 DOI: 10.18231/ 2455-8559.2017.0004

The endocannabinoid system and its role in schizophrenia: a narrative review

Shivananda Palanisamy[1], Paul Brown[2], Ajay Verma Macharouthu[3]

[1]Medical student, University of Dundee, [2]Consultant in Old age Psychiatry, NHS Greater Glasgow & Clyde
[3]Consultant Old age Psychiatry, NHS Ayrshire & Arran, Honorary clinical senior lecturer, University of Glasgow

***Corresponding Author:**
Email: ajjus@aol.com

Abstract

Aim: To provide an overview of the currently understood structure and function of the endocannabinoid system and the putative relationships of endocannabinoid system dysfunction and schizophrenia. To delineate potential novel targets in the endocannabinoid system for therapeutic modulation.

Methods

Design: Narrative review of peer reviewed research articles and authorative texts.

Study (and authorative text) selection and analysis: Several databases including PubMed, Science Direct and University of Dundee library were systematically searched for studies addressing the issues of: (a) an association between cannabis and schizophrenia; (b) an association between any component of the endocannabinoid system and schizophrenia; and (c) possible interventions in schizophrenia by modulating the endocannabinoid system were included. Authorative texts were manually located and information selected according to the same criteria.

Results: This paper provides an overview of the currently known structure and function of the endocannabinoid system. Exogenously administered cannabinoids can produce a range of psychoactive effects including a psychosis with similar clinical features to acute schizophrenia. Additionally, cannabis may contribute to the development of schizophrenia in susceptible individuals. Changes are seen in the endocannabinoid system in schizophrenia and there are putative links between endocannabinoid system dysfunction and the disorder. Phytocannabinoids as well as commercially developed compounds acting on the endocannabinoid system have demonstrable antipsychotic effects.

Conclusions: This review highlights the putative links between endocannabinoid system dysfunction and schizophrenia. Traditional antipsychotic agents have demonstrable effectiveness in treating schizophrenia and were developed in response to the dopamine hypothesis of schizophrenia. However, there remains considerable scope for improvements to be made in the management of this challenging disorder. Aberrant functioning of the endocannabinoid system could represent an exciting therapeutic target for the development of novel effective agents.

Introduction

Schizophrenia is a Greek word which roughly translated means 'the splitting of the mind'. The purpose of the word was intended to describe the apparent disintegration of function between personality, thought, memory and perception. Schizophrenia is a complex disorder with a wide range of clinical features.

The ICD-10 describes Schizophrenia and related mental illnesses as disorders that are 'characterized in general by fundamental and characteristic distortions of thinking and perception with affects that are inappropriate or blunted. Clear consciousness and intellectual capacity are usually maintained although certain cognitive deficits may evolve in the course of time'.[(1)]

The Endocannabinoid System (ECS) is a widespread complex endogenous neurotransmitter system with its own novel ligands and associated receptors. The system is 'omnipresent' across the animal kingdom, found in the simplest of invertebrates such as the sea squirt (*Ciona intestinalis)* through to modern man (*Homo sapiens sapiens).*

The first recorded use of cannabis for medicinal purpose was in 2727 B.C. by the Chinese Emperor Shen-Nung.[(1)] Hemp (a variety of cannabis plant) was used in the treatment of period pains, gout, rheumatism and constipation to name a few. It was later used as an anaesthetic in China in combination with wine.[(2)]

It was only introduced to modern medicine in the 19th century by the Irish physician and scientist, W. B. O'Shaughnessy[(3,4)] who was very much impressed after observing cannabis being used as an analgesic, an anticonvulsant, an antispasmodic, an antiemetic and a hypnotic in India. Medicinal use of cannabis then became widespread and was available over the counter in different preparations.[(4)]

Cannabis was made illegal in the United Kingdom in 1928,[(5)] however the endocannabinoid system has recently come to the forefront of medical research with certain countries changing their stance on drug prohibition. Some advocate for legalization of cannabis for medicinal use as increased attention is being given by medical science to cannabis and the endocannabinoid system as a potential therapeutic target for a range of clinical conditions.

