injections of cocaine were administered following saccharin exposure. The multiple injection procedure enhanced the taste averion normally induced by cocaine, indicating that the temporal properties of a self-administered drug may be important for the induction of a taste aversion. In the third experiment, rats were exposed to one of three drugs (morphine, Valium or Δ^9THC) prior to taste aversion conditioning with either of the three drugs. Depending upon the pre-exposure and conditioning drugs, a taste aversion could still occur indicating that rats can discriminate between different aversive drug properties. When the pre-exposure and conditioning drugs were reversed, however, the taste aversion could be attenuated. This asymmetrical pre-exposure effect may occur as a result of additional negative effects produced by the taste aversion-attenuating drug. Pre-exposure to the more positive drug would not, then, be expected to be as efficient in attenuating the taste aversion induced by the more negative drug.

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Researchers have been attempting to elucidate the basis of voluntary drug use, or drug self-administration, by creating situations for laboratory animals to self-administer drugs. This research aims to shed light on the nature of drug dependence and motivational mechanisms in general. Animals can learn to preferentially ingest drug solutions (e.g. Brown & Amit, 1977; Khavari, Peters, Baity & Wilson, 1975) and to perform an operant behavior which results in a drug injection (e.g. Deneau, Yanagita & Seevers, 1969; Weeks & Collins, 1964; Woods & Schuster, 1968). In these paradigms, a number of factors may be manipulated in order to determine the behavioral and biochemical variables that control the initiation and maintenance of drug self-administration. The fact that laboratory animals self-administer drugs would seem to be contradictory in view of evidence suggesting that self-administered drugs can be aversive to the animals. Rats can develop a conditioned taste aversion (CTA) to a novel flavor when a drug injection follows ingestion of that flavor (Berger, 1972; Cappell, LeBlanc & Endrenyi, 1973). That is, rats learn to avoid a specific taste which is associated with a drug that, otherwise, is self-administered. The same chemical, then, apparently promotes avoidance behavior in one situation (CTA) and a positively-motivated orienting response in another

situation (self-administration). The implication is that a drug can be both aversive and positive. The terms 'aversive' and 'positive' as used here are inferential. Aversion is inferred from the observation that a distinct gustatory stimulus is avoided when it has previously preceded a drug effect. A positive drug effect is inferred from the observation that animals actively engage in a behavior, consummatory or other that causes the drug effect to occur. In the ensuing pages, these inferences will be critically evaluated. The assumption that drugs can either be positive or aversive but not both, is challenged by the fact that self-administered drugs can induce CTAs. For this reason, research in the area of drug aversion can be of considerable importance in broadening our view of the motivational nature of drug effects.

Some basic questions in the area of drug self-administration will be explored in the following pages to assess whether drugs are self-administered for their positive pharmacological properties or to avoid withdrawal symptoms. Some possible pharmacological mechanisms involved in the self-administration behavior will also be examined. Following this analysis, some of the issues related to the role of psychoactive drugs in the induction of CTA will be examined to determine

whether or not CTA is a phenomenon explicable in terms of different parameters from that involved in the drug self-administration paradigm. Some possible physiological mechanisms involved in CTA will also be explored. Finally, there will be a critical review of the concepts that researchers have proposed in order to relate the positive and aversive drug effects to each other.

Drug Self-Administration

A considerable body of literature has evolved demonstrating that laboratory animals self-administer drugs which are self-administered by humans. Table 1 is a representative sample of these experiments. It is not within the scope of this section to exhaustively review the self-administration literature (for reviews see Schuster & Thompson, 1969; Seiden & Dykstra, 1977; Spealman & Goldberg, 1978; Thompson & Pickens, 1975; Wikler, 1973; Woods, 1978). The aim here is to illustrate that drugs can serve as positive reinforcers for laboratory animals and that the magnitude of positive reinforcement varies with the pharmacological agent available for self-administration. Furthermore, some of the evidence implicating a pharmacological basis of drug reinforcement will be reviewed.

TABLE 1

A sample of Self-Administration Experiments

Drug	Species	Route[a]	Prior Drug Experience	Authors and Year[b]
Morphine	Rat	iv	Yes	Weeks & Collins (1964)
			No	van Ree et al. (1978)
		ip	Yes	Headlee, Coppock & Nichols (1955)
		ig	No	Smith, Werner & Davis (1975)
		icv	No	Amit, Brown & Sklar (1976)
		oral	Yes	Khavari & Risner (1975)
				Yanaura & Suzuki (1978)
			No	Alexander et al. (1978)
				Khavari, Peters, Baity & Wilson (1975)
				Kumar, Steinberg & Stolerman (1968)
				Stolerman & Kumar (1970)
	Monkey	iv	Yes	Pozuelo & Kerr (1972)
			No	Deneau et al. (1969)
				Woods & Schuster (1968)
Heroin	Rat	iv	No	van Ree et al. (1978)

TABLE 1 (Continued)

Drug	Species	Route[a]	Prior Drug Experience	Authors and Year[b]
Etonitazene	Rat	oral	Yes	Lewis, Margules & Ward (1975)
			No (Forced-choice)	McMillan et al. (1976)
	Monkey	oral	No	Carroll & Meisch (1978)
Other Opioids	Rat	oral	No (Forced-choice)	McMillan et al. (1976)
Ethanol	Rat	ig	No	Smith, Werner & Davis (1975)
		oral	No	Brown & Amit (1977)
			No (Forced-choice)	Mendelson & Mello (1964)
	Monkey	iv	No	Deneau et al. (1969)
Acetaldehyde	Rat	icv	No	Amit, Brown & Rockman (1977)
Amphetamine	Rat	iv	No	Davis & Smith (1972)
				Davis, Smith & Khalsa (1975)
				Pickens & Harris (1968)
				van Ree et al. (1978)
				Yokel & Wise (1975; 1976)
	Monkey	iv	No	Deneau, Yanagita & Seevers (1969)
	Dog	iv	No	Davis, Smith & Werner (1978)

TABLE 1 (Continued)

Drug	Species	Route[a]	Prior Drug Experience	Authors and Year[b]
Cocaine	Rat	iv	No	deWit & Wise (1977) Pickens & Thompson (1968)
	Monkey	iv	No	Deneau, Yanagita & Seevers (1969) Pickens & Thompson (1970) Wilson & Schuster (1973; 1974)
Barbiturates	Rat	iv	No	Davis, Lulenski & Miller (1968)
	Monkey	iv	No	Deneau, Yanagita & Seevers (1969) Winger, Stitzer & Woods (1975)
	Dog	iv	No	Davis, Smith & Werner (1978)
Methaqualone	Dog	iv	No	Davis, Smith & Werner (1978)

[a] iv = intravenous; icv = intracerebroventricular; ig = intragastric; ip = intraperitoneal

[b] see reference list for complete citation

The Drug as a Positive Reinforcer

A number of investigators have demonstrated that laboratory animals preferentially ingest drug solutions or perform operants which result in the administration of a drug. Self-administered drugs include opiates (Amit, Brown & Sklar, 1976; Deneau, Yanagita & Seevers, 1969; Lewis, Margules & Ward, 1975; Stolerman & Kumar, 1970; van Ree, Slangen & de Wied, 1978; Weeks & Collins, 1964; Mendelson & Mello, 1964), psychomotor stimulants (Deneau et al., 1969; Pickens & Harris, 1968; Yokel & Wise, 1975) and barbiturates (Davis, Lulenski & Miller, 1968; Deneau et al., 1969) among others. Drugs are self-administered orally, intravenously (iv), intragastrically (ig), intraperitoneally (ip) and intracerebroventricularly (icv) (see Table 1). By far, the routes most commonly employed are oral and iv. As is the case with more traditional forms of reinforcement such as food, operant responding for drugs can be controlled by schedules of reinforcement (see Spealman & Goldberg, 1978). In addition, drugs can provide the basis for conditioning of secondary reinforcement (Davis, Smith & Khalsa, 1975). That is, animals respond for the presentation of a stimulus such as a light when it has been contiguously paired with the administration of a drug. By definition, then, drugs can be reinforcers.

What may cause organisms to find a drug reinforcing is a question which has generated controversy in the literature. Essentially, there are two major positions on this question. One, more traditional position, is that drugs are self-administered to avoid withdrawal symptoms (e.g. Weeks & Collins, 1964). In this scheme, the drug is viewed as a negative reinforcer. A second, more recent position, is that drug self-administration occurs as a function of the positive pharmacological effects associated with euphoria (e.g. Amit, Corcoran & White, Note 1; Amit, Sutherland & White, 1975). In this scheme, the drug is viewed as a positive reinforcer. Wikler (1973) has elaborated a conditioning theory of drug dependence which incorporates both the negative reinforcement and positive reinforcement approaches. It will be argued below that, in self-administration situations, drugs are positive reinforcers to laboratory animals as opposed to negative reinforcers, and that positive reinforcement is sufficient to account at least for the acquisition of self-administration behavior. First, however, it is necessary to outline the negative reinforcement position.

The arguments in favor of a negative reinforcement model are based primarily upon results of studies which demonstrate (1) an increased tendency of rats to self-administer opiates after having received drug

experience prior to the self-administration period (Khavari & Risner, 1973a, 1973b; Lewis, Margules & Ward, 1975; Weeks & Collins, 1964; Yanaura & Suzuki, 1978) and, (2) withdrawal symptoms manifesting upon termination of drug self-administration (Khavari, Peters, Baity & Wilson, 1975; Khavari & Risner, 1973a; 1973b; McMillan, Leander, Wilson, Wallace, Fix, Redding & Turk, 1976; Weeks & Collins, 1964). With regards to the first point, it is assumed by proponents of the negative reinforcement model that the animals have become physically dependent as a function of the forced drug administration. The drug is self-administered, therefore, to avoid withdrawal symptoms. With regards to the second point, it is commonly held that the withdrawal symptoms reflect the physical dependence which has maintained the self-administration behavior. McMillan et al. (1976) observed that rats exhibiting withdrawal symptoms precipitated by naloxone (an opiate antagonist) consumed opiate-adulterated solutions after which withdrawal symptoms ceased. McMillan et al. suggested that the resumption of opiate self-administration occurred in order to alleviate withdrawal symptoms.

A major flaw in the negative reinforcement position is the inference of a causal relationship between the potential for withdrawal symptoms and the occurrance of drug self-administration. For the most part, the data

upon which this position rests are correlational. Even if drug-experienced animals tend to self-administer opiates more readily than non-experienced animals, this may be due to habituation to the novelty of the drug (Amit & Baum, 1970) or some other type of related learning such as learned safety. Physical dependence, as defined by withdrawal symptoms, is not a necessary condition for animals to commence self-administration of opiates as demonstrated in studies using non-dependent, naive animals (Amit, Brown & Sklar, 1976; Deneau et al., 1969; Khavari, Peters, Baity & Wilson, 1975; Kumar, Steinberg & Stolerman, 1968; Smith, Werner & Davis, 1975; van Ree et al., 1978; Woods & Schuster, 1968). In fact, van Ree et al. observed no difference in heroin self-administration whether or not rats received prior forced injections of heroin. Furthermore, physical dependence is not a sufficient condition for drug self-administration as exemplified by studies in which cessation of opiate self-administration does not result in the withdrawal syndrome (Amit, Brown & Sklar, 1976; Woods & Schuster, 1968). Related to this point, it is interesting to note that animals voluntarily abstain from drug self-administration even when undergoing withdrawal (Deneau et al., 1969). Another argument against a negative reinforcement model is that drugs which do not produce withdrawal are quite readily

self-administered. These include cocaine (Deneau et al., 1969; deWit & Wise, 1977; Pickens & Thompson, 1968; Woods & Schuster, 1968), amphetamine (Deneau et al., 1969; Pickens & Harris, 1968; van Ree et al., 1978; Yokel & Wise, 1975) and acetaldehyde (Amit, Brown & Rockman, 1977). It seems reasonable to conclude, then, that although withdrawal symptoms may be associated with a particular pharmacological agent, in general, no causal relationship between the withdrawal symptoms and drug self-administration has been conclusively demonstrated. The exception is the study conducted by McMillan et al. (1976) in which withdrawal seemed to promote increased opiate self-administration. At issue here is whether the self-administration behavior was purposefully directed towards relieving withdrawal symptoms or whether a general stress effect promoted self-administration. It is possible that a number of stressors could facilitate drug self-administration. Alexander, Coambs and Hadaway (1978) demonstrated that isolated rats would self-administer morphine to a greater degree than group-housed rats. Although stress might be a factor in drug self-administration, it may be concluded that at least acquisition of drug self-administration behavior does not result from a negatively reinforcing effect of drugs. A more likely alternative is that drugs are positive reinforcers in self-administration

situations. In other words, animals self-administer drugs in order to derive the positive pharmacological effects. That humans report these drug effects to be euphoric is consistant with this hypothesis (Kolb, 1925; Lasagna, Von Felsinger & Beecher, 1955; LeDain, 1973).

Self-Administration Liabilities of Drugs

Not all drugs which humans self-administer are self-administered by laboratory animals. To date, no quantitative measure exists which can rank drugs on the basis of the relative strengths to which they tend to be self-administered. It would be difficult to do so directly from self-administration studies due to changing variables such as different dose parameters, durations of drug action, and preferred routes of administration. What is known, however, is that opiates, stimulants, barbiturates and ethanol can be self-administered by laboratory animals (Table 1). In contrast, cannabinoids and benzodiazepines are not readily self-administered. For instance, Leite and Carlini (1974) demonstrated that rats refused to self-administer marijuana when given the opportunity after prior administration. In parallel, Harris, Waters and McLendon (1974) observed that naive or cannabis--experienced monkeys refused to self-administer the drug. Amit, Corcoran, Charness and Shizgal (1973) failed to detect hashish self-administration in rats, even after

electrical stimulation of the lateral hypothalamus, a manipulation which did increase ethanol self-administration. In this experiment, however, rats had received prior experience with ethanol which could have confounded the results. In another study, Corcoran and Amit (1974) observed that naive rats did not self-administer hashish in either a free-choice or a forced-choice situation, or as a function of lateral hypothalamic stimulation. More recently, van Ree et al. (1978) found that Δ^1THC (a putative active component of cannabis) was poorly self-administered by rats in the same situation that opiates were readily self-administered. These studies suggest that the self-administration liability of cannabinoids are meagre.

The case with benzodiazepines is less clear. The evidence seems to suggest that this class of drug is more readily self-administered than the cannabinoids although the self-administration liability is still quite low. Amit and Cohen (1974) demonstrated that rats did not prefer an orally-ingested diazepam (Valium) solution to water even after electrical stimulation of the lateral hypothalamus. In the study conducted by Amit, Corcoran, Charness and Shizgal (1973), however, rats did self-administer diazepam after lateral hypothalamic stimulation (these animals had received prior

experience with ethanol). In this same study, it may be recalled that hashish was not self-administered. These studies suggest that rats are reluctant to self-administer diazepam although the tendency to do so may be greater than that for cannabis. In monkeys, benzodiazepines are self-administered but not to the same extent as are other drugs suggesting limited reinforcement in these animals. Findley, Robinson and Peregrino (1972) demonstrated that monkeys did self-administer chlordiazepoxide (Librium) although secobarbital was preferentially self-administered. In another experiment, Yanagita and Takahashi (1973) found that diazepam was also self-administered by monkeys but not to the degree that either pentobarbital, alcohol or chloroform were.

In summary, then, one may conclude that, in laboratory animals, the reinforcing effects of opiates, stimulants, barbiturates and ethanol are greater than those of cannabinoids and benzodiazepines. In fact, the reinforcing effects of these latter two seem to be quite limited although benodiazepines may be more reinforcing than cannabinoids.

A Pharmacological Aspect of Self-Administration

The involvement of biogenic amines in drug-reinforced behavior has received a great deal of attention. Catecholamine systems have been implicated in the

self-administration of opiates (Amit & Levitan, 1975; Brown, Amit, Sinyor, Rockman & Ogren, 1978; Davis & Smith, 1972, 1973; Davis, Smith & Khalsa, 1975; Glick & Cox, 1977; Glick, Cox & Crane, 1975; Glick, Zimmerberg & Charap, 1973; Lewis, Margules & Ward, 1975; Pozuelo & Kerr, 1972), ethanol (Amit, Brown & Rockman, 1977; Amit & Levitan, 1975; Myers & Veale, 1972), and psychomotor stimulants (Baxter, Gluckman & Scerni, 1976; Davis & Smith, 1972; Davis, Smith & Khalsa, 1975; deWit & Wise, 1977; Yokel & Wise, 1975; 1976).

The specific role of biogenic amines in opiate self-administration has yet to be defined. Results of studies indicate a mediational role of dopamine (Glick, Cox & Crane, 1975), norepinephrine (Amit & Levitan, 1975; Brown, Amit, Sinyor, Rockman & Ogren, 1978; Davis, Smith & Khalsa, 1975), or an interaction between dopamine and serotonin systems (Glick & Cox, 1977). For ethanol self-administration, norepinephrine has been implicated (Amit, Brown & Rockman, 1977; Amit & Levitan, 1975) as well as an interaction between norepinephrine and serotonin (Rockman, Amit, Carr & Ogren, in press). As far as psychomotor stimulants are concerned, dopamine has also been implicated in self-administration (deWit & Wise, 1977; Yokel & Wise, 1975, 1976) as has norepinephrine (Davis, Smith & Khalsa, 1975). In all probability a

complex interaction between aminergic systems subserve drug self-administration and undoubtedly, other mechanisms also contribute to this behavior. For instance, enkephalins have been directly implicated in morphine self-administration (Belluzzi & Stein, 1977; Stapelton, Lind, Merriman, Bozarth & Reid, 1979). Not withstanding the fact that other mechanisms may mediate drug self-administration, the studies cited above suggest that biogenic amines and, in particular, catecholamines are integrally involved in the behavior. This is of considerable importance when the pharmacological basis of another behavioral drug effect is examined further on, namely, CTA.

