para-tyrosine enhanced the conditioned taste aversion produced by morphine. Other results have demonstrated that alpha-methyl-para-tyrosine blocked a morphine-induced CTA. It is possible that the discrepancy between the studies may be due to an interaction between the nature of the stimulus situation and specific neurotransmitter alterations.

Acknowledgements

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As early as 1925, Kolb concluded that, at least in the initial stages, opiate-seeking behavior was a result of the euphoria or "positive pleasure" derived from the drugs. There is some experimental support for the notion that opiate drugs are self-administered for their positive pharmacological effects. A number of studies have demonstrated morphine self-administration in non-dependent, naive animals. In one study, Deneau, Yanagita and Seevers (1969) demonstrated that naive monkeys would lever-press for morphine injections. Another study (Stolerman & Kumar, 1970) showed that non-dependent rats would orally self-administer a morphine solution but not a quinine solution which had similar gustatory properties. In yet another experiment (Amit, Brown & Sklar, 1976) naive rats lever-pressed for injections of morphine directly into the lateral cerebral ventricle and when the animals were challenged with naloxone, no signs of abstinence were evident. In parallel to the above, Woods and Schuster (1968) observed that when naive monkeys worked for intravenous morphine, and the drug was subsequently removed, no withdrawal symptoms were obvious. From these studies it may be concluded that morphine can act

as a positive reinforcer. Furthermore the studies suggest that animals self-administer morphine for the positive pharmacological effects, not in order to avoid withdrawal.

Weeks and Collins (1964), on the other hand, proposed that escape and avoidance of withdrawal subserved the acquisition of opiate self-administration behavior. This conclusion was based on an experiment in which predependent rats (rats receiving a series of non-contingent morphine injections) voluntarily self-injected intravenous morphine by pressing a lever. When the dose of morphine for which the animals had been pressing was decreased, the daily number of presses increased. Weeks and Collins (1964) argued that the animals increased the number of lever presses in order to escape the abstinence syndrome, however, their data do not necessarily support the conclusion that avoidance or escape from withdrawal was the basis of opiate self-administration. The rats were pre-dependent and therefore, would have had a great deal of opportunity to learn about the drug state prior to learning a response enabling the animals to receive the drug. Since learning about the drug state did not progress

contiguously with learning the drug-seeking behavior, the conclusion that acquisition of drug self-administration is subserved by escape or avoidance of withdrawal is unwarranted. On the other hand, one could argue that avoidance of withdrawal, while not involved in the acquisition of drug self-administration, will nevertheless maintain drug self-administration. This notion, however, is also unlikely. Weeks and Collins (1964) failed to detect signs of abstinence in any of the animals tested, even when the total daily morphine intake was less than 1/60 of that which the animal had been previously self-injecting. In another experiment, Khavari and Risner (1973) demonstrated that pre-dependent rats that failed to maintain consumption of morphine-adulterated food, exhibited signs of withdrawal. If drive reduction was critical for drug self-administration, one would expect the rats to readily consume the morphine-adulterated food in order to relieve withdrawal symptoms. Thus, it is conceivable that avoidance of withdrawal may play no role in opiate self-administration.

Alternatively, it is possible that the animals in Weeks' and Collins' (1964) experiment may have been self-injecting the morphine for its positive properties. Thus it is possilbe that when the unit dose of morphine was lowered in Weeks' and Collins' study (1964), the increased number of lever-presses observed was required in order for an animal to obtain a given level of morphine's positive effects. In this way the morphine could have positively reinforced the bar-pressing responses.

Another intriguing property of morphine is its ability to produce a conditioned taste aversion (CTA). In an experiment conducted by Cappell, LeBlanc and Endrenyi (1973), rats were injected with a relatively low dose of morphine (less than 10 mg/kg, intraperitoneally - i.p.) after exposure to a novel saccharin solution. They found that upon subsequent presentation of the saccharin solution, the intake of saccharin decreased significantly. This CTA phenomenon has also been demonstrated with a variety of other drugs including lithium chloride (LiCl) (Garcia & Ervin,

1968), amphetamine (Cappell & LeBlanc, 1971), chlordiazepoxide, ethanol (Cappell, LeBlanc & Endrenyi, 1973) and methyl-scopolamine (Berger, Wise & Stein, 1973) among many others. That such a wide variety of drugs can induce a CTA is interesting in itself, however, of greater interest is the fact that some of the drugs mentioned are also self-administered even at the identifical dose with which a CTA is produced (Cappell & LeBlanc, 1971).

A number of investigators have used drug pre-exposure paradigms in order to explain the nature of CTAs produced by psychoactive drugs. In one of the earlier of these studies, LeBlanc and Cappell (1974) pre-exposed rats to either morphine or amphetamine a number of times until the animals were determined to be dependent. They then paired an injection of either drug with saccharin and subsequently found that the drug pre-exposure blocked acquisition of a CTA produced by the same drug. In an additional study, Cappell, LeBlanc and Herling (1975) found that amphetamine pre-exposure also attenuated a morphine-induced CTA indicating that there was a degree of commonality between CTAs

induced by both morphine and amphetamine. If morphine- and amphetamine-induced CTA are related one would expect morphine pre-exposure to at least attenuate CTA induced by amphetamine. In the experiment by Cappell et al. (1975), however, morphine pre-exposure failed to attenuate the amphetamine-CTA. It is possible that morphine failed to attenuate the amphetamine-CTA since the initial saccharin intake baseline of the morphine pre-exposure group was considerably lower than that of the amphetamine pre-exposure group, thereby confounding the results. Although there seems to be overlap between morphine and amphetamine, Cappell et al. (1975) found no effects of chlordiazepoxide pre-exposure on either amphetamine- or morphine-CTAs. Unlike the latter two drugs, chlordiazepoxide has not been demonstrated to be dependence-producing (Le Dain, 1973). Similar results have been obtained by Gamzu (Note 1) in which rats receiving three pre-exposures of amphetamine or chlordiazepoxide failed to exhibit a CTA to the same drugs, however, the chlordiazepoxide pre-exposures failed to affect the CTA induced by amphetamine. Thus, there seem to be some differences between CTAs induced by dependence-producing drugs such as morphine and amphetamine and a CTA induced by chlordiazepoxide a drug with little or no dependence-producing

properties.

Although the above studies have shown that pre-exposure to various drugs can differentially affect CTAs, Braveman (1975) has argued that the agent to which the animals are pre-exposed is inconsequential in determining the strength of aversion to the pairing drug, as long as the pre-exposure stimulus itself is capable of producing a CTA. Braveman found that pre-exposure of amphetamine or methylscopolamine, two drugs believed to act on different systems (Berger, Wise & Stein, 1973), attenuated the CTA induced by the other drug. Closer inspection of Braveman's results, however, point to some qualitative differences between the two drugs. For instance, with five drug pre-exposures, methylscopolamine attenuated an amphetamine-CTA by a greater degree than the attenuating effect of amphetamine pre-exposure on a methylscopolamine-CTA. When pre-exposure consisted of seven injections, methyl-scopolamine almost completely blocked the amphetamine-CTA whereas amphetamine produced no significant effect on the methylscopolamine-CTA. Thus, although there is some overlap between the effects of these two drugs on CTA, there also

seem to be differences between them. Berger et al. (1973) concluded that the CTA induced by amphetamine is mediated through different neural mechanisms than that produced by methylscopolamine since amphetamine produced a CTA in rats with area postrema lesions whereas methylscopolamine did not.

