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HOT TOPIC

Roles of Prostaglandins and Cyclooxygenases in Autism Spectrum Disorder: A Comprehensive Review

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Abstract

Purpose of Review Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder with multifaceted etiologies. Emerging evidence implicates dysregulation of prostaglandins and cyclooxygenase (COX) enzymes in ASD pathophysiology. This review aims to explore key mechanisms through which prostaglandins and COX enzymes may influence ASD.

Recent Findings Recent research highlights significant roles for prostaglandins and COX enzymes in modulating Wnt (Wingless and Int-1) signalling pathways, which are known autism susceptibility pathways, as well as in regulating dendritic arborisation and cerebellar function. Polymorphisms in COX genes have also been linked to ASD, indicating a genetic component to this dysregulation. Furthermore, prostaglandins and COX enzymes show potential as biomarkers for ASD.

Summary The accumulated evidence underscores the involvement of prostaglandins and COX enzymes in ASD pathophysiology. This insight offers a deeper understanding of the disorder and may pave the way for more effective diagnostic and treatment strategies.

Keywords Autism spectrum disorder (ASD) · Prostaglandins · Cyclooxygenases (COX) · Neurodevelopment · Neuroinflammation · COX polymorphisms · Wnt pathway

Introduction

Autism Spectrum Disorder (ASD) represents a complex neurodevelopmental condition characterised by persistent deficits in social communication and interaction, as well as restricted and repetitive patterns of behaviours, interests, or activities [1]. The prevalence of ASD has been increasing, with recent estimates suggesting that approximately 1 in 36 children in the United States are affected [2]. The multifaceted nature of ASD's aetiology, encompassing genetic, environmental, neuroinflammation and immunological factors, presents significant challenges in unravelling its underlying mechanisms. Despite significant advancements in understanding its aetiology and pathophysiology, the precise mechanisms underlying ASD remain elusive [3, 4].

Emerging evidence highlights several major pathways implicated in ASD, each intricately linked to neuroinflammation. Dysregulation in transcription and translation processes involving genes such as methyl-CpG binding protein 2 (*MECP2*) and T-box brain transcription factor 1 (*TBR1*), plays a significant role in altering gene expression crucial for neurodevelopment and is associated with microglial activation and cytokine production in ASD [5, 6]. Furthermore,

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disruptions in signal transduction pathways, such as the mammalian target of rapamycin (mTOR) and Wnt (portmanteau formed by combining the names Wingless and Int-1) signalling, affect neuronal development and synaptic plasticity while simultaneously amplifying neuroinflammatory cascades [7, 8]. Similarly, the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB pathway), a key regulator of immune and inflammatory responses, is frequently upregulated in ASD, promoting the release of proinflammatory cytokines such as TNF-α and IL-6, which impair neuronal development and connectivity [9]. Furthermore, epigenetic modifications, such as DNA methylation changes in immune-related genes like *MECP2* and *CHD8*, further link neuroinflammation to ASD's pathogenesis by modulating the expression of inflammatory mediators [10, 11]. This persistent neuroinflammatory state disrupts normal brain development and serves as a crucial link to the involvement of prostaglandins, which act as central mediators of inflammation.

Prostaglandins are bioactive lipid compounds derived from arachidonic acid through the catalytic action of cyclooxygenase (COX) enzymes, specifically cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). These enzymes play crucial roles in various physiological processes, including the modulation of inflammation and immune responses. COX-1 is constitutively expressed and is involved in maintaining homeostatic functions such as gastric mucosal protection and platelet aggregation, whereas COX-2 is inducible and primarily associated with inflammatory responses [12]. In the brain, prostaglandins and COX enzymes are implicated in the regulation of hippocampus cell proliferation, neurogenesis, synaptic plasticity and the maintenance of the blood-brain barrier [13–15]. Prostaglandin E2 (PGE2), in particular, has been shown to modulate neuronal activity and synaptic function. PGE2 exerts its effects through four distinct G-protein-coupled receptors (EP1-EP4), which are differentially expressed in various brain regions and are involved in regulating processes such as neurotransmitter release, synaptic plasticity, and neuroinflammation [16, 17]. Given their involvement in brain development and function, aberrant prostaglandin signalling has garnered increasing attention in the context of neurodevelopmental disorders such as ASD [18]. Dysregulation of Prostaglandin and COX signalling can impact these critical processes, potentially contributing to the cognitive and behavioural challenges observed in people with a diagnosis of ASD.

The potential involvement of prostaglandins and COX in the pathogenesis of ASD is supported by evidence of chronic neuroinflammation observed in individuals with ASD [19]. Elevated levels of PGE2 have been reported in the blood of individuals with ASD, suggesting a role in the disorder's profile [20–22]. Additionally, increased expression of COX-2 has been observed in the blood of individuals with ASD [23]. This chronic inflammatory state may disrupt normal neuronal development and synaptic function, contributing to the pathophysiology of ASD. Furthermore, animal models have shown that COX-2 deficiency leads to behavioural deficits analogous to those seen in ASD, providing further evidence of its role in ASD pathogenesis [24].

Understanding the roles of prostaglandins and COX in ASD could offer novel insights into the mechanisms underlying the disorder and identify potential targets for therapeutic approaches. This review aims to comprehensively examine the current evidence on the involvement of prostaglandins and COX enzymes in ASD, discussing their potential mechanisms and implications for therapy. By elucidating these roles, we hope to contribute to the growing body of knowledge that seeks to unravel the complexities of ASD and pave the way for targeted therapeutic strategies tailored to individuals with ASD.

Methods

Search Strategy

A literature search was conducted to identify and map relevant articles pertaining to prostaglandins and COX in relation to ASD. Peer-reviewed, full-text English academic articles were gathered from electronic databases, including Scopus, MEDLINE via EBSCOhost, and Google Scholar, spanning from as early as 2000 to January 2024. This timeframe ensured the inclusion of both foundational studies and recent advancements, allowing for a comprehensive review of the evolving understanding of prostaglandins and COX in relation to ASD. The search utilised the following set of keywords: [1] autism spectrum disorders or autism or ASD [2] prostaglandin or cyclooxygenase or COX-1 or COX-2 or COX-3. Additionally, references from related review articles and scientific reports were included to supplement the literature search results. Only studies involving prostaglandins or cyclooxygenases in relation to ASD patients or models were included in this review. The findings of the literature search are summarised in Fig. 1.

