Abstract Rationale: Conditioned taste aversion (CTA) produced by drugs of abuse such as morphine and cocaine has been interpreted as representing the rewarding actions of these drugs. Evidence for this interpretation is based, in part, on findings in rats indicating saccharin is a more effective conditioning flavor compared to salt (NaCl). However, our studies with ethanol have found salt to be a highly effective conditioning flavor in mice. Objectives: The present series of studies examined the acquisition of CTA to morphine, ethanol, lithium chloride, and cocaine. Further, saccharin and salt were utilized in each experiment in order to determine effectiveness of each flavor to serve as a conditioning stimulus. Methods: In four separate experiments, adult male DBA/2J mice were acclimated to a 2 h/day water restriction regimen. Subsequently they received four conditioning trials consisting of 1 h access to either 0.15% w/v saccharin or 0.1 M salt followed by 0, 10 or 20 mg/kg morphine (experiment 1), 0, 2, or 4 g/kg ethanol (experiment 2), 0, 1.5 or 3.0 milliequivalents/kg lithium chloride (experiment 3) or 0, 10 or 20 mg/kg cocaine (experiment 4). A fifth flavor access period (trial 5) was not followed by drug exposure. Following trial 5, each subject received 24-h access to the conditioning flavor and water (two-bottle test 1). Control subjects (0 dose groups from each experiment) received a second two-bottle test with 24-h access to both saccharin and salt flavors. Results: Reduced flavor intake and reduced flavor preference was noted in all drug-paired groups in each experiment. However, more rapid development of CTA was seen with the saccharin flavor in morphine- or cocaine-paired groups. In contrast, ethanol-induced CTA appeared more rapidly with the salt flavor. Lithium-induced CTA was modest, and emerged equally with either flavor. Conclusions: CTA induced by morphine or cocaine in mice occurs in a similar pattern to that seen in rats, and these findings agree with an interpretation based on drug reward. In contrast, ethanol-induced CTA is more likely attributable to aversive effects.

Keywords Morphine · Ethanol · Cocaine · Lithium chloride · Conditioned taste aversion · DBA/2J mice

Introduction

Taste conditioning procedures are typically composed of pairings of a distinctive flavor (e.g. saccharin) with subsequent drug exposure. The most frequently reported outcomes are reductions in flavor intake or reductions in preference for the flavor. This effect is produced by many drugs or chemicals, and has been termed conditioned taste aversion (CTA). CTA produced by malaise-inducing drugs such as lithium chloride has been generally accepted as reflecting negative hedonic effects (e.g. Garcia et al. 1974), and this procedure has utility in the assessment of drug toxicity (Riley and Tuck 1985). In addition to toxins, recreationally used drugs (i.e. licit and illicit drugs of abuse) also appear universally to support establishment of CTA (Hunt and Amit 1987). These same drugs are effective reinforcers in self-administration procedures, and are able to support conditioning of place preference at doses also effective in the CTA paradigm (Schuster and Thompson 1969; Meisch and Carroll 1987; Young and Herling 1986; Tzschenkte 1998). These contrasting outcomes of drug self-administration, conditioned reward and conditioned aversion have been the subject of several interpretations. CTAs produced by these drugs may reflect aversive effects which are independent from rewarding properties (Goudie 1987). However, evidence gathered using the taste reactivity proce-
dure indicates drugs such as amphetamine, cocaine, and morphine produce qualitatively different reactions from lithium chloride. Specifically, flavors paired with drugs producing conditioned taste “aversion” elicit behavioral reactions seen after contact with unpalatable tastants (e.g. chin rubbing, gaping, paw treading, Parker 1995). However, drugs that can exert rewarding effects do not produce prominent aversive taste reactions compared to lithium leading to the suggestion that conditioned reductions in flavor intakes produced by these drugs represent avoidance instead of aversion (Parker 1993, 1995).

