

Cannabis Use, Effect And Potential Therapy For Alzheimer's, MS and Parkinson's

ScienceDaily (Oct. 15, 2007) — Cannabis (marijuana) is the most widely produced plant-based illicit drug worldwide and the illegal drug most frequently used in Europe. Its use increased in almost all EU countries during the 1990s, in particular among young people, including school students. Cannabis use is highest among 15- to 24-year-olds, with lifetime prevalence ranging for most countries from 20--40% (EMCDDA 2006).

Recently there has been a new surge in the level of concern about potential social and health outcomes of cannabis use, although the available evidence still does not provide a clear-cut understanding of the issues. Intensive cannabis use is correlated with non-drug-specific mental problems, but the question of co-morbidity is intertwined with the questions of cause and effect (EMCDDA 2006). Prevention is of importance in adolescents, which is underlined by evidence that early-onset cannabis-users (pre- to mid-adolescence) have a significantly higher risk of developing drug problems, including dependence (Von Sydow et al., 2002; Chen et al., 2005).

The illegal status and wide-spread use of cannabis made basic and clinical cannabis research difficult in the past decades; on the other hand, it has stimulated efforts to identify the psychoactive constituents of cannabis. As a consequence, the endocannabinoid system was discovered, which was shown to be involved in most physiological systems -- the nervous, the cardiovascular, the reproductive, the immune system, to mention a few.

One of the main roles of endocannabinoids is neuroprotection, but over the last decade they have been found to affect a long list of processes, from anxiety, depression, cancer development, vasodilatation to bone formation and even pregnancy (Panikashvili et al., 2001; Pachter et al., 2006).

Cannabinoids and endocannabinoids are supposed to represent a medicinal treasure trove which waits to be discovered.

Raphael Mechoulam will tell the discovery story of the endocannabinoid system. His research has not only helped us to advance our understanding of cannabis use and its effects, but has also made key contributions with regard to understanding "neuroprotection," and has opened the door for the development of new drugs.

Endocannabinoid system

In the 1960s the constituent of the cannabis plant was discovered -- named tetrahydrocannabinol, or THC -- which causes the 'high' produced by it (Gaoni & Mechoulam, 1964). Thousands of publications have since appeared on THC. Today it is even used as a therapeutic drug against nausea and for enhancing appetite, and, surprisingly, has not become an illicit drug -- apparently cannabis users prefer the plant-based marijuana and hashish.

Two decades later it was found that THC binds to specific receptors in the brain and the periphery and this interaction initiates a cascade of biological processes leading to the well known marijuana effects. It was assumed that a cannabinoid receptor is not formed for the sake of a plant constituent (that by a strange quirk of nature binds to it), but for endogenous brain constituents and that these putative 'signaling' constituents together with the cannabinoid receptors are part of a new biochemical system in the human body, which may affect various physiological actions.

In trying to identify these unknown putative signaling molecules, our research group in the 1990s was successful in isolating 2 such endogenous 'cannabinoid' components -- one from the brain, named anandamide (from the word 'ananda, meaning 'supreme joy' in Sanscrit), and another one from the intestines named 2-arachidonoyl glycerol (2-AG) (Devane et al., 1992; Mechoulam et al., 1995).

Neuroprotection

The major endocannabinoid (2-AG) has been identified both in the central nervous system and in the periphery. Stressful stimuli -- traumatic brain injury (TBI) for example -- enhance brain 2-AG levels in

mice. 2-AG, both of endogenous and exogenous origin, has been shown to be neuroprotective in closed head injury, ischemia and excitotoxicity in mice. These effects may derive from the ability of cannabinoids to act through a variety of biochemical mechanisms. 2-AG also helps repair the blood brain barrier after TBI.

The endocannabinoids act via specific cannabinoid receptors, of which the CB1 receptors are most abundant in the central nervous system. Mice whose CB1 receptors are knocked out display slower functional recovery after TBI and do not respond to treatment with 2-AG. Over the last few years several groups have noted that CB2 receptors are also formed in the brain, particularly as a reaction to numerous neurological diseases, and are apparently activated by the endocannabinoids as a protective mechanism. Through evolution the mammalian body has developed various systems to guard against damage that may be caused by external attacks. Thus, it has an immune system, whose main role is to protect against protein attacks (microbes, parasites for example) and to reduce the damage caused by them. Analogous biological protective systems have also been developed against non-protein attacks, although they are much less well known than the immune system. Over the last few years the research group of Esther Shohami in collaboration with our group showed that the endocannabinoid system, through various biological routes, lowers the damage caused by brain trauma. Thus, it helps to attenuate the brain edema and the neurological injuries caused by it (Panikashvili et al., 2001; Panikashvili et al., 2006).

Clinical importance

Furthermore it is assumed that the endocannabinoid system may be involved in the pathogenesis of hepatic encephalopathy, a neuropsychiatric syndrome induced by fulminant hepatic failure. Indeed in an animal model the brain levels of 2-AG were found to be elevated. Administration of 2-AG improved a neurological score, activity and cognitive function (Avraham et al., 2006). Activation of the CB2 receptor by a selective agonist also improved the neurological score. The authors concluded that the endocannabinoid system may play an important role in the pathogenesis of hepatic encephalopathy. Modulation of this system either by exogenous agonists specific for the CB2 receptors or possibly also by antagonists to the CB1 receptors may have therapeutic potential. The endocannabinoid system generally is involved in the protective reaction of the mammalian body to a long list of neurological diseases such as multiple sclerosis, Alzheimer's and Parkinson's disease. Thus, there is hope for novel therapeutic opportunities.

Numerous additional endocannabinoids -- especially various fatty acid ethanolamides and glycerol esters -- are known today and regarded as members of a large 'endocannabinoid family'. Endogenous cannabinoids, the cannabinoid receptors and various enzymes that are involved in their syntheses and degradations comprise the endocannabinoid system.

The endocannabinoid system acts as a guardian against various attacks on the mammalian body.

Conclusion

The above described research concerning the endocannabinoid-system is of importance in both basic science and in therapeutics:

- The discovery of the cannabis plant active constituent has helped advance our understanding of cannabis use and its effects.
- The discovery of the endocannabinoids has been of central importance in establishing the existence of a new biochemical system and its physiological roles -- in particular in neuroprotection.
- These discoveries have opened the door for the development of novel types of drugs, such as THC for the treatment of nausea and for enhancing appetite in cachectic patients.
- The endocannabinoid system is involved in the protective reaction of the mammalian body to a long list of neurological diseases such as multiple sclerosis, Alzheimer's and Parkinson's disease which raises hope for novel therapeutic opportunities for these diseases.

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