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Research report

Affective taste responses in the presence of reward- and aversion-conditioned stimuli and their relationship to psychomotor sensitization and place conditioning

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HIGHLIGHTS

- Rewarding and aversive stimuli produce conditioned place preferences and aversions.
- Affective experience of tastants can be assessed by studying orofacial reactions.
- Orofacial reactions in reward and aversion conditioned places predict behavior.
- Has implications for how affective responses to conditioned stimuli guide behavior.

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ABSTRACT

Anecdotal experience and empirical evidence suggest animals approach or avoid conditioned stimuli based on the ability of those stimuli to elicit affective responses or interfere with affective assessments of ongoing stimuli. Thus, this study investigated the relationship between the ability of drug-conditioned environments to induce conditioned place preference or aversion and their ability to influence palatability responses to sucrose and quinine in those same environments. Mice were conditioned to methamphetamine (2 mg/kg), morphine (10 mg/kg) or naloxone (10 mg/kg). Following testing for the expression of place conditioning, palatability responses to sucrose and quinine in the conditioned contexts were assessed. In general, virtually no effects of exposure to drug-conditioned contexts on overall positive or aversive palatability responses were observed. However, in naloxone-conditioned mice, the strength of conditioned place aversion to the naloxone-paired context correlated with aversive taste reactivity responses to quinine in that context. In morphine-conditioned mice, positive reactions to sucrose in the morphine-paired context negatively correlated with positive reactions to sucrose in the vehicle-paired context. Interestingly, the rate of methamphetamine-induced behavioral sensitization during conditioning and positive taste responses to sucrose in the methamphetamine-paired context positively correlated. These studies suggest that conditioned stimuli interact with or modulate the affective experience of ongoing unconditioned stimuli such as tastants, and these may reflect behavioral processes that guide behavior optimally.

1. Introduction

Place conditioning, especially conditioned place preference (CPP), has become an immensely popular method for assessing the rewarding properties of stimuli in laboratory animals [1]. This popularity is due especially to its ease of application, strong predictive validity and lack of alternative models for predicting the affective impact of unconditioned stimuli. A commonly held, but largely unproven, view is that place conditioning derives from an ability of conditioned cues to influence or generate emotional responses leading to approach or avoidance behavior. If indeed conditioned cues acquire such ability, then one may expect them to interfere with the affective assessment of other unconditioned or conditioned stimuli. Certainly, clinical and preclinical studies show that conditioned stimuli can elicit affective changes, or influence the affective assessment of unconditioned stimuli already present. For instance, studies in rodents show that affective responses to tastants such as sucrose and quinine can come under the control of conditioned exteroceptive stimuli such as a tone or odor [2–4] or

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interoceptive stimuli such as taste [5]. Related studies in humans show that emotional state can interfere with taste assessments [6–9].

With this in mind, this study investigated the relationship between the ability of drug-conditioned environments to induce conditioned place preference or aversion (CPA) and their ability to modulate palatability responses to sucrose and quinine in those same environments. The objective was to seek evidence that conditioned stimuli could influence ongoing affective states, such as generated by palatable and aversive tastants, and that such influence would predict any effect of those conditioned cues on behavior. We found that exposure to drug-conditioned stimuli readily guides behavior, i.e. produced place conditioning, but there was little evidence that these conditioned stimuli produce generalized shifts in affective, i.e. palatability, assessments of tastants. However, we found several predictive relationships between palatability responses in the presence of conditioned stimuli and the strength of CPP and CPA, or the rate of behavioral sensitization. These studies suggest that stimuli conditioned to affective events interact with the affective experience of ongoing unconditioned stimuli, and these may reflect behavioral processes that guide behavior optimally.

2. Materials and methods

2.1. Overall experimental design

Detailed descriptions of specific aspects of the experimental design are provided in the sections below. The overall design of this study was to first implant mice with intra-oral cannulae for infusion of tastants, then assess the ability of drugs to induce place conditioning, and finally assess orofacial reactions to tastants when forcibly exposed to the conditioned stimuli that induced the place conditioning. By using this approach, it was possible to determine if (1) drug-conditioned stimuli influenced affective, i.e. palatability, assessments of tastants, and (2) if affective assessments of tastants in the presence of conditioned stimuli predicted the ability of these conditioned stimuli to guide behavior, i.e. induce CPP or CPA. Thus, following recovery from surgery, mice were subjected to a standard conditioning procedure that induced CPP or CPA by pairing a pre-determined compartment of a two-compartment apparatus to one of three drugs, largely as described in our previous studies [10–12]. These drugs were chosen for their ability to produce opposing effects by various pharmacological means. Thus, two drugs that typically produce CPP (morphine or methamphetamine) were compared with a drug that produces CPA (naloxone). The establishment of CPP or CPA was determined by comparing the natural bias of mice to the two compartments before conditioning with the bias induced by conditioning. Locomotion was also measured during conditioning to determine the psychomotor effects of the drugs and any incidences of behavioral sensitization. Together, psychomotor activation, behavioral sensitization and conditioned place preference are considered three fundamental responses to addictive drugs (see [13]). Following testing for place conditioning, the floor of the conditioning apparatus was raised so that mice could be viewed from below while maintaining the visual cues present. Mice were confined to each compartment of the conditioning apparatus for 20 min at a time for two contiguous days to determine the effect of the conditioned stimuli on orofacial reactions to tastants. That is, 10 min into the 20 min confinement period, each mouse received a short infusion of sucrose, during which orofacial reactions were video recorded for later scoring. Ten minutes later, mice were infused with quinine and video recorded again.

