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The Interaction of Psychomotor Stimulants and Sedative Hypnotics in the Conditioned Taste Aversion Paradigm

Daniel Kunin

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ABSTRACT

The Interaction of Psychomotor Stimulants and Sedative Hypnotics in the Conditioned Taste Aversion Paradigm

Daniel Kunin

Specific pairs of drugs such as cocaine and ethanol and nicotine and ethanol are widely used by humans. A variety of existing studies have reported behavioral and pharmacological interactive effects between these pairs of drugs. The present thesis was designed to further examine the potential interactive effects between these pairs of drugs as reflected in two variants of the Conditioned Taste Aversion (CTA) paradigm. Experiment 1 examined the potential for cocaine and ethanol to interact pharmacologically in the pretreatment CTA procedure. These results revealed that while cocaine and ethanol may interact pharmacologically, their interaction was asymmetrical and therefore not cocaethylene mediated. Experiment 2 examined the potential for nicotine and ethanol to interact pharmacologically in the pretreatment CTA procedure. These results demonstrated that nicotine and ethanol interacted pharmacologically in an asymmetrical fashion. Together, these pretreatment effects indicated a pharmacological specificity between pairs of drugs as reflected in their interaction. Experiments 3 and 4 were conducted in order to assess whether cocaine and ethanol as well as nicotine and ethanol were functionally related and endowed with overlapping stimulus properties as reflected in the pre-exposure CTA paradigm. These results demonstrated that both pairs of drugs were functionally related and endowed with overlapping but non-identical

stimulus properties. That is, cocaine less effectively disrupted CTA to ethanol while ethanol more effectively disrupted CTA to cocaine. Similarly, nicotine effectively disrupted CTA to ethanol while ethanol less effectively disrupted CTA to nicotine. Taken together, these asymmetrical pre-exposure effects were thought to be related to the self-administration potential of these drugs.

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INTRODUCTION

Traditionally, alcoholism and other forms of drug abuse have been studied as if they were separate phenomena that occurred in relative isolation from one another (Mello, 1987). Due to the frequency of polydrug abuse it has been suggested that such a singular approach is not tenable (Mello, 1987). According to Kreek (1987) it is rare that a substance abuser will abuse a single substance. In fact, there appears to be increasing evidence that substance abuse frequently involves the use of several drugs concomitantly (Mello &Griffiths, 1987).

In recent years, it has been reported that the combined use of cocaine and alcohol has become a prevalent phenomenon among humans (Grant & Hartford, 1990). According to the 1985 National Survey on Drug Abuse, approximately 12 million individuals co-use alcohol and cocaine (Grant & Hartford, 1990). The combined use of cocaine and alcohol could reflect a summation of their separate reinforcing effects. That is, when used together, cocaine and alcohol may produce more intense and longer lasting euphoric effects (Hearn, Flynn, Hime, Rose, Cofino, Mantero-Atienza, Wetli & Mash, 1991; Hedaya & Pan, 1996). A second reason for the concomitant use of cocaine and alcohol could result from a mutual antagonism. It has been reported that the use of alcohol during a cocaine binge will ameliorate the unpleasant physical sequelae associated with cocaine ingestion namely paranoia and agitation (Hearn,et al. 1991; McCance-Katz, Price, McDougle, Kosten, Black & Jatlow, 1993).

When cocaine is ingested either alone or in combination with other drugs it normally undergoes a rapid transformation to benzoecgonine, ecgonine, ecgonine methyl

ester and norcocaine (Landry, 1992). When cocaine is ingested with ethanol (ethyl alcohol) exclusively, an additional metabolite, cocaethylene is formed (Landry, 1992). It has been demonstrated that cocaethylene can be formed in humans as well as rats after concurrent administration of cocaine and ethanol (McCance-Katz et al. 1993; Hedaya & Pan, 1996).

There is evidence to support the idea that cocaethylene has psychotropic effects in common with cocaine (McCance-Katz et al. 1993). Cocaethylene, like cocaine, has been reported to bind to the dopamine transporter and block dopamine reuptake and thereby, increase extra cellular concentrations of dopamine in the nucleus accumbens (Hearn et al. 1991; Jatlow, Elsworth, Bradberry, Winger, Taylor, Russell & Roth, 1991; Landry, 1992). Such neurochemical activity has been suggested to explain cocaethylene's ability to increase locomotion and sustain its self-administration (Jatlow et al. 1991). Studies investigating the self-administration potential of cocaethylene have demonstrated that cocaethylene is equal to or slightly more potent than cocaine as a reinforcer (Jatlow et al. 1991; Aspen and Winger, 1997). In addition, cocaethylene has been shown to completely substitute for cocaine in the drug discrimination paradigm (Woodward, Mansbach, Caroll & Balster, 1991). More recently, it has been reported that cocaethylene can induce a conditioned place preference (Schecter, 1995). These results can be taken as evidence for cocaethylene's rewarding effects which are characteristic of drugs with abuse potential (McCance–Katz et al. 1993). It would seem to follow then that cocaethylene's reinforcing effects may explain the frequency of combined cocaine and alcohol use in human populations (Schecter, 1995).

The formation of cocaethylene represents the only known example of the body producing a third psychoactive and reinforcing drug exclusively during the coadministration of two drugs of abuse (Landry, 1992). This is of significance in so far as it suggests that cocaethylene may putatively mediate the combined use of cocaine in combination with alcohol through its activation of central reward mechanisms (Hearn et al. 1991; Landry, 1992; Schechter, 1995). Thus, it would appear that the identification of cocaethylene must at least replace the notion that cocaine and ethanol are pharmacologically antagonistic (Landry, 1992).

As was mentioned, the abuse of a single substance is a rare phenomenon. The combined use of ethanol and nicotine in the form of alcoholic beverage and cigarette smoking respectively is widespread (Batel, Pessione, Maitre & Rueff, 1995; Zacny, 1990). In humans, a strong positive relationship between alcohol use and cigarette smoking has been suggested by a number of studies (Griffiths, Bigelow & Liebson, 1976; Maletzky & Klotter, 1974; Zacny, 1990). Heavy drinkers smoke more than light drinkers (Maletzky & Klotter, 1974; Keenan, Hatsukami, Pickens, Gust & Strelow, 1990), and heavy smokers drink more alcohol than light-smokers (Kaprio, Hammer, Koskenvuo, Floderus-Myrhed, Langinvainio & Sarna, 1982). In addition, a number of studies have demonstrated that alcohol pretreatment can increase cigarette smoking in alcoholics and those with no prior history of alcoholism (Glautier, Clements, White, Taylor & Stolerman, 1996; Griffith, Bigelow & Liebson, 1976; Henningfield, Chait & Griffiths, 1984).

The relationship between ethanol and nicotine has also been examined in the laboratory rat. Potthoff, Ellison, & Nelson (1983) examined the effects of a variety of

drugs on the oral intake of ethanol. In this study, rats acclimatized to drinking both water and a 10% ethanol solution were implanted with a slow releasing device containing nicotine and a variety of other drugs. The authors reported that ethanol intake increased only during exposure to nicotine and amphetamine. More recently, Blomqvist, Ericson, Johnson, Engel & Soderpalm (1996) reported that rats given nicotine (0.35 mg/kg s.c) daily increased their oral ethanol intake. The effects of ethanol and nicotine have also been compared in the drug discrimination paradigm. Nicotine has been shown to potentiate ethanol discrimination in the rat (Signs & Shechter, 1986). Finally, cross-tolerance between the effects of nicotine and ethanol has been demonstrated. Short-term treatment with nicotine can result in the development of cross-tolerance to some of the effects of ethanol and short-term treatment with ethanol can result in the development of cross-tolerance to some of nicotine's effects in mice (Burch, deFiebre, Marks & Collins, 1988; Collins, Burch, deFiebre & Marks, 1988).

There are several hypotheses which have attempted to explain the putative interaction between ethanol and nicotine (Zacny, 1990). First, it has been proposed that there may be cross-tolerance between the effects of ethanol and nicotine. That is, one substance may induce tolerance to the effects of the other (Burch, deFiebre, Marks & Collins, 1988; Collins, Burch, deFiebre & Marks, 1988). A second proposed explanation for the interactive effects between ethanol and nicotine is related to drug metabolism; how one drug may effect the metabolism of the other (Zacny, 1990). At present, there is hardly evidence that either one of the two drugs may affect clearance or metabolic rate of the other (Benowitz, Jones & Jacob, 1986; Collins, Burch, deFiebre & Marks, 1988). A third mechanism proposed to account for the interactive effects between ethanol and

nicotine is based on the notion of self-medication (Potthoff, Ellison & Nelson, 1983; Zacny, 1990). According to this notion, the effects of one drug may reflect attempts at self-medication to counteract the effects of another drug. For example, nicotine may promote excessive stimulation, and the sedative effects of ethanol may attenuate these effects. Conversely, ethanol may promote excessive sedation and nicotine's stimulant properties may act to antagonize ethanol's effects.

Conditioned Taste Aversion

One tool that has been used to examine the potential interactive effects between drugs of abuse is the Conditioned Taste Aversion (CTA) paradigm. In the traditional CTA paradigm an animal will be presented with a novel tasting fluid and immediately after receive a treatment consisting of a drug injection. On a later occasion (4-5 day interval) the animal will once again be offered the same fluid. Typically, an animal will tend to avoid this fluid on the second presentation. This reduced preference or intake of the fluid is taken as evidence of a conditioned taste aversion (Goudie, 1979; Hunt & Amit, 1987). Traditionally, it was believed that this reduction in fluid intake as reflected in the CTA procedure was due to the association between the taste of a substance and some aversive property of the treatment drug (Goudie, 1979).

The study of the stimulus properties of drugs within the context of the CTA paradigm was an outgrowth of earlier work in which the CTA was used primarily as a vehicle to study associative learning processes in animals. Typically, this work involved the administration of drugs or treatments with emetic effects such as lithium, apomorphine, and non-pharmacological treatments such as x-irradiation and rapid

rotation. It was demonstrated that rats could learn to associate a novel taste with an internal illness over one trial even with a long delay between two stimulus events (Garcia, Ervin & Koelling, 1966; Nachman, 1970; Nachman & Ashe, 1973). According to Seligman (1970), rodents were predisposed to associate flavors with delayed illness and therefore learning could occur in one trial and with a long delay between the taste and the internal event. The general idea behind this early work was that CTA was induced by toxicity and or some general malaise induced by the various treatments.

The adequacy of the theory that the CTA phenomenon was an index of toxicity or a form of conditioned illness was challenged by various subsequent findings. First, Berger (1972) reported the development of CTAs to a variety of psychoactive drugs such as amphetamine, scopolamine, and chlodiaxepoxide within dose ranges that produced no signs of illness or toxicity. Subsequently, it was demonstrated that a wide variety of drugs particularly those with positive reinforcing properties could produce CTAs within dose ranges that were self-administered (Hunt & Amit, 1987). Additionally, it was found that specific toxic agents failed to produce CTA. For example, Nachman & Hartley (1975) and Ionescu & Buresova (1977) reported that gallamine (a curare derivative), melonate and cyanide all failed to induce a CTA. Berger (1972) also failed to demonstrate a CTA with strychnine.

