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ENDOCANNABINOID SYSTEM INVOLVEMENT IN DRUG ADDICTION, DEPRESSION, AND NEUROTIC DISORDERS

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A b s t r a c t

The aim of this paper is to bring to attention recent evidence on the roles of the central endocannabinoid system in neuropsychopathological conditions such as drug dependence, depression, anxiety, and aggression. Results of pharmacological studies with cannabinoid receptor ligands in rodent behavioural models reported (behavioural sensitisation to drugs of abuse – "open-field test", "agonistic behaviour", "I.V. drug self-administration"; depression – "bilateral olfactory bulbectomy", "repeated social defeat"; aggressiveness, and anxiety – "agonistic behaviour") are expected to show in their outcomes a possibility of predicting therapeutic pharmacological intervention into the endocannabinoid system activity in the above-mentioned neuropsychiatric disorders.

K e y w o r d s

Endocannabinoid system, Potential pharmacotherapy, Dependence, Depression, Anxiety, Pharmacokinetics

INTRODUCTION

Neuropsychopathological changes cannot be evaluated just as an individual health alteration but may negatively influence the whole family and even a society simultaneously. This is concluded by data of large national studies (*1, 2*) showing an increasing number of patients, a decrease in the age of onset (namely in drug addiction), and an increasing budget associated with the treatment and programmes of education and prevention. Therefore, both preclinical (experimental) and clinical research in this field expecting to bring new knowledge on neurobiology of these processes is in the centre of interest all over the globe. As a novel approach for the development of new pharmacotherapeutical agents can, for instance, serve exogenously induced manipulation with the activity of the endocannabinoid system.

MATERIALS AND METHODS

The endocannabinoid system

The endocannabinoid system is a complex of endogenous compounds called endocannabinoids, enzymes of their synthesis and biodegradation, and specific cannabinoid receptors (mediating also effects of cannabinoids known as components of marihuana and hashish from Cannabis sativa). Physiological and pathophysiological roles of the endocannabinoid system are being discovered step by step at present (*3*). It is expected that possibilities of pharmacological manipulation with the activity of the endocannabinoid system (differently than smoking marihuana) on just some of its levels and thus production of more selective effects with minimal adverse influences will be developed (*4, 5, 6, 7*). Within the nervous system endocannabinoids are believed to work as retrograde synaptic messengers (*8, 9*). They are released on demand from neuronal cells, are bound to cannabinoid CB_1 receptors on the presynaptic terminals of neurones of a differential neurotransmitter (e. g. serotonin, glycine, gamma-aminobutyric acid, glutamate, cholecystokinin) and hormonal (corticotropin – ACTH, corticosterone) origin. The activity of cannabinoid receptors then influences a release of these substances. Particularly from the CB_1 cannabinoid receptor localisation it can be predicted that changes of their activity might on one side be involved in various signs of nervous system disorders and, on the other side, there is a belief that exogenous intervention into those mechanisms could be of pharmacotherapeutical importance (*10, 11, 12, 13*).

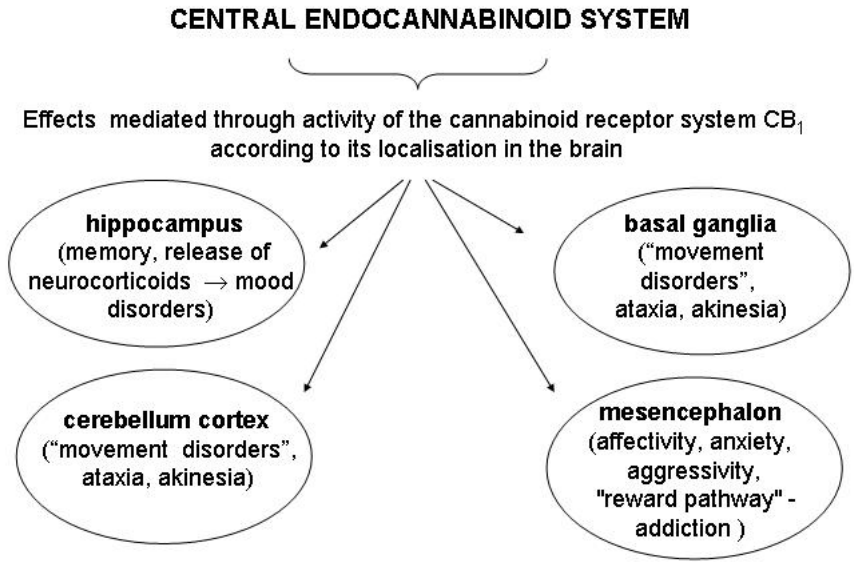
Considering that the neuroprotective role of the endocannabinoid system in the CNS might be employed against different disorders including changes associated with drug dependence, depression and neurotic signs (*13*), the recognised experimental behavioural models of these disorders running for a longer time in our labs offer a guarantee that investigation of pharmacological interventions into its activity and their interactions with other exogenously administered drugs can provide enlargement of knowledge on what has been causing quite a stir worldwide in searching for new drugs.

