg), or saline as previously described. Forty minutes later, a novel 0.1% saccharin solution was presented

in place of the normal drinking water. Immediately following the 20 min drinking period, animals were given ip injections of either distilled water (3 ml/kg), amphetamine (1 mg/kg) or LiCl (3ml/kg of a .15 M solution). A 3 x 3 factorial design was used such that saline pretreated animals received conditioning injections of either distilled water (SAL-VEH, n=8), amphetamine (SAL-AMPHET, n=9) or LiCl (SAL-LiCl, n=7). Similarly, methylatropine pretreated animals received conditioning exposure to either distilled water (MA-VEH, n=8), amphetamine (MA-AMPHET, n=9), or LiCl (MA-LiCl, n=8). And finally, atropine pretreated animals received conditioning injections of either distilled water (AT-VEH, n=8), amphetamine (AT-AMPHET, n=9) or LiCl (AT-LiCl, n=8). Three conditioning days and a final test day were given as in Experiment 5a.

Results and Discussion

Separate statistical analyses were performed on the data of the amphetamine and LiCl treated animals with the vehicle conditioning groups serving as controls for both analyses. One way ANOVAs indicated no significant differences in baseline saccharin intake between treatment groups on the first conditioning day, both for the amphetamine ($F(5,45) = 1.37, p > .7$) and LiCl ($F(5,46) = 1.43, p > .7$) analyses. The data was accordingly expressed as percent change from baseline scores as in the preceding experiment. Separate three way (3 x 2 x 3) ANOVAs with repeated measures was performed on data of the amphetamine and LiCl groups as