Though currently trade is illegal, cannabis can be found in a number of forms. A recent report made by the Home Office highlights the commonly used forms of Cannabis by the British public. Herbal strains that are homegrown and of low potency are the most common,[(6)] however a steady increase in the use of 'sinsemilla' or hydroponic varieties, which are much stronger[(6)] has also been seen. There is also still a

market for hashish or hash, which is cannabis resin that tends to be imported from North Africa.[6] Due to illegality, this market and its products tend to be unregulated resulting in products of variable potencies.

The first compound isolated was Cannabinol, a weak metabolite of Δ^9- tetrahydrocannabinol, this happened very early on in 1895.[3,4] Next came the discovery of Cannabidiol in 1934,[3,4] one of the main cannabinoids found in cannabis. And finally in 1964, Raphael Mechoulam and his team isolated the elusive compound that was responsible for the psychoactive effect of cannabis, Δ^9- tetrahydrocannabinol (Δ^9-THC).[3,4]

Over the years, various other phytocannabinoids have been isolated from Cannabis itself, amounting to 30 and others have been found in different plants such as *Echinacea* spp.[7]

Cannabis can induce significant psychoactive effects. This observation, along with the distribution of cannabinoid receptors across the brain in areas related to higher functions in addition to the importance of the ECS in neurotransmission and emotional regulation give rise to a possible association of the ECS and psychiatric disorder. Exploration of such links could provide potential opportunities for novel therapies.

This article explores the role the ECS may have in the development of schizophrenia specifically as the use of cannabis and this psychiatric disorder have long been associated.

Materials and Method

Relevant research concerning the endocannabinoid system, cannabis and schizophrenia was identified by searching the relevant science databases. A total of 7 databases were searched for publications from 1995 through to the present (2015).

Database search terms used were 'cannabis or endocannabinoid' plus 'schizophrenia or psychosis' anywhere in the title or abstract. No language restrictions were placed. Any studies and reviews that addressed the issue of: (a) an association between cannabis and schizophrenia; (b) an association between any component of the endocannabinoid system and schizophrenia; and (c) possible interventions in schizophrenia by modulating the endocannabinoid system were included.

There is a paucity of research papers on this topic with variable quality. An unsystematic narrative was chosen in order to effectively synthesize and present the main findings from the evidence.

Neuropharmacology of the endocannabinoid system: The current hypothesis of the function of the ECS under normal physiological conditions is to restore homeostatic balance after stress, inflammation or cell damage. This system works in a paracrine fashion, with ligands being produced on demand in a locally and temporally regulated manner from constituents of the cell membrane with the help of specific lipases, being released into the cell surroundings for local effect. Once the ligands have completed their function, they are taken up into cells where they are enzymatically degraded.

1. **Endocannabinoids:** Endocannabinoids (eCBs) are a group of small lipid molecules involved in cell-to-cell signaling, with modulation of neurotransmitters within the CNS. They have also been shown to have activity outside the nervous system. These lipid molecules are derivatives of arachidonic acid; they exist in precursor form within the phospholipid bilayer of cell membranes.

Anandamide is an endocannabinoid occurring in small concentrations. It is a full agonist at CB_1 receptors and although it binds to CB_2 receptors it has shown to have low affinity at this receptor. It modulates cAMP levels thereby inhibiting neurotransmitter release.[8,9,10,11]

When tested in animals, anandamide produced a series of behavioural responses characteristic of classical cannabinoids: anti-nociception, hypothermia and hypo-motility.[11] In low doses, a mixture of stimulant and depressive effects were observed. At high doses, central depression predominantly resulted.[11] Anandamide has various roles within the CNS involving memory, pain relief and reward seeking behaviour. Recent studies have uncovered its importance across different systems in the human body;[9] the process of blastocyst implantation and the regulation of feeding behavior. It has been hypothesized that exercise-induced release of Anandamide may have analgesic effects.[12]

Anandamide is derived from *N*-arachidonoyl phosphatidylethanolamine (NAPE) through various pathways when required.[8,9,10] The most common method of synthesis is by the cleavage of NAPE by a novel phospholipase D (NAPE-PLD), producing Anandamide and phosphatidic acid.[8,9,10]