Claiming further support for his argument, Braveman demonstrated that pre-exposure to stimuli as diverse as LiCl, amphetamine, methylscopolamine or turntable rotation all blocked a CTA induced by turntable rotation. That the above pre-exposure stimuli blocked a rotation-induced CTA, does not discount the possibility that all of these stimuli produced similar effects to those produced by turntable rotation in causing a CTA. For example, rotation can conceivably produce vestibular and gastrointestinal effects such as dizziness and nausea, either of which may be common to any of the chemical pre-exposure stimuli in producing a CTA. Thus, pre-exposure to any chemical stimulus with one or both properties could attenuate the rotation-induced CTA. Aside from this possibility, interpretation of Braveman's experiment is difficult for two reasons. Firstly, the measurement used in the experiment may not

have been adequate to demonstrate differences between the pre-exposure stimuli. Braveman measured whether or not a fixed number of stimulus pre-exposure attenuated the rotation-induced CTA. It would also be important to measure the number of stimulus pre-exposures required to attenuate the CTA. For example, it has been demonstrated that fenfluramine requires eight pre-exposures in order to block its own CTA whereas only four amphetamine pre-exposures are sufficient to abolish its own CTA (Goudie, Taylor & Atherton, 1975). The number of pre-exposures used in Braveman's study (5 pre-exposures) may have been more than adequate for all the stimuli to attenuate the rotation-induced CTA. It is possible, however, that less than five pre-exposures may have resulted in only certain of the stimuli attenuating the CTA. With only one pre-exposure, only rotation pre-exposure itself may have attenuated the CTA. Thus, the pre-exposure stimuli may have been differentiated on the basis of the number of pre-exposures required to attenuate the rotation-induced CTA.

A second problem with Braveman's (1975)

study is a failure to equate the various stimuli in terms of their own abilities to produce a CTA. For example, the dose of LiCl used may have produced a stronger CTA than the dose of amphetamine used. If the dose of LiCl was lowered so that it produced the same strength of CTA as did amphetamine, the LiCl may not have attenuated the rotation-induced CTA to the same extent as amphetamine.

In summary, there are methodological difficulties with Braveman's (1975) experiments which hinder interpretation. Although one cannot rule out that, in pre-exposure studies, the type of pre-exposure stimulus used is inconsequential in determining whether or not a CTA induced by another stimulus is attenuated, the possibility exists that there are qualitative differences in the nature of CTAs induced by various drugs.

There are CTA experiments which clearly illustrate differences between a variety of drugs that produce CTAs - in particular differences between positively reinforcing drugs and those which are not. For instance, a recent study demonstrated that when morphine is infused into the left lateral cerebral ventricle, it

produced a CTA. The same route of LiCl administration, however, failed to produce a CTA (Switzman, Sinyor & Amit, Note 2). Thus, it seems as though there is a central component to the morphine-CTA whereas there may be no central involvement in the LiCl-CTA. Morphine has been shown to have positively reinforcing properties whereas LiCl has been demonstrated to have no positively reinforcing properties (White, Sklar & Amit, 1977). This together with the results of the experiment by Switzman et al. indicate that mechanisms underlying CTAs induced by positively reinforcing drugs are different from the mechanisms of CTAs produced by drugs with no positively reinforcing effects.

Experiments involving biochemical manipulations have been conducted in order to further understand the mechanisms underlying CTA. Roberts and Fibiger (1975) injected amphetamine or LiCl into rats treated with 6-hydroxydopamine, a neurotoxin that selectively destroys catecholamine (CA) nerve terminals. Roberts and Fibiger found that under these conditions, amphetamine failed to produce a CTA, however, LiCl was still capable of inducing a CTA. These

results suggest that CAs subserve the CTA induced by amphetamine, a self-administered drug, whereas CAs do not mediate the CTA induced by LiCl. Sklar and Amit (1977) further investigated the role of CAs in CTAs induced by both self-administered and non-self-administered drugs. They found that AMPT, a tyrosine hydroxylase inhibitor, which lowers brain CA levels, blocked CTAs induced by morphine and ethanol but did not affect LiCl- or Δ^9THC-induced CTAs. Sklar and Amit also explored the degree to which the specific CAs, dopamine (DA) and norepinephrine (NE) participate in the mediation of CTA. Pimozide, a DA receptor blocker, eliminated both morphine and ethanol CTAs while CTAs induced by LiCl and Δ^9THC were unaffected. FLA-57, a dopamine-β-hydroxylase inhibitor which lowers NE levels, blocked only a CTA produced by morphine. The investigators concluded that, while both DA and NE subserve morphine-induced CTA, only DA mediates CTA induced by ETOH. These results along with those of Roberts and Fibiger suggest that CAs mediate CTAs induced by self-administered drugs but not those produced by non-self-administered drugs. In contrast, Coussens, Crowder and Davis (1973)

found that CA depletions with AMPT enhanced, rather than attenuated, a morphine-induced CTA. The discrepancy between the results of Coussens et al. and those of Sklar and Amit (1977) are difficult to explain, however, it is curious that the former group of investigators failed to produce a CTA with an injection of 10 mg/kg of morphine in non-pretreated control animals. Similar doses of morphine used by others have produced a robust CTA (Amit et al., 1977; Cappell, LeBlanc & Endrenyi, 1973).

The CA system is also believed to be involved in the mediation of the positively reinforcing properties of self-administered drugs such as alcohol, amphetamine and morphine. It has been found that AMPT antagonizes ethanol-induced stimulation and euphoria in humans (Ahlenius, Carlsson, Engel, Svensson & Sodersten, 1973). Ethanol self-administration has been attenuated in animals by injections of FLA-57 (Amit, Brown, Levitan & Ogren, Note 3). Davis and Smith (1972) demonstrated that AMPT blocked reacquisition of a bar-pressing response for amphetamine as well as morphine. The effect of AMPT was probably not

due to motor debilitation since a buzzer paired with morphine failed to acquire secondary reinforcing properties when animals were pretreated with AMPT (Davis & Smith, 1973). In a more recent study, the same investigators found that NE depletors, diethyldithiocarbamate (DDC) and U-14,624 also suppressed reacquisition of bar-pressing for both morphine and amphetamine. (Davis, Smith & Khalsa, 1975). Lewis and Margules (1975) demonstrated that AMPT suppressed operant responding for exposure to etonitazene-adulterated water in pre-dependent rats. (etonitazene is a synthetic opiate reported to be one thousand times more potent than morphine). In non-dependent rats, oral morphine self-administration was also blocked by AMPT (Glick, Zimmerberg & Charap, 1973). Glick and Cox (1977) recently found that substantia nigra lesions, which destroy DA neurons, decreased bar-pressing for intravenous morphine in rats. The investigators concluded that the lesions increased sensitivity to the rewarding properties of morphine.

Pozuelo and Kerr (1972) conducted a study in which restrained monkeys lever-pressed for intravenous injections of morphine. When AMPT was administered to these animals, bar-pressing ceased with no signs of withdrawal evident. Pozuelo and Kerr ruled out a sedative action of AMPT on the bar-pressing as the causal agent for the cessation of lever-pressing since injections of sedative drugs failed to decrease morphine intake.

