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Research report

Effects of thalamic hemorrhagic lesions on explicit and implicit learning during the acquisition and retrieval phases in an animal model of central post-stroke pain

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HIGHLIGHTS

- VBC lesions induced thermal hyperalgesia for acquisition and retrieval phases.
- VBC lesions facilitated conditioned place preference in implicit memory.
- VBC lesions did not affect spatial learning in explicit memory.
- VBC lesions did not affect motor function.
- Our data provide some insights for CPSP and learning memory.

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ABSTRACT

Hemorrhagic stroke has many symptoms, including central pain, learning and memory impairments, motor deficits, language problems, emotional disturbances, and social maladjustment. Lesions of the ventral basal complex (VBC) of the thalamus elicit thermal and mechanical hyperalgesia, forming an animal model of central post-stroke pain (CPSP). However, no research has yet examined the involvement of learning and memory in CPSP using an animal model. The present study examined whether VBC lesions affect motor function, conditioned place preference (CPP; implicit memory), and spatial learning (explicit memory) in the acquisition and retrieval phases. The results showed that rats with VBC lesions exhibited thermal hyperalgesia in the acquisition and retrieval phases, indicating that these lesions can induce CPSP. During these phases, the rats with VBC lesions exhibited enhanced (morphine-induced) CPP learning. These lesions did not affect the rats' total distance travelled, time spent, or velocity in the spatial learning tasks. The lesions also did not affect motor function in the rotarod task. Altogether, VBC lesions resulted in CPSP and facilitated CPP (implicit memory). However, the lesions did not affect spatial learning (explicit memory) or motor function. The relationship between CPSP and learning and memory is important for patients who suffer from such central pain. The implications of the present study may provide insights into helping reduce CPSP and its associated symptoms.

1. Introduction

Central post-stroke pain (CPSP) is the most important clinical symptom in hemorrhagic stroke patients [1,2]. In the clinical setting, 8–14% of stroke patients suffer from this symptom [3]. Thalamic nuclei are the hemorrhage location in CPSP patients, and the symptoms are known as "thalamic symptoms," the clinical characteristics of which include sensory loss (deafferentation), hypersensitivity (sensitization and disinhibition), and altered sensations of temperature and pain [4,5]. In addition to these

Abbreviations: ANOVA, analysis of variance; CPP, conditioned place preference; CPSP, central post-stroke pain; HSD, honestly significant difference; rpm, rotations per minute; SEM, standard error of the mean; TES, tris (hydroxymethyl)-methyl-2-aminoethane sulfonate; VBC, ventrobasal complex; VPL, ventral posterolateral; VPM, ventral posteromedial.

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somatosensory dysfunctions, stroke causes disabilities and such associated symptoms as motor deficits, cognitive dysfunction [6], language problems, emotional disturbances, and social maladjustment [7]. These symptoms and disorders are diverse and difficult to treat. Clinical studies have shown that thalamic lesions disrupt performance in explicit and implicit learning and memory tasks [8]. In these studies, however, the relationship between the animal model of CPSP and learning and memory deficits remains unknown. More knowledge of the associations between CPSP and learning and memory is necessary. Data on explicit and implicit learning and memory deficits that underlie thalamic lesion-induced CPSP might provide insights into the development of novel treatments for hemorrhagic stroke in the thalamus.

Clinical studies have shown that the spinothalamocortical pathway is the most likely location of the pathological mechanism of CPSP [9,10]. Thalamic nuclei are the critical brain region that controls CPSP. Researchers have recently developed animal models of CPSP. The ventrobasal complex (VBC; including the ventral posteromedial [VPM] and ventral posterolateral [VPL] portions) of the thalamus plays an important role in the onset of CPSP [11–14]. Our studies have shown that the brain's pain matrix and spinothalamocortical pathway are involved in CPSP, and VBC lesions in the spinothalamocortical pathway lead to thermal and mechanical hyperalgesia [11]. However, the way in which VBC lesions affect learning, memory, and CPSP remains unknown.

Many studies of memory in humans and nonhuman primates have reported that the brain can be divided into a multiple-memory system rather than a single-memory system [15–17]. Different neural substrates may be involved in different memory systems that control explicit and implicit memory [18–20]. For example, the severely amnesic patient HM had damage to the medial temporal lobe, with involvement of the hippocampus and adjacent perirhinal and parahippocampal cortices. He exhibited poor performance in tests of conventional intelligence, immediate digit span memory, related facts, and event recall [18]. This type of memory system stores information through conscious recollection, which is termed "declarative" or "explicit" memory. Additionally, HM showed progressive improvements in motor skills learning, word priming performance, and simple classical conditioned learning, although he still presented impairments in several explicit memory functions. A separate memory system directly mediates motor skills and implicit-related information through performance without conscious recollection [20]. These learned behaviors are implicit and are termed "non-declarative" or "implicit" memory. Importantly, the brain damage that HM incurred in the hippocampus and adjacent brain areas did not affect performance in implicit learning and memory tests. Therefore, the multiple memory systems of the brain can be dissociated into implicit and explicit memory based on damage to separate brain areas.