The finding that a reinforcing drug produced a CTA within dose ranges self-administered has been termed "paradoxical" (Goudie, 1979; Hunt & Amit, 1987). This "paradox" implies that a given drug can be both rewarding as reflected in its self-administration and aversive as reflected in the CTA paradigm. In fact, this paradoxical phenomenon has been shown with a number of self-administered drugs such as morphine

(Cappell & LeBlanc, 1973), amphetamine (Berger, 1972), cocaine (Goudie, Dickens & Thornton, 1978), ethanol (Cappell, LeBlanc & Endrenyi, 1973) and barbiturates (Vogel & Nathan, 1975). A finding that typified the paradox was the observation that the same neurochemical systems involved in drug induced CTA were also implicated in self-administration (Hunt & Amit, 1987). For example, it has been demonstrated that manipulations of catecholamine systems can block the aversive properties of self-administered drugs (Goudie, Thornton & Wheatley, 1975; Roberts & Fibiger, 1975; Sklar & Amit, 1977). Another finding that underscored the paradox was based on the observation that simultaneous reinforcement and aversion could occur. That is, the same injection of either morphine or amphetamine could be both positively reinforcing and aversive as reflected in a CTA (White, Sklar & Amit, 1977; Wise, Yokel & deWitt, 1976). Taken together, the evidence supported the view that CTA inducing and positively reinforcing properties of self-administered drugs were functionally related (Hunt & Amit, 1987).

There have been numerous attempts in the past to resolve the "paradox", yet none appeared to have been successful. Procedural differences between standard CTA and self-administration paradigms involving route of administration of the drugs was thought to play an important part in determining the contrast in drug effects seen in the two paradigms. Specifically, the i.p drug injection was the most common route of drug administration in CTA studies whereas the self-administration procedure typically involved intravenous injections (Hunt & Amit, 1987). Despite these differences, Wise Yokel & deWitt (1976) demonstrated that equating the route of drug-administration did not selectively dissociate the reinforcing from the aversive effects of self-administered

drugs. They reported that amphetamine induced a CTA regardless of whether it was administered i.p or i.v.

It has also been suggested that control (experimenter administration vs. self-administration) over the drug administration may be a critical variable in explaining why drugs have apparently opposing properties. Vogel & Nathan (1975) suggested that the aversive effects of drugs in the CTA paradigm was due to the fact that subject's could not control their drug experience. This suggestion was refuted on the basis of results that demonstrated that CTA could be produced through self-administration (Wise, Yokel & deWitt, 1976).

The fact that drugs could be both positively reinforcing and aversive proved hard for researchers to reconcile because it ultimately challenged the popular conception of hedonic drug properties (Gamzu, 1985). There have been two major positions that have attempted to explain the finding that positive reinforcing drugs also possessed aversive properties, as revealed by their capacity to induce CTA. The first position is the Tolerance hypothesis and the second position is the Novelty hypothesis. Support for both positions has been obtained from CTA pre-exposure studies. In the CTA pre-exposure paradigm, rats are pre-exposed to a drug on one or more occasions prior to taste aversion conditioning trials with the same drug. In general, pre-exposure studies have shown that pre-exposure to a drug can attenuate CTA to the same drug. The pre-exposure effect has been demonstrated with both self-administered and non-self-administered drugs (Berman & Cannon, 1974; Goudie, Taylor & Atherton, 1975; Leblanc & Cappell, 1974).

The tolerance hypothesis holds that all drugs are initially dysphoric and can therefore induce CTAs. However, with continued drug experience, the aversive effects

tolerate and unmask the positive reinforcing effects (Cappell, LeBlanc & Herling, 1975; Goudie, Taylor & Atherton, 1975). There are a number of difficulties with the tolerance hypothesis. First, if pharmacological tolerance were the mechanism by which drug pre-exposure affected aversive conditioning, one would predict a permanent attenuation particularly for self-administered drugs. In fact, the strength of CTA increases with repeated conditioning with both self-administered and non-self-administered drugs (Berman & Cannon, 1974; Riley, Jacobs & Lolordo, 1976). The tolerance hypothesis has also been challenged on the basis of results which demonstrated that when a flavor was paired with a drug prior to conditioning trials with a different flavor, a CTA still occurred to a second flavor (Stewart & Eikelbloom, 1978).

Due to the difficulties inherent with the tolerance hypothesis, Braveman (1975) proposed an associative explanation to account for the pre-exposure results. Braveman (1975) found that pre-exposure to an array of CTA inducing drugs including amphetamine blocked CTA induced by rotation. This finding could not be accounted for in terms of the tolerance hypothesis since rotation was non-pharmacological. According to Braveman (1975), pre-exposure to any CTA inducing agent should at least attenuate the formation of CTA normally induced by another agent as long as both agents could induce taste aversions on their own. Braveman's associative explanation assumes that all pre-exposure effects are symmetrical. This associative explanation was challenged on the basis of several studies which demonstrated asymmetrical pre-exposure effects (e.g. Cappell, LeBlanc & Herling, 1975; Vogel & Nathan, 1976). For example, amphetamine and amobarbital had been shown to interact asymmetrically in the pre-exposure paradigm

(Vogel & Nathan, 1976). Morphine and amphetamine have been reported to interact asymmetrically as well (Cappell, LeBlanc & Herling, 1975).

Braveman (1977) subsequently pointed out that asymmetrical pre-exposure effects could be related to parametric issues. That is, pre-exposure to a weaker aversive stimulus may have less effect on the formation of a CTA to a more potent CTA inducing agent. Moreover, pre-exposure to the more potent stimulus agent may attenuate CTA to a weaker CTA inducing agent. This explanation was ruled out on the basis of a study demonstrating that drugs with equi-aversive potential interacted asymmetrically in the pre-exposure CTA paradigm (Switzman, Fishman, & Amit, 1981).

Several researchers have suggested that the apparent aversive properties of self-administered drugs may reflect the novelty of the drug state (Amit & Baum, 1970; Gamzu, 1977). The novelty hypothesis suggests that a CTA to a self-administered drug is the result of a "fear" response to a novel experience due to first time exposure with a particular drug effect, which subsides over time. This should be distinguished from viewing CTA induction by self-administered drugs as a reflection of their aversive or dysphoric properties. Thus, the difference between the tolerance vs. novelty hypotheses is that the novelty hypothesis implies that the CTA is a function of the internal stimulus complex provided by a drug, including those stimulus properties which can be positively reinforcing (Gamzu, 1977). Conversely, the tolerance hypothesis implicates an aversive component that can be distinguished from a positively reinforcing component, and in fact counteracts it.

The novelty hypothesis can account for the finding that drug pre-exposures can attenuate CTA to the same drug. An apparent difficulty for the novelty hypothesis is the

asymmetrical drug pre-exposure phenomenon. It follows from the novelty hypothesis that in order for a pre-exposed drug to attenuate the formation of a CTA induced by a second drug, the stimulus properties (drug state) of both drugs should be similar. Therefore, reversing the pre-exposure and conditioning drugs should result in the same magnitude of attenuation. This however, does not seem to be the case. As was previously mentioned, a number of studies emanating from different laboratories have demonstrated asymmetrical drug pre-exposure effects between pairs of drugs (e.g. Vogel and Nathan, 1976). The novelty hypothesis has also been challenged by a study which reported that morphine still induced a CTA to a second flavor after having been paired a number of times with another flavor (Stewart & Eikelbloom, 1978). The novelty hypothesis would have predicted a diminished CTA to the second flavor since its novel properties had been experienced during conditioning to the first flavor (Stewart & Eikelbloom, 1978). Even though at present the novelty hypothesis cannot explain all instances of the paradox, it nevertheless has a number of important implications (Gamzu, 1977). First, all drugs that can produce discriminable internal changes (these need not be aversive) should be effective in producing a CTA in drug naïve animals (Gamzu, 1977). Second, pre-exposure with such drugs prior to conditioning training, should at least attenuate subsequent conditioning (Hunt & Amit, 1987). Third, the extent to which two different drug treatments result in discriminably similar internal states, will determine whether pre exposure with one such treatment will at least attenuate CTA to the other. In principle the pre-exposure CTA paradigm may enable the assessment of the degrees of similarity between the stimulus properties of drugs. In other words, the pre-exposure procedure may serve as a useful vehicle to identify common psychopharmacological properties shared by

various drugs, which in turn give rise to CTA (Cappell, LeBlanc, Herling, 1975; Vogel & Nathan, 1976; Switzman, Fishman & Amit, 1981; Ng Cheong Ton, 1983; Aragon, Abitbol & Amit, 1986).

The Pretreatment CTA Paradigm

Another variant of the CTA paradigm is the pretreatment CTA procedure. In this procedure, a pretreatment drug is typically administered prior to conditioning with a second drug but in close temporal proximity (60-90 minutes) in order to permit a pharmacological interaction between the pretreatment and the conditioning drug. It has been argued that if the association between a novel flavor (conditioned stimulus) and a drug treatment (unconditioned stimulus) can be disrupted by pretreatment with a second drug, then both the pretreatment drug and the unconditioned stimulus drug interact pharmacologically. The inability of a pretreatment drug to disrupt taste aversion learning to a second drug (conditioning drug) would suggest that the pretreatment drug was unable to alter the pharmacological effects of the conditioning drug.

Pretreatment effects have also been explained in terms of general interference effects (Domjan, 1980). According to this view, pretreatment with any given drug will disrupt the "causal inference" a rat will make between a taste experience and a subsequent conditioning drug treatment (Domjan, 1980). By definition then, such a view would predict that all pretreatment effects would be symmetrical. This assumption was not borne out. Brown, Amit, Smith & Rockman (1979) demonstrated that morphine and diazepam could interact asymmetrically in the pretreatment paradigm. That drugs may interact asymmetrically argues against the notion that all pretreatment effects are due

merely to general interference effects. In fact it supports the idea that there may be pharmacologically specific and unidirectional interactions between drugs that can be reflected in this paradigm.

The Present Investigation

It has been demonstrated that CTA inducing and positively reinforcing properties of self-administered drugs are functionally related (Switzman, Fishman & Amit; White, Sklar & Amit, 1977). The suggestion therefore has been that the positively reinforcing and "aversive properties" of self-administered drugs are dependent components within the same stimulus complex (Gamzu, 1985; Switzman, 1980). If this indeed is the case, by studying CTA, we may ultimately be tapping into the stimulus properties of drugs, which also underlie their positively reinforcing effects. The present thesis was designed to explore the potential interactive effects between cocaine and ethanol as well as nicotine and ethanol in two variants of the CTA paradigm discussed above.

The goal of the first experiment was to assess whether cocaine and ethanol could interact pharmacologically in the pretreatment CTA paradigm. A further goal of this experiment was to determine whether this potential interaction was cocaethylene mediated. The second experiment was designed to assess whether nicotine and ethanol could interact pharmacologically in the pretreatment CTA paradigm. The third experiment of this thesis assessed whether cocaine and ethanol were functionally related and share common stimulus properties as reflected in the pre-exposure CTA. The final

study of this thesis assessed whether nicotine and ethanol were functionally related as reflected in their interaction in the pre-exposure paradigm.

EXPERIMENT 1

The simultaneous use of cocaine and ethanol appears to be increasingly common (Grant & Hartford, 1990). When cocaine is in the presence of ethanol, a third psychoactive substance, cocaethylene, is formed (Landry, 1992). Cocaethylene, a potent reinforcer in its own right, may explain the ubiquitous combined use of cocaine and alcohol use in humans (Schecter, 1995). The present experiment was designed in order to examine whether cocaethylene may mediate the potential interaction between cocaine and ethanol in the CTA paradigm.

It has been shown that pretreatment with a variety of neurochemical agents may differentially disrupt taste aversion learning to a number of self-administered drugs (e.g., Brown, Smith, Amit & Rockman, 1979). The pretreatment CTA procedure may provide the opportunity to assess whether two drugs present within the organism in close temporal proximity to each other can interact pharmacologically. Experiment 1a was designed to assess the effects of pretreatment with ethanol on the formation of a cocaine induced CTA. In experiment 1a, ethanol was administered 60 minutes prior to conditioning with cocaine. Since the half-life of ethanol administered was roughly 2 hours (Freund, 1967), it could be argued that ethanol and cocaine would have the opportunity to interact pharmacologically. Experiment 1b was designed to assess the effects of pretreatment with cocaine on the formation of an ethanol induced CTA. In this study, cocaine was administered 60 minutes prior to conditioning with ethanol. Since the half-life of the administered cocaine was roughly 60 minutes (Lau, Imam, Ma & Falk,

1991) it could be argued that cocaine would have the opportunity to interact with ethanol pharmacologically.

