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Corticosterone and propranolol's role on taste recognition memory

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ABSTRACT

Taste recognition is a robust procedure to study learning and memory processes, as well as the different stages involved in them, i.e. encoding, storage and recall. Considerable evidence indicates that adrenal hormones and the noradrenergic system play an important role in aversive and appetitive memory formation in rats and humans. The present experiments were designed to characterize the effects of immediate post training corticosterone (Experiment 1) and propranolol administration (Experiment 2 and 3) on taste recognition memory. Administration of a high dose of corticosterone (5 mg/kg, sc) impairs consolidation of taste memory, but the low and moderate doses (1 and 3 mg/kg, sc) didn't affect it. On the other hand, immediate post-training administration of propranolol (1 and 2 mg/kg, ip) impaired taste recognition memory. These effects were time-dependent since no effects were seen when drug administration was delayed 3 h after training. These findings support the importance of stress hormones and noradrenergic system on the modulation of taste memory consolidation.

1. Introduction

Animals organize their past experience as "memories", all that they learn is encoded and stored in their brains, and they preserve the environmental information in order to enable better adaptation to future situations (Ruetti et al., 2009a, 2009b). One of the most adaptive learning that the animals had is related to the intake, since consumption guarantees the subsistence, and certain errors in the selection of food or flavors that they taste could cause irreparable damages and even cause death. From an evolutionary perspective taste memory had a significant relevance since it increases the survival of animals, allowing them to recognize, due to past experiences, what and what is not safe to eat or taste. The subjects had to discriminate among the familiar stimuli and the novel ones to conclude what information requires more attention to be encoded in their long term memory (Bures et al., 1998; Domjan, 1976; Mickley et al., 2000). Fear of novel stimuli is usually observed during the first encounter with a novel stimulus; for example, a novel food with a taste and/or odor-relevant component is usually ingested in significantly lower amounts than a familiar one; after several presentations of the originally novel food, consumption increases, which is interpreted as attenuation of neophobia or habituation to the novel taste and also as appetitive memory for that food (e.g., Núñez-Jaramillo et al., 2010).

Taste recognition is a robust procedure to study learning and memory processes, as well as the different stages involved in it, i.e. encoding, storage and recall (Bérmudez-Rattoni, 2004). Considerable evidence indicates that the noradrenergic system plays an important role in aversive and appetitive memory formation in rats and humans (Cohen and Gotthard, 2011; Do-Monte et al., 2010; McGaugh, 2000; McGaugh and Roozendaal, 2009). In particular, noradrenergic agonists enhance, whereas noradrenergic antagonists impair, learning for many kinds of aversive experiences (Gallagher et al., 1977; Introini-Collison et al., 1996; Izquierdo et al., 1992; LaLumiere et al., 2003).

On other hand, studies performed in our laboratory reported evidence about the role of corticosterone on appetitive reward memory, using a negative contrast paradigm in which animals were exposed to different sucrose solutions. For example, Bentosela et al. (2006) reported that administration of corticosterone (3 mg/kg, sc) immediately (but not 3 h after training) after the change in sucrose solutions concentrations (e.g. 32% a 4%), led to an increase in the size and duration of the contrast effect. Thus, temporal contiguity between the downshift experience and corticosterone administration is necessary for peripheral and/or central glucocorticoids to influence memory consolidation.

Glucocorticoid receptor (GR) agonist administered bilaterally into the nucleus accumbens (NAc) shell after ingestion of an appetitive saccharin drinking solution enhanced long-term retention, in a dose- and time-dependent fashion, of the safe taste experience. Moreover, GR agonist administration into the NAc shell after pairing of the saccharin taste with a malaise-inducing agent enhanced retention of the aversive taste learning experience. Furthermore, concurrent antagonism of β-adrenoceptor activity within the NAc blocked the GR agonist induced retention enhancement on both tasks. Altogether, these findings

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suggest that GR activation interacts with the noradrenergic arousal system within the NAc to enhance memory consolidation of emotionally arousing training experiences regardless of valence (Wichmann et al., 2012).

Besides, it has been demonstrated that propranolol administration (β-adrenergic antagonist) in the insular cortex (IC) and in the basolateral amygdala (BLA) previously to the presentation of a novel flavor impairs memory in attenuation of neophobia paradigm or habituation to novel taste (e.g. the animals do not increases the intake of the novel solution in the following trials; Miranda et al., 2008). This study shows that noradrenergic activity is required in acquisition of a novel taste, but didn't indicates how the administration of the drug is involved in the consolidation of the information.

In line with this background, it is expected that adrenal hormones and the antagonist of its receptors modulate the consolidation of taste memory. For that reason the aim of the present experiments was to evaluate the role of corticosterone and propranolol administration in the consolidation of a taste recognition test (TRT).

2. Material and methods

2.1. Subjects

The subjects were 131 male, experimentally naive Wistar rats, about 3 months old at the start of the experiments. One week before the start of each experiment, animals were placed in individual cages with free access to water and food. The average ad libitum weight was 338 g (range: 239–463 g). The amount of food was gradually reduced across days until the animals reached 85% of their ad libitum weights. This level of deprivation was maintained throughout the duration of the experiment by posttraining supplementary food administered 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). Training trials were conducted between 10:00 and 15:00 h to avoid the peak of the circadian release of corticosterone, which occurs at the onset of the dark period (Romero, 2002). The housing and testing rooms were maintained at constant temperature (around 22 °C) and humidity (around 60–70%). All efforts were made to minimize animal suffering and to reduce the number of animals used.