Based on the hypothesis of the multiple-memory system, simple classical conditioning is known as implicit memory and underlies unconscious information processing [18,19]. In the present study, we used the conditioned place preference (CPP) paradigm, which involves simple classical conditioning [21] and thus is associated with implicit learning and memory. Previous studies have shown that spatial learning is mediated by the hippocampus, and hippocampal lesions or dysfunction induce spatial learning deficits [22,23]. Deficits in spatial learning might be similar to the anterograde amnesia that was experienced by HM, who sustained damage to the hippocampus and adjacent brain areas. Accordingly, impairments in spatial learning likely impair explicit learning and memory. In the spatial learning model in the present study, the animals were placed in a water maze to search for a hidden platform. They must configure the environmental cues or stimuli that they had learned outside the water maze and link these stimuli to form a wide range of tank configurations or representations [24]. After several trials in the training procedure, the well-trained animals needed less time to find the hidden platform. This procedure presumes that animals need to process spatial information through consciousness. It is suitable for the explicit memory requirement that spatial stimuli and information need to be processed using consciousness. Moreover, Pickens and Holland (2004) suggested that conjunctive stimulus representations "may serve as appropriate animal models of human 'declarative memory,' which is also described as heavily dependent on temporal lobe structure, and which also involves binding of temporal, spatial, and object information into single event representations" (p. 655). Therefore, the present study used the CPP paradigm and spatial learning in the water maze task to evaluate implicit and explicit memory, respectively.

In addition to CPSP symptoms, the animal model of CPSP remains uncertain whether brain hemorrhaging causes motor deficits [14,25,26]. Moreover, it has suggested that the location of brain damage is thought to be a critical factor in determining whether motor dysfunction occurs in CPSP. For example, a CPSP study in rats showed that lesions of the VPM and VPL of the thalamus, including the medial lemniscus, induced CPSP symptoms and motor impairments; however, this study did not ablate the motor cortex, associated motor cortex, or internal capsule [26]. Another animal study of intracerebral hemorrhage infused bacterial collagenase into the right basal ganglia, a motor-related brain region. The results showed that animals with intracerebral hemorrhage exhibited motor dysfunction in the open field and rotarod tests [25]. Motor deficits were thus associated with intracerebral hemorrhage. Additionally, a recent study found that lesions of the VBC, without destruction of the motor cortex, produced central pain (i.e., CPSP) but did not induce motor deficits in the rotarod test [14]. Therefore, we evaluated whether VBC lesions in rats affect motor function.

The purpose of the present study was to investigate whether CPSP that is induced by thalamic hemorrhage affects CPP (implicit memory) and spatial learning (explicit memory) during the acquisition and retrieval phases. Moreover, we investigated whether VBC lesions affect motor function in the rotarod test.

2. Methods and materials

2.1. Animals

Forty-seven male Sprague-Dawley rats, weighing 250–350 g, were obtained from the National Laboratory for Animal Breeding and Research Center (Taipei, Taiwan). The rats were individually housed in suspended stainless-steel cages in a colony room with a constant temperature and 12 h light cycle (lights on 6:00 a.m. to 6:00 p.m.). Food and water were provided ad libitum except during the specific treatments described below.

2.2. Experimental surgery

All of the rats were treated in accordance with the animal care guidelines of the American Psychological Association. The rats were subjected to anesthesia and surgery before the acquisition of CPP and spatial learning in Experiment 1 and after the acquisition of CPP and spatial learning in Experiment 2. In Experiment 3, the rats were subjected to anesthesia and surgery before assessing motor function in the rotarod test. Twenty minutes prior to anesthesia, each rat was injected with atropine sulfate (0.1 mg, i.p.) and gentamicin (6 mg, i.p.). The rats were then anesthetized with sodium pentobarbital (50 mg/kg, i.p.). Half of the rats were assigned to the sham group, and the other half were assigned to the VBC lesion group. The VBC lesion group received a 0.5 μl volume of 0.125 U collagenase type IV (Sigma), which was injected into the right VBC of