Anti-inflammatory effects of cannabinoids

Efeitos anti-inflamatórios dos canabinoides

Alexandre Magno da Nóbrega Marinho[1], Ricardo Wagner Gomes da Silva-Neto[1]

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ABSTRACT

BACKGROUND AND OBJECTIVES: The use of cannabinoids for epileptic syndrome and control of side effects associated with chemotherapy is already widespread and supported by several well-controlled clinical trials. However, the use of these drugs in inflammatory pathologies is sometimes underestimated due to lack of scientific knowledge with a high degree of evidence, non-recognition of the endocannabinoid system as an active participant in these diseases, as well as fear of the stereotype surrounding the use of cannabis derivatives. The purpose of this study was to examine the anti-inflammatory and antioxidant effects of endogenous and exogenous cannabinoids on various physiological systems in which these ligands interact.

CONTENTS: Studies cited in this review were obtained by searching Pubmed, Medline, Google Scholar, Scielo, Cochrane Central Register of Controlled Trials (CENTRAL), LILACS, and through the authors' familiarity with the published literature in this area of interest. Clinical, observational and intervention, experimental, qualitative studies and review articles were all included in the search. Articles were identified using the following descriptors: cannabis and tetrahydrocannabinol and cannabidiol and endocannabinoids and anti-inflammatory inflammation and oxidative stress. In addition, a manual revision of relevant references was also performed to capture articles that may not have been picked up through the initial search. The literature investigation was conducted from March 22 to May 2022.

CONCLUSION: Cannabinoids show to be a promising therapeutic option in the context of inflammatory diseases, given the complete and complex relationship between the endocannabinoid system and the immune system. The setback to be overcome in the use of cannabinoids as anti-inflammatory drugs includes the synthesis of non-psychoactive cannabinoid receptor agonists while maintaining potent anti-inflammatory activity. Further studies are needed to increase our understanding of cannabinoids and their intricate effects on immune system disorders.

Keywords: Anti-inflammatory agents, Cannabinoids. Inflammation, Pain.

RESUMO

JUSTIFICATIVA E OBJETIVOS: O uso de canabinoides para síndrome epiléptica e controle de efeitos adversos associados à quimioterapia já é amplamente difundido e apoiado por vários ensaios clínicos bem controlados. Entretanto, o uso destes fármacos em patologias inflamatórias é, por vezes, subestimado pela falta de conhecimento científico com alto grau de evidência, pelo não reconhecimento do sistema endocanabinoide como participante ativo destas doenças, bem como por receio do estereótipo que envolve o uso dos derivados da cannabis. O objetivo deste estudo foi analisar os efeitos anti-inflamatórios e antioxidantes de canabinoides endógenos e exógenos em vários sistemas fisiológicos nos quais esses ligantes interagem.

CONTEÚDO: Estudos citados nesta revisão foram obtidos por meio de buscas feitas nas bases de dados Pubmed, Medline, Google Acadêmico, Scielo, *Cochrane Central Register of Controlled Trials* (CENTRAL), LILACS, e através da familiaridade dos autores com a literatura publicada nesta área de interesse. Estudos clínicos, observacionais e de intervenção, experimentais, qualitativos e artigos de revisão foram todos incluídos na pesquisa. Os artigos foram identificados usando os seguintes descritores: cannabis e tetraidrocanabinol e canabidiol e endocanabinoides e inflamação anti-inflamatório e estresse oxidativo. Ademais, uma revisão manual nas referências relevantes também foi realizada para captura de artigos que podem não ter sido captados por meio da busca inicial. A investigação na literatura foi realizada no período de 22 de março a 17 de maio de 2022.

CONCLUSÃO: Os canabinoides demonstram ser uma opção terapêutica promissora no contexto das doenças inflamatórias, haja vista a completa e complexa relação entre o sistema endocanabinoide e o sistema imune. O revés a ser vencido no uso de ca-

Alexandre Magno da Nóbrega Marinho – https://orcid.org/0000-0003-3885-4338;
Ricardo Wagner Gomes da Silva-Neto – https://orcid.org/0000-0003-4444-9689.

1. Federal University of Campina Grande, Health and Biological Sciences Center, Medicine Academic Unit, Neurology Course, Campina Grande, PB, Brazil.

HIGHLIGHTS

- The cannabinoid system regulates a variety of cellular and physiological processes, and is thus related to regulatory processes including inflammation, metabolism regulation, energetic balance, thermogenesis, neural development, immune function, cardiovascular function, synaptic plasticity and learning, pain, memory, movement, psychomotor behavior, sleep/wake cycles, stress and emotion regulation, and digestion.
- The main anti-inflammatory mechanisms produced by cannabinoids are induction of apoptosis, inhibition of cell proliferation, suppression of cytokine production, and induction of T-regulatory cells.
- Increased levels of anandamide decrease inflammatory responses, suggesting that endocannabinoids are physiologically involved in the attenuation of the immune system. However, there are still poorly understood and sometimes contradictory effects.

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Correspondence to:
Alexandre Magno da Nóbrega Marinho
E-mail: nobrega74@yahoo.com

nabinoides como fármacos anti-inflamatórios inclui a síntese de agonistas de receptores canabinoides que não sejam psicoativos, mantendo a potente atividade anti-inflamatória. Novos estudos são necessários para aumentar a compreensão dos canabinoides e seus efeitos intrincados sobre distúrbios do sistema imunológico.
Descritores: Anti-inflamatórios, Canabinoides, Dor, Inflamação.

INTRODUCTION

The cannabis plant genus, a member of the Cannabaceae family, has three distinct primary species, varying in their biochemical constituents: *C. sativa* (Cs), *C. indica*, and *C. ruderalis*. Its anxiolytic and euphoric properties have been recorded in religious scriptures dating back several millennia, revealing that the use of Cs already held a strong and prominent position in ancient medicine. Its various benefits were documented in Sanskrit and Hindi literature as early as 2000-1400 B.C. and its medicinal use was described in more detail in the Indian Ayurvedic medical literature as early as 900 B.C. Between the centuries I and III, the Greek physicians Claudius Galen (131-201 A.D.) and Pedanius Dioscorides (40-90 A.D.) described medicinal indications.

