v. 4, n. 19, 2024

International Journal of Health Science

PATHOPHYSIOLOGY OF THE ENDOCANNABINOID SYSTEM IN AUTISM SPECTRUM DISORDER: A NARRATIVE REVIEW

Andrey Alves Siqueira de Miranda

INTRODUCTION

As the therapeutic possibility of cannabis gradually gains more emphasis in the national and global media, the population begins to discuss the topic more openly. In addition to already recognized anticonvulsant properties, research shows that cannabinoid agents have an important response on human social behavior [1] [2]. There is also a suggestion to improve social communication and reduce aggressiveness [3] [4]. Because of this, cannabinoid compounds appear as an expectation for the treatment of neurodevelopmental disorders, such as Autism Spectrum Disorder (ASD).

This review aims to discuss changes in the endocannabinoid system in the central nervous system (CNS) of patients with ASD, as well as possible therapeutic mechanisms for the use of cannabinoid agents involved in the treatment of core symptoms of the disorder, taking into consideration, clinical trials or secondary studies that deal with on the proposed topic.

This work is organized as follows: in section 2, we present the methodology used and the review planning, followed by section 3, in which we detail the execution. In section 4, we present a theoretical framework regarding the diagnosis of ASD. Section 5 consists of summarizing the data followed by section 6, where we present a discussion based on the findings of this review.

We close this work in section 7 with conclusions.

REVIEW METHODOLOGY

To carry out this narrative literature review, we followed the protocol of Page et al., 2020, in order to guarantee relevance of the works to be synthesized.

We begin this section by introducing an overview of the method, followed by the research question, and definition of population, intervention, context and outcome. We also detail the search strategy steps, inclusion and exclusion criteria and quality assessment used to make the final selection of the articles that made up this work.

NARRATIVE REVIEW METHOD

This Narrative Review will be based on five steps, namely:

- Step 1 – Automatic Search: This step consists of automatic searching in selected search engines (i.e., Science Direct and Pubmed), organizing the results returned and removing duplicates.
- Step 2 – Title, Abstract and Keywords: This step consists of reading the titles, abstracts and keywords of each article. Articles that are not related to the research questions and/or meet the inclusion/exclusion criteria are discarded (if there is not enough information, the article is left for the next step).
- Step 3 – Introduction and Conclusion: This step consists of reading the introductions and conclusions of each article. Articles that are not related to the research questions and/or meet the inclusion/exclusion criteria are discarded (if there is not enough information, the article is left for the next step). Articles that meet the inclusion criteria are included for quality assessment.
- Step 4 – Reading the article: This step consists of reading the entire article as well as evaluating the quality criteria.
- Stage 5 – Summary of Results: In this stage, data from included articles are analyzed and grouped.

RESEARCH QUESTION

To define the objectives and research questions, four main elements were established, according to an approach known in research circles by the acronym PICO: P) Population (i.e., individuals with Autism Spectrum Disorder); I) Intervention (i.e., administration of cannabis derivatives); C) Context (i.e., treatment of behavioral symptoms); O) Outcome/Outcome (i.e., symptomatic response) [27].

Based on these elements, the main research question was defined as:

> *"What neurological changes to the endocannabinoid system are found in ASD?"*

In addition to the main question, a secondary question was also defined:

> *"What psychopharmacological mechanisms are involved in the possible therapeutic effects on behavioral symptoms of ASD when using cannabis derivatives?"*

SEARCH STRATEGY

Based on the four elements of the main question, keywords and related terms were created as shown in Table 1 [26].

