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Research report

Complex assessment of distinct cognitive impairments following ouabain injection into the rat dorsoloateral striatum

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HIGHLIGHTS

- There is no sufficient therapy to treat patients following focal brain damage.
- Even slight cognitive impairments seem to be crucial for mental well-being.
- We developed the rat model of cognitive deficits resulting from focal brain injury.
- Brain damage impaired habit learning, switching and 'what – where' memory.
- Developed model enables testing of restorative therapy effectiveness and safety.

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ABSTRACT

A stroke in humans may induce focal injury to the brain tissue resulting in various disabilities. Although motor deficits are the most discernible, cognitive impairments seem to be crucial for patients mental well-being. The current lack of effective treatments encourages scientists and clinicians to develop novel approaches. Before applying them in clinic, testing for safety and effectiveness in non-human models is necessary. Such animal model should include significant cognitive impairments resulting from brain lesion.

We used ouabain stereotactic injection into the right dorsolateral striatum of male Wistar rats, and enriched environment housing. To confirm the brain injury before cognitive testing, rats were given a beam-walking task to evaluate the level of sensorimotor deficits. To determine the cognitive impairment after focal brain damage, rats underwent a set of selected tasks over an observation period of 30 days.

Brain injury induced by ouabain significantly impaired the acquisition of the T-maze habit learning task, where 'win–stay' strategy rules were applied. The injured rats also showed significant deficits in the performance of the T-maze switching task, which involved shifting from multiple clues previously relevant to the only one important clue. Focal brain injury also significantly changed 'what – where' memory, tested in the object exploration task, in which a novel object consecutively appeared in the same place while the location of a familiar item was continuously changed.

In conclusion, we developed an animal model of distinct cognitive impairments after focal brain injury that provides a convenient method to test the effectiveness of restorative therapies.

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1. Introduction

A stroke in humans may often induce focal injury to the brain tissue. The exact location and the extent of the lesion in patients may vary and results in diverse functional impairments. Motor deficits following brain damage are most easily discernible and are manifested by the disruption of daily tasks [1,2]. However, cognitive impairments seem to have a greater influence on mental well-being and may significantly worsen the quality of everyday life [3,4]. The current lack of treatment for such impaired functions following focal brain injury encourages scientists and clinicians to develop novel therapies. But, before applying such therapies in

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clinics, each approach must be tested on animals. Thus, the development of adequate non-human models of disease is necessary determine the therapeutic effectiveness and safety.

In animal models of focal brain injury it is crucial to produce repeatable lesion in means of their location and extent. Such a design makes it possible to test restorative treatment(s) which may increase both functional recovery and structural repair. The injury should include selected brain structure. This enables finding functional impairments basing on well-established knowledge concerning role of particular structure to a given behavior. In such model, functional impairments resulting from focal brain damage might also be difficult to trace the treatment benefit because of the spontaneous recovery [5]. Extending the range of the experimental brain damage for this purpose is not a good solution because there is less likelihood that restorative therapy effects would be successful. Developing more sensitive tasks to be performed in the same observation period and in the same animal groups to determine the complex cognitive impairments induced by a relatively small lesion seems to be an urgent necessity. For instance, MacLellan and colleagues looked for complex cognitive deficits following intracerebral hemorrhage [6]. Although they applied several tasks designed to determine distinct cognitive impairments, they did not find any significant impairments resulting from brain damage.

In our model, focal brain injury was induced by a stereotactic injection of ouabain (OUA) into the dorsolateral striatum of rats. The OUA infusion was shown to produce brain damage comparable to that after ischemia [7]. The dorsolateral striatum was selected mainly because it controls motor functions [8] and its injury induced significant sensorimotor deficits [9,10]. Motor impairments are most easily assessed when testing experimental therapy effects on functional recovery, subsequent to brain damage, at various time points, because the dynamics of such impairments can be evaluated.

