Endocannabinoid system: conceptual parameters, history and therapeutic possibilities

Luis Henrique Almeida Castro (nutricao.luishenrique@gmail.com)
PhD in the Health Sciences Graduate Program, Federal University of Grande Dourados
Dourados, Mato Grosso do Sul – Brazil.

Geanlucas Mendes Monteiro
Heath and Development in West Central Region Graduate Program, Federal University of Mato Grosso do Sul
Campo Grande, Mato Grosso do Sul – Brazil.

Ygor Thiago Cerqueira de Paula
Motion Science Graduate Program, Federal University of Mato Grosso do Sul
Campo Grande, Mato Grosso do Sul – Brazil.

Vanessa de Souza Ferraz
Motion Science Graduate Program, Federal University of Mato Grosso do Sul
Campo Grande, Mato Grosso do Sul – Brazil.

Flavia Soares Bezerra Okumoto Nery de Mello
Motion Science Graduate Program, Federal University of Mato Grosso do Sul
Campo Grande, Mato Grosso do Sul – Brazil.

Dayane Aparecida Moisés Caetano Bottini
Motion Science Graduate Program, Federal University of Mato Grosso do Sul
Campo Grande, Mato Grosso do Sul – Brazil.

Nelson Thiago Andrade Ferreira
Motion Science Graduate Program, Federal University of Mato Grosso do Sul
Campo Grande, Mato Grosso do Sul – Brazil.

Tayla Borges Lino
Motion Science Graduate Program, Federal University of Mato Grosso do Sul
Campo Grande, Mato Grosso do Sul – Brazil.

Juliana Vicente de Souza
Motion Science Graduate Program, Federal University of Mato Grosso do Sul
Campo Grande, Mato Grosso do Sul – Brazil.

Gildiney Penaves de Alencar
Heath and Development in West Central Region Graduate Program, Federal University of Mato Grosso do Sul
Campo Grande, Mato Grosso do Sul – Brazil.

Wesley Sebastião da Silva Moraes
Exercise Physiology and Sports Training Graduate Program, Alfredo Torres Institute of Education and Research.
Campo Grande, Mato Grosso do Sul – Brazil.

Fernanda Viana de Carvalho Moreto
MSc., Nutrition, Food and Health Graduate Program, Federal University of Grande Dourados

Abstract

Among the drugs considered illicit in the West, the Cannabis sativa *plant is the most consumed: around 4% of the adult population, 10% of these users are in a situation of dependence. However, the medicinal use of this herb dates back to the early days of the emergence of our own species: some anthropologists theorize that some of the genus Homo has progressed in the struggle for survival with other hominids precisely because of the advanced knowledge – kept to the proper proportions – it possessed of plants like* Cannabis*. Millennia later, science – even focusing intensely on the chemical characterization of its more than 530 bioactive components – was still not able to generate verifiable hypotheses in order to explain two of the most remarkable characteristics of the recreational use of this plant: because small chemical changes potentiated the effect of the drug up to 100 times and, mainly, because it would be virtually impossible for an individual to suffer a lethal overdose of the substance. To overcome this paradigm, some compounds derived from delta-ninetetrahydrocannabinol (Δ9-THC) - the main component of cannabis – were radioactively marked in an experimental study and, after their induction, it was discovered that they had tropism by brain membranes and that their binding was saturated and stereosleptic. Such evidence strongly suggested the existence of endogenous receptors for the drug and it was these findings that led to the discovery of the Endocanabinoid System (SEC): a physiological apparatus made up of endogenous receptors and binders, philogenetically conserved, responsible for several controls related to neuronal homeostasis.*

Keywords: *Cannabis sativa*; Endocannabinoid system; Therapeutic possibilities.