It was hypothesized that if cocaethylene mediates the interaction between cocaine and ethanol, then, as long as cocaine is in the presence of ethanol, one should observe a symmetrical interaction between these drugs. Conversely, asymmetrical results would effectively rule out a cocaethylene, mediated effect.

EXPERIMENT 1A

Materials and Method

Subjects: Subjects were 32 male Wistar rats (Charles River, Quebec) weighing between 275-300 grams at the start of the experiment. The subjects were individually housed in stainless steel cages throughout the experiment in a room regulated for constant temperature and humidity on a 12 hour light-dark cycle. Purina rat chow was available ad lib throughout the experiment. Subjects were acclimatized to the colony room seven days before imposing the restricted water access schedule. Subjects had free access to water throughout the acclimatization period only.

Drugs: Cocaine Hydrochloride (BDH Fine Chemicals) 9 mg/kg was dissolved in 0.9% saline at a concentration of 1 mg/ml. Cocaine was injected i.p. Ethanol (20% v/v) was prepared by diluting 95% ethanol in saline. Ethanol (1.2 g/kg) was injected i.p. Saccharin solution (0.1%) was mixed in tap water.

Procedure: Following one week of acclimatization to the laboratory housing conditions, rats were placed on a 23 hour and 20 minute water deprivation schedule. Tap water was presented to the animals in stoppered plastic tubes fitted with stainless steel ball bearing spouts for 40 minutes beginning at noon each day. The spouts were inserted through the wire mesh in front of the home cages. Rats were presented with water in this manner for 6 consecutive days following the last acclimatization day. Fluid intake was measured to the nearest ml. A single bottle, forced choice drinking procedure was employed. That is, during fluid presentation, each animal was presented with fluid in a single stoppered plastic tube. It followed that during conditioning and drug free test days, animals were only presented with saccharin. A forced choice procedure was used in all

experiments since under these conditions, a CTA is measured as a reduction in consumption of the test substance.

On day 7, animals were randomly assigned to one of 4 treatment groups. A total of 8 animals were assigned to each group. Group Vehicle-Vehicle (V-V) received a single injection of saline 60 minutes prior to the presentation of a novel 0.1% sodium saccharin solution given in place of normal drinking water. Immediately following the 20-minute saccharin exposure session, animals in this group were administered 4 injections of saline spaced 20 minutes apart. Animals assigned to group Vehicle-Cocaine (V-C) were injected with saline 60 minutes prior to the presentation of saccharin and were then administered 4 injections of cocaine (9 mg/kg) spaced 20 minutes apart. This regimen of cocaine administration has previously been shown to produce a CTA (Hunt, Switzman & Amit, 1985). Animals assigned to group Ethanol-Cocaine (E-C) were injected with ethanol (1.2 g/kg) 60 minutes prior to the saccharin presentation and were then administered 4 injections of cocaine (9 mg/kg) spaced 20 minutes apart. Animals assigned to group Ethanol-Vehicle (E-V) received a single injection of ethanol (1.2 g/kg) 60 minutes prior to the presentation of saccharin solution and were then administered 4 injections of saline spaced 20 minutes apart.

On the following days, all animals were maintained on restricted water access. The conditioning procedure (pairing day) which took place on day 7 was repeated on days 10 and 13. Days 16, 19 and 22 constituted drug free test days. On these days animals were presented with saccharin for 20 minutes without a corresponding drug treatment. On intervening days, between conditioning and test days, animals were presented with water for 40 minutes beginning at noon.

Data Analysis: Only animals consuming at least 5 ml of saccharin on the first exposure to saccharin were included in the data analysis. This criterion was set in order to avoid a floor effect. This criterion, in fact, eliminated one animal from group V-V.

In the present experiment, a CTA was defined as a significant reduction in saccharin intake of a given experimental group relative to its own baseline saccharin intake (pairing day 1). A failure to observe an increase in saccharin intake was not considered sufficient evidence to indicate a CTA induced by a given conditioning agent. Since the failure to increase saccharin intake may not, by itself, reflect a taste aversion but rather maintenance of neophobia, the more conservative definition of CTA that incorporates an observable avoidance response was applied to the present data (Hunt, Spivak & Amit, 1985).

Saccharin intake data was analyzed with a 4 x 6 mixed factorial ANOVA with Group as a between subjects factor and Days as the repeated measures factor. Following the omnibus *F* test, tests of simple comparisons (single-df-comparisons) were used in order to probe for CTA. Significance testing was conducted with α=. 05 in this and all subsequent studies.

Results

A two-way (4x6) ANOVA with repeated measures on the Days factor was conducted on saccharin intake data. This analysis yielded a significant Group ($F_{3,28} = 14.343, p < .001$), Days ($F_{5,140} = 25.056, p < .001$) and Group x Days interaction ($F_{15,140} = 6.549, p < .001$) effect. A test of simple main effects revealed that baseline saccharin intake (pairing day 1) did not differ significantly ($p<.05$) between the groups.

However, the same analysis revealed that the groups did in fact differ significantly across all other days.

Within subject single-df-comparisons revealed that group V-V significantly increased ($p < .05$) its saccharin intake on all days relative to baseline saccharin consumption. Group E-V significantly increased its baseline saccharin consumption on test days 1, 2 and 3 relative to baseline. In contrast, group V-C significantly decreased its baseline saccharin consumption on pairing day 3 and test day 1. Group E-C significantly decreased their saccharin consumption on pairing day 3 and test days 1 (see Figure 1).

Between subjects single-df-comparisons revealed that groups V-C and E-C consumed significantly less saccharin than groups V-V and E-V on pairing day 3 and test day 1. In addition, group E-C consumed significantly less saccharin than group V-C on test day 1, suggesting that ethanol augmented a cocaine CTA.

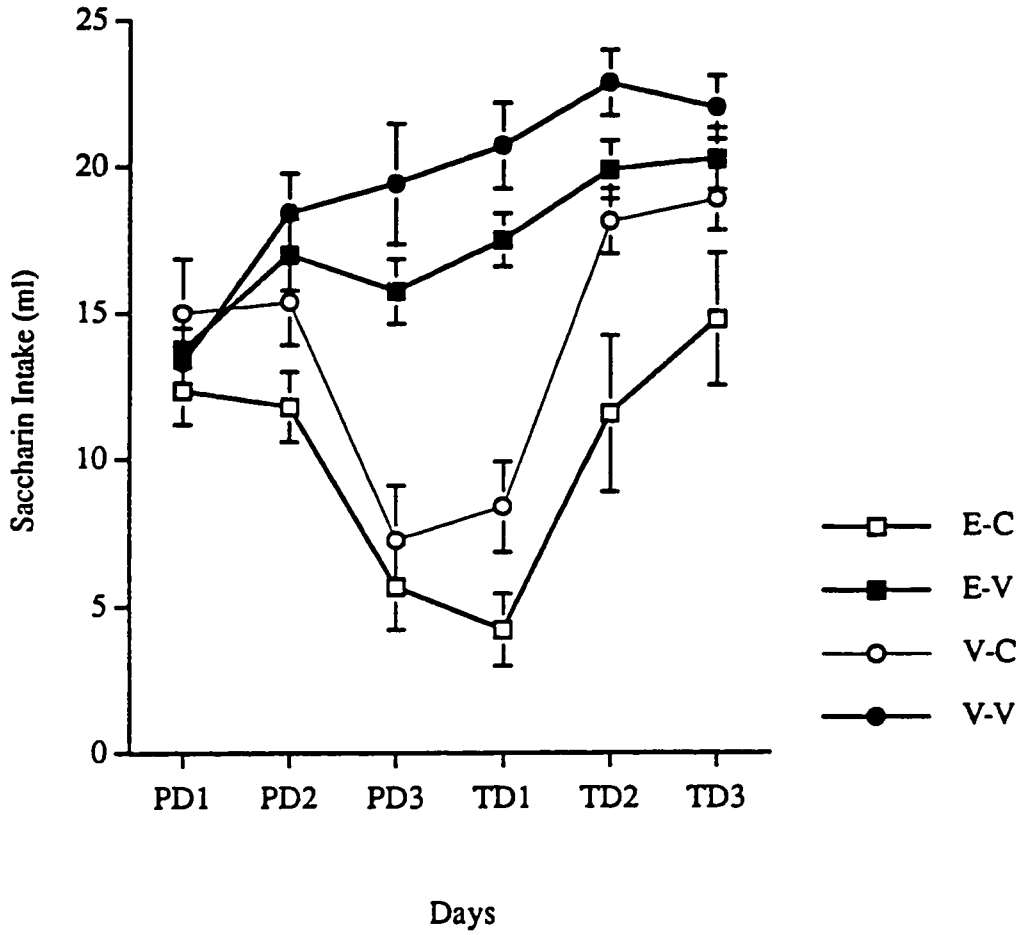

Figure 1. Effects of pretreatment with ethanol on a cocaine induced conditioned taste aversion as reflected in mean consumption of saccharin solution for Pairing Days 1-3 (PD1, PD2, PD3) and Test Days 1-3 (TD1, TD2, TD3). Vertical lines represent the S.E.M.

EXPERIMENT 1B

Materials and Method

Subjects: Subjects were 32 male Wistar rats (Charles River, Quebec) weighing between 275-300 grams at the start of the experiment. Housing conditions were identical to those outlined in experiment 1a. All subjects were acclimatized to the colony room for seven days as in experiment 1a before imposing the restricted water schedule.

Procedure: Following one week of adaptation to the colony room conditions, rats were placed on the same water deprivation schedule as in experiment 1a. Animals assigned to group Vehicle-Ethanol (V-E) were administered a single injection of saline 60 minutes prior to presentation of saccharin and were then injected with a single injection of ethanol (1.2 g/kg) immediately following the 20-minute saccharin exposure. This dose of ethanol has reliably been shown to produce a CTA (Ng Cheong Ton & Amit, 1983). Animals assigned to group Cocaine-Ethanol (C-E) were administered a single injection of cocaine (36 mg/kg) 60 minutes prior to saccharin presentation and were then administered a single injection of ethanol (1.2g/kg) immediately following exposure to saccharin. Animals assigned to group Cocaine-Vehicle (C-V) received a single injection of cocaine (36 mg/kg) 60 minutes prior to presentation of saccharin solution and were then injected with saline immediately following saccharin presentation. Animals assigned to group Vehicle-Vehicle (V-V) were administered a single injection of saline 60 minutes prior to presentation of saccharin solution and were then injected with saline following saccharin exposure.

Data Analysis: As in experiment 1a, only animals consuming at least 5 ml of saccharin on the first pairing day were included in the analysis. No animals were

eliminated from the analysis. As in experiment 1a, CTA was defined as a significant reduction in saccharin intake of a given experimental group relative to its own baseline saccharin intake. Saccharin intake data was analyzed with a 4 x 6 mixed factorial ANOVA as in Experiment 1a. Single-df-comparisons were used in order to probe for CTA.

Results

A two-way (4x6) ANOVA with repeated measures on the Days factor was conducted on saccharin intake data. This analysis yielded significant Group ($F_{3,28} = 10.898, p < .001$), Days ($F_{5,140} = 18.934, p < .001$) and Group x Days interaction ($F_{15,140} = 4.701, p < .001$). Analysis of simple main effects revealed that the groups differed significantly ($p<.05$) in terms of their saccharin intake at baseline as well as all other days. Because initial baseline saccharin differed significantly between the groups, it was deemed inappropriate to subsequently compare groups.

Within subject single-df-comparisons revealed that relative to baseline, group V-V significantly increased ($p < .05$) its saccharin intake on all days except for test day 1. Relative to baseline, group C-V significantly increased its baseline saccharin consumption on all days except for pairing day 3. In contrast, group V-E significantly decreased its baseline saccharin consumption on test day 1. Group C-E significantly increased its saccharin consumption on all days relative to baseline (see Figure 2).

