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Differential Aversive Effects of Heroin and Morphine in the Conditioned Taste Aversion Paradigm

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A Thesis

In

The Department

of

Psychology

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

March 1984

ABSTRACT

Differential aversive effects of heroin and morphine in the conditioned taste aversion paradigm

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The efficacy of heroin to induce a conditioned taste aversion (CTA) as compared to morphine was examined under varying conditions in two strains of rats. In Experiment 1, 'new colony' (pathogen-free) Wistar rats were injected with either heroin (3 mg/kg, 6 mg/kg, or 9 mg/kg) or morphine (9 mg/kg, 15 mg/kg) after saccharin presentation every third day for a total of four conditioning trials. Neither drug induced a significant reduction of saccharin intake at any of the doses used. In Experiment 2, the heroin doses (3 mg/kg, 6 mg/kg, 9 mg/kg) were divided into three injections, spaced 20 minutes apart. This attempt to enhance the drug state did not induce a heroin CTA. In Experiment 3, heroin (5 mg/kg, 10 mg/kg, 15 mg/kg and 20 mg/kg) and equimolar doses of morphine (4.4 mg/kg, 8.8 mg/kg, 13.3 mg/kg and 17.7 mg/kg) were administered to 'old colony' Sprague Dawley rats every five days for a total of five conditioning trials. Heroin induced a CTA at doses of

10 mg/kg and 20 mg/kg, while morphine induced a CTA at 13.3 mg/kg and 17.7 mg/kg. Experiment 4 replicated experiment 3 using 'new colony' Wistar rats. Although heroin did not induce a significant CTA, a change in saccharin consumption over days was noted. Morphine was effective in inducing a CTA at all doses except 4.4 mg/kg. The results of this series of experiments suggest that the induction of heroin CTA appears to be a function of heroin's pharmacological properties as compared to morphine and the temporal- dose parameters used in the specific experimental design.

Acknowledgements

I would like to express my appreciation and gratitude to Dr. Ann Sutherland and to Dr. Zalman Amit for their valuable guidance, support and encouragement throughout the course of these studies.

I would also like to thank the members of my committee, Dr. Peter Shizgal and Dr. Edward Brussell for their supportive feedback.

I am grateful to Dr. Rick Blair for his participation in the supervision of the research, to Karen Spivak for her help in the conduct of the research and to Max Ng Cheong Ton, whose patient help enabled this thesis to be printed.

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For over a decade, the paradigm of drug induced conditioned taste aversion (CTA) has been used in investigating the reinforcing actions of various drugs, as well as facilitating an understanding of the learning process. The results of a majority of these studies have raised issues concerning the aversive effects of drugs that are believed to be positively reinforcing in both animals and humans. The investigation of the reinforcing actions of the various drugs that are abused by humans may lead to a better understanding of drug motivated behaviour.

A CTA is established through a conditioning paradigm in which the conditioned stimulus (CS), a novel flavoured solution, is followed by the unconditioned stimulus (UCS), either injection of certain drugs or other manipulations (see Riley & Baril, 1976). The CTA is measured in terms of reduction of food or fluid intake on subsequent presentation of the novel flavour. In the earliest studies on CTA, the UCSs have been a variety of manipulations such as injections of lithium chloride (LiCl), rotation, or x-irradiation (Braun & McIntosh, 1973; Garcia & Koelling, 1966). Some investigators proposed that CTA may be due to the formation of an association between the conditioned flavour and the illness induced by the manipulation (toxicosis) (Garcia & Koelling, 1966). This proposal was questioned following

findings that: (1) highly toxic drugs such as cyanide, strychnine, and warfarin were not capable of inducing CTA although these drugs did induce symptoms of toxicity such as inactivity, convulsions, diarrhea and paralysis (Nachman & Hartley, 1975); (2) psychoactive drugs (e.g., scopolamine, chlorpromazine) which do not induce the above symptoms or any observable "gastro-intestinal distress" effects, can also induce a CTA (Berger, 1972); (3) self-administered drugs, that is drugs that the animals seek for their supposed positive effects, such as amphetamine (Cappell & LeBlanc, 1971; D'Mello, Stolerman, Booth & Pilcher, 1977; Goudie & Thornton, 1977); morphine (Cappell, LeBlanc & Endrenyi, 1973; Jacquet, 1973); and ethanol (Cappell et al., 1973) are capable of inducing CTA.

While not all non self-administered drugs are capable of inducing CTA, all self-administered drugs investigated to date have induced some degree of CTA, with the notable exception of heroin (Switzman, Hunt & Amit, 1981). The inability of heroin to induce CTA in a single conditioning trial, is surprising when compared to morphine which readily induces CTA. Heroin is rapidly hydrolyzed to morphine in the brain (Goodman & Gilman, 1980; Way, Young & Kemp, 1965) and morphine, therefore, is postulated to be responsible for most of the pharmacological effects of heroin

(Way et al., 1965). In view of the unexpected finding of the inability of heroin to induce a CTA, this thesis will explore the possibility of inducing CTA with heroin under different parameters of the same experimental paradigm.

The characteristics of CTA induced by non self-administered drugs, as compared to self-administered drugs, will be discussed. Particular emphasis will be placed on the 'paradoxical' drugs: i.e., those self-administered drugs that seem to have positive and aversive properties simultaneously. CTAs induced by such drugs appear qualitatively different from CTAs induced by non self-administered drugs. Furthermore, the degree of CTAs induced by self-administered drugs differ among themselves according to the pharmacological properties of the drug and the temporal-dose parameters used.

CTA Induced By Non Self-Administered Drugs

Early studies of CTA induced by aversive treatments were prompted by findings suggesting that the avoidance of the CS, which had been associated with unpleasant interoceptive events might somehow differ from other forms of passive avoidance (Garcia & Koelling, 1966). CTA is readily induced by lithium chloride (LiCl), x-irradiation (Garcia & Koelling, 1966), or rotational stimulation (Braun & McIntosh, 1973) but not as readily induced when paired

with electric shock (Krane & Wagner, 1975; Lasiter & Braun, 1981). Conversely, audio-visual cues are readily made aversive when paired with electric shock but not when paired with toxicosis (Garcia & Koelling, 1966). The learned association of the gustatory cue to the interoceptive event is not necessarily contingent on the close temporal contiguity of the CS and the UCS. CTAs have been induced by CS-UCS intervals of up to 8 hours (Garcia & Koelling, 1966) and the strength of the resulting association is such that the CTA can be sustained for many days following the conditioning trial.

The most frequently used non self-administered illness-inducing drug in the literature is LiCl. LiCl has been demonstrated to induce strong CTAs after one conditioning trial (Grupp, Linseman & Appell, 1976; Nachman & Ashe, 1973) as well as over long CS-UCS intervals (Best & Gemberling, 1977; Gemberling, Domjan & Amsel, 1980; Martin & Timmins, 1980; Steinart, Infurna, Jardula & Spear, 1979). The CTA induced by LiCl can be enhanced by prolonging the drug duration through repeated injections (Domjan, 1980; Domjan, Foster & Gillan, 1979). Repeated conditioning trials will further strengthen a LiCl-induced CTA with the ensuing likelihood of total avoidance of the associated taste (Kulkosky, Sickel & Riley, 1980). A LiCl CTA is not blocked

by pre-exposure to the drug (Braveman, 1975; Domjan & Best, 1977), however, the LiCl-induced CTA can be attenuated to a degree directly related to the pre-exposure dose and inversely related to the conditioning dose (Cannon, Berman, Baker & Atkinson, 1975). This attenuation can be reversed by additional conditioning trials (Cannon et al., 1975; Dacany & Riley, 1982; Riley, Jacobs & Lolordo, 1976). Aversions to LiCl are reliable, varying little among subjects and these aversions are not easily blocked or disrupted by central manipulations (Kimble, Bremiller, Schroeder & Smotherman, 1979; Lorden & Margules, 1977; Lorden & Oltmans, 1978; Mason & Fibiger, 1979; Nonneman & Curtis, 1978; Roberts & Fibiger, 1975; Siegel, 1976; Sklar & Amit, 1977).

The illness-inducing nature of LiCl, with its resulting CTA, has supported the suggestion that the CTA is due to toxicosis. This inference however, cannot explain the inability of substances more poisonous than LiCl (e.g., cyanide, strychnine and warfarin) to induce CTA, suggesting that other factors may also underly CTA induced by emetic agents (Ionescu & Buresova, 1977; Nachman & Ashe, 1973; Nachman & Hartley, 1975). Nachman and Hartley (1975) suggested that the rate of onset of interoceptive cues and the duration of symptoms, as well as the physiological

systems mediating these drug's actions, may be relevant to a drug's potential to condition an aversion to the CS.

The 'toxicity' theory of learned aversions may partially explain the rapidly acquired CTAs induced by emetic drugs. However, findings that the antiemetic scopolamine and drugs such as chlorpromazine, lorazepam and amphetamine, which induce no observable signs of illness, can induce CTAs (Berger, 1972) led to further investigations of the nature of CTA.

CTA Induced By Non-Emetic Psychoactive Drugs

Within the category of psychoactive drugs fall classes of drugs with differing behavioural effects: depressants, anaesthetics, muscle relaxants, anti-convulsants, stimulants, hallucinogens, narcotic agonists and antagonists (Overton, 1982). CTA experiments examining these drugs have revealed differences both between and within drug classes in the nature of the CTAs induced.

Among the psychoactive drugs which have induced CTA are: opiates (Cappell et al., 1973; Farber, Gorman & Reid, 1976; Gorman, De Obaldia, Scott & Reid, 1978; Switzman, Hunt & Amit, 1981); naloxone, an opiate antagonist (LeBlanc & Cappell, 1975; Van der Kooy & Phillips, 1977); amphetamine (Cappell, LeBlanc & Herling, 1975; Carey, 1973; D'Mello, et

al., 1977; Goudie, Thornton & Wheeler, 1976); cocaine (Booth, Pilcher, D'Mello & Stolerman, 1977; Goudie, Dickins & Thornton, 1978); ethanol (Berman & Cannon, 1974; Cappell et al., 1973; Kulkosky et al., 1980); barbiturates (Vogel & Nathan, 1975); cannabinoids (Corcoran, 1973; Corcoran, Bolotow, Amit & McCaughran, 1974; Elsemore, 1972; Elsemore & Fletcher, 1972; Kay, 1975); fenfluramine (Booth et al., 1977; Goudie, Taylor & Atherton, 1975); nitrous oxide (Goudie & Dickins, 1978) and apomorphine (Ahlers & Best, 1971; Brackbill & Brookshire, 1971; Krane, Sinnamon & Thomas, 1976). Since these drugs are not toxic at the doses used to produce a CTA, it seems unlikely that either poisoning per se or gastro-intestinal distress is reponsible for CTAs induced by these drugs.

An important distinction among these psychoactive drugs is that some are readily self-administered by animals while others are not. For example, the self-administration liability of the cannabinoids (Amit, Corcoran, Charness, & Shizgal, 1973; Van Ree, Slangen and deWeid, 1978) and benzodiazepines (Amit & Cohen, 1974) appears to be low. It appears that not only does the self-administration liability of these drugs differ, but also that aversions produced by the non self-administered and the aversions produced by the self-administered drugs differ qualitatively. These

differences are exemplified by the effects of pre-exposure to these drugs on the attenuation or blocking of CTA.

Several investigators have studied the nature of the aversions through the pre-exposure paradigm. In the pre-exposure situation, rats receive experience with a drug one or more times prior to the usual taste aversion conditioning trials. The assumption of this procedure is that if two drugs possess similar properties, prior experience with one drug will interfere with the learning of the association between the novel flavour (CS) and the effects of the other drug (UCS). Corcoran (1973) examined the effect of tetrahydrocannabinol (Δ^9 THC) on three novel tastes, each taste paired with the drug at 10-day intervals. The resulting CTA to the third flavour was not appreciably weaker than the CTA to the first. These results suggest that not only does Δ^9 THC possess aversive properties, but that novelty of the drug experience does not seem to account for the aversiveness. Consistent with this idea, Kay (1975) reports an increase in strength of aversion over repeated trials and with increased doses of Δ^9 THC. In fact, if novelty of the drug experience underlies the CTA induced by THC, the reverse would be expected, i.e. a decrease in the strength of aversion over repeated trials.