1. Introduction

Among the drugs considered illicit in the West, the *Cannabis sativa* plant is the most consumed: around 4% of the adult population, 10% of these users are in a situation of dependence. However, the medicinal use of this herb dates back to the early days of the emergence of our own species: some anthropologists theorize that some of the genus Homo has progressed in the struggle for survival with other hominids precisely

because of the advanced knowledge – kept to the proper proportions – it possessed of plants like *Cannabis*. Millennia later, science – even focusing intensely on the chemical characterization of its more than 530 bioactive components – was still not able to generate verifiable hypotheses in order to explain two of the most remarkable characteristics of the recreational use of this plant: because small chemical changes potentiated the effect of the drug up to 100 times and, mainly, because it would be virtually impossible for an individual to suffer a lethal overdose of the substance.

To overcome this paradigm, some compounds derived from delta-ninetetrahydrocannabinol (Δ9-THC) - the main component of cannabis – were radioactively marked in an experimental study and, after their induction, it was discovered that they had tropism by brain membranes and that their binding was saturated and stereosleptic. Such evidence strongly suggested the existence of endogenous receptors for the drug and it was these findings that led to the discovery of the Endocanabinoid System (SEC): a physiological apparatus made up of endogenous receptors and binders, philogenetically conserved, responsible for several controls related to neuronal homeostasis.

The receptors, according to the order of discovery, were classified into CB1 and CB2: while the former is responsible for most of the psychotropic effects – besides being the most abundant in the Central Nervous System (CNS) – the CB2 receptors have their majority expression in the immune system, in the microglia and in pathological conditions such as chronic pain. Their density is described in Table 1.

Table 1 - Density of CB1 and CB2 receptors.

DENSITY	**RECEPTOR**	
	CB1	**CB2**
Top	Olfactory bulb, hippocampus, lateral striated, striated nuclei and cerebellum	Cells of the immune system
Moderated	Prosencephalus, frontal lobe, parietal and cincture, septum, amygdala, ventromedial hypothalamus, lateral subclair of the interpeduncular nucleus, parabrachial nucleus, solitary tract nucleus and dorsal medulla horn	-
Download	Thalamus, medulla ventral horn and other brain stem nuclei	Microglia

2. Mechanisms of action

The mechanism of action of both are similar and culminate in neuronal hyperpolarization causing a decrease in the release of neurotransmitters in the synaptic cleft: CB1, when active, inhibits adenylciclase which, in turn, leads to a deficit in the conversion of ATP into cAMP by decreasing the action of kinase A (PKA); with the reduction of phosphorylation of potassium channels – generating the output of these ions in presynaptic cells – inhibition of voltage-sensitive calcium channels occurs, leading to neuronal desensitization.

On the other hand, CB2 – which presents a 44% homologous physical-chemical structure to CB1 receptors – has inhibitory activity of Gi proteins which, in turn, inhibit adenylciclase, thus activating the MAPK

protein cascade. Due to these characteristics the SEC constitutes one of the exceptions to the law of dynamic polarization postulated by Ramon and Cajal in 1891 since they follow the retrograde direction of synaptic transmission.

Shortly after the characterization of these receptors, science dedicated itself to the study of endogenous binders for the SEC of which two are the most quantitatively relevant: anandamide (N-araquidonylethanolamide) - Sanskrit terminology for "eternal happiness" - and 2-araquidonilglycerol (2-AG). While the latter presents high selectivity for CB1/CB2 receptors performing total agonist action for them, anandamide is only partial agonist for CB1/CB2 presenting still low affinity for TRPV1.

The synthesis of these binders occurs by means of noncontinuous membrane phospholipid precursors, i.e., they are produced on demand in postsynaptic neurons without prior vesicular storage with direct release into the synaptic cleft or via the bloodstream. Although there is considerable redundancy in this process, the mediation and regulation of the synthesis is done by the accumulation of calcium ions in the postsynaptic neuron being this the limiting step.

