# Palmitoylethanolamide in Autism Spectrum Disorder

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Palmitoylethanolamide (PEA) is a naturally occurring saturated N-acylethanolamine that has proven to be effective in controlling inflammation, depression, epilepsy, and pain, possibly through a neuroprotective role against glutamate toxicity. Here, we systematically reviewed all human and animal studies examining PEA and its biobehavioral correlates in ASD. Studies indicate altered serum/brain levels of PEA and other endocannabinoids (ECBs)/acylethanolamines (AEs) in ASD. Altered PEA signaling response to social exposure and altered expression/activity of enzymes responsible for the synthesis and catalysis of ECBs/AEs, as well as downregulation of the peroxisome proliferator activated receptor-α (PPAR-α) and cannabinoid receptor target GPR55 mRNA brain expression, have been reported. Stress and exposure to exogenous cannabinoids may modulate ECBs/AEs levels and expression of candidate genes for neuropsychiatric disorders, with implications for ASD. Limited research suggests that PEA supplementation reduces overall autism severity by improving language and social and nonsocial behaviors. Potential neurobiological underpinnings include modulation of immune response, neuroinflammation, neurotrophy, apoptosis, neurogenesis, neuroplasticity, neurodegeneration, mitochondrial function, and microbiota activity, possibly through peroxisome proliferator-activated receptor-α (PPAR-α) activation.

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## 1. Introduction

Autism spectrum disorder (ASD) is a complex and multifactorial neurodevelopmental condition affecting those who suffer from it at different levels. Difficulties in social communication and associated tendency to have restrictive interests and repetitive and stereotyped activities are considered the core aspects of the disorder [1], allowing clinicians to make a diagnosis of ASD based on behavioral assessment [2]. However, converging research evidence supports the presence of altered neurobiological parameters such as functional and structural brain abnormalities [3][4], by which gene variants or epigenetic marks lead to the neurocognitive and biobehavioral symptoms consistently reported in ASD [5][6]. It is noteworthy that, even though the pathophysiology of ASD is not completely understood, studies conducted over the last two decades have helped clarify some of the mechanisms of disease progression. In particular, altered inflammatory response [7] and disrupted glutamate signaling [8][9][10]

have been reported, leading the way to the investigation of the effect of molecules targeting the immune-glutamatergic system in improving clinical severity in ASD [11].

Growing evidence indicates that one of the major physiological functions of the cannabinoid signaling system is the modulation of neuroinflammation [12] and glutamate neurotransmission [13]. Both exogenous cannabinoids (e.g., plant-derived cannabinoids Δ9-tetrahydrocannabinol, Δ9-THC, and cannabidiol, CBD) and their endogenous counterparts (e.g., endocannabinoids anandamide and 2-arachidonoylglycerol, 2-AG) interact with the endocannabinoid system, with implications for health and disease [14][15]. Despite promising evidence on the efficacy of Δ9-THC- and CBD-based treatments in the management of ASD-related behavioral problems, it is still limited and requires further investigation [16]. Anandamide (arachidonoylethanolamide) and 2-AG are both derivatives of arachidonic acid, a polyunsaturated fatty acid well known as the precursor of bioactive prostaglandins and other eicosanoids, with anandamide specifically being its ethanolamine [17].

Other ethanolamines of various long-chain fatty acids also naturally occur, and along with anandamide they are collectively referred to as N-acylethanolamines. However, they are more abundant than anandamide in the body and do not bind to cannabinoid receptors, while exerting most of their biological effects by activating the peroxisome proliferator-activated receptor-α (PPAR-α), a nuclear receptor, and PPAR-α-independent pathways involving other receptors such as Transient Receptor Potential Vanilloid 1 (TRPV1) and GPR55 [17][18]. Research evidence suggests that such specific mechanisms of action would account for their anti-inflammatory, analgesic, anticonvulsant, and neuroprotective properties [17][18]. Palmitoylethanolamide (PEA, N-hexadecanoylethanolamide), in particular, is a saturated N-acylethanolamine which has been suggested to be effective in the control of inflammatory responses [19][20], depressive symptoms [21], epilepsy [22], and pain [23], possibly through a neuroprotective role against glutamate toxicity [17].