2.2. Experimental subjects

Male C57BL/6J Jcl mice (Nihon Clea, Tokyo, Japan), 8 weeks of age at arrival, were used. Mice were individually housed with food and water provided ad libitum in a temperature-controlled colony room. All experiments were carried out during the light period (07:00–19:00). Experimental protocols were approved by the RIKEN Brain Science Institute review committee and were in accord with the National Research Council Guide for the Care and Use of Laboratory Animals.

2.3. Tastants and drugs

Sucrose and quinine hydrochloride dihydrate were purchased from Sigma–Aldrich and dissolved in distilled water. Methamphetamine hydrogen chloride (Dainippon Pharmaceutical, Tokyo, Japan), morphine hydrochloride (Sankyo Co, Tokyo, Japan) and naloxone hydrochloride (Sigma–Aldrich) were dissolved in 0.9% NaCl. Methamphetamine, morphine and naloxone doses are expressed as free base amounts corrected for salt and water contents.

2.4. Surgical implantation of oral cannulae

Mice were implanted with chronic bilateral oral cannula under ketamine (100 mg/kg) and xylazine (10 mg/kg) anesthesia, as described previously [14].

2.5. Place conditioning

The place conditioning apparatus consisted of 25 cm × 25 cm × 20 cm ($W \times D \times H$) locomotor activity monitoring boxes divided into two equal sized rectangular compartments. The compartments differed only by the visual stimuli on the walls (black and white horizontal or vertical stripes, 2 cm wide). The floor, consisting of transparent Plexiglas, was placed over bright grey paper to simulate a mirror. During tastant infusions for taste reactivity measurement (see below), the apparatus was temporarily elevated and a mirror placed beneath the transparent floor to allow video recording from underneath. Horizontal locomotor activity and location within the box were monitored by infrared photosensors (16 × 16 array; Truscan, Coulbourn Instruments, Allentown, PA, USA).

On the first day (pre-test), mice freely explored the entire apparatus for 20 min. The time spent in each compartment was recorded. During the following eight days (conditioning), mice received subcutaneous injections of vehicle or drugs and immediately confined for 40 min to one of the two compartments. Conditioning was performed using an unbiased experimental design such that approximately half the mice were assigned to their preferred and half to their unpreferred compartment. All mice received vehicle (0.9% NaCl, 10 ml/kg) on days 1, 3, 5 and 7 of conditioning, and either vehicle (9 mice), methamphetamine (2 mg/kg; 9 mice), morphine (10 mg/kg; 9 mice) or naloxone (10 mg/kg; 8 mice) on days 2, 4, 6 and 8 of conditioning. Preference or aversion to the drug-paired environment was tested (test) the following day (day 10) during a 20 min session identical to the pre-test. Establishment of place conditioning was defined as a statistically significant change in time spent in the drug-paired context between the test and pre-test. Taste reactivity in the conditioning chambers was measured on the two following days (days 11 and 12; see below).

2.6. Taste reactivity testing

For taste reactivity testing, mice received a 0.1 ml infusion over a period of 1 min during which time they were video recorded. For video recording, the entire place conditioning apparatus was elevated and orofacial taste reactivity responses recorded using a video camera directed at a mirror. Mice were habituated to the infusion procedure with drinking water in the home cage for two days. Each day, mice received an infusion of 0.2 M sucrose 10 min following placement in the compartment, followed by an infusion of 0.5 mM quinine 10 min later. The choice to infuse sucrose first, and quinine second was based on previous studies suggesting this order to have the least confounding effects on individual responses to the two tastants and that a 10 min interval is sufficient to allow dissipation of any effect on subsequent responding [15,16]. The concentration of sucrose and quinine were chosen based on data from our laboratory [14], as to elicit an intermediate level of positive and negative reactions, thus allowing changes in either direction. Mice were tested in one compartment per day and the order of the compartment, i.e. drug-paired versus vehicle paired, was randomized. Mice were never presented with sucrose or quinine in the conditioning apparatus before these two days of testing.

Video recordings were analyzed frame-by-frame (30 frames/s) by an observer blind to treatment (tastant or context) as described previously [14]. Positive reactions scored were rhythmic tongue protrusions, non-rhythmic tongue protrusions and paw licking. Aversive reactions recorded were gapes, forelimb flails, headshakes, face wiping and chin rubbing. A time bin scoring procedure was used to ensure that each component made an equal contribution to the final positive and aversive scores [17]. This scoring method, which helps equate scores of different reactions within each category so that more perseverative reactions do not obscure rare but informative reactions, is a more accurate measure of general palatability [18]. Rhythmic tongue protrusion and chin rubbing were scored in 2 s bins (continuous repetitions within 2 s scored as one occurrence). Paw licking and face wiping were similarly scored in 5 s bins. Non-rhythmic tongue protrusions, gapes, forelimb flails, and headshakes, which can occur as single behaviors, were scored as separate occurrences.

2.7. Correlation analysis

Correlation analyses were conducted between various behaviors observed during the conditioning and testing procedure and taste reactivity, focusing on behaviorally meaningful relationships such as those between taste reactivity responses and the strength of place conditioning, and differences in taste reactivity responding between the two conditioned compartments. Behavioral sensitization ratios were calculated by dividing locomotor activity on days 2, 3 or 4 of drug conditioning sessions by locomotor activity on day 1. The place conditioning score (change in time spent in the drug-paired context between the test and pre-test sessions) and the time spent in the drug-paired context during the test session were used as measures of the strength of place conditioning. Regarding taste reactivity testing, positive and aversive responses to either sucrose or quinine in both the drug-paired and vehicle-paired context were included in the analysis. Correlational