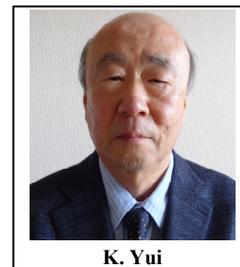


Eicosanoids Derived From Arachidonic Acid and Their Family Prostaglandins and Cyclooxygenase in Psychiatric Disorders

Kunio Yui^{1,*}, George Imataka², Hiroyuki Nakamura³, Naoki Ohara⁴ and Yukiko Naito⁵

¹Research Institute of Pervasive Developmental Disorders, Ashiya University Graduate School of Education, Rokurokusocho 13-22, Ashiya 659-8511, Hyogo, Japan; ²Department of Pediatrics, Dokkyo Medical University School of Medicine, 880 Kitakobayashi, Mibu, 321-0293, Tochigi, Japan; ³Laboratory of Chemical Pharmacology, Graduate School of Pharmaceutical Sciences, Chiba University, Chiba 260-8675, Japan; ⁴School of Pharmacy, Kinjo Gakuin University, Nagoya, 463-8521, Japan; ⁵Department of Genomic Medicine, National Cerebral and Cardiovascular Center, Osaka 565-8565, Japan



Abstract: Arachidonic acid (AA)-derived lipid mediators are called eicosanoids. Eicosanoids have emerged as key regulators of a wide variety of physiological responses and pathological processes, and control important cellular processes. AA can be converted into biologically active compounds by metabolism by cyclooxygenases (COX). Beneficial effect of COX-2 inhibitor celecoxib add-on therapy has been reported in early stage of schizophrenia. Moreover, add-on treatment of celecoxib attenuated refractory depression and bipolar depression. Further, the COX/prostaglandin E pathway play an important role in synaptic plasticity and may be included in pathophysiology in autism spectrum disorders (ASD). In this regard, plasma transferrin, which is an iron mediator related to eicosanoid signaling, may be related to social impairment of ASD. COX-2 is typically induced by inflammatory stimuli in the majority of tissues, and the only isoform responsible for propagating the inflammatory response. Thus, COX-2 inhibitors considered as the best target for Alzheimer's disease.

Keywords: Alzheimer's disease, arachidonic acid, autism spectrum disorder, cyclooxygenases-1 inhibitors, cyclooxygenases-2 inhibitors, depression, eicosanoids, schizophrenia.

1. INTRODUCTION

Arachidonic acid (AA) is an abundant polyunsaturated fatty acid of the membrane phospholipids, where it is stored in the sn-2 position of phosphatidylinositol and/or phosphatidylcholine [1]. AA-derived eicosanoids belong to a complex family of lipid signaling mediators that regulate a wide variety of physiological responses and pathological processes [2], and control important cellular processes, including cell proliferation, apoptosis, metabolism and migration [3]. Eicosanoids perform numerous regulatory functions in the brain and throughout the rest of the body, in particular for the regulation of immune and inflammatory responses [4]. In addition, eicosanoids play a role in regulating mainly immunopathological processes of inflammatory responses and chronic tissue remodeling [5]. Eicosanoid biosynthesis is usually initiated by the activation of phospholipase A₂ (PLA₂) from membrane phospholipids in mammalian cells [5] (Fig. 1). There are four families of eicosanoids—the prostaglandins (PG), prostacyclins (PGI), the thromboxanes (TX) and the leukotrienes (LT) [3]. The AA is transformed by cyclooxygenase (COX) and lipoxygenase (LO) pathways to prostaglandins, thromboxane and leukotriene [6]. AA-derived

eicosanoids from COX and lipoxygenases are important lipid mediators involved in numerous homeostatic and pathophysiological processes [7], including neurodegenerative and neuropsychiatric conditions [8-10] such as schizophrenia [11], autism spectrum disorders (ASD) [12], refractory major depression [13] and Alzheimer's disease (AD) [14, 15]. COX-2 induction and resultant prostaglandin synthesis are often implicated in neurodegeneration [16]. The brain is known to be sensitive to oxidative stress and lipid peroxidation. Lipid peroxidation has been shown to contribute to pathophysiology of many psychiatric disease including neurodegenerative disorders [17] and autism spectrum disorder (ASD) [18, 19]. In this regard, PLA₂ activation induced by oxidative stress contributes to cognitive impairment, neuronal dysfunction and disease [20] and neurodegenerative diseases [21].