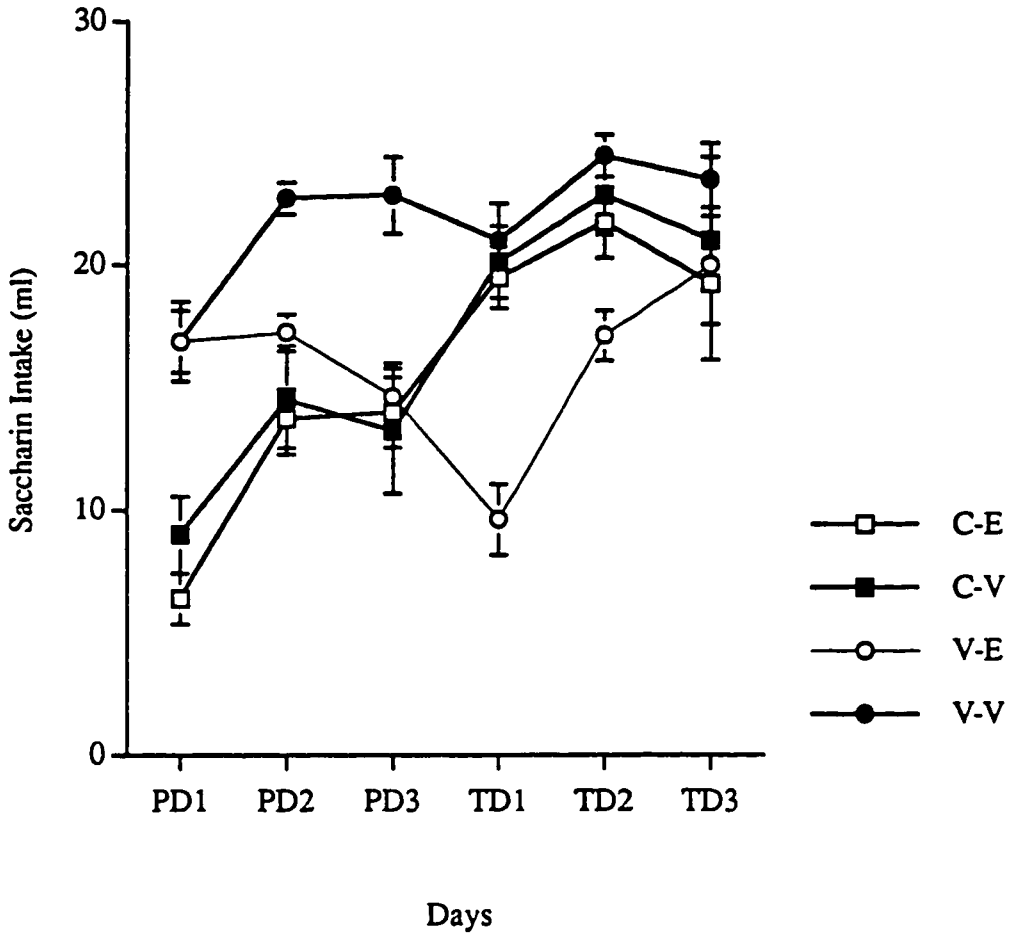

Figure 2. Effects of pretreatment with cocaine on an ethanol induced conditioned taste aversion as reflected in mean consumption of saccharin solution for Pairing Days 1-3 (PD1, PD2, PD3) and Test Days 1-3 (TD1, TD2, TD3). Vertical lines represent the S.E.M.

Discussion

Taken together, the results of experiments 1a and 1b revealed that cocaine and ethanol interacted asymmetrically in the pretreatment CTA paradigm. In experiment 1a it is apparent that ethanol pretreatment failed to block a cocaine induced CTA. In fact, ethanol pretreatment appeared to augment a cocaine induced CTA. In contrast, in experiment 1b, cocaine pretreatment completely blocked the formation of an ethanol CTA. These findings suggest that cocaine and ethanol may interact in a pharmacologically specific fashion as reflected in the pretreatment CTA procedure.

An alternate explanation for the present asymmetry may be related to the idea that in experiment 1b, a CTA was not observed for group C-E because it's baseline saccharin intake was low. It should be noted however that CTA can occur in rats consuming as low as 1 ml of saccharin (Deutsch, 1978).

That cocaine and ethanol may interact asymmetrically eliminates the possibility that in the present study, the interaction between cocaine and ethanol is cocaethylene mediated. That is, if cocaethylene were mediating the behavioral interaction between cocaine and ethanol, then as long as the two drugs were in the presence of one another, regardless of the order in which they were administered, one would expect to see the same behavioral outcome, which was not the case.

EXPERIMENT 2

Ethanol in the form of alcoholic beverages and nicotine in the form of tobacco products are two of the most frequently used psychoactive substances (Zacny, 1990). In humans, correlations between cigarette smoking and alcohol use have been suggested by several epidemiological studies (e.g., Istvan & Matarazzo, 1984). In addition, several studies have demonstrated that alcohol can increase cigarette smoking (Glautier, Clements, White, Taylor & Stolerman, 1996; Griffiths, Bigelow & Liebson, 1976; Henningfield, Chait & Griffiths, 1984). Several studies have also reported on the behavioral similarities between the effects of ethanol and nicotine in animals (e.g. Blomqvist, Ericson, Johnson, Engel & Soderpalm, 1996; Collins, Burch, deFiebre & Marks, 1988; Potthoff, Ellison, & Nelson, 1983; Signs & Schechter, 1986). Experiment 2 was designed to examine the potential interactive effects between ethanol and nicotine in the pretreatment CTA paradigm. Experiment 2a examined the effects of pretreatment with ethanol on the formation of a nicotine induced CTA. Experiment 2b examined the effects of pretreatment with nicotine on the formation an ethanol induced CTA. It was hypothesized that if nicotine and ethanol interact pharmacologically, then pretreatment with ethanol should attenuate the development of a nicotine induced CTA and pretreatment with nicotine should attenuate the development of an ethanol CTA.

EXPERIMENT 2A

Materials and Method

Subjects: Subjects were 32 male Wistar rats (Charles River, Quebec) weighing between 275-300 grams at the start of the experiment. The subjects were individually housed in stainless steel cages throughout the experiment in a room regulated for constant temperature and humidity on a 12 hour light-dark cycle. Purina rat chow was available ad lib throughout the experiment. Subjects were acclimatized to the colony room seven days before imposing the restricted water access schedule. Subjects had free access to water throughout the acclimatization period only.

Drugs: (-) – Nicotine di-d-tartate (Research Biochemical International) in a dose of 1 mg/kg was dissolved in 0.9% saline at a concentration of 1 mg/ml. Nicotine was injected i.p. This dose of nicotine has previously been shown to produce a CTA. Ethanol (20% v/v) was prepared by diluting 95% ethanol in saline. Ethanol was injected i.p. Saccharin solution (0.1%) was mixed in tap water.

Procedure: Following one week of acclimatization to the laboratory housing conditions, rats were placed on a 23 hour and 20 minute water deprivation schedule. Tap water was presented to the animals in stoppered plastic tubes fitted with stainless steel ball bearing spouts for 40 minutes beginning at noon each day. The spouts were inserted through the wire mesh in front of the home cages. Rats were presented with water in this manner for 6 consecutive days following the last acclimatization day. Fluid intake was measured to the nearest ml. A one bottle drinking procedure was used for all drinking sessions.

On day 7, animals were randomly assigned to one of 4 treatment groups. Group Vehicle-Nicotine (V-N) received a single injection of saline 60 minutes prior to minutes prior to presentation of a novel 0.1% sodium saccharin solution given in place of normal drinking water. Immediately following the 20-minute exposure to the saccharin solution, animals in this group were injected with nicotine (1 mg/kg twice-spaced 30 minutes apart). This regimen of nicotine was adapted from Etscorn and Colleagues (1987) who demonstrated that a single injection of nicotine (1 mg/kg) failed to produce a CTA. Animals assigned to group Vehicle-Vehicle (V-V) were injected with saline 60 minutes prior to presentation of saccharin and were then injected with saline (twice spaced 30 minutes apart) immediately following the 20-minute saccharin exposure session. Animals assigned to group Ethanol-Nicotine (E-N) were injected with ethanol (1.2 g/kg) 60 minutes prior to saccharin presentation and then injected with nicotine (1 mg/kg twice spaced 30 minutes apart) immediately following exposure to saccharin. Animals assigned to group Ethanol-Vehicle (E-V) received a single injection of ethanol (1.2 g/kg) 60 minutes prior to presentation of saccharin solution and were then injected with saline (twice spaced 30 minutes apart) immediately following saccharin presentation.

On the following days, all animals were maintained on restricted water access. The conditioning procedure (pairing day) which took place on day 7 was repeated on days 10 and 13. Days 16, 19 and 22 constituted drug free test days. On these days animals were presented with saccharin for 20 minutes without a corresponding drug treatment. On the intervening days, between conditioning and test days, animals were presented with water for 40 minutes beginning at noon.

Data Analysis: Only animals consuming at least 5 ml of saccharin on the first exposure to saccharin were included in the data analysis. The adoption of this criterion eliminated a single animal from group E-V. A CTA was defined in a manner identical to that of previous experiments. Saccharin intake data was analyzed with a 4 x 6 mixed factorial. Single-df-comparisons were used in order to probe for CTA.

Results

A two-way (4x6) ANOVA with repeated measures on the Days factor was conducted on saccharin intake data. The analysis yielded significant Group ($F_{3,27} = 7.366, p < .001$), Days ($F_{5,135} = 8.086, p < .001$) and Group x Days interaction ($F_{15,135} = 5.211, p < .001$) effects. Test of simple main effects revealed that the groups did not differ significantly at pairing day 1.

Within subjects single-df-comparisons revealed that both groups E-V and V-V significantly increased ($p < .05$) their saccharin consumption on all days relative to baseline saccharin intake. In contrast, group V-N significantly decreased its saccharin consumption on test day 1 relative to baseline, which was indicative of a nicotine induced CTA. Group E-N maintained its baseline saccharin intake across all days (see Figure 3).

Between subjects single-df-comparisons revealed that on test days, group V-N consumed significantly less ($p<.05$) saccharin relative to all other groups. In addition, group E-N consumed significantly less saccharin compared to groups E-V and V-V, suggesting that ethanol pretreatment attenuated a nicotine CTA.