Conditioned Taste Aversion (CTA)

In the previous section, evidence was presented demonstrating that certain drugs are self-administered by laboratory animals. The position taken was that the drug-oriented behavior is positively reinforced by the pharmacological effect of the accessable drug and, that the positively reinforcing effect of a drug is mediated at least, in part, by catecholamines. In this section, the behavioral properties of psychoactive drugs will be examined from the perspective of their demonstrated aversive effect. By examining drug aversion,

researchers have attempted to gain a broader understanding about the nature of the stimulus properties, as well as the environmental conditions which contribute to hedonic effects of drugs. The term 'stimulus property' as used here refers to an internal change in state produced by a drug, the quality of which can be discriminated by an organism.

The Drug as an Aversive Agent

Drug aversion is inferred from studies demonstrating the induction of CTA in laboratory rats. In the CTA paradigm, ingestion of a novel-tasting substance precedes the administration of a stimulus which can either be chemical or physical. Aversive properties of the stimulus paired with the flavor is inferred if, upon subsequent exposure, there is a decrease in consumption of the novel-tasting substance. CTA may be induced by a vast array of stimuli (see Riley & Clarke, 1977). This list includes psychoactive drugs such as opiates (Cappell, LeBlanc & Endrenyi, 1973; Jacquet, 1973), naloxone, an opiate antagonist (LeBlanc & Cappell, 1975; van der Kooy & Phillips, 1977), amphetamine (Berger, Wise & Stein, 1973; Cappell, LeBlanc & Herling, 1975), cocaine (Booth, Pilcher, d'Mello & Stolerman, 1977; Goudie, Dickins & Thornton, 1978), ethanol (Cappell, LeBlanc & Endrenyi, 1973; Eckardt, 1975), barbiturates (Vogel & Nathan,

1975), benzodiazepines (Cappell, LeBlanc & Endrenyi, 1973; Gamzu, Note 2; Vogel & Nathan, 1975), cannabinoids (Corcoran, Bolotow, Amit & McCoughren, 1974; Elsemore & Fletcher, 1972; Kay, 1975), fenfluramine (Booth et al., 1977; Goudie, Taylor & Atherton, 1975), methylscopolamine (Berger et al., 1973; Braveman, 1975) and nitrous oxide (Goudie & Dickens, 1978). That such a variety of drugs can induce CTAs is interesting in terms of learning theory. Rats can learn to associate a novel taste with an internal event over one trial (Nachman & Ashe, 1973) even with a long delay between the two stimulus events (Garcia, Ervin & Koelling, 1966; Nachman, 1970). Seligman (1970) proposed that organisms are predisposed to associate flavors with delayed illness, hence, learning can occur in one trial and with a long delay between the taste and the internal event. Seligman's "preparedness" hypothesis has been challenged by results demonstrating the induction of CTA by footshock (Krane & Wagner, 1975). What is of interest here is that many CTA-inducing drugs are also positively reinforcing, as was outlined in the previous section.

Effective Dosages for CTA Induction by Self-Administered Drugs

The phenomenon of CTA induced by self-administered drugs is not necessarily interesting if the dosages employed in CTA studies are beyond those normally

self-administered. In that case, it could be argued that the CTA merely reflects illness produced by a high drug dosage. However, the manifestation of CTA for some self-administered drugs can occur with dosages which are pharmacologically relevant in terms of self-administration. Morphine can be self-administered by rats at a dose of up to 10 mg/kg iv (Weeks & Collins, 1964) or ig (Smith, Werner & Davis, 1975). Morphine can also induce a CTA in rats at a dose as low as 3 mg/kg ip (Cappell, LeBlanc & Endrenyi, 1973). Amphetamine can be self-administered at a dose of 1 mg/kg iv (Pickens & Harris, 1968) and this drug can also induce a CTA at a dose of .32 mg/kg ip (d'Mello, Stolerman, Booth & Pilcher, 1977). Both morphine and amphetamine, then, can induce CTAs well within the range of doses which are self-administered.

It is evident that the route of administration typically used in CTA studies is different from the route used in self-administration experiments. This could account for the fact that, in one situation, the drugs seem to be aversive and, in another, the drugs seem to be positively reinforcing. The same injections of morphine or amphetamine, however, can be both positively reinforcing (as indicated by facilitated operant behavior) and aversive (as indicated by CTA induction) (Reicher & Holman, 1977; White, Sklar & Amit, 1977; Wise, Yokel &

deWit, 1976). It is doubtful, then, that the apparently contradictory behavioral effects of morphine or amphetamine can be accounted for by high-dose toxicity or route of administration.

In demonstrating CTA induction by barbiturates, Vogel and Nathan (1975) have also argued that this drug effect was not merely due to a high dose, citing experiments in which monkeys self-administered anesthetic doses of barbiturates (e.g. Deneau et al., 1969). In the experiment conducted by Vogel and Nathan (1975), a CTA was induced in rats at subanasthetic doses.

Not all self-administered drugs seem to induce CTAs at dosages which are positively reinforcing. It has yet to be demonstrated that ethanol and cocaine can induce taste averions at dosages within the range used in self-administration experiments. Although it has been demonstrated that rats can self-administer approximately 400 mg/kg of ethanol ig in a 10 hr period (Smith, Werner & Davis, 1976), the effective CTA-inducing dose of ethanol is 1200 mg/kg administered ip (Cappell, LeBlanc & Endrenyi, 1973; Sklar & Amit, 1977). The possibility exists that the appropriate conditions for ethanol to induce a CTA at a self-administered dose may not yet have been employed. Alternatively, two other possibilities could account for the fact that a relatively high dose

of ethanol may be required to induce a CTA. First, it is possible that the stimulus properties of a self-administered dose are not amenable to the induction of CTA and, at higher doses, the CTA may be due to a toxic effect (e.g. gastrointestinal malaise and/or intracellular dehydration). Second, as Brown, Amit, Smith and Rockman (1978) suggested, the CTA induced by ethanol may be subserved by the ethanol metabolite, acetaldehyde. Acetaldehyde is metabolized quite rapidly (Sippell, 1974) and in order for a sufficient quantity to be in the system for an adequate period of time, a relatively high dose of ethanol would be required. It is interesting that acetaldehyde is self-administered by rats (Amit, Brown & Rockman, 1977), indicating that this metabolite may mediate the positively reinforcing effect of ethanol as well. It is possible, then that both self-administration and CTA induced by ethanol may in fact be pharmacologically-mediated by acetaldehyde.

The idea that a drug must exert an effect for a prolonged period of time in order for a CTA to occur was originally proposed by Cappell and LeBlanc (1977) and more recently by Goudie and his colleagues (Goudie & Dickins, 1978; Goudie, Dickins & Thornton, 1978). Cocaine, which has a fairly short duration of action (Nayak, Misra & Mulé, 1976), produces a weak CTA at

high doses (Booth et al., 1977; Cappell & LeBlanc, 1977; Goudie, Dickins & Thornton, 1978). This led Goudie and co-workers to hypothesize that duration of drug action may be an important variable for CTA induction. In support of this hypothesis, Goudie and Dickins (1978) demonstrated that the magnitude of the CTA induced by nitrous oxide varied directly with the duration of exposure to a constant level of the gas. Goudie and Dickins further suggested that drug actions of short duration may mediate positive reinforcement. Experimental evidence, however, does not seem to support this latter idea (Davis, Lulenski & Miller, 1968; Winger, Stitzer & Woods, 1975).

In summary, the evidence presented demonstrates that morphine, amphetamine and barbiturates can induce taste aversions at doses which are also self-administered. Ethanol and cocaine have not been demonstrated to induce CTAs within the self-administration dose range. This could be due to the relatively short durations of action of acetaldehyde, a metabolite of ethanol, and of cocaine.

Pharmacological Aspects of CTA

The involvement of biogenic amines in CTA has received some attention. Catecholamines not only seem to mediate drug self-administration, as was outlined previously, but these neurotransmitters also seem to

mediate CTA induction by self-administered drugs.

A number of studies have implicated catecholamine mediation of CTAs induced by self-administered drugs. With the exception of one experiment (Coussens, Crowder & Davis, 1973), the studies demonstrate that functional disruptions of catecholamine systems can attenuate or block the formation of the CTAs (Goudie, Thornton & Wheatley, 1975; Grupp, 1977; Roberts & Fibiger, 1975; 1977; Sklar & Amit, 1977). In contrast, Coussens et al. (1973) found that pretreatment with α-methyltyrosine (AMT, a tyrosine hydroxylase inhibitor which lowers dopamine and norepinephrine levels) enhanced morphine's potential to induce a CTA. In this experiment, however, morphine alone failed to induce a significant CTA bringing into question the effectiveness of the procedure. Other studies have demonstrated that α-methylparatyrosine (AMPT) can block the formation of a CTA induced by morphine, ethanol (Sklar & Amit, 1977) and amphetamine (Goudie, Thornton & Wheatley, 1975). Parallel findings have been reported with 6-hydroxydopamine-treated rats (6-OHDA, a catecholamine neurotoxin). When 6-OHDA was injected icv, the CTA normally induced by amphetamine was greatly attenuated (Roberts & Fibiger, 1975), however, when 6-OHDA was injected into the dorsal tegmental noradrenergic pathway, the amphetamine-induced CTA was not affected (Roberts &

Fibiger, 1977). These results implicate dopaminergic neuronal involvement in the amphetamine-induced CTA. Grupp (1977) found that pimozide (a dopamine receptor blocker) attenuated the formation of a CTA induced by amphetamine which supports the suggestion that dopamine mediates the amphetamine-CTA. Sklar and Amit (1977) demonstrated that pimozide can attenuate CTAs induced by morphine and ethanol implicating dopamine in the aversive effects of these drugs as well. Sklar and Amit also demonstrated that FLA-57 (a dopamine-β-hydroxylase inhibitor which lowers norepinephrine levels) could attenuate morphine- and ethanol-based CTAs, indicating that norepinephrine is also involved in the CTAs induced by these drugs. Roberts and Fibiger (1977) found that 6-OHDA infused into the dorsal tegmental noradrenergic pathway attenuated the acquisition of a morphine-based CTA confirming the involvement of norepinephrine in morphine's CTA. Taken together, these studies demonstrate that catecholamines subserve CTAs induced by self-administered drugs. Whereas dopamine has been implicated in the aversive effects of amphetamine, both dopamine and norepinephrine seem to be involved in the aversive effects of morphine and ethanol. The fact that catecholamines are involved in CTAs induced by self-administered drugs as well as being involved in

self-administration is of theoretical interest. The same drugs not only produce aversion and reinforcement, but the same systems mediate both of these effects.

In contrast with results demonstrating a mediational role of catecholamines in CTAs induced by self-administered drugs, these neurochemical systems do not seem to mediate the acquisition of CTAs induced by non-self-administered drugs. The CTA induced by lithium chloride is not affected by 6-OHDA (Mason & Fibiger, 1979; Roberts & Fibiger, 1975; Stricker & Zigmond, 1974), AMPT, pimozide or FLA-57 (Sklar & Amit, 1977). The CTA induced by cyclophosphamide is not affected by lesions of the locus coeruleus which contains noradrenergic neurons (Sessions, Kant & Koob, 1976). On the other hand, lesions of the raphe nuclei, which contain serotonergic neurons, enhance acquisition of the CTA induced by lithium chloride. This enhancement is reversed by 5-hydroxytryptophan (a serotonin precurser) treatment (Lorden & Oltmans, 1978). The cholinergic system has also been implicated in the lithium chloride--induced CTA. Atropine sulfate, an anticholinergic agent has been shown to attenuate aversive conditioning based on lithium (Deutsch, 1978a). There is no evidence demonstrating the involvement of these systems in CTAs induced by self-administered drugs.

The evidence presented above suggests that systems

which mediate CTAs induced by self-administered drugs are different from those which mediate CTAs induced by non-self-administered drugs. This idea, which has been proposed by other investigators (e.g. Berger et al., 1973; Amit, Levitan, Brown & Rogan, 1977), is substantiated by other evidence. Berger et al. demonstrated that lesions of the area postrema blocked the formation of a CTA induced by methylscopolamine but not by amphetamine. Since methylscopolamine crosses the blood-brain barrier poorly, Berger et al. suggested a peripheral mode of action for methylscopolamine as opposed to a central mode of action for amphetamine. In a recent experiment, McGlone, Ritter and Kelley (1979) similarly demonstrated that area postrema lesions disrupted the formation of CTAs induced by scopolamine and lithium chloride but not amphetamine. Amit, Levitan, Brown and Rogan (1977) investigated the putative role of the hippocampus in CTA. These authors found that, when morphine, ethanol or Δ^9THC were infused into the dorsal hippocampus, only Δ^9THC induced a CTA. These studies suggest that the anatomical substrates of CTAs induced by self-administered drugs are different from those which underlie the CTAs induced by non-self-administered drugs. In general, the results obtained in the diverse number of experiments presented above support the conclusion that the nature of CTAs

induced by self-administered drugs is different from that of non-self-administered drugs.

The Relationship Between Positive Reinforcement and Aversion

The evidence presented thus far demonstrates that certain pharmacological agents can be positively reinforcing to laboratory animals. Furthermore, it seems that catecholaminergic systems mediate at least to some extent, the positively reinforcing properties of drugs. Evidence was then presented demonstrating that positively reinforcing drugs can also induce CTAs suggesting that these drugs also have aversive properties. What is particularly intriguing is that CTAs can be induced within a dose range that supports self-administration. Moreover, catecholaminergic systems seem to mediate the aversive effects of self-administered drugs in addition to their positively reinforcing effects. Catecholamines do not seem to be involved in the aversive effects of non-self-administered drugs. This, along with other data, suggest that the nature of the aversion observed with self-administered drugs is qualitatively different from that observed with non-self-administered drugs.

How can the same chemical stimulus be both positively reinforcing and aversive? How can one account for the

fact that the same neurochemical systems mediate these seemingly opposite hedonic properties? To date, no explanation can sufficiently answer these questions. Researchers, being faced with this puzzle have resorted to the term 'paradox' as a reflection of our current understanding about this complex phenomenon (e.g. Goudie, in press; Sklar & Amit, 1977).

There have been two major positions on this issue. One position (the tolerance hypothesis) holds that aversion and positive reinforcement are relatively distinct temporal components of the drug effect (Cappell, LeBlanc & Herling, 1975; Goudie, Taylor & Atherton, 1975). The second position (the novelty hypothesis) holds that aversion and positive reinforcement reflect related, or even the same components, of the drug effect (Amit & Baum, 1970; Gamzu, 1977; Vogel & Nathan, 1976). In the ensuing pages, these positions will be outlined and critically evaluated.

Tolerance to Aversive Drug Effects

The drug tolerance hypotheses suggest that, initially, drugs are pharmacologically aversive (dysphoric) to rats and, therefore, they can induce CTAs. With drug experience, however, the aversive pharmacological effect tolerates and unmasks the positively reinforcing effect of the drugs (Cappell, LeBlanc & Herling, 1975; Goudie, Taylor & Atherton, 1975). Goudie et al. (1975)

specifically commented that the extent to which an aversive drug effect tolerates may determine the degree of positive reinforcement produced by a drug. Although there are a number of serious problems with the idea of tolerance as a mechanism by which an aversive stimulus can acquire positively reinforcing properties, the idea is appealing in light of human reports and animal experimental evidence. For instance, it has been noted that humans report dysphoria associated with initial drug experiences and that the dysphoria eventually decreases (Kolb, 1925).

Support in the animal literature for a drug tolerance hypothesis arises primarily from CTA pre-exposure studies. In these studies, rats typically receive prior exposure to a drug one or more times before taste aversion conditioning occurs. Drug pre-exposure can attenuate or block the formation of a CTA. This effect has been demonstrated with drugs which are highly self-administered and those which are not. Included among these drugs are morphine (LeBlanc & Cappell, 1974), amphetamine (Goudie, Taylor & Atherton, 1975; LeBlanc & Cappell, 1974), ethanol (Berman & Cannon, 1974), amobarbital (Vogel & Nathan, 1976), diazepam (Gamzu, Note 2), chlordiazepoxide (Cappell, LeBlanc & Herling, 1975) and lithium chloride (Cannon, Berman, Baker & Atkinson, 1975). Results from pre-exposure studies demonstrate

that CTAs induced by self-administered drugs are more readily attenuated by pre-exposure than CTAs induced by non-self-administered drugs. For instance, a single pre-exposure to ethanol (Cannon et al., 1975) or amobarbital (Vogel & Nathan, 1976) can attenuate the formation of CTAs induced by these drugs whereas a few pre-exposures to lithium chloride do not have a strong attenuating effect on taste aversion conditioning (Riley, Jacobs & Lolordo, 1976). Elsemore (1972) demonstrated that although 7 pre-exposures to Δ^9THC attenuated conditioning based on that drug, the effect was not significant from placebo pre-exposed controls. Finally, Goudie, Taylor and Atherton (1975) observed that 4 pre-exposures to amphetamine blocked an amphetamine-CTA whereas 8 pre-exposures to fenfluramine merely attenuated a fenfluramine-CTA. These studies can be interpreted to support the idea that the extent to which aversive drug properties tolerate may determine the degree of positive reinforcement.

As was mentioned above, there are a number of problems with the idea of tolerance to drug aversion. These issues, to be outlined below, have led the proponents of the tolerance hypothesis to re-examine this proposal (Cappell & LeBlanc, 1977; Goudie, in press).

