Use of cannabinoids in orphan diseases: potential for the treatment of pediatric epilepsy and Duchenne's muscular dystrophy

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Research performed on plant cannabinoids since the discovery of the main psychoactive constituent of cannabis, D^9-tetrahydrocannabinol (THC), has been dominated by studies on this compound. Yet, the several existing varieties of *Cannabis sativa* contain almost one hundred different cannabinoids. Recently, the pharmacology of some of these compounds, i.e. cannabidiol (CBD), D^9-tetrahydrocannabivarin (THCV), cannabidivarin (CBDV), cannabigerol (CBG), cannabichromene (CBC), etc., has been increasingly investigated. Most plant cannabinoids do not interact directly with THC specific binding sites in mammals, i.e. the cannabinoid CB1 and CB2 receptors, but hit multiple targets, including thermo-sensitive transient receptor potential (TRP) channels (e.g. TRPV1, TRPV2 and TRPA1), nuclear receptors (e.g. PPARg) and orphan G-protein-coupled receptors (e.g. GPR55). Furthermore. they inhibit the enzymatic hydrolysis or, more frequently, the cellular reuptake of endocannabinoids, or, through some of their several targets, can indirectly counteract THC actions in the brain. Therefore, they are in principle capable of indirectly modulating CB1 and CB2 receptor activity.

Based on recent preliminary data indicating that pure CBD dramatically reduces seizures in rare forms of pediatric epilepsy (e.g. Dravet's syndrome), and on own results showing that manipulation of CB1 receptors can remodel skeletal muscle differentiation *in vitro* and *in vivo* in mice, my group has recently investigated the effects of synthetic pharmacological tools specific for TRP channels and CB1 receptors, as well as of non-THC plant cannabinoids, in preclinical models of neuronal hyperactivity and muscular dystrophy. I will report on the results obtained in some of these studies, which strengthen the case for the therapeutic use of cannabinoids in orphan diseases such as Dravet's syndrome and Duchenne's muscular dystrophy.