

## Endocannabinoidome tone in Multiple Sclerosis patients

Alessandro Rabbito, Michał Biernacki, Alina Kułakowska, Joanna Tarasiuk, Elzbieta Skrzydlewska and Barbara Mroczko

Medical University of Białystok, Poland

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system, caused by an autoimmune response against myelin that leads to progressive neurodegeneration and disability. Although recent studies have provided new data on molecular mechanism underlying the onset of the disease, there is still a gap in the knowledge about lipid derivatives participating in development of MS. In this context, endocannabinoid system may be important. Endocannabinoids are a class of bioactive lipids derivatives, among which AEA and 2-AG, are the most abundant endocannabinoids in human body and the first ones to have been discovered. Beyond these two major endocannabinoids there are other related compounds considered as endocannabinoids and endocannabinoids-like molecules, members of a more big family of lipid derivatives molecules that compose the endocannabinoidome. Considering that, one of the most interesting properties probably is the entourage effect, several studies reported that these molecules can enhance endocannabinoids levels/biological activity. Furthermore, these bioactive lipids are not just entourage molecules, but reveal also functions by activating different receptors.

The endocannabinoid system is a biological system composed of endocannabinoids, which are endogenous lipid-based retrograde neurotransmitters that bind to cannabinoid receptor proteins, and cannabinoid receptors that are expressed throughout the vertebrate (including the brain) central systema nervosum and peripheral systema nervosum. The ECS remains under preliminary research, but could also be involved in regulating physiological and cognitive processes, including fertility, pregnancy, pre- and postnatal development, various activity of system, mood, and memory, appetite, pain-sensation, and in mediating the pharmacological effects of cannabis.

Two primary cannabinoid receptors are identified: CB1, first cloned in 1990; and CB2, cloned in 1993. CB1 receptors are found predominantly within systema nervosum and brain, also as in peripheral organs and tissues, and are the most molecular target of the endogenous partial agonist, anandamide (AEA), also as exogenous THC, the foremost known active component of cannabis. CBD may be a phytocannabinoid that acts as a rather weak antagonist at both CBRs and a stronger agonist at TRPV1 and antagonist at TRPM8. It's also known to be a negative allosteric modulator at CB1. CBD has been found to counteract a number of the negative side effects of THC.

Multiple sclerosis (MS) may be a demyelinating disease during which the insulating covers of nerve cells within the brain and medulla spinalis are damaged. This damage disrupts the power of parts of the systema nervosum to transmit signals, leading to a variety of signs and symptoms, including physical, mental, and sometimes psychiatric problems. Specific symptoms can include diplopia, blindness in one eye, muscle weakness and trouble with sensation or coordination. MS takes several forms, with new symptoms either occurring in isolated attacks (relapsing forms) or build up over time (progressive forms). Between attacks, symptoms may disappear completely; however, permanent neurological problems often remain, especially with the advancement of the disease. While the cause is unclear, the underlying mechanism is assumed to be either destruction by the system or failure of the myelin-producing cells.

Proposed causes for this include genetics and environmental factors like being triggered by a virus infection. MS is typically diagnosed supported the presenting signs and symptoms and therefore the results of supporting medical tests.

The three main characteristics of MS are the formation of lesions within the central systema nervosum (also called plaques), inflammation, and therefore the destruction of myelin sheaths of neurons. These features interact during a complex and not yet fully understood manner to supply the breakdown of nervous tissue and successively the signs and symptoms of the disease. Cholesterol crystals are believed to both impair myelin repair and aggravate inflammation. MS is believed to be an immune-mediated disorder that develops from an interaction of the individual's genetics and so far unidentified environmental causes. Damage is believed to be caused, a minimum of partially, by attack on the systema nervosum by an individual's own system.

The relative effectiveness of various treatments is unclear, as most have only been compared to placebo or a little number of other therapies. Direct comparisons of interferons and glatiramer acetate indicate similar effects or only small differences in effects on relapse rate, disease progression and resonance imaging measures. Alemtuzumab, natalizumab, and fingolimod could also be simpler than other drugs in reducing relapses over the short term in people with RRMS. Natalizumab and interferon beta-1a (Rebif) may reduce relapses compared to both placebo and interferon beta-1a (Avonex) while Interferon beta-1b (Betaseron), glatiramer acetate, and mitoxantrone can also prevent relapses. Evidence on relative effectiveness in reducing disability progression is unclear. All medications are related to adverse effects which will influence their risk to profit profiles.

Over 50% of individuals with MS may use complementary and medicine, although percentages vary counting on how medicine is defined. Regarding the characteristics of users, they're more frequently women, have had MS for a extended time, tend to be more disabled and have lower levels of satisfaction with conventional healthcare. The evidence for the effectiveness for such treatments in most cases is weak or absent. Treatments of unproven benefit employed by people with MS include dietary supplementation and regimens, vitamin D, relaxation techniques like yoga, herbal medicine (including medical cannabis), hyperbaric oxygen therapy, self-infection with hookworms, reflexology, acupuncture, and mindfulness. Evidence suggests vitamin D supplementation, regardless of the shape and dose, provides no benefit for people with MS; this includes for measures like relapse recurrence, disability, and MRI lesions while effects on health-related quality of life and fatigue are unclear.

**Methodology & Theoretical Orientation:** The aim of this studies was investigate the dysregulation of endocannabinoidome tone, in biological fluids as CSF and serum, in MS patients. The concentrations of endocannabinoids and endocannabinoid-like molecules were assessed, after SPE lipid extraction, using ultra-performing liquid chromatography tandem mass spectrometry in positive-ion mode.

**Findings:** These preliminary results obtained analyzing a panel of more than 10 endocannabinoids and endocannabinoid like molecules, confirm that there is an alteration in endocannabinoidome tone in MS.

**Conclusion & Significance:** Although several studies reported changes in endocannabinoids tone in neurological/neurodegenerative diseases, but there are very few papers concerning a big panel of endocannabinoid like molecules in serum and CSF of MS patients. Because the alterations are different between molecules, further investigations with a bigger group of patients are needed.