In addition, tolerance does not seem to develop to the

aversive properties of Δ^9 THC. Eight pre-exposure trials to 10 mg/kg of Δ^9 THC did not attenuate the acquisition of a CTA (Elsemore, 1972). However, Switzman, Fishman and Amit (1981) report that prior exposure to THC did attenuate a CTA induced with this drug. It appears that neither novelty nor tolerance accounts for the aversion induced by Δ^9 THC. It is possible that the metabolism of the drug may be important to explain the aversive effects of cannabinoids on CTA. Pretreatment with SKF 525A (proadafan), a non-specific microsomal enzyme inhibitor believed to slow down drug metabolism, attenuates Δ^9 THC induced CTA (Corcoran, 1973). It may be that the metabolites of the cannabinoids, rather than the parent compounds, were responsible for the drug's abililty to induce a CTA. Goudie, Kelley, Taylor and Wheeler (1975), however, point out that SKF 525A, previously assumed not to affect behaviour itself, does have a sedative effect and may potentiate a drug's efffect on behaviour. While the precise mechanism involved in CTAs induced by cannabinoids remains unknown, infusion of the drug into the dorsal hippocampus produces an aversion comparable to intraperitoneal (IP) administration; this suggests that a central component may be involved in peripherally induced CTAs, particularly those induced by cannabis (Amit, Levitan, Brown & Rogan, 1977).

Benzodiazepines

Pre-exposure studies have demonstrated that the benzodiazepines differ among themselves. Chlordiazepoxide does not block the acquisition of a CTA induced by amphetamine or morphine (Cappell et al., 1975). Diazepam, however, does attenuate the stronger aversion normally induced by morphine (Switzman, Fishman & Amit, 1981). Interestingly, pre-exposure to morphine does not attenuate a diazepam-induced CTA (Brown, Amit, Smith & Rockman, 1979; Switzman, Fishman & Amit, 1981). Such unexpected cross-over effects are not consistent with the hypotheses which attribute the effects of one drug on the CTA induced by another drug to relative toxicity, relative magnitude of aversions, novelty of drug effects or impaired association, in acquisition of CTA (Brown, Amit, Smith & Rockman, 1979; Switzman, Fishman & Amit, 1981). These issues will be explored in a further section.

Switzman, Fishman and Amit (1981) suggest that the differential interference of doses of diazepam, morphine and THC, drugs that induce comparable degrees of aversion, may be due to the influence of the temporal properties of drugs. Morphine and THC have similar duration of action. Longer acting drugs may be more effectve in blocking CTA than shorter acting drugs. Morphine, however, is reliably self-

administered (Amit, Brown & Sklar, 1976; Amit, Corcoran, Amir & Urca, 1973) and THC rarely self-administered (Amit, Corcoran, Charness & Shizgal, 1973; Van Ree et al., 1978). Since the positive reinforcing properties of diazepam and THC differ from those of morphine, these drugs may also possess different or additional aversive properties not possessed by morphine. The evidence implies that aversions induced by the poorly self-administered benzodiazepines and cannabinoids differ qualitatively from those aversions conditioned with the readily self-administered drugs such as ethanol and morphine.

CTA Induced By Self-Administered Drugs

While not all non self-administered psychoactive drugs induce CTA (Ionescu & Buresova, 1977; Nachman & Hartley, 1975), most of the self-administered drugs have been effective in inducing some degree of CTA. Psychoactive drugs that have been self-administered by experimental animals include barbiturates (Deneau, Yanagita & Seevers, 1969), ethanol (Brown & Amit, 1977; Eckardt, 1975), amphetamine (Davis & Smith, 1973a; Yokel & Wise, 1976), cocaine (De Wit & Wise, 1977; Roberts & Koob, 1982), morphine (Amit, Brown & Sklar, 1976; Davis & Smith, 1973b; Glick & Cox, 1977; Stolerman & Kumar, 1970; Van Ree et al.,

1978) and heroin (Van Ree & de Wied, 1977; Van Ree et al., 1978). These drugs have been examined in the taste aversion paradigm in an attempt to elucidate their reinforcing actions.

Barbiturates

Vogel & Nathan (1975) demonstrate CTA with a variety of barbiturates (amobarbitol, hexobarbitol, phenobarbitol) using a wide range of doses. They found that the higher doses induced stronger aversions than lower doses. However, these aversions could not be predicted by observation of the behavioral effects (e.g., anaesthesia) of the drugs, nor could they be attributed to the drug's direct actions, since testing was done after these pharmacological actions had ceased. Vogel and Nathan (1976) found that prior exposure to amobarbitol attenuated the amobarbitol-induced CTA. Since they found that the attenuation was not accompanied by a corresponding reduction of induced sleep-time tolerance to the drug's effect cannot account for this attenuation; amobarbitol induces sleep and a reduction of sleeptime would be indicative of the development of tolerance to the drug. Instead, animals pretreated with the drug were found to sleep as long as drug-naive animals.

Ethanol

Ethanol induces an aversion in a single trial at higher doses (e.g., 1200 mg/kg) but not at lower doses (e.g.,300 or 600 mg/kg) (Cappell et al., 1973). Cannon et al., (1975) found that exposure to ethanol would attenuate CTA. The attenuation of the ethanol-induced CTA was described as a positive function of the pre-exposure dose and an inverse function of the conditioning dose (Cannon et al., 1975).

Kulkosky et al. (1980) report that the weak CTA induced by ethanol in a single trial can be strengthened by repeated conditioning trials to the point of total avoidance of the conditioned taste. In contrast, morphine does not suppress consumption completely even after repeated trials (Barber et al., 1976; Riley, Jacobs & LoLordo, 1978).

The mechanisms mediating an ethanol-induced CTA remain unclear. Administration of ethanol into the dorsal hippocampus does not induce an aversion as would the same dose if given intraperitoneally (IP) (Amit et al., 1977). Intracerebroventricular (ICV) infusion of acetaldehyde, the major metabolite of ethanol, does not induce CTA although IP injection does (Brown, Amit, Smith & Rockman, 1978). Brown et al. (1978) suggest that the aversiveness of acetaldehyde may be due to peripheral toxicosis even though the positive reinforcing effects appear to be central, since naive rats

will self-administer acetaldehyde ICV (Brown, Amit & Rockman, 1979). Although these studies suggest that the positively reinforcing and aversive effects of acetaldehyde are mediated by two separate mechanisms, manipulations of the central catecholamine system block both the reinforcing effects of ethanol and the acquistion of CTA. This seems to suggest that a common mechanism may link the peripheral and central effects of this drug. Sklar & Amit (1977) suggest central mediation of aversiveness by the same mechanisms which mediate positive reinforcement.

Amphetamines and Cocaine

Amphetamines and cocaine, classified as psychomotor stimulants with similar behavioural effects, differ in their potency to induce CTA. Amphetamine can induce a significant CTA in a single trial at moderate doses (Berger, 1972; Booth et al., 1977; Cappell & LeBlanc, 1971), while cocaine induces CTA in a single trial only at very high doses (Goudie et al., 1978). Amphetamine-induced CTA is enhanced by repeated conditioning trials (Stolerman & D'Mello, 1978), while cocaine remains a relatively weak aversive agent (Goudie et al., 1978). Switzman (1981) found no CTA with 20 mg/kg of cocaine paired with saccharin, while Foltin & Schuster (1982) report that 10 conditioning trials on alternate days resulted in a weak CTA. In contrast,

amphetamine has been shown to induce CTA at a dose of 3.2 mg/kg in a single trial and at 1 mg/ kg after a third trial (Booth et al., 1977) or over four trials when ingested orally at a range of concentrations (Sanger, Greenshaw, Thompson & Mercer, 1980). Amphetamine consistently induces a CTA more reliably than cocaine.

Morphine and Heroin

Although a number of investigators have reported morphine to be an effective UCS in conditioning aversions (Cappell et al., 1973; Farber et al., 1976; Jacquet, 1973; Parker, Failor & Weidman, 1973; Sklar, & Amit, 1977; Sinyor, Switzman & Amit, 1980; Switzman, Hunt & Amit, 1981; White, Sklar & Amit, 1977), morphine-induced aversions often take more than one trial to develop and are typically incomplete even after repeated conditioning trials. A CTA can be induced with as little as 3 mg/kg (Blair & Amit, 1981, Cappell & LeBlanc, 1973; Switzman, Fishman & Amit, 1981) or not be apparent after the initial trial at doses of 10-80 mg/kg (Riley et al., 1978). This variability indicates that morphine-induced CTAs are not necessarily dose-dependant (Farber et al., 1976). CTAs with morphine have been induced by administering the drug by subcutaneous implantation of pellets (Manning & Jackson, 1977) as well as IP (e.g., Jacquet, 1973; Parker et al., 1973; White et al., 1977).

Experiments using other narcotic drugs to induce CTAs are rare. Heroin examined in only one study to date, did not induce a CTA at any of a wide range of doses (Switzman, Hunt & Amit, 1981).

The Self-Administration/Taste-Aversion Paradox

The finding that a self-administered drug induces a CTA appears quite paradoxical: how could the same drug dosage be simultaneously aversive and positive reinforcing? Since different parameters are used in studying CTA and self-administration, it has been suggested that the aversiveness attributed to self-administered drugs may be an artifact of the CTA paradigm (Cappell et al., 1973). That this is not the case is clear from studies which show that the same injection of amphetamine or morphine can serve as a positive reinforcer and simultaneously induce a CTA (Switzman, Amit & White & Fishman, 1978; White et al., 1977; Wise, Yokel & De Wit, 1976).

Explanations of the aversive effects of self-administered drugs in the CTA paradigm remain highly controversial. Researchers attempt to explain the 'paradox' in terms of the novelty of the drug state, or tolerance to the aversive properties of the drug. The tolerance or habituation hypothesis postulates that the aversion and

positive reinforcement reflect different temporal components of a drug's effect (Cappell et al., 1975; Dacanay & Riley, 1982; Goudie, Taylor & Atherton, 1975; LeBlanc & Cappell, 1974; Riley et al., 1976). According to the novelty hypothesis, the aversive and positive reinforcing components of a drug effect are closely related (Amit & Baum, 1970; Gamzu, 1974; Rudy, Rosenberg & Sandell, 1977; Vogel & Nathan, 1976). The experimental literature pertaining to the tolerance hypothesis and the novelty hypothesis will be outlined below.

The Tolerance Hypothesis

The tolerance hypothesis suggests that initially, drugs are pharmacologically aversive to naive rats and can therefore induce an aversion. Subsequently, the aversive effect tolerates with drug experience, unmasking the positively reinforcing effect of the drugs (Cappell et al., 1975; Goudie, Taylor & Atherton, 1975). Goudie, Taylor & Atherton (1975) point out however, that tolerance to the aversive effects of drugs should be distinguished from tolerance acquired to a drug's more general pharmacological properties. For example, while attenuation of morphine-induced analgesia with drug experience is specific to the conditioning environment, attenuation of morphine CTA

through pre-exposure is not environmentally specific (Stewart & Eikelboom, 1978). Tolerance to the aversive quality of a drug does not seem to determine whether the animal will acquire a CTA and to what degree, since repeated conditioning trials will subsequently enhance the CTA attenuated by pre-exposure for both self-administered and non self-administered drugs (Berman & Cannon, 1974; Riley et al., 1976). Furthermore, pairing of the pre-exposure doses of a drug with one taste will prevent the pre-exposure from interfering with the CTA induced by the drug to a different flavour during conditioning (Stewart & Eikelboom, 1978).