However, the first scientific report on cannabis was published only in 1839 by the Irish physician William O'Shaughnessy, which marked the first traces of its popularization. By providing evidence of its therapeutic efficacy and safety for pathological conditions such as child convulsions and cholera, he was essential in laying the groundwork for medical research and use[1-8]. A major obstacle to the use of Cs was the fact that the active ingredient, cannabidiol (CBD), had not yet been described. It was first isolated from cannabis in 1940, and its structure was reported in 1963.

Nevertheless, the psychoactive effect of Cs overshadowed its possible therapeutic effects. The structure of the main psychoactive phytocannabinoid, Δ-9-tetrahydrocannabinol (THC), was determined in Israel by Mechoulam and Gaoni in 1964. Mechoulam's discovery promoted the exploration of a new receptor system, the endocannabinoid system. At the present time, this system comprises a few known endocannabinoids (mainly, N-amino acid ethanolamine [AEA] and 2-amino acid ethanolamine [2-AG]), possessing two primary cannabinoid receptors (CB1R and CB2R). Through these and receptors in other systems, endocannabinoids modulate the release of neurotransmitters and cytokines[9-15].

Regarding the function, the ubiquitous nature of the cannabinoid system regulates a variety of cellular and physiological processes, and is thus related to regulatory processes including inflammation, regulation of metabolism, energetic balance, thermogenesis, neural development, immune function, cardiovascular function, synaptic plasticity and learning, pain, memory, movement, psychomotor behavior, sleep/wake cycles, regulation of stress and emotion, and digestion. Studies to date indicate that the main potentials in the therapeutic use of the endocannabinoid system are linked to neuromodulation, modulation of the autonomic nervous system (ANS), immune system, and microcirculation[13,16-20].

The present study's objective was to examine the anti-inflammatory and antioxidant effects of endogenous and exogenous cannabinoids on various physiological systems in which these ligands interact.

CONTENTS

The present narrative review was prepared as a comprehensive theoretical resource to achieve the described objectives. The use of cannabinoids for epileptic syndrome and control of adverse effects associated with chemotherapy is already widespread and supported by several well-controlled clinical trials. However, the use of these drugs in inflammatory diseases is sometimes underestimated due to lack of scientific knowledge with a high degree of evidence, non-recognition of the endocannabinoid system as an active participant in these diseases, and fear of the stereotype surrounding the use of cannabis derivatives. Therefore, the present study provides a basis to contribute to the scientific community by deepening the comprehension of the mechanisms involved in the anti-inflammatory effects promoted by cannabinoids and by providing substrate for the development of possible clinical and public health guidelines.

Studies mentioned in this review were obtained by searching the Pubmed, Medline, Google Scholar, Scielo, Cochrane Central Register of Controlled Trials (CENTRAL) and LILACS databases, as well as the authors' familiarity with the literature published in this area of interest. Clinical, observational and intervention, experimental, qualitative studies and review articles were all included in the search. Articles were identified using the following descriptors: cannabis and tetrahydrocannabinol and cannabidiol and endocannabinoids and inflammation and anti-inflammatory and oxidative stress. In addition, a manual search of relevant references was also performed to capture articles that may not have been picked up through the initial search. The literature search was conducted from March 22 to May 17, 2022.

Endocannabinoid system

Endogenous cannabinoids act as natural ligands for cannabinoid receptors expressed in mammalian tissues, thus constituting an important lipid signaling system called the endocannabinoid system. Cannabinoid receptor agonists are very heterogeneous and can be divided into four groups, according to the difference in chemical and structural composition: classical, non-classical, aminoalkylindol and eicosanoids. The classical group consists of the phytocannabinoids (Δ-9-tetrahydrocannabinol [THC], cannabinol [CBN], cannabidiol [CBD], among others) and their synthetic analogues. The eicosanoid group is mainly made up of the endocannabinoids (arachidonylethanolamine [anandamide or AEA], 2-araquidonylglycerol [2-AG], among others), ligands of the cannabinoid system produced by human cells. The other two groups, non-classical and aminoalkylindol, consist of synthetic cannabinoids[21,22].

Endocannabinoids are derivatives of arachidonic acid combined with ethanolamine or glycerol. These products are synthesized on demand from phospholipid precursors that integrate the cell membrane in response to increased intracellular calcium levels. The prototypical endogenous cannabinoids are 2-AG and anandamide or AEA. Both are eicosanoids produced from arachidonic acid-containing phospholipids, such as phosphatidylinositol 4,5-biphosphate and phosphatidylethanolamine, respectively. These ligands have both complementary and divergent functions.

While 2-AG is a full agonist at both cannabinoid receptors (CB1R and CB2R), anandamide exerts partial agonism.

Other lesser known endocannabinoids include dopamine N-araquidonoil (NADA) and glycerol 2-araquidonoil ether (noladine), both of which bind strongly to CB1R. In addition, ethanolamine arachidonoil (virodamine) has been identified as a full CB2R agonist and possesses antagonistic activity on CB1R[23-28]. Exogenous cannabinoids, however, comprise both naturally occurring phytocannabinoids and synthetic cannabinoids. Exogenous cannabinoids are compounds isolated from the Cannabis genus and make up more than 100 chemicals, among which THC and CBD are the most abundant and most frequently used. THC has a high affinity for both CB1R and CB2R. In contrast, CBD has a higher affinity for CB2R. In addition, CBD possesses pain modulation effect by anti-inflammatory properties and may be able to counteract negative effects of THC on memory, mood and cognition[29-31].

In addition to the transmitters that serve as ligands for the cannabinoid receptors, the endocannabinoid family also comprises the enzymes for biosynthesis and degradation of the ligands. Enzymes known to hydrolyze the endocannabinoids include fatty acid amide hydrolase (FAAH), monoglyceride lipase, and N-acylethanolamine[12].

The cannabinoid receptors, CB1R and CB2R, are G-protein coupled heterotrimeric and both are expressed in the periphery and the central nervous system (CNS). However, CB1R expression is predominant in the CNS, especially in presynaptic nerves, while CB2R is mainly expressed in immune cells. Both are activated by endogenously produced lipophilic ligands. Nevertheless, CB1R and CB2R receptors are also coupled to a variety of ion channels in the cell membrane: inward rectifier potassium channels and calcium channels[11,32,33].