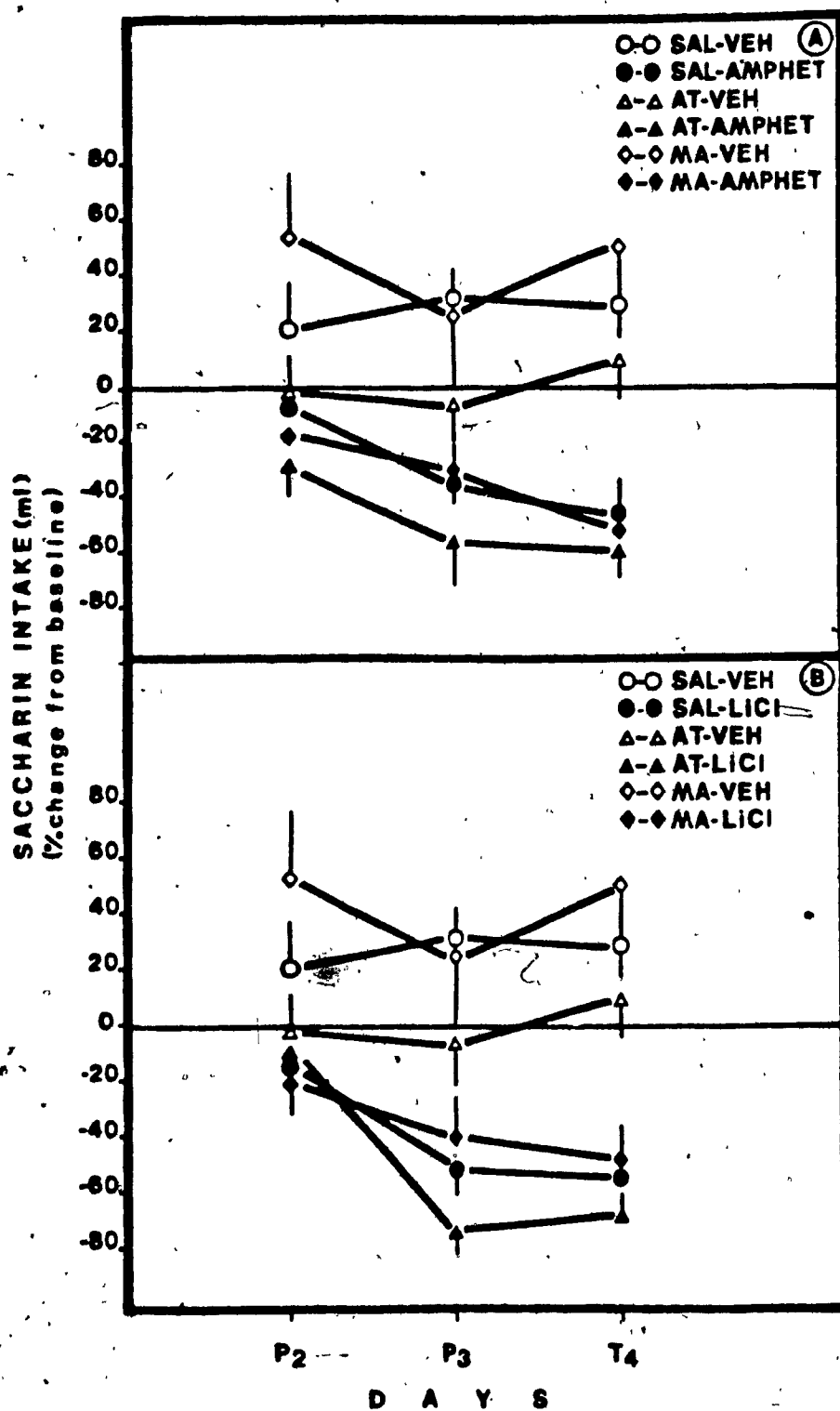


Figure 8. Saccharin intake (ml) expressed as percent change from baseline saccharin consumption (on P₁) of animals pretreated with either saline (SAL), atropine (AT) or methyl-atropine (MA) and conditioned with either vehicle (VEH) or amphetamine (AMPHET; see Panel A), or lithium chloride (LiCl; see Panel B).

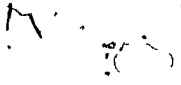


mentioned above.

The ANOVA for the amphetamine conditioned animals (and appropriate vehicle control groups, see Fig 8, panel A) revealed significant main effects of Pre-treatment ($F(2,45) = 3.26, p < .01$), of Conditioning ($F(1,45) = 36.51, p < .01$), and of Days ($F(2,90) = 6.87, p < .01$). A significant Conditioning x Days interaction was also evident ($F(2,90) = 7.98, p < .01$). Examination of the data of the vehicle conditioned animals suggests a similar pattern of effects as observed in Experiment 5a. Dunnett's tests indicated that only the MA-VEH group showed an increased saccharin consumption (on Days P2 and T4). In amphetamine conditioned animals, a significant decrease from baseline intake levels was evident for the SAL-AMPHET and MA-AMPHET groups only on the final Test day (T4). In contrast, the atropine pretreated, AT-AMPHET group exhibited a significant reduction in saccharin consumption on Days P3 and T4. Thus, while all amphetamine conditioned animals exhibited an amphetamine CTA, the atropine pretreatment would appear to have, if anything, served to enhance this CTA. When considered together with the previous atropine blockade of a morphine CTA observed in Experiment 5a, these data seem to provide a confirmation of the predicted findings from the study of Davis and Smith (1975), in which atropine blocked morphine but enhanced amphetamine self-administration. These data, therefore, seem to provide strong support for the hypothesis of a functional relationship between these SA drugs' positive reinforcing and CTA-inducing properties.

A three-way ($3 \times 2 \times 3$) ANOVA, with repeated measures performed on the LiCl conditioned and vehicle control groups (see Fig 8, panel B) revealed significant main effects only of Conditioning ($F(1,41) = 38.08, p < .01$) and of Days ($F(2,82) = 11.47, p < .01$) and a significant Conditioning \times Days interaction ($F(2,82) = 9.72, p < .01$). Dunnett's tests indicated that both the SAL-LiCl and AT-LiCl groups exhibited a significant reduction in saccharin intake on Days P3 and T4, while the MA-LiCl group exhibited this reduction only the final test day, T4. It is not clear, at present, how to account for this apparent attenuative effect of methylatropine pretreatment. Additionally, the present data are in conflict with an earlier report by Deutsch (1978) indicating that atropine pretreatment served to block a LiCl-induced CTA. However, in this study by Deutsch, an atropine dose of 100 mg/kg was used in comparison to the 0.6 mg/kg atropine dose used here. Such a contrast in dose level clearly provides a means to explain the apparent discrepancy between the two studies.

In summary, the results of Experiments 5a and 5b would appear to provide a confirmation of the hypothesis that the neurochemical mechanisms involved in the positive reinforcing and CTA-inducing properties of the SA drugs morphine and amphetamine are functionally related. The present data would also appear to add to the evidence suggesting differences in the neurochemical mediation of morphine and amphetamine CTAs. Roberts and Fibiger (1977)

found that neurotoxic lesions of the dorsal noradrenergic bundle served to disrupt a morphine but not an amphetamine CTA. Also, while naloxone pretreatment serves to attenuate a morphine CTA (Van Der Kooy & Phillips, 1977), a similar naloxone pretreatment was found not to alter an amphetamine-induced CTA (Goudie & Denielweek, 1980). The present findings, indicating an atropine pretreatment blockade of a morphine CTA and apparent enhancement of an amphetamine CTA, would therefore appear consistent with the evidence suggesting differential involvement of neurochemical systems mediating both the aversive (CTA-inducing) and positive reinforcing (Davis & Smith, 1975) properties of these two SA drugs.



