Cannabinoids and muscle weakness – Investigating the function of CB1 receptors in mammalian skeletal muscle

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The presence of CB1 cannabionid receptors (CB1R) has been shown in skeletal muscle, but it is yet to be cleared whether they have any significance in the regulation of muscle contractions. Muscle contractions are evoked by the elevation of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) during a process called excitation-contraction coupling. CB1-mediated signaling can interefere with this process in several ways. CB1-knockout (CB1-KO) mice showed hypoactivity, however it is questionable whether this was solely originated by effects on the central nervous system or impairment of skeletal muscle function also contributes to this. It was also shown that treatment by cannabinoid agonists attenuates the contractions of frog skeletal muscle. Our aim was to study the role of CB1R in mammalian skeletal muscle, and the effects of cannabinoid drugs on Ca^{2+}-transients.

Running ability (average and maximal speed, distance) of control and CB1-KO mice was tested by activity-wheel-tests and *in vivo* muscle force of the animals was tested by grip-tests and hang-tests. Ca^{2+} transients evoked by KCl-depolarization in the presence of cannabinoid agonists were studied on enzymatically isolated flexor digitorum brevis (FDB) fibers of control and CB1-KO mice.

CB1-KO mice performed worse in all the behavior tests compared to control. Depolarization-evoked Ca^{2+}-transients were significantly higher in FDB fibers isolated from CB1-KO mice (847.8±98.2 nM, n=47) compared to control (375.6±59.9 nM, n=32, $p<0.01$). On control FDB the second transients after the CB1 agonist WIN55,212 treatment were significantly smaller than in untreated fibers.

On the basis of the $[Ca^{2+}]_i$ measurements we can conclude that CB1R-mediated signaling contributes to the regulation of skeletal muscle contractions, but as the main cause of the worse muscle performance of CB1-KO mice the effects mediated by the absence of CB1R in the central nervous system can neither be ruled out. These results can contribute to the identification of the side effects of medically used cannabinoid drugs on skeletal muscle.

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