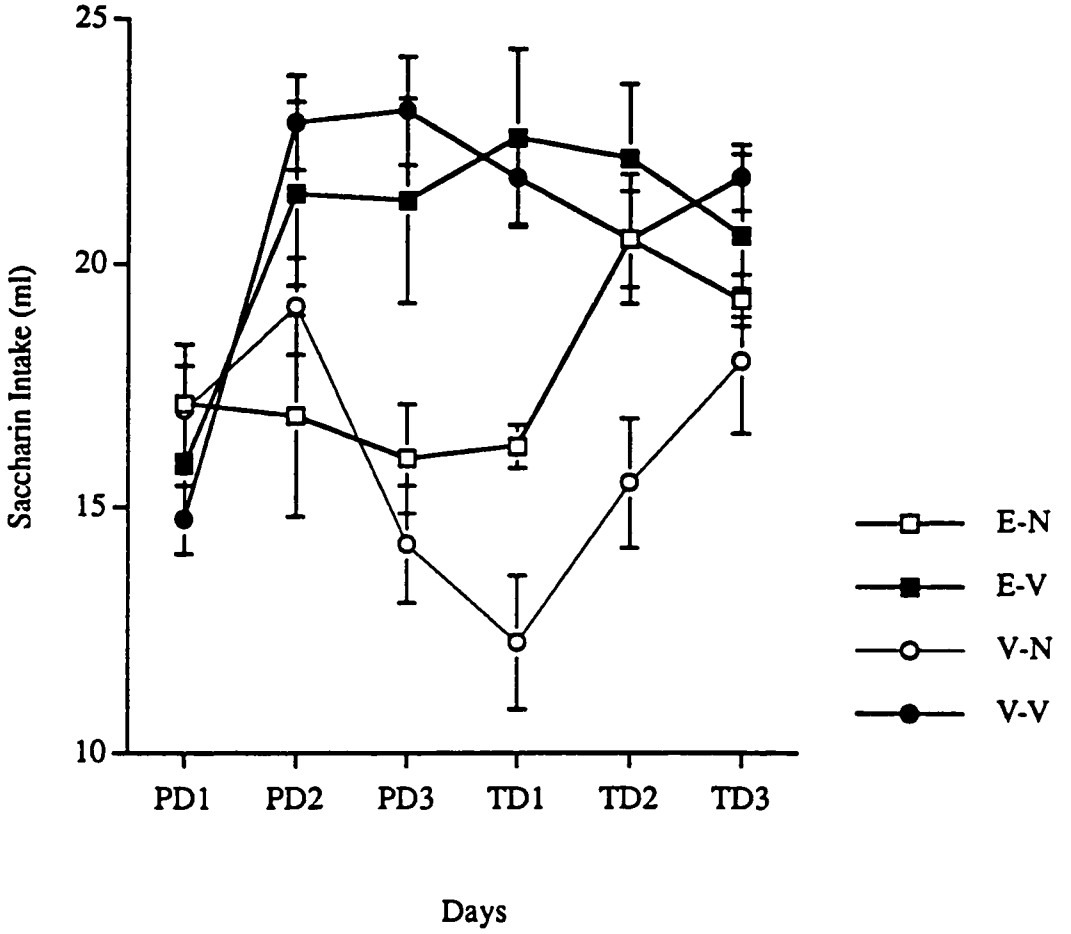

Figure 3. Effects of pretreatment with ethanol on a nicotine induced conditioned taste aversion as reflected in mean consumption of saccharin solution for Pairing Days 1-3 (PD1, PD2, PD3) and Test Days 1-3 (TD1, TD2, TD3). Vertical lines represent the S.E.M.

EXPERIMENT 2B

Materials and Method

Subjects: Subjects were 32 male Wistar rats (Charles River, Quebec) weighing between 275-300 grams at the start of the experiment. Housing conditions were identical to those outlined in Experiment 2a. All subjects were acclimatized to the colony room for seven days as in Experiment 2a before imposing the restricted water schedule.

Procedure: The experimental procedure was identical to experiment 2a. Animals were randomly assigned to one of 4 groups. Animals assigned to group Vehicle-Ethanol (V-E) were administered a single injection of saline 60 minutes prior to presentation of saccharin and then administered a single injection of ethanol (1.2 g/kg) immediately following the 20-minute saccharin exposure. Animals assigned to group Nicotine-Ethanol (N-E) received a single injection of nicotine (2 mg/kg) 60 minutes prior to saccharin presentation and then received a single injection of ethanol (1.2 g/kg) immediately following exposure to saccharin. Animals assigned to group Nicotine-Vehicle (N-V) received a single injection of nicotine (2 mg/kg) 60 minutes prior to presentation of saccharin solution and were then injected with saline immediately following saccharin presentation. Animals assigned to group Vehicle-Vehicle (V-V) were injected with saline 60 minutes prior to presentation of saccharin solution and then injected with saline following saccharin exposure. As in experiment 2a, there were three conditioning days and three drug free test days.

Data Analysis: No animals were eliminated from the data analysis. A CTA was defined as in previous experiments. Saccharin intake data was analyzed with a 4 x 6 mixed factorial. Single-df-comparisons were used in order to probe for CTA.

Results

A two-way (4x6) ANOVA with repeated measures on the Days factor was conducted on saccharin intake data. The analysis yielded significant Group ($F_{3,28} = 6.077, p < .001$), Days ($F_{5,140} = 18.017, p < .001$) and Group x Days interaction ($F_{15,140} = 6.196, p < .001$) effects.

Within subjects single-df-comparisons revealed that groups N-V and V-V significantly increased ($p < .05$) their saccharin consumption on all days relative to baseline saccharin intake. In contrast, group V-E significantly decreased their baseline saccharin consumption on pairing days 2 and 3, as well as test day 1. Group N-E significantly increased their saccharin intake on all days relative to baseline (see Figure 4).

Between subjects single-df-comparisons revealed that group V-E consumed significantly less ($p<.05$) saccharin compared to all other groups on pairing day 2, 3 and test day 1. In addition, group N-E did not differ from groups N-V or V-V on pairing day 2, 3 and test day 1, suggesting that nicotine completely blocked the formation of an ethanol induced CTA.

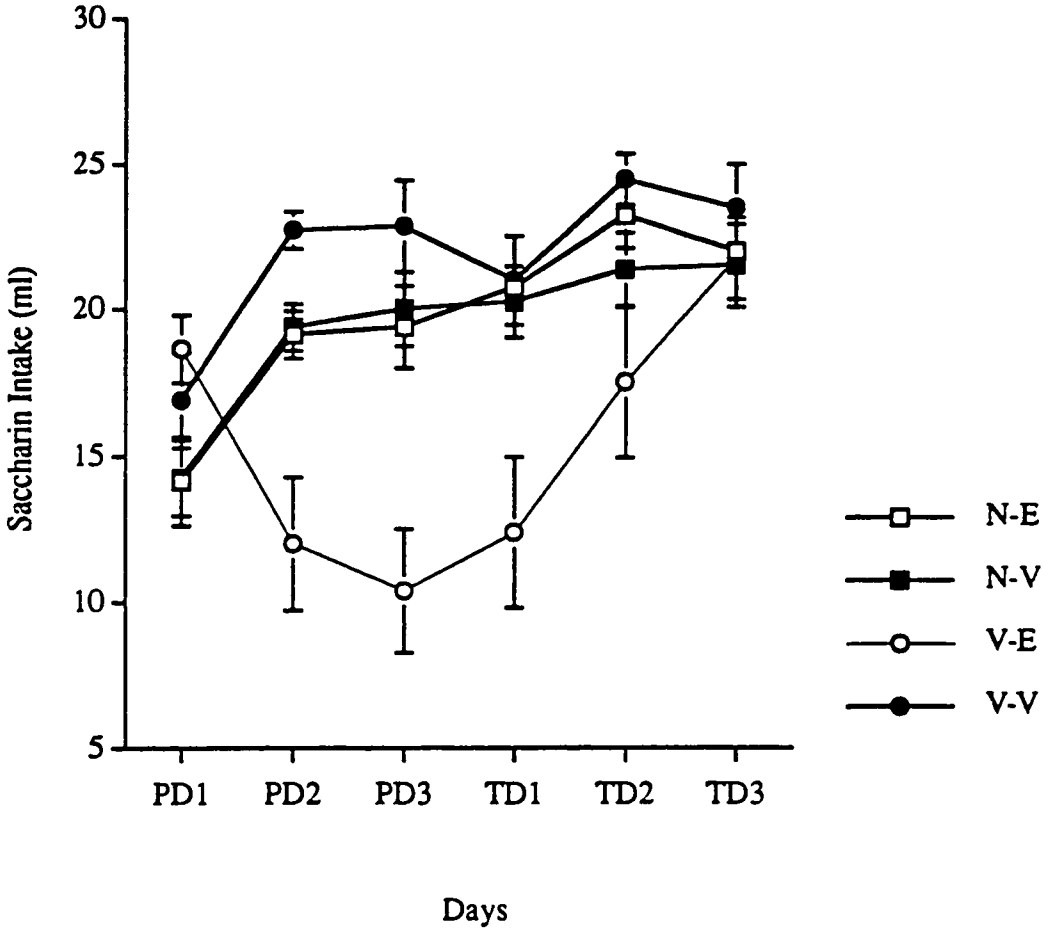

Figure 4. Effects of pretreatment with nicotine on an ethanol induced conditioned taste aversion as reflected in mean consumption of saccharin solution for Pairing Days 1-3 (PD1, PD2, PD3) and Test Days 1-3 (TD1, TD2, TD3). Vertical lines represent the S.E.M.

Discussion

Taken together, the results of experiments 2a and 2b demonstrated that ethanol and nicotine interacted asymmetrically in the pretreatment CTA paradigm. In experiment 2a, ethanol pretreatment attenuated the formation of a nicotine induced CTA whereas, in experiment 2b nicotine pretreatment completely blocked the formation of an ethanol induced CTA.

A tentative explanation for the present asymmetry between nicotine and ethanol may be related to the pharmacologically specific nature of this relationship. It has been suggested that nicotine may antagonize the impairing effects of ethanol (Zacny, Mitchell, Cramblett & deWitt, 1996). For example, several studies have demonstrated that nicotine may attenuate the psychomotor-impairing effects of ethanol (Leigh, 1982; Leigh & Tong, 1976; Tong, Knott, McGraw & Leigh, 1974). Additionally, a number of studies have shown that nicotine may counteract certain detrimental effects of ethanol on several cognitive skills such as reduction in alertness and speed of decision making (e.g., Lyon, Tong, Leigh & Clare, 1975; Michel & Battig, 1989). The rewarding relationship between these substances has also been shown to be unidirectional. That is, nicotine may enhance the reinforcing effects of ethanol but not vice versa (Glautier, Clements, White, Taylor & Stolerman, 1996; Zacny, Mitchell, Cramblett & deWitt, 1996). Altogether, the directional effects between ethanol and nicotine in the pretreatment CTA appears to be consistent with existing literature regarding the nature of their interaction.

EXPERIMENT 3

Experiment 3 was conducted in order to examine whether cocaine and ethanol are functionally related with common psychopharmacological effects. The pre-exposure variant of the CTA paradigm formed the basis of the following set of experiments. As outlined earlier in this thesis, the pre-exposure CTA paradigm may provide an opportunity for the assessment of the functional similarities between drugs. In the pre-exposure paradigm, drug stimuli being compared are typically never in the system long enough to provide an opportunity for a pharmacological interaction between them. Therefore, any similarities in drug effects must reflect overlapping stimulus properties between substances being compared.

Experiment 3a examined the effect of ethanol pre-exposure on the formation of a cocaine induced CTA. Experiment 3b examined the effect of cocaine pre-exposure on the formation of an ethanol induced CTA. It was hypothesized that if cocaine and ethanol are functionally related and endowed with overlapping stimulus properties, then pre-exposure to ethanol should at least attenuate a cocaine induced CTA and cocaine pre-exposure should at least attenuate an ethanol CTA. Such results by definition would exclude cocaethylene as the agent inducing CTA in the pretreatment paradigm because at no time would cocaine or ethanol be present in the animals simultaneously.

EXPERIMENT 3A

Materials and Method

Subjects: Thirty-two male Wistar rats (Charles River, Quebec) weighing between 275-300 grams at the start of the experiment. The animals were individually housed in stainless steel cages throughout the experiment in a room regulated for constant temperature and humidity on a 12 hour light-dark cycle. Purina rat chow was available ad lib throughout the experiment. Subjects were acclimatized to the colony room seven days before imposing the restricted water access schedule. Subjects had free access to water throughout the acclimatization period only.

Drugs: Cocaine Hydrochloride (BDH Fine Chemicals) 18 mg/kg was dissolved in 0.9% saline at a concentration of 1 mg/ml. Cocaine solution was injected i.p. Ethanol was injected in a concentration of 20% v/v and was prepared by diluting 95% ethanol in saline. Ethanol solution was injected i.p. Saccharin solution (0.1%) was mixed in tap water.