## 2. Development and Findings

This is the first systematic review of all studies exploring the biobehavioral correlates of palmitoylethanolamide (PEA) in autism spectrum disorder (ASD) in humans and animals. Previous reviews have mainly addressed the potential role of neuroinflammation and altered glutamate signaling in ASD etiopathogenesis, indicating that, in subjects with genetic predispositions, atypical neurodevelopment may arise from a complex interplay between (neuro)inflammatory processes, mitochondrial dysfunction, oxidative stress and altered expression of glutamate signaling [24]. Interestingly, research evidence converges on the crucial role of exogenous cannabinoids and endocannabinoids in modulating such neurobiological systems, including neuroinflammation [12] and glutamate neurotransmission [13]. Overall, this review demonstrates that PEA may be involved in ASD, as indicated by interventional studies of the positive biobehavioral effects of PEA supplementation in both humans and animals as well as observational studies reporting aberrancies in the PEA signaling pathway at different levels.

PEA supplementation in humans as both monotherapy [25][26] and add-on therapy to antipsychotic medication [27] has been shown to reduce overall autism severity [25][26] by improving both expressive language (*what* the child says) [25] and inappropriate speech (*how* the child says it) [27], as well as modulating atypical behavior [25][26][27] and

immune response [25]. Similarly, PEA supplementation in different animal models of autism and related conditions has been suggested to be effective in improving social and nonsocial behaviors [26][28][29] as well as in modulating a number of neurobiological processes including neuroinflammation [26], neurotrophy [28], apoptosis [26], neurogenesis [26], neuroplasticity [26], neurodegeneration [29][30], mitochondrial function [28], and microbiota activity [28]. Importantly, PEA administration resulted in an activation of the peroxisome proliferator activated receptor-α (PPAR-α) [28], whose downregulation may decrease antioxidative and anti-inflammatory processes, also altering energy homeostasis, mitochondrial fatty acid metabolism, and regulation of genes coding proteins that are involved in glutamate homeostasis and cholinergic/dopaminergic signaling in the brain, with implications for neurodevelopmental conditions [31]. The hippocampus is one of the brain areas where such modulatory effects of PEA are mostly reported. Further studies are needed to investigate the role of the PEA-induced modulation of the hippocampal system in improving the brain spatiotemporal framework within which sensory, emotional, and cognitive aspects of an experience are processed in ASD, with implications for comprehension and language production [32]. This is of paramount importance, as structural, functional, and neurochemical alterations in the hippocampus have been suggested as candidate biomarkers for the diagnosis of ASD in childhood [33].

Another line of research identified lower serum levels of PEA and other endocannabinoids (ECBs)/acylethanolamines (AEs) in humans suffering from ASD, independently of sociodemographic and clinical characteristics [34]. Similarly, studies performed in animal models of autism and related conditions suggested an altered response of the PEA signaling in the face of social exposure [35], altered expression and activity of the enzymes responsible for the synthesis and catalysis of ECBs/AEs [35][36], and downregulation of PPAR-α [35][36] and the cannabinoid receptor target GPR55 mRNA expression in the brain [35]. Interestingly, animals exposed to stress and administered with exogenous cannabinoids showed variations in their ECB/AE levels and expression of genes implied in neuropsychiatric disorders [37].

The findings of this systematic review have to be seen in light of some limitations. Research in the field is still too limited, especially in humans (2 of the 4 human studies are case reports, leaving a single experimental study conducted in a youth population with ASD), and further studies are needed to fully address the relevance of PEA for the different clinical phenotypes of ASD and whether the potentially beneficial effects of PEA are mediated by a protective role of the compound against altered neuroinflammatory responses and glutamate toxicity, which have been suggested to be involved in the pathophysiology of ASD [7][8][9][10]. Additionally, whether the PEA concentration profile can be used as a biomarker for ASD remains to be tested, and future longitudinal studies will have to investigate its clinical utility in monitoring response to treatment. Moreover, as the available evidence does not allow excluding a placebo effect [38], further clinical trials in larger samples are needed to fully explore the efficacy and tolerability of PEA supplementation in ASD. Finally, even though the systematic review followed the PRISMA statement, no review protocol was registered.

# 3. Conclusions

PEA may be useful in improving language difficulties and stereotypic behavior as well as in controlling hyperactivity and irritability which co-occur frequently in ASD. Notably, no serious adverse effects were observed with the

administration of the compound in all human studies reviewed here, making PEA supplementation a potentially valid and reasonably safe therapeutic intervention in ASD.

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