2.2. Behavioral procedures

Rats were trained in 4 conditioning boxes (MED Associates, Fairfax, VT). Each box was measured 24.1 cm in length, 29.2 cm in width, and 21 cm in height. The floor was made of aluminum bars (0.4 cm in diameter, 1.1 cm apart from center to center). In the center of a lateral wall, there was a 5-cm hole, 3.5 cm deep, 1 cm above the floor level, 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 just in front of the tip of the sipper tube, inside this hole. Goal-tracking time (measured in 0.01-s units) was automatically recorded by a computer that measured the cumulative amount of time that the photocell was activated during the trial. This measure correlates with fluid intake for the two sucrose concentrations used in this experiment (Mustaca et al., 2002) and it has been used concurrently with fluid intake yielding the same results (Papini et al., 1988; Riley and Dunlap, 1979). Each box was enclosed in a sound and light-attenuating cubicle equipped with a source of white noise and diffused house light.

The TRT procedure had 2 trials, during training (trial 1), all rats received access to 4% sucrose solution; in this trial the animals acquired the information of the taste, this is the acquisition or encoding stage, after this trial ends starts the consolidation process. 24 h later the test trial was conducted to evaluate the taste recognition memory, by exposing to the animals to the sucrose solution again (trial 2). In this last trial the recovery of the first trial information is retrieved, this stage is considered as the recognition (or recall) one. On each trial, the sipper tube was manually introduced into the box before rats were placed in the conditioning box. Training and test trials lasted 5 min starting from the first interruption of the photocell located by the sipper tube. Sucrose solution (*w*/*v*) was prepared by mixing 40 g of commercial sugar in 1 L of tap water. Animals were tested in squads of four. The order of the squads was randomized across days. Each box was swept with a damp towel after each training trial.

2.3. Drug administration

To prepare corticosterone (from Sigma-Aldrich Laboratories, Saint Louis, MO), ethanol 100% was diluted in 0.9% isotonic saline to a 5% ethanol concentration. Corticosterone was then diluted in this vehicle to the target dose. Controls received the same volume of 5% ethanol in isotonic saline. This drug was administered subcutaneously (sc).

Propranolol (from Sigma-Aldrich Laboratories, Saint Louis, MO) was diluted in isotonic saline to the target dose. Controls received the same volume of isotonic saline. This drug was administered intraperitoneally (ip). The doses of both drugs were selected from previous research and preliminary experiments (Bentosela et al., 2006; Campbell et al., 2008; Crowe et al., 1991; Ruetti et al., 2009b).

2.4. Experimental designs

Three experiments were performed, each of them with an inter-subject design. The Experiment 1 evaluate the effect of corticosterone on the TRT, the Experiment 2 the role of propranolol in the TRT, and the Experiment 3 discarded possible unspecific effects that propranolol could have and bias the results of the second experiment. The following paragraphs detailed the rationality of each design.

High circulating levels of corticosterone during and immediately after an emotionally arousing event, but not after relatively neutral events, are known to modulate memory consolidation and/or retrieval (Okuda et al., 2004). In taste recognition of saccharin corticosterone enhances the retention of the safe taste (Wichmann et al., 2012). According to this research, the goal of the first experiment was to investigate the effect of several doses of corticosterone on a taste recognition test. Immediately after trial 1, different groups of animals were injected with corticosterone 1 mg/kg (group named C1; $n = 10$) or 3 mg/kg (group named C3; $n = 10$) or 5 mg/kg (group named C5; $n = 10$) or vehicle (group named VEH; $n = 10$), in an inter-subject design. With this administration the goal was to affect the consolidation of the taste memory.

The administration of β-adrenergic antagonist also modulates memory consolidation, causing an amnesic effect in animals (McGaugh, 2000; Sun et al., 2011). Consistent with this, the goal of the second experiment was to evaluate the propranolol's effect in the taste recognition test. Immediately after the first trial, different groups of animals were injected with propranolol 1 mg/kg (group named P1; $n = 10$) or 2 mg/kg (group named P2; $n = 10$) or vehicle (group named VEH; $n = 10$), in an inter-subject design. With this administration the goal was to affect the consolidation of the taste memory.

To confirm the propranolol's effect on memory consolidation, the 3rd experiment was carried out. This last design tested possible unspecific effects that the drug administration should have. There were four groups, the first one received the administration of propranolol immediately after the first trial, in a dose of 1 mg/kg (group named P immed, $n = 15$); the second group of animals received the administration of the vehicle immediately after the first trial (group named VEH immed, $n = 15$), the third group was administered with propranolol 1 mg/kg but 3 h after the first trial was ended to test possible unspecific effects of the drug (group named P 3 h, $n = 15$) and the last group received the application of vehicle after 3 h (group named VEH 3H, $n = 16$).