



Research report

Influence of the anteromedial thalamus on social defeat-associated contextual fear memory

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ABSTRACT

The ventral part of the anteromedial thalamic nucleus (AMv) is heavily targeted by the dorsal premammillary nucleus (PMd), which is the main hypothalamic site that is responsive to both predator and conspecific aggressor threats. This PMd-AMv pathway is likely involved in modulating memory processing, and previous findings from our group have shown that cytotoxic lesions or pharmacological inactivation of the AMv drastically reduced contextual fear responses to predator-associated environments. In the present study, we investigated the role of the AMv in both unconditioned (i.e., fear responses during social defeat) and contextual fear responses (i.e., during exposure to a social defeat-associated context). We addressed this question by placing N-methyl-D-aspartate (NMDA) lesions in the AMv and testing unconditioned fear responses during social defeat and contextual fear responses during exposure to a social defeat-associated context. Accordingly, bilateral AMv lesions did not change unconditioned responses, but decreased contextual conditioning related to social defeat. Notably, our bilateral AMv lesions also included, to a certain degree, the nucleus reuniens (RE), but single RE lesions did not affect innate or contextual fear responses. Overall, our results support the idea that the AMv works as a critical hub, receiving massive inputs from a hypothalamic site that is largely responsive to social threats and transferring social threat information to circuits involved in the processing of contextual fear memories.

1. Introduction

Social interactions are essential for defining access to sexual partners, territories and nutritional resources [see 1]. The definition of social hierarchy is established aggressively, with different physiological and behavioral consequences for defeated animals and winners [2].

Defeated animals present clear defensive responses when re-exposed to a potential aggressor or to a context previously associated with a social defeat [3–7]. Studies conducted in our laboratory showed that defeated animals avoid cages in which they had been defeated and performed a careful exploration of the environment through risk assessment behaviors [7]. Importantly, social defeat has been proposed to be an animal model of depression [8], resulting in similar behavioral and neuroendocrine changes to those found in depressed patients [9].

Combining the results of behavioral, neuronal immediate early gene activation, lesion, and neuroanatomical experiments, we have delineated a putative circuit that is involved in both innate and contextual defense responses in a subordinate conspecific [7,10,11]. During social defeat, the dorsal premammillary nucleus (PMd) is the hypothalamic site that presents the most striking activation, which appears to be

particularly confined to the dorsomedial part of the nucleus [10,11]. The dorsomedial part of the PMd receives strong inputs from specific regions of the lateral hypothalamic area (i.e., the juxtaparaventricular and juxtadorsomedial regions), which upregulate Fos expression during social defeat and likely convey septo-hippocampal information that encodes the environmental boundary restriction imposed by the presence of a dominant aggressor [11]. Moreover, the dorsomedial part of the PMd is further influenced by the conspecific-responsive circuit of the medial zone of the hypothalamus (including the medial preoptic area, the ventrolateral part of the ventromedial nucleus and the ventral premammillary nucleus), which is also mobilized during social defeat and integrates conspecific cues conveyed by the medial amygdalar nucleus [10]. Interestingly, PMd lesions block the passive components of social defense (i.e., freezing and sustained on the back position), as seen during a confrontation with a dominant aggressor [10]. It is noteworthy that the PMd is believed to influence the mnemonic processes related to contextual defensive responses [12,13] and likely involves the projection branch to the ventral part of the anteromedial nucleus (AMv) [14].

The anterior thalamic nuclei have been shown to support multiple

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and complementary forms of learning. In humans, the anterior thalamic nuclei, along with mammillary body atrophy, have been implicated in the amnesic symptoms of Korsakoff's syndrome and are required for normal episodic memory [15–17]. In rodents, there is considerable evidence from both lesion and electrophysiological studies that the anterior thalamic nuclei are involved in navigation and spatial memory, especially when distal cues are essential for a successful performance [18–21]. Moreover, the anterior thalamic nuclei influence hippocampal-dependent non-spatial tasks, such as those required to solve a temporal order problem and sample a sequence of successive odors [22], as well as the ability to use contextual information to resolve conflicts in an olfactory list learning task [23].

Previous studies from our group have shown that cytotoxic lesions or pharmacological inactivation of the anteromedial thalamic nucleus drastically reduced contextual fear responses to predator-associated environments [24,25]. However, it remains to be determined whether the AMv is involved in contextual fear in socially defeated animals. Thus, as we have previously shown for predator threats, we presently investigated whether the AMv works as an effective hub to convey social threat information from hypothalamic sites to systems involved in the processing of contextual fear memory. In the present investigation, we addressed this question by placing N-methyl-D-aspartate (NMDA) lesions in the AMv and testing both unconditioned fear responses during social defeat and contextual fear responses during exposure to a social defeat-associated context.

