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A Runner's high depends on cannabinoid receptors in mice

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Exercise is rewarding, and long distance runners have described a Runner's high as a sudden pleasant feeling of euphoria, anxiolysis, analgesia and sedation. Mechanisms leading to a Runner's high are not understood to date. A popular belief has been that endogenous endorphins mediate the beneficial effects of running. However, running exercise increases blood levels of both: ß-endorphin (an opioid) and anandamide (an endocannabinoid). Aim of the present thesis has been to study and model a Runner's high in mice.

Firstly, we established an experimental paradigm to show that a Runner's high phenotype occurs in mice after 5 hours of acute running. Using this protocol, mice revealed less anxiety in dark-light box, analgesia in hotplate testing and post exercise sedation compared to non-running animals.

In a second experiment we injected mice with endocannabinoid or endorphin antagonists aiming at preventing a Runner's high. We discovered that running-induced anxiolysis was prevented by central CB1 antagonism and running-induced reduction of thermal pain sensitivity was absent after both, peripheral and central CB1 and CB2 blockade.

In a next step we used mutant mice lacking CB1 receptors on forebrain GABAergic neurons and examined running and anxiety-like behavior. Thus we could demonstrate that CB1 receptors on forebrain GABAergic neurons are essential for running-induced anxiolysis.

Immunohistochemical experiments revealed increased c-Fos expression in the dentate gyrus after running, that was significantly reduced in mice with a pharmacological inhibition of central CB1 receptors and in mice lacking CB1 receptors on GABAergic neurons. This indicates running-induced increased hippocampal neuronal activity mediated by endocannabinoid signaling.

We thus demonstrate that cannabinoid receptors are crucial for a Runner's high in mice. These experiments unravel a biological mechanism for a myth among sportsmen longing for their "Runner's high" experience.