General Discussion

It has been proposed that a qualitative distinction may be established between CTAs induced by SA drugs and CTAs induced by other, primarily emetic agents. Of particular interest to psychopharmacologists is the seemingly contradictory notion that the CTA-inducing, aversive stimulus properties of psychoactive drugs such as morphine, ethanol, amphetamine and cocaine may be functionally related to these drugs' well known positive reinforcing properties. The fact that the same drug can act both as a positive reinforcer and as an aversive agent can, in itself, be viewed as paradoxical (Cappell & LeBlanc, 1977; Gamzu, 1977; Goudie, 1979). The 'paradoxical' nature of this phenomenon was further augmented by the observation that the same presentations of morphine or amphetamine have been shown both to induce CTA and act simultaneously as a positive reinforcer in the same animal (Reicher & Holman, 1977; White et al., 1977; Wise et al., 1976). The involvement of the same neurotransmitter systems in what would commonly be considered to be two behaviorally distinct and opposing motivational processes serves to even further accentuate the apparent complexity of these drugs as reinforcing stimuli.

The results of Experiment 1 would appear both to potentially extend the list of behavioral criteria by which a qualitative distinction can be made between emetic CTAs and CTAs induced by SA drugs, and also to provide further empirical support for the notion that there is an important

similarity between the positive reinforcing and CTA-inducing properties of SA drugs such as morphine. The first point is apparent in that while a clear dose-response relationship is observable in the disruption of a LiCl-induced CTA by LiCl pre-exposure (Cannon et al., 1975), it was found that no such dose-response relationship was evident in the case of morphine preexposure effects on a morphine CTA. While a wide range of morphine doses examined in this study were dissimilar in their capacity as CTA-inducing agents, these doses were however equipotent as preexposure agents serving to attenuate a subsequent morphine CTA. These data, therefore, suggest that an unequivocal, qualitative distinction can be assumed between CTAs induced by emetic drugs such as LiCl, and CTAs induced by positive reinforcing drugs such as morphine.

Second, the findings of Experiment 1 appear to add to the evidence assuming an important similarity between the positive reinforcing and CTA-inducing stimulus properties of SA drugs such as morphine. It was shown that preexposure to low doses of morphine, known to be within the range of doses maintaining self-administration in animals (Weeks & Collins, 1964) but not within the dose range inducing CTA, served to disrupt a subsequent morphine CTA. Implicit in an associative interference explanation of this preexposure phenomenon is the idea that the strength of the disruptive effects of drug preexposure is determined by the similarity of the psychopharmacological impact of the two agents

involved in preexposure and conditioning treatments (Cannon et al., 1977). Given the findings of Experiment 1, it would follow logically that the positive reinforcing (but non-aversive) stimulus properties of the morphine preexposure dose shares important discriminative similarities with a higher morphine dose capable of inducing a reliable CTA. Thus, it would appear that a CTA induced by a SA drug such as morphine may involve a discrimination of the drug's more general stimulus properties, incorporating those potentially related to positive reinforcement, rather than simply reflect some more or less discrete, noxious component of the drug's action. This idea has previously been most strongly supported by findings that SA drugs may be simultaneously aversive (CTA-inducing) and positive reinforcing (Reicher & Holman, 1977; White et al., 1977; Wise et al., 1976).

In Experiment 2, a further testing of this notion was provided. It was found that a low, non-aversive dose of morphine was equally capable of maintaining a previously established morphine CTA as was continued exposure to a high, CTA-inducing drug dose. This low dose of morphine was within a dose range self-administered by animals (Weeks & Collins, 1964). It would therefore appear that exposure to the predominantly positive reinforcing stimulus properties is alone sufficient to maintain a previously established morphine CTA. As in Experiment 1, the findings of Experiment 2 may be seen to contribute further evidence supporting the

thesis that a significant commonality exists between the CTA-inducing and positive reinforcing stimulus properties of SA drugs.