'Crossover' effects demonstrate that prior exposure to one drug will attenuate the aversion normally formed to a second drug, whereas prior exposure to the second drug will have no effect on an animal's acquisition of an aversion to the first (Switzman, Fishman & Amit, 1981; Vogel & Nathan, 1976). This asymmetry has been demonstrated using amphetamine and morphine (Cappell et al., 1975), amphetamine and amobarbitol (Vogel & Nathan, 1976) and various other drugs. For example, amphetamine attenuates a morphine CTA; however, morphine does not attenuate an amphetamine CTA (Cappell et al., 1975). Pre-exposure to morphine does not block CTA induced by diazepam or Δ^9 THC, but does block a morphine CTA (Brown, Amit, Smith & Rockman, 1979; Cappell et

al., 1975; LeBlanc & Cappell, 1974; Switzman, Fishman & Amit, 1981). Conversely, THC attenuates both a morphine and a diazepam CTA (Brown, Amit, Smith & Rockman, 1979; Switzman, Fishman & Amit, 1981). The evidence indicates that less readily self-administered drugs will effectively attenuate aversions to more readily self-administered drugs, but not the reverse (Switzman, Fishman & Amit, 1981).

The Novelty Hypothesis

It has been suggested that CTA may reflect the novelty of the drug effect, implying that the drugged state is itself aversive to naive subjects (Amit & Baum, 1970; Vogel & Nathan, 1976). This novelty hypothesis would predict a lesser aversion from habituated subjects (Amit & Baum, 1970).

Evidence that pre-exposure to the conditioning drug can block or attenuate the CTA seems to support the novelty hypothesis. Drugs whose effects attenuate or block CTA through familiarity with the conditioning drug included: morphine (LeBlanc & Cappell, 1974; Switzman, Fishman & Amit, 1981); amphetamine (Goudie, Thornton & Wheeler, 1976; LeBlanc & Cappell, 1974); diazepam and chlordiazepoxide (Gamzu, 1974); amobarbitol (Vogel & Nathan, 1976); ethanol (Amit, Ziskind & Baum, 1973; Cannon et al., 1975) and fenfluramine (Goudie, Taylor & Atherton, 1975).

Some of the evidence against the novelty hypothesis can be drawn from 'crossover' studies, demonstrating that pre-exposure to one drug may block or attenuate the CTA induced by pairing another (still novel) drug with the taste. The hypothesis would predict a CTA with each novel drug regardless of the pre-exposure drug. Gamzu (1974) reports that pre-exposure to diazepam will prevent development of a CTA in response to chlordiazepoxide and Vogel and Nathan (1976) found that an amobarbitol CTA is attenuated by pre-exposure to amphetamine, although amphetamine pre-exposure did not attenuate an amobarbitol-induced CTA. Pre-treatment with diazepam has been found to block development of a CTA in response to morphine (Brown, Amit, Smith & Rockman, 1979) and chronic prior exposure to amphetamine to attenuate a morphine-induced CTA (Cappell et al., 1975). These studies do not necessarily contradict the novelty hypothesis. Although the conditioning drug in the pre-exposure studies is novel, the animal may not be discriminating between the pre-exposure drug and the conditioning drug. Both drugs may be operating through common mechanisms and although different, have similar effects. In the case of drugs operating via different mechanisms, the novelty hypothesis may account for the resulting CTAs.

Investigations of the mechanisms mediating CTA of self-

administered drugs lend further support to the novelty hypothesis. Sklar & Amit (1977) suggest that the aversive properties of self-administered drugs might be a function of the novelty of the drug's positive reinforcing properties in naive rats. This hypothesis would predict a common mechanism mediating both the aversive and the positively reinforcing effects of self-administered drugs. A variety of studies have implicated the central catecholamine (CA) systems in the mediation of CTA by self-administered drugs. Brain lesions in central CA regions can attenuate CTAs (Amit, Corcoran, Amir & Urca, 1973; Glick & Cox, 1977), as can pharmacological blockade of CA receptors by pimozide (Grupp, 1977; Sklar & Amit, 1977); depletion of CA levels in the brain by alpha-para-methyl-tyrosine (AMPT) (Brown, Amit, Sinyor, Rockman & Ogren, 1978; Goudie, Thornton & Wheatley, 1975) and destruction of CA pathways by infusions of 6-hydroxy-dopamine (6-OHDA) (Brown & Amit, 1977; Roberts & Fibiger, 1975). Furthermore, such manipulations of the CA system do not block the induction of CTAs by non self-administered emetic drugs such as LiCl (Lorden & Margules, 1977; Mason & Fibiger, 1979; Roberts & Fibiger, 1975, 1977; Sklar & Amit, 1977).

These studies indicate the both the positively reinforcing and the aversive effects of self-administered

drugs may be mediated by the same or related central mechanisms. Further research into the precise loci of pharmacological effects of drugs may serve to resolve the so-called paradoxical effects of self-administered drugs in the CTA paradigm. If the CTA induced by self-administered drugs is centrally mediated, closer examination of the rate of onset to peak brain activity and the duration of action of the drug in the central nervous system seems important in understanding the differences in efficacy of these drugs to induce CTA.

Temporal Considerations of Self-Administered Drugs

Various investigators have hypothesized that the difference in temporal properties of self-administered drugs (the rate of onset to peak brain activity and the duration of action in the CNS) may underlie the efficacy of these drugs to induce CTA (Goudie, 1978; Switzman, Hunt & Amit, 1981). Goudie (1978) suggested that the duration of action of a drug might play a role in determining its potency to induce CTA, a possibility which was also considered by Nachman & Hartley (1975) with regard to differences in CTA potency evidenced by toxic drugs. This hypothesis is supported by evidence that two readily self-administered psychomotor stimulants, amphetamine and cocaine, differ greatly in CTA potency. Amphetamine has a longer duration

of action than cocaine (Goudie, 1979) and is effective in CTA induction in doses as low as .32 mg/kg (D'Mello et al., 1977) while cocaine is a very weak aversive agent, inducing CTA only at a high dose of 36 mg/kg (D'Mello, Goldberg, Goldberg & Stolerman, 1979; Goudie et al., 1978). It seems that a drug with a longer duration of action is more aversive in the CTA paradigm than a drug with a shorter duration of action. Goudie & Dickins (1978) further support the duration of action theory by demonstrating that the aversive potency of nitrous oxide, which equilibrates in the brain within minutes, is directly related to the duration of exposure to the drug over a period of up to 4 hours. Similarly, a relationship has been postulated between the low aversive potency of ICV administration of acetaldehyde and its short duration of action (Brown, Amit, Smith & Rockman, 1978). It has also been shown that administration of a dose of LiCl divided into two spaced injections to prolong its duration of action will induce a stronger aversion than the same dose administered in a single injection (Domjan, 1980; Domjan et al., 1979).

The duration of action hypothesis seems to be contradicted by the minimal difference in potency to induce CTA between the cocaine-analogue WIN 35428 and the shorter-duration cocaine (D'Mello et al., 1979). This despite the

fact that the relative potencies of these two drugs were found to be consistent with their effects on operant responding (D'Mello et al., 1979).

In the case of the opiates, morphine and heroin, the lack of CTA potency demonstrated by heroin as compared to morphine has also been attributed to heroin's more rapid rate of onset (Switzman, Hunt & Amit, 1981). Heroin crosses the blood-brain barrier at a quicker rate than does morphine (Oldendorf, Hyman, Braun & Oldendorf, 1972); thus it is possible that heroin's quicker rate of onset accounts for its lack of potency in inducing CTA (Switzman, Hunt & Amit, 1981). This difference in rate of onset may also account for the weak CTA induced by cocaine as compared to amphetamine, since cocaine has a more rapid rate of onset than amphetamine (Nayak, Misra & Mule, 1976).

The importance of the rate of onset to CTA induction is further supported by Hunt, Amit, Switzman & Sinyor (1983). They demonstrate that ICV administration of morphine, which causes a more rapid rate of onset to peak brain activity than IP injection, does not induce a CTA, although IP administration of morphine does induce a CTA fairly reliably (Jacquet, 1973; White et al., 1977). Hunt et al. (1983) administered naloxone, (an opiate antagonist) IP in combination with the cerebral infusion of morphine and

succeeded in obtaining a CTA. These results may be attributed to the gradual binding of morphine to the opiate receptors as the naloxone occupying the receptor sites gradually dissipates. Since naloxone has a relatively short half-life (Goodman & Gilman, 1980), the morphine molecule would still be intact when the naloxone in the system has been eliminated. Thus, when experimentally slowing down the rate of onset of ICV morphine, a CTA may occur (Hunt et al., 1983). It seems that the potency of a drug to induce a CTA may be related to the rate of onset of the drug as well as the duration of action. Drugs with longer duration of action and perhaps slower rates of onset induce more reliable CTAs. It seems that although all self-administered drugs except heroin have been shown to induce some degree of CTA, the differences in their temporal properties may underlie the degree of the CTAs induced.

The previous discussion seems to indicate that the effects of non self-administered and self-administered drugs in the CTA paradigm differ, that the effects of self-administered drugs seem to be mediated by central mechanisms and that the potency of drugs to induce CTAs may be related to their temporal properties. Repeated conditioning trials, varied dosages and the intervals between trials apparently effect the degree of CTA induced by various drugs. More

specifically, CTAs induced by both non self-administered and self-administered drugs can be enhanced by division of the total drug dose into spaced injections, by repeated conditioning trials and by extension of the interval between conditioning trials.

Despite extensive literature on the phenomenon of CTA, relatively little work has been done using heroin as the UCS. Switzman, Hunt & Amit (1981) report that although heroin is a more potent analgesic than morphine, heroin failed to induce a CTA in a single-trial paradigm. The failure of heroin to induce a CTA, while morphine in comparable dosages does, is surprising since heroin, a diacetyl derivative of morphine, is believed to convert to morphine in the CNS (Way, Young & Kemp, 1965). Perhaps as in the case of cocaine, a weak aversive agent, heroin can induce a CTA when conditions are enhanced.

The present experiments are designed to investigate the parameters that may facilitate a heroin CTA as compared with morphine. Experiment 1 examines heroin and morphine over repeated trials with a two-day interval between conditioning trials. In experiment 2, doses of heroin are administered in repeated injections, spaced at twenty minute intervals. Experiments 3 and 4 examine a wide range of doses of heroin and morphine in two different strains of rats, over repeated

trials with 5 days between trials. A CTA is determined as a decrease in saccharin consumption relative to baseline intake. An additional saline-treated group is included. This criterion of a decrease from baseline intake, with the inclusion of a saline-treated group has been reported by other researchers as evidence of a CTA (Carey, 1973; Dacanay & Riley, 1982; Kulkosky et al., 1980; Riley et al., 1976; Riley et al., 1978; White et al., 1977). The addition of the saline-treated group serves two purposes: firstly, to establish a basis for a true difference due to drug treatment and, secondly, to establish the pattern of drinking a novel flavour by saline-treated control animals. Animals are known to be neophobic to novel flavours (Siegel, 1974). Over repeated exposures, this neophobic response is decreased and consumption of the novel flavour is usually increased (Rozin & Kalat, 1971).

EXPERIMENT 1

Almost all self-administered drugs investigated in the CTA paradigm to date have induced some degree of CTA. These self-administered drugs include ethanol (Cappell et al., 1973; Kulkosky et al., 1980), amphetamine (Cappell & LeBlanc, 1971; D'Mello et al., 1977), morphine (Jacquet, 1973; Riley et al., 1979; Switzman, Hunt & Amit, 1981; White et al., 1977) and cocaine (Foltin & Shuster, 1981; Goudie et al., 1978). Heroin is the one self-administered drug examined in the CTA paradigm that has not induced a CTA. Recently, Switzman, Hunt & Amit, (1981) have reported that morphine was more effective than comparable doses of heroin in inducing a CTA in a single trial. These results are surprising, since heroin is hydrolized to morphine in the brain and is therefore believed to depend on morphine for its pharmacological actions (Goodman & Gilman, 1980; Wasacz, 1981; Way et al., 1965). Furthermore, since heroin is a more potent analgesic than morphine (Goodman & Gilman, 1980; Switzman, Hunt & Amit, 1981) and is more easily discriminated by rats (Overton, 1982; Overton & Batta, 1977), it is expected that heroin would induce a CTA as morphine does. Heroin is believed to have greater positively reinforcing properties than other self-administered drugs (Van Ree et al., 1978). These positively

reinforcing effects may mask any aversive properties of heroin which would make detection of the aversiveness difficult for the rat. Therefore, more than one exposure to heroin may be necessary for the rat to develop a CTA to the novel flavour. The number of flavour-drug presentations has been reported to influence the strength of CTAs induced by various drugs. For example, both ethanol- and morphine-induced CTAs are reported to increase over repeated saccharin-drug pairings (Kulkosky et al., 1980; Riley et al., 1978). The present experiment examines the effect of repeated conditioning trials on the efficacy of heroin as compared to morphine to induce a CTA.

