Behavioural Brain Research 284 (2015) 94–102

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Differential contribution of perirhinal cortex and hippocampus to taste neophobia: Effect of neurotoxic lesions

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HIGHLIGHTS

- Perirhinal lesions impair neophobic response to novel 0.3% and 0.5% saccharin solution.
- Perirhinal lesions do not affect neophobic response to novel 0.7% saccharin solution.
- Hippocampus lesions before novel saccharin do not impair neophobic response.
- Hippocampus lesions 24 h after saccharin do not affect consolidation of taste memory.

ARTICLE INFO

Article history:
Received 21 November 2014
Received in revised form 2 February 2015
Accepted 6 February 2015
Available online 16 February 2015

Keywords:
Taste
Neophobia
Perirhinal cortex
Hippocampus
Learning
Memory

ABSTRACT

Although the perirhinal cortex (Prh) has been extensively related to recognition memory, little is known about its specific role in taste memories. The main aim of the present series was therefore to examine the effect of neurotoxic lesions of the Prh on taste neophobia, a phenomenon consisting of a low intake of a novel food until its postingestive consequences are determined. The results showed that Prh-lesioned rats consumed significantly more novel saccharin in trial 1 than control subjects when a saccharin solution of 0.3% (expt. 1a) and 0.5% (expt. 1b) was presented. However, when the saccharin concentration was high and qualitatively more aversive, Prh lesions did not affect the neophobic response (0.7%, expt. 1c) and the lesioned and control animals consumed a similar amount of the fluid during the first and subsequent test trials. In all three experiments, Prh-lesioned and control rats showed a comparable intake at asymptote. Experiment 2 and 3 showed that neurotoxic lesions to the dorsal hippocampus prior to or 24 h after the intake of the novel taste (0.3% saccharin) had no effect on the initial occurrence of the neophobic response or on the consolidation of safe taste memory, respectively. These findings support a dissociation of functions between the Prh and the hippocampus in taste neophobia. Also, the data suggests that the Prh plays an essential role in detecting the novelty of the new tastant.

1. Introduction

The ability to remember tastes is one of the most important evolutionary developments in animals and it is crucial to their survival. When an animal encounters a food, the first thing it does is determine whether the nutrient is novel or familiar. If rats conclude that a food is novel and that they therefore have no knowledge about subsequent postingestive consequences, they are reluctant to consume the novel tastant and will thus consume less of it [1–3]. This innate phenomenon is called gustatory neophobia and its function is to protect the animal against the consumption of large amounts of a potentially aversive/toxic new tastant. If the new food has no negative consequences, the initial neophobic response diminishes progressively upon repeated presentations of the taste (habituation or attenuation of the neophobia) and the tastant comes to be considered safe and familiar [4–7]. However, it may happen that consumption of the new food is followed by gastrointestinal illness. In this case rats develop conditioned taste aversion (CTA) and show decreased intake of the food the next time they encounter it [8–11].

Little is known about the neural system underlying the phenomenon of taste neophobia. Using a variety of methods, including mostly c-fos expression and permanent or temporary lesions, it has been proposed that the basolateral amygdala and the insular cortex are the central components of this circuit, although the gustatory thalamus and the medial amygdala might also play a certain role [12–15]. Supporting the essential involvement of the basolateral amygdala and insular cortex, permanent lesions to this region

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http://dx.doi.org/10.1016/j.bbr.2015.02.017
0166-4328/

cause an elevated intake of the novel taste at the initial encounter and an intake comparable to that of controls at asymptote after presentation of the taste over several successive days [13,14,16–18].

In addition to the 'classical' regions mentioned above, there is recent data suggesting that the perirhinal cortex (Prh) may play some type of role in gustatory neophobia. First, neuroanatomical studies have clearly established strong reciprocal connections between the insular cortex-Prh and the basolateral amygdala-Prh, meaning that the Prh might cooperate with the above structures in some aspects of taste neophobia [19–23]. Second, behavioral studies have demonstrated that Prh lesions produce a profound impairment in the performance of the spontaneous novel object preference task and in a variety of similar tasks, suggesting that the Prh plays an essential role in judging the prior occurrence of individual items, that is, in recognition memory [24–30]. Third, electrophysiological recording studies have identified novelty neurons in the Prh; i.e. neurons that respond differently to the first presentation of novel stimuli as compared to subsequent presentations of the same or to presentations of familiar stimuli [31]. Other studies, using immunohistochemical imaging for c-fos expression, have detected greater activation of the Prh by novel, as opposed to familiar, individual stimuli [32–34]. These data provide a possible neural substrate for the detection/recognition of the novelty of a taste and, consequently, in the production of the neophobic response. Fourth, one study showed a profound disruption of CTA acquisition when the Prh was inactivated by the infusion of tetrodotoxin 60 min prior to the presentation of the conditioned stimulus but not when the toxin was infused immediately after saccharin drinking [35]. This CTA deficit could be viewed as a secondary consequence of a possible taste neophobia deficit in which rats with Prh inactivation treat the novel taste presented (the conditioned stimulus) as familiar, producing a retardation in acquisition due to a latent inhibition-like effect [36,37].