Anandamide has a short half-life explaining why it is found in low concentrations. It is taken up into cells via a lipid transport protein (EMT)[8,9,10,13] and then enzymatically degraded immediately after it is produced. The enzyme responsible for degradation, Fatty Acid Amide Hydrolase (FAAH) hydrolyses Anandamide into a free fatty acid and ethanolamine.[8,9,10,13]

2-arachidonoylglycerol (2-AG) is another endocannabinoid found in larger concentrations within the CNS; concentrations of more than 170 times that of Anandamide have been noted.[13] 2-AG binds to both CB_1 and CB_2 receptors and acts as a full agonist, again producing effects characteristic of classical cannabinoids.[8,9,10,13] 2-AG has been viewed as an unlikely mediator of psychotropic effects however as it binds more efficaciously to the receptors it has been hypothesized that it has more important effects on neurotransmission than Anandamide.[16]

The biosynthesis of 2-AG occurs via various pathways. 2-AG is produced from its precursor, phosphatidylinositol bisphosphate (PIP2),[8,9,10] by the sequential action of two enzymes; phospholipase C (PLC) followed by one of two diacylglycerol lipases (DAGL).[11,12,13] It can also be synthesized via the combined actions of a phospholipase C and phospholipase A_1.[11,12,13]

Exogenously added 2-AG is degraded rapidly by a variety of cells to yield arachidonic acid and glycerol.[8,9,10] The key enzyme catalyzing the breakdown of 2-AG is monoacylglycerol lipase (MAGL).[8,9,10] The same lipid carriers that facilitate the uptake of Anandamide are responsible for the uptake of 2-AG into cells.

2. **Cannabinoid Receptors:** The cannabinoid receptors are part of the G-protein-coupled superfamily of receptors.[14,15] They are primarily coupled to G_0/G_i G-proteins and hence their common signaling pathways include the inhibition of Adenylyl Cyclase, activation of mitogen-activated (MAP) kinases, inhibition of voltage gated Ca^{2+} channels and activation of G protein-gated inward rectifying K^+ channels (GIRK).[14,15,16]

CB_1 receptors are found in high densities mostly within the CNS;[14] they have a receptor density 10 to 50 times greater than that of dopaminergic and opioidergic receptors.[14,15,17] The CB_1 receptor is found to be located on the terminal ends of central and peripheral neurons and as well as on glial cells.[14,15,17] CB_1 receptors are believed to have a physiological role in the regulation of higher mental functions such as perception, learning, emotional states and memory processes.

CB_2 receptors are found in tissues with immune system functions including the spleen, tonsils, bone marrow and on leukocytes,[14,15,17] with the highest expression detected in B-lymphocytes. They have also been found on microglia in the amygdala, hippocampus, hypothalamus and cerebellum.[18] The CB_2 receptors inhibit immune cell function and so are anti-inflammatory. Within the CNS, CB2 receptors have been postulated to exert a neuro-protective effect.[17]

Recently the CB_2 receptor has been implicated in a more central function.[19] It may be involved in emotional control and reactions to stress. However these functions are yet to be investigated.

Functional interactions between the ECS and other monoaminergic and peptidergic systems have been shown, with the purpose of the endocannabinoids being to modulate the release of the various other monoaminergic and peptidergic neurotransmitters.

The endocannabinoid system also has a role in synaptic plasticity. This phenomenon is thought to play an important function in the formation of new memories and aid in the ability to learn.[20-24]

Current research is beginning to show that synaptic plasticity mediated by the ECS might play an important part in maintaining homeostasis, with regard to physiological and behavioural responses to acute and prolonged stress.