CB1R is highly expressed in most regions of the CNS, with densities that rival other neurotransmitter and neuromodulatory receptors. In addition to the CNS, CB1R expression has been reported in the somatic, sympathetic, parasympathetic, and enteric nervous systems. It is presented in both inhibitory GABAergic and excitatory glutamatergic neurons. The activation of this receptor, in a dose-dependent manner, can produce subsequent decrease of Ca2+ entry into the cell, without involvement of cyclic adenosine 3',5'-monophosphate (cAMP), producing its final effect, the reduction of neurotransmitter release. This mechanism may be related to the ability of CB1 receptor agonists to impair cognition and memory, and alter the control of motor function and nociception[34,35].

CB2R, on the other hand, is expressed at very low levels inside the central nervous system (CNS) under physiological conditions. However, pathological conditions characterized by a neuroinflammatory state have resulted in a positive regulation of CB2R levels in glia cells, such as microglia. This receptor is also expressed at high levels in immune cells and lymphoid tissues that participate in the innate and adaptive immune response. The presence of cannabinoid receptors is different on each immune cell, being expressed, from most abundant to scarcest, on B cells, natural killer (NK) cells, monocytes, neutrophils, CD8+ and CD4+ lymphocytes[36].

As a common mechanism, the cannabinoid receptors CB1 and CB2 also act to regulate the phosphorylation and activation of different members of the mitogen-activated protein kinase (MAPK) family, including kinases 1 and 2 regulated by extracellular signals. MAPK, in turn, controls gene expression related to cell proliferation, motility, adhesion and apoptosis, as well as glucose metabolism. Both receptors share the ability to modulate the release of chemical messengers. By acting on CB1 receptors, cannabinoids interact with various neurotransmitters in the CNS and can modulate their release, while controlling the release of inflammatory cytokines by acting on CB2R, regulating the immune system[37-40].

One of the non-CB1/CB2 receptors with cannabinoid binding capacity is the transient receptor vanilloid type 1 (TRPV1), also called the capsaicin receptor. This is a non-selective cation channel present in sensory neurons of the skin, heart, blood vessels, and lungs. TRPV1 is associated with the transmission and modulation of pain through primary afferent and perivascular sensory neurons[12,41,42]. In addition to this, additional pathway receptors have been shown to be involved in cannabinoid signal transduction. These include peroxisome proliferator-activated receptors (PPAR), G-protein receptor 55 (GPR55), as well as nicotinic receptors, serotoninergic receptor (5-HT1A) and adenosine A2A (Figure 1)[15,43].

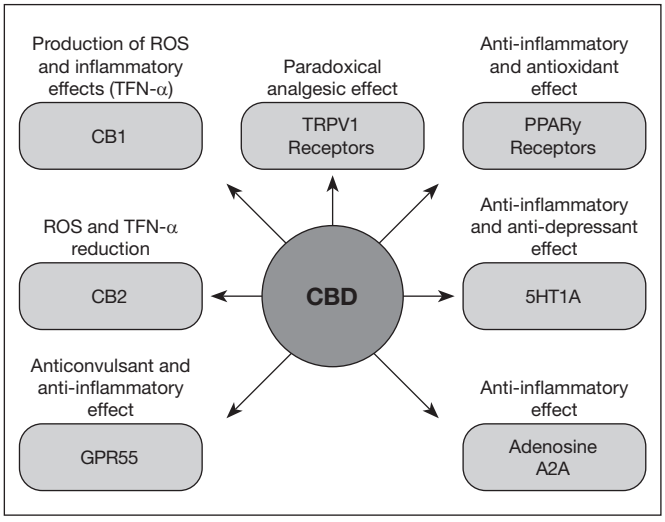

Figure 1. Main effects of cannabidiol on various membrane receptors

Cannabinoids and inflammation

Activation of glial CB1R and CB2R promote an anti-inflammatory state, elevating anti-inflammatory cytokines and also decreasing levels of pro-inflammatory cytokines. CB2R, present primarily in immune cells, plays an integral role in regulating humoral and cell-mediated immunity. Cannabinoids apparently act on inflammation through mechanisms different from those of agents such as nonsteroidal anti-inflammatory drugs (NSAIDs), thus free of the adverse effects associated with them.

Studies show that prenylated flavones, non-cannabinoid derivatives of the cannabis genus, are 30 times more potent than aspirin in inhibiting cyclooxygenase (COX), the well-established anti-inflammatory drug. THC is 80 times more potent than aspirin and twice as potent as hydrocortisone. Ajulemic acid (AJA), a

synthetic cannabinoid, is 50-100 times more potent than THC as an analgesic, having 12 times more affinity for CB2R than for CB1R, which makes it non-psychoactive in therapeutic doses[44].
Among the effects of cannabinoid derivatives, immune modulation referring to the suppression of tumor necrosis factor alpha (TNF-α) and other cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin 6 (IL-6), interferon-gamma (IFN-γ), and interleukin 12 (IL-12) produces a potent anti-inflammatory activity. CBD reduces TNF-α production and induces a reduction in FAAH activity while increasing the production of anandamide, an anti-inflammatory endocannabinoid. THC has been observed to produce anti-inflammatory effects by antagonizing with TNF-α[45-47].
The main anti-inflammatory mechanisms produced by cannabinoids are induction of apoptosis, inhibition of cell proliferation, suppression of cytokine production, and induction of T-regulatory cells (Tregs).

Induction of apoptosis
Under normal conditions, apoptosis is necessary to maintain homeostasis and involves morphological changes (cell shrinkage, nuclear fragmentation, and pore formation in the plasma membrane) as well as molecular changes (induction of caspases and extravasation of cytochrome c)[48].
Both anandamide and THC, for example, induce apoptosis in T and B lymphocytes. However, THC, with greater immunosuppressive potency, promotes additional apoptosis in macrophages and antigen-presenting cells through regulation of BCL2 protein activity and caspases. Cannabidiol, on the other hand, induces apoptosis in T cells, CD4+ and CD8+, producing reactive oxygen species (ROS) and activating caspases 8 and 3[48-52]. In opposition to immune cells, cannabinoids can protect apoptosis in CNS cells, conferring neuroprotection. The mechanisms of immunosuppression by cannabinoids occur through partial activation of CB2R and probably also CB1R[53].

