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Research report

Atropine-induced, state-dependent learning for spatial information, but not for visual cues

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Abstract

This study investigates state-dependent learning employing atropine. The reaction of rats to (1) the presentation of novel stimuli, (2) habituation to intermittent presentations of the same stimulus at the same local, (3) spatial change at the site of stimulus presentation, and (4) a visual stimulus change, was investigated in the straight alleyway test, controlling for the possible development of behavioral and/or pharmacological tolerance. Our findings reveal that rats habituated to stimulus presentation at a specific location, when under an atropine effect, do react to stimulus presentation at another location, or to a different stimulus, when under an atropine effect, indicating that this drug does not interfere with the acquisition of spatial or visual information. Differently, however, rats habituated to stimulus presentation at a specific location in the absence of an atropine effect are unable to react to spatial change when under the atropine effect, but do react to a visual stimulus change. This suggests that atropine interferes either with the retrieval of previously acquired spatial information or with the comparison of previously acquired spatial information with current information, but does not interfere with visual recognition. These findings reveal that atropine interferes with the use of spatial information acquired in the absence of a drug effect.

Keywords: Memory; Hippocampus; Atropine sulfate; Muscarinic cholinergic antagonist; Drug-state dependent; State-dependent learning; Spatial discrimination; Exploratory behavior

1. Introduction

The cholinergic system plays an important role in learning and memory processes. Drugs that impair the function of the central cholinergic system usually impair memory [3,5,6,13,22,23,24,26,27]; conversely, drugs that potentiate central cholinergic function may, under certain circumstances, enhance memory [7,14]. The participation of central cholinergic systems in modulating cognitive functions has received experimental attention in studies on humans [3], monkeys [24] and rats [6,7,12,13,16,26,27]. Most address the enhancing properties of the cholinergic system on spatial memory acquisition and/or retention. A possible cholinergic effect on the retrieval of spatial *versus* non-spatial stored memories, using tasks that impose similar behavioral demands for spatial and non-spatial information, and controlling for pharmacological and behavioral tolerance, has not been considered. In the present study, a state-dependent-learning protocol (see [20], and below) was employed to examine the possible effect of cholinergic blockade on the retrieval of spatial and non-spatial stored memories, using atropine.

State-dependent learning refers to the retrieval of information acquired in the same sensory context and physiological state as that present during encoding ([1,9,20,21,25]). Such learning is commonly characterized in pharmacological studies employing a 2×2 experimental design in which groups of animals are first trained under either a drug (D) or no-drug (N) effect, and then tested for recall under either the same drug (D) or no-drug (N) effect, according to the pairings N-N, N-D, D-N and D-D. Interpretation of the main drug effects depends on the behavioral outcomes (for details, see [20]). For example, poor performance during testing by groups exposed to a drug state change (N-D and D-N) accompanied by normal performance in groups not exposed to a drug state change (N-N and D-D)

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reveals state dependency. Differently, while poor performance during testing by animals receiving a drug before the training session (D-N and D-D) suggests the occurrence of acquisition disruption, poor performance during testing under the drug effect (N-D and D-D) suggests that the drug interferes with the retrieval of previously learned material. In addition, poor testing performance in the N-D condition associated with normal performance in the D-D and D-N conditions may suggest (1) that the drug interferes with the retrieval of information stored in the absence of the drug, and that retrieval of information stored under the drug effect is possible when acquisition occurs under the drug effect, (2) the occurrence of behavioral tolerance, *i.e.*, temporary performance impairments that occur when the drug is first administered, allowing the animal to learn how to deal with the debilitating effect of the drug, or (3) the occurrence of pharmacological tolerance, *i.e.*, after the initial drug application the animals develop drug tolerance that minimizes the effect of a subsequent dose. In the present study, the drug and no-drug administration schedule was planned to control for these possibilities (see below).