The above experiments established that depletion of CAs disrupts responding for morphine and that the decrease in morphine-seeking behavior may be a function of the concomitant decrease in the positively reinforcing properties of the drug. Thus, it seems that CAs may not only subserve morphine aversion, but also the positively reinforcing properties of this drug.

Although CAs seem to underlie aversion induced by morphine and other self-administered drugs, as well as the reinforcing value of these drugs, the nature of the relationship between positive reinforcement and aversion remains unclear. Recently, two experiments have been conducted in an attempt to elucidate this

relationship. In one experiment, rats were trained to lever-press for injections of amphetamine. After the animals had been pressing consistently, apomorphine was substituted for the amphetamine. Prior to receiving the apomorphine, the animals were water-deprived and were presented with a novel saccharin solution. The rats continued to press for the apomorphine injections and when they were subsequently presented with the saccharin again, fluid consumption was significantly reduced (Wise, Yokel & deWit, 1976). Since the animals continued to self-administer apomorphine and, at the same time, exhibited a CTA induced by the same drug, the authors concluded that a single drug was capable of producing both positive reinforcement and aversion in the same paradigm. It is difficult to judge whether or not the animals were actually continuing to press for amphetamine or whether they were pressing as a direct result of apomorphine reinforcement. This ambiguity seriously limits the conclusion of Wise et al. regarding simultaneous reinforcement and aversion.

Another recent study was conducted using running speed as a measure of positive reinforcement and amount of flavored food eaten as the measure of aversion (White, Sklar & Amit, 1977). Animals were allowed to run down a straight alley for saccharin-flavored food, consumption of which was followed by an injection of either morphine or LiCl. White et al. found that the LiCl-injected animals reduced their running speed and decreased the amount of food eaten. These results indicated that LiCl was highly aversive. The morphine group also ate less food, however, the running speed of this group increased significantly above control levels. The investigators concluded that, while the reduced food intake reflected aversion produced by morphine, the increased running speed indicated positive reinforcement. Thus, the same morphine injection yielded signs of aversion as well as positive reinforcement.

Based on the experiments discussed here, it is suggested that CTAs induced by self-administered drugs, such as morphine, are qualitatively different from the aversion

produced by non-self-administered drugs such as LiCl or poorly self-administered drugs such as Δ^9THC. It is further proposed that both positive reinforcement and aversion are mediated by the CAs since CA depletions attenuate self-administration as well as CTA. In previous experiments CA depletions reduced the strength of aversion produced by self-administered drugs in paradigms dissimilar to those in which positive reinforcement was affected. If positive reinforcement and aversion are related, then a single CA manipulation should affect both, when they are manifested in the same paradigm.

The runway procedure used by White et al. provides an excellent paradigm to determine if the same CA depletion could attenuate both the positively reinforcing and aversive properties of a self-administered drug. The following experiments were conducted to further examine the relationship between the positive reinforcing and aversive properties of morphine, and the role of CAs therein.

Experiment I

A number of studies have demonstrated that morphine can be positively reinforcing (Amit, Brown & Sklar, 1976; Deneau, Yanagita & Seevers, 1969; Woods & Schuster, 1968). On the other hand, morphine can also be aversive since animals learn to avoid a novel-tasting substance associated with the drug (Cappell, LeBlanc & Endrenyi, 1973; Jacquet, 1973). The apparent paradox, that morphine can be positively reinforcing as well as aversive, has been the target of investigation in many experiments. A number of these experiments have demonstrated differences in the nature of CTAs induced by positively reinforcing drugs and drugs which are not positively reinforcing (Amit, Levitan, Brown & Rogan, 1977; Berger, Wise & Stein, 1973; Cappell, LeBlanc & Herling, 1975; Goudie, Taylor & Atherton, 1975; Roberts & Fibiger, 1975; Sklar & Amit, 1977; Switzman, Sinyor & Amit, Note 2).

In a recent study, White, Sklar and Amit (1977) demonstrated simultaneous positive reinforcement and aversion produced by a single morphine injection. Food-deprived rats were placed in a straight runway and were allowed to

run for a distinctly flavored food which was paired with an injection of morphine. The investigators found that the morphine-injected rats ran faster than control animals but ate less of the food.

The present experiment is a reinvestigation of the morphine reinforcement-aversion paradox as reflected in the runway experiment described above. Unlike the study by White et al., the running speed in this experiment was stabilized prior to the experimental manipulation. It has been found that once rats stabilize running speed, a shift in the magnitude of reinforcement produces a concomitant change in speed corresponding to the direction of the reinforcement shift (Crespi, 1942; Zeaman, 1949). For example, Crespi found that when the amount of food available in the goal box was increased, the animals increased running speed. Similarly, when less than the original amount of food was available, a decrease in running speed occurred. Hence, if morphine injections produce additional reinforcement in the runway situation, one would expect the rats to increase their running speed after it had stabilized to some degree, barring

a ceiling effect.

Method

Subjects

Subjects were 16 male Wistar rats weighing 250-300 g at the start of the experiment. The animals were separately housed in stainless steel cages with free access to Purina laboratory chow and water prior to the onset of the experiment.

Drugs and Materials

Morphine hydrochloride (May & 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 experiment called for flavored food, the mash was adulterated with Sanka decaffeinated coffee such that 100 g of ground lab chow was mixed with 200 mls. of a 4% (w/v) Sanka/water solution.

The experiment was conducted in a straight wooden runway (16 cm. wide with walls 30 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 alley was 183 cm. long and both the start and

goal boxes were 18 cm. in length. 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 running time meters (Type 6335A, Gonrac Corp.) were used to measure running speed. The first timer measured the latency to leave the start box and the second one measured the running time down the alley. A photoelectronic relay system (mod. no. V-942, Veritas) controlled the meters. Lifting the start box door depressed a microswitch which started the first running time meter. When a rat broke the light beam focussed on the photocell outside the start box door, the first timer was stopped and, simultaneously, a 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 the times on both meters yielded the total running time.

Procedure

Food was removed from the home cages 24 hours prior to the onset of the experiment. Throughout the study, the animals received a one hour

supplement of plain mash in the home cage at least ½ hour after being run each day.

The experiment consisted of three phases. In the first phase, which lasted two consecutive days, the rats were allowed to adapt to the runway apparatus: Each animal was placed in the start box for 30 seconds, after which the door was opened allowing the rat to move freely in the runway for ten minutes. During this time, the animal had free access to a dish of plain mash which was located in the goal box. The second phase of the experiment was instituted to allow the animals to stabilize their running speed. The criteria for stabilization were (1) that on three consecutive days, the total running time ranged within one second or (2) that the total running time was less than five seconds for three consecutive days, whichever occurred first. Again, the rat was placed in the start box for 30 seconds and, thereupon, the door was opened. When the animal entered the goal box, in which there was plain mash, the goal box door was closed trapping the animal inside. The goal box was then removed from the rest of the apparatus and placed aside for ten minutes. If an animal could not be

trapped on the first trial, it was discarded from the study. Once an animal had stabilized it was randomly assigned to either of two groups, Group M (n=6) or Group R (n=10), for the third phase of the experiment which lasted six consecutive days. On each day, the rats were run as was described for phase two except that the mash was flavored with Sanka and the animals received an intraperitoneal injection after the ten minute eating period. Group M received 9 mg/kg (1 cc/kg) of morphine and Group R was injected with a volume of Ringer's solution equivalent to the morphine injection. Following the injections, the rats were replaced in the goal box without food for 50 additional minutes whereupon they were removed and returned to their home cages.