Inhibition of cell proliferation
Inhibition of lymphocyte proliferation may be induced by direct effects on immune cells, and not mediated by CB1R and CB2R. While low doses of THC stimulate T cells, high doses induce inhibition of the response to lipopolysaccharides (LPS), T cell mitogens, and anti-CD3 antibodies. THC can suppress immune functions and increase susceptibility to infections[54-56].

Suppression of cytokine production
Cytokines are the signaling proteins synthesized and secreted by stimulating immune cells. They are the modulating factors that balance the initiation and resolution of inflammation. Cannabinoids induce downregulation of cytokine production and disruption of the well-regulated immune response. In addition, cannabinoids can affect the host immune response and resistance by disrupting the balance between cytokines produced by T-helper, Th1 and Th2 subsets. Cannabinoids also exert their immunosuppressive effects by decreasing inflammatory products, including nitric oxide (NO), TNF-α, gamma interferon-induced protein 10 (CXCL10), chemokine CCL2, and chemokine CCL5. In addition, cannabinoids can regulate the migration and differentiation of monocytes into M1 or M2 macrophage phenotypes, as well as their ability to produce cytokines, chemokines, and other immune mediators[57-60].
Anandamide reduces the production of several interleukins (IL) such as IL-2, IL-6, IL-8, IL-12 and monocytes induced by LPS and also blocks LPS triggered activation of LPS and I-KB kinase of nuclear factor kappa B (NFkB), a protein complex that controls DNA transcription, cytokine production and cell survival[61]. Cannabidiol also reduces prostaglandin E2 and COX activity. THC, on the other hand, altered the Th1 destructive immunity by Th2 protective immunity, even less effectively than cannabidiol, and also showed immunosuppressive effects on dendritic cells. This occurs through suppression of IL-12p40 production and inhibition of expression of maturation markers such as MHCII, CD86 and CD4[51,62-65].
When AJA is in the peripheral blood, it reduces the production of the pro-inflammatory cytokine IL-1b, as well as the steady-state levels of IL-6 mRNA and its subsequent secretion by LPS-stimulated macrophages. IL-6 is a multifunctional cytokine that contributes to inflammation and tissue injury in a variety of diseases. However, AJA did not reduce TNF-α production in these studies[66]. Finally, increased levels of anandamide decrease inflammatory responses, suggesting that endocannabinoids are physiologically involved in attenuating the immune system[7]. However, there are still poorly understood and sometimes contradictory effects.

Induction of regulatory T-cells
Exogenous cannabinoids have been shown to suppress T-cell-mediated immune responses, mainly by inducing apoptosis and suppressing inflammatory cytokines and chemokines. THC can increase the number of Treg Foxp3+ cells, inducing them to inhibit cytokine production. This suggests that Treg cells, unlike other T cells, may be resistant to THC-induced apoptosis and can suppress the activation of T cells that eventually escape apoptosis. This further supports the notion that the endogenous cannabinoid system is protective against inflammatory changes[67,68].

Cannabinoid system and oxidation
Antioxidant activity of CBD has been shown in the redox state, direct or indirectly, through components of this system. The imbalance between oxidants and antioxidants leads to oxidative stress in lipids, nucleic acids, and proteins, which results in changes in the structure of these components, disrupting their molecular interactions and signal transduction pathways[69]. Oxidative modifications play an important role in the functioning of redox-sensitive transcription factors, such as nuclear factor erythroid 2 (NRF2) and NFkB. Therefore, they play a role in the regulation of pathological conditions characterized by imbalances in the redox system and inflammation, such as cancer, inflammatory diseases, and neurodegenerative diseases[70,71].
Like other antioxidants, CBD interrupts free radical chain reactions by capturing these molecules or transforming them into less active forms[8], also reducing oxidative conditions by preventing the formation of superoxide radicals, which are mainly ge-

nerated by xanthine oxidase (XO) and NADPH oxidase (NOX1 and NOX4). In experimental models of chronic inflammation, CBD promoted reduced NO levels[72].

CBD also reduces ROS production by chelating transition metal ions, thus decreasing amyloid formation in neurons[9]. It increases the mRNA level of superoxide dismutase (SOD) and the enzymatic activity of copper (Cu), zinc (Zn) and manganese-dependent superoxide dismutase (Mn-SOD), which are responsible for superoxide radical metabolism in experimental models[74].

When lowering ROS levels, CBD also protects non-enzymatic antioxidants through the prevention of their oxidation. This is relevant because glutathione cooperates with other low molecular weight compounds in antioxidant action, especially with vitamins such as A, E and C[75].

Repeated doses of CBD in inflammatory conditions increase peroxidase and glutathione reductase activity, resulting in decreased malonaldehyde levels[72]. The high affinity of CBDs for cysteine residues is a possible explanation for this observation[76]. It is known that under oxidative conditions, changes in enzyme activity can be caused by oxidative modifications of proteins, especially aromatic and sulfur amino acids[10]. CBD also aids in the action of antioxidant enzymes by preventing reduction in the levels of microelements, such as Zn or selenium [Sn], which are normally lowered under pathological conditions. These elements are necessary for the biological activity of some proteins, especially enzymes such as SOD or glutathione peroxidase[78].

Finally, it s possible to observe that cannabinoids can interact with the body's natural antioxidant system. This mechanism constitutes an accessory pathway by which the endocannabinoid system acts with anti-inflammatory effects.

NON-CANNABINOID RECEPTORS AND INFLAMMATION

TRP receptors

It has also been shown that CBD can affect redox balance and inflammation through modulation of mammalian transient receptor potential (TRP) channels[77,80]. CBD activates vanilloid receptors (TRPV), directly or indirectly, by increasing the level of endogenous AEA, one of the agonists of TRPV1[81]. This agonism causes desensitization, producing the "paradoxical analgesic activity" similar to that of capsaicin[72]. It has been suggested that there is a relationship between TRPV1 molecular signaling and oxidative stress[82] because ROS and the products of lipid peroxidation can regulate the physiological activity of TRPV1 by oxidizing its thiol groups[83]. Consequently, CBD not only activates TRP through a direct agonist-receptor interaction, but also by reducing the level of oxidative stress. In addition, it activates other vanilloid receptors, such as TRPV2 and the potential receptor subtype of ankarin protein 1 (TRPA1), while antagonizing the TRP-8 receptor (TRPM8)[79].

