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Cannabinoids and monoamine neurotransmission with focus on monoamine oxidase

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ABSTRACT

Progress in understanding the mechanisms of action of cannabinoids was made after discovery of cannabinoid receptors and finding their endogenous ligands. New findings are obtained using both endogenous cannabinoids and plant or synthetic cannabinoids. Activation of cannabinoid receptors on synaptic terminals results in regulation of ion channels, neurotransmitter release and synaptic plasticity. Neuromodulation of synapses by cannabinoids is proving to have a wide range of functional effects, making them potential targets as medical preparations in a variety of illnesses, including some neurodegenerative and mental disorders. Brain monoamines are involved in many of the same processes affected by neuropsychiatric disorders and by different psychotropic drugs, including cannabinoids. Basic information is summarized in the paper about mechanisms of action of cannabinoids on monoaminergic systems, with a view to inhibition of monoamine oxidase.

1. Introduction

Cannabinoids form a group of substances originally found in cannabis plant but they refer to any substance which is specifically recognized by the cannabinoid systems in the body (reviewed by Howlett et al., 2002; Lambert and Fowler, 2005). Currently, there are three general types of cannabinoids: 1. herbal cannabinoids, e.g. Δ^9-tetrahydrocannabinol (Δ^9-THC, THC), cannabinol, cannabidiol, 2. endogenous cannabinoids, e.g. anandamide (AEA), 2-arachidonoylglycerol (2-AG), and 3. synthetic cannabinoids, e.g. WIN 55,212-2, CP 55,940, HU-210, JWH-018 (reviewed by Fišar, 2009a). The endocannabinoid system consists of cannabinoid receptors, endogenous ligands and several proteins responsible for synthesis and degradation of endocannabinoids. The physiological functions of the cannabinoid system are very complex and involve motor coordination (basal ganglia), memory (hippocampus), appetite, pain modulation (hindbrain), neuroprotection, and maintenance of homeostasis, among others (reviewed by Marsicano and Lutz, 2006; Pacher et al., 2006; Tasker, 2006).

1.1. Phytocannabinoids

It was demonstrated in the 1960s that Δ^9-THC is the most significant constituent of cannabis from a pharmacological and toxicological point of view. The exact chemical structure of Δ^9-THC was described in 1964 (Gaoni and Mechoulam, 1964) and its complete synthesis (a mixture of (−)- and (+)-optical isomers) was published in 1965 (Mechoulam and Gaoni, 1965). Demonstration of the existence of cannabinoid receptors in the central nervous system (CNS) in 1988 (Devane et al., 1988) and the discovery of the first endogenous cannabinoids (Devane et al., 1992; Mechoulam et al., 1995) were key events in understanding of molecular mechanisms of action of cannabinoids.

The action of low doses of Δ^9-THC is characterized by a mixture of depressive and stimulative effects on the CNS. Abuse of cannabis drugs leads to a series of mental and physical changes. While acute effects of cannabis are well-known, knowledge of the influence of chronic cannabis use on cognitive function, neurochemical processes, endocrine and immune systems is not so well-understood (reviewed by Grotenhermen, 2007; Hall and Solowij, 1998; Iversen, 2003).

The acute effects of psychotropic cannabinoids depend on dose, route of administration, previous experience of the cannabis user and individual susceptibility to psychotropic action of Δ^9-THC, and also on the state of abuser state of mind at the time of taking the drug. Serious adverse effects usually occur only with higher doses (>20 mg of Δ^9-THC) but they may also occur with lower doses due to high interindividual variability in response to cannabinoids (reviewed by Grotenhermen, 2007; Hall and Solowij, 1998). Cannabis has a marked negative effect on short-term memory but it seems that the ability to recall previously learned information is not disturbed. Acute effects of cannabis on working memory disappear after 3–4 h; the degree of damage to memory and other intellectual functions due to regular use of high doses of cannabinoids is still subject to research.