In both phases two and three, total running time was recorded for each animal and the food dish was weighed directly before placing the animal in the runway and immediately after the dish was removed from the goal box.

Results

Food consumption and running speed for each test day are presented in Figures 1 and 2 respectively. These are expressed in terms of percent change from baseline. Test days were the last five days in phase three of the experiment.

The mean amount of food eaten on the last two days of phase two and the first day of phase three was used as a baseline for each animal. There was no significant difference between Group M and Group R in baseline food intake ($t=.3257$; $dF=14$, $p > .1$). The percent of baseline food scores for the test days were logarithmically transformed. Analysis of variance was carried out on these scores. As Figure 1 illustrates, the mean amount of food consumed by Group M was consistently below the mean amount of food eaten by Group R for every test day. This effect approached significance (two-way analysis of variance: $F=4.016$; $dF=1/14$; $p < .065$). There was no significant change in the amount of food eaten over days ($F=.3923$; $dF=4/56$; $p > .8$) for either of the groups ($F=.2129$; $dF=4/56$; $p > .9$).

The baseline running speed for each animal was obtained by calculating the mean running score

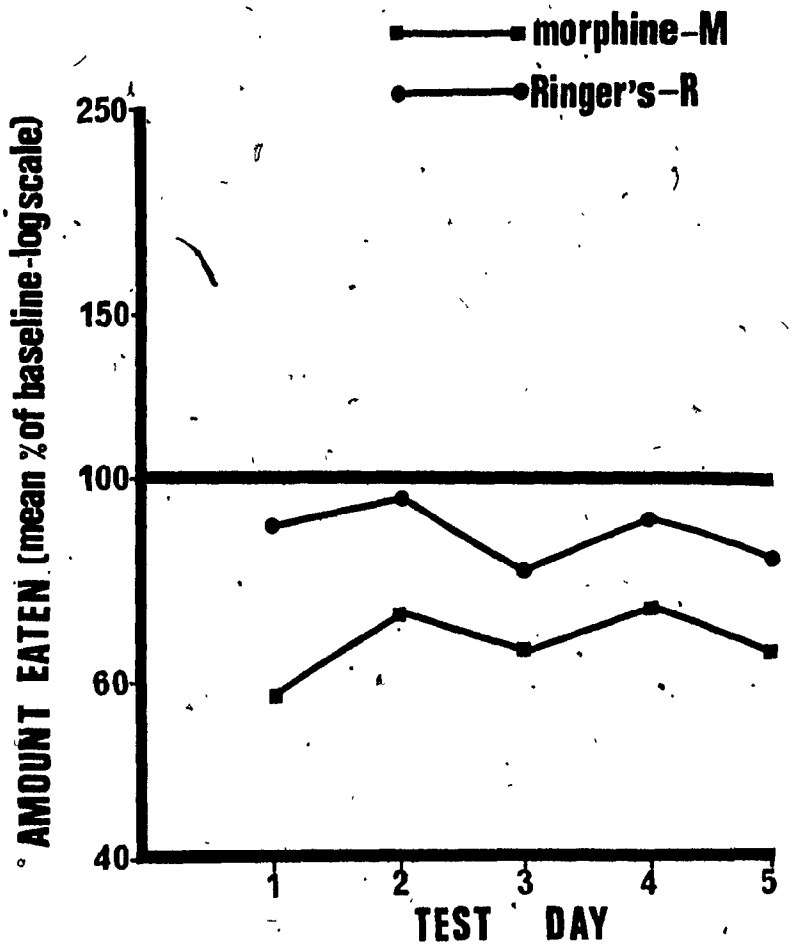

Figure 1. Mean percent of baseline amount of food eaten in the goal box for the morphine and Ringer's groups.

on the same three days used to determine the food baseline. There was no significant difference between the baseline running scores for Group M and Group R ($t=1.02$; $dF=14$, $p > .1$). In order that an increase in running speed could be reflected by an ascending curve, the reciprocal of the percent of baseline running scores were calculated. These scores were then logarithmically transformed for statistical analysis. Analysis of variance was carried out on these scores. As can be seen from Figure 2, Group M ran faster than Group R on all test days except the first (two-way ANOVA: $F=5.2021$; $dF=1/14$; $p < .039$). Both the days effect ($F=2.340$; $dF=4/56$; $p < .0661$) and the Group x days interaction ($F=2.3551$; $dF=4/56$; $p < .0637$) approached significance.

The raw data for this experiment appear in Appendix A.

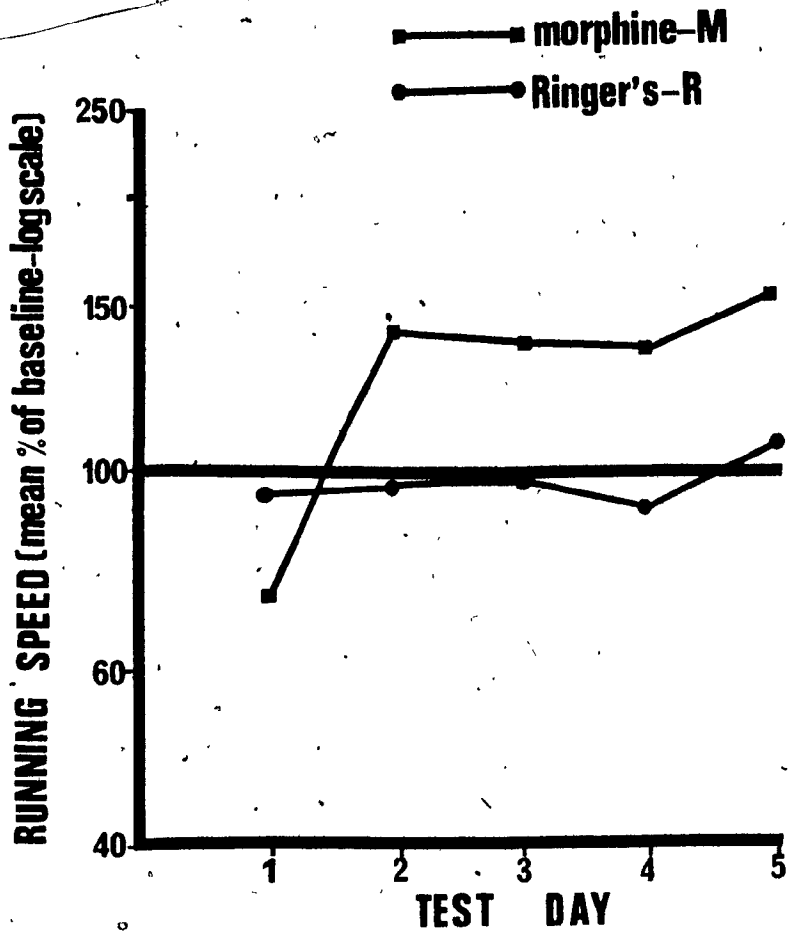

Figure 2. Mean percent of baseline running speed for the morphine and Ringer's groups.