In contrast to views relating drug-induced CTA to experience of negative hedonic consequences, at least two alternative theoretical accounts have been offered to explain CTA produced by self-administered drugs. Both accounts are based on the general notion that rewarding effects of drugs per se underlie the production of CTA. Hunt and Amit (1987) propose self-administered drugs produce conditioned “taste shyness.” In this account, novel drug stimulus properties paired with a novel taste come to elicit avoidance of the flavor. Flavor avoidance is based on a general alarm reaction to the novel stimulus. These same drug stimulus properties are also thought to subserve reinforcement in self-administration procedures (Hunt and Amit 1987). A more recent view is based on a process termed “reward comparison” (Grigson 1997). This interpretation is related to the concept of anticipatory contrast, in which consumption of a preferred solution (e.g. saccharin) is reduced in situations when it predicts availability of a more preferred sucrose solution (Flaherty and Checke 1982). Thus, in the CTA paradigm, reductions in intake of a preferred flavor represent greater preference for the drug. That is, the hedonic value of saccharin is comparatively less than the hedonic value of a drug. A similar outcome (i.e. reductions in saccharin intake) occurs when saccharin access predicts the presentation of a more preferred sucrose solution (see discussion in Grigson 1997). Regarding drug-induced CTA, evidence for the reward comparison hypothesis comes, in part, from studies in rats utilizing a highly preferred saccharin flavor and a less preferred and presumably neutral salt flavor as the conditioned stimulus. Reinforcing drugs such as morphine and cocaine elicit greater CTA to a saccharin flavor compared to a salt flavor. In contrast, the aversive drug lithium chloride produces comparable CTA to both flavors (cf. Grigson 1997).

The purpose of the present series of experiments was to examine the acquisition of CTA in mice using either saccharin or salt as the conditioning flavor. Several drugs of abuse (i.e. morphine, ethanol, cocaine), in addition to LiCl were used as unconditioned stimuli. Although saccharin appears more effective compared to salt as a conditioning stimulus with morphine or cocaine (Grigson 1997), data from this laboratory suggest salt is a more effective stimulus compared to saccharin when ethanol was used as the unconditioned stimulus (Risinger and Cunningham 1995). However, these studies also differed in the species used (rats or mice), and our previous work did not compare the saccharin and salt flavors within the same experiment. Thus, in the present work we examined the acquisition of CTA using both saccharin and salt flavors within each experiment. In accord with Grigson (1997), we postulated more effective conditioning with the saccharin flavor when either morphine or cocaine was used as the unconditioned stimulus. We expected saccharin and salt to show comparable conditioning to lithium chloride. For ethanol, we postulated greater conditioning with salt compared to saccharin, in accord with our previous findings (cf. Risinger and Cunningham 1995).

Materials and methods

Subjects

Adult male DBA/2J mice were obtained from the Jackson Laboratory (Bar Harbor, Maine, USA) at 7 weeks of age and allowed to acclimate to the animal colony for 1 week before procedures began. Mice were housed individually in hanging stainless-steel cages (24×18×18 cm) with wire mesh front and bottoms. The colony room was maintained on a normal 12-h light-dark cycle (lights on at 0700 hours) at an ambient temperature of 21±1°C. All procedures were conducted during the light phase. Lab chow was available continuously in the home cages. Daily access to fluids was restricted as described herein. Animal housing, care, and procedures followed the Guide for the Care and Use of Laboratory Animals (National Research Council 1996).

Drugs

Morphine sulfate, ethanol, and cocaine hydrochloride were mixed in saline. Lithium chloride was mixed in sterile distilled water. Morphine, lithium and cocaine concentrations were varied to achieve a 10 ml/kg volume of injection. Ethanol was prepared as a 20% v/v solution and dose manipulated by varying the volume of injection (cf. Linakis and Cunningham 1979).

Procedure

Four separate experiments were conducted, differing only in the drug used as the unconditioned stimulus. In each experiment, subjects were adapted to a water restriction schedule (2 h water per day) over a 7-day period. At 48-h intervals over the next 10 days, separate groups of mice received 1-h access to either a solution of NaCl (0.1 M in tap water) or saccharin (0.15% w/v in tap water) between 0900 and 1000 hours. After all but the last flavor exposure, all mice received drug treatment (n=9–10/group). Drug treatments (all injections IP) for each experiment were as follows: experiment 1, morphine (0, 10, 20 mg/kg); experiment 2, ethanol (0, 2, 4 g/kg); experiment 3, lithium chloride (0, 1.5, 3.0 mg/kg); experiment 4, cocaine hydrochloride (0, 10, 20 mg/kg). Drug doses were chosen on the basis of literature values in rats or mice and were expected to produce CTA. All mice also received 30-min access to tap water 5 h after each flavor access period, in order to prevent dehydration. Two-hour access to tap water was given on intervening days.

Following the last flavor access period, mice were given 24-h access to water. Subsequently, each mouse was given 24-h access to both the conditioning flavor and to water (i.e. two-bottle test). Position of the tubes (left/right) was counterbalanced in each drug-treatment group. Following this test, saline treated subjects in each experiment (i.e. 0 mg/kg groups) were given simultaneous 24-h access to both saccharin and salt flavors. Measures were corrected for evaporation in all experiments was corrected by comparing fluid loss from bottles placed on an empty cage.