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Cholinergic transmission underlies modulation of frustration by open field exposure

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ABSTRACT

Frustration can be defined as an emotional state generated by the omission or devaluation in the quantity or quality of an expected appetitive reward. Thus, reactivity to a reward is affected by prior experience with the different reinforcer values of that reward. This phenomenon is known as incentive relativity, and can be studied by different paradigms. Although methodologically simple, the exploration of a novel open field (OF) is a complex situation that involves several behavioral processes, including stress induction and novelty detection. OF exposure can enhance or block the acquisition of associative and non-associative memories. These experiments evaluated the effect of OF exploration on frustration and the role played by the cholinergic system in this phenomenon. OF exploration before first or second trial of incentive downshift modulated the expression of frustration. This effect of OF was blocked by the administration of scopolamine either before or after OF exploration. These results indicate that the cholinergic system is involved in the acquisition and consolidation of OF information.

1. Introduction

Frustration is an emotional reaction found after a given expectation is violated (Amsel, 1962). This emotional state can be assessed in laboratory animals through the consummatory successive negative contrast paradigm (cSNC; Flaherty, 1996; Justel et al., 2012a,b; Papini et al., 2015; Ruetti et al., 2009). In a cSNC animals that have had extensive access to an appetitive, highly sweetened sucrose solution (e.g., 32%), are suddenly exposed to a devaluation of this expected reward (e.g. they are given a 4% sucrose solution). Animals that experience this switch exhibit a sudden drop in sucrose acceptance, suggesting they evaluate the value of the current reinforcer against the reactivated memory of the previously experienced reward. These animals show several neurobiological alterations, including enhanced corticosterone release (Flaherty et al., 1985) and alterations in opioid transmission (Pellegrini et al., 2005). Aggressive behavior is significantly enhanced after the shift (Papini et al., 2006), whereas sexual and social behaviors are severely affected (Freidin and Mustaca, 2004; Mustaca et al., 2000). Altogether, this evidence suggests that the cSNC is a reliable model for assessing frustration responses. It has been suggested that the experimental frustration resulting from cSNC induces emotional, cognitive 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 et al., 2006; Ruetti et al., 2009).

The cSNC is modulated by several behavioral and pharmacological treatments, including neonatal stress (Ruetti et al., 2010), sexual contact (Freidin and Mustaca, 2004; Freidin et al., 2005), and by drugs that act on GABA (Becker and Flaherty, 1982; Kamenetzky et al., 2008; Justel et al., 2012a,b), opioid (Pellegrini et al., 2005; Wood et al., 2005) and cannabinoid receptors (Genn et al., 2004; for a review see Papini et al., 2015; Justel et al., 2014a).

Animals exposed to a novel environment, but not those accustomed to it, exhibit several behavioral reactions, including stress and novelty detection responses (Thiel et al., 1998). Novelty exposure, in turn, is a potent modulator of memory processes. For instance, Liu et al. (2015) found facilitated extinction of fear conditioning in animals that had been exposed to a novel environment 1 h before extinction (also see Menezes et al., 2015). An earlier study revealed greater appetitive learning in invertebrates when training sessions occurred in a novel environment (Kemenes and Benjamin, 1994).

Given this background, it should not be a surprise that the exploration of a novel open field (OF) can enhance or block memory acquisition

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(Justel and Psyrdellis, 2014; Myskiw et al., 2014), depending on factors such as timing of treatment (e.g., before or after learning acquisition or testing; Blake et al., 2011; Boccia et al., 2005; Izquierdo and McGaugh, 1985, 1987; Netto et al., 1985; Yang and Tang, 2011). Altogether, it seems that novelty exposure – as delivered via application of OF – can be used as a useful tool for the analysis of memory acquisition, consolidation, and retrieval (Izquierdo et al., 2003).

It has been recently 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 (Justel et al., 2014b). On the other hand, exposure to the OF prior to the second downshift trial enhanced the frustration effect (Justel et al., 2014c). OF did not affect sucrose intake when the frustration effect was absent, i.e. a violation in the expectation of reward was needed to observe the effect of novelty. Both effects were blocked by the nonselective beta blocker propranolol, administered either before or after the OF (Justel et al., 2014c). The first and second post-shift trials of cSNC are functionally different and seemed to reflect primary or unconditional frustration and conditioned frustration, respectively (Amsel, 1992). Several studies indicate that pharmacological or behavioral treatments affect behavior differently when given during each trial (Becker, 1986; Becker and Flaherty, 1982, 1983; Flaherty, 1990; Flaherty et al., 1997; Pellegrini et al., 2005; Wood et al., 2005; for a review Ruetti and Justel, 2010).