Method

Subjects. Subjects were 42 male Wistar rats ('new colony' 'pathogen-free') weighing 275-300 gms at the beginning of the experiment. Animals were housed individually in stainless steel cages in a temperature-regulated room (21 C) with a 12-hour day-night cycle (light on from 0800 hr. to 2000 hr.). Food (Purina Lab Chow) and water were made available ad lib. The animals were handled for 4 days before the beginning of the experiment.

Drugs and injections. Heroin (diacetyl morphine hydrochloride) (Macfarlan Smith Ltd.) and morphine hydrochloride (Merck, Sharpe and Dohme Canada Ltd.) were

dissolved in injectable physiological saline solution (Abbot Laboratories). All injections were administered intraperitonneally (IP) in a volume of 3 ml/kg. Treatment groups were as follows: saline, (n=7); heroin, 3 mg/kg H, (n=9), 6 mg/kg H (n=10), 9 mg/kg H (n=6), or morphine, 9 mg/kg M (n=5), 15 mg/kg M (n=5).

Procedure. Following 6 days of adaptation to laboratory conditions, animals were placed on a 23.5 hr fluid deprivation schedule in their home cage. For the following 6 days, tap water was available to the rats for a 30-minute period at 0900 hrs. All fluids (i.e., water or saccharin) were presented in stoppered plastic test tubes fitted with stainless steel ballbearing spouts inserted through the wire mesh in front of the cage.

On days 7, 10, 13 and 16 at 0900 hrs., a 0.1% (w/v) saccharin solution was substituted for water. Within 2 minutes following the 30-minute saccharin presentation, animals received IP injections of their respective drug dosages. Following the fourth and final pairing day and two additional water days, saccharin was once more presented for the 30-minute period without a subsequent drug injection. All saccharin consumption was measured and recorded in mls.

Results

Results of this experiment are presented in Figure 1.

The means with the standard errors of the means are presented in Table 1 (see Appendix A). A one-way analysis of variance on absolute intake of saccharin yielded no significant difference between groups on day 1 (baseline) ($F(5,36) = .4809$, $p > .25$).

A two-way analysis of variance on saccharin consumption between groups over the five test days, revealed no significant difference between groups ($F(5,36) = 2.43023$, $p > .05$) and no significant effect of days ($F(4,144) = 1.26997$, $p > .25$). The drug x day interaction, however, was highly significant ($F(20,144) = 2.22617$, $p < .005$). Post hoc analysis (simple main effects) exploring this interaction on each of the 4 test days yielded a significant difference in saccharin intake between groups on day 4 ($F(5,180) = 3.55$, $p < .01$), and day 5 ($F(5.180) = 4.69$, $p < .01$). Post hoc Tukey tests revealed that rats treated with 6 mg/kg H and 9 mg/kg H drank significantly less saccharin than saline-treated rats on day 4 ($p < .04$). Only the 6 mg/kg H group remained significantly different from saline-treated animals on day 5 ($p < .01$). Both 9 mg/kg M and 15 mg/kg M groups drank significantly less saccharin than the saline group on day 5 ($p < .01$).

It is important to note that although these groups drank significantly less saccharin than the saline group,

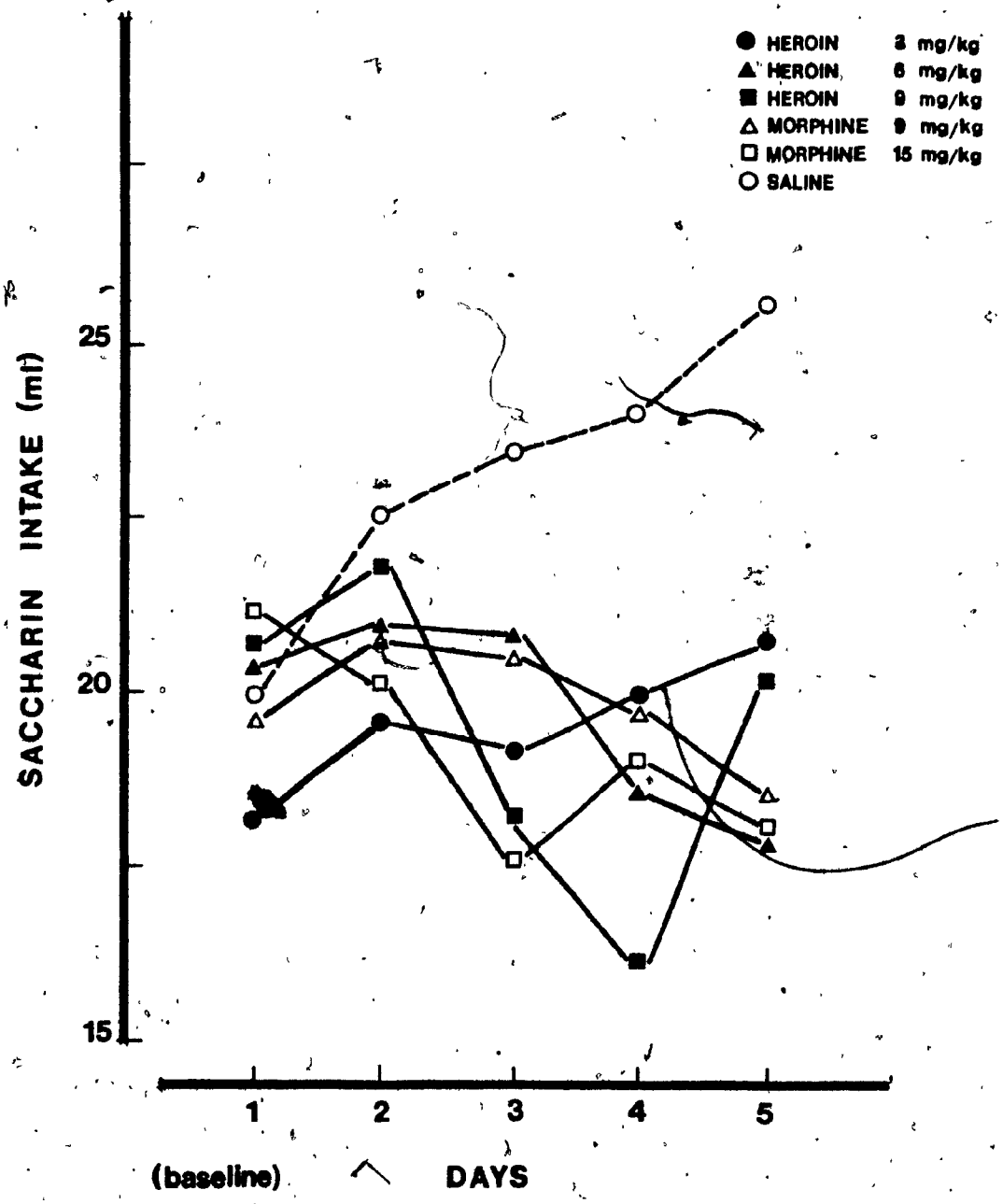

Figure 1. Means of saccharin intake of groups receiving injections of saline, heroin or morphine over repeated trials (two water-days between trials).

none of the groups decreased their saccharin intake as compared to their own baseline consumption (Tukey, $p > .05$). Therefore, it appears that the significant drug x day interaction is a function of the proportional difference between a drug group and the saline group on any particular day. A CTA, defined as a significant decrease in consumption from baselin intake was not induced by either heroin or morphine.

Discussion

In the present experiment, neither morphine nor heroin induced a CTA. The finding that morphine in this study did not induce a CTA is surprising. Several studies have reported that morphine is an effective CTA inducing agent (Blair & Amit, 1981; Cappell & Leblanc, 1973; Switzman, Hunt & Amit, 1981; White et al., 1977). Furthermore, researchers have demonstrated that repeated conditioning trials increase morphine's reliability to induce CTA (Riley et al., 1978) and further strengthen the CTA of drugs such as LiCl and ethanol (Kulkosky et al., 1980). Different factors such as strain of rats and parameters used, may account for the inefficacy of morphine to induce a CTA in this experiment. These factors will be explored further in Experiments 3 and 4.

It remains unclear as to why heroin does not induce a

CTA over repeated conditioning trials. Increasing the duration of the drug effect by dividing the total drug dose into spaced injections has been demonstrated to enhance the CTA induced by LiCl, a reliable CTA-inducing agent (Domjan et al., 1979) as well as enhancing the CTA of a weak aversive agent such as cocaine (Switzman, 1981). The next experiment was designed to investigate the possibilty of inducing a heroin CTA with repeated injections over repeated conditioning trials.

EXPERIMENT 2

In Experiment 1, administration of heroin over repeated trials did not result in a significant reduction of saccharin consumption. Heroin as yet, has not been effective as a CTA inducing agent. Perhaps the parameters under which heroin can condition an aversion remain to be established.

Distribution of the drug dose over repeated injections has been reported to enhance the weak CTA induced by cocaine (Switzman, 1981) and to strengthen the reliable CTA induced by LiCl (Domjan et al., 1979). Based on these findings, the present experiment examines the efficacy of heroin to induce a CTA when the total dose of drug is administered in repeated injections.

Method

Subjects. Subjects were 38 male Wistar ('new colony') rats weighing 275-300 gms at the beginning of the experiment. Animals were housed as described previously in experiment 1. Food (Purina Lab Chow) and water were made available ad lib. The animals were handled for at least 4 days before the beginning of the experiment.

Drugs and injections. Heroin (diacetyl morphine hydrochloride) (MacFarlan Smith Ltd.) was dissolved in

injectable physiological saline solution (Abbot Laboratories). All injections were administered intraperitoneally (IP) in a volume of 1 ml/kg. Treatment groups were as follows: saline (n=9); heroin, 3 mg/kg H (n=10), 6 mg/kg H (n=10) and 9 mg/kg H (n=9).

Procedure. The procedure was similar to that of Experiment 1. Animals received 4 saccharin-drug pairings at three day intervals, with water presented on the intervening days. In contrast to experiment 1, only heroin was administered, and the total dose of drug was divided into three injections administered at 20-minute intervals.

Results

A one-way analysis of variance on day 1 (baseline) intake of saccharin revealed a significant difference between groups ($F(3,34) = 4.16255$, $p < .05$). The data for the 5 days were therefore analyzed in a two-way analysis of co-variance. Analysis of covariance makes an adjustment of the means so that the data can be analysed taking into account how the groups differed on baseline intake before experimental manipulation. The mean scores of the first covariate (baseline scores) and the adjusted means of each test day are represented in Figure 2 (see Appendix A). The original and the adjusted means of each group on each day and the standard errors of the means are presented in Table