Among prostaglandins, prostaglandin E (PGE) has closely related to Wnt signaling, which regulates crucial aspects of cell fate determination, cell migration, cell polarity, neural patterning and organogenesis during embryonic development [22] in prenatal development of the nervous systems [23], and a predictive biomarker in ASD [24]. Moreover, PLA₂ activity may play a crucial role in neurodegeneration and also be essential in prevention of neuropsychiatric diseases [25]. Additionally, animal studies reported that PLA₂-related signaling pathway mediated long-term potentiation induction [26].

*Address correspondence to this author at the Research Institute of Pervasive Developmental Disorders, Ashiya University Graduate School of Education, Rokurokusocho 13-22, Ashiya 659-8511, Hyogo, Japan; Tel: +81 78 791 8981; Fax: +81 797 23 1901; E-mail: yui16@bell.ocn.ne.jp

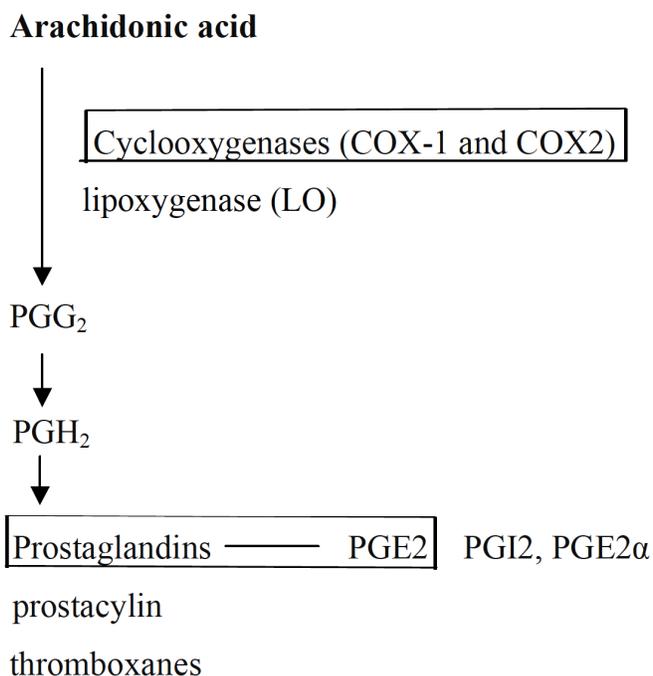


Fig. (1). Synthesis pathways for eicosanoids from arachidonic acid (Harizi *et al.*, 2008. [5]). Arachidonic acid (AA) is released from membrane phospholipids by phospholipases, especially cytosolic phospholipase A2 (cPLA2). The AA is transformed by cyclooxygenase (COX) and lipoxygenase (LO) pathways to prostaglandins, thromboxane and leukotriene. This review addressed the role of COX, and prostaglandins and PGE2.

Eicosanoids families are modulated by neuroglia such as microglia and astrocyte. Eicosanoids are produced by microglia [27]. Microglia are a type of glial cell that are the resident macrophages of the brain and spinal cord, and thus act as the first and main form of have active immune defense in the central nervous system. PGE synthesis may be related to activation of microglia [28]. Microglia are a major source of PGE2 production through the COX-2 pathway [29]. PLA2 enhances PG synthesis *via* increased availability of AA, the through the COX pathway in astrocyte [30]. Astrocytes in the hypothalamus release PGE₂ in response to cell–cell signaling initiated by neurons and glial cells in human brain [31]. PGD2 mediates microglia/astrocyte interaction [32].