Inclusion and Exclusion Criteria

The inclusion criteria were established via discussion within the research team, and used to identify studies explicitly investigating prostaglandins or COX enzymes in ASD patients, as well as in vivo and in vitro models. Exclusion criteria encompassed non-English articles, studies not directly addressing prostaglandins or COX in the context of ASD, and duplicate studies to prevent redundancy.

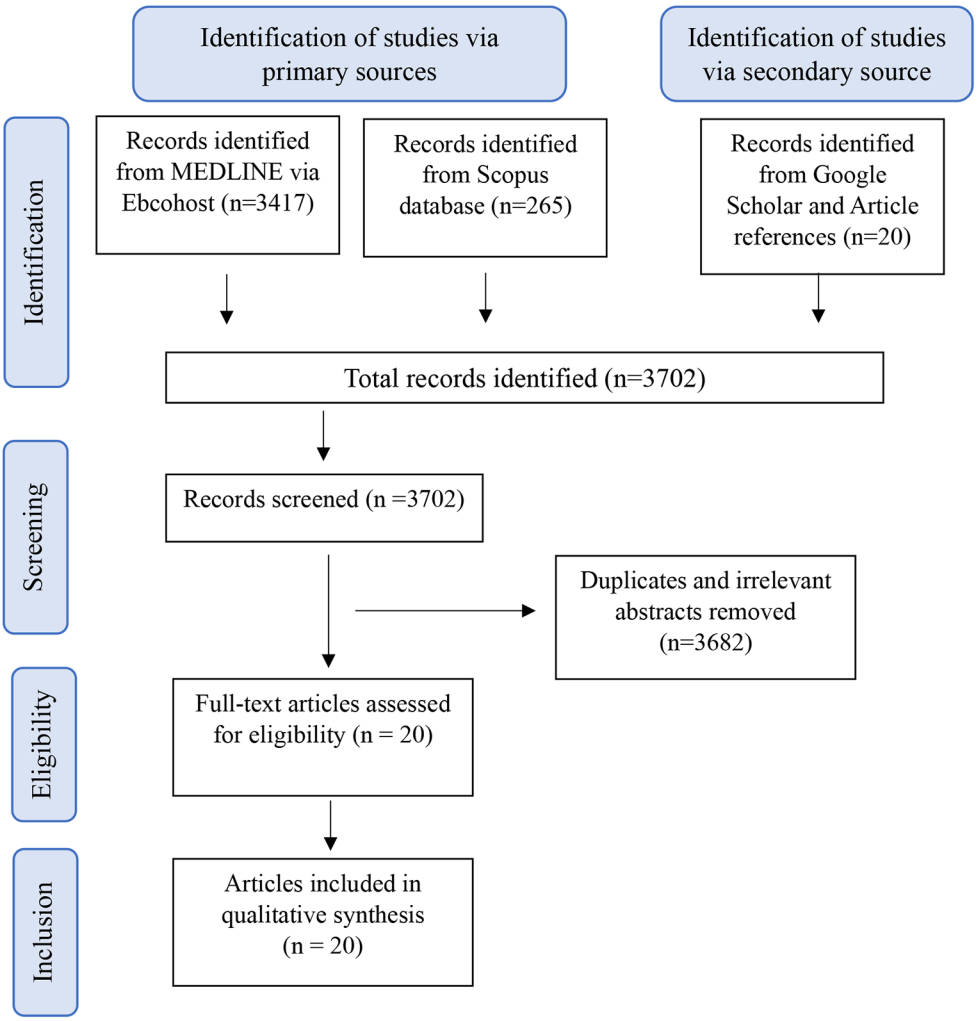

Fig. 1 Flowchart of the literature search and selection process

Data Selection and Bias Minimization

Two independent reviewers (D.A.M.K. and S.Z.A.) screened titles and abstracts for relevance to the inclusion criteria. Any disagreements were resolved through consensus or consultation with a third reviewer (W.S.W.S.). The full texts of articles deemed potentially relevant were then thoroughly and independently evaluated for eligibility. This process was designed to minimise selection bias and ensure a rigorous review.

Data Synthesis

Data from the included studies were extracted using a standardised form detailing study design, sample characteristics, intervention details, and outcomes related to prostaglandin or COX involvement in ASD. The extracted data are comprehensively presented in the Table of Evidence section, providing a clear overview of the evidence collected and facilitating comparison across studies.

Finding and Discussion

COX Polymorphisms and ASD

Polymorphisms in the COX gene have been linked to multiple neurological diseases and neurodevelopmental conditions, including ASD. COX enzymes are essential for the production of prostaglandins, which are significant regulators of inflammation and neuronal activity in the brain [18]. Changes in the expression or function of the COX gene could interfere with the development of the nervous system, leading to the development of ASD. COX is involved in the transformation of arachidonic acid into prostaglandin H2, which serves as the precursor for prostaglandins and thromboxane [25]. There are two primary isoforms of COX, which are COX-1 and COX-2. COX-1 is consistently present and plays a role in generating prostaglandins, while COX-2 is a version that can be activated in response to certain stimuli [26, 27]. In addition, the COX-2 enzyme could also facilitate the production of PGE2, which stimulates cell

growth, prevents cell death, promotes the formation of new blood vessels, and has a role in the development of cancer and inflammation [28].

In Rett syndrome, a neurodevelopmental disorder once classified under ASD, the pattern of COX-2 immunoreactivity in the cortex is disrupted, resulting in a decrease in the number of COX-2-positive neurons distributed randomly in the brain [29]. Unlike the typical increase in COX-2 associated with inflammatory processes, Rett syndrome is characterised by a decline in COX-2-positive neurons across the cortex, which is associated with abnormal early dendritic development and organisation [29]. Such a reduction is also found in conditions like Down syndrome [30], where similar dendritic anomalies are observed, suggesting a unique, non-inflammatory role for COX-2 in neurodevelopmental disorders. Furthermore, COX-2 may have a significant impact on long-term potentiation, a well-established mechanism of synaptic plasticity and subsequent cognitive processes such as learning and memory [31]. A previous study using a rat model involved the targeted destruction of basal forebrain cholinergic neurons during the first week after birth. This intervention resulted in reduced levels of hippocampal COX-2 in adulthood, accompanied by impaired social memory. These findings are particularly pertinent to autism spectrum disorders (ASDs), as impaired social memory is a core deficiency often observed in individuals with ASDs [32]. Furthermore, it has been postulated that certain types of ASDs may be associated with an imbalanced or atypical immunological response. Given that cytokines and other substances produced during immunological activation have broad impacts on neural pathways and can modify behaviours like mood and sleep, it is plausible that COX-2 has a role in these atypical immune processes in ASD [33].

