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Original article

The role of transient receptor potential vanilloid type 1 in unimodal and multimodal object recognition task in rats

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ABSTRACT

Background: The role of transient receptor potential vanilloid type 1 (TRPV1) channels in learning and memory processes has recently been recognized. In the present study, the role of this receptor in the multisensory integration process was investigated.
Methods: This study was done using 96 male Wistar rats, which were kept in a reverse 12–12 h dark/light cycle. Unimodal and multimodal object recognition task was performed by four variations of the spontaneous object recognition (SOR) test including standard SOR, tactile SOR, visual SOR, and cross-modal visual-tactile SOR (CMOR). AMG9810 (selective TRPV1 antagonist) was injected into the right lateral cerebral ventricle prior to sample and choice phases of SOR. A discrimination ratio was calculated to assess the preference of the animal for the novel object.
Results: Results demonstrated that administration of AMG9810 prior to the sample phase, as encoding phase, and prior to the choice phase, as retrieval phase, impaired discrimination between the novel and the familiar objects in all standard SOR, tactile SOR, visual SOR, and CMOR tasks (all $p < 0.05$).
Conclusion: The results of this study showed that TRPV1 receptors might be implicated in both unimodal and cross-modal encoding of information in rats.

Introduction

Learning and memory are basic properties of animals' nervous system. They can be achieved by analyzing sensory inputs from the environment. These inputs could be conveyed to the nervous system by one or different sensory modalities. The nervous system integrates segregated information from different sensory systems and gives us the ability to perceive, recognize, and understand our environment [1]. Recently, Winters and colleagues developed a spontaneous tactile-to-visual task called cross-modal object recognition (CMOR) [2], which facilitates studying learning and memory processes. It relies on information conveyed through one sensory modality (visual or tactile) or through integration of two (visual and tactile) modalities. Perirhinal cortex and posterior parietal cortex, which mainly process visual and tactile features of the objects respectively, are the most important brain regions involved in the CMOR task [3].

Transient receptor potential (TRP) ion channel includes a large family of receptors and is classified into six subfamilies [4]. The vanilloid receptor subtype 1 (TRPV1) is the best and oldest characterized member of the TRP family [5]. TRPV1 has broad distribution in the brain and is expressed in many regions of the brain including cortex, hippocampus [6], and sensory neurons [7]. This channel is activated by capsaicin, low pH, and high temperature [8]. TRPV1 is involved in a wide variety of physiological functions such as pain perception, bladder control, body temperature maintenance, and itching [4,9]. Recent studies demonstrated that TRPV1 has a role in synaptic plasticity and memory processes. For example, TRPV1 knock-out mice had reduced long-term potentiation (LTP) in the hippocampus and exhibited impaired hippocampus-dependent learning [10]. Moreover, activation of the TRPV1 facilitated LTP, suppressed long-term depression (LTD), and protected against the acute stress-induced memory deficit in spatial memory retrieval test [11]. In another study, it was shown that TRPV1-induced LTD in the hippocampal

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interneurons may have a role in learning [12]. In contrast, injection of TRPV1 agonists or antagonist into the ventral hippocampus was reported with no significant effect on acquisition or retrieval of memory in the Morris water maze [13].

Previous studies showed the essential role of different receptors in learning and memory and also in multisensory integration, including the muscarinic [14], D1 [15], and *N*-methyl-D-aspartate receptor (NMDA) [16] receptors. This study aimed to evaluate the effects of intracerebroventricular (*icv*) administrations of the TRPV1 antagonist on multiple facets of object processing and multisensory object recognition in rats.

Materials and methods

Animals

In this study, we used 96 adult male Wistar rats (200–250 g). Four rats were housed in each standard cage. Rats were maintained on a reverse 12–12 h dark/light cycle (8:00 A.M. lights off; 8:00 P.M. lights on). All behavioral testing procedures were done during the dark phase of the cycle (9–11 A.M.). The animal house temperature was set at 24 ± 2.0 °C. Animals were randomly allocated into two experiments A and B (see below for details). Each experiment included eight groups. Each animal received the treatment only once. The number of animals was 5–10 per experimental group. All of the experimental procedures were carried out in accordance with the guidelines for the care and use of laboratory animals observed in the Rafsanjan University of Medical Sciences and the European Communities Council Directive of 24 November 1986 (86/609/EEC).