Procedure: Following one week of acclimatization to the laboratory housing conditions, rats were placed on a 23 hour and 20 minute water deprivation schedule. Tap water was presented to the animals in stoppered plastic tubes fitted with stainless steel ball bearing spouts for 40 minutes beginning at noon each day. The spouts were inserted through the wire mesh in front of the home cages. Water was presented in this manner at the same time daily and was measured to the nearest ml. A one bottle drinking procedure was used for all drinking sessions.

After 3 days of adaptation to the water deprivation schedule animals were randomly assigned to one of four treatment groups. The pre-exposure injections were

administered on days 4, 5 and 6, 60 minutes following the 40-minute water session. Animals assigned to groups Ethanol-Cocaine (E-C) and Ethanol-Vehicle (E-V) were pre-exposed to a single injection of ethanol (1.2 g/kg) while animals assigned to groups Vehicle-Cocaine (V-C) and Vehicle-Vehicle (V-V) were pre-exposed to saline. On day 7, 24 hours after the last pre-exposure injections, rats were presented with a novel tasting 0.1% (w/v) saccharin solution for 20 minutes at noon. Within one minute after completion of the saccharin drinking session, animals in groups E-C and V-C were injected twice with cocaine (18 mg/kg per injection spaced 30 minutes apart) while animals in groups E-V and V-V were injected with saline in the same manner. Data gathered in pilot experiments in our laboratory indicated that 2 injections of cocaine 18 mg/kg spaced 30 minutes apart produced a reliable CTA. A second and third pairing between saccharin solution and drug or vehicle injections was repeated on days 10 and 13. Days 16, 19 and 22 constituted drug free test days. On these days animals were presented with saccharin for 20 minutes with no corresponding drug treatment. On intervening days, between conditioning and test days, animals were presented with water for 40 minutes beginning at noon.

Data Analysis: Only animals consuming at least 5 ml of saccharin on the first exposure to saccharin were included in the data analysis. This criterion eliminated no animals from the data analysis of this experiment. A CTA was defined as a significant reduction in saccharin intake of a given experimental group relative to its own baseline saccharin intake. Saccharin intake data was analyzed with a 4 x 6 mixed factorial. Single-df-comparisons were used in order to probe for CTA.

Results

A two-way (4x6) ANOVA with repeated measures on the Days factor was conducted on saccharin intake data. This analysis yielded significant Group ($F_{3,25} = 6.723, p < .001$), Days ($F_{5,125} = 14.777, p < .001$) and Group x Days interaction ($F_{15,125} = 4.464, p < .001$) effect. Test of simple main effects showed that the groups did not differ significantly ($p > .05$) from each other at baseline.

Within subjects single-df-comparisons revealed that group V-V significantly increased ($p < .05$) its baseline saccharin intake on all days except for test days 1 and 3. Group E-V significantly increased its saccharin consumption on all days relative to baseline. In contrast, saccharin consumption decreased significantly for group V-C on test day 1 relative to baseline, which was indicative of a cocaine induced CTA. Baseline saccharin intake significantly increased for group E-C on all days except for pairing day 2.

Between subjects single-df-comparisons revealed that group V-C consumed significantly less saccharin ($p < .05$) relative to all other groups on test day 1. In addition, on this day, saccharin consumption for group E-C did not differ significantly from control groups V-V and E-V suggesting that ethanol completely blocked a cocaine induced CTA.

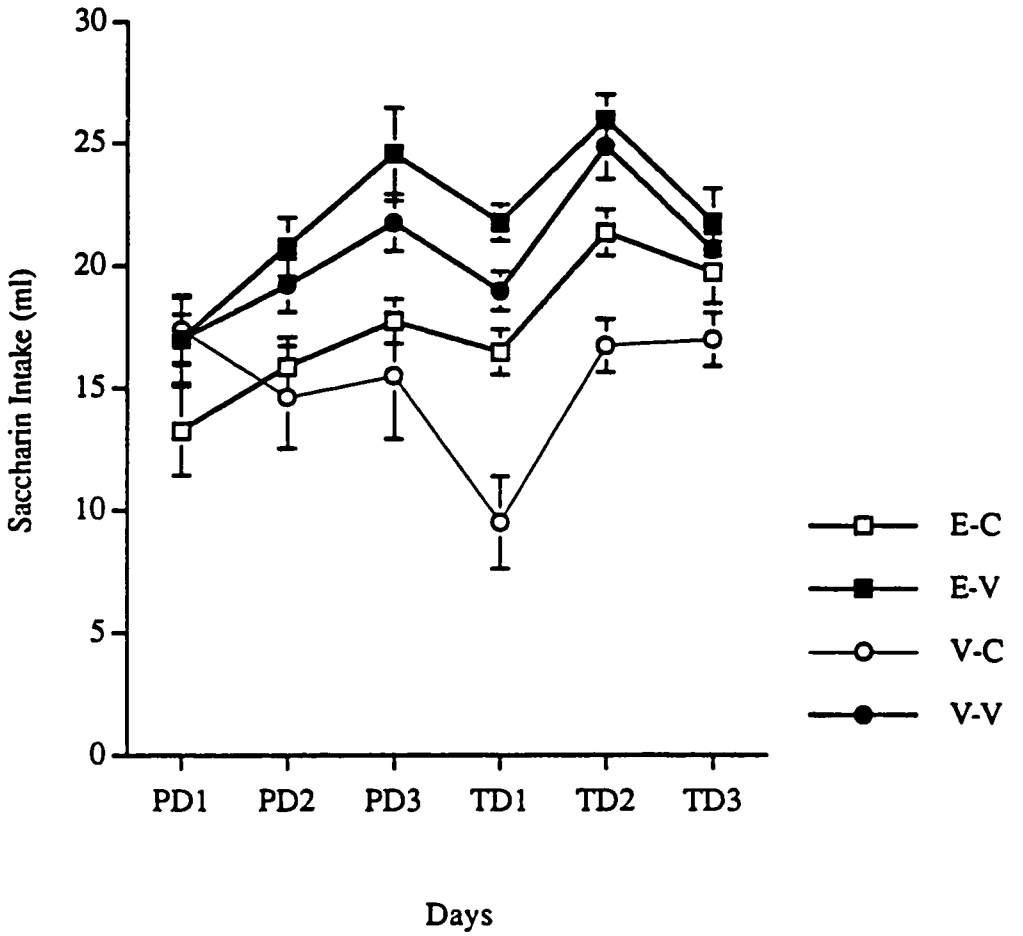

Figure 5. Effects of pre-exposure to ethanol on a cocaine induced conditioned taste aversion as reflected in mean consumption of saccharin solution for Pairing Days 1-3 (PD1, PD2, PD3) and Test Days 1-3 (TD1, TD2, TD3). Vertical lines represent the S.E.M.

EXPERIMENT 3B

Materials and Method

Subjects: Subjects were 33 male Wistar rats (Charles River, Quebec) weighing between 275-300 grams at the start of the experiment. Housing conditions were identical to those outlined in experiment 3a. All subjects were acclimatized to the colony room for seven days as in experiment 3a before imposing the restricted water schedule.

Procedure: Following one week of adaptation to the laboratory housing room conditions, rats were placed on the same water deprivation schedule as in experiment 3a. However, in this experiment, animals assigned to groups Cocaine-Ethanol (C-E) and Cocaine-Vehicle (C-V) were pre-exposed to a single injection of cocaine (36 mg/kg) while animals assigned to groups Vehicle-Ethanol (V-E) and Vehicle-Vehicle (V-V) were pre-exposed to saline. On day 7, 24 hours after the last pre-exposure injections, rats were presented with a novel tasting 0.1% (w/v) saccharin solution for 20 minutes at noon. Within one minute after completion of the saccharin session, animals assigned to groups C-E and V-E received a single injection of ethanol (1.2 g/kg), while animals assigned to groups C-V and V-V were injected with saline. As in experiment 3a, a second and third pairing between saccharin solution and drug or vehicle injections was repeated on days 10 and 13. Days 16, 19 and 22 constituted drug free test days.

Data Analysis: As in experiment 3a, only animals consuming at least 5 ml of saccharin on the first pairing day were included in the analysis. No animals were eliminated from the data analysis. As in experiment 3a, CTA was defined as a significant reduction in saccharin intake of a given experimental group relative to its own baseline saccharin intake. Saccharin intake data was analyzed with a 4 x 6 mixed factorial

ANOVA as in Experiment 3a. Single-df-comparisons were used in order to probe for CTA.

Results

A two-way (4x6) ANOVA with repeated measures on the Days factor was conducted on saccharin intake data. This analysis yielded no significant Group ($F_{3,29} = .961, p > .05$) effect. Conversely, significant Days ($F_{5,145} = 15.595, p < .001$) and Group x Days interaction ($F_{15,145} = 4.125, p < .001$) effects were observed. Test of simple main effects revealed that saccharin consumption for the groups did not differ significantly ($p > .05$) at baseline.

Within subject single-df-comparisons revealed that group V-V significantly increased ($p < .05$) its baseline saccharin consumption on pairing day 3 and test days 2 and 3. Group C-V significantly increased its saccharin consumption on all days relative to baseline. In contrast, group V-E significantly decreased its saccharin consumption on test day 1 relative to baseline suggesting an ethanol induced CTA. Group C-E significantly increased its baseline saccharin intake on pairing days 2 and 3, as well as on test day 2.

Between subjects single-df-comparisons revealed that on test day 1, group V-E consumed significantly less ($p < .05$) saccharin compared to groups C-V and V-V but not C-E suggesting that cocaine merely attenuated the formation of an ethanol induced CTA.

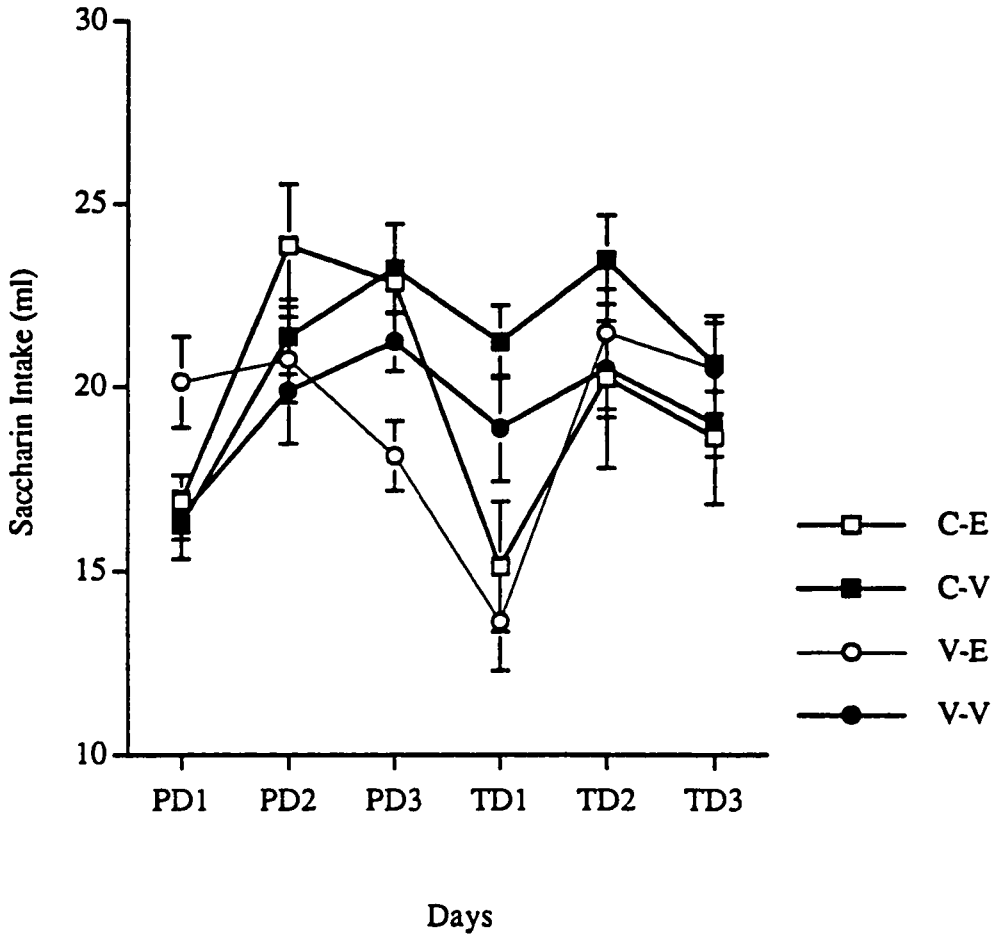

Figure 6. Effects of pre-exposure to cocaine on an ethanol induced conditioned taste aversion as reflected in mean consumption of saccharin solution for Pairing Days 1-3 (PD1, PD2, PD3) and Test Days 1-3 (TD1, TD2, TD3). Vertical lines represent the S.E.M.