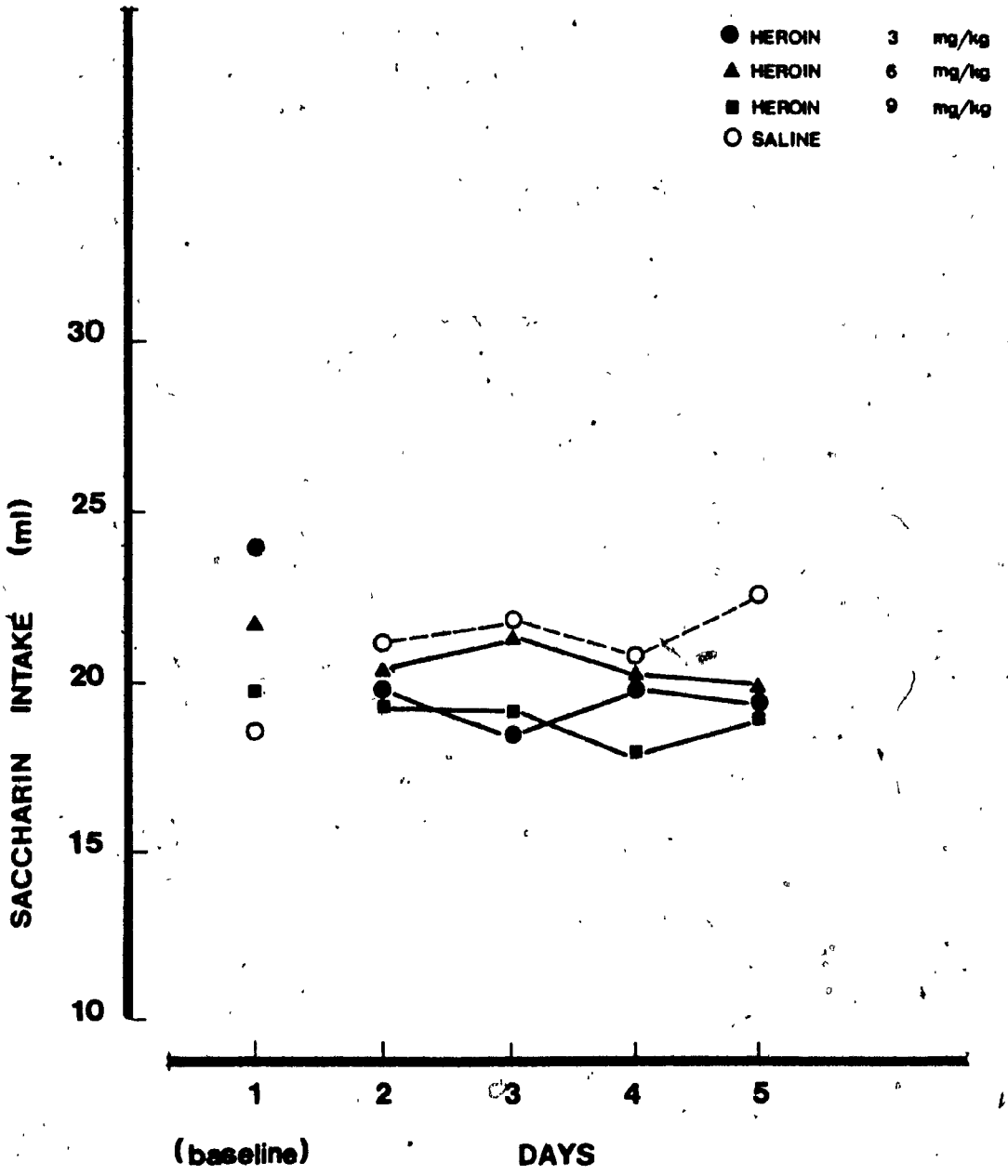

Figure 2. Means of saccharin intake of groups receiving saline and total doses of heroin divided into 3 spaced injections. (Baseline means and adjusted means according to analysis of covariance).

2. The adjusted means show what part of the variation due to baseline differences is removed. The analysis revealed no main effect of drugs ($F(3,33) = .96$, $p > .05$), no significant effect of days ($F(3,102) = .46$, $p > .05$) and no significant drug x day interaction ($F(9,102) = .52$, $p > .05$). Repeated injections of heroin did not decrease saccharin consumption.

Discussion

In the present experiment, administering the drug dose in repeated injections did not induce a CTA. It is unclear why heroin under enhanced conditions does not induce a CTA under conditions that enhance CTAs induced by other reliably self-administered drugs such as cocaine. Several factors may account for the results of this experiment. Perhaps, in the case of heroin, the parameters set out in this experiment are not effective for eliciting the aversive effects, if they exist, of heroin.

A second consideration is the strain of rats used. A problem recently encountered in research with laboratory rats in the Montreal area, is the differential responding to experimental manipulations of the 'new colony' (pathogen-free) rats and old colony rats. The 'pathogen-free' rats used in this study and in Experiment 1 were prone to sickness and appeared to be more 'finicky' and

hyperexcitable than the 'old colony' rats previously used in the laboratory. One of the reasons for this difference may be that the 'old colony' rats receive more handling at the breeding farms as a result of the more frequent changes of bedding and water bottles, while 'pathogen-free' rats are administered water by an automatic water system. Perhaps these 'new colony' rats are in an agitated state that interferes with the ability to discriminate the aversive properties of heroin. Ng Cheong Ton (1982) also reported differential responses between 'old colony' and 'new colony' animals to chronic treatment with amphetamine and naltrexone in the open field. 'New colony' rats were more sensitive to interference even under white noise conditions. It seems possible then, that the 'new colony' rats used in this study may also be less sensitive than other breeds of rats to the effects of heroin in the CTA paradigm, and that 'old colony' rats may be more responsive to the aversive stimulus properties of heroin.

EXPERIMENT 3

Researchers have reported varied degrees of CTA depending upon the parameters used. Repeated conditioning trials are reported to enhance CTAs induced by morphine (Riley et al., 1978), ethanol (Kulkolsky et al., 1980) and LiCl (Kulkosky et al., 1980). In addition, the length of the interval between conditioning trials seems to be an important parameter (Domjan, 1980; Garcia & Koelling, 1966). Repeated conditioning trials with a two day interval did not result in a heroin CTA in Experiments 1 and 2. Switzman, Hunt & Amit (1981) report a failure to induce a heroin CTA in a one-trial learning paradigm with 5 days between conditioning and test days. Perhaps an extension of the paradigm used by Switzman, Hunt & Amit (1981) to include repeated conditioning trials with five intervening days would result in a heroin CTA.

It is also possible, as discussed in experiment 2, that the agitated behaviour of the 'new colony' (pathogen-free) rats may be interfering with the ability of these rats to discriminate any aversive stimuli due to the association of the flavour and the drug. If this is the case, the more stable 'old colony' animals may more easily discriminate the stimulus properties of heroin.

The present experiment is designed to examine

heroin and morphine as aversive agents in 'old colony' rats, over repeated conditioning trials with 5 day intervals between trials.

Method

Subjects. Subjects were 72 male Sprague Dawley ('old colony') rats weighing 275-325 gms at the beginning of the experiment. Animals were housed and handled as described in Experiments 1 & 2, in temperature regulated rooms. Food (Purina Lab Chow) and water were made available ad lib.

Drugs and injections. Heroin (diacetyl morphine hydrochloride) (MacFarlan Smith Ltd.) and morphine hydrochloride (Merck, Sharpe and Dohme, Canada Ltd.) were dissolved in injectable saline solution (Abbot Laboratories). All injections were administered intraperitoneally (IP) in a volume of 1 ml/kg. Treatment groups were as follows: saline (n=8); heroin: 5 mg/kg H (n=8), 10 mg/kg H (n=8), 15 mg/kg H (n=7) and 20 mg/kg H (n=9); and morphine: 4.4 mg/kg M (n=8), 8.8 mg/kg M (n=8); 13.3 mg/kg M (n=8), 17.7 mg/kg M (n=8). It should be noted that the doses of morphine chosen were equimolar to the heroin doses used in this experiment.

Procedure. Following one week of adaptation to laboratory conditions, animals were placed on a 23.5 hour fluid deprivation schedule. During the following 6 days,

tap water was available to the rats for a 30-minute period. All fluids (i.e. water or saccharin) were presented in stoppered plastic test tubes fitted with stainless steel ballbearing spouts inserted through the wire mesh in front of the cage as in experiments 1 and 2.

On Day 7, a 0.1% (w/v) saccharin solution was substituted for the water. Within 2 minutes following the 30-minute saccharin presentation, animals received IP injections of their respective doses. This procedure was repeated every sixth day for a total of 5 saccharin-injection pairings. Water was presented on the 5 intervening days for the 30-minute period. Following the fifth and final pairing, and after an additional 5 water days, saccharin was once more presented without a subsequent drug injection.

All saccharin consumption was measured and recorded in mls.

Results

Results of this experiment are presented in Figures 3 and 4. The data from the heroin-treated groups (Fig. 3) and the morphine-treated groups (Fig. 4) are presented separately for purposes of clarity. The mean saccharin consumption with the standard errors of the means for each group on baseline day and five test days is presented in

Table 3 (see Appendix A).

A one-way analysis of variance on baseline scores reveals no significant difference on day 1 (baseline) among any of the groups ($F(8,63) = .86895$, $p > .05$).

A two-way analysis of variance yielded a highly significant main effect of drug ($F(8,63) = 6.0925$, $p < .0001$), a significant effect of days ($F(5,315) = 26.4869$, $p < .0001$) and a significant drug x days interaction ($F(40,315) = 2.4015$, $p < .0001$). Post hoc (simple main effects) tests yielded significant differences between groups on day 3 ($F(8,378) = 6.0$, $p < .001$), on day 4 ($F(8,378) = 5.54$; $p < .001$), on day 5 ($F(8,378) = 5.73$, $p < .001$) and on day 6 ($F(8,378) = 8.40$, $p < .001$). There was no significant difference in saccharin intake on day 2, after the first conditioning trial. Further exploration of the significant drug x day interaction with post hoc Tukey tests revealed that all the heroin- and morphine-treated groups drank significantly less saccharin than the saline-treated group on days 3, 4, 5 and 6, with the exception of 5 mg/kg H, 15 mg/kg H, 4.4 mg/kg M and 8.8 mg/kg M on day 4 and 4.4 mg/kg M on day 5.

In exploring the effect of repeated conditioning trials on saccharin consumption, post hoc Tukey tests revealed that a significant CTA was established with the administration of

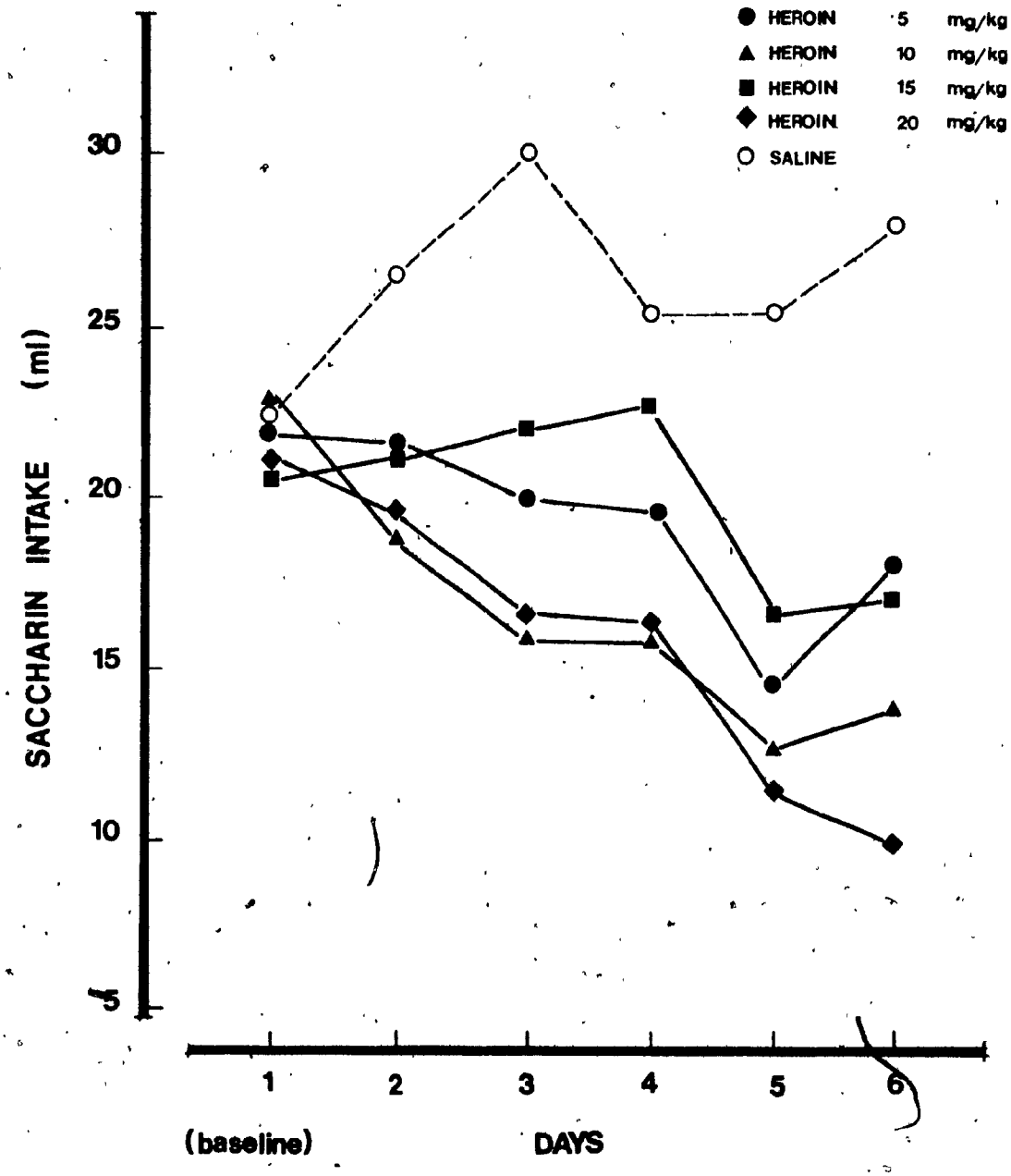

Figure 3. Means of saccharin intake of groups receiving injections of saline or heroin over repeated trials (five water-days between trials).