P	*"autism"*
I	*"cannabis", "cannabidiol"*
C	*"self-harm", "self-agression"*
O	*"treatment"*

Table 1 – Key words

To construct the search keywords, the terms were combined as follows: 1) terms from the same element were grouped by the logical OR operator; and 2) the sets of terms of the four elements were grouped by the logical operator AND. Initially, the resulting search term only generated results on the Science Direct platform, and there were no articles in the Pubmed search engine. Because of this, the keywords for searching on this platform were simplified [27] [26]. Therefore, the final search terms were defined as:

ScienceDirect

((autism OR autism) AND (treatment OR treatment) AND (cannabidiol OR cannabis) AND (auto aggression OR self-harm OR self-aggression))

Pubmed

((autism OR autism) AND (treatment OR treatment) AND (cannabidiol OR cannabis))

INCLUSION AND EXCLUSION CRITERIA

To filter the results obtained in the searches, inclusion and exclusion criteria were defined according to the methodology proposed by Kitchenham & Charters, 2007, described in Table 2. Articles published on the aforementioned platforms during the period between the year 2000 and the year 2022 [28].

#	**Inclusion criteria**
1	Primary or secondary studies
2	Studies that talk about the use of cannabis derivatives to treat autism
3	Articles that deal with clinical trials
4	Articles that deal with the therapeutic response to cannabis-derived medications in humans or animal models
#	**Exclusion Criteria**
5	Studies without peer review (pre-print)
6	Duplicate studies (only one copy will be kept)
7	Articles not written in English or Portuguese
8	Gray literature (for example: private technical reports and non-peer reviewed chapter books)
9	Redundant articles by the same author
10	Outside the scope of the review

Table 2 - Inclusion and Exclusion Criteria

QUALITY ASSESSMENT

To guarantee the quality of the selected studies, criteria were applied to assess their credibility, completeness and relevance [28]. All selected articles were evaluated according

to the 10 criteria shown in Table 3. For each of the criteria it is possible to assign a score between 0 and 1 and the final score for each article is computed through the average of these scores. Results lower than 60% of the total value will be excluded.

#	Quality Criteria	Possible answers
1	Does the study present a convincing rationale?	Yes =1 | No=0 | Partially=0.5
2	Does it have a good theoretical basis?	Yes =1 | No=0 | Partially=0.5
3	Was it based on research or is it simply about "lessons learned" or an expert's report?	Yes=1 | No=0
4	Were the research objectives clearly defined?	Yes =1 | No=0 | Partially=0.5
5	Was the proposed technique or solution clearly described?	Yes =1 | No=0 | Partially=0.5
6	Was the study empirically evaluated?	Yes =1 | No=0 | Partially=0.5
7	Does the study propose any tools?	Yes=1 | No=0
8	Is there a discussion about the study results?	Yes =1 | No=0 | Partially=0.5
9	Were the limitations of the study discussed?	Yes =1 | No=0 | Partially=0.5
10	Does the study add scientific value to the research area?	Yes =1 | No=0 | Partially=0.5

Table 3 - Quality Assessment Criteria

REVIEW EXECUTION

This Narrative Review was carried out from September 2022 to December 2022. In Stage 1 of the process, the search term was entered in the two selected engines: Science Direct and Pubmed. From this phase, 683 articles were obtained, 579 from Science Direct and 104 from Pubmed. Of these, 4 were duplicates and were excluded from the process, leaving 679 articles.

In Stage 2 of the review, titles, abstracts and keywords were analyzed according to the exclusion criteria and 639 articles were removed from the review. In Stage 3 of the review, the introduction and conclusion of the remaining 40 articles were analyzed according to the exclusion criteria and 16 articles were excluded, totaling 24 articles under analysis. In Stage 4, the articles were read in their entirety and evaluated according to the quality criteria. One article did not reach 60% of the maximum score and was excluded, leaving 23 articles for summarization.

AUTISTIC SPECTRUM DISORDER

Autism spectrum disorder is a heterogeneous syndromic group with multiple neurodevelopmental phenotypes designated by social communication disorders and restricted and reiterated patterns of behavior [8].

In the United States, the prevalence of the disorder is around 1%. Around 15% of the spectrum appears to be associated with genotypic changes. Fragile X syndrome is the most common of these, occurring in 2 to 3% of patients with ASD. It is an X-linked recessive hereditary disorder. Tuberous sclerosis also occurs at a similar frequency, affecting 2% of ASD [8].