Genetic studies support the association between COX-2 polymorphisms and ASD. A case-control study demonstrated the possible association of COX-2 rs2745557 polymorphism with increased risk of ASD among Kazakh children [34]. Based on PCR-RLFP analysis, the A allele was found to be associated with an increased risk of developing ASD (OR = 1.57, 95% CI = 0.44–5.61, $p = 0.49$). Additionally, there was an increased possibility of developing ASD in individuals with the AA genotype compared to those with either GG or GA genotypes (OR = 1.52, 95% CI = 0.13–18.03, $p = 0.74$) and for AA + GA genotypes vs. the GG genotype (OR = 1.62, 95% CI = 0.35–7.45, $p = 0.53$). However, this study did not find any statistically significant difference due to the small sample size, which consisted of 27 autistic children (AC) and 23 healthy siblings (controls).

Moreover, in the Korean population, rs2745557 polymorphism and GAAA haplotype (combination of four polymorphisms rs4648308 + rs5275 + rs2745557 + rs689466) were significantly associated with ASD [35]. This study examined the differences in social interaction, communication, repetitive behaviour, and restricted interest across different genotypes of rs2745557 using the ADOS and ADI-R assessments. The results demonstrated a substantial preference for the A allele in individuals with ASD. Subjects with the GG genotype experience significantly more severe overactivity/agitation on the ADOS compared to those with the AG genotype. Additionally, subjects with the AG genotype have significantly higher qualitative abnormalities in communication in nonverbal subjects on the ADI-R compared to those with the GG genotype (t = 4.00, $p < 0.001$ and t = 6.51, $p < 0.001$, respectively).

Studies have also shown that the amount of COX-2 in the hippocampus is linked to neuronal activity and synaptic plasticity [36, 37]. In addition, the COX-2 enzyme is known to be activated during seizures and has a role in altering the synaptic connections associated with the development of epilepsy [38, 39]. Given that COX-2 is an enzyme that can be activated, the genetic variation of PTGS2 (prostaglandin-endoperoxide synthase 2) impacts the production of inflammatory prostaglandin, which in turn may affect an individual's risk of developing ASDs. Taken together, the evidence suggests that COX-2 polymorphisms may play a significant role in the development of ASD. Disruptions in COX-2 expression or function, as seen in animal models, can lead to impaired cognitive processes and social memory deficiencies commonly observed in individuals with ASDs. Genetic studies, though limited by sample size, further indicate that specific COX-2 polymorphisms, such as rs2745557, may increase the risk of ASD, particularly in certain populations. While the exact mechanisms remain to be fully elucidated, the association between COX-2 polymorphisms and ASD provides a compelling avenue for further research. Future studies with larger sample sizes and diverse populations are essential to confirm these findings and explore potential therapeutic targets for ASD based on COX-2 modulation.

COX/PGE2 Signalling Pathway and ASD

COX and PGE2 are found to interact with other signalling pathways implicated in ASD. The Wnt signalling pathway, in particular, is interrelated with COX/PGE2 and models of autism. This connection is crucial for understanding ASD, as Wnt controls several crucial neural processes, including dendritic development, synaptic function, and neuronal plasticity [40]. The reported mechanism involves the interaction of the COX/PGE2 pathway with the Wnt pathway through Protein Kinase A (PKA) and Phosphatidylinositol 3-Kinase (PI-3 K), both of which are essential for neuronal development and synapse formation which are associated with ASD [41].

In a study, COX-1 and COX-2 knockout mice (COX-$1^{-/-}$ and COX-$2^{-/-}$) were used as a model, and the offspring brains were isolated at embryonic days 16 and embryonic days 19, followed by microarray analysis. Based on whole-genome microarray analysis, the majority of genes associated with ASD were downregulated, and eight of the genes were associated with canonical and non-canonical Wnt signalling pathways (integral pathways for neural development). These findings were supported by the dysregulation of phosphorylation of β-catenin at Serine-552 (S552), at COX-$2^{-/-}$ embryonic days 16 and embryonic days 19 model. These data indicate that β-catenin, a key regulator of the Wnt signalling pathway, induced alterations in COX-$2^{-/-}$ at embryonic days 16 and embryonic days 19 through the PGE2/PKA-dependent mechanism [42]. The study confirms the crosstalk between COX-PGE2 and Wnt signalling pathways in the brain, both considered as autism susceptibility pathways. Wnt signalling normally induces the expression of various regulatory pathways involved in neural cell fate specification, cell proliferation, migration, axon guidance, and synapse formation [40, 43]. Thus, based on COX knockout mice (COX$^{-/-}$) models, this pathway was affected, potentially causing disturbances in neuronal migration, axon guidance, and neural connectivity in the brain. Consequently, this could result in the development of ASD.

In addition, another study using COX-2 knockout mice demonstrated the correlation between abnormal COX-2/PGE2 signalling and autism-related behaviours in males and females at juvenile (4–6 weeks) or adult (8–11 weeks) stages [24]. Male COX-$2^{-/-}$ mice exhibited prominent autism-related behaviours in most behavioural tests. During the open field test, COX-$2^{-/-}$ mice exhibited increased locomotion compared to control mice, suggesting heightened levels of hyperactivity. Additionally, adult male COX-$2^{-/-}$ mice spent less time in the centre of the field, indicating increased anxiety-related behaviours. In addition, the COX-$2^{-/-}$ mice exhibited a higher frequency of marble burying, particularly among males, indicating elevated levels of anxiousness and repetitive behaviours. Adolescent male COX-$2^{-/-}$ mice showed a higher frequency of falls in the inverted screen test, indicating the presence of motor impairments. These studies showed that male and female mice with a deficiency in the COX-2 enzyme are associated with autism. Furthermore, male COX-$2^{-/-}$ mice demonstrated increased expression *Wnt2* gene. Wnt2 is an active signalling molecule of the Wnt pathway, increased levels of Wnt2 may have a role in altered sociability recorded in this study and affect the interplay between the COX-2/PGE2 and Wnt signalling pathways [24].