Drugs

AMG9810 [(E)-3-(4-t-butylphenyl)-*N*- (2, 3-dihydrobenzo[b] [1,4]dioxin-6-yl) acryl amide] (AMG) was purchased from Tocris Bioscience (UK). AMG is an antagonist with high selectivity that blocks all known modes of TRPV1 activation [17]. Based on our previous study, we used AMG at the dose of 30 μg/rat [18]. The drug was dissolved in dimethyl sulfoxide and sterile 0.9% saline (up to 10%, v/v) and Tween 80. The experimenter was blind to the identity of the drug being administered. Drug and vehicle administrations were counterbalanced across the groups.

Surgical procedures and drug microinjection

Rats were deeply anesthetized by intraperitoneal (*ip*) administration of ketamine (90 mg/kg) and xylazine (4 mg/kg). Midline cranial hair was shaved and then the animal was fixed on a stereotaxic apparatus (Stoelting, USA). Bregma point was considered as zero and the stainless steel guide cannula (22-gauge) was implanted in the right lateral ventricle according to these coordinates: AP = −1.5, L = 1.5, VD = 3.5 [19]. Then, a guide cannula was fixed to the skull with acrylic dental cement and two small stainless steel screws. For prevention of obstruction, a stylet of the same length was placed inside the guide cannula. Animals spent seven days of recovery after the surgery.

On the test days, 5 μl of the drug solution or vehicle was injected into the right ventricle of each rat during a 2 min period. The injections were done *via* a 27-gauge needle (1 mm below the tip of the guide cannula) connected to a 10 μl Hamilton microsyringe. Needles were left in place for an additional 60 s to prevent the drug backflow. Administrations were done in a room separated from the experiment room. Drug solution or vehicle was coded so that the experimenter did not know the type of intervention.

Y-maze apparatus

We used a Y-shape maze for studying cross-modal object recognition behavior. The protocol is documented elsewhere [20,21]. Briefly, the maze was made of non-transparent Plexiglas and had three arms (each of them, 40 cm high, 27 cm long, and 10 cm wide). In the start arm, there was a guillotine door located at 18 cm from the rear of the arm, and the rats were first confined in the start arm by this door. In the two other remaining arms (choice arms), there were notches located 9 cm from the rear of the arms. These notches allow the experimenter to restrict the physical

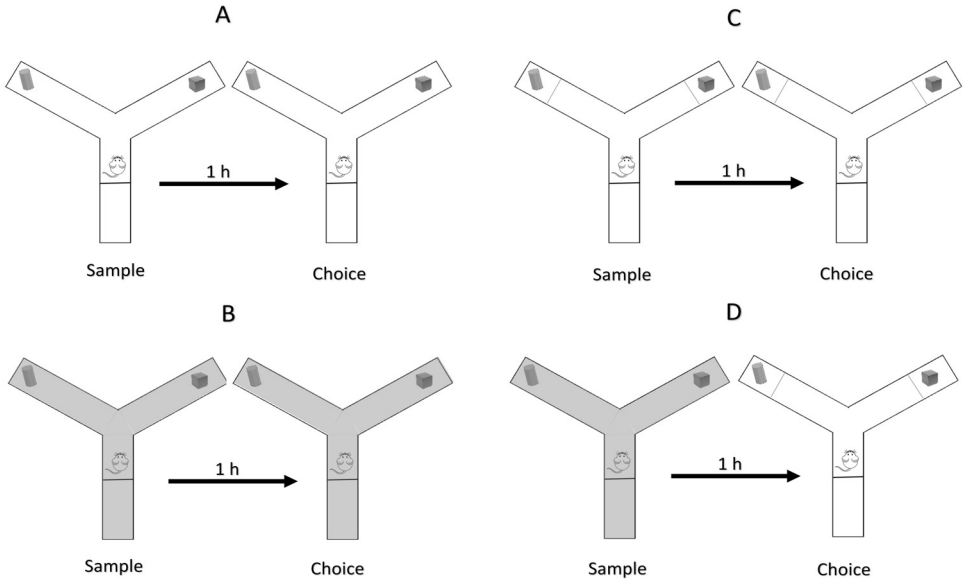

Fig. 1. Schematic illustration of the four spontaneous object recognition (SOR) tasks used in this study. A: standard SOR task; both phases were run in white light, and animals had full access to the visual and tactile properties of the objects. B: tactile SOR; both phases were run in red dim light, and animals had access only to the tactile properties of the objects. C: visual SOR; both phases were run in white light, and two transparent barriers were in front of the objects. D: cross-modal object recognition (CMOR) task; the sample phase was done similar to B and the choice phase was done similar to C. The delay between sample and choice phases of SOR was 1 h.