An Argument Against Tolerance: An Associative Explanation

If pharmacological tolerance was the mechanism by which drug pre-exposures affected aversive conditioning, one would expect to see a permanent attenuation, especially for self-administered drugs. Although drug pre-exposures do attenuate CTAs, the strength of the CTA increases with repeated conditioning trials. This holds true for self-administered drugs (Berman & Cannon, 1974) and non-self-administered drugs (Riley, Jacobs & Lolordo, 1976). A pharmacological tolerance hypothesis is also challenged by results obtained in another type of pre-exposure situation. When a flavor is paired with a drug prior to conditioning trials with a different flavor, a CTA can still occur to the second flavor. Again, this holds true for self-administered drugs (Stewart & Eikelboom, 1978) and non-self-administered drugs (Mikulka, Leard & Klein, 1977). Other results are also problematic for a tolerance hypothesis. Cappell and LeBlanc (1977) demonstrated that the attenuation of CTAs normally induced by morphine or amphetamine is not affected by massing or spacing pre-exposure injections. A tolerance hypothesis would predict that massed pre-exposure trials should more effectively attenuate a CTA.

Based on the studies presented above, it would seem plausable to conclude that a mechanism other than

pharmacological tolerance may underlie the drug pre-exposure effect. Braveman (1975) proposed an associative explanation to account for the pre-exposure results. Braveman found that pre-exposures to a variety of CTA-inducing agents, including amphetamine, blocked the formation of a CTA induced by turntable rotation. This finding would be extremely difficult to account for in terms of a tolerance hypothesis, especially since rotation is a non-pharmacological stimulus. Braveman proposed a number of possibilities, all of which are associative in nature, to account for these and other pre-exposure results. Braveman's central argument is that the learning of an association between a flavor and its aversive consequences is impaired by the relatively low correlation between the presentation of a flavor and an aversive agent. In Braveman's framework, the animal learns that an aversive consequence follows tasting a novel flavor. The nature of the aversive stimulus is unimportant. What is important is learning the association. Then, according to Braveman, pre-exposure to any CTA-inducing agent should at least attenuate the formation of CTA normally induced by any other agent. In other words, no matter what the pre-exposure and conditioning agents are, attenuation of CTA should occur as long as both can induce aversions.

This associative explanation can be challenged on

the basis of two studies which demonstrate asymmetrical pre-exposure effects. An asymmetrical pre-exposure effect occurs if pre-exposure to drug A attenuates a CTA normally induced by drug B but pre-exposure to drug B does not affect the CTA induced by drug A. According to Braveman's explanation, if pre-exposure to drug A attenuates the CTA induced by drug B, then the reverse should also occur. However, Cappell, LeBlanc and Herling (1975) demonstrated the pre-exposures to amphetamine attenuated aversive conditioning based on itself and morphine whereas pre-exposures to morphine only attenuated aversive conditioning based upon morphine and not amphetamine. In the same study, Cappell et al. demonstrated that pre-exposures to chlordiazepoxide, which attenuated conditioning based upon itself, did not affect an amphetamine-based CTA. Vogel and Nathan (1976) demonstrated that pre-exposure to amphetamine attenuated the CTA normally induced by amobarbital but that pre-exposure to amobarbital did not attenuate the CTA induced by amphetamine. The fact that pre-exposure to drug A attenuated aversive conditioning based upon drug B but not the reverse, indicates that an associative explanation cannot fully account for the drug pre-exposure effect. In addition, the studies conducted by Cappell, LeBlanc and Herling (1975) and Vogel and Nathan (1976)

do not support a tolerance hypothesis since cross-tolerance or symmetry would be predicted.

Braveman (1977) has attempted to reconcile the asymmetrical pre-exposure data with an associative explanation by pointing to a potential confounding variable. Braveman's point was that if a relatively more potent CTA-inducing agent was pre-exposed, then one could expect that the CTA normally induced by the less potent conditioning agent would be readily attenuated. If a relatively less potent CTA-inducing agent was pre-exposed, then one could expect that the CTA normally induced by the more potent conditioning agenc would be less affected. Cannon et al. (1975) demonstrated a direct relationship between the strength of the pre-exposure dose of lithium chloride and attenuation of CTA. In the experiments demonstrating asymmetrical pre-exposure effects, it is difficult to assess the relative CTA-inducing potencies of the drug dosages due to the nature of the data presentation.

There is no question that in order for a CTA to occur, an animal must associate the gustatory stimulus with the subsequent internal change produced by a drug. What does remain open to question, however, is whether associative interference can totally account for the effect of pre-exposure on the formulation of a CTA. Evidence

already presented suggests that an associative explanation cannot account for all of the observations in pre-exposure experiments. For instance, relatively few pre-exposures of a self-administered drug can attenuate the CTA induced by that drug as opposed to a requisite greater number of pre-exposures for a non-self-administered drug (Goudie, Taylor & Atherton, 1975). Probably the greatest problem with an associative explanation in terms of the general issue in this thesis is its inability to explain how an otherwise positively reinforcing drug, such as amphetamine, can induce a CTA.

Novelty of Drug Effects

A number of investigators (Amit & Baum, 1970; Gamzu, 1977; Vogel & Nathan, 1976) have suggested that the so-called aversion induced by psychoactive agents reflects the novelty of the drug effect. This is to be distinguished from viewing CTA induction by these drugs as aversive or dysphoric per se. In terms of a novelty hypothesis, the CTA may be indicative of fear induced by a novel drug state which, after a number of experiences, habituates (Amit & Baum, 1970). Although it has been argued that a novelty hypothesis is merely a more general statement of a tolerance hypothesis (Cappell & LeBlanc, 1977), there is an important distinction between the two. A novelty hypothesis implies that the CTA is a

function of the internal stimulus complex provided by a drug, including those same stimulus properties which can be positively reinforcing. In contrast, a tolerance hypothesis implicates an aversive component which can be distinguished from the positively reinforcing component. Of course, not all drugs have positive pharmacological effects, as assessed by their self-administration liabilities. For these drugs, it has been suggested that the CTA actually reflects a dysphoric drug effect (Vogel & Nathan, 1976).

The novelty hypothesis can account for the fact that drug pre-exposures attenuate the formation of CTAs and that, in general, fewer pre-exposures are required for self-administered drugs than for non-self-administered drugs. With self-administered drugs, the novelty habituates. With non-self-administered drugs, the aversion remains constant and, therefore, any attenuation that may occur is purely a function of associative interference. The novelty hypothesis as originally stated (Amit & Baum, 1970), however, runs into the same difficulties as the tolerance hypothesis. It is difficult for a novelty hypothesis to explain asymmetrical pre-exposure effects. In order for the pre-exposed drug to attenuate the formation of a CTA induced by another drug, the stimulus properties underlying CTA of the

two drugs should be similar. This being the case, reversing the pre-exposure and conditioning drugs should also result in attenuation. Yet, the results obtained by Cappell, LeBlanc and Herling (1975) as well as Vogel and Nathan (1976) are contrary to this prediction. Another problem for a novelty hypothesis is the demonstration that morphine still induced a CTA to a second flavor after having been paired a number of times with another flavor (Stewart & Eikelboom, 1978). In accordance with a novelty hypothesis one might predict that the CTA associated with the second flavor should be attenuated as the drug state is not as novel. Finally, a point of particular contention is the fact that cocaine, even at very high dosages, produces only a minor taste aversion (Booth et al., 1977; Goudie, Dickins & Thornton, 1978). If the stimulus properties which comprise the positively reinforcing effect of cocaine are responsible for the manifestation of a CTA, then one would expect to see a stronger CTA within a dose range which is self-administered. It is possible, however, as was mentioned earlier, that the relatively short duration of cocaine activity is not amenable for the manifestation of a CTA.

It seems, then, that there are a number of problems with a novelty hypothesis as well as a tolerance hypothesis. None of these formulations can easily

account for all of the CTA data which have been generated.

Simultaneous Positive Reinforcement and CTA

Three recent experiments have demonstrated that injections of self-administered drugs can be simultaneously reinforcing and aversive (Reicher & Holman, 1977; White et al., 1977; Wise, Yokel & deWit, 1976). Wise et al. permitted rats to lever-press for injections of amphetamine after having ingested a novel-tasting saccharin solution. Upon subsequent exposure to the saccharin, a CTA was observed. Hence, injections of amphetamine which positively reinforced lever-pressing also induced a CTA. Reicher and Holman found that injections of amphetamine in one side of a shuttlebox not only induced a preference for the location of the injection in the shuttlebox but also induced a CTA in the same animals. Finally, White et al. demonstrated that injections of morphine in the goal box of a runway increased running speed down the alleyway on subsequent trials and also induced a CTA to the flavored food consumed in the goal box prior to the injections. These studies clearly demonstrate that the same drug injections can be both positively reinfocing and aversive in the same animals at the same time. This effect is not artifactual since lithium chloride, in the runway situation, produces a decrease in running speed as well as a CTA (White et al., 1977). Furthermore,

rats avoid a place associated with lithium chloride (Berk & Miller, 1978).

The fact that simultaneous positive reinforcement and aversion can occur, suggests that the internal stimulus complex produced by self-administered drugs may, at the same time, mediate both effects. This would seem to rule out the idea that the aversive drug effect tolerates prior to the development of a drug's positively reinforcing effect. What does remain open to question is whether the positively reinforcing and aversive properties of a drug are independent components within the same stimulus complex or whether they represent partially dependent components. Catecholamine experiments would suggest the latter since identical neurochemical interventions disrupt both CTA and self-administration. However, if they are distinct components, then it would be interesting to determine what environmental cues promote the discrimination of either positive reinforcement or aversion. If, on the other hand, the two behavioral effects are interrelated, then the implication is that by studying CTA we are, in fact, tapping into the stimulus properties of drugs which also underlie their positively reinforcing effects. In either case, the phenomenon of simultenous reinforcement and aversion certainly challenges our current understanding

about hedonic drug properties.

Towards a Further Understanding

A number of issues have been discussed under the question: what is the relationship, if any, between drug aversion and positive reinforcement? As was illustrated, there is no comprehensive answer to this question. Hypotheses have been proposed to account for the finding that a drug can be both positively reinforcing and aversive. These hypothesis (tolerance and novelty), however, cannot account for all of the data generated over the past decade. It is clear that in order to further understand the relationship between positive reinforcement and aversion, some outstanding issues must be clarified.

Based on the evidence presented in this thesis, it may be suggested that the positively reinforcing and aversive effects of self-administered drugs are somehow related. The same neurochemical systems seem to mediate both effects, which can occur in the same animal at the same time. If positive reinforcement and aversion are related, then why does cocaine not induce a CTA at moderate doses comparable to that of amphetamine (Booth et al., 1977)? Is duration of action an important component, as Goudie and Dickins (1978) have argued?

The position held in this paper is that the nature

of the aversion induced by self-administered drugs is qualitatively different from that induced by non-self-administered drugs. The neural bases for the aversions seem to be different as well as their behavioral profiles in pre-exposure studies. The fact that pre-exposure to one drug does not necessarily attenuate the formation of CTA based upon another drug would seem to indicate that differences between drugs can be reflected in the CTA pre-exposure paradigm. However, as Braveman (1977) pointed out, the possibility of differentially aversive drug dosages confounding results of these studies limit interpretation. By controlling this aspect, would cross-over pre-exposure effects between drugs with different pharmacological profiles be symmetrical, as Braveman suggests?

The first experiment of this thesis assesses whether or not there is a relationship between drug reinforcement and aversion in the runway situation described by White et al. (1977). A further goal in Experiment 1 will be to assess the relative contribution of the gustatory stimulus to both positively- and aversively-motivated behaviors. In the second study, some of the parameters involved in promoting a cocaine-CTA will be examined. The final study is a cross-over pre-exposure experiment using three drugs with different pharmacological

profiles (morphine, Valium (diazepam) and Δ^9THC). When equivalently-aversive dosages are used, would CTA be attenuated only when the pre-exposure and conditioning drug was the same? If not, would the observed attenuation be symmetrical or asymmetrical? Together and individually, these three studies should answer some basic questions to elaborate the nature of CTAs induced by psychoactive drugs.

Experiment 1

It is well-established that morphine can induce a CTA to a novel-tasting substance (e.g. Cappell et al., 1973; Farber et al., 1976; Jacquet, 1973) suggesting that this drug has aversive properties. A number of studies have been directed at understanding the aversive properties of positively reinforcing drugs such as morphine. The quality of CTA produced by positively reinforcing drugs has been distinguished from the type of CTA produced by drugs with no demonstrated positively reinforcing properties (Amit, Levitan, Brown & Rogan, 1977; Berger et al., 1973; Goudie, Taylor & Alherton, 1975; Riley et al., 1978; Roberts & Fibiger, 1975; Sklar & Amit, 1977). Properties of self-administered drugs which produce aversion may be at least partly responsible for the production of positive reinforcement. For instance, neurochemical interventions which disrupt CTA induced by positively reinforcing drugs are similar or identical to interventions which disrupt drug self-administration (LeBlanc & Cappell, 1975; Roberts & Fibiger, 1975; Sklar & Amit, 1977).

In a recent experiment, White et al. (1977) attempted to elaborate the nature of the relationship between morphine's positively reinforcing and aversive properties.

These investigators set out to determine whether or not the same morphine injections could be simultaneously positively reinforcing and aversive. Food-deprived rats were allowed to run down a straight runway for a novel-tasting food located in the goal box. Consumption of the food was followed by an injection of morphine. Over subsequent trials, with this same procedure carried out on each trial, the rats ate less food and ran faster. Thus, the same series of morphine injections produced signs of positive reinforcement and aversion.

The present experiment further examines the relationship between aversion, as reflected by decreased food consumption, and positive reinforcement, as seen by an increase in running speed.

Methods

Subjects

Subjects were 30 male Wistar rats weighing 275-325 g at the start of the experiment. The animals were individually housed in stainless steel cages with free access to Purina laboratory chow and water prior to the onset of the experiment.

Drug and food

Morphine hydrochloride (May and Baker Can. Ltd.) was dissolved in a vehicle of injectable Ringer's solution

(Abbott Laboratories Ltd.).

During the experiment, the only food available to the animals was wet mash comprising ground lab chow and water. When the paradigm required the use of flavored food, the mash was adulterated with decaffeinated coffee (Sanka) such that each gram of ground lab chow was mixed with 1 ml of a 4% (w/v) coffee/water solution.

Apparatus

The experiment was conducted in a straight wooden runway (19 cm wide with walls 29 cm high) consisting of a start box, alley and goal box. Vertically-sliding doors separated the start box and goal box from the alley between the boxes. The lengths of the start box, alley and goal box were 19.3 cm, 181 cm and 24 cm, respectively. The goal box and its sliding door could be detached from the end of the alley and placed aside with a rat in it when necessary.

Two digital timers, calibrated in units of 1/10 sec were used to measure running time. The first timer measured latency to leave the start box and the second one measured running time down the alley. A photoelectronic relay system controlled the timers. Lifting the start box door depressed a microswitch which started the first timer. When a rat broke the beam of light focussed on the photocell outside the start box

door, the first timer was stopped, and simultaneously the second timer was activated. Deactivation of the second timer occurred when the rat broke the light beam which crossed the entrance to the goal box. Summing both times yielded the total running time.

Procedure

Food was removed from the home cages 24 hr prior to the onset of the experiment. Throughout the experiment, the animals received a 1/2 hr supplement of plain mash in the home cages at least 1/2 hr after being run each day.

There were 3 stages to the experiment. In the first stage, which lasted two consecutive days, the rats were allowed to adapt to the runway apparatus. Each animal was placed in the start box and within 5 sec the door was lifted allowing the rat to move freely in the runway for 10 min. During this time, animals had free access to plain mash located in the goal box. The second stage of the experiment which also lasted two consecutive days, was instituted to enable each animal to stabilize its running speed. The rat was placed in the start box, the door was opened and, when the animal entered the goal box (in which there was plain mash), the goal box door was lowered, trapping the animal inside. The goal box was then removed from the rest of the apparatus and placed aside for 10 min. The third stage of the experiment

lasted 6 consecutive days. In this stage, the mash was flavored with coffee for 2 of the groups. One of these groups (Group FM; n = 10) received i.p. injections of morphine immediately after the 10 min eating period and the second group (Group FR; n = 8) received i.p. injections of the Ringer's vehicle solution. Two additional groups continued to receive plain mash in stage 3 of the experiment. One of these groups (Group UM; n = 7) received i.p. injections of morphine immediately after the 10 min eating period and the second group (Group UR; n = 5) received i.p. injections of Ringer's. All injections were administered in a volume of 1 ml/kg. The dose of morphine was 9 mg/kg. Following injections, all animals were replaced in the goal box and left there without food for 50 additional min.

In both stages 2 and 3, total running time was recorded for each animal. The food container placed in the goal box was weighed directly before placing an animal in the runway and immediately after the 10 min eating period.

Results

Both eating and running scores are expressed as percentage change from baseline. Individual baseline scores were obtained from day 1 of stage 3 of the

experiment.

The percentage of baseline eating scores were logarithmically transformed and a two-way analysis of variance was carried out on these scores.

In order for an increase in running speed to be reflected by an ascending curve, the reciprocal of the percentage of baseline running scores was calculated. These scores were then logarithmically transformed, and a two-way analysis of variance was carried out on these scores.

It was found in pilot studies that animals with baseline running times greater than or equal to 10 sec usually ran with considerable variability throughout the experiment, independently of the type of treatment received. It was, therefore, decided a priori that animals not running less than 10 sec would be removed from the experiment.