Psychiatric Disorders: It is well established that cannabis can induce a range of psychiatric features in healthy human subjects, including psychotic symptoms resembling those found in schizophrenia.[25] The acute effects of cannabis include euphoria, relaxation, heightened sensory awareness and feelings of detachment.[25,26] It can also cause unwanted effects such as paranoia, panic, a fear of dying, a feeling of loss of control, depersonalization and derealisation,[25,26] though these effects are short lived. There are several ways in which cannabis has been shown to precipitate a psychosis.[25]

A large one-off dose can cause an acute toxic psychosis, with symptoms like confusion and hallucinations, remitting after abstinence.[25] A chronic psychosis is seen in heavy users of cannabis; these people suffer from repeated short psychotic episodes and can display evidence of a chronic psychotic state.[25]

Long-term use may lead to an organic psychosis, which partially remits after abstinence leaving a residual state known as amotivational syndrome.[25] This syndrome is characterized by personality deterioration and the loss of the drive and energy to work, but it must be taken into account that the evidence for the syndrome comes from largely uncontrolled studies and therefore the existence of such a syndrome is uncertain.[25]

Cannabis or Δ^9-THC can worsen psychotic symptoms in those who already have a diagnosis of Schizophrenia thereby contributing to a poorer outcome, with increased chance of relapse. Additionally it has been shown that antipsychotics are not as effective in a patient concurrently abusing cannabis.

There are studies that show that cannabis use may itself contribute to the development of the illness in individuals susceptible to psychosis. Also people more likely to develop Schizophrenia are those who are also more likely to abuse cannabis. There is difficulty differentiating as to whether cannabis and cannabinoids are one in a multitude of other risk factors for developing the illness or a drug of abuse for individuals with schizophrenia trying to cope with the negative symptoms of the illness.

This tells us that the ECS and disruption of its function may play a crucial part in the pathophysiology of Schizophrenia. With the further elucidation of the function of the ECS, its receptors and ligands, more studies were attempted to find links between this system and schizophrenia.

One postmortem study, conducted by Zavitsanou et al,[27] using a radiolabeled ligand selective for CB_1 receptors in brains of recently deceased schizophrenia

patients has shown a 64% increase in CB_1 receptor density in the anterior cingulate cortex, an area of the brain important for normal cognition and involved in motivation and attention, as when compared to controls.[27]

Another study, Dean et al,[28] using a radiolabeled nonspecific CB_1 receptor agonist identified an increase in CB_1 receptor density in the dorsolateral prefrontal cortex (Brodmann area 9, DLPFC) that was independent of prior cannabis use. Seeing as both these areas in which CB_1 receptor density is increased are involved in higher functioning it is not surprising that the possibility of endocannabinoid dysfunction may indeed lead to schizophrenia.

Eggan and Hashimoto et al[29] studied CB_1 receptor MRNA and protein expression in the brains of schizophrenic patients, which showed results that were different to the previous studies; CB_1 receptor MRNA and protein expression, was found to be reduced. The DLPFC is known to have an increased CB1 receptor density, compared to other areas of the brain; here the ECS works to suppress GABA. According to this study, Schizophrenia is characterized by impairments in working memory that have been associated to reduce GABA neurotransmission in the DLPFC.[29] This reduction is hypothesized to represent a compensatory action by the Endocannabinoid System to enhance GABAergic neurotransmission in the DLPFC.

A 2004 study by Giuffrida et al[30] measured CSF anandamide levels across a number of different participants; healthy volunteers, antipsychotic naïve first episode paranoid schizophrenia patients, schizophrenia patients treated with antipsychotics as well as dementia and affective disorder patients. The antipsychotic naïve group of schizophrenia patients showed a level of Anandamide in their CSF eight times greater than that of controls. Patients treated with typical antipsychotics showed no difference in their CSF Anandamide levels as when compared with controls; however those treated with atypical antipsychotics showed levels similar to the antipsychotic naïve group; possibly due to the difference in receptor targets between the different antipsychotics. Affective disorder and dementia patients showed levels similar to controls.

This study also showed that increased levels of CSF anandamide were negatively correlated with positive symptoms.[30] The current hypothesis is that Anandamide may act to re-exert homeostatic control by serving as an inhibitory feedback signal to counter the hyperdopaminergic state in psychosis.

A more recent study by Koethe and Giuffrida et al[31] further examined the relationship between CSF eCB levels and the development of psychosis. This time they found that raised levels of CSF Anandamide in the prodromal states of psychosis increased the transition time to acute psychosis whilst lower CSF Anandamide meant a shorter transition time. This study suggests that the ECS exhibits a protective role in early schizophrenia as seen from the up-regulation of Anandamide and correlation with transition time to psychosis and presence of symptoms.