Another evidence suggests a potential link between the Wnt signalling pathway, prostaglandin synthesis, and ASD pathogenesis. Treatment with PGE2 on mouse neuroectodermal (NE-4 C) stem cells, which serves as a model to study neural differentiation and development, upregulates the expression levels of Wnt-target genes (*Ctnnb1*, *Ptgs2*, *Ccnd1*, *Mmp9*) previously associated with ASD [44]. Furthermore, in this study, PGE2 was found to interact with Wnt through PKA and PI-3 K as mediators. This interaction of PGE2 via Wnt signalling may relate to its possible impact during prenatal neurodevelopment. In another study, it was shown that PGE2 treatment to mouse NE-4 C stem cells induces the progression of NE-4 C stem cell differentiation into neuronal-lineage cells, which suggests the promotion of neurogenesis [45]. In this study, PGE2 was also reported to regulate the Wnt-target genes (*Ctnnb1*, *Ptgs2*, *Ccnd1*, *Mmp9*, *Wnt3*, *Tcf4*), which further suggests the role of PGE2 and Wnt in ASD. Meanwhile, another study demonstrated that PGE2 elevates intracellular calcium levels and calcium spontaneous fluctuation levels in the cell soma and growth cones of differentiated neuroectodermal (NE-4 C) stem cells and affects the neurite extension length, which could potentially impact early nervous system development [46].

In summary, abnormalities in the COX-PGE2 signalling pathway are strongly implicated in the development of ASD, as evidenced by studies involving COX-1 and COX-2 knockout mice. Studies discussed above demonstrate the relation to critical neurodevelopmental processes, such as Wnt signalling, neuronal migration, and synapse formation, which are essential for proper brain function. The interaction between COX-2/PGE2 and Wnt pathways, along with the behavioural and molecular changes observed in COX-2-/- mice, underscores the importance of this signalling axis in the aetiology of ASD.

PGE2 Treatment/COX-2-Deficient Knockin mice Relation to Dendritic Arborisation

Two recent studies [47, 48] investigate the role of PGE2 signalling in cerebellar development and its potential link to ASD. These studies explore the impact of both COX-2 deficiency and perinatal PGE2 exposure on dendritic morphology and cerebellar function.

The first study highlights the importance of COX-2 signalling for normal cerebellar development [47]. COX-2 knockout mice (COX-$2^{-/-}$) exhibited abnormal dendritic branching, with increased local arborisation and decreased arborisation at distal regions compared to wild-type mice. This suggests altered synaptic connectivity near the cell body in COX-$2^{-/-}$ mice. Interestingly, the study revealed sex-dependent effects. While healthy females had thicker dendrites, COX-$2^{-/-}$ males showed the opposite trend, potentially contributing to sex differences in ASD linked to excitatory/inhibitory (E/I) imbalances. The study also

found significant sex disparities in spine density. While control males exhibited a higher density of mature spines, COX-$2^{-/-}$ mice displayed the opposite pattern, suggesting disrupted cerebellar development through altered spine morphology. Additionally, COX-$2^{-/-}$ mice displayed self-fasciculation of dendrites, potentially impacting neuronal connectivity. These findings suggest that COX-2 deficiency disrupts the actin cytoskeleton, a crucial regulator of dendritic structure and spine development. This disruption may contribute to abnormal cerebellar development and potentially influence ASD development, particularly in males.

The second study focused on the effects of perinatal PGE2 exposure on cerebellar development [48]. Offspring exposed to PGE2 exhibited increased dendritic arborisation, particularly near the soma, and a higher spine density with a bias towards mature spines. This suggests potential disruption of E/I balance within the cerebellum due to prenatal PGE2 exposure. Interestingly, PGE2 exposure also eliminated the sex difference observed in control spine maturity, suggesting a reduction in oestrous cycle-driven spine shape changes in females. This finding highlights the potential influence of PGE2 on sex hormones and brain development, impacting susceptibility to ASD. Furthermore, PGE2 exposure resulted in motor coordination deficits, particularly in males. This finding aligns with the role of sensorimotor integration in ASD and suggests that PGE2 exposure may render males less efficient in motor planning. Additionally, PGE2 exposure disrupted cerebellar-dependent behaviours differently in males and females, potentially due to sex hormone interactions. Similar to the COX-2 deficiency study, PGE2 exposure downregulated cytoskeletal protein expression (beta-actin and spinophilin). This suggests potential cytoskeletal dysfunction that might underlie the observed motor abnormalities and potentially contribute to ASD-related motor impairments.

These studies [47, 48] provide compelling evidence for the involvement of COX-2/PGE2 signalling in cerebellar development and its potential link to ASD. Both studies highlight the importance of sex as an analytical factor, as sex differences significantly influence the effects of COX-2 deficiency and PGE2 exposure. Further research is needed to explore the underlying mechanisms by which COX-2/PGE2 signalling regulates dendritic morphology and cerebellar function, particularly in the context of sex hormones and their interaction with the developing brain. Understanding these mechanisms can pave the way for the development of novel therapeutic strategies targeting the COX-2/PGE2 pathway for ASD treatment, with a focus on potential sex-specific approaches.

Prostaglandin and COX as Potential Biomarkers for ASD

Prostaglandins, particularly PGE2 and COX-2, have garnered increasing attention as potential biomarkers for ASD. Elevated levels of PGE2 have been consistently observed in several studies involving ASD patients, indicating a strong association between prostaglandin dysregulation and the pathophysiology of ASD [20–22]. Furthermore, receiver operating characteristic (ROC) curve analyses have been employed to assess the diagnostic potential of PGE2, COX-2, prostaglandin-EP2 receptors, and microsomal prostaglandin E synthase-1 (mPGES-1) in ASD. These studies have demonstrated that the mentioned biomarkers can effectively differentiate ASD patients from healthy controls with high sensitivity and specificity [20, 22, 23]. A significant correlation has also been identified between levels of PGE2, COX-2, and mPGES-1 and sensory processing dysfunction in ASD patients [22]. Furthermore, another study proves that a combination of mPGES-1 and phosphatidyl ethanolamine could distinguish the degree of sensory profile impairment in ASD patients [49].