Flavored Food

It was observed that some animals injected with morphine reduced their food intake whereas other animals did not demonstrate a reduction in food intake. Based on this observation and the suggestion that morphine's aversive and positively reinforcing effects may be related (e.g. Sklar & Amit, 1977), it was decided that morphine-injected animals would be divided into subgroups. One subgroup would consist of subjects in which food intake

had diminished. The second subgroup would contain subjects that did not demonstrate a decrease in food intake. Running speeds of these subgroups would then be compared with the Ringer's control group in order to further evaluate the relationship between flavored food intake and running speed. The following method was employed in order to assign subjects into either subgroup: the standard deviations (S.D.) of the mean daily eating scores for the control group (FR) were calculated; an animal was considered to have displayed a CTA if, on any day, an eating score fell below 2 S.D. units of the control group mean for that day. No subject from Group FR met this criterion. In contrast, 7 out of the 10 subjects in Group FM did meet the criterion. Hence, the morphine group was subdivided into group FM-low (n = 7), consisting of morphine-injected animals in which food intake was reduced, and group FM-high (n = 3), consisting of morphine-injected animals in which there was no reduction in food intake. Figure 1 presents flavored food consumption for Group FM-low , Group FM-high and Group FR.

There was a significant treatment effect (Figure 2) on the running

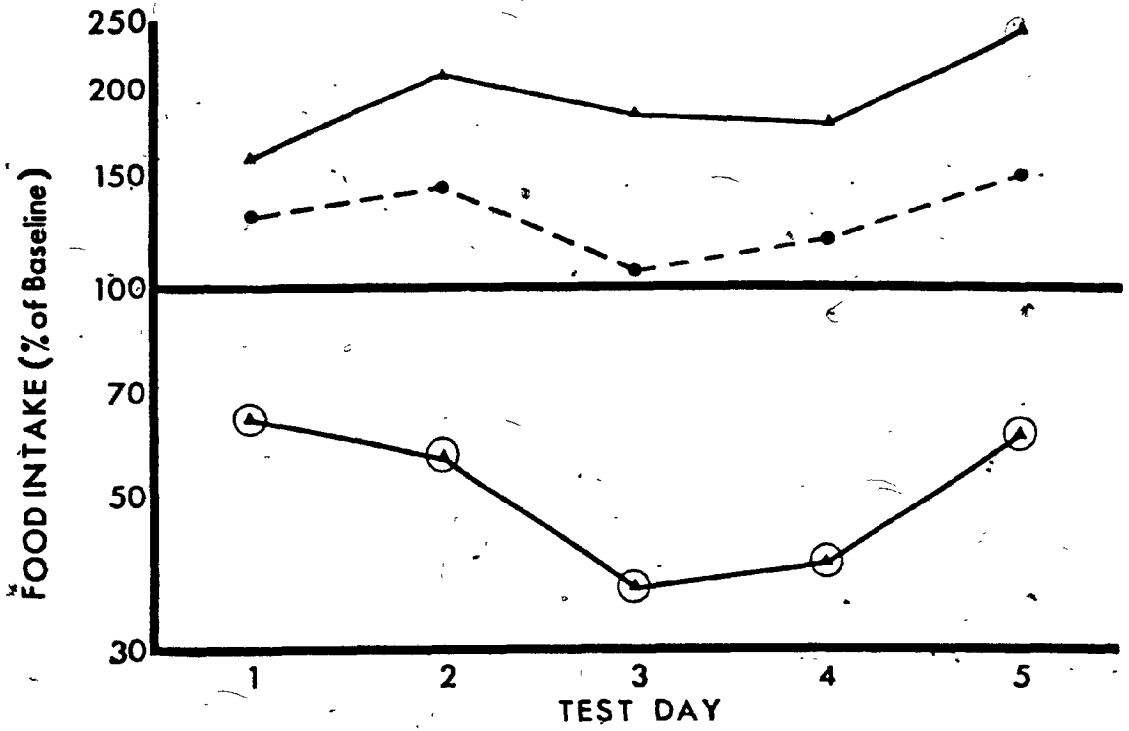

Figure 1. Mean percent of baseline amount of food eaten in the goal box for Group FM-low (solid line-circled triangles), Group FM-high (solid line-triangles) and Group FR (broken line).

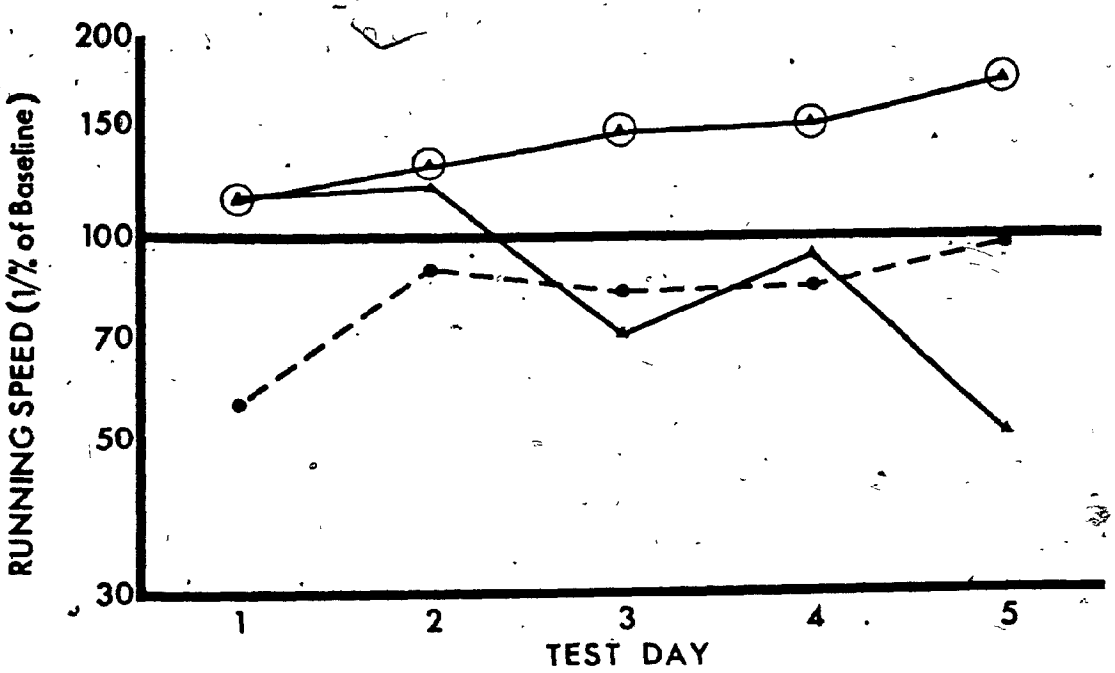

Figure 2. Mean percent of baseline running speed for Group FM-low (solid line-circled triangles), Group FM-high (solid line-triangles) and Group FR (broken line).

speeds ($F(2,15) = 5.0484$, $p<.025$) such that group FM-low ran significantly faster than Group FR ($F(2,15) = 9.2$, $p<.05$). There was no significant difference in running speed between Group FM-high and Group FR ($F(2,15) = .0609$, $p>.25$).

Unflavored Food

Since morphine injected animals receiving flavored food were placed into subgroups consisting of animals reducing food intake and animals not reducing food intake, a parallel subdivision of morphine-injected animals receiving unflavored food was conducted. The S.D. of each daily mean eating score for the unflavored food control group was calculated. An animal was considered to have reduced food intake if, on any day, an eating score fell below 2 S.D. units of the control group (UR) mean for the day. No subject in the Ringer's control group met the aversion criterion. On the other hand, 3 out of 7 subjects in the morphine group did meet the criterion. Thus, the morphine group was subdivided into Group UM-low ($n = 3$) and Group UM-high ($n = 4$). Figure 3 presents flavored food consumption for Group UM-low, Group UM-high and group FR.

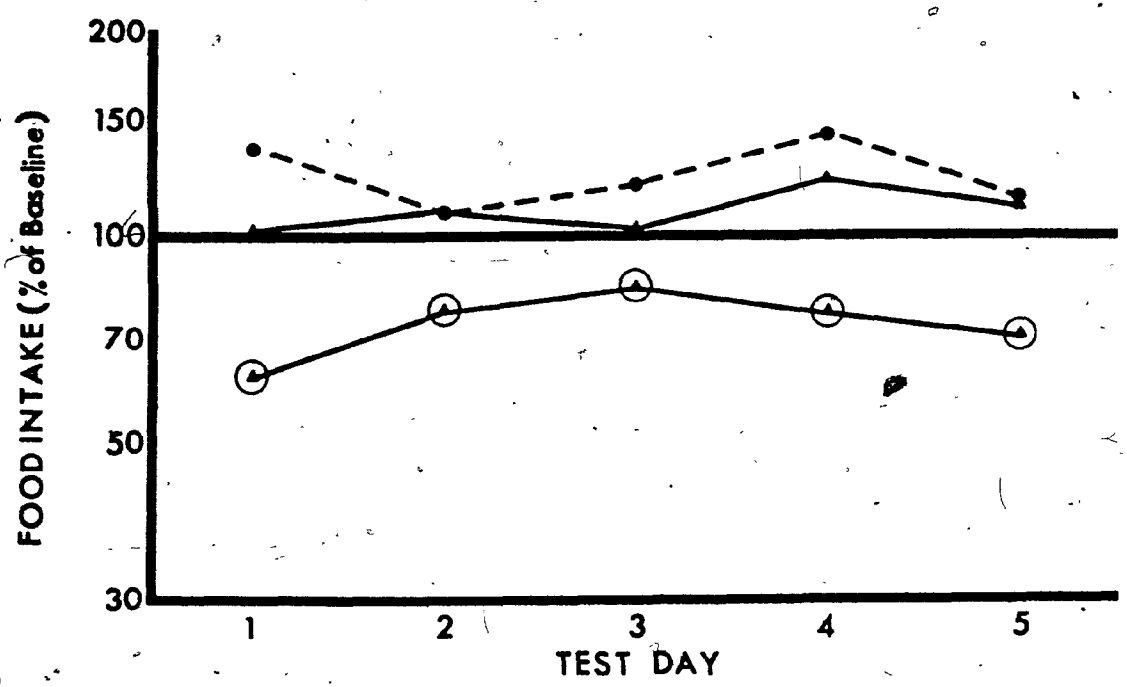

Figure 3. Mean percent of baseline amount of food eaten in the goal box for Group UM-low (solid line-circled triangles), Group UM-high (solid line-triangles) and Group UR (broken line)

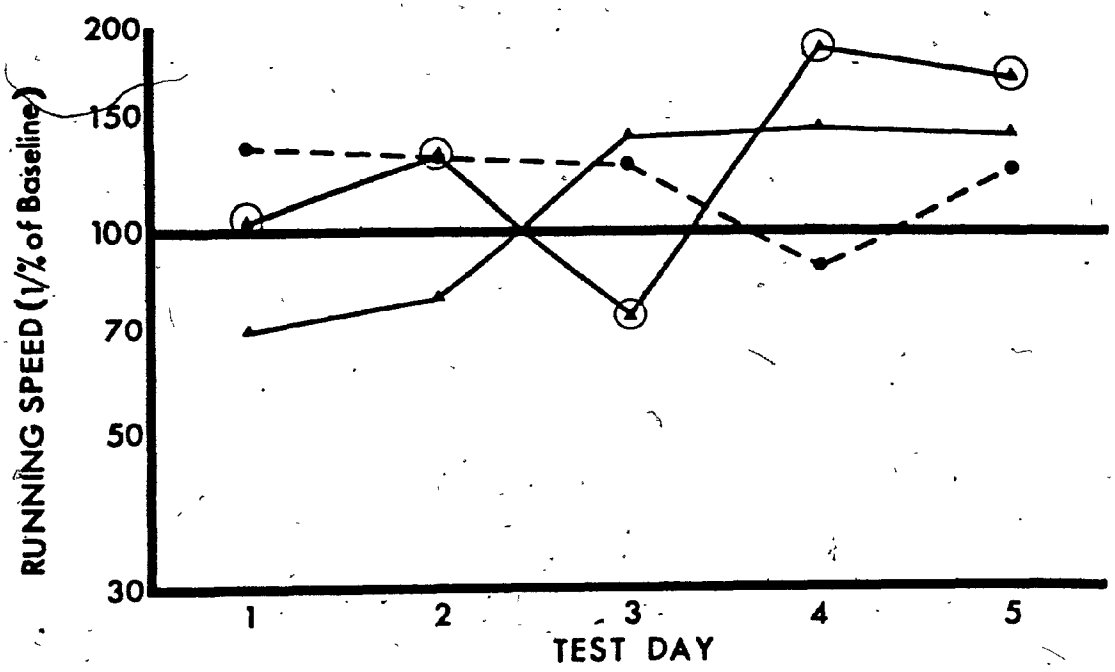

Figure 4. Mean percent of baseline running speed for Group UM-low (solid line-circled triangles), Group UM-high (solid line-triangles) and Group UR (broken line).

The running scores for Group UM-low, Group UM-high and Group UR are presented in Figure 4. The analysis of variance revealed a significant groups x days interaction ($F(8,36) = 2.2761$, $p<.05$). On the first test day, Group UM-high ran significantly slower than Group UM-low and Group UR (Newman-Keuls, $p<.05$). On the fourth test day Group UM-high as well as Group UM-low ran significantly faster than Group UR (Newman-Keuls, $p<.05$).

Discussion

The variability of morphine's effect on flavored food consumption is consistent with results of other CTA studies (e.g. Riley et al., 1978) in which large variance in saccharin-water drinking produced by a wide dose range of morphine injections has been reported. As Riley et al. note, such variability rarely occurs when LiCl is used as the aversion-inducing agent. It is, therefore, possible that some of the properties of morphine that produce CTA are qualitatively different from the aversion-inducing properties of drugs such as LiCl.

As a result of the variable eating response, and the possible relationship between CTA and positive reinforcement (e.g. Sklar & Amit, 1977), morphine-injected animals receiving flavored food were subdivided into Group FM-low,

consisting of subjects in which morphine produced a CTA and Group FM-high, in which morphine failed to produce a CTA. It was found that Group FM-low ran faster than their own baseline running speed and the control group running speed across the 5 test days. In contrast, Group FM-high ran below their own baseline on the last 3 test days and did not differ from the control group. These results suggest that there is a relationship between the discriminative cues which produce a CTA and the increase in running speed. When CTA was observed in rats, running speed increased; when no CTA was evident, there was no increase in running speed. It seems, therefore, that the same morphine injections can, simultaneously, provide a stimulus for a response from which we infer positive properties and for a different response from which we infer aversive properties. It is doubtful that the increase in running speed could be interpreted as a motor activation produced by morphine since the animals received injections after having run down the alley approximately 24 hr after the previous injection. It is equally improbable that the increase in running speed is related to frustration experienced in the goal box since LiCl injected in the runway situation produces a dramatic decrease in food intake as well as a concommitant decrease in running speed (White et al., 1977). Thus,

the increased running effect observed in the present experiment may best be explained in terms of morphine's, much studied, positively reinforcing properties (e.g. Deneau et al., 1969; Woods & Schuster, 1968).

In order to further examine the aversion-reinforcement problem, the effect upon running speed of altering cues related to CTA was assessed. If the discriminative cues related to CTA are also involved in the increase observed in running speed, then reducing the salience of the food cue might also affect running speed.

When the eating scores for Group UM-low and Group FM-low are compared (Figures 1 and 3), it can be seen that the magnitude of the effect in Group UM-low was less than that seen in Group FM-low. Furthermore, a smaller proportion of the subjects fell into the "low" subgroup from Group UM (3/7 subjects) than from Group FM (7/10 subjects). Therefore, the morphine-produced reduction in eating was greater when the food was flavored. The running effect seen in the unflavored food groups on the first 3 test days bear little or no relationship to their levels of food consumption. On the fourth test day, however, both groups UM-low and UM-high ran significantly faster than Group UR. In addition, Group UM-low had a faster mean running time than Group UM-high and, although this difference was not significant, it was maintained on

the last test day. It is, thus, possible that in the previous phase of the experiment, the flavored food provided an additional cue, not only for the aversive effect, but also for the positively reinforcing effect of morphine. The flavored food may have enhanced the discriminability of the positive stimulus properties of morphine resulting in increased running speed.

The results of the present experiment suggest that CTA and positive reinforcement produced by morphine are functionally related. It is possible that the novel flavor of the food enhanced the discriminability of the drug state that produced both CTA and increased running speed. The morphine cue may have been enhanced by the distinct flavor of the food. Animals which successfully associated the drug state with the novel food taste could have increased running speed down the alley as a result of the enhanced discriminability of the positive pharmacological effect of morphine. The CTA produced in these animals may be a function of the novelty of the drug state which became associated with the food. What determines that some animals display positive reinforcement and aversion whereas others do not, still remains open to question.

Experiment 2

Conditioned taste aversion (CTA) to a novel-tasting substance can be induced by a variety of stimuli. Included among a broad spectrum of agents are radiation (Smith, 1971), rotation (Braveman, 1975), lithium chloride (Nachman & Ashe, 1973), and psychoactive drugs such as barbiturates (Vogel & Nathan, 1975), chloridiazepoxide, morphine, alcohol (Cappell et al., 1973), and amphetamine (Booth et al., 1977). Some of these pharmacological agents which induce CTA such as alcohol, morphine and amphetamine, are also self-administered. It is doubtful that the CTAs induced by self-administered drugs result from a toxic reaction to the drug since both taste aversion and positive reinforcement have been observed with the same morphine injections (White et al., 1977) or amphetamine injections (Reicher & Holman, 1977).

Cocaine has been distinguished from other positively reinforcing drugs in terms of CTA-inducing liability. Cocaine produces a relatively weak CTA compared to other drugs. In two recent experiments, Goudie, Dickins and Thornton (1978) and Booth et al. (1977) with different procedures obtained only moderate decreases in saccharin intake even though relatively high doses of cocaine were administered. It seems, then, that the effect of cocaine is weak in the CTA paradigm. This is particularly

intriguing since amphetamine, another psychomotor stimulant, can produce quite a robust CTA at a relatively low dose (Booth et al., 1977; Goudie, Taylor & Atherton, 1975).