Our previous work (Justel et al., 2014b, 2014c) indicated that the exploration of an OF prior to the first or second encounter with the devaluated solution modulates the expression of cSNC, and pinpointed the role played by the noradrenergic system in the phenomenon. The aim of the present study was to evaluate the role of the cholinergic system in the OF effect on frustration, during the first and second encounter with the downshifted sucrose solution. The effect of administering scopolamine hydrochloride (SCOP), a muscarinic cholinergic antagonist, immediately *before* OF exposure was analyzed in Experiments 1 and 3. Experiments 2 and 4, in turn, examined the effect of SCOP administered *after* the OF experience. These manipulations were meant to affect the acquisition and consolidation of the OF-related memory, respectively.

The central cholinergic system has been implicated in learning and memory processes (Klinkenberg and Blokland, 2010; McGaugh and Roozendaal, 2002, 2009; Robinson et al., 2011) and particularly in the facilitating effects of novelty exposure on memory acquisition. Acetylcholine levels in the cortex and hippocampus have been observed to be greater in rats exposed to a novel open field than in control counterparts (Aloisi et al., 1997; Giovannini et al., 1998; Thiel et al., 1998; Popovic et al., 2015). While the vast majority of the research has reported SCOP-induced memory impairments (Klinkenberg and Blokland, 2010), some have indicated a facilitation of memory after SCOP administration (Roldan et al., 2001). Popovic et al. (2015) administered SCOP immediately after the acquisition of a step-through passive avoidance task. A SCOP-induced memory impairment was found when animals were tested 24 h after the training (i.e. rats given SCOP exhibited shorter latencies than controls to step-through to the compartment associated with the electric shock). SCOP treated animals, however, exhibited significantly higher latency to step-through to the compartment when the test was performed 48 h after the training trial. In other words, under these circumstances SCOP administration resulted in better memory retention. Another study exposed animals to a novel, nose-poking task during consolidation of an avoidance task. SCOP administration in-between tasks impaired acquisition of the nose-poke task but spared the consolidation of the avoidance learning (Blake et al., 2011).

Based on previous results, the hypotheses were that the OF applied before the first or second downshift trial would exert opposite effects on frustration (inhibition and facilitation, respectively). It was relatively uncertain whether SCOP would facilitate or block these effects (Blake et al., 2012; Izquierdo and McGaugh, 1985; Popovic et al., 2015; Roldan et al., 2001).

2. Materials and methods

2.1. Experimental subjects

Two hundred and twenty 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, which were approximately 120 days old at the start of the experiment, were individually housed and had ad libitum access to water. They were weighed daily and the average ad libitum weight was 361 g (range: 274–496 g). The amount of food was gradually reduced over 7 days until animals reached 85% of its ad libitum weight. All animals reached the target weight by day 7. 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. Thus, animals were kept under food deprivation for a total of 15 days. Animals were maintained in a 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). In the center of a lateral wall was a 5 cm hole, 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 sipper tube protruded 2 cm into the box. A photocell was located in front of the tip of the sipper tube inside this hole. Time in contact with the sipper (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 contact with the sipper exhibits a significant correlation with fluid intake (Mustaca et al., 2002). Moreover, several studies have concurrently used contact with the sipper and fluid intake and yielded comparable results with either dependent variable (Papini et al., 1988; Papini and Pellegrini, 2006; Riley and 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.

Four open fields were used as means of exposure to novelty. They were made of gray acrylic (50 × 50 × 50 cm), and divided in 9 equal squares. They were located in the floor of the room. Animals were exposed to the regular ambient noise of the experimental room (i.e., no white noise was employed). A light bulb (100 W) was suspended on top of the apparatus to provide illumination.

2.3. Behavioral procedures

After 7 days of food deprivation, the animals were exposed to the assigned sucrose concentration in their home cage. A habituation day was first conducted. The water bottle was filled with 20 mL of the corresponding sucrose solution and made available for 40 min. This procedure was intended to attenuate taste neophobia. The next day the cSNC, which was composed of two phases, began. (1) Pre-shift phase: the animals were exposed to the 32% or 4% sucrose solution 5 min each day for 5 days/trials. This phase was meant to facilitate the encoding of an appetitive memory. (2) Post-shift phase: 24 h after the last pre-shift trial, all 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. After the post-shift phase