Discussion

The results of this experiment provide additional support for the view that self-administered drugs can have simultaneous positively reinforcing and aversive properties (White et al., 1977; Wise et al., 1976). Animals given morphine in the goal box increased their running speed when compared to control animals and, at the same time, decreased the consumption of a flavored food.

Although the lowered food intake of the morphine group only approached significance, a number of points should be considered. In the present experiment, consumption of flavored food for Group M decreased to a level about 35 percent below baseline. White et al. (1977), in an almost identical paradigm, demonstrated a decrease in food consumption for the morphine group by approximately 30 percent below baseline. Thus, the morphine animals in this experiment ate slightly less than the morphine group in the experiment conducted by White et al. The eating data in this experiment may not have been as significant as those results obtained by White et

al. because the Ringer's animals in this experiment ate less food than the comparable control animals in the study of White et al. Therefore, when an intergroup comparison was conducted in this experiment, the net CTA produced by morphine was less significant than that produced in White et al.'s experiment. Thus, the relatively diminished CTA effect seen here may be, at least, partially attributed to the lower food intake of the Ringer's animals. One might argue that morphine animals should have also proportionately decreased their food intake thus enabling a more significant CTA to have been produced. Data gathered in other experiments, however, indicate that the CTA induced by similar doses of morphine as the one used here does not generally decrease intake below about 2/3 of baseline intake (Amit, Levitan, Brown & Rogan, 1977; Jacquet, 1973; White et al., 1977). This "floor" effect coupled with the diminished food intake of the Ringer's group could explain why the CTA in the present study did not achieve the same level of significance as was attained in the study conducted by White et al. There may still be some reservations about the eating

data, however, it may be pointed out that the directionality of the results in this experiment are the same as in the previous runway experiment (White et al., 1977): the morphine rats increased running speed and at the same time ate less food. If this phenomenon was transient, the chances of achieving the same directionality of results twice in a similar, but not identical paradigm would be small.

It is difficult to explain why the Ringer's group ate so little food in the present experiment, however, it is quite possible that the flavor of the food contributed to this effect (in the experiment by White et al. the mash was adulterated with saccharin).

A number of hypotheses have been proposed to account for the apparent paradoxical effects of morphine. It has been suggested that initial drug experiences induce fear in the animals (Amit & Baum, 1970).

The novelty of the drug state itself, rather than any noxious properties of morphine, may be the basis of the aversive component in CTA. Gamzu (Note 1) suggested that any novel internal state is perceived harmful until proven otherwise.

A novelty hypothesis would imply that morphine is not aversive in the same way as LiCl, which may produce gastrointestinal discomfort in animals. Hence, from a psychobiological viewpoint, it is conceivable that the strength of a LiCl-induced CTA would be greater than a morphine-induced CTA since there should be a stronger association between gustatory and gastrointestinal stimuli than between gustatory and non-digestive stimuli. The data bear this out. The CTA produced by morphine is much less robust than a LiCl-induced CTA (White et al., 1977). Even though the novelty hypothesis is sufficient to differentiate between CTAs induced by self-administered and non-self-administered drugs, it fails to explain why animals increase running speed for a drug that may, at the same time, be perceived as harmful. Goudie et al. (1975) proposed an Aversive Tolerance hypothesis to deal with the problem of aversion produced by self-administered drugs. Their explanation is that the aversive drug effects, which initially predominate (even in a self-administration paradigm), tolerate allowing the drug to become increasingly rewarding.

Accordingly, the self-administration liability of a drug is reflected in the amount of time required for the aversive effects to tolerate. This explanation could not account for the results of this experiment since on the first day the morphine group ran below their own baseline whereas on subsequent days the running speed had significantly increased. The shift in running speed was sudden and the Aversive Tolerance hypothesis would predict a concomitant increase in the amount of food eaten which did not occur. In the context of Aversive Tolerance, it is difficult to understand why an animal would persistently approach a stimulus (the goal box) associated with a drug (Beach, 1957) that produces a sign of aversion. In discussing CTAs induced by self-administered drugs, Cappell and LeBlanc (1977) suggested that non-gustatory stimuli are less likely to produce an avoidance response and are prone to either indifferent or approach behaviors. In contrast CTAs produced by drugs reflects the animals' predisposition to avoid a novel gustatory stimulus paired with the drug. In the runway situation, the animals avoided the gustatory

stimulus paired with the morphine and at the same time approached the place associated with the morphine with decreased latency on all days except the first. Whether or not a pre-wired mechanism determining response bias exists as Cappell and LeBlanc suggested, the question still remains: what is the relationship between positive reinforcement and aversion in self-administered drugs?

There have been suggestion that a single mechanism may underlie both the positively reinforcing and aversive properties of morphine (LeBlanc & Cappell, 1975; Sklar & Amit, 1977), however, specifications about such a mechanism have been vague. A dual-mechanism hypothesis has also been proposed (White et al., 1977) suggesting that morphine activates a neural reinforcement mechanism which facilitates learning independently from the affective state produced by morphine. This mechanism would be responsible for the increase in running speed. The CTA, on the other hand, occurs as a result of the drug state having been associated with the novel food. White et al. proposed that, in this way, both positive reinforcement and aversion can be demonstrated

simultaneously. It remains to be determined whether one or more mechanisms can best account for the positively reinforcing as well as aversive properties of morphine. The following experiment was designed to examine this issue.

Experiment II

The previous experiment supported the demonstration by White et al. (1977), that the same series of morphine injections can be both positively reinforcing and aversive. The aversion produced by morphine seems to be of a different nature from that produced by non-reinforcing drugs. For example, CA depletions produced by alpha-methyl-para-tyrosine (AMPT), a tyrosine hydroxylase inhibitor, blocked a morphine-induced CTA without affecting CTAs produced by LiCl and Δ^9THC (Sklar & Amit, Note 3). AMPT has also been shown to suppress morphine self-administration in rats (Davis & Smith, 1972) as well as in monkeys (Pozuelo & Kerr, 1972). Thus, the same CA manipulation disrupted both self-administration and CTA in different paradigms. It is, therefore, possible that the CA system may mediate both the positively reinforcing and aversive properties of morphine.

It follows from the above experiments that CA depletions should attenuate the positively reinforcing and aversive components of morphine when both are displayed in the same paradigm. The present experiment was designed to determine if

CA depletions affect both positive reinforcement and aversion produced in a single paradigm by the same series of morphine injections.

Method

Subjects

Subjects were 59 male Wistar rats weighing 250-300 g at the start of the experiment. The animals were separately housed in stainless steel cages with free access to Purina lab chow and water prior to the onset of the experiment.

Drugs and Materials

Morphine hydrochloride (May & Baker Can. Ltd.) was dissolved in injectable Ringer's solution (Abbott Laboratories Ltd.) and d-l-alpha-methyl-para-tyrosine (AMPT) methyl esther (Sigma Chemical Co.) was microsuspended in Ringer's solution. The food source and apparatus were the same as in Experiment 1.

Procedure

The procedure was identical to that described in Experiment I with the exception of phase three in which all groups were pretreated with two intraperitoneal injections, eight and six hours before being run in the runway each day.

Three groups of animals were run: Group A-M (n=9), Group R-M (n=8) and Group A-R (n=7). Group A-M and Group A-R received pre-treatment

with 75 mg/kg of AMPT per injection. Group R-M was injected with an equivalent volume of Ringer's solution.

