Therapeutic potential of modulators of cannabinoid receptors in cerebellar ataxias

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Scientific Abstract

Cerebellar ataxias (CAs) are a group of human disorders affecting ability to control motor output and are typically associated with degeneration of Purkinje cells (PCs), the principal neurones of the cerebellum. A predominant mechanism underlying PC degeneration is the hyperexcitability of innervating synaptic pathways. We will use *in vitro* electrophysiological techniques in animal models of ataxia to investigate neurotransmission in cerebellar brain slices. More specifically, we will use intracellular patch-clamp and extracellular multi-electrode array (MEA) recordings in a Friedreich's Ataxia model (decreased expression of the mitochondrial protein, frataxin) and the *ducky* cerebellar ataxia model (mutation in the $\alpha 2\delta 2$ calcium channel subunit). Electrophysiological experiments will assess changes in synaptic transmission and thereby determine if agents that affect neuronal excitability may offer the potential to treat CAs. Here, we will investigate how modulation of cannabinoid CB_1 receptors affects PC excitability. We have access to a number of plant-derived cannabinoids, including the CB_1 receptor antagonist, Δ^9-tetrahydrocannabivarin (Δ^9-THCV), which we have recently shown to cause a potent reduction in network excitability in the cerebellum. We will use a range of synthetic and plant-derived cannabinoids to test the hypothesis that modulation of CB_1 receptors represents a viable therapeutic strategy to treat CAs.

Lay Summary

Cannabis plants contain many different compounds (cannabinoids) and there is a growing interest in developing medicines from individual cannabinoids that have beneficial therapeutic effects but lack the alteration in mental processes associated with cannabis abuse. Several cannabinoids have been shown to reduce the over-excitation of nerve cells that may lead to their degeneration, loss of function and ultimately cell death. The cerebellum is the part of the brain that controls movement and balance, and dysfunction in this region is associated with many ataxias. Within the cerebellum there are receptors for cannabinoids, which are activated by cannabinoids naturally produced within the brain and deficits in this system can have adverse affects on cerebellum function. External cannabinoids (e.g. from plants) also act on these receptors and have been shown to cause changes in nerve cell excitability. This project will test the hypothesis that cannabinoid compounds represent a viable therapeutic strategy to treat cerebellar ataxias.

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