Discussion

Taken together, the results of experiments 3a and 3b revealed an asymmetrical interaction between cocaine and ethanol in the pre-exposure paradigm. In experiment 3a, ethanol pre-exposure blocked the formation of a cocaine induced CTA but in experiment 3b, cocaine pre-exposure attenuated the formation of an ethanol induced CTA. The present asymmetrical results suggest that there are functional similarities between cocaine and ethanol, which reflect overlapping but not identical stimulus properties shared by these drugs as reflected in the pre-exposure paradigm.

The present interaction between cocaine and ethanol cannot be mediated by cocaethylene. As mentioned earlier, cocaethylene is produced exclusively in the presence of cocaine and ethanol (Landry, 1992) and in the present set of experiments, cocaine and ethanol were not in the animal simultaneously. In fact, the last pre-exposure injection came 24 hours prior to conditioning with either one of the drugs serving as the unconditioned stimulus. As it is certain that cocaine and ethanol were not present in the animal in any appreciable amount after 24 hours, the possibility that the present interaction is mediated pharmacologically through the production of cocaethylene would appear to be remote.

EXPERIMENT 4

Experiment 4 was conducted in an attempt to examine whether nicotine and ethanol were functionally related and share common stimulus properties. Experiment 4a examined the effects of pre-exposure to ethanol on the formation of a nicotine induced CTA. Experiment 4b examined the effects of nicotine pre-exposure on the formation of an ethanol induced CTA. It was hypothesized that if pre-exposure to ethanol or nicotine could disrupt the acquisition of CTA to nicotine or ethanol respectively, then the effects of nicotine and ethanol must be viewed as functionally related, through the involvement of common stimulus properties. A failure of ethanol or nicotine pre-exposure to disrupt taste aversion learning based upon nicotine or ethanol respectively would suggest a complete dissimilarity between the effects of ethanol and nicotine.

EXPERIMENT 4A

Materials and Method

Subjects: Thirty-two male Wistar rats (Charles River, Quebec) weighing between 275-300 grams at the start of the experiment. The animals were individually housed in stainless steel cages throughout the experiment in a room regulated for constant temperature and humidity on a 12 hour light-dark cycle. Purina rat chow was available ad lib throughout the experiment. Subjects were acclimatized to the colony room seven days before imposing the restricted water access schedule. Subjects had free access to water throughout the acclimatization period only.

Drugs: (-) – Nicotine di-d-tartate (Research Biochemical International) 1 mg/kg was dissolved in 0.9% saline at a concentration of 1 mg/ml. Nicotine was injected i.p. Ethanol was injected in a concentration of 20% v/v and was prepared by diluting 95% ethanol in saline. Ethanol was injected i.p. Saccharin solution (0.1%) was mixed in tap water.

Procedure: Following one week of adaptation to the laboratory housing room conditions, rats were placed on the same water deprivation schedule as in experiment 3b. After 3 days of adaptation to the water deprivation schedule animals were randomly assigned to one of four treatment groups. The pre-exposure injections were administered on days 4, 5 and 6; 60 minutes following the 40 minute water session. Animals assigned to groups Ethanol-Nicotine (E-N) and Ethanol-Vehicle (E-V) were pre-exposed with a single injection of ethanol (1.2 g/kg) while animals assigned to groups Vehicle-Nicotine (V-N) and Vehicle-Vehicle (V-V) were pre-exposed to saline. On day 7, 24 hours after the last pre-exposure injections, rats were presented with a novel tasting 0.1% (w/v)

saccharin solution for 20 minutes at noon. Within one minute after completion of the saccharin session, animals in groups E-N and V-N were injected twice with nicotine (1 mg/kg per injection spaced 30 minutes apart) while animals in groups E-V and V-V were injected with saline in the same manner. A second and third pairing between saccharin solution and drug or vehicle injections was repeated on days 10 and 13. Days 16, 19 and 22 constituted drug free test days. On intervening days, animals were presented with water for 40 minutes beginning at noon.

Data Analysis: Only animals consuming at least 5 ml of saccharin on the first exposure to saccharin were included in the data analysis. This criterion eliminated no animals from the data analysis. A CTA was defined as in previous experiments. Saccharin intake data was analyzed with a 4 x 6mixed factorial. Single-df-comparisons were used in order to probe for CTA.

Results

A two-way (4x6) ANOVA with repeated measures on the Days factor was conducted on saccharin intake data. The analysis yielded significant Group ($F_{3,28} = 4.298, p < .05$), Days ($F_{5,140} = 6.657, p < .001$) and Group x Days interaction ($F_{15,140} = 3.001, p < .001$) effects. Tests of simple main effects revealed that the groups did not differ significantly ($p > .05$) in baseline saccharin consumption but did differ significantly on paring day 3, test day 1 and 2.

Within subjects single-df-comparisons revealed that both groups E-V and V-V significantly increased ($p < .05$) their saccharin consumption on all days relative to baseline saccharin intake. In contrast, group V-N significantly decreased its saccharin

consumption on test day 1 relative to baseline, which was indicative of a nicotine, induced CTA. Group E-N maintained its baseline saccharin consumption across all days.

Between subjects single-df-comparisons revealed that group V-N consumed significantly less ($p<.05$) saccharin compared to all other groups on test day 1. However, on this same day, group E-N consumed less saccharin compared to control group E-V. test day 2. This pattern of results suggested that suggested ethanol pre-exposure attenuated a nicotine induced CTA.

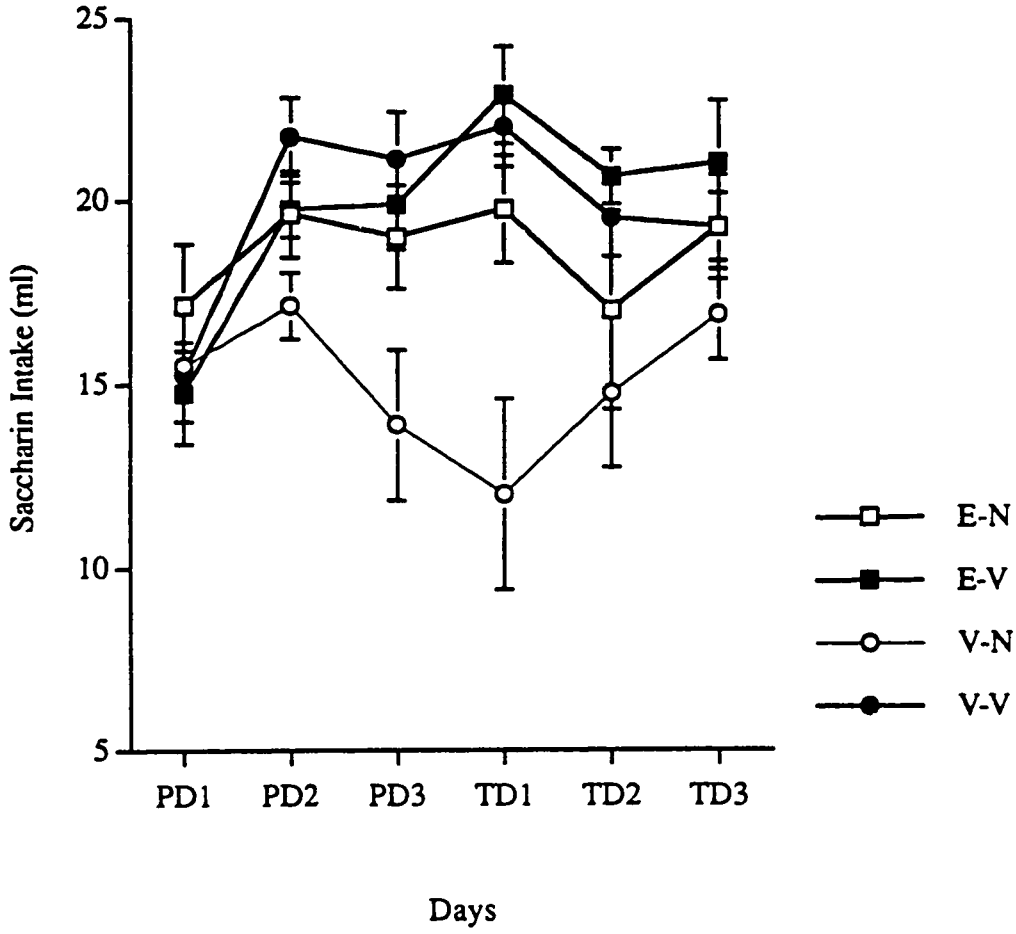

Figure 7. Effects of pre-exposure to ethanol on a nicotine induced conditioned taste aversion as reflected in mean consumption of saccharin solution for Pairing Days 1-3 (PD1, PD2, PD3) and Test Days 1-3 (TD1, TD2, TD3). Vertical lines represent the S.E.M.

EXPERIMENT 4B

Materials and Method

Subjects: Subjects were 32 male Wistar rats (Charles River, Quebec) weighing between 275-300 grams at the start of the experiment. Housing conditions were identical to those outlined in experiment 4a. All subjects were acclimatized to the colony room for seven days as in experiment 4a before imposing the restricted water schedule.

Procedure: Following one week of adaptation to the laboratory housing room conditions, rats were placed on the same water deprivation schedule as in experiment 4a. In fact, procedures were identical to experiment 4a. However, animals assigned to groups Nicotine-Ethanol (N-E) and Nicotine-Vehicle (N-V) were pre-exposed to a single injection of nicotine (2 mg/kg) while animals assigned to groups Vehicle-Ethanol (V-E) and Vehicle-Vehicle (V-V) were pre-exposed to saline. On day 7, 24 hours after the last pre-exposure injections, rats were presented with a novel tasting 0.1% (w/v) saccharin solution for 20 minutes at noon. Within one minute after completion of the saccharin session, animals assigned to groups N-E and V-E received a single injection of ethanol (1.2 g/kg), while animals assigned to groups N-V and V-V were injected with saline. As in experiment 4a, a second and third pairing between saccharin solution and drug or vehicle injections was repeated on days 10 and 13. Days 16, 19 and 22 constituted drug free test days.

Data Analysis: Only animals consuming at least 5 ml of saccharin on the first exposure to saccharin were included in the data analysis. This criterion eliminated no animals from the data analysis of this experiment. A CTA was defined as in previous

experiments. Saccharin intake data was analyzed with a 4 x 6mixed factorial. Single-df-comparisons were used in order to probe for CTA.

Results

A two-way (4x6) ANOVA with repeated measures on the Days factor was conducted on saccharin intake data. This analysis yielded significant Days ($F_{5,140} = 12.788, p < .001$) and Group x Days interaction ($F_{15,140} = 5.334, p < .001$) effects. There was no significant Group effect ($F_{3,28} = 2.499, p > .05$). Test of simple main effects revealed that the groups did not differ significantly ($p<.05$) in their baseline saccharin intake.