It has also been well documented that the dorsolateral striatum, in both humans and rodents, is crucial in habit-learning processes [11]. In rats, the ability to learn the 'win–stay' radial maze task was shown to be impaired after a dorsolateral striatum lesion [12] and lidocaine injection [13]. Yin and coworkers showed that the bilateral injury of the rat dorsolateral striatum significantly impaired T-maze habit learning task, which requires turning toward the same direction [14]. In case of a unilateral lesion, like the one in our model, the latter type of task is not useful because of the bias induced by brain injury [9,10,15–19]. To assess learning deficits caused by OUA focal brain injury, we introduced the T-maze habit learning task. Our task is a simplified version of the 'win–stay' radial maze task and does not require turning in the same direction. By using an equal number of left and right turns, it was possible to differentiate unilateral brain injury-induced bias from the learned habit. We employed a T-maze rather than a radial maze to make it easier for experimental animals to learn the task. This modification makes it possible to perform several tests in a relatively short observation time period. Such a design is useful in assessing experimental therapy effects on various aspects of functional recovery following focal brain injury.

The changes inherent in everyday life require continuous switching or attention set-shifting to adapt. Such processes are defined as cognitive flexibility [20] in which the striatum was shown to be involved. D'Amore and colleagues found that the bilateral infusion of BDNF into the central striatum significantly improved strategy-set-shifting in instrumental learning [21]. Ragozzino and coworkers showed that the dorsomedial striatum is involved in behavioral flexibility, as measured by the reversal-learning task [22,23]. Moreover, appetitive motivation was shown to act on the striatal dopaminergic system and to influence cognitive flexibility [24]. In our experiment, just after completing the T-maze habit learning task, we used the T-maze switching task to test the ability to adapt. Our task required shifting from several relevant clues in the habit learning task (like turn direction, the previously visited T-maze arm, a visual clue) to only one significant clue (visual). Such switching requires paying attention to visual information only, because the previously important turn direction and 'win–stay' strategy become irrelevant.

'What,' 'where,' and 'when' information is categorized as episodic memory and is crucial in recalling unique events from an individual's personal past [25]. The striatum was shown to be involved in episodic encoding [26,27]. In humans, stroke may induce episodic memory disorders, disturbing the quality of everyday life [3]. In rodents, episodic-like memory could be assessed using tasks based on spontaneous novelty preference and objects, as well as their location recognition [28,29]. The rat striatum was shown to be involved in object identification, as indicated by NMDA receptor subtype expression [30]. Following the T-maze habit learning and switching tasks training, we used the object exploration task, which combined the 'what' and 'where' design in one test. Examining the effects of experimental therapies on recovery from slight 'what – where' memory deficits may provide valuable information about improvements in a patient's everyday life after focal brain injury.

2. Materials and methods

2.1. Animals

We used male Wistar rats, weighing about 250 g at the beginning of the study, were used under a 12/12 h light/dark cycle. The animal handling and experimental procedures were approved by IV Local Ethics Committee on Animal Care and Use (Ministry of Science and Higher Education). As we previously described [9,10], the rats (both OUA and control) were kept in a large enriched environment home cages (70 cm × 41 cm × 56 cm), 7–8 rats per cage. The cages contained various equipment such as beams, platforms, branches, ladders etc. We introduced enriched environment housing 4 days before brain surgery to ensure sufficient handling. In a single experimental set one enriched environment cage of rats was used i.e. six OUA injured animals (two OUA and four OUA + experimental teatment) and one or two control rats. Food and water were provided *ad libidum* throughout the all experiments.

2.2. Surgery

The stereotactic OUA injection procedure was preformed as previously described [7,9,10]. Briefly, rats were positioned within a stereotactic frame (Stoelting) under general anesthesia (3.6% chloral hydrate, 10 ml/kg b.w. given i.p.). After placement of a burr hole on the right side of the cranium, 1.5 μL of 5 nmol ouabain solution was injected intracerebrally at a rate of 1 microliter/min via a Hamilton needle (gauge 33) at the following coordinates: AP = 0.5; L = 3.8; and V = 4.7 [41], according to bregma, using an infusion pump (Stoelting). After the injection, the needle was kept i*n situ* for an additional 5 min to avoid back-flow of the injected solution. Then, the needle was removed and the skin was sutured.

2.3. Focal brain injury evaluation

To confirm that the experimental brain injury occurred before cognitive testing, we evaluated the level of motor impairments. As previously described [9,10], the animals were trained to walk along a narrow wooden beam (14 mm wide, 80 cm long, elevated 50 cm above the cushioned floor) before the brain damage. The rats were tested 2 days after the OUA lesion was induced, as well as 7, 15 and 30 days following brain damage [9,10], (data not shown in this paper). The performance of the task was video recorded.

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