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Measures of the aversive effects of drugs: A comparison of conditioned taste and place aversions

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ABSTRACT

The present experiments directly compared the ability of the conditioned taste and place aversion designs (CTA and CPA, respectively) to measure the aversive effects of lithium chloride (LiCl) in male Sprague–Dawley rats. In the CTA assessment (Experiment 1), rats were given one of two novel tastes paired with LiCl (0, 0.18, 0.32, 0.56 or 1 mEq/kg) and the alternate novel taste paired with vehicle the next day. This was repeated three times, followed by a final two-bottle test. In the CPA assessment (Experiment 2), rats were given LiCl at the same doses and placed on one side of an unbiased two-chambered apparatus, followed by vehicle injection and placement on the opposite side on alternating days. This was repeated three times followed by free access to both sides in an assessment of relative preference. LiCl induced robust, dose-dependent taste aversions with rats receiving 0.32 mEq/kg or greater consuming a smaller percentage of the drug-paired taste than that of controls. LiCl did not induce place aversions at any dose with LiCl- and vehicle-treated subjects displaying comparable preferences for the drug-paired side. The basis for the differences of the two designs in indexing LiCl's aversive effects was discussed.

1. Introduction

The aversive effects of various compounds have been extensively assessed in a variety of animal models (Kimeldorf et al., 1960; van der Kooy et al., 1983; Parker and Rennie, 1992; Ettenberg, 2009), the two most common being the conditioned taste aversion (CTA) and conditioned place aversion (CPA) procedures. In the CTA design, an animal is given access to a novel solution and then injected with a drug (Garcia et al., 1955; Freeman and Riley, 2008). On a subsequent exposure, the animal avoids consumption of the taste, presumably due to its association with the drug's aversive effects (Garcia and Ervin, 1968; Revusky and Garcia, 1970; Riley and Tuck, 1985; Rozin and Kalat, 1971; for an alternative interpretation, see Grigson, 1997). In the CPA procedure, the animal is injected with a drug prior to being placed on one side of a two-chambered apparatus (and the vehicle before placement on the other side). Under these conditions, the animal subsequently spends significantly more time on the vehicle-paired than the drug-paired side, an effect argued to be a function of the association of the chamber with the drug's aversive effects (van der Kooy et al., 1983; Stewart and Grupp, 1986).

The CTA and CPA designs are both purported to measure a drug's aversive effects; however, it is not known if the two procedures are comparable in this assessment. Work with drugs of abuse in the taste and place conditioning preparations suggests that the two designs may not be similar in this respect, in that many drugs of abuse, e.g., ethanol (Chester and Cunningham, 1999; Green and Grahame, 2008), cocaine (Isaac et al., 1989), methamphetamine (Gubner et al., 2013), morphine (Bechara et al., 1987; Simpson and Riley, 2005), nicotine (Rauhut et al., 2008) and caffeine (Steigerwald et al., 1988; Brockwell et al., 1991) produce both a CTA and a conditioned place preference (CPP), an index of the rewarding effects of drugs (Mucha et al., 1982; Tzschentke, 2007) at the same dose and route of administration. Importantly, such effects can be seen in the same animals when concurrently tested in a combined CTA/CPP design (Reicher and Holman, 1977; Simpson and Riley, 2005; Verendeev and Riley, 2011), indicating that such drugs have multiple stimulus effects (Verendeev and Riley, 2012). In other words, the production of robust CTAs and CPPs by a variety of drugs of abuse suggests that a drug's rewarding effects may mask its aversive effects in the place conditioning procedure, thereby impacting the ability of this procedure to index such effects (for a related discussion, see Murray and Bevins, 2010).

Although it may be difficult to compare CTAs and CPAs with drugs of abuse, several studies have made comparisons between the two designs using a manipulation with clear aversive, but no rewarding, effects. For example, in a review by Garcia et al. (1961) on the ability of radiation to induce CTAs and CPAs, the CTA design appeared to be more sensitive than the CPA procedure in assessing radiation's aversive effects (as indexed by the minimal effective dose and the number of trials to produce conditioning in each preparation). However, several differences in the experimental procedures among the studies preclude any general conclusions regarding the relative sensitivities of the two

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designs in assessing radiation's aversive effects, e.g., taste aversions were measured as a reduction in consumption from a preconditioning baseline, whereas place aversions were measured as a preference between the drug- and vehicle-associated chambers. Further, different doses were used across the studies making it difficult to determine whether the procedures would be equally sensitive to the same dose. Finally, due to differences between the two study designs with respect to number of trials, exposure durations and exposure rates, the extent of change in taste and place aversions attributable to each of these factors cannot be determined.