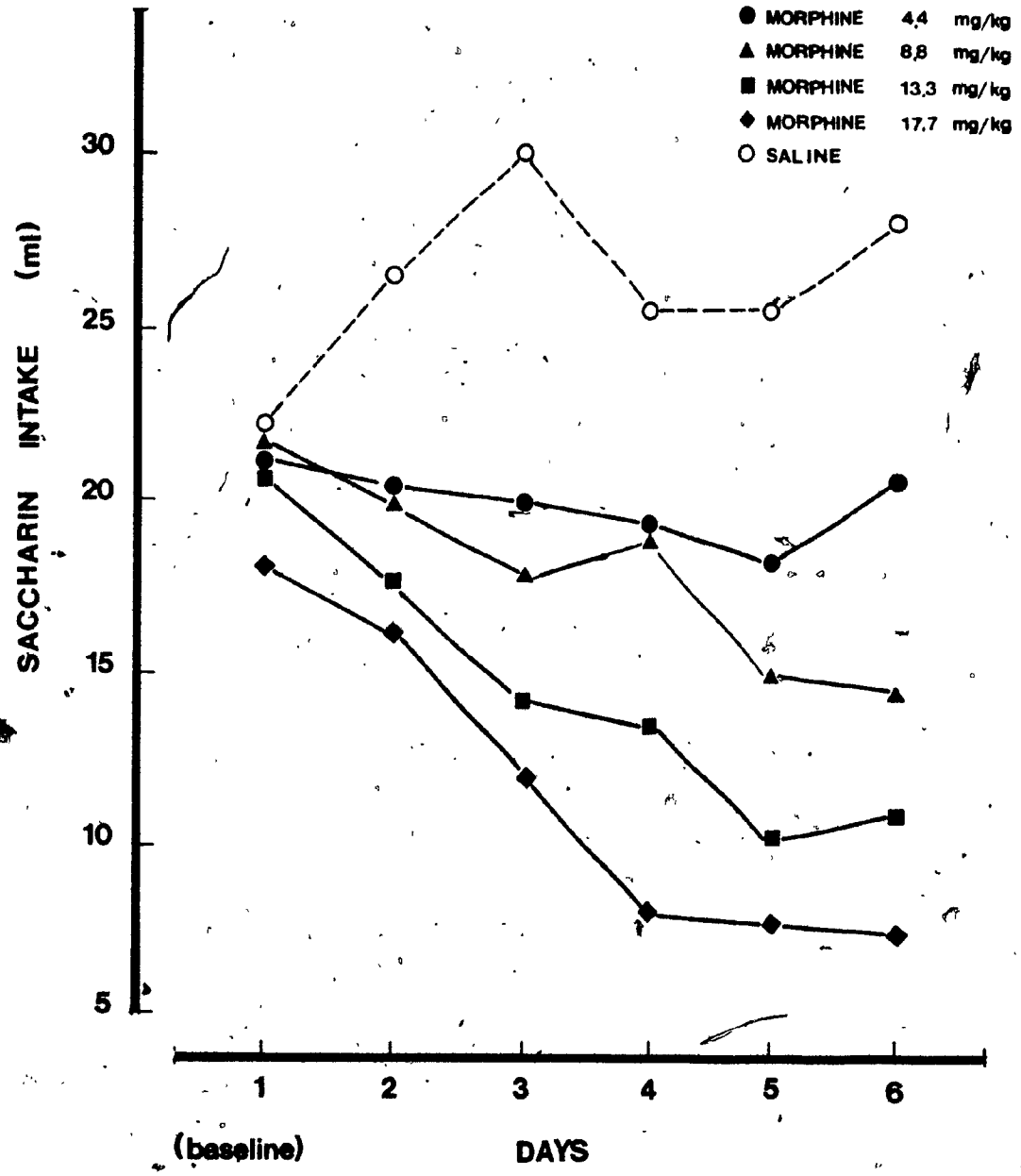

Figure 4. Means of saccharin intake of groups receiving injections of saline or morphine over repeated trials (five water-days between trials).

doses of 10 mg/kg H and 20 mg/kg H. These groups significantly reduced their saccharin consumption on day 5 and day 6 when relative to baseline intake ($p<.05$). Of the morphine-treated animals, the 13.3 mg/kg M drank significantly less on day 4, day 5, and day 6 than on day 1 (baseline) ($p<.05$). The 17.7 mg/kg M group also significantly decreased consumption from baseline on day 4, day 5 and day 6 ($p<.05$). The effect of doses of 13.3 mg/kg M and 17.7 mg/kg M was consistent. Saccharin intake of these groups decreased progressively over days (Figure 4).

A comparison of equimolar doses of heroin and morphine revealed the following. The 13.3 mg/kg M group drank significantly less saccharin than the 15 mg/kg H group on day 3 and day 4 ($p<.05$), and the 17.7 mg/kg M group drank significantly less on day 4 than the 20 mg/kg H. The 17.7 M group also drank significantly less than all other groups on this day. Since none of the groups differed on baseline measures, this would indicate that the morphine-treated animals showed a greater aversion to saccharin than the heroin-treated animals. Furthermore, the morphine groups demonstrate a more rapidly acquired CTA than heroin-treated groups. A CTA induced by morphine was revealed on day 4, while a heroin induced CTA was acquired on day 5.

Discussion

The results of the present experiment indicate that under certain conditions, heroin does induce a CTA to a novel flavour. Morphine in equimolar doses however, was a more effective CTA inducing agent. A CTA was induced by morphine after three conditioning trials, while heroin induced a CTA after four trials. Furthermore, of the groups that did demonstrate a CTA to saccharin, morphine-treated rats drank significantly less saccharin than rats injected with equimolar doses of heroin. Morphine induced an aversion progressively over days in a dose response manner (Figure 4). Increased doses of morphine induced decreased intake over days. This dose response relationship was not evident in the heroin-treated groups. 10 mg/kg H and 20 mg/kg H induced reliable CTAs, while 15 mg/kg H was ineffective.

It is not known why the effects of these doses of heroin differ. It is also unclear why heroin is a more potent drug than morphine in other behavioural measures such as analgesia (Switzman, Hunt & Amit, 1981) and less potent as a CTA-inducing agent. Since the aversive properties of the drug are inferred behaviourally through the reduction of fluid intake subsequent to the conditioning trials, heroin may be a less aversive agent to the animals than morphine.

Nevertheless, the results of the present experiment provide the first indication that heroin can induce a CTA. Whether the CTA induced by heroin in this study is a function of the strain of rats used or the parameters used in this experiment remains to be explored.

EXPERIMENT 4

In Experiment 3, reliable CTAs were induced with both heroin and morphine. Morphine has been demonstrated to induce CTAs in numerous reports (Riley et al., 1978; Switzman, Hunt & Amit, 1981; White, Sklar & Amit, 1977). Results of Experiment 3, however, present the first evidence that heroin can induce CTA. Conditions in Experiment 3 differed from those in the previous research (i.e., Switzman, Hunt & Amit, 1981; Experiment 1 and Experiment 2 of present research). 'Old colony' animals were used in Experiment 3 as well as differing parameters. Five days intervened between repeated conditioning trials. The present experiment examines which of the above factors can account for the heroin-induced CTA, by replicating Experiment 3 , using 'new colony' animals.

Methods

Subjects. Subjects were 63 male Wistar rats ('new colony, pathogen-free'), weighing 275-300 gms at the start of the experiment. Animals were housed as described in experiment 1 in temperature regulated rooms. The animals were handled for at least 4 days before the beginning of the experiment.

Drugs and injections. Heroin (diacetyl morphine hydrochloride) (Macfarlan and Smith Ltd.) and morphine

(Merck, Sharpe and Dohme Canada Ltd.) were dissolved in injectable physiological saline solution (Abbot Laboratories). All injections were administered IP in a volume of 1 ml/kg. Treatment groups were as follows: saline, (n=7); heroin: 5 mg/kg H (n=7), 10 mg/kg H (n=7), 15 mg/kg H (n=7) and 20 mg/kg H (n=7) and morphine: 4.4 mg/kg M (n=7), 8.8 mg/kg M (n=7), 13.3 mg/kg M (n=7) and 17.7 mg/kg M (n=7). As in experiment 3, doses of morphine were equimolar to the heroin doses used.

Procedure. The procedure used was identical to Experiment 3. Animals received a total of five saccharin-drug pairings. All saccharin consumption was measured and recorded in mls.

Results

The results of this experiment are presented in Figure 5 and Figure 6. As in Experiment 3, the data of the heroin groups and the morphine-treated groups are presented separately. The mean saccharin consumption with the standard error of the means are presented in Table 4 (see Appendix A).

A one way analysis of variance revealed no significant difference in saccharin intake on day 1 (baseline) between groups ($F(8,54) = .63059$, $p > .05$).

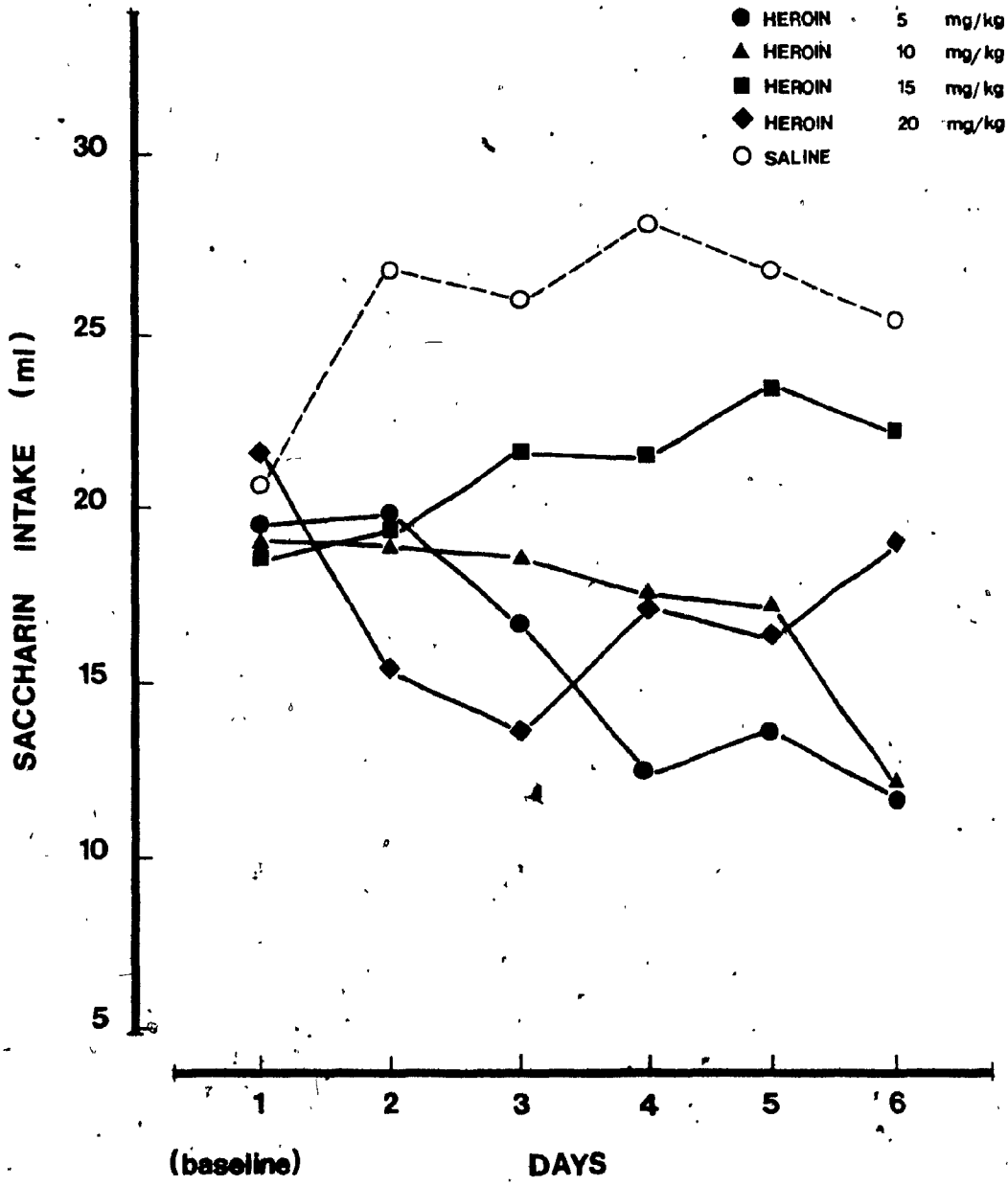

Figure 5. Means of saccharin intake of groups receiving injections of saline or heroin over repeated trials (five water-days between trials).