Following the ten minute eating period in the goal box, Groups A-M and R-M both received 9 mg/kg of morphine whereas Group A-R received an injection of Ringer's solution.

Assays

Thirty-six rats were run for assay purposes in order to assess the degree of brain CA depletions produced by the AMPT injections in the experiment. These rats received two intraperitoneal injections of AMPT (75 mg/kg/injection) at 10:00 A.M. and 12:00 A.M. each day. Control animals received the same schedule of Ringer's injections. At 6:00 P.M. on each of six consecutive days, five AMPT and one Ringer's animal were sacrificed and their brains removed. Thus, animals killed on day one were injected only on that day while animals killed on day six had been injected on six consecutive days including the day on which they were killed.

All of the rats were food-deprived 24 hours prior to sacrificing the first group of rats. Each day, animals not killed on that day were

given plain mash in the home cage for one hour the time during which the other animals were being sacrificed. Once the brains were extracted, they were frozen until a spectrophotofluorometric assay was conducted for both DA and NE.

Results

Behavioral

Food consumption and running speed for each test day are presented in Figures 3 and 4 respectively. These are expressed in terms of percent change from baseline. As was the case in Experiment I, the last five days in phase three were the test days.

The mean amount of food eaten on the last two days of phase two and the first day of phase three was chosen as the food baseline for each animal. There was no significant difference between any of the groups in baseline food intake (one-way ANOVA: $F=.7616$; $dF=2/21$, $p > .1$). The percent of baseline food scores for the test days were logarithmically transformed for statistical analysis. There was a significant treatment effect on the amount of food eaten (two-way ANOVA: $F=4.5959$; $dF=2/21$, $p < .022$). Group A-R ate significantly more food than both Groups A-M and R-M (Scheffé, $p < .05$). In addition, Group A-M ate less food than Group R-M (Scheffé, $p < .05$). The amount of food consumed did not significantly change over days

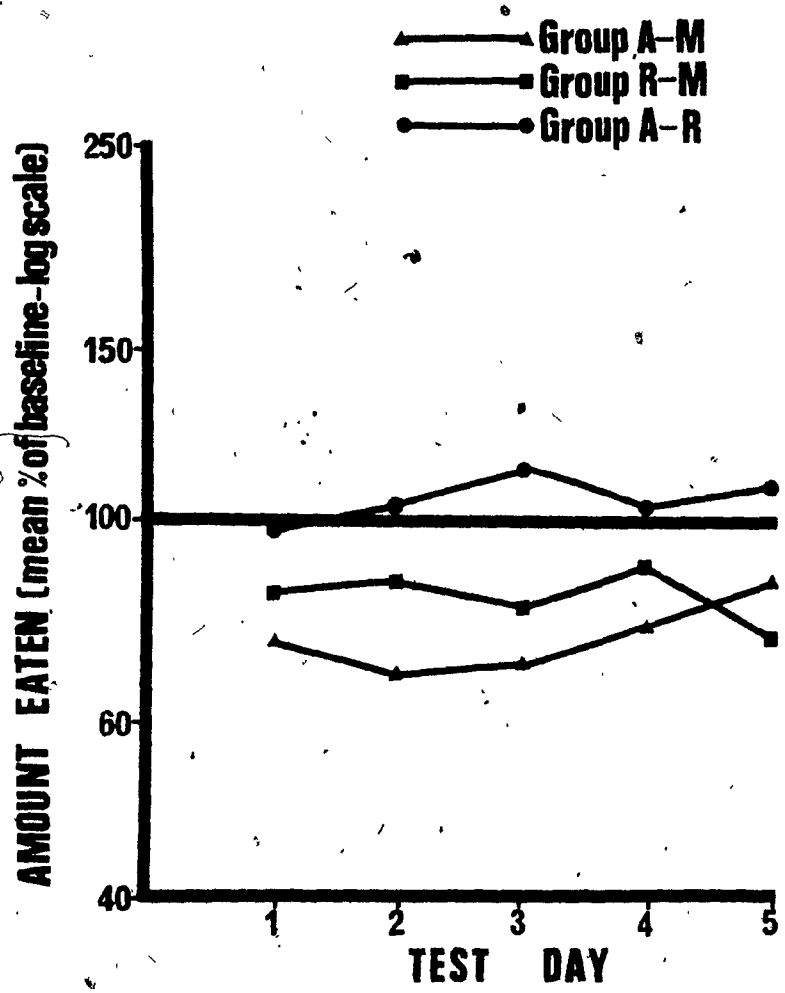

Figure 3. Mean percent of baseline amount of food eaten in the goal box for Group A-M, Group R-M and Group A-R.

($F=.3220$; $dF=4/84$, $p > .8$) for any group ($F=.6259$; $dF=8/84$, $p > .75$).

The baseline running speed for each animal was obtained by calculating the mean running time on the same days used to determine the food baseline. There was no significant difference between the baseline running scores for any of the groups (one-way ANOVA: $F=1.234$; $dF=2/21$, $p > .1$). As in Experiment I, the reciprocal of the percent of baseline running scores were logarithmically transformed for statistical analysis. There was no significant treatment effect on running speed for any of the groups (two-way ANOVA: $F=.1008$; $dF=2/21$, $p > .9$). Similarly, there was no significant change in running speed over days ($F=2.188$; $dF=4/84$, $p > .077$), as well as no significant Group x days interaction ($F=.8946$; $dF=8/84$, $p > .52$).

Assay

Due to technical problems, assay data from one AMPT-treated and one Ringer's animal are missing. As can be seen in Table 1, AMPT reduced brain CAs below control levels. This effect was highly significant for both DA (one-way ANOVA:

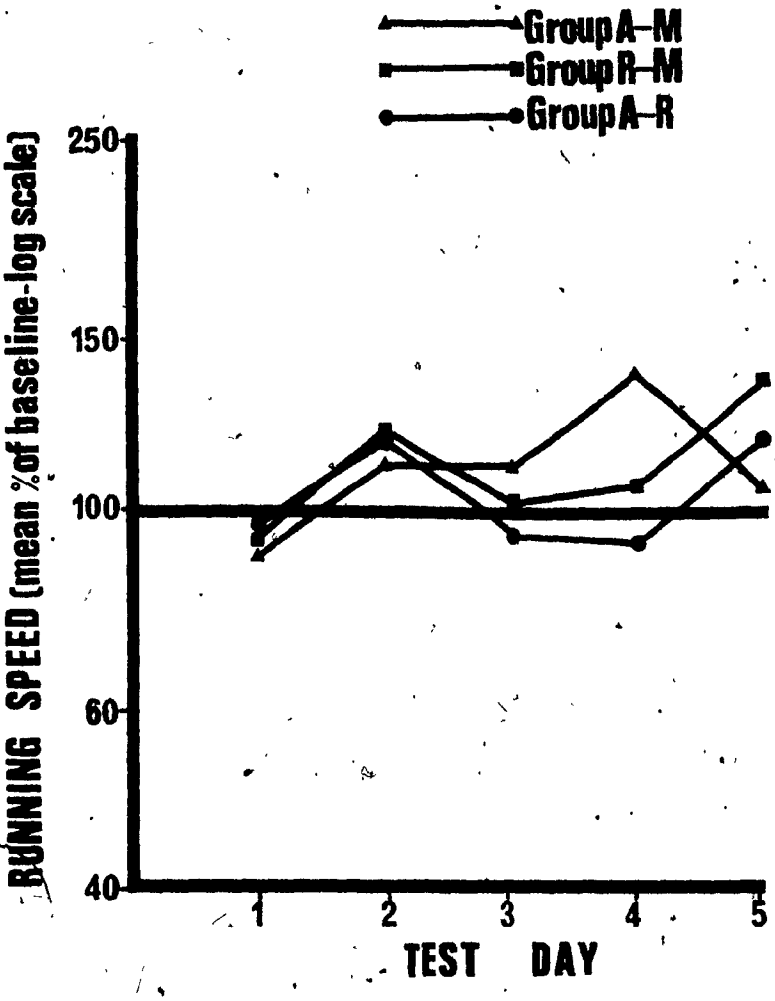

Figure 4. Mean percent of baseline running speed for Group A-M, Group R-M and Group A-R.