The disorder is usually identified when patients are in the second year of life. In cases of significant neurodevelopmental impairment, it can be identified before 12 months. In those who present milder symptoms, the diagnosis may only become evident after 24 months of life [9].

The DSM-V diagnostic criteria for autism spectrum disorder involve persistent deficits in social communication and social interaction (Criterion A) and restricted, repetitive patterns of activities, behavior, or interests (Criterion B). Such symptoms appear early in the development period and cause daily socio-functional impairment (Criteria C and D). This condition is not better explained by global developmental delay or even intellectual disability (Criterion E). Symptoms manifest as soon as environmental demand overrides the individual's social response capacity. Learned strategies can mask symptoms into adulthood at the latest.

The condition of the disorder varies according to the severity of the symptoms, age group and level of development [9]. Rett syndrome and childhood disintegrative, Asperger's, and pervasive developmental disorders not otherwise specified will be included under the diagnostic rubric of autism spectrum disorder[8].

SUMMARIZATION

The endocannabinoid system is composed of a specific group of receptors and neurotransmitters that provide, in general, modulation of brain hyperactivity [5]. This system promotes important action in the processes of neuronal plasticity involved in memory, learning and behavior [6] [7]. These neurotransmitters modulate a broad part of neuronal functioning, which, in turn, are altered in ASD [31]. Its behavioral modulation property and its repercussions on ASD will be explored in this section.

ENDOCANNABINOID SYSTEM

Endocannabinoids, in general, carry out retrograde neurotransmission in hyperactive neuronal circuits, modulating the release of neurotransmitters in the cleft.

Thus, its synthesis in postsynaptic neurons is determined by demand. With the activation of the type 1 cannabinoid receptor (CB1) in presynaptic neurons, there is a reduction in synaptic activity in the circuit in question.

After action of endocannabinoids, specific membrane transporters reuptake neurotransmitters by facilitated diffusion to the postsynaptic neuron and immediately hydrolyze them [11][7]. Fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) degrade anandamide and 2-AG, respectively [5]. Anandamide acts as a partial agonist at CB1 and type 2 cannabinoid receptors (CB2). On the other hand, 2-AG proves to be the main cannabinoid. Even though it has lower affinity for cannabinoid receptors, it is present in concentrations around 200 times higher than its analogue. 2-AG acts as a full agonist of CB1 and CB2 receptors and has greater selectivity towards them. Alternatively, anandamide exerts negative feedback on the synthesis of 2-AG [7]. CB1s are expressed in high density in the basal ganglia, hippocampus, cortex, hypothalamus, and limbic cortex. Such brain structures respectively modulate motor activity, motor coordination, thinking, appetite and sedation [14].

CB1 is a G protein-linked receptor, while CB2 is present in macrophages and the spleen, providing an immunomodulatory effect [12]. CB2 receptors are not widely expressed in the central nervous system (CNS) under normal conditions. Its presence in glial cells occurs in contexts of neurological pathologies [10]. Regarding CB2, these are expressed in cells and tissues, which are associated with the immune and inflammatory response [18]. Palatine tonsils, spleen, some CNS cells and glial cells are structures where we can find CB2. However, CB2 is not normally expressed in neurons, with its massive presence being more common in pathological neurological and psychiatric conditions [19]. Furthermore, this receptor is not found in the brain stem, so Cannabis has minimal effects on respiratory and cardiac functions [8].

ENDOCANNABINOID SYSTEM AND CANNABIS DERIVATIVES

There are two main components that make up the set of substances derived from Cannabis: cannabidiol (CBD) and THC [12] [13]. THC naturally binds to the CB1 receptor and has a strong affinity for it [5] [14]. This interaction is responsible for the psychoactive effect of the "high" sensation [12] [7]. THC also has an action on CB2 receptors [12].

CBD, however, does not act directly

on CB1 [13]. It has the pharmacological property of inhibiting FAAH, increasing the concentration of anandamide in the synaptic cleft [15] [16]. Thus, CBD has an indirect action on the cannabinoid system. Additionally, the molecule can modulate the system GABA-glutamate, which studies suggest is unbalanced in ASD [17].

