Long-term protective effect of wheel running on cocaine reactivity

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INTRODUCTION

Epidemiological and experimental studies suggest that regular physical exercise could play a protective role on the vulnerability to seek and consume drugs of abuse (1-3).

However, some aspects of physical activity observed in humans are often absent in animal studies like the cessation of this behavior.

Psychomotor sensitization was used as a classical model to assess the vulnerability to the neurobehavioral alterations induced by chronic administration of drug.

The aim of this experiment was to study the effect of the loss of running wheel (used to model physical exercise) on cocaine sensitization in male C57BL/6J mice after a long period of free access.

METHODS

Two blocks of identical experiments were realized for this study (N=72, n=12). Early adolescent mice (35 days old) were single-housed with a running wheel (exercised mice n=48) or in standard condition (sedentary mice n=24) for 5 weeks. Running wheels (Fig.2) were then removed for half of exercised mice (« loss » groups) 3 days before the testing began.

The experiment consisted in several phases:

(1) the measure of exploratory activity induced by the novelty (day 1),
(2) the measure of psychomotor activity under saline (day 2) and after the first injection of cocaine (day 3)
(3) the establishment of psychomotor sensitization over 13 once-daily injections of cocaine (days 4 to 15)
(4) a long-term expression test 30 days after the last cocaine session (day 45). Each session lasted 30 min.

Cocaine HCl was dissolved in an isotonic saline solution (0.9% NaCl) at 8mg/kg and was injected via intraperitoneal route (i.p.) in a volume of 0.01ml/g body weight. The control treatment (saline solution) was administered in the same volume and manner.

Locomotor activity was measured in eight custom-made activity-meters that were each transected by two infrared photobeams (Fig.1). A mouse had to traverse the full distance between the beams for each activity count.

Figure 1. Activity-meter

Figure 2. Running wheel

ANOVAs were performed on locomotor activity scores and post hoc comparisons were used in order to assess any relevant differences between experimental groups. Statistical significance was conventionally set from $p<0.05$.

RESULTS

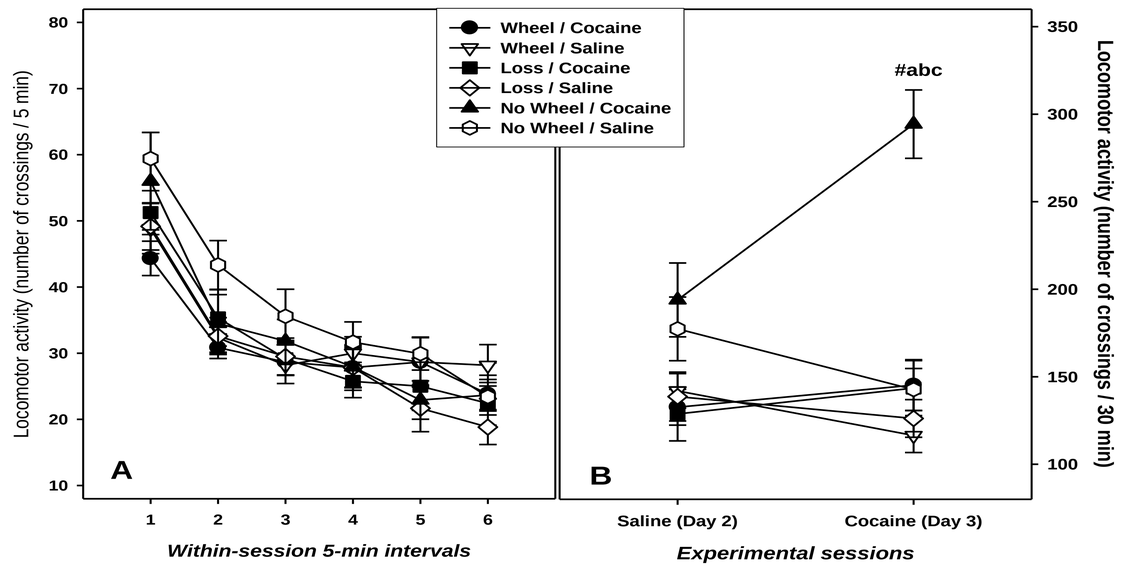

Figure 3. (A) Time-course of novelty-induced activity as a function of six 5-min intervals. There was no significative difference between experimental groups.