F=.0977; dF=6/27, p < .0001) and NE (F=13.5673; dF= 6/27, p < .0001).

Table 1

Mean Daily Brain Catecholamine Levels Following AMPT Over Six Consecutive Days

Group	n	Absolute Level DA[a]	Absolute Level NE[a]	Percent Depletion From Control Level DA	Percent Depletion From Control Level NE
Ringer's Control	5	422.1	256.7		
AMPT					
One Day	5	88.0	100.1	79.2	61.0
Two Days	5	123.4	90.3	70.9	64.8
Three Days	5	150.9	108.0	64.3	57.9
Four Days	5	144.5	99.1	65.8	61.4
Five Days	5	112.8	74.4	73.3	71.0
Six Days	4	138.2	96.5	67.7	62.4

[a]Expressed in ng/gm tissue.

Discussion

As can be seen from Figures 2 and 4, there are discrepant results in the running speed. Group M in Experiment I increased running speed to a level of between 130 and 155 percent of baseline whereas the comparable group in Experiment II, Group R-M, had scores which ranged between 100 and 140 percent over baseline. These results suggest that when morphine was administered in the runway, pretreatment with a Ringer's injection produced lower and more variable running speeds than no injection pretreatment. This finding is difficult to interpret in the present context; it is impossible to determine whether the additional injections, the handling associated with them, or some other variable produced the effect. Curiously, animals pretreated with AMPT had somewhat faster running speeds and more variability between days than non-treated animals receiving Ringer's in the goal box. This may seem

puzzling since AMPT has been reported to suppress responding for a positive reinforcer. For example, Seiden, MacPhail and Ogelsby (1975) reported that AMPT decreased bar-pressing for water in fluid-deprived rats indicating that CA depletions produced a deficit in appetitive responding. In another experiment, however, Saper and Sweeney (1973) found contrasting results: AMPT enhanced learning of a black-white discrimination task in which rats were required to approach and enter the appropriately-shaded goal box at the end of an alley. The discrepancy between the results of Seiden et al. and those of Saper and Sweeney may be resolved by viewing the problem in terms of the type of paradigms implemented as well as the adequate response required in the situation. Seiden et al. used a free-operant paradigm in which the adequate response was bar-pressing; Saper and Sweeney used a discrete-trial paradigm in which rats were required to approach and enter the appropriate goal box. Hence, the measurement used in each of the experiments was considerably different. The effect of a manipulation on an animal's performance may depend very much upon the nature of the task as well as the way in

which it is measured.

The results obtained for running speed in the present experiment are equivocal since pretreating animals with an injection seemed to increase variability in running speed for all groups. This may be a cause for the insignificant treatment effect on running speed.

AMPT pretreatment enhanced the morphine-induced CTA since Group A-M ate significantly less food than Group R-M. This effect cannot be attributed to an attenuation of feeding behavior in general produced by AMPT since Group A-R ate consistently above baseline except for the first test day where eating was only slightly below baseline (Figure 3). The CTA results in the present experiment concur with results obtained by Coussens, Crowder and Davis (1973) in which morphine produced a CTA when rats were pretreated with AMPT but not in non-pretreated animals. In contrast, the present results conflict with those of Sklar and Amit (1977) in which AMPT pretreatment blocked a morphine-induced CTA in rats. This discrepancy may be due to differences in the stimulus situations in which the pairings took place,

thus altering the AMPT pretreatment effect upon the CTA. In Sklar and Amit's study, the drug pairing occurred in the home cage whereas in this experiment as well as the experiment by Coussens et al., drug pairings occurred outside the home cage: Coussens et al. paired in an opaque plastic cylinder and in this study, pairing occurred in the runway. Hence, it is possible that there was an increase in the salience of the situation which may have interacted with the AMPT pretreatment to enhance the CTA.

It is doubtful that differences in drug injection doses and schedules account for the divergent results. The dose of AMPT and morphine in this experiment were identical to the doses used in the experiment conducted by Sklar and Amit (1977); the schedule of AMPT injections were also the same; the CA depletions were similar; and the pairing procedure was similar. Although the conditional stimulus (CS) paired with the morphine, as well as the consummatory response required to ingest the flavored substance, differed in this experiment from the Sklar and Amit's experiment, it is doubtful that this element was crucial in determining the

directionality of the results. The CS used in the experiments carried out by Sklar and Amit as well as Coussens et al. (1973) was saccharin-flavored water. In the present experiment the CS was Sanka-flavored mash. If the quality of the CS and the consummatory response were critical variables, the results of Coussens et al. as well as those of Sklar and Amit should have been similar. Furthermore, one would have expected the present experiment to have yielded results different from both of the others.

It seems, therefore, that neither the quality of the CS in these experiments nor the consummatory response were major causes in determining the results. It is, hence, suggested that exteroceptive cues may be critical variables in determining the properties of CTAs induced by self-administered drugs. It is possible that CAs may be differentially involved in CTAs produced by these drugs depending upon the nature of the situation in which the initial learning occurs.

It is difficult to consider the results of the present experiment in terms of a single versus dual mechanisms underlying aversion and

positive reinforcement since the running speed data are ambiguous. The CTA results do, however, indicate that CAs may not participate to the same degree in drug aversion for all situations. In order to attain a more comprehensive understanding of the catecholaminergic role in aversion produced by self-administered drugs, questions regarding situational variables must be considered.

General Discussion

The results of the first experiment provide additional support for the view that the same series of morphine injections can produce both an increase in running speed in the runway and a decrease in the amount of flavored food eaten in the goal box. It would appear that the same series of morphine injections can produce both positively reinforcing and aversive effects. The second experiment demonstrated that CA depletions produced by AMPT failed to attenuate the aversive properties of morphine. In fact, AMPT pretreatment enhanced the morphine-induced CTA.