Cappell and LeBlanc (1977) suggested that the failure of cocaine to induce a reliable CTA may be due to the relatively short half-life of the drug (Nayak, Misra & Mulé, 1976). Goudie and Dickins (1978) recently demonstrated that rats would display a stronger aversion to a novel saccharin solution paired with nitrous oxide when the gas was administered at longer rather than shorter durations. It is possible, then, that temporal properties of drugs may be partly responsible for the induction of CTAs. If duration of drug action is an important contributing factor for the production of a CTA, then one would expect that prolonged exposure to cocaine should produce a stronger CTA than short-duration exposure to the drug. Cappell and LeBlanc (1977) demonstrated that 4 spaced cocaine injections following saccharin exposure produced a fairly robust CTA, confirming the notion that duration of action may be an important variable. These investigators, however, also found that a single high dose of cocaine followed by 3 saline injections also produced a CTA whereas a single high-dose injection alone did not. It was suggested that in the spaced

cocaine injections group, the initial cocaine injection followed by the subsequent handling and injection procedure interacted to induce the CTA. Although this in fact may be the case, it should be noted that Cappell and LeBlanc used a dose of cocaine which they report to be 50% of the LD50. It is possible, therefore, that the interaction they observed was merely a function of the high dose used followed by the extensive handling. The critical question would seem to be whether or not a similar interaction would occur with a lower dose of cocaine.

The present series of experiments were designed to further clarify some of the parameters which enable cocaine to induce a relatively robust CTA. In Experiment 2a, a different number of spaced injections were administered to different groups of rats following saccharin exposure in order to assess whether or not the CTA would increase in magnitude with the number of injections administered. In Experiment 2b, a constant number of spaced injections were administered at different dosages following saccharin exposure in order to assess the nature of the dose-response relationship. Experiment 2c was designed to determine whether, (a) a single high dose of cocaine would induce the same magnitude of CTA as would 4 spaced dosages equal in total to the single dose and, (b) whether additional

saline injections would interact with a moderate dose of cocaine to induce a greater CTA as compared to the moderate dose of cocaine alone. With the exception of a different drug dosage, this latter phase is essentially a replication of the study conducted by Cappell and LeBlanc (1977).

Experiment 2a

Method

Subjects

Subjects were 40 male Wistar rats (Canadian Breeding Farms) weighing 250-300 g at the start of the experiment. The animals were individually housed in stainless steel cages with free access to Purina Lab Chow and water prior to the onset of the experiment.

Drugs and Materials

Cocaine hydrochloride (May & Baker Can. Ltd.) was dissolved in injectable saline solution (Abbott Laboratories) in a concentration of 20 mg/ml. Drinking fluids were delivered to the animals in glass test tubes with ball-bearing spouts. The spouts were inserted through the wire mesh of the cages.

Procedure

The paradigm was derived from that of Goudie, Dickins and Thornton (1978). Following a one-week adaptation to

the laboratory, the animals were placed on a 23½ hr fluid deprivation schedule for a period of five days. On each day at the same time, the rats were exposed to 1/2 hr of water. On the sixth day, a 0.1% (w/v) saccharin solution was substituted for the water afterwhich the animals received their respective injection regimes. Two more such saccharin-injection pairings ensued with two water days intervening between each. Following the third and final pairing day, and with two additional water days intervening, the saccharin was once more presented for 1/2 hr. Thus, there were 4 saccharin presentations, the first three of which were followed by injections.

Groups

Eight rats were assigned to each of 5 groups. One group received a single injection of cocaine (20 mg/kg) on each pairing day. A second group received two injections of cocaine (20 mg/kg per injection) spaced 20 min apart on every pairing day. The third, fourth and fifth groups received 3, 4 and 5 injections of cocaine respectively on each pairing day. For these groups, each injection also consisted of 20 mg/kg cocaine spaced 20 min apart. The first injection was administered within a few minutes after removel of the saccharin for all of the groups.

Results and Discussion

Baseline fluid intakes on the first saccharin day did not significant differ between the groups ($F(4,95) = .0896$, $p>.25$, simple main effects test). As Figure 5 illustrates, saccharin intakes decreased over days for all multiple injection groups ($F(3,105) = 101.979$, $p<.0001$). The group receiving two spaced injections drank significantly less saccharin than the single-injection group on days 2 and 4 (Newman-Keuls, $p<.05$). The group receiving three spaced injections differed from all groups on day 3 and was significantly below the two-injection group on day 4 (Newman-Keuls, $p<.05$). Both the four- and five-injection groups drank consistantly less than the three-injection group, however, the difference was statistically significant on day 3 only (Newman-Keuls, $p<.05$).

The results obtained in the present experiment demonstrate that cocaine can produce a predictable and orderly decrease in saccharin intake in a CTA paradigm. As the number of injections administered increased, the strength of the CTA also increased. When a single cocaine injection was administered, no decrease in saccharin intake was observed, however, when 4 or 5 spaced injections were administered, the effect of cocaine was sufficiently

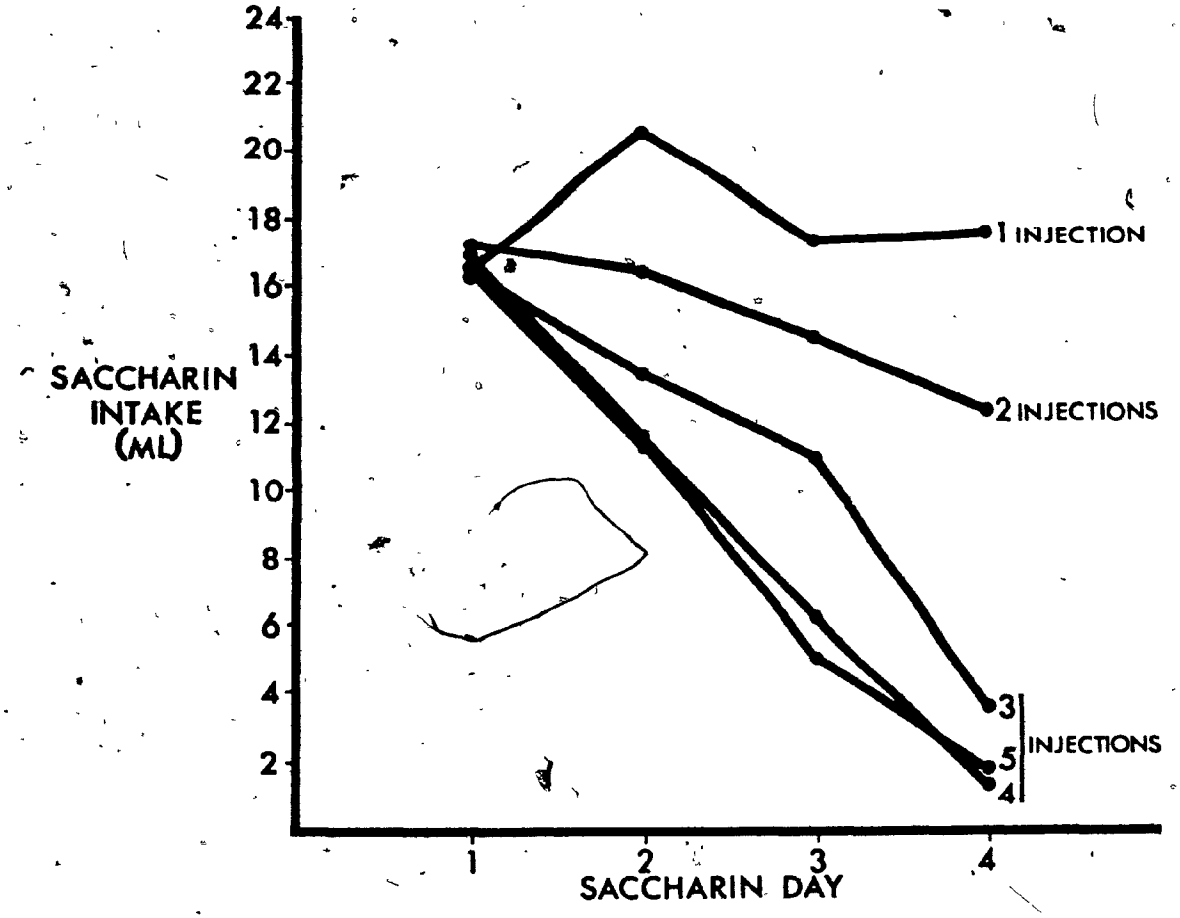

Figure 5. Saccharin intake over the four saccharin days for groups receiving a single or multiple injections of cocaine.

potent to have suppressed saccharin intake to a mean of less than 2 ml on the fourth day. Cocaine, then, can be a powerful aversive agent when administered over an extended period of time.

The total dose of the five-injection group was 100 mg/kg which, if administered in a single injection, would be lethal to most, if not all rats (Cappell & LeBlanc, 1977). That none of the animals died would argue for the fact that metabolism of the drug was rapid enough in all groups to accomodate the injection regime. This would further argue that blood levels of cocaine did not reach high proportions. The decrease in saccharin intake observed was, in fact, a CTA rather than a long-term effect of cocaine on fluid intake. Water intake was not observed to decrease on the days following the pairing days. To illustrate this, on the day prior to the first pairing, the mean water intake for the five-injection group was 16 ml. On the day following the first pairing, the mean water intake was 15.9 ml and on the day following the third pairing, the mean water intake was 18 ml.

Experiment 2b

Method

Subjects and Procedure

Twenty three male Wistar rats were randomly assigned to three different groups. The procedure was the same as that described in Experiment 2a.

Groups

Each of the three groups received 5 spaced injections following each saccharin exposure and, as in Experiment 1, the injections were spaced 20 min apart. One group (n = 8) received 5 spaced injections of saline (1 ml/kg each injection). A second group (n = 8) received 5 spaced injections of cocaine at a dose of 5 mg/kg (1 ml/kg) for each injection. A third group (n = 7) received 5 spaced injections of cocaine at a dose of 10 mg/kg (1 ml/kg) for each injection.

Results and Discussion

The results are presented in Figure 6. For purposes of comparison, the five injection group (20 mg/kg per injection) from Experiment 2a is included. Baseline fluid intakes on the first saccharin day did not differ between the groups ($F(3,95) = 2.54$, $p>.05$, simple main effects test). As is evident, the saline group did not decrease

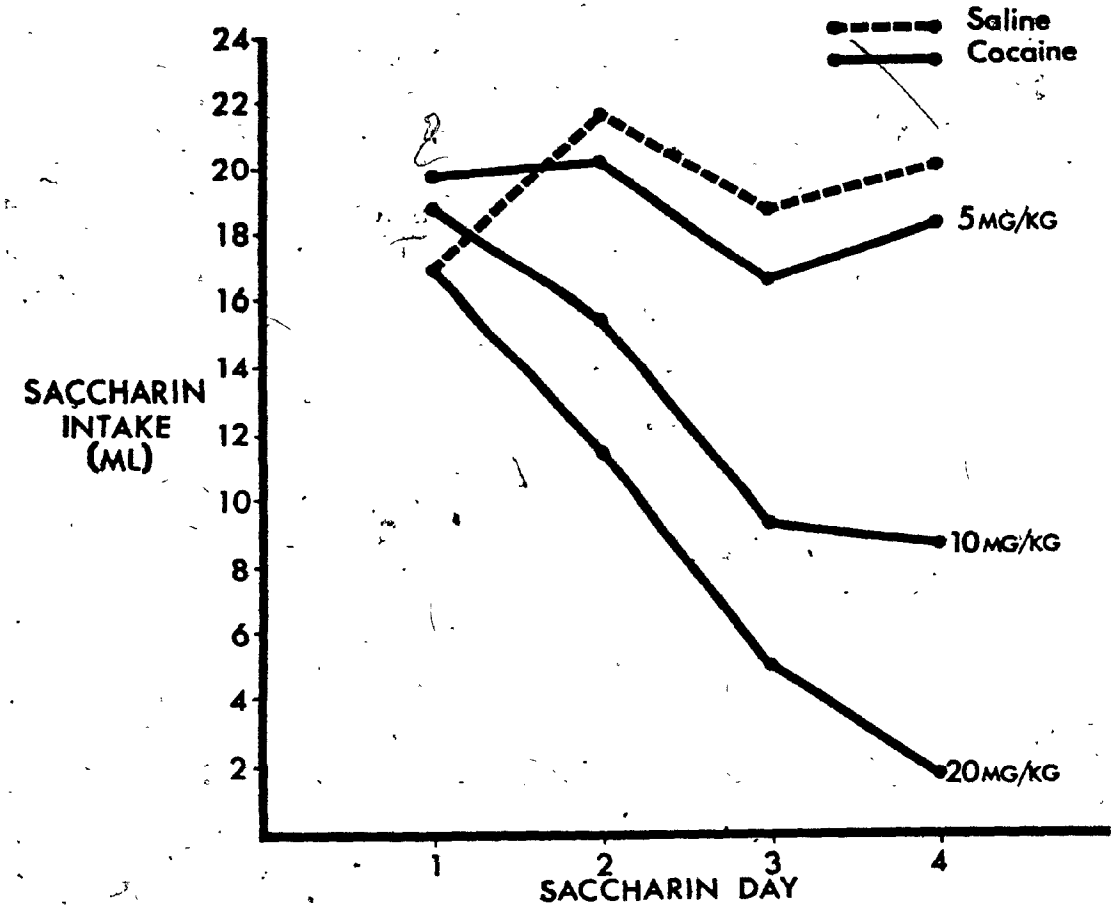

Figure 6. Saccharin intake over the four saccharin days for groups receiving five spaced injections of either saline or cocaine at one of three dosages.

saccharin intake whereas all of the cocaine-injected groups did so in a dose-dependent fashion ($F(3,26) = 46,1357$, $p<.0001$). Over the last three saccharin days, each cocaine group significantly differed from each other (Newman-Keuls, $p<.05$). Although the 5 mg/kg cocaine group drank consistently less saccharin than the saline group, the only significant difference occurred on day 3 (Newman-Keuls, $p<.05$).

The results obtained in the present experiment demonstrate that multiple injections of cocaine can produce a CTA at lower doses. The orderly dose-response relationship parallels that observed when amphetamine is used in CTA experiments (Booth et al., 1977). Furthermore, it may be observed that multiple saline injections do not induce a CTA, confirming the results of Cappell and LeBlanc (1977), and indicating that stress of the injection regime alone cannot account for the CTA observed in the other groups.

Experiment 2c

In Experiments 2a and 2b, it was demonstrated that cocaine can induce a strong CTA when administered in multiple injections, that the strength of the CTA varies directly with the number of injections administered, and that the CTA induced by multiple injections of cocaine

is dose-dependent. It is impossible, however, to draw any firm conclusions about the role of the "duration of the drug effect". Three variables changed in each group of the first experiment: duration of drug effect, number of injections administered, and total dose injected after the saccharin presentation. Cappell and LeBlanc (1977) demonstrated an interaction between the administration of cocaine and successive injections of saline which enhanced the CTA. These investigators, however, used a high dose of cocaine (36 mg/kg). The present experiment was designed to assess the relative contribution of the three variables outlined above upon the formation of CTA induced by cocaine. One group received four spaced injections of cocaine at a moderate dose and a second group received a single injection equal to the total dose received by the former group. A third group received one injection of the moderate dose followed by three spaced saline injections. A fourth group received one injection of the moderate dose alone. These third and fourth groups were run to determine whether the additional saline injections would produce an exaggerated effect. A fifth control group received four spaced saline injections.

Method

Subjects and Procedure

Fifty male Wistar rats were randomly assigned to the five different groups. The procedure was the same as that described in Experiment 2a.

Groups

Group MC received 4 injections of cocaine spaced 20 min apart on each pairing day. The dose of each injection was 9 mg/kg (1 ml/kg) thus yielding a total dose on each pairing day of 36 mg/kg. Group HC received a single injection of 36 mg/kg (1 ml/kg) of cocaine on each pairing day. Group CS received 4 injections spaced 20 min apart on each pairing day. The first injection consisted of cocaine at a dose of 9 mg/kg (1 ml/kg) and the subsequent three injections consisted of saline (1 ml/kg per injection). Group LC received a single injection of 9 mg/kg (1 ml/kg) cocaine on each pairing day. Finally, Group S received 4 spaced injections of saline (1 ml/kg per injection) on each pairing day.