In a further investigation of the morphine preexposure phenomenon examined in Experiment 1, the findings of Experiment 3, provide a demonstration that, like morphine discrimination (Shannon & Holtzman, 1976), morphine CTA (Van Der Kooy & Phillips, 1977) and opiate self-administration (Weeks & Collins, 1976), the disruptive effects of morphine preexposure on a morphine CTA appear to be mediated by naloxone-sensitive opiate receptors. The interpretation of the results presented for Experiment 1 would necessarily require such a consistent involvement of the same neurochemical systems in each of these phenomena. Therefore the findings of Experiment 3 strengthen the notion that an important commonality exists amongst these various stimulus properties of morphine.

In Experiment 4, preexposure to centrally (icv) administered morphine, prior to taste aversion conditioning with peripherally administered morphine, was found to result in a subsequent increase of saccharin intake in both saline conditioned (control) and morphine conditioned animals. Such an effect was not observed in experiment 1, in which preexposure to peripherally administered morphine served, if anything, to suppress initial saccharin intake. This unexpected pattern of results in Experiment 4 clearly accentuates the inherent complexity of the behavioral

effects of psychoactive, SA drugs such as morphine which apparently can be modified substantially due to central (icv) versus peripheral routes of drug administration.

In Experiment 5, central cholinergic systems previously shown to be involved in the positive reinforcing effects of morphine and amphetamine (Davis & Smith 1975) were shown to be similarly involved in mediating these drugs' CTA-inducing properties. Such a finding provides further support for the 'paradoxical' notion that there is a functional relationship between those neurochemical systems mediating the behaviorally distinct positive reinforcing and CTA-inducing effects of these SA drugs. Furthermore, the failure of the peripherally-acting cholinergic antagonist, methyl-atropine to alter morphine or amphetamine CTAs adds to earlier evidence indicating that central rather than peripheral systems are involved in mediating such CTAs (e.g., Berger et al., 1973; Van Der Kooy, 1984). As well, the failure of either cholinergic antagonist to alter a LiCl-induced CTA, provides an additional demonstration of the distinction between CTAs induced by SA drugs contrasted with primarily emetic drugs which constitute a central theme of this thesis.

An increasingly prevalent notion within the human drug abuse literature concerns the involvement of 'mixed euphoric/dysphoric' effects of SA drugs in the maintenance of drug self-administration (Meyer & Mirin, 1979; Mello, 1983). For instance, Meyer and Mirin (1979) have published reports of increased (presumably dysphoric) agitation and

'cravings.' during heroin self-administration in humans within an experimental setting. Increased dysphoria and anxiety associated with opiate and alcohol intake have also been reported during a period of chronic intoxication (Mello, 1983). At high doses of cocaine there are also reports of dysphoria and anxiety accompanied by a desire for more cocaine (Resnick et al., 1977). In view of such reports, it is theoretically possible to postulate that CTAs induced by SA drugs may reflect their dysphoric properties. Such a notion, of mixed euphoric/dysphoric effects of SA drugs would not be inconsistent with the point, argued elsewhere in this thesis, that the aversive stimulus effects of SA drugs are functionally related to these drugs' positive reinforcing properties. A closer integration of such an hypothesis with available animal CTA and drug self-administration data would appear to require the additional consideration of some form of 'stimulus relevance' idea (see Cappell & LeBlanc, 1977; Revusky, 1977). It would follow from such a consideration that different (euphoric/dysphoric) components of a SA drug stimulus would be more or less discriminable under contrasting gustatory or exteroceptive stimulus conditions. Exposure to a complex pharmacological stimulus following potent gustatory input provided by presentation of a novel taste stimulus may be discriminated differently from an identical exposure to the same drug without the associated gustatory stimulation. Since gustatory input has been

reported to reach the thalamus, amygdala and hypothalamus (Norgren, 1976), considered together with electrophysiological evidence suggesting potential modulatory input of these regions to the solitary nucleus during taste aversion conditioning (Chang & Scott, 1984), it would appear at least plausible that gustatory stimulation may potentially serve to modulate stimulus properties of a subsequently administered SA drug. While clearly speculative, the role of the solitary nucleus in a general arousal system (Koella, 1974) may be seen in this context as consistent with the hypothesis that gustatory stimulation might result in some form of neurophysiological activation which, in turn, could serve as a modulatory influence upon exposure to a psychoactive drug. Such a notion is not inconsistent with the apparent discriminative complexity of SA drugs such as opiates (Colpaert, 1978). For instance, Colpaert Niemegeers and Janssen (1976) found that, in a drug discrimination paradigm, animals trained on a saline/fentanyl discrimination responded on the drug-appropriate lever when presented with apomorphine. However, animals initially trained to discriminate between saline and apomorphine subsequently failed to generalize this drug discrimination to fentanyl. It may be, then, that under certain conditions, an animal's prior drug (or perhaps, taste) history may change how various components of a drug stimulus complex are discriminated. There is also evidence from the human drug literature to indicate that the stimulus properties of