PPAR receptors

PPARγ are members of a family of nuclear receptors that modify gene transcription in response to a variety of signaling pathways. They are expressed on immune system cells, such as monocytes and macrophages, and regulate inflammatory responses through inhibitory effects on the expression of inflammatory cytokines and eicosanoids. It participates in modulating inflammation by inducing proteosomal degradation by ubiquitination of p65, which causes inhibition of pro-inflammatory gene expression, such as cyclooxygenase-2 (COX2) expression and some pro-inflammatory mediators, such as TNF-α, IL-1β and IL-6, as well as inhibition of NFkB-mediated inflammatory signaling[84]. For this reason, acting through the PPARγ receptor, CBD shows anti-inflammatory and antioxidant properties.

Moreover, its direct activity is enhanced by the action of AEA and 2-AG, which are also PPARγ agonists and whose levels are elevated by these cannabinoids[85]. In addition to its ability to bind to CB2R, AJA binds to PPAR-γ, consequently suppressing the promoter activity of IL-8, a chemoattractant cytokine with specificity for the neutrophil, the main cell involved in acute inflammation.

GPR55 Receptors

CBD acts as an antagonist of GPR55, which, when inactivated, reduces the intracellular level of calcium ions, and probable anticonvulsant effect[86]. Moreover, it has been shown that mice knockout for GPR55 have elevated levels of anti-inflammatory interleukins (IL-4, IL-10, and IFN-α)[87], while high expression of GPR55 reduces ROS production[88].

5-HT1A receptors

CBD has direct affinity for the human 5-HT1A receptor[89], and it also can indirectly induce this receptor by increasing the level of AEA[90]. When activated, the 5-HT1A receptor can act as a membrane antioxidant by capturing ROS[91]. Therefore, through activation of 5-HT1A, CBD can neutralize phospholipid peroxidation and thus participate in the protection of biomembranes against oxidative and, consequently, inflammatory modifications.

Adenosine A2A receptors

CBD is also an agonist of the adenosine A2A[92] receptors. Adenosine and its agonists exhibit anti-inflammatory activity in vivo[93]. Therefore, adenosine release is one of the mechanisms of immunosuppression during inflammation[94], and adenosine receptor agonists reduce TNF-α[95,96] levels.

CONCLUSION

Cannabinoids are a promising therapeutic option in the context of inflammatory diseases, given the complete and complex relationship between the endocannabinoid system and the immune system. The setback to be overcome in the use of cannabinoids as anti-inflammatory drugs includes the synthesis of cannabinoid receptor agonists that are non-psychoactive while maintaining potent anti-inflammatory activity. While most studies have focused on the effect of cannabinoids on cytokines, apoptosis and Th1 cells, further investigations into their effect on Th17 cells, dendritic cells, natural killer cells, B cells and Foxp3+ regulatory T cells are critical, as these cells play important roles in regulating and mediating the response to inflammatory or autoimmu-

ne diseases. Moreover, the interaction with adhesion molecules, co-stimulatory molecules, and chemokines, require further study to increase the comprehension of cannabinoids and their intricate effects on immune system disorders.

AUTHORS' CONTRIBUTIONS

Alexandre Magno da Nóbrega Marinho
Project Management, Methodology, Writing - Preparation of the original, Writing - Review and Editing, Supervision, Visualization
Ricardo Wagner Gomes da Silva-Neto
Methodology, Writing - Preparation of the original, Writing - Review and Editing, Visualization