Results and Discussion

Results obtained in this experiment are presented in Figure 7. There was no significant difference between the groups in baseline saccharin intakes ($F(4,116) = .09$,

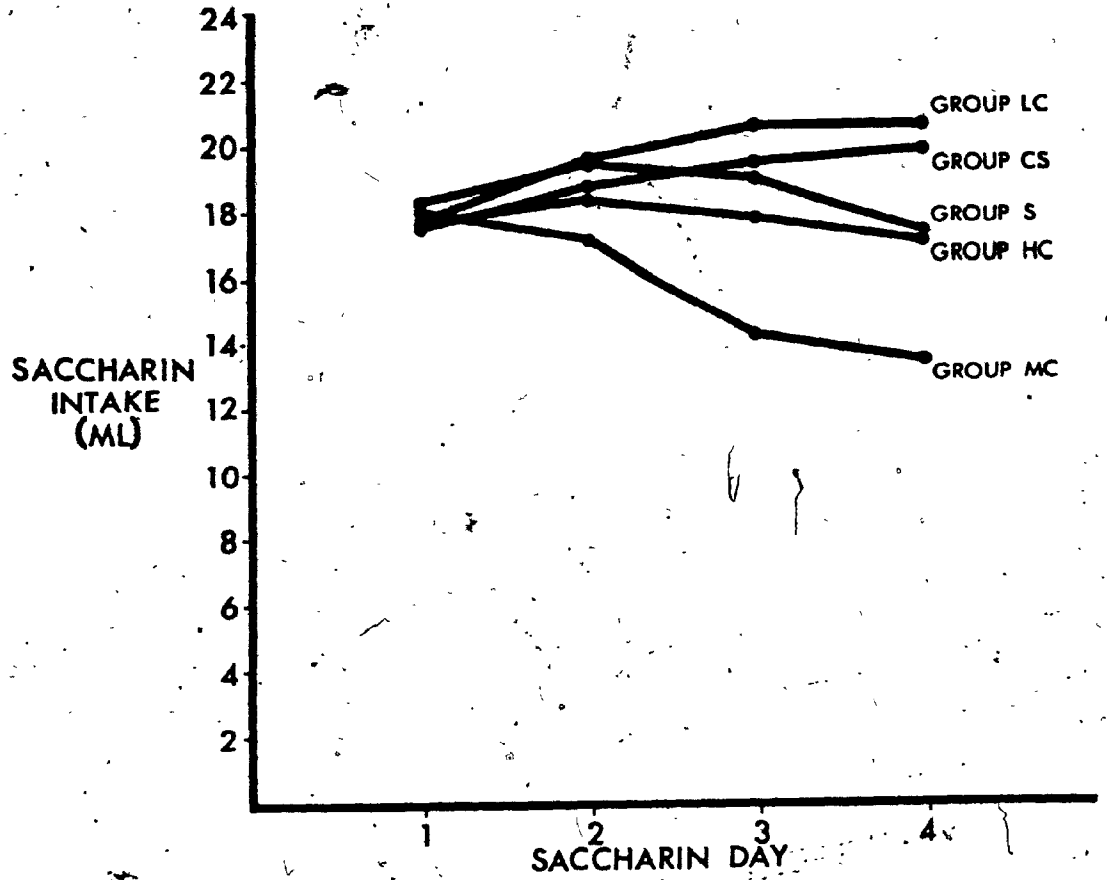

Figure 7. Saccharin intake over the four saccharin days for Groups MC (four spaced cocaine injections), HC (single 36 mg/kg cocaine injection), CS (9 mg/kg cocaine injection plus three saline injections), DC (single 9 mg/kg cocaine injection) or S (four spaced saline injections).

$p>.25$, simple main effects test). The analysis of variance revealed a significant main effect of groups ($F(4,45) = 3.28$, $p<.02$) as well as a significant groups x days interaction ($F(12,135) = 2.84$, $p<.002$). Only Group MC significantly decreased saccharin intake below baseline (Newman-Keuls, $p<.05$). Groups LC and CS gradually increased saccharin intake above baseline (Newman-Keuls, $p<.05$) whereas Groups HC and S did not change from baseline intake. Thus, whereas Group MC developed a significant CTA, none of the other groups did so. On days 3 and 4, Group MC drank below all other groups (Newman-Keuls, $p<.05$). The only other difference between any of the groups occurred on day 4 where Group LC drank significantly more saccharin than Group S, HC or MC (Newman-Keuls, $p<.05$)

The finding of primary interest in this experiment is that only the multiple injection cocaine group (Group MC) developed a significant CTA. Group HC, which received a single injection of cocaine equivalent to the total dose of the multiple injection group (Group HC), did not develop a significant aversion. Neither did the group receiving multiple saline injections (Group S). Furthermore, it made no difference if rats were given 3 additional saline injections following a single dose of cocaine (Group CS) or if they received the single dose

of cocaine alone (Group LC). It would seem that results demonstrating an interaction between cocaine and additional saline injections (Cappell & LeBlanc, 1977) may only occur when the dose of cocaine injected is high. Although a stress effect of multiple injections cannot be ruled out completely as contributing to the observed CTA in Group MC, this variable cannot completely account for the magnitude of the CTA observed.

Discussion

Taken together, the results of the Experiment 2a, 2b and 2c suggest that duration of drug action may be an important contributing factor for the production of CTA by self-administered drugs (Cappell & LeBlanc, 1977; Goudie & Dickins, 1978). From the results obtained in this study, it is not clear whether duration per se is critical or whether the degree of drug activity over time is important. In this study, it is possible that the blood level of cocaine may have gradually increased with the number of injections administered. Thus, the steepness of the slope of blood cocaine concentrations over time may be partly responsible for the magnitude of the CTA observed. Although Goudie and Dickins (1978) found that increasing the duration of exposure to nitrous oxide at a constant dose facilitated the formation of a

CTA, the magnitude of the effect was fairly weak.

The results obtained in the present series of experiments demonstrate that cocaine, like amphetamine, can produce a fairly robust CTA. An intriguing question is whether or not an enduring drug effect is inherently aversive (Goudie & Dickins, 1978) or is more easily associated with a novel taste.

Experiment 3

The fact that lithium chloride can induce a CTA (Nachman & Ashe, 1973) may be explained in terms of its noxious gastrointestinal effects and, thus, it is not surprising to find that the drug is aversive in the CTA paradigm. Neither is it difficult to account for results demonstrating the induction of CTA by psychoactive agents such as Valium (Gamzu, 1977) or tetrahydrocannabinol (Elsmore & Fletcher, 1972). These drugs are poorly self-administered by rats (Amit & Cohen, 1974; Corcoran & Amit, 1974; van Ree, Slangen & de Wied, 1978) indicating that rats do not find these drugs to be highly positive or rewarding. Drugs with relatively high self-administration liabilities in rats, such as morphine (Stolerman & Kumar, 1970; Weeks & Collins, 1964) and amphetamine (Yokel & Pickens, 1973; 1974), however, can also induce CTAs (Berger, 1972; Cappell, LeBlanc &

Endrenyi, 1973). It has proven difficult for researchers to reconcile the fact that a drug can be both positively reinforcing and aversive (Goudie, in press).

One of the strategies employed by investigators to examine the basis of drug aversion and, in particular, the aversive properties of self-administered drugs, has been the CTA pre-exposure paradigm. In the pre-exposure situation, rats receive experience with a drug one or more times prior to taste aversion conditioning trials. Typically, it has been found that drug pre-exposure can attenuate or block the formation of CTA (Cannon, Berman, Baker & Atkinson, 1973; Cappell, LeBlanc & Herling, 1975; Goudie, Thornton & Wheeler, 1976; Riley, Jacobs & LoLordo, 1976). Furthermore, as the number of pre-exposures increase, the attenuation of CTA also increases (Cannon et al., 1973). The pre-exposure effect on aversive conditioning has been explained in terms of pharmacological tolerance (Goudie, Taylor & Atherton, 1975; LeBlanc & Cappell, 1974), habituation to the novelty of the drug state (Amit & Baum, 1970; Gamzu, 1977; Vogel & Nathan, 1976), and impaired association between a novel taste and a drug effect as a function of the non-contingent drug pre-exposures (Braveman, 1975).

It is difficult for a tolerance hypothesis to account for results demonstrating that pre-exposure to aversive

stimuli different from that paired with a novel flavor can attenuate conditioning (Braveman, 1975). Results obtained by Cappell and LeBlanc (1977) are also problematic for a tolerance hypothesis. These investigators found no difference between massed and spaced pre-exposure trials upon conditioning with either morphine or amphetamine. A novelty hypothesis could account for the results obtained by Cappell and LeBlanc (1977) as well as the results obtained by Braveman (1975) if one assumed that the stimulus properties of the pre-exposure and conditioning stimuli were similar. However, even with such an assumption, a novelty hypothesis could not explain the fact that pre-exposure effects can be asymmetrical. For instance, Cappell, LeBlanc and Herling (1975) have demonstrated that pre-exposures to amphetamine attenuated CTA induced by morphine, however, pre-exposures to morphine did not attenuate CTA induced by amphetamine. Similarly, Vogel and Nathan (1976) have demonstrated that pre-exposures to amphetamine attenuated CTA normally induced by amobarbital but that pre-exposures to amobarbital did not attenuate the CTA normally induced by amphetamine. These results are also problematic for an associative explanation where the emphasis is placed on the impaired association between a drug and a novel-tasting substance as a function of drug

pre-exposure (Braveman, 1975). If one drug can attenuate the formation of CTA induced by a second drug, then the reverse should also be true. Braveman (1977) has pointed out, however, that the asymmetrical pre-exposure effects may be related to parametric problems. For example, pre-exposing an animal to a weaker aversive stimulus may have relatively little effect on the formation of CTA induced by a more potent agent whereas pre-exposing the more potent agent might attenuate or block formation of CTA induced by the weaker agent. Thus, if the relative CTA-inducing potencies of the drugs were different, one might expect an asymmetrical pre-exposure effect no matter how similar the two stimuli were. In fact, Cannon et al. (1975) demonstrated this when lithium chloride was used in the pre-exposure and conditioning phases.

In the present experiment, the effect of pre-exposing equipotent dosages of three different pharmacological agents on the formation of CTAs induced by the drugs was assessed. Each drug was administered in the pre-exposure phase as well as the conditioning phase of the experiment. The drugs employed were morphine, Valium and Δ^9-tetrahydrocannabinol (Δ^9THC). All of these drugs can induce CTAs (Cappell, LeBlanc & Endrenyi, 1973; Elsmore & Fletcher, 1972; Gamzu, 1977), yet the drugs are pharmacologically dissimilar (Goodman & Gillman, 1975).

Furthermore, morphine has a relatively high self-administration liability in laboratory rats. Valium and cannabis, however, are not readily self-administered by laboratory rats. The present experiment attempts to answer the question, can different properties of drugs be reflected in the CTA pre-exposure situation and, if so, will the pre-exposure drug affect conditioning based only upon itself?

Method

Subjects

The subjects were 173 male Wistar rats weighing 230-325 g at the start of the experiment. The animals were individually housed in stainless steel cages with free access to Purina lab chow and tap water prior to the onset of the experiment.

Drugs and Materials

Morphine hydrochloride (May and Baker of Can., Co.) was dissolved in a vehicle of Ringer's solution. Valium was provided by Hoffman-La Roche Ltd. of Canada, and Trans Δ^9-tetrahydrocannabinol (Δ^9THC, 95% pure) was provided by the Department of National Health and Welfare, Canada. The Δ^9THC was diluted in a vehicle of propylene glycol (19 parts) and 95% ethanol (1 part). Data gathered in pilot experiments indicated that 9 mg/kg of morphine

(1 ml/kg), 10 mg/kg of Valium (2 ml/kg) and 4 mg/kg of Δ^9THC (0.5 ml/kg) would induce equivalent magnitudes of CTAs. Hence, these drug dosages were used throughout the experiment.

Saccharin sodium was dissolved in tap water (0.1% w/v). All drinking fluids were presented to the animals in glass test tubes with double ball-bearing spouts inserted into rubber stoppers. The fluids were presented in the home cages.

Procedure

Following a one-week adptation period to the laboratory, the rats were placed on a 23 hr 40 min fluid deprivation schedule. The animals were exposed to 20 min of water exposure between 1200 h and 1300 h each day for 7 consecutive days. The pre-exposure injections were administered following the 20 min drinking period on days 2, 4 and 6 of the experiment. On day 8 of the experiment (pairing day), the rats were presented with a novel-tasting saccharin solution for 10 min and 2 min after removal of the tube containing the saccharin, the rats were injected in a manner described below. For 5 consecutive days following the pairing day, the animals continued to receive 20 min of water per day. The saccharin was reintroduced (test day) six days after the pairing day. CTA was defined by a significant decrease in saccharin

intake on test day when compared to that on pairing day. Fluid intake was measured throughout the experiment.

The experiment was carried out in 4 parts. In part one of the experiment, the dosages of morphine, Valium and Δ^9THC were assessed for their relative CTA-inducing potencies. It was important to evaluate that the dosages used were equivalent in terms of their relative CTA inducing liabilities in order to rule out a potential confound of different drug potencies. In part one of the experiment, the experimental animals received pre-exposure injections of Ringer's (1 cc/kg) and on pairing day the rats were injected with either morphine, Valium or Δ^9THC. The control groups also received pre-exposure injections of Ringer's and on pairing day the rats were injected with either the Ringer's vehicle or the propylene glycol-ethanol vehicle. In part two of the experiment, rats received pre-exposure injections of morphine and pairing day the rats were injected with either morphine, Valium, Δ^9THC or Ringer's. In part three of the experiment, rats received pre-exposure injections of Valium and on pairing day the rats were injected with either morphine, Valium, Δ^9THC or Ringer's. In part four of the experiment, rats received pre-exposure injections of Δ^9THC and on pairing day the rats were injected with either morphine, Valium, Δ^9THC or Ringer's.

TABLE 2

Sample sizes and treatment groups in Experiment 3

Pre-exposure Treatment	Conditioning Treatment				
	Propylene Glycol	Ringer's	Morphine	Valium	Δ^9THC
Ringer's (Part 1)	8	10	11	10	10
Morphine (Part 2)		10	10	10	9
Valium (Part 3)		10	10	11	11
Δ^9THC (Part 4)		10	10	12	11

Table 2 presents a summary of the groups run and their sizes.

Results

Part One, Ringer's Pre-Exposure

Pairing day and test day saccharin intakes are presented in Figure 8. The analysis of variance revealed a significant interaction between drug treatments and days ($F(4,43) = 29.78$, $p<.0001$) as well as a significant main effect of drug treatments ($F(4,43) = 15.14$, $p<.0001$) and a significant main effect of days ($F(1,43) = 28.05$, $p<.0001$). On pairing day, the baseline saccharin intakes between the groups did not differ significantly (simple main effect post hoc test: $F(4,83) = 1.21$, $p>.25$, however, on test day, sccharin intake significantly changed from that on pairing day for each group. The two vehicle control groups significantly increased their saccharin intakes (Ringer's, $F(1,42) = 9.82$, $p<.005$; propylene glycol-ethanol, $F(1,42) = 19.81$, $p<.001$). In contrast, the morphine group significantly decreased saccharin intake ($F(1,42) = 34.12$, $p<.001$) as did the Valium group ($F(1,42) = 48.32$, $p<.001$) and the Δ^9THC group ($F(1,42) = 35.15$, $p<.001$). As Figure 8 illustrates, the maghitude of the decrease in saccharin intakes for the 3 drug groups were comparable. The morphine group decreased intake

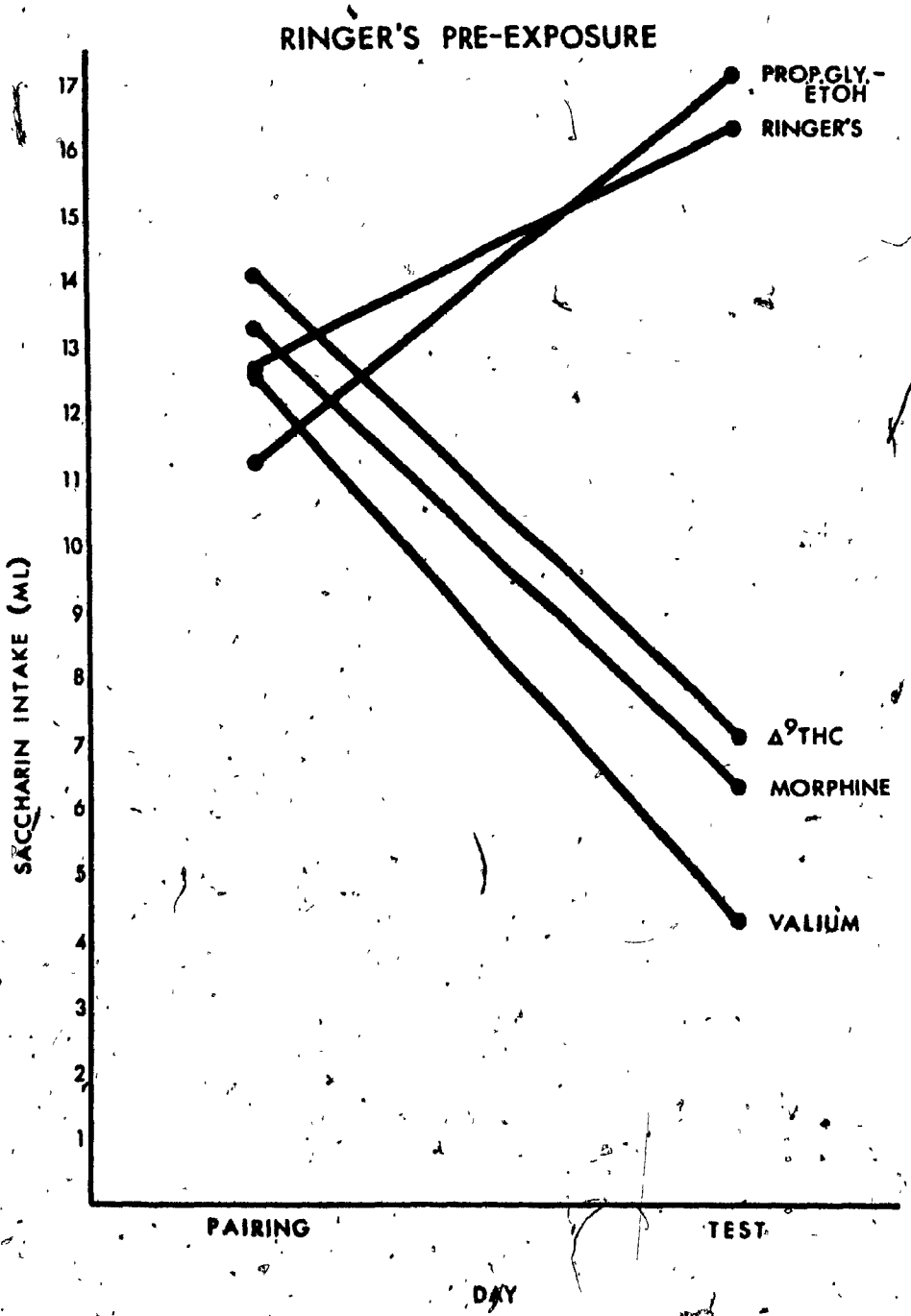

Figure 8. Pairing and test days saccharin intake for Ringer's pre-exposure groups. Pairing day injection for each group is indicated on the right-hand side of the Figure.

from pairing day to test day by a mean of 6.6 ml, the Valium group decreased by a mean of 8.2 ml and the Δ^9THC group decreased by a mean of 7.0 ml. These difference scores did not differ significantly ($F(2,28) = 0.44$, $p>.25$).