The most marked psychic effects of THC can be divided into four groups: 1. affective (euphoria, cheerfulness, anxiety, panic), 2. sensoric (increased perception of external stimuli and one's own body),

Abbreviations: AEA, anandamide; 2-AG, 2-arachidonoylglycerol; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; CREB, cAMP response element-binding protein; GABA, γ-aminobutyric acid; GPCR, G protein-coupled receptor; HU-210, 11-hydroxy-Δ^8-THC-dimethylheptyl; MAO, monoamine oxidase; PKA, protein kinases type A; SERT, serotonin transporter; Δ^9-THC, THC, Δ^9-tetrahydrocannabinol.

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3. somatic (feeling of the body floating or falling), and 4. cognitive (disturbed time perception, impaired short-term memory and attention). Impaired cognitive functions are more marked among those who started to use cannabis during adolescence (Pope et al., 2003). Recent studies of cannabis users in the unintoxicated state evidenced that long-term heavy cannabis use is associated with impaired memory function. The evidence suggests impaired encoding, storage, manipulation and retrieval mechanisms (reviewed by Solowij and Battisti, 2008).

Investigations of recovery of cognitive function with abstinence from cannabis have produced conflicting evidence, with some studies suggesting persistent deficits in specific cognitive functions beyond the period of acute intoxication (Bolla et al., 2002; reviewed by Solowij and Michie, 2007). However, many findings do not support the hypothesis that long-term heavy cannabis use causes irreversible cognitive deficits (Pope et al., 2001; reviewed by Grant et al., 2003).

Cannabis also has a large number of physical effects, e.g. lowering of body temperature, reddened conjunctivae, reduced tear flow, decreased intraocular pressure, tachycardia, increased oxygen demands, vasodilatation, orthostatic or postural hypotension, hypertension, bronchodilation, hyposalivation, reduced bowel movement and delayed gastric emptying, changes in hormonal and immune system etc. THC influences cardiovascular system through CB_1 receptors located both in blood cell and in hearth tissue (reviewed by Fišar, 2009b). Elevation of static heartbeat, as far as about 60% during first 30 min after smoking cannabis, can be dangerous for men with cardiovascular disorder.

Psychoactive cannabinoids increase risk of traffic accidents and risk of psychotic symptoms among vulnerable persons (reviewed by Koethe et al., 2009; Leweke and Koethe, 2008). Most of these effects are dependent on dose and route of administration and are attributable to a modulation of endocannabinoid system in the brain, via specific interactions with their receptors (reviewed by Pertwee et al., 2010) with the subsequent activation of different signaling pathways.

1.2. Endocannabinoids

Endogenous cannabinoids (endocannabinoids) are lipophilic signaling molecules which are synthesized de novo from membrane phospholipids and released in response to postsynaptic depolarization or activation of metabotropic glutamate receptors. They meet the criteria for listing as neurotransmitters, but unlike classic neurotransmitters they are not synthesized in the cytosol of neuron and are not stored in synaptic vesicles. Endocannabinoids are widely distributed in the brain and throughout the body. *sn*-2-Arachidonoylglycerol (2-AG) (Mechoulam et al., 1995; Sugiura et al., 1995) is the most prevalent endogenous ligand of cannabinoid receptors in mammals, and anandamide (*N*-arachidonoylethanolamide, AEA) (Devane et al., 1992) has been the most explored. Additional putative endocannabinoids are noladin ether (2-arachidonoyl glyceryl ether), virodhamine (*O*-arachidonoyl ethanolamine), *N*-arachidonoyl dopamine, oleamide, *N*-oleoyl dopamine and others (reviewed by Pertwee 2005). Anandamide, 2-AG and several other endogenous cannabinoids are derived from arachidonic acid (all-*cis* 5,8,11,14-eicosatetraenoic acid, 20:4), which is one of the unsaturated fatty acids found in the phospholipids of the cell membrane. It seems that endocannabinoids play an important role in brain reward system and in emotional response to stress.