positive reinforcing drugs are not readily discriminable, particularly when dissociated from previously experienced environmental cues (Lasagna, Von Felsinger & Beecher, 1973; Van Dyke & Byck, 1982). Curiously, experienced opiate users have reported using the magnitude of the initial nausea occurring following drug intake as a positively correlated cue for predicting the intensity of the subsequent drug 'high' (Stolerman & Kuhar, 1972). However, a direct parallel of this 'good sick' phenomenon in humans with CTA in animals would seem to be obviated by the findings presented in Experiment 2 of this thesis. In this study, it was found that a morphine CTA, initially induced by higher, CTA-inducing doses of morphine could subsequently be reliably maintained over repeated conditioning trials by exposure to lower, non CTA-inducing, doses of morphine. These data suggest that the hypothetically more discriminable, dysphoric stimulus effects of higher morphine doses are not necessary for maintenance of a taste aversion response. Conversely, it was demonstrated in Experiment 1, that preexposure to low morphine doses are as effective as preexposure to high doses in disrupting a morphine CTA. Reliable self-administration of such a low morphine dose has, however, been established (Weeks & Collins, 1964). Thus, it appears that the discriminable, potentially 'dysphoric', CTA-inducing stimulus properties of SA drugs such as morphine may be inextricably associated with other, potentially 'euphoric' positive reinforcing properties of

these drugs.

There is also evidence within the human drug literature to suggest that the initial exposure to potential drugs of abuse are predominantly aversive rather than euphoric in nature (Jaffe & Martin, 1980; McAuffle, 1975; Tecce & Cole, 1974). This is consistent with the hypothesis that drug-novelty, associated with an unfamiliar, drug-induced change of state, may be an important factor underlying the induction of CTA by SA drugs (Amit & Baum, 1970; Gamzu, 1977). Such an account is consistent with the reports of disruption of CTA by drug preexposure (Gamzu, 1977; Vogel & Nathan, 1976). While this hypothesis would predict that increasing drug familiarity over repeated conditioning trials should result in a decreasing magnitude of CTA, the appearance of such an effect may be dependent on the temporal pattern of such drug exposures (Colle & Amit, 1985; but see Riley et al., 1978). As well, in at least one report of non-contingent drug preexposure given prior to drug self-administration in rats, no facilitation of acquisition of the drug-taking behavior was observed (Deneau, Yanagita & Seevers, 1969; see also Woods & Schuster, 1973) as would be predicted by the hypothesis of drug-novelty aversion. As previously argued (Cappell & LeBlanc, 1977), while intuitively appealing, a problematic aspect of this hypothesis is that it would appear difficult to adequately test the possible contribution of such a novelty factor without concomitantly introducing other confounding factors,

such as drug tolerance.

As suggested by Goudie (1979), the 'paradoxical' nature of CTA induced by SA drugs may be conceptualized as a contradiction of the expectation that stimuli associated with a drug's positive reinforcing actions should eventually take on secondary positive reinforcing properties. For instance, classically conditioned reinforcing properties of an exteroceptive, auditory stimulus paired with morphine or amphetamine injections have been reported in the animal literature (Davis & Smith, 1974; Coussens, 1974). Similar effects have been reported in humans, the so-called 'needle-freak' phenomenon (Levine, 1974). Injection of saline or water served to elicit drug-like euphoria, apparently due to secondary conditioned properties associated with the drug injection procedure. However, there are reports by human drug abusers that suggest that other pre-injection stimuli (e.g., presentation of drug preparation paraphernalia) may be aversive (see Grabowski & Cherek, 1983). Insofar as the novel taste CS in taste aversion conditioning may be considered as a distinctive pre-injection stimulus, such reports are, then, compatible with a confirmation of the paradox described above. It would appear that pre-injection stimuli may potentially be both positive reinforcing and aversive in nature. An important limitation for such an interpretation, however, may be the rapid (one trial) acquisition of CTA, in that in the human reports cited by Grabowski and Cherek, (1983), repeated

exposure to the particular pre-injection stimuli presumably took place. Despite this difficulty, it is interesting to note that in a runway paradigm in which morphine-conditioned animals were found to exhibit simultaneously both a CTA to novel tasting food and increased running speed to reach the goal-box where this food was presented, the presence of the novel taste appeared to enhance the discriminability of the positive reinforcing properties of morphine (Switzman et al., 1978). Animals conditioned with morphine that were not exposed to the novel taste (and hence did not exhibit a CTA), did not as readily exhibit an increase in running speed. Although these data would appear contradictory, it may be postulated that the taste stimulus may act both as a discriminative cue, facilitating approach behavior, and also as a more proximal, pre-injection cue, eliciting consummatory avoidance behavior.