2. Materials and methods

2.1. Animals

Adult male Wistar rats (N = 34) weighing approximately 300 g (3–4 months old) were used as intruders; adult Long Evans male rats (N = 5) weighing approximately 600 g (9–12 months old) were used as residents and were housed with Long Evans female rats (N = 5) weighing approximately 350 g (3–5 months old). Both lineages were obtained from local breeding facilities. The animals were housed under a controlled temperature (23 °C) and illumination (12-h cycle) in animal quarters and had free access to water and a standard laboratory diet.

2.2. Ethics

Experiments were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23, 1996). All experimental procedures had been previously approved by the Committee on the Care and Use of Laboratory Animals of the Institute of Biomedical Sciences – University of São Paulo, Brazil (Protocol number 085/2012). In the present study, the experiments were planned to minimize the number of animals used and their suffering. In addition, all surgical procedures were performed under deep anesthesia, and analgesic and antibiotic medication were given postoperatively.

2.3. Surgery

For the lesion procedure, rats were deeply anesthetized with sodium pentobarbital (Cristália; Itapira, SP, Brazil; 40 mg/kg, i.p.) and were placed in a stereotaxic apparatus. Bilateral iontophoretic deposits of a 0.15 M solution of N-methyl-D-aspartate (NMDA, Sigma, St. Louis, MO, USA) were bilaterally centered in the ventral part of the anteromedial thalamic nucleus (n = 10; coordinates: anteroposterior 1.40 mm from bregma; laterolateral, ± 1.0 mm from the midline of the sagittal sinus; dorsoventral 6.1 mm from the surface of the brain) or in the rostral half of the nucleus reuniens (n = 10; coordinates: anteroposterior, 1.40 mm from bregma; laterolateral, 0.0 mm from the midline of the sagittal sinus; dorsoventral 6.30 mm from the surface of the brain) using the

stereotaxic coordinates from *The Brain Maps: structure of the rat brain* [26]. In addition, in 7 other animals, control saline injections were performed bilaterally at the same coordinates used for the ventral part of the anteromedial thalamic nucleus. NMDA deposits were performed over a 15-min period through a glass micropipette (30 µm tip diameter) using a constant-current device (model CS3, Midgard Electronics, Canton, MA, USA) set to deliver –10 µA, with 7-s pulse and interpulse durations (for NMDA lesion protocol see [27]). Animals received postoperative analgesics (Ibuprofen; Medley; Campinas, SP, Brazil; 30 mg/kg in drinking water) and antibiotics (Pentabiótico®; Zoetis; Campinas, SP, Brazil; 0.1 ml/100 g, i.p.). After a 1-week post-surgical period, the animals were placed in the experimental apparatus.

2.4. Experimental apparatus and procedure

The experimental protocol presently used to investigate innate and contextual fear related to social defeat followed Faturi and Rangel et al. [7]. The experimental apparatus was made of clear Plexiglas and consisted of a 25 × 25 × 25 cm home cage connected to another 25 × 25 × 25 cm chamber (the food compartment) by a hallway that was 12.5 cm wide and 100 cm long, with 25-cm high walls. Between the home cage and hallway, there was a sliding door (12.5 cm wide and 26 cm high) that remained closed most of the time, except for when animals were allowed to explore the remainder of the apparatus. For 10 days before the testing procedures (habituation period), the intruders were isolated and lived in the home cage, and then at the beginning of the dark phase, the home cage door was opened and animals were allowed to explore the remainder of the apparatus and obtain food pellets that were stored in the food compartment. To maintain the animals in an active state without eating, during all of the habituation and testing periods of the intruders, all pellets in the home cage were removed 3 h before the test. After the testing procedures, the food pellets were returned to the home cage. The resident male, an adult Long Evans rat, had been housed in a 25 × 25 × 25 cm cage together with a female Long Evans rat for at least three weeks prior to the social encounter with the intruder. To prevent pregnancy and discharge of pups, the females housed with the resident males had been previously hysterectomized under deep anesthesia (mixture of ketamine and xylazine; 1:2 v/v; 1 ml/kg body weight) by severing the uterine horns at the tubo-vaginal junction and at the anterior end of the cervix, but their ovaries remained intact. After a 2-week recovery period, the sterilized females were housed with the resident males.

The testing procedure consisted of three phases. Phases 1 and 3 consisted of a 5-min observation period during the last day of habituation (Phase 1) and context exposure (Phase 3). Phase 2 consisted of a 10-min observation period during the social defeat procedure. During the tests, animals were recorded with a horizontally mounted video camera.

2.4.1. Phase 1 – last day of habituation

On the last day of habituation (day 10), we observed the intruder in a familiar environment during the beginning of the dark period. To maintain the animals in an active state without eating, no food pellets were offered.

2.4.2. Phase 2 – social defeat

On the 11th day, the food compartment had been replaced by the home cage of a resident male. On the defeat day, the female was removed, and once the Wistar male intruder had entered the resident's cage, the cage's door was closed and the resident started attacking the intruder in less than 1 min. Only experienced resident males were used in the present study. After the first resident attack with a painful experience (i.e., a bite), residents and intruders were left together for a 10-min period. Only intruders that had suffered a clear social defeat were used for further analysis.

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