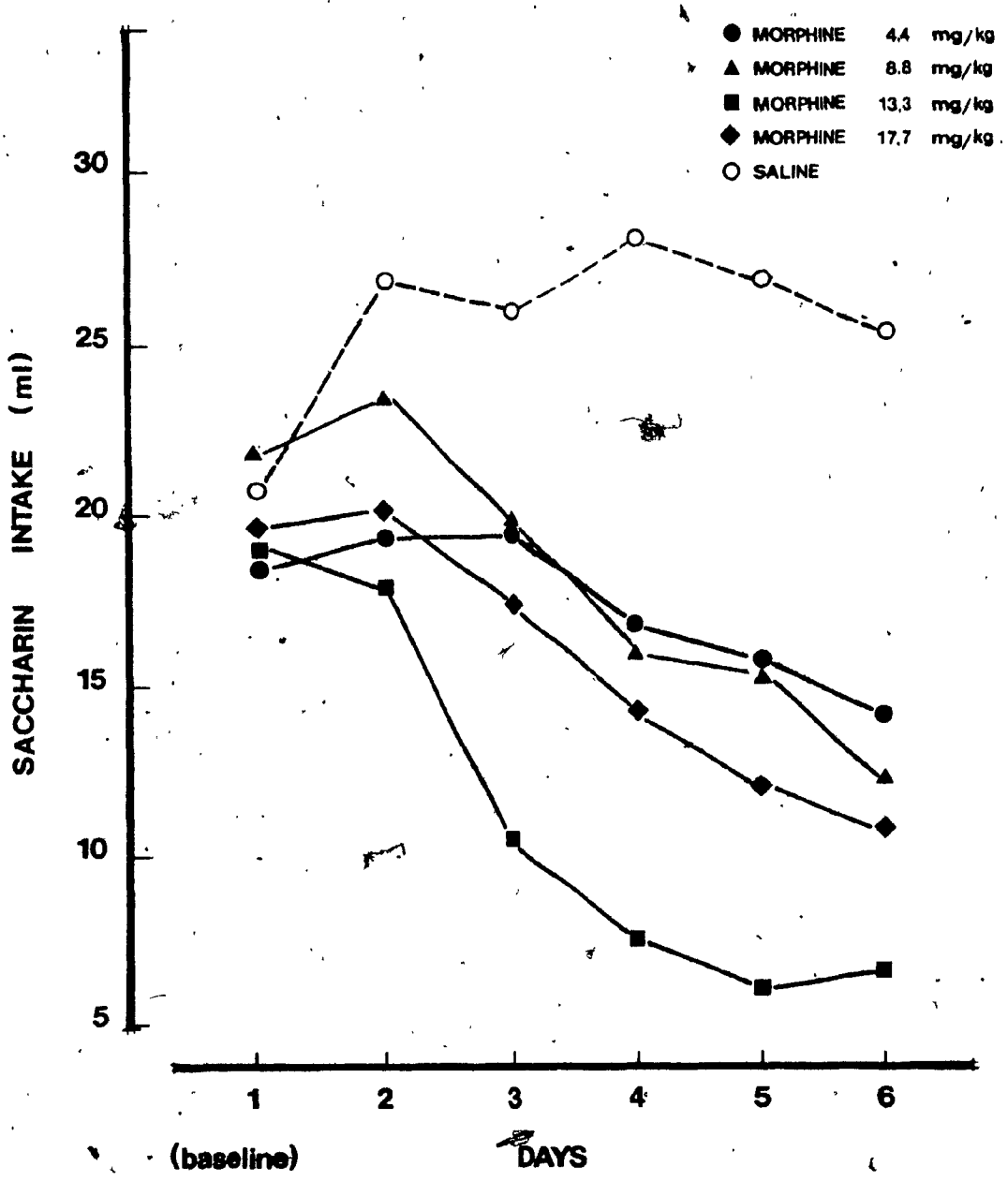

Figure 6. Means of saccharin intake of groups receiving injections of saline or morphine over repeated trials (five water-days between trials).

A two way analysis of variance on baseline and 5 test days yielded a highly significant main effect of drugs ($F(8,54) = 7.89202$, $p < .0001$); a significant effect of days ($F(5,270) = 12.4489$, $p < .0001$), and a highly significant drug x day interaction ($F(40,270) = 2.73214$, $p < .0001$). Groups differed significantly on all test days (post hoc simple main effects).

Further exploration of the significant drug x day interaction with post hoc Tukey tests revealed that all groups drank significantly less saccharin than the saline group on day 4, day 5, and day 6 ($p < .05$), with the exception of the 20 mg/kg H group on day 6 ($p > .05$) and 15 mg/kg H ($p > .05$) on all days. The 15 mg/kg H did not differ from the saline-treated control group at any point. The 20 mg/kg H, however, also differed significantly from saline on day 2 ($p < .01$) and day 3 ($p < .01$). Since groups did not differ on baseline measures, it appears that the dose of 20 mg/kg H had some effect on saccharin intake after one conditioning trial. As seen in Figure 5, this effect attenuated on day 4 and on subsequent test days. There were no significant differences among the drug groups, with the exception of the 13.3 mg/kg M group. This group drank significantly less saccharin than the 4.4 mg/kg M, and 8.8 mg/kg M groups on day 3, and than all the groups except for the 17.7 mg/kg M

and 5 mg/kg H on day 4 and day 5; and less than the 20 mg/kg H group on day 6. It is apparent that this dose of morphine is most effective in the reduction of saccharin intake.

In exploring the effect of repeated conditioning trials on saccharin consumption, post hoc Tukey tests revealed tha CTA was established with the morphine-treated animals at doses of 8.8 mg/kg M, 13.3 mg/kg M and 17.7 mg/kg M. The 8.8 mg/kg M and 17.7 mg/kg M showed a significant decrease on day 6 as compared with baseline measures ($p < .05$). The 13.3 mg/kg group, however, significantly reduced consumption on day 3 ($p < .05$) and further decreased intake on day 4, day 5, and day 6 ($p < .01$) relative to their baseline measure.

None of the heroin-treated animals demonstrated a significant CTA. The 20 mg/kg H group, however, approached a significant difference from baseline on day 3 ($p = .05$). Furthermore, as seen in Figure 5, the 5 mg/kg H group also tend to decrease intake over days. Although the reduction of saccharin intake of both the 20 mg/kg H and 5 mg/kg H groups were not statistically significant, the tendency for heroin to induce a decrease in saccharin consumption seems evident (Fig. 5). The fact that there was a large difference in consumption in these animals as compared with the consumption of the saline-treated animals, indicates that heroin had some effect although not significant on

saccharin intake.

Discussion

Contrary to the results of Experiment 3, heroin-treated animals did not demonstrate a significant CTA in this experiment, while morphine-treated animals did. The 5 mg/kg H, 10 mg/kg H and 20 mg/kg H treated animals did, however, differ significantly from saline-treated controls. Although the tendency to reduce consumption in the above groups is evident (Figure 5), morphine remains a more reliable CTA-inducing agent. The optimal dose of morphine in this experiment seems to be 13.3 mg/kg M.

Morphine induced a CTA in this experiment as well as in Experiment 3 and 5 mg/kg H and 20 mg/kg H groups demonstrated a tendency to decrease saccharin consumption, it seems therefore, that the strain of rats used are not a relevant factor influencing the production of CTA with morphine and heroin in this study. The results of this experiment and that of Experiment 3 seem to indicate that the parameters of repeated conditioning trials separated by 5 days were more conducive to inducing a CTA with morphine and heroin than were trials separated by two days as in Experiment 1. Neither morphine nor heroin induced a CTA in Experiment 1 in "new colony" rats.

The results of the present experiment seem to indicate

that CTAs induced by morphine and heroin are influenced by the specific parameters used.

General Discussion

The present research was designed to explore the efficacy of heroin to induce a CTA as compared to morphine. Several factors that have been reported (e.g. Riley et al., 1978; Domjan, 1980) to influence the reliablity of various drugs to induce CTA were examined. These include the number of conditioning trials, the schedule of drug administration, the intertrial interval, and the strain of rats used.

The results of the present experiments provide the first evidence that heroin can induce a CTA, although less reliably than comparable doses of morphine. The question of why heroin and morphine differ in the CTA paradigm remains unanswered. However, the results of the present studies suggest that heroin and morphine-induced CTAs are influenced by the pharmacological properties of the drugs and the temporal-dose parameters used in the specific experiment.

In Experiment 1, 9 mg/kg M, 15 mg/kg M, and 3 mg/kg H, 6 mg/kg H, and 9 mg/kg H did not induce CTAs when administered over repeated conditioning trials with two day intervals between trials. Others have reported that repeated conditioning trials have facilitated CTA induction with self-administered drugs such as morphine (Riley et al., 1978) and ethanol (Kulkosky et al., 1980) and further strengthen already established aversions induced by non

self-administered drugs such as LiCl (Kulkosky et al., 1980).

It has been suggested that longer acting drugs are more potent in inducing CTAs than shorter acting drugs (Goudie, 1978; Switzman, Hunt & Amit, 1981). For example, both amphetamine (D'Mello et al., 1977), and Δ^9THC (Corcoran, 1973; Elsemore, 1972; Switzman, Fishman and Amit, 1981) have been shown to be more effective in inducing CTAs than shorter acting drugs such as cocaine (Goudie et al., 1978; Switzman, 1981)).

Increasing the duration of the drug effect by administering the total drug dose over repeated injections has been demonstrated to be effective in inducing a CTA with the weak aversive agent, cocaine (Switzman, 1981) and in strengthening the potency of the CTA produced by LiCl (Domjan et al., 1979). In Experiment 2, the total dose of heroin was distributed over three injections in the identical paradigm as that of Experiment 1. No CTA was observed at either the 3 mg/kg H, 6 mg/kg H or 9 mg/kg H dose. As discussed previously, this procedure has been reported to facilitate the induction of a CTA with cocaine, a self-administered drug, with a short duration of action and a rapid rate of onset (Switzman, 1981).

The failure to observe a heroin CTA in experiments 1

and 2, in conjunction with the surprising failure of morphine to induce a CTA in Experiment 1, raised questions regarding the strain of rats used and the temporal-dose parameters used in these experiments. Both these issues were examined in Experiments 3 and 4. These two experiments were identical to each other with the exception of the strain of rats used. Conditioning trials in both experiments were separated by 5 water days in contrast to Experiments 1 and 2 in which 2 days intervened between conditioning trials. 'Old colony' Sprague Dawley rats were used in Experiment 3, while 'new colony' Wistar rats were used in Experiment 4.

The results of Experiment 3 provide the first evidence of a heroin-induced CTA. A significant reduction of saccharin intake was observed in groups treated with 10 mg/kg H and 20 mg/kg H. In Experiment 4, 5 mg/kg H and 20 mg/kg H treated rats showed a tendency to decrease saccharin consumption (see Figure 5), although this was not statistically significant.