The perspective provided in this review addressed the role of COX in neuropsychiatric disorders such as schizophrenia, major depression, ASD and Alzheimer disease.

2. THE ROLE OF AA-DERIVED EICOSANOIDS IN NRURONAL FUNCTION AND DISEASE

2.1. The Role of Eicosanoids in Neuronal Systems

Downstream targets of the activity of a key set of lipid-modifying enzymes, such as prostaglandin synthase, constitute a complex lipid signaling network with multiple nodes of interaction and cross-regulation. Imbalances in this network contribute to the pathogenesis of human diseases including psychiatric disorders [3].

2.2. The Relationship between Phospholipase A2 and Schizophrenia

Neurotransmitter systems of schizophrenia were modulated by the activation of PLA2 [33]. PLA2 enzyme activities and *in vivo* brain membrane breakdown specific to schizophrenia are biological processes mediated by three PLA2 isomers such as PLA2G6A, PLA2G4A and PLA2G2A [33]. These three PLA2 enzymes lie downstream of activation of neurotransmitter pathways implicated in schizophrenia, such as dopaminergic, serotonergic or glutamatergic systems [33].

A previous study on the efficacy of PLA2 in schizophrenia revealed that baseline intracellular PLA2 activity was significantly increased in 35 young drug-naïve and treated first episode patients as compared to 22 healthy controls. Baseline intracellular PLA2 activity was also associated with severity of negative symptoms and lower functioning at baseline [34]. Furthermore, baseline intracellular PLA2 activity was associated with improvement in negative symptoms and functioning within the first 12 weeks of treatment with second-generation antipsychotics [34]. Thus, intracellular PLA2 activity has been considered as a potential predictor of treatment response for different antipsychotic agents [34].

2.3. Efficacy of COX Inhibitors in Psychiatric Disorders

COX is the key enzyme that converts AA to PG play an important role in the nervous system *via* production of downstream signalling molecules such PGE [12]. COX-2/PG2 pathway play an important function in synaptic plasticity and refining of mature neuronal connections [12]. Altered COX-2 levels have been found in psychiatric disorders [12]. COX inhibitors are known to influence the immune system in a way that may redirect imbalance of this system [35] and might have additive or even synergistic neuroprotectant effect [28]. Thus, COX inhibitors have therapeutic potential for schizophrenia [36, 37].

2.3.1. Efficacy of COX-inhibitors in Schizophrenia

Increasing evidence from clinical research studies on COX-2 inhibitors points to an advantageous effect of add-on therapy to atypical antipsychotic neuroleptics in schizophrenia, especially in the early stages of the disease [38] through their effects in reducing PGE₂, type-2 cytokine and kynurenic acid production and strengthening glutamatergic neurotransmission [39]. In previous clinical study, COX-2 inhibitor such as celecoxib in addition to amisulpiride, which is atypical antipsychotic, induced a significantly better outcome in the 25 patients with schizophrenia (mean age \pm SD: 26.2 \pm 7.7 years) compared to 25 patients (mean age \pm SD: 30.9 \pm 8.1 years) treated with amisulpiride plus placebo [36]. Particularly, a significantly superior therapeutic effect was observed in negative symptoms in the celecoxib plus amisulpiride group [36]. Update, five clinical studies reported efficacy of COX-2 inhibitor such as celecoxib in schizophrenia. Table 1 summarized these double-blind randomized-placebo-controlled trials. Taking a view of these clinical studies, celecoxib has been reported to be effective add-on treatment to atypical neuroleptics such as risperidone and amisulpiride

Table 1. Summaries of findings of clinical trial of celecoxib.

