Evaluation of long-term functional deficits following transient cerebral ischemia in two mouse strains

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Introduction

Cerebral ischemia is induced in more than 80% of human stroke. This neurovascular disease is responsible for long-term functional disabilities such as sensorimotor, cognitive and behavioral impairments. To date, although improving survivors' health remains a major concern, no efficient pharmacological treatment to enhance functional recovery following transient focal cerebral ischemia has been successfully approved. This lack of treatment could partly explained by the absence of animal models designed to study long-term effects of cerebral ischemia. In this work, a battery of behavioral tests was established and used to compare 2 common mouse strains in order to provide a reliable animal model of cerebral ischemia.

Experimentation and results

Experimental design

27 C57Black/6H and 33 129S2/SvPas adult male were subjected either to a MCAo or *sham* surgery. Briefly, MCAo consists of filament insertion into the right internal carotid artery. The filament is held in place 30 minutes before removal.

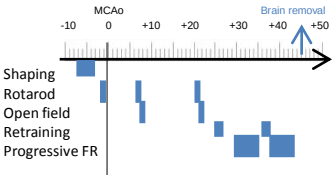

Figure 1 : Day 0 refers to surgery. Horizontal bars represent the testing period for a given behavioral test. Some tests required a training and/or an assessment of the baseline performance before surgery (from D-7 to D-1). Most tests were performed after surgery (D+7 to D+39).

Sensorimotor testing

In the rotarod test, mice were placed on an accelerated rod and fall latency were recorded. Spontaneous locomotion was assessed in a square open-field (50 x 50 cm): total path length was quantified using a video-tracking device (Viewpoint©).

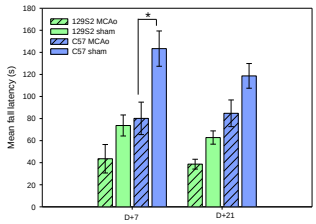

Figure 2 : performance on the rotarod expressed as the mean fall latency (±SEM). * indicates a significant difference (p<0,05).

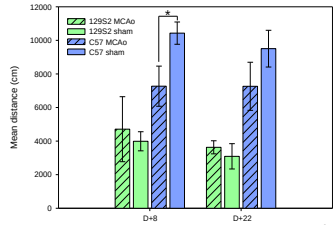

Figure 3 : spontaneous locomotor activity in open field expressed as the mean total distance (±SEM) travelled over 60 minutes. * indicates a significant difference (p<0,05).

Transient sensorimotor deficits were detected only in C57 mice. Ischemic mice expressed shorter fall latency on the rod and they were impaired in spontaneous locomotor activity.

Progressive fixed-ratio schedule

Food-deprived C57 mice were subjected to a continuous FR1 schedule until reaching a performance criterion of 20 lever-presses in two consecutive sessions. For progressive schedule, mice went through 5 incrementing ratios (5, 10, 15, 20, 30) spread on 5 sessions.

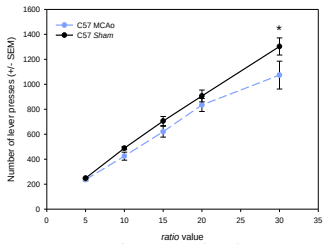

Figure 4: number of lever presses (±SEM) in a progressive FR schedule. * indicates a significant difference (p<0,05).

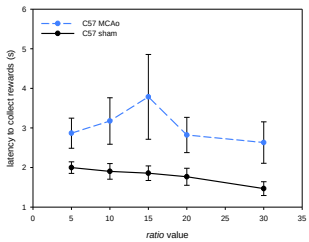

Figure 5: latency to collect rewards (±SEM) in a progressive FR schedule.

Ischemic C57 mice showed persistant disturbance of endurance when the ratio value was high and trouble in executive functioning (switching between instrumental and feeding behavior).

Immunohistochemistry

D+46: animals were perfused; brains were then removed and cut into 50µm slices. Cerebral injury was revealed using NeuN staining and total infarcted volume was assessed using optical microscopy.

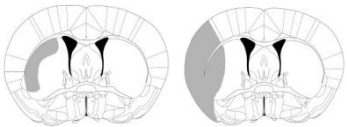

Figure 6 : extension of ischemic damage in 129S2 (left) and C57 (right) brains (Bregma +0,14mm).

Ischemic lesion was localized in the dorsolateral part of the ipsilateral striatum in both strains with recurrent cortical damages in C57 mice.

Conclusions

- C57 mouse strain is the most suitable animal model to evaluate long-term deficits and functional recovery after cerebral ischemia
- Striatal damages appear responsible for transient sensorimotor and long lasting cognitive impairments since the motor cortex seems relatively spared by ischemic lesion in 129Sv mice
- Operant conditioning tests are more sensitive than sensorimotor tests to detect subtle disabilities