Morphine, on the other hand, induced significant CTAs in both Experiments 3 and 4, although the optimal dose differed in both experiments. In Experiment 3, 13.3 mg/kg M and 17.7 mg/kg M induced reliable CTAs with the 17.7 mg/kg M being the optimal dose. In Experiment 4, lower doses of

morphine induced significant CTAs (8.8 mg/kg M, 13.3 mg/kg M and 17.7 mg/kg M), with the 13.3 mg/kg M being the optimal dose. It seems that, according to the results of Experiments 3 and 4, morphine was more effective as a CTA inducing agent in 'new colony' Wistar rats. These results however, are contradicted by the results of Experiment 1. Doses of 9 mg/kg M and 15 mg/kg M did not induce a CTA in 'new colony' Wistar rats in that experiment. The possiblity exists that 'new colony' rats are unpredictable and unreliable subjects in the CTA paradigm. However, in Experiments 3 and 4, morphine induced a CTA in both strains of rats, and heroin induced a CTA in 'Old colony' rats (Experiment 3) and a tendency to reduce intake in 'new colony' rats (Experiment 4). It seems therefore, that the induction of a heroin and morphine CTA was not due to the strain of rats used in this study, but rather to the temporal-dose parameters. More specifically, repeated conditioning trials separated by five day intervals seems more effective in inducing a CTA with morphine and heroin than trials separated by two days (Experiment 1), and furthermore, than one conditioning trial in the case of heroin (Switzman, Hunt and Amit (1981).

The quality of CTAs induced by various psychoactive drugs seems to indicate that these drugs vary in their

efficacy to induce CTA in some type of hierarchical order that may be related to their self-administration liability. Although it has been reported that positive reinforcement, as inferred by increased running speed, is directly related to degree of aversion (Switzman et al., 1978; White et al., 1977), a comparison of the results of self-administration studies and CTA studies indicates that CTAs induced by non self-administered drugs are stronger, more reliable and more consistent than CTAs induced by self-administered drugs. Within the category of self-administered drugs, drugs that are less readily self-administered, such as THC (Amit, Corcoran, Charness & Shizgal, 1973; Van Ree et al., 1978) induce stronger, more reliable CTAs that are less readily blocked or attenuated (Elsemore. 1972) than drugs that are more reliably self-administered, such as morphine (Switzman, Fishman & Amit, 1981). The results of this study indicates that heroin also falls into this hierarchy, in that heroin is a less reliable CTA-inducing agent than morphine.

Furthermore, the drugs that have longer duration of action and slower rates of onset seem to be more aversive in the CTA paradigm than quicker acting drugs. For example, the difference in the ability of cocaine and amphetamine to induce a CTA has been linked to the differences in their temporal properties. Cocaine has a faster rate of onset and

a shorter duration of action than amphetamine (Goudie, 1979) and is less effective in inducing a CTA (D'Mello et al., 1979; Goudie et al., 1978).

Heroin and morphine may be compared to cocaine and amphetamine in their CTA inducing ability in that they also differ in their temporal properties. Heroin is an opioid derivative that converts to morphine in the brain (Goodman & Gilman, 1980; Wasacz, 1981; Way et al., 1965). However, heroin crosses the blood-brain barrier more rapidly (peak brain levels are reached within fifteen minutes) than morphine (peak brain levels are reached within approximately one hour) (Oldendorf et al., 1972). This difference in the temporal properties between heroin and morphine may underlie the differences between these two drugs in their ability to induce CTA. The rate of onset of both heroin and cocaine is very rapid (Nayak et al., 1976; Way et al., 1965) and both these drugs are weak CTA inducing agents. It may be that in order for a drug to induce a CTA, the time to peak activity must be gradual as opposed to sudden.

Although heroin is more potent in other measures, such as analgesia (Switzman, Hunt & Amit, 1981), morphine seems more potent in the CTA paradigm. The aversive element elicited by the conditioning of a novel flavour with a drug that causes an aversion to that flavour has as yet not been

described. If the aversion is found to be identified as an aversive property inherent in the drug, morphine may be found to have additional aversive properties not possessed by heroin that underlie morphine's potential to induce CTA.

It remains unclear exactly how the pharmacological properties of a drug relate to its efficacy as a CTA inducing agent. It may be that the discriminability of the positively reinforcing properties of a drug and the discriminability of the aversive properties of a drug are related. Heroin is more easily discriminated than morphine by rats as a positive reinforcer (Overton & Batta, 1977; Overton, 1982; Van Ree et al., 1978) and less easily discriminated than morphine as an aversive agent (Switzman, Hunt & Amit, 1981).

The results of the present study indicate that heroin like other self-administered drugs, can induce a CTA. Heroin's relative weakness when compared to morphine in the CTA paradigm appears to depend on several factors that include the temporal properties of the drug's actions and the specific temporal-dose parameters used.

Further research into these factors and the mechanisms that underlie CTA would be fruitful in understanding the reinforcing actions of self-administered drugs.

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APPENDIX A

Tables for the means and standard errors of the mean of saccharin intake.

TABLE 1

Mean Amount of Saccharin Consumed on 4 Conditioning Days and Test Day (Day 5)

GROUP	n	DAYS 1(B)	2	3	4	5
3 mg/kg Heroin	9	18.2 (1.5)	19.6 (1.4)	19.2 (0.7)	20.0 (1.3)	20.8 (0.9)
6 mg/kg Heroin	10	20.2 (1.7)	20.9 (1.1)	20.7 (1.0)	18.4 (1.1)	17.7 (1.0)
9 mg/kg Heroin	6	20.5 (1.2)	21.8 (0.9)	18.2 (2.0)	16.2 (2.4)	20.2 (2.0)
9 mg/kg Morphine	5	19.6 (0.6)	20.8 (1.7)	20.4 (1.2)	19.6 (1.1)	18.4 (0.4)
15 mg/kg Morphine	5	21.2 (1.5)	20.2 (1.7)	17.6 (1.5)	19.0 (2.0)	18.0 (1.3)
Saline	7	20.0 (0.9)	22.6 (1.2)	23.4 (1.3)	24.1 (1.4)	25.6 (1.1)

Note: Number in parentheses indicates corresponding standard error of the mean.

TABLE 2

Mean Amount of Saccharin Consumed on 4 Conditioning Days and Test Day (Day 5) of Rats Receiving Repeated Injections (adjusted cell means)

		DAYS				
GROUP	n	1(B)	2	3	4	5
3 mg/kg Heroin	10	23.9 (0.7)	19.9 (1.1)	18.3 (0.7)	19.9 (1.0)	19.7 (0.9)
6 mg/kg Heroin	10	20.7 (1.4)	20.3 (1.1)	21.1 (0.9)	19.9 (0.9)	19.8 (1.1)
9 mg/kg Heroin	9	19.7 (0.6)	19.4 (1.3)	19.0 (1.6)	17.9 (1.6)	19.4 (2.0)
Saline	9	18.4 (1.6)	21.0 (1.6)	21.2 (1.9)	20.4 (2.0)	22.3 (1.9)

Note: Numbers in parentheses indicate standard error of the mean.

TABLE 3

Mean Amount of Saccharin COnsumed on Five Conditioning and Test Days (Day 6). (Sprague Dawley)

GROUP	n	DAYS					
		1(B)	2	3	4	5	6
5.0 mg/kg Heroin	8	21.9 (1.6)	21.6 (1.4)	19.9 (1.7)	19.6 (1.9)	14.4 (1.5)	18.0 (2.3)
10.0 mg/kg Heroin	8	22.0 (1.7)	18.4 (2.3)	15.6 (2.1)	15.5 (2.6)	12.4 (2.8)	13.6 (3.1)
15.0 mg/kg Heroin	7	20.2 (2.0)	21.6 (2.8)	21.9 (3.0)	22.4 (3.3)	16.7 (3.4)	17.0 (3.7)
20.0 mg/kg Heroin	9	20.8 (0.8)	19.3 (1.6)	16.2 (2.2)	15.6 (2.5)	11.2 (2.5)	9.9 (2.5)
4.4 mg/kg Morphine	8	21.1 (1.3)	20.4 (1.6)	19.9 (0.9)	19.3 (1.6)	18.1 (1.9)	20.5 (1.7)
8.8 mg/kg Morphine	8	21.4 (1.4)	19.8 (2.3)	17.8 (2.8)	18.8 (3.2)	14.8 (2.9)	14.2 (3.2)
13.3 mg/kg Morphine	8	20.9 (1.2)	17.6 (1.7)	14.0 (2.3)	13.3 (2.0)	10.3 (2.1)	10.8 (2.7)
17.7 mg/kg Morphine	8	18.0 (1.0)	16.1 (2.5)	11.8 (1.6)	8.0 (1.1)	7.8 (2.0)	7.5 (1.6)
Saline	8	21.9 (0.7)	26.5 (1.6)	30.0 (0.8)	25.4 (3.4)	25.4 (1.9)	28.0 (1.6)

Note: Numbers in parentheses indicate corresponding standard error of the mean.

TABLE 4

Mean Amount of Saccharin Consumed on 5 Conditioning Days and Test Day (Day 6). (Wistars)

GROUP	DAYS					
	1(B)	2	3	4	5	6
5.0 mg/kg Heroin	19.3 (1.5)	19.8 (2.5)	16.7 (2.1)	12.4 (2.5)	13.6 (2.6)	11.7 (1.6)
10.0 mg/kg Heroin	19.1 (1.6)	18.8 (1.3)	18.6 (1.7)	17.4 (2.9)	17.1 (3.3)	11.7 (2.4)
15.0 mg/kg Heroin	19.1 (1.0)	19.4 (1.5)	21.4 (2.6)	21.3 (1.1)	23.1 (2.6)	22.0 (2.4)
20.0 mg/kg Heroin	21.3 (1.2)	15.1 (1.6)	13.3 (2.3)	17.4 (3.5)	16.1 (3.9)	18.1 (3.6)
4.4 mg/kg Morphine	18.6 (1.7)	19.3 (1.0)	19.7 (1.8)	17.0 (2.0)	15.7 (2.8)	14.3 (3.0)
8.8 mg/kg Morphine	21.9 (1.0)	23.4 (0.7)	19.7 (0.6)	16.9 (2.4)	15.6 (1.8)	12.3 (2.3)
13.3 mg/kg Morphine	19.3 (0.9)	17.9 (1.0)	10.6 (1.8)	7.6 (1.5)	6.4 (1.4)	6.6 (1.3)
17.7 mg/kg Morphine	19.7 (1.3)	20.1 (3.4)	17.8 (2.6)	14.3 (3.0)	12.4 (3.0)	10.7 (3.4)
Saline	20.7 (2.1)	26.9 (1.1)	26.3 (1.0)	28.3 (0.8)	27.1 (0.7)	25.4 (1.2

Note 1: n = 7 for all groups

Note 2: Numbers in parentheses indicate corresponding standard error of the mean.

APPENDIX B

Summary tables for the analyses of variance

TABLE 1

Analysis of Variance

Experiment 1

Source	df	MS	F
Drug	5	78.0307	2.43023
Subjects within groups	36	32.1084	
Days	4	10.6476	1.26997
Drugs x Days	20	18.6645	2.22617*
Days x subjects within groups	144	8.38416	

*$p < .005$

TABLE 2

Analysis of Variance

Experiment 2

Source	df	MS	F
Drug	3	33.63895	.96
error	33	34.92532	
Days	3	4.59442	.46
Drug x Days	9	5.22726	.52
error	102	10.07121	

TABLE 3

Analysis of Variance

Experiment 3

Source	df	MS	F
Drug	8	838.758	6.09250*
Subjects within groups	63	137.671	
Days	5	468.443	26.48690*
Drug x Days	40	42.4726	2.40150*
Days x Subjects within groups	315	17.6859	

*p<.0001

TABLE 4

Analysis of Variance

Experiment 4

Source	df	MS	F
Drug	8	660.759	7.89202*
Subjects within groups	54	83.7249	
Days	5	274.549	12.4489*
Drug x Days	40	60.2546	2.73214*
Days x Subjects within groups	270	22.0540	

*p<.0001