REFERENCES

1. Crocq MA. History of cannabis and the endocannabinoid system. Dialogues Clin Neurosci. 2020;22(3):223-8.
2. Baron EP. Comprehensive review of medicinal marijuana, cannabinoids, and therapeutic implications in medicine and headache: what a long strange trip it's been. Headache J Head Face Pain. 2020;55(6):885-916.
3. Li HL. An archaeological and historical account of cannabis in China. Econ Bot. 1973;28(4):437-48.
4. Russo E. Cannabis for migraine treatment: the once and future prescription? An historical and scientific review. Pain. 1998;76(1-2):3-8.
5. Schultes RE, Klein WM, Plowman T, Lockwood TE. Cannabis: an example of taxonomic neglect. Bot Mus Lealf Harv Univ. 1974;23(9):337-67.
6. Indian Hemp Drugs Commission Report - Note by Mr. G. A. Grierson [Internet]. [citado 25 de abril de 2022]. Available at: https://www.druglibrary.org/schaffer/library/studies/inhemp/6app1.htm
7. UNODC - Bulletin on Narcotics - 1957 Issue 1 - 002 [Internet]. [citado 25 de abril de 2022]. Available at: https://www.unodc.org/unodc/en/data-and-analysis/bulletin/bulletin_1957-01-01_1_page003.html.
8. Brunner TF. Marijuana in ancient greece and rome? The literary evidence. Bull Hist Med. 1973;47(4):344-55.
9. Burstein S. Cannabidiol (CBD) and its analogs: a review of their effects on inflammation. Bioorganic Med Chem. 2015;23(7):1377-85.
10. Mechoulam R, Gaoni Y. A Total Synthesis of dl-Δ1-tetrahydrocannabinol, the active constituent of hashish. J Am Chem Soc. 1965;87(14):3273-5.
11. Pertwee RG. Cannabinoid pharmacology: the first 66 years. Br J Pharmacol. 2006;147(Suppl 1):S163-71.
12. Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, Gibson D, Mandelbaum A, Etinger A, Mechoulam R. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science. 1992;258(5090):1946-9.
13. Serrano A, Parsons LH. Endocannabinoid influence in drug reinforcement, dependence and addiction-related behaviors. Pharmacol Ther. 2011;132(3):215-41.
14. De Petrocellis L, Di Marzo V. An introduction to the endocannabinoid system: from the early to the latest concepts. Best Pract Res Clin Endocrinol Metab. 2009;23(1):1-15.
15. Battista N, Tommaso M Di, Bari M, Maccarrone M. The endocannabinoid system: an overview. Front Behav Neurosci. 2012;6-9.
16. Aggarwal SK. Cannabinergic pain medicine: a concise clinical primer and survey of randomized-controlled trial results. Clin J Pain. 2013;29(2):162-71.
17. de Fonseca FR, del Arco I, Bermudez-Silva FJ, Bilbao A, Cippitelli A, Navarro M. The endocannabinoid system: physiology and pharmacology. Alcohol Alcohol. 2005;40(1):2-14.
18. MacCarrone M, Gasperi V, Catani MV, Diep TA, Dainese E, Hansen HS, Avigliano L. The endocannabinoid system and its relevance for nutrition. Annu Rev Nutr. 2010;30:423-40.
19. Greco R, Gasperi V, Maccarrone M, Tassorelli C. The endocannabinoid system and migraine. Exp Neurol. 2010;224(1):85-91.
20. Howlett AC. Efficacy in CB 1 receptor-mediated signal transduction. Br J Pharmacol. 2004;142(8):1209-18.
21. Pertwee RG. Pharmacological actions of cannabinoids. Handb Exp Pharmacol. 2005;168:1-51.
22. Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA, Felder CC, Herkenham M, Mackie K, Martin BR, Mechoulam R, Pertwee RG. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol Rev. 2002;54(2):161-202.
23. Basith S, Cui M, Macalino SJY, Park J, Clavio NAB, Kang S, Choi S. Exploring G protein-coupled receptors (gpcrs) ligand space via cheminformatics approaches: impact on rational drug design. Front Pharmacol. 2018;9:128.
24. Di Marzo V, De Petrocellis L. Why do cannabinoid receptors have more than one endogenous ligand? Philos Trans R Soc B Biol Sci. 2012;367(1607):3216-28.
25. Bisogno T, Melck D, Bobrov MYu, Gretskaya NM, Bezuglov VV, De Petrocellis L, Di Marzo V. N-acyl-dopamines: novel synthetic CB(1) cannabinoid-receptor ligands and inhibitors of anandamide inactivation with cannabimimetic activity in vitro and in vivo. Biochem J. 2000;351 Pt 3(Pt 3):817-24.
26. Hanus L, Abu-Lafi S, Fride E, Breuer A, Vogel Z, Shalev DE, Kustanovich I, Mechoulam R. 2-arachidonyl glyceryl ether, an endogenous agonist of the cannabinoid CB1 receptor. Proc Natl Acad Sci U S A. 2001;98(7):3662-5.
27. Porter AC, Sauer JM, Knierman MD, Becker GW, Berna MJ, Bao J, Nomikos GG, Carter P, Bymaster FP, Leese AB, Felder CC. Characterization of a novel endocannabinoid, virodhamine, with antagonist activity at the CB1 receptor. J Pharmacol Exp Ther. 2002;301(3):1020-4.