1.3. Synthetic cannabinoids

A series of extremely potent cannabinoid receptor agonists and cannabinoid receptor antagonists/inverse agonists has been synthesized. Thus, synthetic cannabinoids are particularly useful in experiments to determine the relationship between the structure and activity and they facilitate behavioral and neurobiological research with cannabinoids (reviewed by Fišar, 2009a).

The most investigated synthetic analogue of classical phytocannabinoids has been 11-hydroxy-Δ^8-THC-dimethylheptyl (HU-210). HU-210 has affinities for CB_1 and CB_2 receptors that exceed those of these other cannabinoids. As a result, it is a particularly potent cannabinoid receptor agonist. *R*-(+)-WIN55,212 is the most highly studied compound of the class of aminoalkylindoles (D'Ambra et al., 1992). It displays high affinity for CB_1 and CB_2 receptors and shows higher relative intrinsic activity as compared with Δ^9-THC.

There is increasing amount of synthetic substances with cannabimimetic properties; more than 100 compounds show cannabinoid receptor activity. However, little data is available on the psychological and other risks of synthetic cannabinoids. The physical withdrawal phenomena and dependence syndrome after consumption of synthetic cannabinoids are similar to phytocannabinoids (Zimmermann et al., 2009; reviewed by Seely et al., 2011; Vardakou et al., 2010). It seems likely that they can cause psychosis in vulnerable individuals (Every-Palmer, 2011).

2. Molecular mechanisms of action of cannabinoids

Neurochemical events for cannabinoid action could be classified into direct (immediate) effects, early (intermediate) effects, and long-term (delayed) effects. Immediate receptor effects of cannabinoids are followed by early events, such as changes of availability of neurotransmitters, alteration of neurotransmitter receptors activation, and changes in intracellular signaling pathways, including activation of transcription factors. Long-term effects are linked to changes of gene expression of neurotrophic factors and other cellular proteins.

There are two types of G protein coupled cannabinoid receptors, CB_1 and CB_2, which were cloned and confirmed endogenously. However, cannabinoids activate more distinct cannabinoid receptors, such as GPR55 and transient receptor potential vanilloid type 1. Recent data also suggest that CB_1 receptors form homo- and heteromeric complexes with certain other receptors (reviewed by Pertwee et al., 2010). Available findings show that CB_1 receptors in the brain are responsible for the psychotropic properties of the cannabinoids, including the reward effect, tolerance and physical addiction (reviewed by Tanda and Goldberg, 2003). Both receptor types are coupled with $G_{i/o}$ proteins, negatively to adenylate cyclase ($G\alpha_{i/o}$-dependent inhibition) and positively to mitogen-activated protein kinase ($G\beta\gamma$-dependent activation). cAMP is an important second messenger for transfer of signals for the activation of various neurotransmitter receptors (Table 1), and participates in regulating cellular functions via activation of A-type protein kinases (PKA). PKA activity is related to many cellular functions, including synaptic plasticity and cell survival (reviewed by Bosier et al., 2010). Further, CB_1 receptors are connected via $G_{i/o}$ proteins to ion channels, negatively with N-type and P/Q-type calcium channels, and positively with various types of potassium channels (reviewed by Demuth and Molleman, 2006). Inhibition of calcium channels can explain cannabinoid induced reduction of release of neurotransmitters from presynaptic terminals. However, there are evidences that CB_1 receptors can also stimulate adenylate cyclase via G_s proteins, induce receptor mediated Ca^{2+} fluxes and stimulate phospholipases in some experimental models (reviewed by Turu and Hunyady, 2010).

Localization of cannabinoid receptors is determining their physiological functions. CB_1 receptors are found predominantly in the brain but they also occur in the spinal cord and peripheral nervous system. CB_1 receptors are thought to be the most highly expressed G protein-coupled receptors (GPCRs) in the brain. They are especially located in the area of synapses, and one of their functions involves modulation of neurotransmitter release. CB_1 receptor positive terminals target both the dendritic and somatic surfaces of neurons. These receptors are abundant on GABAergic neurons (Bodor et al., 2005). Receptor distribution along the axonal membrane was determined using