As we already know, the function of the ECS in the periphery is mainly related to immune function and several hypotheses have involved immune system dysfunction in the development of psychotic illness. It has also been reported that function of the ECS in the periphery mirrors that of central endocannabinoid function in neuroinflammatory diseases.[32]

Bioque et al tested this hypothesis. Their study compared the expression of CB2 receptors and the activity of eCB synthesis enzymes on peripheral blood mononuclear cells (PBMC) between healthy controls and patients with first episode psychosis.[33] The patients with first episode psychosis showed reduced expression of CB_2 receptors and decreased activity of eCB synthesis enzymes as when compared to the controls.[33] The enzymes regulating the breakdown of eCBs like FAAH and MAGL were showing increased activity but not so much as to be statistically significant.[33] This study suggests that peripheral endocannabinoid dysfunction is present in psychosis.

Therapeutic Modulation: The phytocannabinoid, cannabidiol has come across as the most attractive option in the therapy of Schizophrenia with studies showing that it exerts clinically relevant antipsychotic effects with marked safety and tolerability. One human therapeutic-exploratory study was conducted and it showed that the antipsychotic effect produced by administration of cannabidiol had similar effectiveness to a standard antipsychotic. Cannabidiol has been shown to be inhibitory to FAAH, resulting in enhanced Anandamide signaling, which may explain its antipsychotic effects.[34]

The novel enzyme NAPE-PLD, a crucial enzyme in the synthesis of Anandamide, could be manipulated in order to increase levels of Anandamide in tissue. The enzymes responsible for the breakdown of endocannabinoids, FAAH and MAGL, could be inhibited to stop hydrolysis of both Anandamide and 2-AG. In fact the FAAH inhibitor URB597 has been shown to reduce social deficits in animal models.[35,36]

The lipid carrier that facilitates re-uptake has displayed substrate specificity, is saturable and can be blocked by the action of drugs like AM 4048 allowing for increased levels of endocannabinoids.[36]

CB_2 receptor modulation could also represent a possible therapeutic target. Stimulation of these receptors could possibly help in Schizophrenia as reduced expression of CB_2 receptors correlates with ECS dysregulation which is a probable cause of psychosis. CB_2 agonists like beta-caryophyllene[36,37] are now under scrutiny.

CB_1 receptor antagonists including Rimonabant have been trialed on humans previously but the

resultant effects did not make much improvement on existing therapies.[36,38]

As for biomarkers of the disease, measurement of the level of Anandamide in the CSF appears to be the best candidate. Studies have been conducted on anandamide levels in the prodromal state of psychosis and they have shown that higher levels of the ligand in the CSF correlate with a longer transition time to psychosis.[29] Anandamide could in future serve as a biomarker in relation to predicting the development of psychosis.

Discussion

There is substantial evidence that implicates dysfunctional dopaminergic neurotransmission in the genesis of psychotic symptoms including hallucinations and delusions. Many antipsychotic drugs have been developed in response to the dopaminergic hypothesis of schizophrenia although it is widely acknowledged that schizophrenia is a highly complex psychiatric disorder with a range of abnormal neurotransmitter systems and other abnormalities. Indeed, effective antipsychotic drugs have pharmacological action in multiple neurotransmitter systems in the brain in addition to dopamine neurotransmission. Current antipsychotic drugs have maximal effectiveness against so called 'positive' features of schizophrenia with more disappointing results seen in the attempted treatment of 'negative' features of schizophrenia and the cognitive deficits seen in this disorder.

This review has emphasised the putative links between endocannabinoid system dysfunction and schizophrenia as well as the demonstrable antipsychotic effects of cannabidiol and commercially developed compounds with specific pharmacological action at multiple receptor sites of the endocannabinoid system.

Further study of the role of the endocannabinoid system in the pathogenesis of schizophrenia could lead to the development of novel therapeutic agents which would be a welcome addition to the armamentarium we have to treat this challenging and complex disease.