Another subtype of prostaglandin, 8-iso-PGF2α, and prostaglandin-H2 D-isomerase was found to be significantly elevated in individuals with autism [50, 51]. Another study revealed that the levels of a subtype of prostaglandin-H2 D-isomerase, hematopoietic prostaglandin D2 synthase levels were lower in patients with ASD compared to healthy controls. Moreover, ROC analysis and predictive curves indicated that hematopoietic prostaglandin D2 synthase lacked sufficient predictive power to be considered a reliable neuroinflammatory biomarker for ASD [52].

In animal studies, findings further support the observations from human research on prostaglandins in ASD. For instance, in a mouse model of idiopathic autism prenatally exposed to the neurotoxic pesticide chlorpyrifos, a significant elevation in PGE2 levels was observed in their offspring at Postnatal Days (PND) 21 and 70, with notable increases specifically in male mice at PND 21 [53]. This pattern suggests that environmental factors can induce neuroinflammatory responses via prostaglandin pathways in susceptible genetic models, echoing findings in human studies where increased levels of prostaglandins were linked to ASD. Conversely, in a separate experiment using a valproic acid-induced model of ASD, a significant reduction in the expression of the prostaglandin EP3 receptor was observed in critical brain regions such as the prefrontal cortex, hippocampus, and cerebellum [54]. This reduction in receptor expression, contrasting with the elevated prostaglandin levels noted in the first study, suggests a complex, potentially compensatory mechanism in prostaglandin signalling within

ASD pathology. Similarly, human studies recorded lower PGE2-EP2 receptors in ASD patients, while their blood exhibited higher prostaglandin and COX-2 levels [22].

Neuroinflammation has been recognised as a contributing factor in both neurodegenerative and neurodevelopmental disorders. Prostaglandins and COX are central players in neuroinflammatory processes, and there is emerging evidence that they may serve as biomarkers for neurodegenerative diseases such as Alzheimer's [55–57]. Similarly, PGE2 and COX may be explored as early screening biomarkers for autism risk, aiding in early detection and intervention. However, further research is essential to validate these findings across larger and more diverse populations and to explore the feasibility of incorporating PGE2 measurements into routine clinical practice for the diagnosis and prognosis of ASD.

Therapeutic Potential of COX-2 Inhibitors in ASD

The involvement of prostaglandins and COX enzymes in ASD pathogenesis presents promising therapeutic avenues, particularly through COX-2 modulation, which has shown potential in addressing various neuropsychiatric disorders [38, 58]. COX-2 inhibitors, such as celecoxib, have demonstrated therapeutic effects in conditions like major depressive disorder (MDD) and schizophrenia [59]. A study suggests that inhibiting prostaglandins may play a palliative role in schizophrenia, with recent approaches incorporating anti-inflammatory agents like aspirin alongside antipsychotic medications to enhance treatment efficacy [60].

COX-2 inhibitors have been shown to directly influence the serotonergic system in the central nervous system (CNS) and indirectly modulate immune processes. For example, rofecoxib, a COX-2 selective inhibitor, increased serotonin levels in the frontal and temporoparietal cortices of rats, indicating a potential antidepressant effect [61]. These findings are further supported by a study involving celecoxib, which showed reductions in cytokine levels and improved behavioural outcomes in animal models of depression [62]. Clinical trials in humans also confirmed that celecoxib, when used adjunctively with antidepressants like fluoxetine or sertraline, significantly improved depression symptoms, with the improvement correlating with reduced proinflammatory cytokine levels, such as IL-6 [63].

In the context of ASD, COX-2 inhibitors may modulate neurodevelopment by altering the Wnt signalling pathway and dendritic arborisation, potentially restoring normal neurodevelopment. Further research is needed to validate these hypotheses and fully understand the underlying mechanisms of ASD treatment. Additionally, the relationship between COX-2 and the serotonergic system could be explored further as a potential avenue for behavioural treatments in ASD. Investigating specific modulators of PGE2 receptors (EP receptors) may also offer a more refined approach to prostaglandin signalling, optimising the interaction between COX and prostaglandins in neuronal development while minimising side effects [64].

Overall, COX-2 modulation offers a promising therapeutic strategy for neurodevelopmental disorders such as ASD. However, comprehensive studies are required to better define its efficacy and safety across these conditions.

Table of Evidence

The 20 studies identified were analysed and categorised based on their study type. Table 1 presents in vitro studies, Table 2 summarises in vivo studies, and Table 3 compiles human studies, all focused on prostaglandin and COX involvement in autism spectrum disorder.

Invitro Study

Table 1 In vitro studies on prostaglandin or COX involvement in Autism Spectrum disorder (ASD)

Study setting	Study Model	Study parameter	Findings	Conclusion	References
PGE2 (1 µM) treatment to NE-4 C cells for 24 h.	Mouse neuroectodermal (NE-4 C) stem cells.	1. Wnt-target genes (*Ctnnb1*, *Ptgs2*, *Ccnd1*, *Mmp9*). 2. Cellular characteristics.	PGE2 treatment: Modulates canonical Wnt signalling pathways via PKA and PI-3 K activation in NE-4 C stem cells. Increases the final distance from the origin, path length travelled, and the average speed of migration in Wnt-activated cells. Induce phenotype modification of Wnt-induced NE-4 C cells, corresponding to modified cell splitting behaviour. Upregulates the expression levels of Wnt-target genes (*Ctnnb1*, *Ptgs2*, *Ccnd1*, *Mmp9*) previously associated with ASD.	PGE2 and Wnt signalling interact in neuronal cells, with PKA and PI-3 K as possible mediators. This interaction may significantly impact prenatal neurodevelopment.	[44]
PGE2 (1 µM) treatment to NE-4 C cells for 24 h.	Mouse neuroectodermal (NE-4 C) stem cells.	1. Cell differentiation. 2. Expression of Wnt-regulated genes previously associated with neurodevelopmental disorders (*Ptgs2*, *Mmp9*, *Ccnd1*, *Wnt3*, *Tcf4*).	PGE2 increases the proliferation of undifferentiated NE-4 C stem cells. PGE2 promotes the progression of NE-4 C stem cell differentiation into neuronal lineage cells. In undifferentiated stem cells, PGE2 downregulates Ptgs2 expression and upregulates Mmp9 and Ccnd1 expression. In differentiating neuronal cells, PGE2 causes upregulation of Wnt3, Tcf4, and Ccnd1. The convergence of the PGE2 and the Wnt pathways is also apparent through increased expression of active β-catenin.	PGE2 affects the development of neurons and the expression of Wnt target genes.	[45]
PGE2 (0.1 µM, 1 µM, and 10 µM) treatment to NE-4 C cells for 3 and 24 h.	Mouse neuroectodermal (NE-4 C) stem cells.	1. Calcium level. 2. Spontaneous calcium fluctuation levels. 3. Neurite extension length.	PGE2 elevates intracellular calcium levels and calcium spontaneous fluctuation levels in the cell soma and growth cones of differentiated neuroectodermal (NE-4 C) stem cells and affects the neurite extension length.	PGE2 might negatively affect intracellular calcium dynamics in differentiated neuronal cells and potentially impact early nervous system development.	[46]

