



## Exercise Biochemistry Review

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### Endocannabinoid CB1 receptor-mediated abnormal enhancement of rat corticostriatal glutamatergic pathway participates in exercise fatigue Regulation

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**Objective** By monitoring the expression of CB1 receptor protein and key regulatory protein RGS4 in the endocannabinoid system (eCBs), and the changes in the transmission efficiency of Corticostriatal glutamatergic pathway and movement ability after microinjection of CB1 receptor agonist WIN 55212-2 into the lateral ventricles in rats, this study investigates the possible mechanism of striatal eCBs regulation of exercise fatigue. The results may provide experimental basis for further improving the theory of exercise fatigue and indicate new targets for the regulation of exercise fatigue.

**Methods** 74 adult male Wistar rats were randomly divided into control group (Control) and 1-day fatigue group (1 FG), 3-day fatigue group (3FG) and 7-day fatigue group (7FG) after 3 days rearing. The Control group was in a quiet state and the exercise fatigue group performed exhaustive exercise for 1 day, 3 days and 7 days, respectively. After the induction of exercise fatigue, the expression of CB1 receptor and RGS4 in rat striatum was determined by Western blotting technique. WIN 55212-2 (2mM, 5 $\mu$ L) microinjection into the lateral ventricle plus the stimulation-induced electrophysiological technique was used to determine the effect of CB1 receptor activation on the evoked spike discharges in striatal MSNs.

**Results** (1) The results of Western blotting showed that there was no significant change in the expression of CB1 receptor and RGS4 protein in the striatum of rats in 1FG compared with Control group ( $P > 0.05$ ). But the expression of CB1 receptor and RGS4 in the striatum was significantly increased in both FG and 7FG compared with Control group ( $P < 0.01$ ).

(2) The results of stimulation-induced electrophysiological experiment plus microinjection of lateral ventricle showed that the evoked spike frequency of MSNs in striatum of Control group ( $2.35 \pm 0.66$ Hz) at 1h after injection of WIN55212-2 was not significantly different from that before injection ( $2.43 \pm 0.49$ Hz) ( $P > 0.05$ ), that the evoked discharge frequency of MSNs in striatum of rats in 1FG ( $2.63 \pm 0.54$ Hz) was decreased at 10~20min after injection of WIN55212-2 ( $2.16 \pm 0.43$ Hz), but no significant difference was found ( $P > 0.05$ ), that the evoked discharge frequency of MSNs in the striatum of rats in 3FG was decreased at 10~20min after injection of WIN55212-2 ( $2.16 \pm 0.43$ Hz), that the evoked discharge frequency of MSNs in the striatum of 3FG ( $10.57 \pm 2.12$ Hz) was significantly decreased at 10~20min ( $7.05 \pm 1.84$ Hz) after injection ( $P < 0.01$ ), and it was basically restored to the pre-injection level by the time of 50~60min injection ( $10.47 \pm 2.83$ Hz), and that the evoked discharge frequency of MSNs in the striatum of 7FG ( $21.7 \pm 3.28$ Hz) was significantly decreased at 10~20min after injection ( $15.14 \pm 1.94$ Hz) ( $P < 0.01$ ), and it was basically recovered at 50~60min after injection ( $19.12 \pm 2.89$ Hz) ( $P > 0.05$ ).

(3) The experimental results of exercise fatigue showed that the time of exercise to fatigue in 7FG group after microinjection of WIN 55-212-2 in lateral ventricle ( $138.91 \pm 8.76$ min) was significantly longer than that in artificial cerebrospinal fluid (aCSF) group ( $127.51 \pm 9.45$ min) ( $P < 0.05$ ), the time of exercise to fatigue in the 1FG group ( $105.33 \pm 8.99$ min) was not significantly different from that in the aCSF injection group ( $105.59 \pm 10.34$ min) ( $P > 0.05$ ), the time of exercise to fatigue in

3FG group( $118.16 \pm 7.99$ min) was longer than that in aCSF injection group ( $107.5 \pm 10.31$ min), but there was no statistical significance ( $P > 0.05$ ).

**Conclusions** Exercise-induced fatigue could increase the expression of CB1 receptor protein and key regulatory protein RGS4 in the striatum and decrease the function of eCBs, which mediated the abnormal enhancement of the transmission efficiency of the corticostriatal glutamatergic pathway and participated in the central regulation of exercise-induced fatigue, and showed an obvious fatigue accumulating effect. The enhancement of the function of eCBs in the striatum of exercise fatigue rats could inhibit the transmission efficiency of rat corticostriatal glutamatergic pathway, and to a certain extent played a role in delaying exercise fatigue. Striatal eCBs may be a new target for central regulation of exercise fatigue.