The AMPT enhancement of the morphine-CTA in the second experiment parallels results obtained by Coussens et al. (1973) in which AMPT increased morphine's ability to produce a CTA. It is proposed that the divergence of the results in this study as well as those of Coussens et al. with results obtained by Sklar and Amit (1977) may be a function of the differences in the exteroceptive cues present during the drug pairing. More specifically, in the experiment conducted by Sklar and Amit, the pairing occurred in a familiar environment

(the home cage) whereas pairings in this experiment as well as that of Coussens et al. occurred in a less familiar environment. It is possible that there may be differential CA involvement in the morphine-CTA depending upon situational variables. The degree to which the specific neurochemicals (i.e. DA or NE) and their various pathways are involved in the morphine-CTA may be functionally related to the nature of the stimulus situation. This idea is indirectly supported by recent results obtained by White (Note 4). In White's experiment, rats could obtain electrical brain stimulation by performing one of three tasks: running in a four-sided square alley in which a photobeam on each side had to be broken; flicking the tail from side to side in a restraining cage; a standard bar-pressing situation. Each rat learned to perform all the tasks and was then pretreated with pimozide or FLA-57 on different occasions. When the rats received pimozide running was greatly depressed, bar-pressing was disrupted to a lesser extent and there was no effect of pimozide on the tail flick. Pretreatment with

FLA-57 abolished the tail flick, depressed bar-pressing to a similar extent as did pimozide, and had no effect on running. Thus, only certain responses for the same reinforcer, brain stimulation, were affected by each drug. The response which was most affected by one drug, was least affected by the other. Thus, it is possible that the role of CAs in morphine aversion also varies depending upon the nature of the situation in which conditioning occurs.

Although there have been experiments indicating that exteroceptive cues are irrelevant in affecting CTAs (Garcia, McGowan, Ervin & Koelling, 1968; Slotnick, Brown & Gelhard, 1977), these studies have not altered neurotransmitter levels. It is possible that when CAs are depleted, the role of exteroceptive cues may become increasingly critical in CTAs induced by morphine. This may be tested by conducting CTA experiments in which CAs as well as situational variables are systematically manipulated.

Sklar and Amit have proposed that the aversion produced by morphine is functionally related to the positive reinforcement. If this

is true, one would expect an enhancement of running speed corresponding to the increase seen in the CTA produced by AMPT pretreatment in this experiment. AMPT, however, had no effect on running speed. This may have been a function of the increased variability in running speed produced by pretreatment with an injection. Alternatively, it is possible that there is more than one basic physiological substrate mediating positive reinforcement and aversion produced by morphine. There may be some overlap in systems subserving various classes of responses (i.e. classes of appetitive and avoidance response) and this is indicated by experiments previously mentioned in which CA depletions attenuated both appetitive and avoidance responses in different paradigms. The degree of overlap may be determined in part by situational variables as well as variations in the response which is being measured. Thus, a more systematic examination of the interaction between physiological manipulations, stimulus situations and demand characteristics of a situation is needed.

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APPENDIX A

Raw Scores For Experiment I

TABLE 1

Total Running Time On Baseline And Test Days

Group	Day							
	Baseline Day Running Time (sec.)			Test Day Running Time (sec.)				
	1	2	3	1	2	3	4	5
Ringer's								
	3.1	3.6	3.4	3.3	2.9	3.8	2.7	3.2
	3.0	3.1	3.6	4.5	5.3	4.2	5.3	3.9
	3.1	2.7	2.6	2.6	3.1	3.4	3.1	2.6
	2.2	2.4	2.3	2.5	3.5	2.7	2.4	2.1
	3.2	2.5	2.4	2.7	2.4	2.8	2.6	2.2
	3.4	3.5	2.6	2.9	5.1	8.7	4.4	4.4
	4.4	3.4	3.3	4.5	2.8	3.5	2.7	2.9
	4.0	4.0	5.6	3.7	4.3	3.6	4.8	4.5
	4.1	4.6	3.5	4.7	[illegible]	9.4	8.4	3.5
	4.3	4.3	3.6	5.4	3.5	4.6	4.0	3.4
Morphine								
	3.0	2.3	3.3	2.9	1.9	2.1	1.9	1.8
	5.8	3.0	3.1	5.8	3.4	2.7	3.3	1.7
	3.7	3.3	2.8	10.5	2.5	3.1	3.9	2.0
	2.7	5.5	2.9	6.5	2.5	2.6	2.3	2.3
	3.0	3.0	4.0	3.5	2.6	3.8	3.6	2.9
	4.5	4.1	9.2	5.1	5.4	3.8	3.8	7.8

TABLE 2

Amount Of Food Consumed On Baseline And Test Days

Group	Day							
	Baseline Day Food Consumption (g)			Test Day Food Consumption (g)				
	1	2	3	1	2	3	4	5
Ringer's								
	19	19	17	13	21	13	14	12
	22	23	21	15	18	19	17	19
	23	18	12	26	30	25	21	22
	21	25	23	17	15	15	14	21
	21	22	22	26	15	23	18	15
	21.5	16	19	28	16	11	9	6
	14	18	18	13	20	21	20	21
	18	20	18	20	14	24	20	12
	19	15	13	7	15	18	20	19
	20	16	14	15	19	18	21	17
Morphine								
	14	13	13	8	8	5	13	10
	13	10	24	11	16	17	13	13
	18.5	18	19	7	9	10	18	17
	24	18	23	8	16	17	19	15
	15	16	22	15	15	10	16	13
	18	17	21	15	13	8	4	5

APPENDIX B

Raw Scores For Experiment II

TABLE 1

Total Running Time On Baseline And Test Days

Group	Day								
	Baseline Day Running Time (sec.)			Test Day Running Time (sec.)					
	1	2	3	1	2	3	4	5	
R-M									
	6.3	5.7	12.2	5.7	3.6	2.9	2.9	2.4	
	7.1	8.0	5.3	4.7	4.0	4.8	4.0	3.2	
	5.0	4.8	7.5	3.8	2.8	3.5	5.3	3.5	
	5.6	5.2	2.8	3.4	8.1	4.0	3.5	3.6	
	3.5	2.0	2.4	11.1	3.2	6.9	7.4	4.4	
	3.3	2.9	2.7	2.8	2.6	13.9	3.5	2.4	
	3.5	2.6	2.6	5.1	2.9	2.6	4.4	2.3	
	3.5	4.0	3.8	2.8	2.5	2.1	2.1	3.7	
A-M									
	2.4	3.1	3.3	2.7	3.2	2.5	2.6	2.0	
	3.4	3.2	3.3	3.3	4.4	3.1	2.3	4.9	
	2.7	2.3	5.1	7.1	4.1	3.1	3.3	2.6	
	2.9	2.2	2.6	3.0	2.0	1.7	2.3	2.4	
	2.5	4.4	4.0	2.7	2.2	7.8	1.7	1.5	
	6.0	5.8	2.6	4.2	3.0	2.6	2.6	2.7	
	3.2	3.5	7.5	6.2	3.8	3.7	3.7	10.0	
	4.9	2.5	5.5	3.1	3.7	3.5	2.4	3.1	
	2.5	3.6	2.8	4.3	2.8	2.9	2.2	3.2	
A-R									
	3.7	4.7	6.6	3.5	3.0	2.9	3.4	2.6	
	2.8	2.6	7.3	4.2	5.4	4.3	4.2	4.3	
	3.6	2.3	5.0	2.0	2.2	2.6	2.3	2.2	
	3.9	4.0	5.4	10.3	2.6	4.0	2.6	2.0	
	3.6	3.0	3.4	4.2	3.1	2.7	6.4	3.1	
	4.2	4.2	4.4	3.5	3.2	11.5	6.5	7.0	
	2.9	4.0	4.3	2.6	3.0	3.6	5.8	2.3	