In addition to the above considerations, over the past two decades experimental data have suggested that the Prh might contribute to both memory and perception [38–41]. This view is known as the 'perceptual-mnemonic hypothesis' of the medial temporal lobe [42–44]. In support of this hypothesis, strong evidence shows that damage to the Prh impairs normal performance in tasks designed to tap perceptual functions regardless of the sensory modality used [45–49]. Under this perspective, Prh lesions might affect the perceptual abilities of the rats when a new tastant is presented at a low concentration, altering the normal gustatory neophobic response of the animals. This last idea constitutes yet another reason to investigate whether the Prh contributes to taste neophobia.

Despite of the aforementioned studies, little is known about Prh participation in taste neophobia. To the best of our knowledge to date no study has investigated the effect of permanent Prh lesions on gustatory neophobia. The present study was undertaken to determine whether neurotoxic lesions in this cortical region influence the neophobic reaction to a novel tastant (0.3%, 0.5% and 0.7% saccharin: experiments 1a, 1b and 1c, respectively). Since the dorsal hippocampus, another mediotemporal lobe region, has been related in previous studies to taste neophobia using intrahippocampal infusions of anisomycin [50], in experiments 2 and 3 of the present series we examined the effect of permanent lesions to the dorsal hippocampus on taste neophobia when the lesions were sustained before or after the presentation of the novel taste.

2. Material and methods

2.1. Animals

The subjects were 90 male Wistar rats from Harlan Laboratories (Barcelona, Spain). Specifically, the number of animals per experiment was (n lesioned vs. n controls): Experiment 1a = 9 versus 9; experiment 1b = 9 versus 9; experiment 1c = 14 versus 10; experiment 2 = 8 versus 7; experiment 3 = 8 versus 7. The rats (270–290 g) were individually housed in plastic cages (480 × 265 × 210 mm, floor area 940 cm^2, Tecniplast, Italy) and maintained on a 12:12 h light:dark cycle (lights on at 8:00 am) at a constant temperature of 22 ± 1 °C. Rats were given *ad libitum* food and water until experiments started. All experimental procedures were performed in conformity with European (86/609/EEC) and Spanish (2005) legislation and were approved by the Ethics Committee for animal research of the University of Granada.

2.2. Surgery

2.2.1. Perirhinal lesions

Under the effect of sodium pentobarbital anesthesia (50 mg/kg, i.p., Sigma Chemical, St. Louis, Missouri), the rats were placed in a David Kopf stereotaxic apparatus (mod. 900, David Kopf Instruments, Tujunga, California) with the incisor bar adjusted so that lambda and bregma were level. Rats were randomly assigned to either an experimental or a control group. The lesioned subjects received bilateral injections of N-methyl-D-aspartic acid (NMDA, Sigma–Aldrich, Madrid, Spain, PBS, pH 7.4, 0.07 M) through the insertion of a 30-gauge stainless steel cannula in eight sites of the perirhinal cortex. The cannula was oriented laterally at 26° from the vertical. The coordinates were derived from the atlas of Paxinos and Watson [51] and based on the anatomical location of the perirhinal cortex, as delineated by Burwell and colleagues [20,52–54]. The anteroposterior (AP) stereotaxic coordinates were calculated relative to bregma, the lateral (L) relative to the midline and the dorsoventral (V) relative to the top of the skull: AP = −2.5, L = ±2.4, V = 9.8; AP = −3.6, L = ±2.9, V = 9.8; AP = −4.8, L = ±3.3, V = 9.8; AP = −5.8, L = ±2.8, V = 9.8. NMDA was administered in a 0.3 μl volume at each site through the cannula, which was attached to a 1-μl Hamilton microsyringe (Teknokroma, Barcelona, Spain). Delivery of the solution was carried out with a Harvard Apparatus pump set (model 22, Panlab-Harvard Apparatus, Barcelona, Spain) at an infusion rate of 0.1 μl/min. The cannula was left *in situ* for an additional 6 min before being withdrawn. The control groups received identical surgical procedures, which the exception that equivalent volumes of phosphate-buffered saline (PBS) were infused into the Prh.

2.2.2. Hippocampal lesions

The initial procedure was the same as that used for the perirhinal lesions. The dorsal hippocampus was damaged at four different antero-posterior sites in relation to the interaural zero point (see [51]): AP = +5.9, L = ±1.6, V = +6.2; AP = +4.8, L = ±2.5, V = +6.5; AP = +3.8, L = ±3.2, V = +6.5; AP = +3.0, L = ±4.0, V = +5.4. The procedure for the bilateral injections of N-methyl-D-aspartic acid (NMDA, Sigma–Aldrich, Madrid, Spain, PBS, pH 7.4, 0.07 M) was the same as that used for the perirhinal lesions.

2.3. Behavioral procedure

2.3.1. Experiments 1a, 1b and 1c. Effect of Prh lesions on taste neophobia (0.3%, 0.5% and 0.7% saccharin solution)

All behavioral testing occurred in the home cages. After recovering from surgery, animals were placed on a water-restriction schedule of 15-min of water access in the morning followed 6 h later by a second 15-min period of water access in the afternoon. After 3 days of this habituation program, on the fourth day the first presentation of the novel stimulus took place. Specifically, in experiments 1a, 1b and 1c, the animals were presented with a solution of sodium saccharin (Sigma–Aldrich, Madrid, Spain) at 0.3%, 0.5% and 0.7%, respectively, for 15 min. In experiment 1a the animals