ENDOCANNABINOID INVOLVEMENT IN NEURODEGENERATIVE DISORDERS AND NEUROPATHIC PAIN

VINCENZO DI MARZO

Endocannabinoid Research Group, Institute of Biomolecular Chemistry, CNR , Via Campi Flegrei 34, 80078, Pozzuoli (NA)

The activity of the endocannabinoid system, in terms of the levels of the endocannabinoids and of cannabinoid receptors, or of the functional coupling of the latter to a biological response, undergoes to dramatic remodelling during pathological conditions. In the CNS, these changes, depending also on the nature of the disorder, can be either transient or long-lasting, occur only in those tissues involved in the pathological condition, and usually aim at restoring the physiological homeostasis by reducing excitotoxicity, neuroinflammation and neuronal death. In animal models of neuropathic pain, endocannabinoid levels are elevated in both spinal and supra-spinal regions to counteract nociception and, perhaps, to retard nerve degeneration. However, during some chronic or degenerative neurological disorders, prolonged activation of the endocannabinoid system might also contribute to the symptoms of the pathology. This occurs in some animal models of Parkinson's and Alzheimer's disease. By contrast, there are also examples, such as in experimental models of Huntington' chorea and multiple sclerosis, where endocannabinoid signalling is impaired, and this phenomenon also seems to contribute to disease symptoms.

Whilst acute changes of the tissue levels of the endocannabinoids reflect the "on demand" nature of their biosynthesis and release, and hence are effected mostly through intracellular calcium-mediated regulation of the biosynthetic enzymes, chronic changes seem to be mostly due to longer-lasting alterations in the expression of anabolic and catabolic enzymes.

The possibility of obtaining therapeutic advantage from endocannabinoid plasticity in neurological disorders will be discussed. In particular, examples of the beneficial effects of CB_1 receptor blockers or inhibitors of endocannabinoid inactivation in experimental models of Parkinson's and Alzheimer's disease, multiple sclerosis and neuropathic pain will be provided.