Design	Treatment, Subject Characteristics	Duration	Efficacy	Interleukin	References
RCT	celecoxib + risperidone (2-6 mg/day) or placebo (n=25) Acute exacerbation	5 weeks	PANSS, significant group effect	Soluble IL-2 no significant different	Muller (n=25) <i>et al.</i> , 2004
RCT	celecoxib + risperidone (3.0 mg/day) (n=25) or placebo (n=25) out patients with chizophrenia	8 weeks	PANSS, no significant group effects	NA	Rapaport <i>et al.</i> , 2004
RCT	celecoxib (400 mg/day+risperidone (2-6 mg/day) (n=25) or placebo (n=25) Acute exacerbation	5 weeks	PANSS, significant effect on cognition	NA	Muller <i>et al.</i> , 2005
RCT	celecoxib (400mg) + risperidone (6 mg) (n=30) or placebo (n=30) Chronic	8 weeks	PANSS-positive symptoms and general psycho-psychopathology, significant effect.	NA	Akhondzadeh <i>et al.</i> , 2007
RCT	celecoxib (400 mg) + amisulporide amisulporide (200-1000mg or placebo (n=30) Chronic	8 weeks	PANSS-negative symptoms and general psycho-psychopathology, significant effect	NA	Muller <i>et al.</i> , 2010

RCT: Randomized Controlled Trial; PANSS: Positive and Negative Syndrome Scale; NA: no available.

for 5-8 weeks in patients with acute exacerbation [40, 41] or chronic schizophrenia [36, 42] (Table 1). Whereas, another double-blind placebo-controlled trial did not find improvement of celecoxib (400 mg/day for 8 weeks) add-on atypical neuroleptics such as risperidone (3.0 mg/day) or olanzapine (12.6 mg/day) in 18 outpatients with schizophrenia [43]. In this regard, a recent review article commented that results on efficacy of celecoxib in schizophrenia were very heterogeneous, ranging from negative to strong positive effects [44]. The treatment cohorts did not differ on any clinical outcome measures. Review of the data of the previous add-on therapy [36, 40-42] suggests that the psychopathology ratings for the celecoxib augmentation group and placebo group were converging with time. Celecoxib augmentation might potentiate the speed of response but not the overall magnitude of response [43]. Future studies are necessary to elucidate the relationship between doses and treatment periods of atypical neuroleptics and the augmentation effects using a large sample size.

2.3.2. Mechanisms of Action of COX-2 Inhibitors in Schizophrenia

The main mechanism of action underlying the efficacy of COX-2 inhibitors in schizophrenia is inhibiting conversion of AA into active prostanoids such as PGE₂, prostanooids D₂, prostanooids I₂ and others [45]. Increases or imbalances in cytokines may be related to produce vulnerability to schizophrenia [46]. Thus, cytokine modulation may offer the promise of tailored psychopharmacologic intervention based on individual peripheral and central neuroimmune biomarker profiles [47] (Table 2). Therapeutic effects of COX-2 inhibitors may depend on reducing PGE₂, type-2 cytokine and kynurenic acid production and strengthening glutamatergic neurotransmission [39]. Moreover, the immunological imbalance in an inflammatory state combined with increased PLA₂ production and increased COX-2 expression may be involved in the

mechanisms of action of COX-2 inhibitors [48]. The immune response in schizophrenia is confounded by factors partly disease-inherent such as disease duration, chronicity, prevailing symptoms and response to medical treatment [36]. Whereas, another study reported that celecoxib (400 mg/day) add-on treatment to risperidone (mean dose, 3.6 mg/day) or olanzapine (mean dose, 15.0 mg/day) for 8 weeks did not alter any of the cytokine parameters such as IL-6 and TNF- α in 14 patients with schizophrenia compared to 14 normal healthy controls [49]. The relationship between the long duration of disease, treatment resistance and higher IL-6 levels may be related to different immune response possibly linking place in different stages of diseases [36]. In this regard, the blunted type-1 response, which promotes the cell-mediated immune directly against intracellular pathogens, is found primarily in early stages of schizophrenia. While, in later stages of disease, an autoimmune process might additionally play a role in immune function [36]. The findings of the previous many studies shown in Table 2 suggest that schizophrenia is associated with a systemic imbalance in the plasma or serum levels of pro-inflammatory/anti-inflammatory prostaglandins in favor of former [50].