ENDOCANNABINOID SYSTEM AND ASD

Studies suggest that the endocannabinoid system modulates emotional responses and social interaction, functions typically impaired in ASD. Associated with this context, laboratory profiles of ASD in animals demonstrated an imbalance in the endocannabinoid neurotransmitter system. Other evidence also suggests that children with ASD have lower serum levels of endocannabinoids when compared to children with typical neurodevelopment [6]. Other studies observed changes in the same serum levels persisting into adulthood [31].

A widely accepted assumption deals with a possible excitatory-inhibitory (E-I) imbalance in neural circuits [20]. This would occur due to local hyper connectivity and deficiency in long-range connections. The E-I imbalance may result from glutamatergic hyperactivity or reduced GABAergic neurotransmission [21] [20]. The consequence of this deregulation would be defective synaptic plasticity and an epileptogenic neuronal pattern. Therefore, patients with ASD have 25 times more epilepsy than the general population, especially in syndromic forms [20]. E-I imbalance can determine behaviorally neurodivergent and abnormal sociability, as well as irritability and stereotyped and repetitive behaviors. Behavioral and social changes observed in ASD are attributed to an increased E-I ratio in the PFC [22].

In a functional brain MRI study focusing on the effects of CBD and cannabidivarin in the treatment of patients with ASD, a GABA-mediated inhibitory response was found distinct from those belonging to the control group [31]. The result of this research converges with previous studies that highlight distinctions between the basal functioning of the GABAergic system in individuals with ASD and neurotypical people. Furthermore, CBD has been shown to alter oscillation amplitude and frequency, as well as brain connectivity in the adult CNS in anatomical areas often associated with autism. However, in this case, glutamatergic excitatory mechanisms did not differ between the two groups (patients and control).

Poleg, S. et al., 2021, suggests the possibility of defining animal genetic models of ASD, since research on twins indicates that the disorder has a genetic scope. This way, Shank3 mutant mouse models could help decipher more mechanisms associated with the endocannabinoid system [5]. SHANK3 (SH3 and multiple ankyrin repeat domains 3) is a structural protein made up of a signaling cytoskeleton molecule, which connects receptors and clusters many ion channels. It also binds structural proteins, enzymes, and signaling molecules. SHANK3 aims to connect all of these mechanisms to postsynaptic neuronal density. SHANK3 is also known as proline-rich synapse-associated protein 2 (ProSAP2).

When SHANK3 acts on glutamatergic synapses, there is a simultaneous action on all glutamatergic receptors. This action is mediated by proteins postsynaptic proteins such as GKAP (Guanylate-kinase-associated protein) and Homer PSD95 [5]. Therefore, it has an indirect action on NMDA, AMPA, and metabotropic glutamate receptors. SHANK3 also communicates with postsynaptic adhesion molecules, such as Neuroligins. The SHANK3 protein is relevant in spinogenesis (formation

of dendritic spikes), which establishes brain development and the storage of information in its neuronal circuits, originating, in part, from the individual's experiences [5] [23]. Furthermore, it participates in the development of synapses and organizes glutamatergic postsynaptic density [5].

The InsG3680 Shank3 mutation is an alteration identified in individuals with ASD that promotes almost complete loss of the SHANK3 protein [5]. In mouse models with this mutation, visible autistic behaviors occur, such as impaired sociability and anxiety. In approximately 30% of adult homozygous mice, repetitive self-grooming behaviors caused skin lesions.

After 3 weeks of treatment with Avidekel (cannabis extract oil with a high concentration of CBD), there was a reduction in the amount of cleaning performed by mutant mice by more than 70%, when compared to the control group.

ASD has two relevant clinical characteristics: neuroimmune system maladjustment and inflammation. Patients with ASD demonstrate increased inflammatory activity. Furthermore, individuals with ASD present an upregulation in the density of CB2 receptors and an increase in CB2 protein levels in peripheral blood mononuclear cells [24]. In this case, the CB1 receptors and the FAAH enzyme were unchanged [25].