The medial septum is known to project cholinergic fibers to the hippocampus; such projection seems to be critically involved in the septo-hippocampal processing of spatial information [2,10,11,18,19,28]. Congruently, the administration of muscarinic cholinergic blockers induces consistent impairments of performance in spatial tasks; to illustrate, the use of atropine, a muscarinic cholinergic antagonist, impairs the performance of rats in the radial arm maze [23], the tree-table maze [5], the traditional water maze [22], and the water T-maze [14]. These findings raise intriguing questions. For instance, are these marked atropine effects specifically related to the use of hippocampus-dependent spatial tasks? Would such atropine effects occur if non-spatial tasks were used? Does atropine interfere with the acquisition or retrieval of spatial information?

O'Keefe and Nadel [18] proposed that the hippocampus provides a cognitive map of the environment. They distinguished alternative strategies used by animals to navigate through the environment, and suggested that more than one strategy may be used simultaneously to solve spatial tasks. According to these authors, while place (or locale) strategies involve cognitive mapping, guidance (or taxon) strategies depend on a particular prominent object or stimulus that indicates the goal location; egocentric orientation strategies are based on the rotation of the body axis relative to other axes. O'Keefe and Nadel [18] postulated that such strategies would be served by different neural systems; the hippocampus would be necessary for place learning.

According to this view, hippocampal damage should disrupt place discrimination while sparing discriminations that do not require the place dimension. Xavier et al. [30] evaluated this hypothesis by testing rats with dorsal hippocampectomy in a behavioral task that enabled assessment of their ability to deal with either spatial or non-spatial information, but whose response requirements are the same for both types of information. The animals were trained to run a shuttle-alleyway for food up to an assymptotic level of performance. Subsequently, several testing sessions were run to evaluate (1) exploratory behavior directed to the place at which novel, distracting visual stimuli (black cards on the walls) were presented in the alleyway, (2) the reduction in exploratory activity (habituation) to the intermittent presentation of the same stimulus at the same location, (3) reaction to presentation of the same stimulus (to which the rats had become habituated) at a novel location in the alleyway, and (4) reaction to the presentation of a different stimulus (black and white checkered cards on the walls, instead of black cards) at the location where the stimulus had been presented previously (and to which the rats had become habituated). The findings were straight-forward; like the controls, hippocampectomized rats did explore the black cards, did habituate to intermittent presentation of this stimulus at the same location, and did react to its substitution by the black and white checkered cards, indicating that damage to the hippocampus does not disrupt ability to explore novelty, to habituate to repetitive presentations of the same stimulus, or to compare the representation of a previously presented stimulus, stored in memory, with a current novel stimulus. In contrast, and differing from their controls, rats with damage to the hippocampus do not react to the location change for stimulus presentation, suggesting that the ability to compare a previous location of stimulus presentation, which for control rats was stored in memory, with a current one, was disrupted in hippocampectomized rats.

Xavier et al. [29] emphasized some of the advantages of the straight alleyway task in investigating cognitive functions. The fact that the behavioral response is unrelated to the reinforcement but, rather, competes with it renders this response a good index of exploratory activity. In addition, the exact same response is measured for the different cognitive functions under evaluation; thus, impairments following only one specific manipulation cannot be ascribed to the behavioral output. Finally, as stated by Xavier et al. [29], "both extra- and intra-maze cues can be manipulated either alone or in association, allowing tests of rats' capacity (1) to code external events, store this information in the form of a representation, and pay particular attention to places that are changing; and (2) to detect and react to spatial and directional-contextual changes independently of their own direction of locomotion in the maze." (p. 172).

The purpose of the present experiments was to associate the protocol for state-dependent learning using atropine with the testing of rats in the straight alleyway task to evaluate whether cholinergic blockade interferes with either the acquisition or retrieval of information, and whether similar effects occur when spatial and non-spatial information are processed. A 2×2, state-dependent, learning experimental design was used, including the pairings N-N, N-D, D-N and D-D, both to detect a change in the location of stimulus presentation and to detect a change in the visual pattern of the stimulus. These detections respectively require comparison between a previous location of stimulus presentation with a current one, and comparison between a previously presented stimulus and a current one. The experimental design controlled for the possible occurrence of behavioral and/or pharmacological tolerance.