Invivo Study

Table 2 In vivo studies on prostaglandin or COX involvement in Autism Spectrum disorder (ASD)

Study setting	Study Sample	Marker	Findings	Conclusion	References
Chlorpyrifos (6 mg/kg/bw) treatment on gestational days 14 to 17 by intraoral gavage on C57 strain and BTBR T+tf/J mice (mice model of idiopathic autism).	C57 strain and BTBR T+tf/J mice (mice model of idiopathic autism) pups.	1. Prostaglandin E2 brain level.	Treatment with Chlorpyrifos increased PGE2 levels in strain- and age-dependent manner, with PGE2 elevated in BTBR T+tf/J mice at Postnatal days (PND) 21 and 70. At PND 21, CPF effects were sex-dependent with the increase only associated with male mice.	In the mice model of idiopathic autism, the BTBR T+tf/J strain is highly vulnerable to environmental stressors during the gestational period and PGE2 signalling may be the mediator involved.	[53]
Gene analysis on COX-1 and COX-2 knockout mice (COX-$1^{-/-}$ and COX-$2^{-/-}$) offspring during embryonic days 16 and 19.	COX-1 and COX-2 knockout mice offspring.	1. Genotyping analysis. 2. Microarray analysis. 3. Gene Ontology: Biological Process (GO: BP). 4. Kyoto Encyclopedia of Genes and Genomes (KEGG).	Both COX-/- models revealed gene networks that are associated with dendrite and synaptic transmission functions. Genes related to Wnt pathways which are implicated in ASD are differentially expressed (*Wnt1*, *Wnt2*, *GSK3β*, *Ctnnb1* (β-catenin), *APC*, *TCF* (isoform), *Prickle1*, *Prickle2*, and *PLC* (isoform) in both models at 2 embryonic days 16. The level of PKA-phosphorylated β-catenin (S552), a major activator of the Wnt pathway was increased in the COX-2 embryonic days 16 model.	The COX-PGE2 pathway plays a crucial role in prenatal brain development due to the dysregulation of many important biological pathways and ASD-associated genes in the COX-/- mice. COX models show interactions with pathways strongly implicated in ASD, such as lipid and synaptic pathways and the Wnt pathway during early brain development.	[42]
16,16-dimethyl prostaglandin E2 (0.2 mg/kg) subcutaneous injection on embryonic day 11.	C57BL/6 mice offspring at embryonic day 16 (E16), embryonic day 19 (E19) and postnatal day 8 (P8).	1. Wnt-target genes (*Mmp7*, *Wnt2*, and *Wnt3a*). 2. Genes regulator (PKA-activated phospho-β-catenin-Ser-552 and nonphospho (active) β-catenin (Ser33/37/Thr41).	Wnt-target genes expression: *Mmp7* upregulated at E16 and downregulated at E19 and P8. *Wnt2* is downregulated at E16 and upregulated in E19 and P8. *Wnt3a* upregulated at E16, E19 and P8. Genes regulator expression: Upregulation at E16, downregulation at P8 of phospho-β-catenin (Ser552). Downregulation of non-phosphor β-catenin at P8.	Prenatal exposure to PGE2 affects the Wnt-target genes and genes regulator during critical periods of the developing brain (embryonic day 16, 19, and early postnatal day 8).	[65]
Behavioural and genotyping test.	Male and female COX-2 knock-out mice (COX-$2^{-/-}$). COX-$2^{-/-}$ Mice differentiated into Young mice (4–6 weeks) or adult (8–11 weeks) ages.	1. Open field test. 2. Marble burying test. 3. Inverted screen test. 4. Three-chamber sociability test. 5. Genotyping.	Autism-related behaviours were prominent in male COX-$2^{-/-}$ mice for most behavioural tests. 1. Open field test: COX-$2^{-/-}$ mice travelled more than controls indicating elevated hyperactivity and adult males (COX-$2^{-/-}$ mice spent less time in the centre, indicating anxiety-linked behaviours. 2. Marble burying test: COX-$2^{-/-}$ mice buried more marbles, with males burying more than females, suggesting increased anxiety and repetitive behaviours. 3. Inverted screen test: Young male (COX-$2^{-/-}$ mice fell more frequently indicating motor deficits. Three-chamber sociability test: Adult female COX-$2^{-/-}$ mice spent less time in the novel mouse chamber indicating of social abnormalities. 5. Genotyping: Male COX-$2^{-/-}$ mice showed altered expression of several autism-linked genes: Wnt2, Glo1, Grm5 and Mmp9.	Disrupted COX-2/PGE2 signalling in the developing brain may lead to autism-related behaviours, showing age-related differences and having a greater impact on males. Male COX-2 knockout mice displayed increased hyperactivity, anxiety, repetitive behaviours, motor deficits, and social abnormalities. COX-2 knockout mice could serve as a reliable model system for studying specific types of autism.	[24]

Table 2 (continued)