28. Cravatt BF, Giang DK, Mayfield SP, Boger DL, Lerner RA, Gilula NB. Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. Nature. 1996;384(6604):83-7.
29. Pertwee RG, Howlett AC, Abood ME, Alexander SP, Di Marzo V, Elphick MR, Greasley PJ, Hansen HS, Kunos G, Mackie K, Mechoulam R, Ross RA. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB_1 and CB_2. Pharmacol Rev. 2010;62(4):588-631.
30. Hill AJ, Williams CM, Whalley BJ, Stephens GJ. Phytocannabinoids as novel therapeutic agents in CNS disorders. Pharmacol Ther. 2012;133(1):79-97.
31. ElSohly MA, Slade D. Chemical constituents of marijuana: the complex mixture of natural cannabinoids. Life Sci. 2005;78(5):539-48.
32. Today VDM-D discovery, 2008 undefined. CB1 receptor antagonism: biological basis for metabolic effects. Elsevier [Internet]. [citado 25 de abril de 2022]; Available at: https://www.sciencedirect.com/science/article/pii/S135964460800305X.
33. Pagotto U, Marsicano G, Cota D, Lutz B, Pasquali R. The emerging role of the endocannabinoid system in endocrine regulation and energy balance. Endocr Rev. 2006;27(1):73-100.
34. Howlett AC. Cannabinoid receptor signaling. Handb Exp Pharmacol. 2005 [citado 25 de abril de 2022];168:53–79. Available at: https://link.springer.com/chapter/10.1007/3-540-26573-2_2.
35. Iversen L. Cannabis and the brain. Brain. 2003;126(6):1252-70.
36. Lee SF, Newton C, Widen R, Friedman H, Klein TW. Differential expression of cannabinoid CB2 receptor mRNA in mouse immune cell subpopulations and following B cell stimulation. Eur J Pharmacol. 2001;423(2-3):235-41.
37. Howlett AC. Cannabinoid receptor signaling. Handb Exp Pharmacol. 2005;168:53-79.
38. Pertwee RG. Pharmacology of cannabinoid CB1 and CB2 receptors. Pharmacol Ther. 1997;74(2):129-80.
39. Borges RS, Batista J Jr, Viana RB, Baetas AC, Orestes E, Andrade MA, Honório KM, da Silva AB. Understanding the molecular aspects of tetrahydrocannabinol and cannabidiol as antioxidants. Molecules. 2013;18(10):12663-74.
40. Marsicano G, Moosmann B, Hermann H, Lutz B, Behl C. Neuroprotective properties of cannabinoids against oxidative stress: role of the cannabinoid receptor CB1. J Neurochem. 2002;80(3):448-56.
41. De Petrocellis L, Di Marzo V. Role of endocannabinoids and endovanilloids in Ca2+ signalling. Cell Calcium. 2009;45(6):611-24.
42. Di Marzo V, Petrosino S. Endocannabinoids and the regulation of their levels in health and disease. Curr Opin Lipidol. 2007;18(2):129-40.
43. Klein TW. Cannabinoid-based drugs as anti-inflammatory therapeutics. Nat Rev Immunol. 2005;5(5):400-11.
44. Malfait AM, Gallily R, Sumariwalla PF, Malik AS, Andreakos E, Mechoulam R, Feldmann M. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. Proc Natl Acad Sci U S A. 2000;97(17):9561-6.
45. Burstein S, Varanelli C, Slade LT. Prostaglandins and cannabis-III. Inhibition of biosynthesis by essential oil components of marihuana. Biochem Pharmacol. 1975;24(9):1053-4.
46. Burstein S, Taylor P, El-Feraly FS, Turner C. Prostaglandins and cannabis-V. Identification of p-vinylphenol as a potent inhibitor of prostaglandin synthesis. Biochem Pharmacol. 1976;25(17):2003-4.
47. Klein TW, Lane B, Newton CA, Friedman H. The cannabinoid system and cytokine network. Proc Soc Exp Biol Med. 2000;225(1):1-8.
48. Hengartner MO. The biochemistry of apoptosis. Nature. 2000;407(6805):770-6.
49. McKallip RJ, Lombard C, Martin BR, Nagarkatti M, Nagarkatti PS. Δ9-Tetrahydrocannabinol-induced apoptosis in the thymus and spleen as a mechanism of immunosuppression in vitro and in vivo. J Pharmacol Exp Ther. 2002;302(2):451-65.
50. Do Y, McKallip RJ, Nagarkatti M, Nagarkatti PS. Activation through cannabinoid receptors 1 and 2 on dendritic cells triggers NF-κB-dependent apoptosis: novel role for endogenous and exogenous cannabinoids in immunoregulation. J Immunol. 2004;173(4):2373-82.
51. Lu T, Newton C, Perkins I, Friedman H, Klein TW. Cannabinoid treatment suppresses the T-helper cell-polarizing function of mouse dendritic cells stimulated with Legionella pneumophila infection. J Pharmacol Exp Ther. 2006;319(1):269-76.
52. Lee CY, Wey SP, Liao MH, Hsu WL, Wu HY, Jan TR. A comparative study on cannabidiol-induced apoptosis in murine thymocytes and EL-4 thymoma cells. Int Immunopharmacol. 2008;8(5):732-40.
53. Molina-Holgado F, Molina-Holgado E, Guaza C, Rothwell NJ. Role of CB1 and CB2 receptors in the inhibitory effects of cannabinoids on lipopolysaccharide-induced