In summary, CTAs induced by SA drugs such as morphine would appear to be qualitatively distinct from CTAs induced by primarily emetic agents. Such a distinction is established on the basis of physiological, neurochemical and behavioral evidence. Physiological investigations of CTAs induced by SA drugs, in general, indicate that these CTAs do not simply reflect the potentially noxious (peripherally toxic) actions of these SA drugs (e.g., Berger et al., 1973). Behaviorally, in contrast to emetic CTAs, CTAs induced by SA drugs generally are lower in magnitude and show a greater between-subject variability of the taste

aversion response (e.g., Farber et al., 1976), and are more susceptible to disruption by drug preexposure (Switzman et al., 1981). CTAs induced by SA drugs appear to exhibit a curvilinear dose-response curve (Farber et al., 1976), in contrast to the linear dose-response function seen in emetic CTAs (Nachman & Ashe, 1973). As well, whereas the magnitude of disruption of a CTA induced by prior drug preexposure would appear to be dose-dependent, no such dose-response relationship was observable in similar drug preexposure disruption of a CTA induced by the SA drug, morphine (Experiment 1). Furthermore, a functional relationship has been postulated to exist between the neurochemical systems mediating the positive and CTA-inducing properties of SA drugs. This notion is based primarily on the mounting evidence demonstrating that specific pharmacological manipulations which block the positive reinforcing effects of these drugs also attenuate these drugs' CTA-inducing properties. (e.g., Experiment 5). The evidence derived from the animal literature supports the view that, rather than being separate and dichotomous, the aversive (CTA-inducing) and positive reinforcing stimulus properties of SA drugs may involve common discriminative characteristics. Such a conclusion is inferred from several reports that the same injection of a SA drug can act simultaneously both as a positive reinforcer and as a CTA-inducing agent in the same animal (e.g., Switzman et al., 19xx). In addition, a low, non-aversive dose of morphine, known to be within the dose

range self-administered by animals (Weeks & Collins, 1964), was shown to be capable of maintaining a previously established morphine CTA (Experiment 2). Indeed, in one study, a positive relationship was found between the magnitude of a positive reinforced behavior (running down an alleyway) and the magnitude of the CTA induced by the same drug exposure (Switzman et al., 1978). As discussed above, reports from the human drug literature appear to confirm that the positive reinforcing properties of SA drugs do not simply reflect purely 'euphoric' stimulus properties (Meyer & Mirin, 1979; Mello, 1983). In the context of the present discussion, the 'rewarding' aspects of exposure to SA drugs may be postulated to be inextricably tied to concomitant exposure to other stimulus properties of these drugs which are not accompanied by such euphoric 'feelings of well-being'. According to this view, a novel taste stimulus, previously associated with exposure to a SA drug, may elicit a form of approach/avoidance conflict. Instead of reflecting a simple conditioned taste aversion, such a pattern of response induced by a SA drug may more accurately be described as a conditioned taste shyness. The latter description is, in fact, more consistent with available data concerning behavioral patterns observed in CTAs induced by SA drugs (Parker, 1984; Switzman, personnel communication; Stolerman & D'Mello, 1978). In addition to providing a possible explanation of the paradoxical nature of CTA induced by SA drugs, this taste-shyness hypothesis serves to

underscore the qualitative distinction between CTAs induced by SA drugs and emetic agents established earlier. Moreover, such an interpretation brings into sharper focus important questions concerning the potentially complex motivational stimulus properties of psychoactive, self-administered drugs, so widely abused in modern society. A question of primary relevance in this regard concerns the need to identify neurophysiological and perhaps, environmental variables which may serve to differentially modulate the apparently interrelated aversive and positive reinforcing properties of these drugs. Ultimately, the continued investigation of CTAs induced by SA drugs would appear invaluable in order to more comprehensively understand the intricacies of drug-motivated behavior and of motivational processes in general.

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