Study setting	Study Sample	Marker	Findings	Conclusion	References
Sex-dependent differences in dendritic and dendritic spine morphology in cerebellum neurons at postnatal day 25.	COX-2 knockout mice (COX-$2^{-/-}$) offsprings.	1. Genotyping. 2. Golgi-COX staining method.	COX-$2^{-/-}$ mice have increased dendritic arborisation closer to the cell soma and increased dendritic looping. Sex-dependent effect of the COX-$2^{-/-}$ on dendritic thickness, dendritic spine density, dendritic spine morphology, and the expression of β-actin and the actin-binding protein Spinophilin.	Changes in COX-2/PGE2 signalling lead to impaired morphology of dendrites and dendritic spines in a sex-dependent manner and may contribute to the pathology of the cerebellum seen in individuals with ASD.	[47]
16,16-dimethyl prostaglandin E2 (0.25 µg/g) subcutaneous injection on gestational day 11.	C57BL/6 mice offspring.	1. Cerebellar cell density. 2. Dendritic arborisation. 3. Cytoskeletal protein β-actin expression. 4. Motor behaviour study.	Decreased cerebellar cell density at gestational day 11 (in males and females) and at gestational day 16 (in females only. At postnatal day 30, there is an increase in dendritic arborisation and a decrease in the expression level of the cytoskeletal protein β -actin and N-Cadherin. Motor function test: 1. Adhesive sticker test PGE2-male specific increase in swipes per second, demonstrating reduced motor coordination in these mice. 2. Grid walking test Sex-dependent effect of PGE2 on motor coordination in the grid walking test. 3. Cylinder test Reduced number of steps taken for male mice but no gender differences for forelimb touches and rear number.	Maternal exposure to PGE2 causes disruptions in dendritic cells postnatally in male and female offspring, which correspond to abnormal expression levels of β-actin, spinophilin, and N-cadherin. PGE2-exposed male offspring exhibited abnormal cerebellar-related motor function.	[48]
Pregnant mice were injected with valproic acid (VPA) 500 mg/kg intraperitoneally at 12.5 d gestation. The offspring were tested at the age of 5–6 weeks old for their social interaction behaviour.	Mice.	1. Prostaglandin EP3 receptor mRNA expression. 2. Duration of sniffing behaviour.	Compared to the naive, mice born to dams treated with VPA demonstrated a significantly shorter duration of sniffing behaviour (model of social interaction). The expression of prostaglandin EP3 (EP3) receptor mRNA was significantly lower in the prefrontal cortical, hippocampal and cerebellar areas of the mice born to VPA-treated dams.	This study provides evidence of the role of prostaglandin as an essential part of neuroinflammation in the pathology of ASD.	[54]

Human study

Table 3 Human studies on prostaglandin or COX involvement in Autism Spectrum disorder (ASD)

Study setting	Study Sample	Marker	Findings	Conclusion	References
Blood plasma measurement.	151 Korean family trios.	1. Genetic analysis. 2. ADOS and ADI-R diagnostic algorithms.	An allele of rs2745557 (associated with COX-2 encoding) is preferentially transmitted in ASD. GAAA haplotype (associated with COX-2 encoding) is associated with ASD. Genotypes of rs2745557 in relation to specific symptoms: 1. qualitative abnormalities in communication in nonverbal subjects are higher for subjects with the AG than the GG genotype. 2. Overactivity/agitation is higher for GG than AG.	rs2745557 preferentially transmitted in ASD and may be associated with the symptom phenotypes of ASD, including overactivity/agitation and qualitative abnormality in communication in nonverbal subjects.	[35]
Blood plasma measurement.	20 male autistic patients. 20 male healthy control participants. Age: 4–12 years old.	Plasma level: 1. Prostaglandin E2 (PGE2). 2. Cysteinyl leukotriene. 3. 8 isoprostane.	PGE2, leukotrienes and isoprostanes are elevated in autistics compared to controls. Receiver Operating Characteristic (ROC) curve analysis shows satisfactory values of area under the curve (AUC), which could reflect the high degree of specificity and sensitivity of the altered PGE2, leukotrienes and isoprostanes as predictive biomarkers in autistic patients from Saudi Arabia.	PGE2, leukotrienes and isoprostanes as potential predictive biomarkers for ASD.	[20]
Blood plasma measurement.	121 ASD patients and 110 healthy controls. Age: 3–17 years old.	Plasma levels: 1. Prostaglandin E2 (PGE2). 2. n-3 docosahexaenoic acid (DHA). 3. n-6 arachidonic acid (AA). Composition of n-3 polyunsaturated fatty acids (PUFA) in red blood cell membrane phospholipids.	Higher plasma levels of prostaglandin E2 (PGE2) in a subset of the ASD patients. Lower levels of AA and DHA in ASD patients. The percentage of PUFA was lower in ASD patients.	Abnormal lipid metabolism is linked to autism.	[21]
Blood plasma measurement.	Set 1 involves 35 autistic and 38 healthy control participants. Set 2, 29 autistic and 16 healthy control participants.	Set 1 biomarker: Phosphatidylethanolamine, phosphatidylserine, phosphatidylcholine, mitogen-activated protein kinase kinase 1(MAP2K1), interleukin 10, interleukin 12, nuclear factor kappa B (NF-κB). Set 2 biomarker: Prostaglandin E2, prostaglandin E2 receptor 2 (PGE2-EP2), membrane-bound prostaglandin E synthase 1 (mPGES-1), cyclooxygenase 2 (COX-2), cytosolic phospholipase A2 (cPLA2). Experimental method: 1. Library identification 2. Behavioral assessment (questionnaire).	Autistic and healthy control subjects can be effectively distinguished using two sets of biomarkers. Set 2 biomarker was shown to be able to separate severely impaired sensory profiles of ASD patients from those with mild or moderate impairment, which was apparent by visual inspection of Principle component analysis (PCA) and Multi-dimensional scaling (MDS) plots. Set 1 biomarkers were not able to differentiate sensory profile groups among the ASD patients studied. A combination of membrane-bound prostaglandin E synthase 1, mPGES-1, and phosphatidyl ethanolamine is the best predictor of the degree of sensory profile impairment. Library identification resulted in 100% correct assignments of both autistic and control participants based on either set 1.	The two selected biomarker sets effectively differentiated autistic individuals from healthy controls, demonstrating their potential to predict autism severity accurately. These biomarkers were successful in correctly classifying the study population as either control or autistic, as well as in categorising autistic patients according to the degree of sensory profile impairment.	[49]

