

Therapeutic cannabinoids in multiple sclerosis: immunomodulation revisited

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Cannabinoids are compounds with pleiotropic properties that act on the cannabinoid receptors, CB1 and CB2, and are divided into endocannabinoids, the endogenous ligands of these receptors, synthetic cannabinoids and phytocannabinoids. The latter are derived from the plant *Cannabis sativa*. The therapeutic and psychoactive properties of this plant have been observed and used for centuries. Of the over 60 compounds that are unique to *Cannabis sativa*, the substances that have been attributed the greatest therapeutic potential are Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD), both of which, used alone or combined with each other, have become approved drugs.

Cannabinoids have immunomodulatory and anti-inflammatory properties, neuroprotective properties proven in multiple experimental systems (in part due to the ability to modulate excitatory neurotransmitter release), and the ability to improve symptoms such as pain, spasticity, and neurogenic bladder disturbance. In addition, CBD has antiepileptic effects due in part to the same mechanisms through which spasticity and pain are relieved and neuroprotection is thought to occur.

The immunomodulatory actions of cannabinoids have been attributed mainly to effects on CB2, expressed in large part in the immune system, and the neuroprotective and psychotropic effects to CB1, expressed more in the nervous system.

These properties have made cannabinoids attractive candidates as therapeutic agents in multiple sclerosis (MS), an immune-mediated disease of the central nervous system (CNS), characterised histologically by focal and diffuse inflammation, demyelination, and axonal loss and damage, and clinically by multiple neurological symptoms among which spasticity, pain and neurogenic bladder are prominent.

The therapeutic potential of cannabinoids in MS has also been supported by studies in experimental autoimmune encephalomyelitis (EAE), its experimental animal model, where a combination of neuroprotective, immunomodulatory, and symptomatic effects have been demonstrated.

In MS, large trials of oral cannabis extracts and THC have failed to delay significantly disease progression and spasticity [1], and immunological studies of patients in these trials did not show peripheral immunological effects. It was suggested that the dose of drug required for a significant immunomodulatory effect would have been too high for clinical application.

Nabiximols, a 1:1 combination of THC and CBD licensed for the treatment of moderate spasticity in MS, has never been tested in trials to determine its effect on disease progression or immunological effects. However, patients with MS who are responders (experiencing a positive effect on spasticity usually from the first dose), benefit substantially long-term from the relief of spasticity by the drug. Nabiximols is administered as an oromucosal spray and has significantly different pharmacokinetics and pharmacodynamics compared to oral cannabis preparation. Whether this has a different impact on the patients' immune system has not been explored until now [2].

In this issue of the European Journal of Neurology, Sorosina and colleagues publish the first study of gene expression profiling in peripheral blood under nabiximols. After one month's treatment with nabiximols for MS-associated spasticity, they demonstrate modest but interesting transcriptomics changes. The immunological changes appear to be more pronounced in the patients who are clinical

responders. The genes that are down-regulated encode pro-inflammatory molecules, and gene ontology and network analysis identify NF- κ B transcriptional regulator as a hub molecule. As the critical role of NF- κ B in multiple inflammatory processes including MS is known, the finding of its down-regulation in this study adds plausibility to these modest, short term results obtained by Sorosina and colleagues in a small group of patients. Other down-regulated molecules including MAPK14 and TP53 also have plausible roles in inflammation and MS. Up-regulated genes are involved in synthesis pathways and ribosomal function, which suggests that the observed changes are not simply due to a general effect of nabiximols in transcriptional suppression.

The fact that the gene expression effect was more pronounced in the responders suggests a correlation between the clinical and immunological effect. There are several possible implications and interpretations. First, it suggests that the regulation and level of CB receptor expression and their signalling has similar features in the CNS and immune system. Thus, if this is confirmed and validated, biomarkers to predict the clinical response could be tested in the future in the peripheral blood. Second, assuming that anti-spasticity effects are largely CB1 mediated, it means either that CB1 or CB2 (the latter mainly on immune cells) are co-regulated or that there is sufficient CB1 expression in immune cells in MS to mediate the immunological effects seen. Indeed, we have demonstrated that both CB1 and CB2 are up-regulated on immune cells in MS and this may be through up-regulated inflammatory cytokines such as TNF, IL-1, and IL-6 [4]. Finally it indicates that if cannabinoids reach sufficient concentrations in the periphery to bind to the already up-regulated CB receptors on immune cells, they may provide *in vivo* immunomodulation. For nabiximols, the paper by Sorosina and colleagues represents the first step to suggest that this is feasible. For oral cannabinoids, we have shown that administration with lipids delivers them more effectively to the immune system via the intestinal lymphatics, and they reach sufficient concentrations in the lymph to suppress the proliferation and the increased amounts of inflammatory cytokines produced by immune cells of people with MS [5]. Such a strategy could be exploited therapeutically in the future.

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