Pro-inflammatory cytokines are currently emerging as possible diagnostic markers for ASD. Recently, it was discovered in children aged 3 to 9 years diagnosed with ASD, the presence of high serum levels of pro-inflammatory cytokines and chemokines, such as IL-1β (interleukin...), IL-6, IL-17, IL-12p40 and IL-12p70 and tumor necrosis factor-α (TNF-α) compared to children with typical neurodevelopment [24]. Inflammatory profiles have been suggested as predictors of specific phenotypes of symptomatic severity in ASD. Mild symptomatic conditions showed higher levels of IL-12p40, while moderate symptomatic conditions showed higher levels of TNF-α. Furthermore, there is a gender distinction in inflammatory patterns, since the inflammatory cytokines TNF-α, IL-6 and IL-17 were upregulated in males, which did not occur in females, compared to age-matched healthy controls. and sex.

Neuroinflammation may indicate an important mechanism in the pathophysiology of ASD. Human post-mortem samples from autistic individuals, as well as animal models, show elevated levels of IL-6 in the brain [24]. Other changes found in patients with ASD include abnormal expression of cytokines and pro-inflammatory chemokines, macrophage migration inhibitory factor and platelet-derived growth factor, whether in peripheral blood, cerebrospinal fluid or brain tissues. These cytokines can participate in the formation of excitatory and inhibitory synapses, in order to produce anatomical abnormalities. Despite the evidence, a large proportion of autistic children enrolled in these studies were already treated with psychotropic drugs, such as atypical antipsychotics. Therefore, the increase in cytokine levels may also be a response to these medications.

Another hypothesis is raised, associating the pro-inflammatory state of ASD patients with the gut-brain axis. This axis promotes bidirectional communication between the brain and the gastrointestinal tract via the vagus nerve, enteric and immune systems [24]. However, some microbiota metabolites also interfere with this connection. The intestinal microbiota influences the neurodevelopment of mammals since the beginning, regulating essential behaviors and functions. Therefore, dysregulations of this intestinal microbiota can predispose to acute and even chronic inflammation, which can be involved in

neuropsychiatric disorders, such as ASD.

Patients with ASD have food selectivity, which can influence the nutritional pattern of their diet, reflected in the composition of their intestinal microbiota [24]. Clinical evidence states that half of the individuals on the spectrum have altered permeability of the intestinal barrier and dysbiosis of the intestinal microbiota, leading to gastrointestinal problems.

In this context, it has been suggested that immunological abnormalities in ASD may be related to pro-inflammatory processes triggered by casein and gluten proteins that sensitize the damaged intestinal barrier. Thus, stimulation of the inflammatory cascade generates pro-inflammatory cytokines and monocytes and these reach the CNS, where they trigger a process of neuroinflammation.

In support of this hypothesis, fecal samples from children with ASD identified aggressive forms of Candida spp., compared to their healthy controls [24]. Another study carried out with Microbiota Transfer Therapy (MTT), showed important improvements in ASD-related symptoms and gastrointestinal symptoms, with beneficial effects of MTT even after two years of treatment.

According to Carbone et al., 2020, work carried out on animals indicates that germ-free mice (GF) have a compromised and disorganized immune system architecture, making them more exposed to infections than their conventional counterparts. GF animals show decreased sociability with unknown partners and this behavior is modified after intestinal colonization with several commensal bacteria [24]. In addition, colonization of the intestine of mice by the bacteria Lactobacillus reuteri (L. reuteri) improved symptoms similar to those of ASD.

Finally, the clinical trial by Aran, A. et al., 2021, looks at the administration of complete cannabis extract containing CBD and THC in a 20:1 ratio [29]. The proof-of-concept, double-blind, randomized study with a control group included 150 children and adolescents, with severe symptoms in 78.7%, according to ADOS-2. Under this formulation, there was an improvement in challenging behavior and parental stress in 49% of patients, with greater statistical significance than placebo ($p = 0.005$). However, in the group that received pure cannabinoids, the favorable response in 38% did not demonstrate statistical significance ($p = 0.08$).