Table 3 (continued)

Study setting	Study Sample	Marker	Findings	Conclusion	References
Urine sample.	8 ASD subjects and 8 age- and gender-matched healthy controls. Age: 5 to 15 years old.	1. Protein detection through mass spectrometry. 2. Ingenuity pathway analysis: (IPA).	Prostaglandin-H2 D-isomerase, alpha 1-acid glycoprotein, kininogen-1 isoform 2, leucine-rich alpha-2-glycoprotein 1 and immunoglobulin fragment Fab New lambda light chain has been detected to be increased in ASD subjects compared to controls. IPA analysis recorded molecules that are associated with signalling pathways related to the inflammation, which are chemokine CX3C ligand, trefoil fector2, inducible T-cell costimulator ligand, kallikrein-related peptidase 3 and plasminogen.	This study identifies particular proteins of interest in individuals with ASD compared to control subjects.	[51]
Blood plasma measurement.	24 autistic patients. 24 healthy controls.	1. 8-Iso-Prostaglanding F2 α (8-iso-PGF2α). 2. Paraoxonase 1.	8-iso-PGF2α levels are significantly higher in autistic individuals. No correlation was found between 8-iso-PGF2α and Paraoxonase 1. 8-iso-PGF2α and Paraoxonase 1 do not correlate with clinical or neuroimaging data.	8-iso-PGF2α, which is non-COX mediated PUFA oxidation is increased in ASD subjects.	[50]
Blood plasma measurement.	47 male patients with ASD. 46 healthy controls.	1. Plasma level of prostaglandin E2, COX-2, microsomal. prostaglandin E synthase-1 (mPGES-1). 2. Expression of prostaglandin PGE2 EP2 receptors and nuclear kappa B (NF-κB). 2. Receiver operating characteristic analysis.	Significantly higher levels of PGE2, COX-2, mPGES-1, and NF-κB in ASD patients. Significantly lower PGE2-EP2 receptors in ASD patients. A significant correlation was recorded for PGE2, COX-2, and mPGES-1 with the dysfunction in sensory processing. ROC analysis together with predictiveness diagrams shows a positive area under the curve for PGE2, COX-2, mPGES-1, PGE2-EP2 receptors and NF-κB in ASD patients.	The study proves the role of the PGE2 pathway and neuroinflammation in ASD. PGE2, COX-2 and mPGES-1 are potential biomarkers of autism severity.	[22]
Genotyping study.	27 children with ASD (8.63 ± 6.72 years) 23 healthy individuals (10.26 ± 7.33 years).	1. The rs2745557 genotype study by polymerase chain reaction-restriction fragment length polymorphism.	An allele was associated with an increased risk of ASD. Increased risk of ASD was found for the AA genotype vs. the combined GG + GA genotypes and AA + GA genotypes vs. the GG genotype. However, the associations identified were not significant due to the small number of study groups.	The rs2745557 polymorphism of the COX-2 gene could be explored more for possible contribution to the genetic predisposition to ASD.	[34]
Blood plasma measurement.	38 ASD children and 32 age-matched healthy controls.	1. Analysis of TGFβ2, Heat shock protein 70 (HSP70), and hematopoietic prostaglandin D2 synthase (H-PGDS). 2. ROC analysis. 3. Correlation to sensory deficit.	Higher HSP70, TGFβ2 and lower H-PGDS in ASD subjects compared to controls. No differences were recorded among ASD subjects for each biomarker. ROC analysis and predictiveness curves showed that HSP70 or H-PGDS could not be used as a predictive neuroinflammatory biomarker for ASD. Combining TGF-β2and HSP70 in one ROC curve increases the AUC value and might be used as predictors of variation between the ASD and neurotypical control groups. Predictiveness curves show all biomarkers have insufficient predictive power.	The study shows the potential of TGF-β2, HSP70, and H-PGDS as diagnostic biomarkers for ASD but not among subgroups of ASD exhibiting different stages of sensory disabilities.	[52]
Blood plasma measurement.	40 male autistic patients (2–12 years old). 40 male healthy control participants (2–13 years old).	Cyclo-oxygenase-2, prostaglandin-EP2 receptors α-synuclein value and AUC value.	Higher level of COX-2 and prostaglandin-EP2 receptors in autistic patients. No significant difference was recorded for the α-synuclein value. Prostaglandin -EP2 recorded a satisfactory AUC of (0.875), COX-2 recorded a fair value (0.776) and a poor value for α-synuclein (0.609). The PGE2-EP2 predictive curve showed good value. An increase in AUC of 0.917 was recorded when α-synuclein was combined with PGE2-EP2.	COX-2 and prostaglandin-EP2 receptors show higher specificity and sensitivity, as shown by ROC curve analysis, which shows potential as predictive biomarkers in autistic patients.	[23]

Conclusion

The collective evidence supports the hypothesis that prostaglandins and COX enzymes play a significant role in the pathogenesis of ASD, particularly when considering findings from in vitro and in vivo studies. Dysregulation of these biochemical compounds is associated with ASD symptoms. Prostaglandins and COX enzymes modulate Wnt signalling pathways and regulate dendritic arborisation and cerebellar function, which are critical to neurodevelopment. Additionally, polymorphisms in COX genes have been linked to ASD, suggesting a genetic component. Elevated prostaglandin levels, particularly PGE2 and COX-2, show promise as biomarkers for ASD, potentially aiding in early diagnosis and prognosis.

Limitations and Future Directions

Despite these advances, specific mechanisms by which prostaglandins affect complex human neurodevelopment and pathology in ASD remain unclear, with current understanding primarily derived from animal and in vitro models. This gap highlights the need for further research into the direct effects of prostaglandins/COX in human subjects. Future studies should focus on translating these preclinical findings into human models to clarify the causal pathways, potentially employing techniques such as advanced neuroimaging modalities, human-derived pluripotent stem cell models, longitudinal clinical cohort studies, and integrative multi-omics analyses.

In summary, enhancing our understanding of prostaglandin and COX enzyme dysregulation could lead to a deeper comprehension of ASD pathophysiology and pave the way for more effective diagnostic and therapeutic strategies, ultimately improving the quality of life for individuals with ASD.

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