For the production of anandamide, N-acyltransferase (NAT) is activated by converting phosphatidylethanolamine and phosphatidylcholine into N-araquidonylphosphatidylethanolamine (NAPE), leading to hydrolysis of NAPE by N-araquidonylphosphatidyl-ethanolamine-phospholipase-D (NAPE-FLD), generating anandamide; already in the case of 2-AG, the main route is that of phospholipase-C-beta-diacylglycerol-lipase: FLCβ converts membrane phosphoinositide into 1,2-diacylglycerol which, when hydrolysed by DAGL, forms the endocanabinoid.

3. Therapeutic possibilities

One of the actions described by the SEC, however, is its relationship with the pleasure circuit. In the classical view abuse drugs trigger this circuit by means of second order dopamine neurons in the ATV-NAc axis either by direct action on the dopamine terminals or indirectly under the modulatory inputs; today, however, it is accepted that endocanabinoids contribute to the motivational homeostasis by defining a setpoint acting on the control inputs of the pathway leading to an inversely proportional relationship: The SEC acts maintaining the motivational homeostasis while the exogenous cannabinoids lead to the disturbance of the pathway by neuromodulatory destructuring and alteration of the setpoint of the circuit leading the individual to the behavior called drug seeking & drug taken.

Moreover, the completion of the SEC in sites relevant to memory and its action in modulating it becomes relevant with regard to the promotion and construction of the kidnapping of GABA in order to make it difficult to solidify aversive memories. The interference performed in this process by Δ9-THC, with LTD blocking and consequent translocation of the setpoint for extinction of aversive memories, may significantly alter the impact of memories related to the reward system.

Moreover, in recent years new models have been postulated regarding this system so that there is suspicion, with a reasonable degree of legitimacy, of the existence of at least one more endogenous cannabinoid receptor called until then "putative receptor type CB3" besides the characterization of more binders still little described. The hypothesis that unassociated factors are triggers of mechanisms integral to the ESA is also hypothesized: it is described, for example, that certain membrane disorders are capable of activating

the cascade of pre-synaptic hyperpolarization reaction in an effect equivalent to receptors of type CB1 and CB2.

In this way, the SEC has a general modulatory effect in decisive ways, as seen, in the phenomena related to drug abuse disorders since it collaborates to the establishment of setpoints in multiple neuronal processes; drugs with the modulatory activity of the SEC, therefore, may compose in the coming years a therapeutic focus in the prophylaxis of disorders related to a wide spectrum of neuronal pathologies, from the drug abuse disorder itself to even Alzheimer's.

4. Competing Interests

The authors declare no competing interests.

5. References

Ameri A. The effects of cannabinoids on the brain. Prog Neurobiol. 1999;58(4):315-48.

Bonfa L, Vinagre RC, de Figueiredo NV. Cannabinoids in chronic pain and palliative care. Rev Bras Anestesiol, 2008;58(3):267-79. English, Portuguese.

Cooper ZD, Haney M. Cannabis reinforcement and dependence: role of the cannabinoid CB1 receptor. Addict Biol. 2008;13(2):188-95.

Dennis M, Babor TF, Roebuck MC, Donaldson J. Changing the focus: the case for recognizing and treating Cannabis use disorders. Addiction. 2002;97(Suppl 1):4-15.

Di Marzo V, Bisogno T, De Petrocellis L. Endocannabinoids: new targets for drug development. Curr Pharm Des. 2000;6(13):1361-80.

Fattore L, Fadda P, Spano MS, Pistis M, Fratta W. Neurobiological mechanisms of cannabinoid addiction. Mol Cell Endocrinol. 2008;286(1-2 Suppl 1):S97-107.

Hazekamp A. Medicinal use of Cannabis: a review. Leiden, The Netherlands: Leiden University, Department of Plant Metabolomics; 2008.

Pacher P, Bátkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol Rev. 2006;58(3):389-462.

Vandrey R, Haney M. Pharmacotherapy for Cannabis dependence: how close are we? CNS Drugs. 2009;23(7):543-53.

Zuardi AW. History of Cannabis as a medicine: a review. Rev Bras Psiquiatr. 2006; 28(2):153-7.