A recent clinical trial (SILVA E.A.D. Junior et al., 2022) demonstrated the safety of CBD-rich cannabis extract administered in a study with 60 patients with ASD [32]. The extract was administered to 31 children with only 3 of them experiencing mild adverse events. Likewise, in Aran, A. et al., 2021, there is no reference to severe aversive events, in addition to not observing a relevant frequency of mild side effects. The most common adverse effects reported in this study include drowsiness, reduced appetite, weight loss, tiredness, euphoria and anxiety [29]. In SILVA E.A.D. Junior et al., 2022, mild adverse events similar to those mentioned above are reported.

DISCUSSION

Since several studies suggest the involvement of E-I imbalance in the development of neurodivergent behaviors and abnormal sociability, it is possible that the action of anandamide on presynaptic CB1 receptors downregulates hyperexcitability and modifies such symptoms [11] [22]. Irritability and stereotyped and repetitive behaviors express some of these changes [22]. In this context, the direct action of THC on the same CB1 receptors can act in synergy with anandamide, reducing the excitability of hyperactivated systems.

Furthermore, in line with the above, genetic animal models of ASD indicate

that SHANK3 mutant mice showed improvement in repetitive behaviors under the administration of cannabis extract oil with a high concentration of CBD [5]. Taking into consideration, that this synaptic protein acts on glutamatergic synapses, the action of endocannabinoids on CB1 receptors may contribute to the regulation of excitatory neurotransmission.

On the other hand, an association of ASD with a systemic pro-inflammatory state opens up space for the therapeutic use of CBD in this group of patients. The molecule may allow the modulation of possible neuroimmune changes, through the increase of anandamide in the synaptic cleft and its action on CB2 receptors. In some cases, animal models indicate a possible association of immune dysregulation of the gut-brain axis with deficits in socialization capacity, so that immune modulation via CB2 receptors could improve sociability [24]. THC also acts on CB2 receptors and has ways to confirm this mechanism.

As stated above, the clinical trial by ARAN, A. et al., 2021 suggests that there is a pharmacodynamic interaction between the cannabinoid systems associated with CBD and THC, so that the isolated action of another cannabinoid would not be sufficient to promote a satisfactory behavioral response [29].

Safety and tolerance are important points to be evaluated, as neurodivergent populations are more sensitive to pharmacotherapy and have greater vulnerability to aversive events [30]. Therefore, the low expression of CB2 in the brain stem indicates the possibility of minimal effects of CBD on respiratory and cardiac functions [8].

However, therapeutic application in humans still does not have a medical-scientific consensus on indication criteria. ARAN, A. et al., 2021, in their clinical trial, suggests the application of these drugs aimed at cases of refractory disruptive behaviors [29].

CONCLUSION

In this work we carried out a narrative review of the literature with the aim of observing evidence on the pathophysiology of ASD within the scope of the endocannabinoid system, as well as the therapeutic response mechanisms under the administration of cannabis agents in this disorder.

This review took into consideration, the current literature from the year 2000 to 2022. Searches were carried out in research engines: Science Direct and Pubmed. After analysis according to the inclusion and exclusion criteria, of the 683 articles obtained, 23 articles remained for summarization.

The results of the articles obtained indicated evidence that associates brain circuits modulated by the endocannabinoid system and ASD symptoms, such as stereotyped and repetitive behaviors resulting from dysregulation of the glutamate-GABAergic system. Furthermore, there is evidence that the immunological dysregulation present in a wide range of patients with Autism is associated with defects in the modulation of CB2 receptors, as well as being related to changes in socialization.

Thus, there is evidence of great therapeutic value of cannabis compounds. However, despite advances, more clinical trials need to be carried out due to the need to establish a more robust pharmacological profile on these substances, in addition to determining more specific therapeutic profiles for the indication of treatment.

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