Subsequently, direct comparisons between CTA and CPA procedures using the classical emetic lithium chloride (LiCl) have been made (see Lett, 1985; Mucha and Herz, 1985; Risinger and Cunningham, 2000) and it again appears that a drug's aversive effects are more likely to be detected with taste conditioning than place conditioning. In the study by Lett, for example, rats received a novel taste in their home cage for 15 min and were then placed on one side of a two-chambered apparatus. Five minutes after placement in the chamber, each rat was injected with LiCl and immediately returned to the same chamber for an additional 25 min. On alternate days, rats received the same treatment, but were given a different novel taste in the home cage and placed on the opposite side of the experimental apparatus from their location on the previous trial. After six conditioning trials, taste and place conditioning were tested on the same day, revealing a significantly more pronounced LiCl-induced CTA than CPA. Although suggestive of differences in the ability of taste and place conditioning to index LiCl's aversive effects, there were no assessments of control baselines for taste or side preferences with which to compare the taste and place aversions. Such a comparison would allow for a determination of changes within each procedure relative to its own controls, thus establishing an aversion. This relative change could then be directly compared between designs to determine which procedure was more sensitive. Moreover, the design tested taste and place conditioning in the same animals which may have reduced the likelihood that place conditioning would occur as a result of masking or blocking of place conditioning (Revusky, 1971; Lett, 1989; Esmoris-Arranz et al., 1997; though see King and Riley, 2013; for a review of blocking see Kamin, 1969). That is, an animal that consumes saccharin followed by an injection of LiCl may rapidly form a strong association between the taste of saccharin and the onset of illness. When subsequently put in the place conditioning compartment, the rat's ability to associate illness with the compartment may be impaired because of the previously acquired taste-illness association.

In a related study by Mucha and Herz (1985), one group of rats received on alternate days a pairing of one flavor cue with LiCl and a pairing of a different flavor cue with vehicle (three trials for each condition). A second group of rats received on alternating days a pairing of LiCl with one set of floor cues and a pairing of vehicle with a different set (again, three trials for each condition). Under these two procedures, LiCl produced a taste aversion at 20% of the dose required to induce a place aversion. Similar to Lett (1985), however, no control groups were run to compare with the drug-treated animals (to indicate relative strengths of the aversions). Further, different metrics were used for the different procedures, i.e., taste preference scores were calculated as the differences between volumes consumed of the drug-paired and vehicle-paired flavors as a percentage of total fluid intake, while place preference scores were calculated as the amount of time spent on the vehicle-paired side subtracted from the amount of time spent on the drug-paired side. Moreover, the dose range and number of doses used for each procedure were different making direct comparisons over the full dose–response curve difficult.

More recently, Risinger and Cunningham (2000) compared LiCl-induced conditioned taste and place aversions in adult males of two different mice strains, DBA/2J (D2) and C57BL/6J (B6). In the CTA procedure, different groups of mice received four trials in which access to a 0.2 M NaCl solution was followed by an intraperitoneal (IP) injection of one of four different doses of LiCl. In their CPA design, each mouse received four pairings of a distinctive floor cue (grid vs. hole) immediately after receiving an IP injection of one of three different doses of LiCl. In a direct comparison between the CTA and CPA designs, taste aversions were detected at 1.5 mEq/kg, half the dose required to induce a significant CPA (3.0 mEq/kg), for the D2 mice (no differences were seen in the B6 strain). Although this suggests that the taste aversion design is more sensitive in indexing LiCl's aversive effects (at least for the D2 mouse strain), taste conditioning was assessed by a change in fluid consumption relative to the animal's own baseline, while place conditioning was measured relative to a control group. Given that such measures, i.e., differences from one's own baseline vs. a control baseline, have been reported to yield different minimally effective doses in other work (Dacanay et al., 1984), it is not clear that the results can be directly compared.

In an attempt to circumvent the abovementioned issues with the previous studies, the present experiments assessed and compared LiCl-induced taste aversions (Experiment 1) and place aversions (Experiment 2) in adult male Sprague–Dawley rats. Specifically, in each experiment the preference for the drug-paired stimulus (taste and place in Experiments 1 and 2, respectively) was determined relative to vehicle-treated animals in each experiment. This allowed an assessment of an aversion as a significant difference from the control baseline and further allowed direct comparisons between the taste and place conditioning procedures (as the percent change from controls). To match as closely as possible the conditioning procedures in the CTA and CPA designs, animals in the CTA procedure were given one of two equally preferred tastes and injected with LiCl and the second taste followed by vehicle while in the CPA assessment the animals were injected with LiCl and confined to one of two equally preferred sides and injected with vehicle and confined to the other side. The specific temporal order in which the conditioned stimuli (taste and place) were given in relation to the injection of LiCl matched the procedures typically used in the assessment of taste and place aversions (see Revusky and Garcia, 1970; Tzschentke, 1998; Tzschentke, 2007). Q7 Further, separate groups of animals were used for each experiment to eliminate the possibility of the interference of one conditioning procedure by the other. Finally, comparable doses and conditioning parameters were used for the two assessments.

2. Materials and methods

2.1. Method

2.1.1. Subjects

Eighty-four experimentally naïve, male Sprague–Dawley rats (Harlan Laboratories, Indianapolis, IN) arrived at the facility on postnatal day (PND) 21. Upon arrival, subjects were group housed in OptiRat Plus polycarbonate bins (23 × 44 × 21 cm, $n = 3$ per bin in both experiments) and maintained on a 12:12 light–dark cycle (lights on at 0800 h) and at an ambient temperature of 23 °C. All experimental procedures occurred during the light phase, and unless otherwise stated, food and water were available ad libitum. The study was approved by the Institutional Animal Care and Use Committee at American University and followed the National Research Council's *Guide for the Care and Use of Laboratory Animals* (2011) and the *Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research* (2003).

2.1.2. Apparatus

Place aversion conditioning was conducted in eight identical San Diego Instruments Place Preference Systems, San Diego, CA, each consisting of two main chambers (28 × 21 × 34.5 cm) connected by a smaller middle chamber (14 × 21 × 34.5 cm). One of the main chambers featured a white aluminum diamond plate floor with white walls; the other conditioning chamber featured a hair-cell-textured black plastic floor and black walls; the smaller middle chamber consisted of

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