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Propranolol reverses open field effects on frustration

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ABSTRACT

Reactivity to a reward is affected by prior experience with different reinforcer values of that reward, a phenomenon known as incentive relativity. Incentive relativity can be studied via the consummatory successive negative contrast (cSNC) paradigm, in which acceptance of 4% sucrose is assessed in animals that had been exposed to 32% sucrose. These downshifted animals usually exhibit significantly less sucrose acceptance than animals that always received the 4% sucrose solution. In previous work, we found that exploration of a novel open field (OF) before the first trial with the downshifted solution attenuated the contrast effect. The goal of the present experiments was to expand the knowledge on the effects of OF exposure on cSNC. We evaluated the effect OF exposure before the second downshift trial and assessed the mediational role of the adrenergic system in the effects of OF during the first and second trial of cSNC. The results indicate that OF applied before the first or second downshift trials exert opposite effects and that the adrenergic system is involved in the acquisition and consolidation of the OF information.

1. Introduction

Rats exposed to a sudden downshift in sucrose concentration (e.g. from 32% to 4%) display reduced consummatory behavior than rats kept in continuous access to the lower sucrose concentration (Flaherty, 1996; Justel, Ruetti, Bentosela, Mustaca, & Papini, 2012; Justel, Ruetti, Mustaca, & Papini, 2012; Ruetti, Justel, Mustaca, & Papini, 2009). This phenomenon, referred to as consummatory successive negative contrast (cSNC), can be modulated by anxiolytic compounds (Becker & Flaherty, 1982; Justel, Ruetti, Bentosela, et al., 2012; Justel, Ruetti, Mustaca, et al., 2012; Kamenetzky, Mustaca, & Papini, 2008), and by drugs that act on opioid (Pellegrini, Wood, Daniel, & Papini, 2005; Wood, Daniel, & Papini, 2005), and cannabinoid neurotransmitter systems (Genn, Tucci, Parikh, & File, 2004). cSNC is based on the hypothesis that fear and frustration have functional similarities. Frustration induces emotional, behavioral, neuroendocrine, and physiological effects that are similar to those induced by the anticipation or presentation of exteroceptive nociceptive stimuli (Amsel, 1962; Daly, 1969; Gray, 1987; Konorsky, 1964; Papini, Wood, Daniel, & Norris, 2006). Cognitive mechanisms are also involved in frustration (Ruetti et al., 2009). In cSNC the animal evaluates the current reinforcer against the reactivated memory of the previously experienced reward. Animals subjected to cSNC are not exposed to explicit aversive stimuli but instead experience downshift of the reward magnitude of a known reinforcer.

Several studies indicate that pharmacological or behavioral treatments affect behavior differently when given during the first or second post-shift trial (Becker, 1986; Becker & Flaherty, 1982, 1983; Flaherty, 1990; Flaherty, Coppotelli, & Potaki, 1997; Pellegrini et al., 2005; Wood et al., 2005; for a review Ruetti & Justel, 2010), which suggests functional dissociation between these phases of cSNC (Amsel, 1992). Administration of naltrindole (a delta opioid receptor antagonist) before the first shift trial enhances cSNC, yet naltrindole has no effect when administered before the second shift trial (Pellegrini et al., 2005). Conversely, ethanol administration (Becker & Flaherty, 1982) on post-shift day 2, but not on post-shift day 1, reduced cSNC. These results suggest that different transmitters systems are involved in the expression of cSNC during the first and second post-shift trial (Papini et al., 2006).

The exploration of a novel open field (OF) can enhance or block the acquisition of associative and non-associative memories (Justel & Psyrdellis, in press). The direction of the effect is determined by several factors, including timing of treatment (e.g., before or after learning acquisition or testing; Blake, Boccia, Krawczyk, & Baratti, 2011; Boccia, Blake, Acosta, & Baratti, 2005; Izquierdo &

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McGaugh, 1985, 1987; Netto, Dias, & Izquierdo, 1985; Yang & Tang, 2011). It has been found that exposure to an OF 1 h, but not immediately before the first downshift trial (from 32% to 4% sucrose solution), inhibited the expression of cSNC. Animals that explored the OF drank more of the downshifted reward than controls not exposed to the apparatus, an effect that persisted for up to three recovery trials. OF interfered with incentive downshift even when OF exposure occurred 6 h before the downshift, and repeated exposure to OF did not deteriorate this effect. The interference was also observed after a larger discrepancy between the pre- and shift incentive values of sucrose and after a more prolonged pre-shift phase (Justel, Pautassi, & Mustaca, 2014).

The study by Justel et al. (2014) indicated that exploration of an OF prior to the first encounter with the devaluated solution modulates the expression of cSNC. It is, however, still unknown if OF modulates cSNC during the second exposure to the downshifted reward. This important question was analyzed in Experiment 1 of the present study. Subsequently, we assessed the mediational role of the noradrenergic system in the effects exerted by OF exposure upon frustration, during the first and second post-shift trial. Animals were given propranolol (PROP), a drug that blocks epinephrine and norepinephrine effects at the β1- and β2-adrenergic receptor. The effect of administering PROP immediately *before* OF exposure was analyzed in Experiment 2 and 4. Experiments 3 and 5, in turn, examined the effect of the adrenergic antagonist administered *after* the OF experience. These manipulations were meant to affect the acquisition and consolidation of the OF-related memory, respectively.