Part Two, Morphine Pre-Exposure

Pairing day and test day saccharin intakes are presented in Figure 9. The analysis of variance revealed a significant interaction between drug treatments and days ($F(3,35) = 10.5$, $p<.0001$) as well as a significant main effect of drug treatments ($F(3,35) = 4.754$, $p<.008$). On pairing day, the baseline saccharin intakes did not differ significantly between the groups (simple main effect post hoc test: $F(3,68) = 0.37$, $p>.25$). The group injected with Valium on pairing day decreased saccharin intake significantly on test day ($F(1,35) = 12.66$, $p<.005$) as did the Δ^9THC-injected group ($F(1,35) = 14.07$, $p<.001$). Although the group injected with morphine on pairing day tended to increase saccharin intake on test day, this effect was not significant ($F(1,35) = 3.39$, $p>.05$). In parallel, the Ringer's-injected group did not significantly change saccharin consumption on test day ($F(1,35) = 4.10$, $p>.05$).

Part Three, Valium Pre-Exposure

Pairing day and test day saccharin intakes are

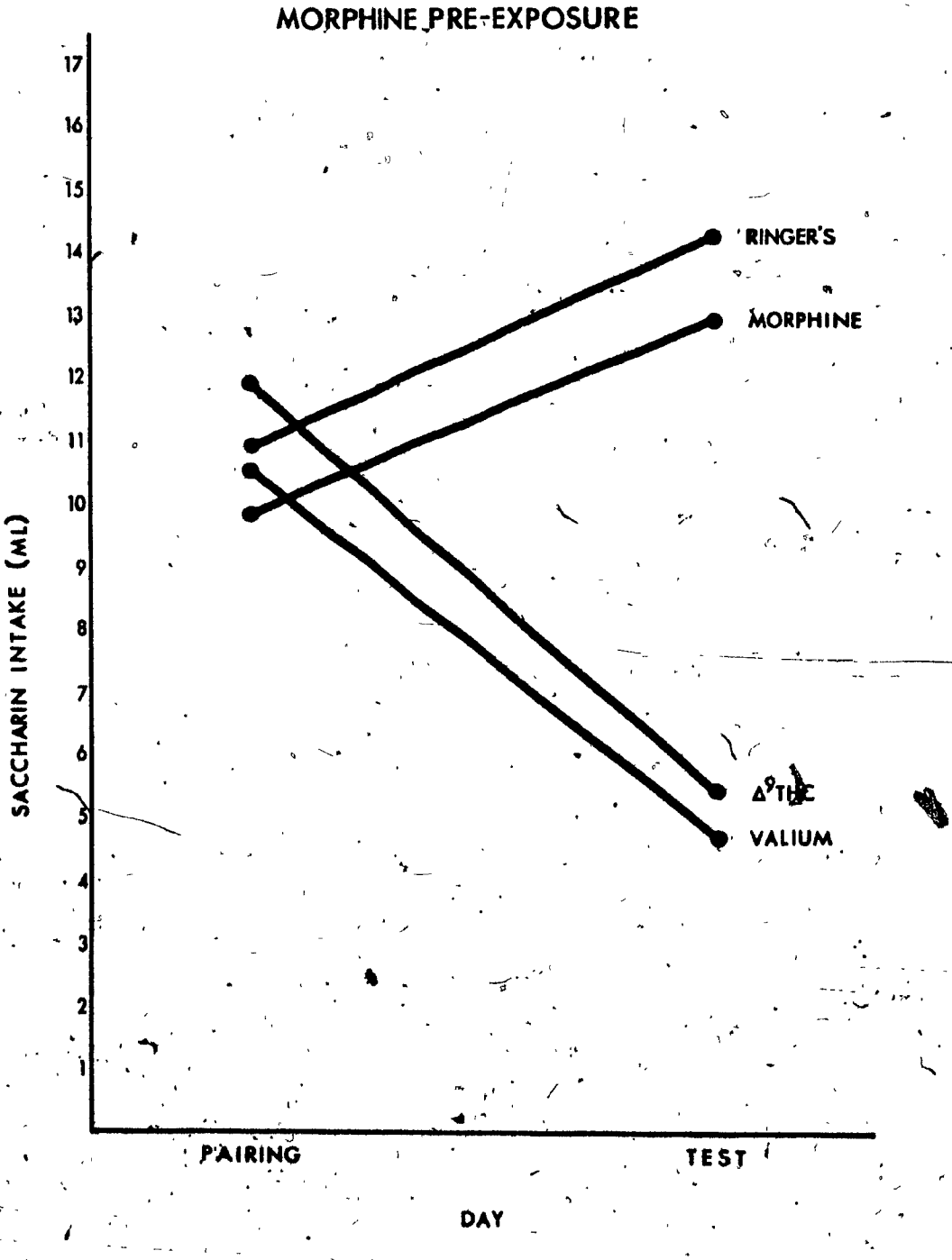

Figure 9. Pairing and test days saccharin intake for morphine pre-exposure groups. Pairing day injection for each group is indicated on the right-hand side of the Figure.

van Ree, Slangen & de Weid, 1978). Valium, as well, is not readily self-administered by rats (Amit & Cohen, 1974), although more so than cannabis (Amit et al., 1973). In contrast with these two drugs, morphine has a relatively high self-administration potential in rats (e.g. Stolerman & Kumar, 1970; van Ree et al., 1978; Weeks & Collins, 1964). In view of the self-administration studies, it is interesting to note that, in the present experiment, the Δ^9THC-CTA was most resistant to attenuation by drug pre-exposure, followed by the Valium-CTA and, finally, the morphine-CTA, which was quite readily attenuated by drug pre-exposure. This parallels the self-adminisration data where cannabis seems to be least readily self-administered followed by Valium and then morphine. Thus, it may be possible to employ crossover pre-exposure experiments to rank the relative self-administration liabilities of psychoactive drugs. For example, the CTA normally induced by drug A may be attenuated by pre-exposures to drug B, however, the CTA normally induced by drug B may not be significantly attenuated by pre-exposures to drug A. One might predict, therefore, that drug A has a greater self-administration liability than drug B provided, of course, that the dosages used produced equivalent magnitudes of CTAs.

General Discussion

It has been suggested that the positively reinforcing and aversive effects of self-administered drugs are in some way related (LeBlanc & Cappell, 1975; Sklar & Amit, 1977, Wise et al., 1976). A number of studies have demonstrated that neurochemical interventions which disrupt positive reinforcement produced by drugs also disrupt CTAs induced by the same drugs (e.g. Goudie, Thornton & Wheatley, 1975; Roberts & Fibiger, 1975; Sklar & Amit, 1977). These studies suggest a functional relationship between the positively reinforcing and aversive properties of drugs. Other studies have demonstrated positive reinforcement and CTA in the same animals at the same time (Reicher & Holman, 1977; White et al., 1977; Wise et al., 1976). These studies also point to a relationship between positive reinforcement and CTA induced by self-administered drugs. Amit and Baum (1970) as well as others (Gamzu, 1977; Vogel & Nathan, 1976) suggested that the so-called drug aversion or CTA reflects the novelty of the drug state. This implies that the stimulus properties of a drug which underlie CTA are identical to, or overlap with, the stimulus properties which are positively reinforcing.

In Experiment 1, when morphine induced a CTA in

rats, running speeds increased in the same rats. When morphine failed to induce a CTA, running speeds did not increase. Running speed is known to vary directly with the magnitude of reinforcement obtained in the goal box (Crespi, 1952). This, together with the fact that rats can learn to orient towards a place in which morphine was experienced (Beach, 1957), would suggest that the increased running speeds observed in Experiment 1 are indicative of morphine's positively reinforcing effect. That morphine selectively produced an increase in running speed for animals that developed a CTA, supports the idea that CTA and positive reinforcement are functionally related. It is possible that the controlling stimuli (both interoceptive and exteroceptive) which promote one behavioral effect, also underlie the other. The fact that there was considerable variability in morphine's CTA-inducing and positively reinforcing effects is consistant with other observations (Farber, Gorman & Reid, 1976; Riley et al., 1978; van Ree et al., 1978). In Experiment 1, it was also demonstrated that altering the cue value of the food paired with the morphine decreased the magnitude of the aversion as well as decreasing the number of rats displaying the aversion. The paradigm used may be viewed as a taste pre-exposure situation as animals received limited but not extensive

experience with the unflavored wet mash prior to the morphine injections. In a taste pre-exposure situation, CTAs are typically attenuated (Kalat, 1974). That some animals did develop an aversion to the unflavored food is not surprising in light of reports that animals can develop aversions to unflavored tap water (Elkins, 1974) or to unflavored wet mash (Garcia, Hankins, Robinson & Vogt, 1972). In the unflavored wet mash condition, the running speeds of the animals were generally more variable. This would suggest that the association between a novel taste and morphine can not only induce a greater magnitude of aversion but it can also provide an additional cue for the positively reinforcing effect of morphine.

The relationship between the CTAs and running speeds observed in Experiment 1 could be explained in terms of a novelty hypothesis. It would seem to be outside the scope of a novelty hypothesis, however, to account for the breakdown in the relationship when the food was left unflavored. In terms of a novelty hypothesis, there is no reason to suspect why the running speeds would be more variable. It is possible that a change in the quality of the food at the same time as the onset of morphine injections could generate a greater degree of predictability about the occurrance of the morphine effect. This would not only facilitate an association

between the food and the morphine, but also between the overall runway situation and the morphine. On the other hand, when the quality of the food was unaltered, the predictability of the ensuing morphine effect could decrease, impeding the association between the food and the morphine as well as the overall situation and the morphine. Thus, depending upon the relative expectancy generated by the food cue, an animal could more or less develop a CTA as well as an increase in running speed.

If CTA and positive reinforcement are related, then it is peculiar that cocaine, which is highly self-administered (Pickens & Thompson, 1968), normally induces only a moderate CTA (Booth et al., 1977; Goudie, Dickins & Thornton, 1978). It has been proposed that cocaine's short duration of action may not be amenable to the induction of CTA (Cappell & LeBlanc, 1977; Goudie et al., 1978). In Experiment 2 of this thesis, the aversion-inducing potential of cocaine was examined. Cocaine induced a robust CTA when administered in multiple spaced injections but when a single high dose of cocaine was administered, no significant CTA was evident. The results obtained in Experiment 2 lend support to the idea that duration of drug action may be an important variable for the induction of CTA. That a high dose of cocaine did not induce a significant CTA

in Experiment 2 is at odds with results obtained by Goudie et al. (1978) demonstrating that the same dose could induce a weak CTA. A possible explanation for the discrepancy is that Goudie et al. used female rats whereas the subjects in Experiment 2 were male rats. In our laboratory, we have observed that a greater magnitude of CTA can be induced by cocaine in female rats (Note 3).

Drug actions of long duration may be inherently aversive or may be more readily associated with a novel flavor. The former possibility is less likely since rats will self-administer drugs consistantly over prolonged periods of time (e.g. Smith, Werner & Davis, 1976; Weeks & Collins, 1964). Duration of drug action alone, however, would seem to be insufficient to account for CTA induction. For instance, it has been demonstrated that leucine-enkephalin, a short-acting endorphin induces a moderate and variable CTA whereas, d-ala-leucine--enkephalinamide, a long-action leucine-enkephalin analogue produces no observable CTA (Switzman, Hammer, Shizgal & Amit, 1977). This would seem to argue against a duration of action hypothesis, however, it is entirely possible that the chemical nature of a drug, in addition to its duration of action, may determine a drug's CTA-inducing potential. A component of the chemical nature of a drug which may permit it to induce a CTA

may be rate of onset. Both in the case of cocaine and the enkephalins, the rate of onset is very rapid (Nayak et al., 1976; Snyder & Childers, 1979). It is possible that in order for a drug to induce a CTA, the time to peak activity must be gradual as opposed to sudden. In Experiment 2, when cocaine was administered over multiple injections, it is conceivable that each additional injection of cocaine caused an increase in cocaine levels. Whether duration of action per se or an interaction between duration of action and rate of onset determines, in part, the CTA-inducing liability of a drug is not clear. It would be difficult to separate the two components.

The goal of this thesis has been to examine the nature of CTAs induced by self-administered drugs and to elaborate the relationship between positive reinforcement and CTA. A fundamental argument made in this thesis is that the nature of the CTAs induced by self-administered drugs is qualitatively different from that induced by non-self-administered drugs. Results obtained in Experiment 3 support this idea. It was demonstrated that the morphine-CTA was most readily attenuated by pre-exposure, whether morphine, Valium or Δ^9THC served as the pre-exposure drugs. The Valium-CTA was less susceptible to attenuation and the Δ^9THC-CTA was least readily attenuated by pre-exposure. Self-administration

studies demonstrate that morphine is highly self-administered whereas Valium and Δ^9THC are not although, Valium seems to be more readily self-administered than cannabis. It would seem that the relative susceptibility of the drug-induced CTA to attenuation correlates with the drug's self-administration liability. Goudie, Taylor and Atherton (1975) have similarly observed that an amphetamine-based CTA was more readily attenuated by pre-exposures than a fenfluramine-based CTA. Goudie, Taylor and Atherton suggested that the aversive effects of self-administered drugs tolerate with experience but that the aversive effects of non-self-administered drugs do not. For reasons previously mentioned, a tolerance hypothesis would not seem to be tenable. An alternative view is that there is a qualitative difference between the aversion induced by self-administered drugs as opposed to that induced by non-self-administered drugs. That is, the stimulus properties of self-administered drugs which induce a CTA may be, to some extent, different from the aversive properties of non-self-administered drugs. In this case, animals should be capable of discriminating between drugs with different stimulus properties in the CTA paradigm. If a pre-exposure and conditioning drug have similar properties, then the CTA should be attenuated. If a pre-exposure and conditioning drug have very

different properties, then the CTA should still occur. The problem becomes more complicated if an asymmetrical pre-exposure effect occurs, as was the case in Experiment 3. Although asymmetrical pre-exposure effects have been observed in other studies (Cappell, LeBlanc & Herling, 1975; Vogel & Nathan, 1976), it is not clear, as Braveman (1977) pointed out, if the drug dosages used were equal in terms of CTA-inducing potencies. This can be ruled out in Experiment 3 as the dosages used were equiaversive. In Experiment 3, morphine pre-exposures did not attenuate aversive conditioning based on Valium or Δ^9THC; Valium pre-exposures did attenuate aversive conditioning based on morphine, and Δ^9THC still induced a CTA; Δ^9THC pre-exposures attenuated aversive conditioning based on morphine and Valium. These results demonstrate that rats can discriminate between drugs in a CTA paradigm but that the discrimination is not necessarily bi-directional. If rats were merely discriminating between different drug effects, then in the case of morphine and Valium, for example, one would expect to see morphine pre-exposures having the same effect on the Valium-CTA as Valium pre-exposures did on the morphine-CTA. Rats may be relationally-judging between the relative hedonic effects of two drugs. For instance, when rats are pre-exposed to morphine and then receive a conditioning trial with

Valium, a CTA may result because the Valium is less positive to the rats than the morphine which had been previously experienced. When rats are pre-exposed to Valium and then receive a conditioning trial with morphine, the CTA may be attenuated because, relative to the animals' experience with Valium, morphine is more positive. Given that morphine's 'aversive' effect is functionally related to its positively reinforcing effect (Experiment 1), it is possible that Valium and Δ^9THC are less positive due to an additional aversive component. If one conceives of the stimulus complex produced by a drug as a set, the stimulus properties of morphine which induce a CTA may be contained within those which induce the Valium CTA which, in turn, may be contained with those which induce the Δ^9THC-CTA. Whereas the stimulus properties of morphine are euphoric, the stimulus properties of Valium and Δ^9THC may be increasingly dysphoric due to the addition of the aversive components.

When a conditioning drug is the same as the pre-exposure drug, an associative explanation is sufficient to account for the observed attenuation (Braveman, 1975). When a conditioning drug is different than a pre-exposure drug, a CTA may result only if a distinct additional stimulus component is associated with the conditioning

drug. Because of the additional negative internal cues, the salience of the taste-drug pairing may be increased. A greater number of pre-exposures would then be required in order for a CTA to be attenuated by pre-exposures to the same drug. The fact that self-administered drugs such as morphine, ethanol and cocaine do not induce CTAs comparable in magnitude to lithium chloride (Cappell, LeBlanc & Endrenyi, 1973; Farber, Gorman & Reid, 1976; Goudie, Dickins & Thornton, 1978; Riley et al., 1978) suggests that these self-administered drugs are not as salient in the CTA paradigm. Thus, these drugs may be less associable with a novel flavor and the CTAs more labile when a neurochemical intervention such as catecholamine depletions ensue. If the stimulus properties of drugs which underlie CTA are functionally related to those that underlie positive reinforcement, then catecholamine manipulations should affect both behaviors. Catecholamine manipulations, however, should have little or no effect on the CTA induced by a drug such as Δ^9THC because of the additional salient aversive component which is not mediated by catecholamines.