References

1. ICD 10 Version: 2015. Chapter V, Mental and Behavioural Disorders (F00 - F99); Schizophrenia, Schizotypal and delusional disorders (F20 - F29).
2. Touw M. The religious and medicinal uses of cannabis in China, India and Tibet. *Journal of Psychoactive Drugs.* 1981;13(1):23-34.
3. Di Marzo V. A brief history of cannabinoid and endocannabinoid pharmacology as inspired by the work of British scientists. *Trends in Pharmacological Sciences.* 2006;27(3):134-140.
4. Robson P. Therapeutic aspects of cannabis and cannabinoids. *The British Journal of Psychiatry*. 2001;178(2):107-115.
5. Blanchard S. How Cannabis was Criminalised [Internet]. Independent Drug Monitoring Unit. 2016. Available from: http://www.idmu.co.uk/historical.htm
6. Hardwick S, King L. Home Office Cannabis Potency Study [Internet]. 1st ed. St. Albans: Home Office Scientific Development Branch; 2008. Available from: http://www.dldocs.stir.ac.uk/documents/potency.pdf.
7. Gertsch J, Pertwee R, Di Marzo V. Phytocannabinoids beyond the Cannabis plant - do they exist? *British Journal of Pharmacology*. 2010;160(3):523-529.
8. Alexander S, Kendall D. The life cycle of the endocannabinoids: formation and inactivation. In: Alexander S, Kendall D. (eds) *Current Topics in Behavioral Neurosciences*. 1st edition. Berlin, Germany: Springer-Verlag; 2009. p3-35.
9. Hillard C. Biochemistry and pharmacology of the endocannabinoids arachidonylethanolamide and 2-arachidonylglycerol. *Prostaglandins & Other Lipid Mediators*. 2000;61(1-2):3-18.
10. Vemuri V, Makriyannis A. Endocannabinoids and their synthetic analogs. In: Reggio P. H. *The Cannabinoid Receptors*. 1st edition. New York: Humana Press; 2009. p21-48.
11. Fride E, Mechoulam R. Pharmacological activity of the cannabinoid receptor agonist, anandamide, a brain constituent. *European Journal of Pharmacology*. 1993;231(2):313-314.
12. Sparling P, Giuffrida A, Piomelli D, Rosskopf L, Dietrich A. Exercise activates the Endocannabinoid System. *Neuro Report*. 2003;14(17):2209-2211.
13. Sugiura T, Kobayashi Y, Oka S, Waku K. Biosynthesis and degradation of anandamide and 2-arachidonoylglycerol and their possible physiological significance. *Prostaglandins, Leukotrienes and Essential Fatty Acids (PLEFA).* 2002;66(2-3):173-192.
14. Yao B, Mackie K. Endocannabinoid receptor pharmacology. In: Alexander S, Kendall D. (eds) *Current Topics in Behavioral Neurosciences*. 1st edition. Berlin, Germany: Springer-Verlag; 2009. p37-63.
15. Marcu J, Console-Bram L, Abood M. Current cannabinoid receptor nomenclature and pharmacological principles. In: Van Bockstaele E. J. (ed) *Endocannabinoid Regulation of Monoamines in Psychiatric and Neurological Disorders*. 1st edition. New York: Springer; 2013. p25-54.
16. Scotter E, Graham S, Glass M. Cannabinoid receptor signal transduction pathways. In: Reggio P. H. *The Cannabinoid Receptors*. 1st edition. New York: Humana Press; 2009. p153-171.
17. Cabral G, Griffin-Thomas L. Emerging role of the cannabinoid receptor CB2 in immune regulation: therapeutic prospects for neuroinflammation. *Expert Reviews in Molecular Medicine*. 2009;11:e3.
18. Cabral G, Raborn E, Griffin L, Dennis J, Marciano-Cabral F. CB2 receptors in the brain: role in central immune function. *British Journal of Pharmacology*. 2008;153(2):240-251.
19. Marco E, Laviola G. The Endocannabinoid System in the regulation of emotions throughout lifespan: a discussion on therapeutic perspectives. *Journal of Psychopharmacology*. 2011;26(1):150-163.
20. Mackie K. Endocannabinoid-mediated synaptic plasticity. *Endocannabinoid Regulation of Monoamines in Psychiatric and Neurological Disorders*. 1st edition. New York: Springer; 2013. p11-24.
21. Patel S, Hillard C. Endocannabinoids as modulators of synaptic signaling. In: Reggio P. H. *The Cannabinoid Receptors.* 1st edition. New York: Humana Press; 2009. p281-308.
22. Alger B. Endocannabinoid signaling in neural plasticity. In: Alexander S, Kendall D. (eds) *Current Topics in*