(B) Acute psychomotor reactivity. Locomotor activity on saline day and the first session of 8mg/kg cocaine administration. Sedentary mice were highly stimulated by the first cocaine injection unlike exercised mice and those who lost the possibility to run.

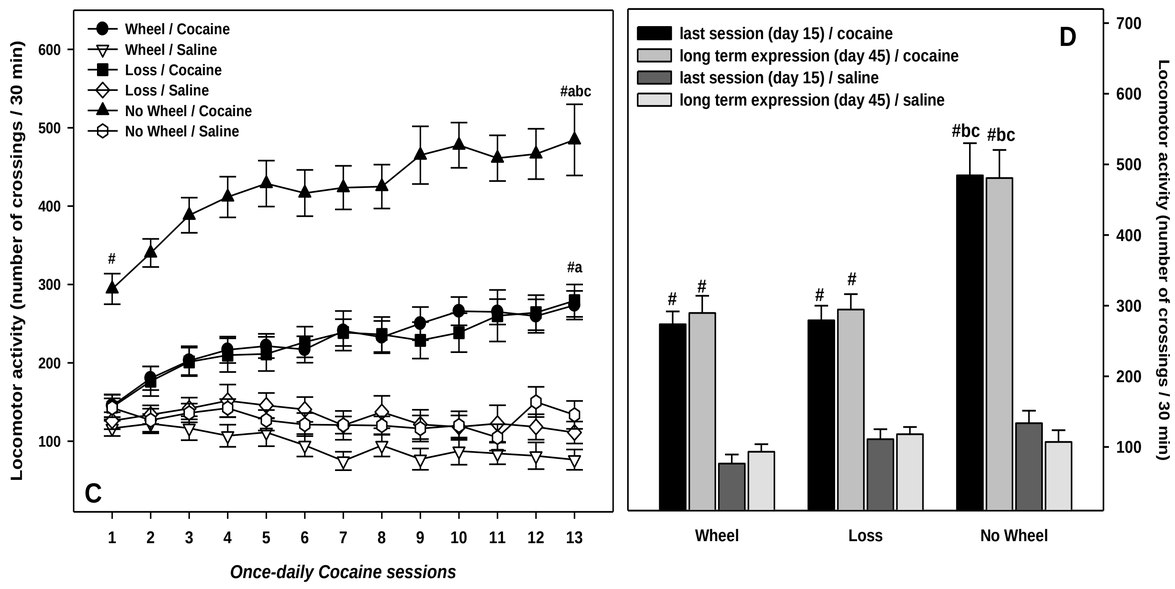

Figure 4. (C) Development of psychomotor sensitization induced by repeated administrations of 8mg/kg cocaine. All cocaine groups displayed sensitization to its stimulating effects. However, sedentary mice showed a global reactivity much higher than both other groups which presented an identical pattern of progression.

(D) Locomotor activity on the last cocaine session and the long-term expression test. There was no difference between these two sessions and between-groups differences were maintained.

Significantly different from the (#) corresponding saline group, (a) first session, (b) « wheel-cocaine » group, (c) « loss-cocaine » group. Data are expressed as mean SEM.

DISCUSSION

Whereas experimental groups did not differ in their spontaneus activity, exercised mice were clearly less sensitive to the stimulating effects of 8mg/kg cocaine (i.p.) than sedentary counterparts after both single and chronic injections. Although sensitization developpment was observed in these mice, one can note that sedentary mice were particularly sensitive to the hyperlocomotor effect of acute administration. Because of this elevated baseline score, sensitization were not different between both groups (parallel curves). With regards to the existing litterature, the much less overall reactivity of exercised mice might be considered as a less sensitivity to the addictive-like effect of cocaine.

Most importantly, it was surprising to observe that the cessation of running activity had no effect. Indeed, those mice displayed similar scores to mice that maintained a physical activity during the experiment. Despite a long period of cocaine administrations (13 days), mice who did not maintained physical exercise expressed an identical pattern to exercised mice. One can suggest that the duration of running period and the time interval between the loss of the wheel and administration of cocaine could be determining parameters for any effect of the cessation of physical exercise.

Five weeks of running performed during adolescence (critical period of maturating brain) may induce neuroadaptations that underlie on a later stage a protective long term effect to cocaine stimulation.

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