Results obtained in the experiments presented in this thesis indicate that the relationship between CTA and positive-reinforcement produced by self-administered drugs is complex. It is possible that the stimulus

properties of self-administered drugs which underlie positive reinforcement are related to those which underlie CTA. Both these effects seem to be bound, at least to some extent, to environmental cues. The salience of a self-administered drug effect for CTA induction may depend, in part, upon its temporal properties. In general, self-administered drugs may not be as salient in the CTA paradigm as non-self-administered psychoactive drugs. The latter may have additional aversive components. The extent of the additional aversive components may not only determine the salience of a drug in a CTA paradigm, but may also cause a drug to have a relatively low self-administration liability.

In summary, it would seem that the nature of the CTA produced by self-administered drugs is qualitatively different from that produced by drugs with low self-administration liabilities. The stimulus properties of self-administered drugs which promote the CTA may be related to those which underlie the drugs' positively reinforcing effects. These stimulus properties alone, however, may not be sufficient to promote the formation of CTA. The temporal nature of a self-administered drug may also determine it potential as a CTA-inducing agent. Another factor that may determine the CTA-inducing potential of any psychoactive drug may be additional

dysphoric properties. This may not only enhance a drug's ability to produce a CTA but may also decrease a drug's ability to be positively reinforcing. These ideas can be further specified in future research.

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APPENDIX A

Raw Scores for Experiment 1

TABLE 1

Amount of Food Consumed (g) on Baseline and Test Days For Flavored Food Groups

	Day					
Group	Baseline	1	2	3	4	5
Ringer's						
	6.4	11.6	11.2	5.6	13.0	15.7
	8.7	10.6	16.3	10.5	17.3	21.0
	12.1	13.7	17.6	13.8	16.5	13.0
	20.4	13.9	14.9	14.2	12.9	14.5
	10.8	15.1	13.6	16.2	11.8	18.2
	16.3	20.8	22.5	16.8	20.8	26.2
	8.0	17.0	22.8	9.5	9.8	17.5
	18.3	19.9	15.8	18.2	11.3	16.3
Morphine						
	16.5	9.8	2.9	1.6	1.7	1.5
	15.8	12.2	16.9	10.0	13.7	14.7
	7.9	7.7	13.0	12.9	14.0	17.5
	8.1	12.6	17.6	11.2	8.9	15.8
	11.8	10.9	9.6	6.6	7.6	11.3
	17.7	10.1	15.2	16.7	14.0	21.5
	5.3	13.8	14.1	14.0	15.0	17.7
	20.3	9.8	14.3	7.6	6.6	21.2
	13.2	14.4	13.7	6.6	5.6	13.7
	10.2	3.8	2.1	1.5	2.4	3.3

TABLE 2

Total Running Time (sec) on Baseline and Test Days for Flavored Food Groups

Group	Day					
	Baseline	1	2	3	4	5
Ringer's						
	2.7	3.6	2.3	2.8	2.7	3.5
	4.5	3.8	2.7	3.2	3.1	2.3
	3.8	5.6	4.6	4.5	4.3	3.7
	3.3	3.6	3.1	7.8	2.7	2.8
	3.4	6.1	2.3	2.9	2.8	3.5
	2.9	13.9	14.0	3.5	4.4	3.5
	3.3	14.2	5.2	9.0	5.1	5.0
	3.2	4.3	2.6	2.6	10.5	4.2
Morphine						
	4.2	3.8	9.8	5.5	2.6	3.4
	7.0	2.4	4.2	4.1	2.9	2.3
	3.2	2.8	3.3	4.0	4.0	5.6
	4.0	3.1	2.8	8.6	3.9	2.7
	5.9	4.7	2.7	3.3	2.4	2.6
	4.1	6.0	2.7	2.2	3.9	2.2
	3.4	3.3	2.8	3.6	3.5	2.2
	3.0	2.6	2.9	2.6	2.6	2.5
	4.6	4.4	2.4	2.8	5.5	2.5
	3.6	4.7	3.0	2.6	2.5	3.2

TABLE 3

Amount of Food Consumed (g) on Baseline and Test Days for Unflavored Food Groups

	Day					
Group	Baseline	1	2	3	4	5
Ringer's						
	10.0	18.8	17.7	14.1	16.8	11.8
	13.4	21.2	17.2	19.8	22.0	16.9
	11.9	16.9	12.4	11.2	19.6	13.0
	16.6	17.2	13.4	15.6	19.7	18.3
	22.0	23.1	17.1	29.2	23.5	23.8
Morphine						
	16.2	17.3	19.9	15.7	17.5	17.9
	17.7	8.1	18.2	16.7	13.4	11.6
	20.3	12.4	9.6	13.2	13.7	14.6
	12.8	11.8	12.2	12.0	14.6	14.4
	11.3	14.0	12.8	13.5	14.4	11.5
	15.0	12.6	14.5	14.6	13.6	11.6
	12.6	11.3	11.2	13.1	15.7	15.5

TABLE 4

Total Running Time (sec) on Baseline and Test Days for Unflavored Food Groups

	Day					
Group	Baseline	1	2	3	4	5
Ringer's						
	3.8	4.0	3.5	5.4	12.9	3.3
	3.1	2.2	4.3	2.7	1.7	2.2
	8.5	2.9	2.7	4.8	9.4	3.2
	3.0	2.2	2.4	1.9	3.3	1.7
	3.2	4.1	2.9	2.5	2.8	7.2
Morphine						
	3.2	3.1	3.8	2.5	2.3	2.5
	3.9	3.4	4.5	3.0	2.0	2.0
	2.9	4.5	2.3	2.4	2.2	2.9
	2.6	3.8	7.4	2.8	2.8	2.9
	3.3	6.7	3.6	2.7	2.7	2.7
	6.6	4.4	3.5	3.2	2.7	2.9
	5.1	3.4	3.7	2.2	2.1	1.9

APPENDIX B

Raw Scores for Experiment 2

TABLE 1

Fluid Intakes (ml) for Groups in Experiment 2a from the Day prior to the First Saccharin-Injection Pairing Onward

	Day										
Group	5	6[a]	7	8	9[a]	10	11	12[a]	13	14	15[a]
Single Injection											
	16	18	18	18	20	19	19	16	16	19	18
	12	19	16	14	19	15	17	17	18	15	17
	15	17	18	19	22	18	19	15	16	18	17
	14	15	15	16	17	17	20	14	15	20	15
	17	16	18	22	23	22	21	19	16	19	23
	15	17	18	16	20	17	18	19	19	13	21
	21	18	19	17	23	20	20	19	14	22	15
	12	15	14	17	21	17	20	18	18	19	15
Two Injections											
	6	14	19	19	17	17	17	11	16	16	9
	21	22	20	25	20	23	23	15	23	20	10
	17	10	19	20	13	17	17	8	20	21	5
	16	18	17	22	15	19	19	19	18	17	19
	16	17	17	21	10	22	33	12	20	22	7
	25	20	19	27	17	24	24	18	23	23	22
	18	22	18	28	23	21	20	18	24	25	15
	20	15	19	17	15	21	20	16	19	16	12

TABLE 1 (Continued)

Group	Day 5	6[a]	7	8	9[a]	10	11	12[a]	13	14	15[a]
Three Injections											
	21	18	20	20	13	20	21	17	17	18	21
	18	15	16	21	15	13	20	14	17	19	4
	17	21	15	21	14	17	20	8	18	21	3
	18	17	21	20	14	17	17	3	21	28	1
	14	18	19	21	18	21	18	13	20	21	3
	21	14	17	15	11	22	17	17	16	18	3
	20	15	25	23	14	19	22	11	23	21	3
	18	14	17	15	9	19	19	5	17	19	1
Four Injections											
	13	11	12	15	10	15	18	11	16	14	1
	18	16	18	16	11	14	18	9	19	17	1
	15	18	18	22	13	15	18	6	29	20	1
	16	17	18	21	14	18	18	11	28	18	4
	17	14	16	19	11	17	19	3	16	17	1
	17	13	21	18	8	16	21	1	21	19	0
	18	20	20	22	12	18	22	2	25	16	0

TABLE 1 (Continued)

Group	Day 5	6[a]	7	8	9[a]	10	11	12[a]	13	14	15[a]
Five Injections											
	10	26	15	19	18	19	18	6	19	19	2
	14	15	18	20	8	20	15	4	18	20	2
	16	20	17	14	13	17	16	8	19	20	0
	14	14	16	17	11	17	21	3	15	20	3
	15	13	14	19	21	18	18	3	20	20	1
	16	15	14	16	13	17	14	4	20	18	3
	18	15	19	15	7	17	16	5	18	16	1
	16	18	14	19	11	9	13	7	15	21	3

[a] Rats received saccharin on these days

TABLE 2

Fluid Intakes (ml) for Groups in Experiment 2b from the Day Prior to the First Saccharin-Injection Pairing Onward

	Day										
Group	5	6[a]	7	8	9[a]	10	11	12[a]	13	14	15[a]
Saline											
	14	15	22	21	25	18	23	24	21	22	22
	12	18	13	17	25	15	21	18	17	17	21
	15	21	17	18	21	17	16	16	19	20	20
	15	12	17	16	20	15	15	17	14	21	17
	17	17	20	21	25	19	23	20	20	22	18
	16	18	15	17	18	14	19	20	20	20	22
	14	18	16	19	18	17	20	17	16	18	20
Cocaine 5 mg/kg											
	14	20	19	17	20	18	16	14	17	19	18
	14	21	9	23	22	20	21	16	22	18	18
	16	19	20	20	21	20	22	17	23	20	20
	17	21	20	21	19	20	25	18	21	20	19
	13	18	17	18	19	17	21	12	20	18	18
	18	19	16	17	20	19	18	19	18	16	18
	14	21	19	20	20	21	27	20	17	[redacted]	20

TABLE 2 (Continued)

Group	Day 5	6[a]	7	8	9[a]	10	11	12[a]	13	14	15[a]
Cocaine 10 mg/kg											
	15	17	18	15	14	20	19	4	17	17	5
	10	19	19	19	14	22	18	6	23	22	4
	13	19	17	17	16	16	18	7	16	17	11
	16	19	20	21	18	19	21	20	20	18	15
	12	21	16	18	18	16	19	11	19	16	9
	17	18	16	23	15	20	19	4	17	17	4
	19	20	18	16	15	21	20	12	24	24	9
	13	18	13	19	14	15	20	10	20	22	4

[a] Rats received saccharin on these days

TABLE 3

Fluid Intakes (ml) for Groups in Experiment 2c from the Day Prior to the First Saccharin-Injection Pairing Onward

	Day										
Group	5	6[a]	7	8	9[a]	10	11	12[a]	13	14	15[a]
S											
	21	22	24	16	22	20	21	16	21	22	13
	22	21	24	24	20	23	27	20	24	25	15
	18	18	22	21	15	17	21	19	18	15	17
	18	10	22	22	19	18	20	21	20	23	20
	22	21	22	22	23	21	20	17	25	22	19
	19	25	25	21	22	20	21	26	19	21	23
	20	19	25	21	27	19	24	22	23	24	21
	15	18	22	17	14	18	20	14	19	21	12
	18	15	20	18	17	19	19	21	15	21	15
	17	15	17	15	15	17	20	14	15	18	19
LC											
	16	18	18	18	18	17	19	19	16	18	18
	14	12	21	22	18	21	24	27	27	24	23
	16	17	21	15	19	17	20	18	17	20	20
	20	23	22	23	24	22	22	22	21	19	20
	25	21	28	20	20	20	25	22	24	23	22
	16	13	19	16	18	18	19	18	20	20	18
	16	15	18	16	17	18	15	16	15	18	18
	22	18	22	20	21	20	20	20	21	20	21
	25	21	24	20	19	23	23	23	19	21	22
	15	19	22	22	21	25	20	20	22	26	23

TABLE 3 (Continued)

Group	Day										
	5	6[a]	7	8	9[a]	10	11	12[a]	13	14	15[a]
CS											
	17	21	20	18	18	18	22	21	24	21	19
	17	15	21	20	18	20	22	22	20	22	19
	20	17	20	17	16	18	20	15	20	19	13
	23	20	20	20	21	18	20	19	18	19	21
	22	19	26	19	23	26	23	19	23	21	24
	19	17	18	17	15	20	18	19	18	19	20
	24	18	25	16	18	21	24	17	19	22	15
	22	19	21	17	23	20	22	21	20	21	23
	15	11	18	16	18	20	22	22	19	18	23
	15	19	18	20	18	20	19	19	22	23	21
HC											
	21	17	23	24	21	24	25	21	25	25	22
	22	19	22	23	20	21	20	16	20	25	15
	17	19	19	15	14	15	19	17	17	16	16
	23	11	21	20	17	23	23	15	24	23	15
	25	20	28	22	27	30	25	24	27	26	24
	19	12	17	16	12	15	14	14	15	17	12
	23	21	24	16	19	18	22	18	20	20	16
	19	20	18	21	18	20	19	14	23	22	15
	19	18	20	14	18	17	18	19	19	16	16
	22	21	22	19	18	21	23	20	21	20	19

TABLE 3 (Continued)

Group	Day 5	6[a]	7	8	9[a]	10	11	12[a]	13	14	15[a]
MC											
	18	20	22	32	22	22	19	16	21	21	21
	17	19	22	19	17	18	21	11	29	21	7
	17	15	16	17	10	18	19	14	19	19	9
	15	15	21	22	18	21	18	13	18	22	16
	19	18	22	20	20	21	23	15	23	23	12
	18	17	20	18	11	18	23	11	20	21	12
	20	19	18	19	18	17	20	14	21	21	15
	20	19	18	17	16	19	20	12	20	16	9
	21	18	23	21	20	24	22	21	19	19	15

[a] Rats received saccharin on these days

APPENDIX C

Raw Scores for Experiment 3

TABLE 1

Fluid Intakes (ml) for Ringer's Pre-Exposure Groups

Group	Day 7	8[a]	13	14[b]
Ringer's				
	12	13	16	18
	15	15	15	16
	15	11	12	15
	13	11	14	17
	12	15	16	18
	15	9	15	17
	11	10	14	18
	10	14	12	16
	9	16	14	13
	12	13	13	16
Propylene-Glycol				
	18	15	20	21
	16	8	16	19
	16	13	15	13
	14	12	17	17
	18	12	14	16
	16	11	17	19
	13	9	15	15
	12	10	14	17

Group	Day 7	8[a]	13[c]	14[b]
Valium				
	14	9	11	3
	18	13	15	3
	15	15	14	10
	12	13	14	3
	15	15	13	4
	16	9	16	4
	15	12	15	8
	18	13	16	2
	15	13	14	5
	11	13	12	1
Δ^9THC				
	12	14	16	8
	14	15	15	11
	10	13	13	6
	11	12	11	2
	13	13	17	16
	12	13	16	6
	8	20	15	12
	14	12	12	2
	13	19		2
	10	10	11	6

TABLE 1 (Continued)

Group	Day 7	8[a]	13	14[b]
Morphine				
	14	19	14	17
	15	10	15	7
	13	15	15	4
	15	13	19	4
	8	12	14	5
	12	11	12	4
	13	11	17	11
	12	9	11	5
	14	12	14	5
	11	14	13	8
	11	16	13	4

[a] Pairing day

[b] Test day

[c] Due to technical problems, data is missing for this day

TABLE 2

Fluid Intakes (ml) for Morphine Pre-Exposure Groups

	Day					Day			
Group	7	8[a]	13	14[b]		7	8[a]	13	14[b]
Ringer's	14	14	8	17	Valium	11	9	19	8
	9	8	14	12		16	12	18	0
	10	8	14	10		9	9	13	2
	13	11	15	14		9	10	13	1
	11	12	18	20		12	10	14	1
	13	12	17	17		11	13	15	4
	15	15	18	23		12	13	15	3
	16	11	18	11		10	10	16	9
	10	6	16	8		10	7	12	6
	10	12	17	10		9	12	17	3
Morphine	13	9	18	15	Δ^9THC	12	15	17	1
	15	12	17	14		13	10	17	1
	12	8	18	17		12	10	16	1
	16	10	14	8		13	13	16	20
	11	10	14	15		10	15	16	2
	12	11	11	13		12	12	17	20
	15	11	8	10		13	10	11	2
	13	11	16	17		9	9	14	1
	11	6	11	5		12	13	15	1
	16	11	15	15					

[a] Pairing day

[b] Test day

TABLE 3

Fluid Intakes (ml) for Valium Pre-Exposure Groups

	Day					Day			
Group	7	8[a]	13	14[b]		7	8[a]	13	14[b]
Ringer's	9	10	17	20	Valium	13	11	9	8
	8	8	13	11		9	11	10	9
	9	6	12	12		7	9	5	5
	5	7	8	14		10	11	10	12
	10	10	14	15		10	11	13	9
	12	12	15	17		14	11	15	14
	8	10	10	10		9	9	13	10
	8	8	15	15		5	5	9	5
	7	7	11	10		6	7	11	4
	7	7	12	16		5	10	9	8
						6	6	12	9
Morphine	3	5	10	9	Δ^9THC	13	13	9	8
	3	6	11	8		8	9	12	1
	6	7	12	3		9	10	10	3
	9	8	14	7		11	8	16	4
	2	5	10	2		12	8	14	2
	9	8	14	5		7	9	11	3
	8	9	16	8		10	6	10	1
	7	9	9	8		9	8	9	3
	6	7	9	9		7	9	10	10
	8	9	14	10		9	9	12	7
						8	9	11	14

[a] Pairing day

[b] Test day