Within subjects single-df-comparisons revealed that saccharin consumption increased significantly ($p<.05$) for all groups except for group V-E on all days relative to their own baseline saccharin intake. In contrast, group V-E significantly decreased their baseline saccharin consumption on pairing day 3 as well as test day 1 suggesting an ethanol induced CTA.

Between subjects single-df-comparisons revealed that group V-E consumed significantly less saccharin compared to all other groups at pairing day 3 and test day 1. In addition, group N-E did not differ significantly from groups N-V and V-V on these days. Altogether, this pattern of results suggested that nicotine pre-exposure completely blocked the formation of an ethanol induced CTA.

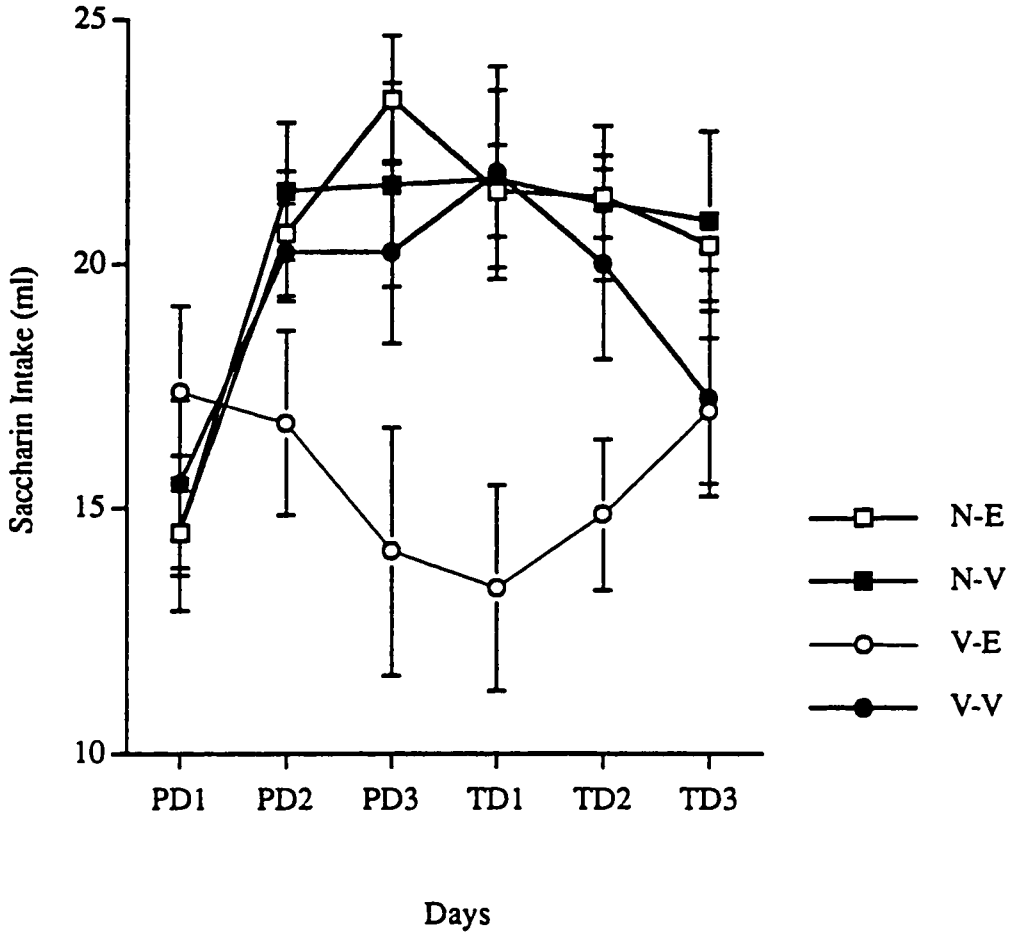

Figure 8. Effects of pre-exposure to nicotine on an ethanol induced conditioned taste aversion as reflected in mean consumption of saccharin solution for Pairing Days 1-3 (PD1, PD2, PD3) and Test Days 1-3 (TD1, TD2, TD3). Vertical lines represent the S.E.M.

Discussion

The results of experiments 4a and 4b demonstrated that ethanol and nicotine interacted asymmetrically in the pre-exposure paradigm. Experiment 4a revealed that ethanol pre-exposure attenuated the formation of a nicotine induced CTA, while experiment 4b suggested that nicotine pre-exposure blocked the formation of an ethanol induced CTA. These results suggested that nicotine and ethanol are functionally related and endowed with overlapping but non-identical properties.

GENERAL DISCUSSION

One of the goals of this thesis has been to assess whether cocaine and ethanol as well as nicotine and ethanol interact pharmacologically in the pretreatment CTA paradigm. In this variant of the CTA paradigm, a pretreatment drug is administered in close temporal proximity but prior to taste aversion conditioning with a second drug injection so as to permit a pharmacological interaction between the pretreatment and conditioning agents. It follows that if a pretreatment drug can disrupt (presumably as a result of an alteration or elimination of its pharmacological effects) taste aversion learning to a conditioning drug, then the two drugs could possibly interact pharmacologically. Results of experiments 1 and 2 in fact suggested that cocaine and ethanol as well as nicotine and ethanol interacted pharmacologically.

An additional goal of this thesis was to determine whether cocaethylene mediated the observed interaction between cocaine and ethanol in the pretreatment paradigm. In fact, the asymmetrical results observed in experiment 1 ruled out the possibility that cocaethylene mediated the interaction between cocaine and ethanol in the pretreatment CTA paradigm.

The present asymmetrical pretreatment effects observed between cocaine and ethanol as well as nicotine and ethanol suggested the possibility of pharmacologically specific interactions between these drugs. This view is in contrast with that proposed by Domjan (1980) which suggested that pretreatment effects are due mainly to the fact that a pretreatment drug can induce a "malaise" which may reduce the effectiveness of the association between the CS (taste stimulus) and a subsequent drug injection. If, as

Domjan (1980) suggested, pretreatment effects are due merely to interference effects without regard for pharmacological interactions, then all drugs tested in the pretreatment paradigm will cancel each other out in a symmetrical manner (assuming each produces similar amounts of malaise). It is difficult to explain the specificity and asymmetry in pretreatment effects between cocaine and ethanol as well as nicotine and ethanol using such a model.

The goal of experiment 3 was to determine whether cocaine and ethanol may be functionally related and also share common stimulus properties. This was investigated using the CTA pre-exposure paradigm and rested on the assumption that the extent to which two different drugs result in discriminably similar internal states, will determine whether pre-exposure to one drug treatment will attenuate CTA to the other. The results of experiment 3 demonstrated that cocaine and ethanol were functionally related and endowed with overlapping properties, independent of the possible formation of cocaethylene. Experiment 4 examined whether nicotine and ethanol were functionally related at least as reflected in the pre-exposure CTA paradigm. These results revealed that nicotine and ethanol were also functionally related and endowed with overlapping stimulus properties.

Pre-exposure effects have been interpreted by some as reflecting pharmacological tolerance (Cappell & LeBlanc, 1977). The drug tolerance hypothesis suggests that self-administered drugs are initially dysphoric which is ultimately why they produce CTA. With experience, the drug's aversive effects tolerate and unmask the positive reinforcing effects (Cappell, LeBlanc & Herling, 1975). The tolerance hypothesis can explain the fact that pre-exposure to a drug may disrupt CTA to the same drug. The tolerance hypothesis

may also support the notion that pre-exposure to one drug may attenuate a CTA based upon a second drug, as long as there is symmetrical cross-tolerance. In other words, if pre-exposure to one drug attenuates conditioning induced by a second drug, then reversing the order of the pre-exposure and conditioning drug should result in an equivalent degree of attenuation. It seems unlikely that the asymmetrical pre-exposure effects between cocaine and ethanol as well as nicotine and ethanol could be explained in terms of pharmacological tolerance.

Pre-exposure effects have been explained by some as reflecting associative effects (Braveman, 1977). According to Braveman, in order for a CTA to occur, an animal must learn that an aversive consequence follows tasting a novel flavor. This is achieved by pairing a novel flavor with an aversive agent. For Braveman, the nature of the aversive agent is not important. Instead, learning the association between the flavor and its aversive consequence is most significant. Therefore, pre-exposure to any drug should serve to disrupt CTA to any other drug as long as both drugs can produce equivalent magnitudes of aversion. This view is similar to that proposed by Domjan. The asymmetrical pre-exposure effects observed between cocaine and ethanol as well as nicotine and ethanol proved difficult for an associative interference explanation.

The present asymmetrical pre-exposure effects also prove problematic for the novelty hypothesis. The novelty hypothesis assumes that in order for a pre-exposed drug to attenuate CTA to a second drug, the stimulus properties underlying both drugs must be similar. Therefore, if one drug disrupts taste aversion learning induced by a second drug, then, reversing the pre-exposure and conditioning drugs should result in an equivalent degree of CTA attenuation, which was not observed.

The present asymmetrical pre-exposure effects between ethanol and cocaine and ethanol and nicotine may reflect overlapping but non-identical stimulus properties between these pairs of drugs. It is conceivable that both ethanol and cocaine as well as ethanol and nicotine may act on common substrates to induce a CTA, but that ethanol has other CTA inducing effects which are uncommon to cocaine, and nicotine has other CTA inducing effect which are uncommon to ethanol.

Switzman, Fishman & Amit (1981) proposed that drugs with greater dysphoric properties (as reflected by their capacity to enhance a drug's ability to produce a CTA) may not only cause CTA to be more resistant to attenuation, but may also lower a drug's self-administration potential. Furthermore, drugs that are less readily self-administered should also be more resistant to attenuation in the CTA. In fact, Switzman, Fishman & Amit (1981) demonstrated that CTA induced by Δ^9-THC was most resistant to attenuation by drug pre-exposure, followed by valium CTA and morphine CTA which were readily attenuated by drug pre-exposure. This data paralleled self-administration data where cannabis was shown to be least readily self-administered followed by valium and then morphine.

In experiment 3, it was observed that cocaine CTA was more effectively attenuated by ethanol pre-exposure than an ethanol CTA was attenuated by a cocaine pre-exposure. It can be argued that relative to ethanol, cocaine has greater self-administration potential. It is possible therefore that those elements that make ethanol less readily self-administered as compared to cocaine, also render it more resistant to attenuation in the CTA paradigm. In experiment 4, it was demonstrated that ethanol CTA was more effectively attenuated by nicotine pre-exposure as compared to nicotine CTA which was

less easily disrupted by ethanol pre-exposure. This observation is interesting in light of the fact that nicotine is presumed to be a weaker reinforcer as compared to other classically reinforcing drugs such as ethanol. It is conceivable that the stimulus properties of nicotine that make it less readily self-administered relative to other drugs also make it more resistant to attenuation by drug pre-exposure.

Conclusions

The results of the studies reported here indicate that specific pairs of drugs whose use is frequently combined by humans are related to each other as reflected in their interaction in two variants of the CTA paradigm. The first set of experiments revealed that cocaine and ethanol as well as nicotine and ethanol are capable of exerting their effects by interacting pharmacologically in the pretreatment variant of the CTA paradigm. The second set of experiments revealed that cocaine and ethanol as well as nicotine and ethanol are functionally related and endowed with overlapping stimulus properties. The fact that these pairs of drugs have overlapping psychopharmacological effects may have relevance to their frequent co-abuse in humans. It is conceivable that the use of one drug may act as a cue to stimulate the use of a second drug as a result of activation of a common mechanism. This may be particularly important for individuals attempting to abstain from these drugs.

It has also been shown in this thesis that drugs which are more readily self-administered may be more readily disrupted in the pre-exposure CTA. Conversely, drugs that are less readily self-administered may also be less readily disrupted in CTA paradigm presumably due to their additional "dysphoric" properties. It follows that the pre-exposure CTA procedure may serve as a useful vehicle to compare the rewarding or

self-administration capacity of drugs with abuse potential (Switzman, Fishman & Amit, 1981).

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