Behavioral Neurosciences. 1st edition. Berlin, Germany: Springer-Verlag; 2009. p141-172.
23. Gerdeman G, Lovinger D. Emerging roles for endocannabinoids in long-term synaptic plasticity. *British Journal of Pharmacology*. 2003;140(5):781-789.
24. Viveros M, Marco E, Llorente R, López-Gallardo M. Endocannabinoid System and synaptic plasticity: implications for emotional responses. *Neural Plasticity*. 2007;2007:1-12.
25. Johns A. Psychiatric effects of cannabis. *The British Journal of Psychiatry*. 2001;178(2):116-122.
26. Ashton C. Pharmacology and effects of cannabis: a brief review. *The British Journal of Psychiatry*. 2001;178(2):101-106.
27. Zavitsanou K, Garrick T, Huang X. Selective antagonist [3H]SR141716A binding to cannabinoid CB1 receptors is increased in the anterior cingulate cortex in schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2004;28(2):355-360.
28. Dean B, Sundram S, Bradbury R, Scarr E, Copolov D. Studies on [3H]CP-55940 binding in the human central nervous system: regional specific changes in density of cannabinoid-1 receptors associated with schizophrenia and cannabis use. *Neuroscience*. 2001;103(1):9-15.
29. Eggan S, Hashimoto T, Lewis D. Reduced cortical cannabinoid 1 receptor messenger RNA and protein expression in schizophrenia. *Archives of General Psychiatry*. 2008;65(7):772-784.
30. Giuffrida A, Leweke F, Gerth C, Schreiber D, Koethe D, Faulhaber J et al. Cerebrospinal anandamide levels are elevated in acute schizophrenia and are inversely correlated with psychotic symptoms. *Neuropsychopharmacology*. 2004;29(11):2108-2114.
31. Koethe D, Giuffrida A, Schreiber D, Hellmich M, Schultze-Lutter F, Ruhrmann S et al. Anandamide elevation in cerebrospinal fluid in initial prodromal states of psychosis. *The British Journal of Psychiatry*. 2009;194(4):371-372.
32. Centonze D, Battistini L, Maccarrone M. The Endocannabinoid System in Peripheral Lymphocytes as a Mirror of Neuroinflammatory Diseases. *Current Pharmaceutical Design*. 2008;14(23):2370-2382.
33. Bioque M, GarcÃa-Bueno B, MacDowell K, Meseguer A, Saiz P, Parellada M et al. Peripheral Endocannabinoid System dysregulation in first-episode psychosis. *Neuropsychopharmacology*. 2013;38(13):2568-2577.
34. Leweke F, Piomelli D, Pahlisch F, Muhl D, Gerth C, Hoyer C et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Translational Psychiatry*. 2012;2(3):e94.
35. Seillier A, Martinez A, Giuffrida A. Phencyclidine-induced social withdrawal results from deficient stimulation of cannabinoid CB1 receptors: implications for schizophrenia. *Neuropsychopharmacology*. 2013;38(9):1816-1824.
36. Kucerova J, Tabiova K, Drago F, Micale V. Therapeutic potential of cannabinoids in schizophrenia. *RPCN*. 2014;9(1):13-25.
37. Gertsch J, Leonti M, Raduner S, Racz I, Chen J, Xie X et al. Beta-caryophyllene is a dietary cannabinoid. *Proceedings of the National Academy of Sciences*. 2008;105(26):9099-9104.
38. Meltzer H, Arvanitis L, Bauer D, Rein W. Placebo-controlled evaluation of four novel compounds for the treatment of schizophrenia and schizoaffective disorder. *American Journal of Psychiatry*. 2004;161(6):975-984.