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Research report

Effects of ibotenic acid lesions of the mediodorsal thalamus on memory: relationship with emotional processes in mice

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Abstract

The effects of ibotenic acid lesions of the mediodorsal nucleus of the thalamus (MD) on memory and fear reactivity in mice were studied. In the first experiment, MD subjects were submitted to a behavioral design allowing to study the relationship between memory and anxiety [Krazem A, Borde N, Beracochea D. Effects of diazepam and beta-CCM on working memory in mice: relationship with emotional reactivity. Pharmacol Biochem Behav 2001;68:235–44; Beracochea D, Krazem A, Jaffard R. Methyl beta carboline-3-carboxylate reverses the working memory deficits induced either by chronic alcohol consumption or mammillary body lesions in mice. Psychobiology 1995;23:52–8]. In a second experiment, MD-lesioned subjects were submitted to a GO/NOGO temporal alternation task involving two intertrial intervals (ITIs: 0 and 30 s). Lesioned subjects exhibited large bilateral mediodorsal thalamic lesions with small damage into the centromedial thalamic nucleus. In the first experiment, MD-lesioned animals performed normally a sequential alternation task involving fixed ITIs over seven successive trials (5 or 30 s); in contrast, MD-lesioned subjects exhibited deficits in the sequential task involving the same but mixed ITIs (30–5 s versus 5–30 s) the deficit being observed for the last trials of the series, regardless the ITIs used. MD lesions increased fear reactivity in an elevated-plus maze, and scores of anxiety were negatively correlated with performance in the mixed alternation schedule. The second experiment involving non spatial information extended results of the first experiment in showing that the deficit of MD-lesioned animals was not dependent on the ITIs separating trials. Overall, our data show that MD-lesioned subjects exhibit a cognitive impairment characterized by a difficulty to maintain an alternation rule in situations involving procedural variance, and this deficit could stem primarily from an increase of fear reactivity.

Keywords: Anxiety; Learning processes; Spatial and non spatial memory; Stress; Thalamus

1. Introduction

The thalamus is a complex set of nuclei sustaining various higher brain functions such as learning and memory, as well as emotion. More specifically, the thalamus is involved in the stress response [1–3] and recent studies have reported an increase of corticotropin-releasing hormone messenger RNA [4] in the posterior thalamus and the centromedial nucleus of the thalamus following acute stress. Lesions of the anteroventral or the anteromedian nucleus of the thalamus have also been found to reduce the endocrine response of the HPA axis to stress whereas damage to the anterodorsal induced the opposite effects [5,6].

The medio dorsal nucleus of the thalamus (MD) is a prominent part of the thalamus, and damage to the MD have been associated with the global amnesic syndrome observed in diencephalic amnesia [7–10]. Numerous authors have sug-

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gested that the cognitive impairments resulting from MD lesions resulted from an indirect frontal cortex dysfunction [11,12]. In contrast, the implication of the MD in working memory processes as well as to delay-dependent forgetting is still discussed [11,13–17,38]. As yet, the exact contribution of the MD itself to emotional processes remains unclear, insofar as lesion studies showing such a role also affect neighboring areas, which can differentially act on emotion. Nevertheless, it has been shown that MD lesions induced changes in emotionality [18–20] and impairments in stimulus-reward associations [21] as well as in the ability to utilize specific action-outcome associations [22]. We already showed that MD lesions in mice produced an increase of fear reactivity in an elevated-plus maze [23] and several studies have found that the MD is involved in the stress response and fear conditioning [1,2,24].

As yet, studies centered on the relationship between the emotional consequences and the memory impairments resulting from MD lesions are very scarce [25]. Therefore, the main goal of our study is to determine if the memory deficits resulting from MD lesions are related to their emotional consequences. For that purpose, MD-lesioned mice of the present study were submitted to a behavioral design already used in previous pharmacological experiments, which allowed to study the relationship between delay-dependent memory performance and anxiety-like reactivity. Indeed, we already showed that diazepam administration produced in the same subject a decrease of fear reactivity in an elevated-plus maze which was significantly positively correlated with an increase of proactive interference in a sequential alternation task [26]; inversely, we showed that the injection of an inverse agonist of the benzodiazepine receptor increased fear reactivity in the plus maze and concomitantly, reduced interference in the same memory task [26]. The same behavioral design allowed us to show that mammillary bodies lesions or chronic alcohol consumption produced a decrease of fear reactivity in the elevated-plus maze and concomitantly produced an increase of interference in the alternation task [27]. Thus, in so far as the modulation of sequential alternation rates by interference is sensitive to the emotional effects of a drug, one could expect that lesions of brain structures that affect emotion might similarly act on the memory component of the alternation task. Interestingly, most of the tasks used at present to study memory in MD-lesioned animals have used food-deprived subjects, stimulus-reward associations or instrumental conditioning, these tasks involving a motivational component that can be affected by the lesion; in our behavioral design, the alternation task used to assess memory does not required the use of any reinforcement nor food deprivation, in so far as the alternation behavior is sustained by a strong innate component.

As the alternation task involves the use of spatial/environmental cues, a second experiment was performed using temporal alternation patterning (GO/NOGO) in a straight alley. This experiment was aimed at determining if memory processes are differentially affected by MD lesions in a non spatial task, as compared to the spatial one. Indeed, previous experiments from our team already showed that MD lesions in the rat did not produced a delay-dependent deficit in the temporal alternation task [28]. However, since the straight alley used allowed a free access to environmental spatial cues, even irrelevant to perform the task, one could think that these cues could interfere with performance. In addition, we wanted to determine if the same effects of MD lesions would be observed in mice, as compared to our previous study performed in the rat [28]. Thus, the straight alley used in the present study was entirely covered with an opaque roof to avoid exposure to the environmental spatial cues during each run. As for experiment 1, each subject was also submitted to exploration of the elevated-plus maze task at the end of the memory task, in order to evaluate fear reactivity and to perform correlation analyses between memory performance and fear reactivity scores.

2. Methods

2.1. Behavioral tasks

2.1.1. Spatial task

Spontaneous alternation (SA) is the innate rodents tendency whereby over a series of successive trials run in a T-maze, mice alternated at each trial the choice of the visited goal-arm, except for the first trial. Such a procedure allowed to distinguish between the ability to alternate per se (second trial of a series, free from any interference) from the progressive inability to do so as the number of trials increased. In the latter case, repetitive testing (i.e. sequences of more than two trials) constitutes a potent source of proactive interference (PI) since a correct response on trial N (which depends on information received in trial N-1) may be influenced by all previous information received from trial 1 to N-2. In this paradigm, the sensitivity to interference is studied by the evolution of SA rates over successive trials, using fixed or mixed delay intervals, as described below.

2.1.2. Apparatus and general procedure

All testing was conducted in a T-maze constructed of grey Plexiglas. Stem and arms were 35 cm long, 10 cm wide and 25 cm high. The starting box (10 cm × 12 cm) was separated from the stem by a vertical sliding door. Horizontal sliding doors were placed at the entrance of each arm. Light inside the apparatus (90 lux) was provided by a lamp positioned 2 m above the stem. Both goal arms and the central alley of the maze were equipped with photoelectric cells allowing to detect the location of the subject and its choice. The opening and closing of the doors were automatically monitored by a computer, which also allowed the opening of the start-arm as a function of the temporal intertrial interval (ITI) imposed by the experimenter.

Three days before the beginning of testing on the sequential SA task, animals were given two free exploration sessions