The rationale for targeting the noradrenergic system is that this transmitter is involved in learning and memory (McGaugh & Roozendaal, 2002, 2009), and modulates novelty-induced arousal (Sara, Vankov, & Hervé, 1994). Based on previous results (Izquierdo & McGaugh, 1985; Justel et al., 2014; Sara, Dyon-Laurent, & Hervé, 1995; Spreng, Cotecchia, & Schenk, 2001; Sun, Mao, Wang, & Ma, 2011), the hypotheses were that the OF applied before the first or second downshift trial would exert opposite effects on cSNC (inhibition and facilitation, respectively); and that PROP would block these effects.

2. Materials and methods

2.1. Experimental subjects

Two-hundred and fifty-six male Wistar rats, born and reared at the vivarium of Instituto de Investigaciones Médicas Alfredo Lanari (IDIM-CONICET, Buenos Aires, Argentina) were used. The animals were approximately 120 days olds at the start of the experiment. They were individually housed and had ad libitum access to water. They were weighed daily and the average ad libitum weight was 353 g (range: 252–446 g). The amount of food was gradually reduced over days until each animal reached 85% of its ad libitum weight. This level of deprivation was maintained throughout the experiment by administering the appropriate amount of food at least 20 min after the end of the daily trial. Animals were kept in a daily light–dark cycle of 12 h (lights on at 07:00 h). The housing and testing rooms were maintained at a constant temperature (around 22 °C) and humidity (around 60–70%).

2.2. Apparatus

The rats were given access to sucrose in five boxes (24 × 29 × 21 cm; MED Associates, St. Albans, VT, USA). The floor consisted of aluminum bars (0.4 cm diameter, 1.1 cm apart from center to center). The center of one of the lateral walls featured a hole (5 cm diameter, 3.5 cm deep and 1 cm above the floor), through which a sipper tube could be manually introduced from the outside. When fully inserted, the tube protruded 2 cm into the box. A photocell was located in front of the tip of the sipper tube. Goal-tracking time (measured in 0.01 s increments) was automatically recorded by a computer that measured the cumulative amount of time that the photocell was activated during the trial. Previous studies that employed the sucrose concentrations used in the present experiments indicated that goal-tracking time exhibits a significant correlation with fluid intake (Mustaca, Freidin, & Papini, 2002). Moreover, several studies have concurrently used goal-tracking time and fluid intake and yielded comparable results with either dependent variable (Papini, Mustaca, & Bitterman, 1988; Papini & Pellegrini, 2006; Riley & Dunlap, 1979). Each box was enclosed in a sound- and light-attenuating cubicle that featured white noise and diffused light. Sucrose solutions (w/v) were prepared by mixing 320 or 40 g of commercial sugar in 1 L of tap water to obtain the final 32% and 4% sucrose solutions, respectively.

An open field was used as means of exposure to novelty. It was made of grey acrylic (50 × 50 × 50 cm), and divided in 9 equal squares. A light bulb (100 W) was suspended on top of the apparatus to provide illumination.

2.3. Behavioral procedures

cSNC training began when the animals were at the target weight. A day before the first trial each animal was exposed to sucrose, to attenuate taste neophobia. Specifically, a bottle was filled with 20 ml of the corresponding sucrose solution and made available for 40 min in the homecage. cSNC was composed of two phases. (1) Pre-shift phase: The animals were exposed to the 32% (Experimental groups) or 4% (Controls groups) sucrose solution 5 min each day for 5 days/trials. This phase was meant to facilitate the encoding of an appetitive memory of the solution. (2) Post-shift phase: Twenty-four hours after the last pre-shift trial, the rats had access to a 4% sucrose solution for 5 min each day for 3 days/trials. Responses to sucrose were tested in daily 5-min trials. Each trial began the first time the photocell was activated. After 5 min, the animal was taken to the housing cage, and the conditioning box was cleaned with a damp towel.

OF exposure (duration: 5 min) was performed 1 h before the first or second downshift trial (depending on the experiment). Control (CTRL) and experimental animals were given similar handling and transportation. The only difference between the groups was that experimental, but not control, animals were exposed to the OF. Specifically, animals in the experimental group were gently placed in the center of the apparatus and allowed free exploration for 5 min. The controls remained in their homecages.

2.4. Drug administration

Propranolol hydrochloride (PROP) was purchased from Sigma Aldrich Laboratories; and administered intraperitoneally (dose: 4.5 mg/kg; volume: 1.0 ml/kg; vehicle: physiological saline). PROP or vehicle (VEH) were administered immediately after or 15 min before OF or CTRL condition (according to the experiment and to the experimental condition). According to previous experiments (Angrini, Leslie, & Shephard, 1998; Stuchlik, Petrasek, & Vales, 2009), 4.5 mg/kg PROP does not induce motor activation, motor depression or sedation.

2.5. Experimental designs

The first Experiment employed a 2 (sucrose solution given during the pre-shift phase: 32% or 4%) × 2 (Treatment: exposure or not to the open field; OF and CTRL groups respectively) factorial