nitric oxide release in astrocyte cultures. J Neurosci Res. 2002;67(6):829-36.
54. Klein TW, Newton C, Zhu W, Daaka Y, Friedman H. Δ9-tetrahydrocannabinol, cytokines, and immunity to Legionella pneumophila. Proc Soc Exp Biol Med. 1995;209(3):205-13.
55. Derocq JM, Ségui M, Marchand J, Le Fur G, Casellas P. Cannabinoids enhance human B-cell growth at low nanomolar concentrations. FEBS Lett. 1995;369(2-3):177-82.
56. Yebra M, Klein TW, Friedman H. Δ9-tetrahydrocannabinol suppresses concanavalin a induced increase in cytoplasmic free calcium in mouse thymocytes. Life Sci. 1992;51(2):151-60.
57. Klein TW, Newton CA, Nakachi N, Friedman H. Δ9 Tetrahydrocannabinol treatment suppresses immunity and early IFN-γ, IL-12, and IL-12 receptor β2 responses to Legionella pneumophila Infection . J Immunol. 2000;164(12):6461-6.
58. Srivastava MD, Srivastava BIS, Brouhard B. Δ9 Tetrahydrocannabinol and cannabidiol alter cytokine production by human immune cells. Immunopharmacology. 1998;40(3):179-85.
59. Correa F, Docagne F, Mestre L, Clemente D, Hernangómez M, Loría F, Guaza C. A role for CB2 receptors in anandamide signalling pathways involved in the regulation of IL-12 and IL-23 in microglial cells. Biochem Pharmacol. 200;77(1):86-100.
60. Montecucco F, Burger F, Mach F, Steffens S. CB2 cannabinoid receptor agonist JWH-015 modulates human monocyte migration through defined intracellular signaling pathways. Am J Physiol Heart Circ Physiol. 2008;294(3):H1145-55.
61. Sancho R, Calzado MA, Di Marzo V, Appendino G, Muñoz E. Anandamide inhibits nuclear factor-κB activation through a cannabinoid receptor-independent pathway. Mol Pharmacol. 2003;63(2):429-38.
62. Watzl B, Scuderi P, Watson RR. Influence of marijuana components (THC and CBD) on human mononuclear cell cytokine secretion in vitro. Adv Exp Med Biol. 1991;288:63-70.
63. Hollister LE. Marijuana and immunity. J Psychoactive Drugs. 1992;24(2):159-64.
64. Bidinger B, Torres R, Rossetti RG, Brown L, Beltre R, Burstein S, Lian JB, Stein GS, Zurier RB. Ajulemic acid, a nonpsychoactive cannabinoid acid, induces apoptosis in human T lymphocytes. Clin Immunol. 2003;108(2):95-102.
65. Cabral GA, Dove Pettit DA. Drugs and immunity: cannabinoids and their role in decreased resistance to infectious disease. J Neuroimmunol. 1998;83(1-2):116-23.
66. Parker J, Atez F, Rossetti RG, Skulas A, Patel R, Zurier RB. Suppression of human macrophage interleukin-6 by a nonpsychoactive cannabinoid acid. Rheumatol Int. 2008;28(7):631-5.
67. Rieder SA, Chauhan A, Singh U, Nagarkatti M, Nagarkatti P. Cannabinoid-induced apoptosis in immune cells as a pathway to immunosuppression. Immunobiology. 2010;215(8):598-605.
68. Hegde VL, Hegde S, Cravatt BF, Hofseth LJ, Nagarkatti M, Nagarkatti PS. Attenuation of experimental autoimmune hepatitis by exogenous and endogenous cannabinoids: involvement of regulatory T cells. Mol Pharmacol. 2008;74(1):20-33.
69. Kim EK, Jang M, Song MJ, Kim D, Kim Y, Jang HH. Redox-mediated mechanism of chemoresistance in cancer cells. Antioxidants. 2019;8(10):471.
70. Chio IIC, Tuveson DA. ROS in cancer: the burning question. Trends Mol Med. 2017;23(5):411-29.
71. Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, Squadrito F, Altavilla D, Bitto A. Oxidative Stress: Harms and Benefits for Human Health. Oxid Med Cell Longev. 2017;2017:8416763.
72. Costa B, Trovato AE, Comelli F, Giagnoni G, Colleoni M. The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain. Eur J Pharmacol. 2007;556(1-3):75-83.
73. Iuvone T, Esposito G, Esposito R, Santamaria R, Di Rosa M, Izzo AA. Neuroprotective effect of cannabidiol, a non-psychoactive component from Cannabis sativa, on β-amyloid-induced toxicity in PC12 cells. J Neurochem. 2004;89(1):134-41.
74. Vomund S, Schäfer A, Parnham MJ, Brüne B, Von Knethen A. Nrf2, the master regulator of anti-oxidative responses. Int J Mol Sci. 2017;18(12):2772.
75. Gęgotek A, Ambrożewicz E, Jastrząb A, Jarocka-Karpowicz I, Skrzydlewska E. Rutin and ascorbic acid cooperation in antioxidant and antiapoptotic effect on human skin keratinocytes and fibroblasts exposed to UVA and UVB radiation. Arch Dermatol Res. 2019;311(3):203-19.
76. Jastrząb A, Gęgotek A, Skrzydlewska E. Cannabidiol regulates the expression of keratinocyte proteins involved in the inflammation process through transcriptional regulation. Cells. 2019;8(8):827.
77. Wall SB, Oh JY, Diers AR, Landar A. Oxidative modification of proteins: An emerging mechanism of cell signaling. Front Physiol. 2012;3:369.
78. Fouad AA, Albuali WH, Al-Mulhim AS, Jresat I. Cardioprotective effect of cannabidiol in rats exposed to doxorubicin toxicity. Environ Toxicol Pharmacol. 2013;36(2):347-57.
79. De Petrocellis L, Ligresti A, Moriello AS, Allarà M, Bisogno T, Petrosino S, Stott CG, Di Marzo V. Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. Br J Pharmacol. 2011;163(7):1479-94.
80. Pellati F, Borgonetti V, Brighenti V, Biagi M, Benvenuti S, Corsi L. Cannabis sativa L. and nonpsychoactive cannabinoids: their chemistry and role against oxidative stress, inflammation, and cancer. Biomed Res Int. 2018;2018.
81. Muller C, Morales P, Reggio PH. Cannabinoid ligands targeting TRP channels. Front Mol Neurosci. 2019;11:487.
82. Miller BA, Zhang W. TRP channels as mediators of oxidative stress. Adv Exp Med Biol. 2011;704:531-44.
83. Ogawa N, Kurokawa T, Fujiwara K, Polat OK, Badr H, Takahashi N, Mori Y. Functional and structural divergence in human TRPV1 channel subunits by oxidative cysteine modification. J Biol Chem. 2016;291(8):4197-210.
84. Vallée A, Lecarpentier Y, Guillevin R, Vallée JN. Effects of cannabidiol interactions with Wnt/β-catenin pathway and PPARγ on oxidative stress and neuroinflammation in Alzheimer's disease. Acta Biochim Biophys Sin (Shanghai). 2017;49(10):853-66.
85. Huang J, Tabbi-Anneni I, Gunda V, Wang L. Transcription factor Nrf2 regulates SHP and lipogenic gene expression in hepatic lipid metabolism. Am J Physiol Gastrointest Liver Physiol. 2010;299(6):G1211-21.
86. Marichal-Cancino BA, Fajardo-Valdez A, Ruiz-Contreras AE, Mendez-Díaz M, Prospero-García O. Advances in the Physiology of GPR55 in the Central Nervous System. Curr Neuropharmacol. 2017;15(5):771-8.
87. Staton PC, Hatcher JP, Walker DJ, Morrison AD, Shapland EM, Hughes JP, Chong E, Mander PK, Green PJ, Billinton A, Fulleylove M, Lancaster HC, Smith JC, Bailey LT, Wise A, Brown AJ, Richardson JC, Chessell IP. The putative cannabinoid receptor GPR55 plays a role in mechanical hyperalgesia associated with inflammatory and neuropathic pain. Pain. 2008;139(1):225-36.
88. Balenga NA, Aflaki E, Kargl J, Platzer W, Schröder R, Blättermann S, Kostenis E, Brown AJ, Heinemann A, Waldhoer M. GPR55 regulates cannabinoid 2 receptor-mediated responses in human neutrophils. Cell Res. 2011;21(10):1452-69.
89. Russo EB, Burnett A, Hall B, Parker KK. Agonistic properties of cannabidiol at 5-HT1a receptors. Neurochem Res. 2005;30(8):1037-43.
90. Haj-Dahmane S, Shen RY. Modulation of the serotonin system by endocannabinoid signaling. Neuropharmacology. 2011;61(3):414-20.
91. Azouzi S, Santuz H, Morandat S, Pereira C, Côté F, Hermine O, El Kirat K, Colin Y, Le Van Kim C, Etchebest C, Amireault P. Antioxidant and membrane binding properties of serotonin protect lipids from oxidation. Biophys J. 2017;112(9):1863-73.
92. McPartland JM, Duncan M, Di Marzo V, Pertwee RG. Are cannabidiol and Δ9-tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review. Br J Pharmacol. 2015;172(3):737-53.
93. Noji T, Takayama M, Mizutani M, Okamura Y, Takai H, Karasawa A, Kusaka H. KF24345, an adenosine uptake inhibitor, suppresses lipopolysaccharide-induced tumor necrosis factor-alpha production and leukopenia via endogenous adenosine in mice. J Pharmacol Exp Ther. 2002;300(1):200-5.
94. Haskó G, Cronstein BN. Adenosine: an endogenous regulator of innate immunity. Trends Immunol. 2004;25(1):33-9.
95. Carrier EJ, Auchampach JA, Hillard CJ. Inhibition of an equilibrative nucleoside transporter by cannabidiol: a mechanism of cannabinoid immunosuppression. Proc Natl Acad Sci U S A. 2006;103(20):7895-900.
96. Ribeiro A, Ferraz-de-Paula V, Pinheiro ML, Vitoretti LB, Mariano-Souza DP, Quinteiro-Filho WM, Akamine AT, Almeida VI, Quevedo J, Dal-Pizzol F, Hallak JE, Zuardi AW, Crippa JA, Palermo-Neto J. Cannabidiol, a non-psychotropic plant-derived cannabinoid, decreases inflammation in a murine model of acute lung injury: role for the adenosine A(2A) receptor. Eur J Pharmacol. 2012;678(1-3):78-85.