Endocannabinoid system involvement in drug addiction, depression, anxiety, and aggressiveness

For about two decades our laboratory has been interested in the research of psychotropic effects of cannabinoids using rodent behavioural models of drug dependence ("I.V. drug self-administration", "open-field test", "agonistic behaviour"), depression ("bilateral olfactory bulbectomy", "chronic social defeat"), anxiety, and aggressiveness ("agonistic behaviour"). The results published in the field of pharmacology research on drug dependence, depression and neurotic disorders – type of anxiety and aggressiveness (*13–18*) showed that the endocannabinoid system is involved in these diseases (*19, 20, 21, 22*, and others). The investigation of selective cannabinoid receptor ligands and compounds indirectly influencing the activity of endocannabinoids (modulating their turnover – eg. inhibitors of endocannabinoid anandamide transporter VDM 11 and UCM 707, anandamidase inhibitor MAFP, and FAAH inhibitor palmitoylisopropylamide) can provide a suggestion for their potential pharmacotherapeutical utilisation in clinics.

RESULTS

In our earlier studies we registered a behavioural cross-sensitisation (*23*) by the cannabinoid agonist methanandamide to methamphetamine antiaggressive effects in the mouse model of social agonistic behaviour (*16, 24*) and to a stimulatory influence on locomotion in the open-field test (*17, 25*). On the other hand, that development of sensitisation was suppressed by the CB1 cannabinoid receptor blocker AM251 (*16, 17*). These results are in agreement with cross-sensitisation confirmed with tetrahydrocannabinol to other drugs of abuse – opioids (*26, 27*) and also suggest the risk of higher vulnerability of cannabinoid users to the abuse of methamphetamine. At the same time the results confirmed our earlier outcomes of the "I.V. drug



Scheme 1.
Endocannabinoid system activity involvement in regulation of addiction and affective disorders, (depression, anxiety, aggressivity).

self-administration" experiment in which the intake of methamphetamine was inhibited in the case of pretreatment with the cannabinoid receptor antagonist AM 251 (*15*). This altogether may predict that CB_1 receptor blockers may be of therapeutic use in addicts. Worldwide there is increasing concern paid to gender differences in susceptibility to drugs of abuse (*29*).

In agreement with various other studies (*29, 30, 31*) we demonstrated in our models an antidepressant-like efficacy of antiepileptics of the 3rd generation (*32-35*), and also of a selective antagonist of cannabinoid CB1 receptor antagonist rimonabant (*36, 37*).

Agonistic mouse behaviour is accepted as a model for testing the anxiolytic and antiaggressive drug activities (*38*). This model has been well established in our lab for a longer time (*39, 40*). Changes of mouse sociable, defensive-escape, aggressive, and locomotor behavioural acts and postures were analysed after administration of compounds with differential affinity and intrinsic activity to cannabinoid receptor subtypes CB1 and CB2. Mixed CB1, 2 agonists (HU210, anandamide) elicited biphasic effects – at low doses stimulation of aggressive behaviour in timid mice, and at higher doses inhibition of aggressiveness in aggressive mice (*14*). A marked inhibitory influence on aggressiveness in aggressive mice was also produced by the

selective agonists of CB1 receptors (noladine, methanadamide) at all doses tested, and to some extent by a putative CB2 receptor agonist (palmithoylethanolamide). In the timid mice, all agonistic ligands of cannabinoid receptor subtypes tested (mixed CB 1, 2 or selective CB1 or selective CB2 ligands) caused proaggressive effects (*41, 42*).

CONCLUSIONS

Thus experimental research on the effects of agents specifically influencing the activity of the recently discovered endocannabinoid system in animal models of drug dependence, depression, anxiety, and aggressiveness suggests that an alteration of the central endocannabinoid system activity might result in changes of these neuropsychopathological conditions, and that exogenous manipulation with the endocannabinoid system activity could therefore be of pharmacotherapeutical benefit.

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