2.4. The Efficacy of COX-2 Inhibitors in Major Depression, Bipolar Depression and Refractory Major Depression

2.4.1. Summaries of the Efficacy of COX-2 Inhibitors in Major Depression

There are two review articles on the efficacy of COX-2 inhibitors or non-selective COX inhibitors. Five randomized controlled trials (four unipolar depression studies and one bipolar depression study) has reported that the add-on celecoxib treatment had a statistically significant decrease in means of the Hamilton Depression Rating Scale score at week 4 and week 6. The add-on celecoxib treatment also showed higher remission rates compared with the placebo group [51]. Thus, celecoxib can be considered as an effective

Table 2. Biomarkers of treatment with COX-2 inhibitors in schizophrenia.

Subjects Characteristics	Results of Biomarkers	
Chronic schizophrenia (n = 25) Healthy normal controls (n = 25)	Plasma levels of IL-2: significantly increased Plasma levels of IL-6: no significantly Correlated to SANS and duration of illness	Kim <i>et al.</i> 2000
Paranoid schizophrenia (n = 24) Healthy normal controls (n = 24)	Serum levels of cytokines (IL-6, IL-8 and IFN- γ): significantly increased Serum levels of IL-2, IL-4 and IFN- α : no significant changes	Kamińska <i>et al.</i> , 2001
Schizophrenia (n = 2298) Healthy controls (n = 1858) A research of computerized Literature databases PubMed and EMBASE	Periopheral levels of IL-1RA, sIL-2R and IL-6: significantly increased Periopheral levels of IL-2: significantly decreased Periopheral levels of IFN- γ , IL-4, IL-1RA, IL-2, soluble IL-2receptor and IL- β : no significant changes	Potvin <i>et al.</i> , 2008
Schizophrenia (n = 28) Celecoxib 400 mg/day vs. olanzapine	No alterations of blood TNF-alpha and IL-2 levels	Bresee <i>et al.</i> , 2006

SANS: The Scale for the Assessment of Negative Symptoms. IL-2, IL-6 and IFN- γ are known as cytokines.

add-on treatment for unipolar depressive patients [51]. While, a current review article has reported that the efficacy of COX-2 and non-selective COX inhibitors on depressive symptoms appears to be inconsistent [52]. According to this review article, 4 of a total of 6 randomized controlled trials showed a significant effect of COX-2 inhibitors [52]. In addition, in a total of 5 studies exploring the efficacy of non-selective COX inhibitor, the randomized controlled trials failed to show a significant result [52]. Among the 3 cohort studies, one showed a positive result and the other 2 showed no effect [52]. With regard to these inconsistent findings, significant methodological heterogeneity (i.e. age range, sex, presence of antidepressant use, method of depression measure, severity of depressive symptoms, duration and study design (randomized controlled trial vs. cohort) has been suggested. Further high quality research is needed to explore the effects of COX-2 inhibitors and non-selective COX inhibitors as monotherapy or add-on treatment to various antidepressants [52].

2.4.2. The Efficacy of COX-2 Inhibitors in Refractory Major Depression

It is well known that number of patients with major depression do not respond adequately to current antidepressant pharmacological treatments [53]. Recent studies suggested that inflammatory processes may contribute to pathophysiological processes, since increased levels of pro-inflammatory cytokines and PGE2 have been found in a subset of patients with major depression [53]. In this regard, add-on treatment with COX-2 inhibitors enhance the efficacy of both reboxetine and fluoxetine in treatment-resistant depression. A previous study examined the acute effects of a combined treatment with celecoxib and reboxetine and fluoxetine on noradrenaline, dopamine and 5-HT output in the medial prefrontal cortex in rats [53]. Acute effects of a combined treatment with celecoxib significantly potentiated the efficacy of reboxetine and fluoxetine on increases in cortical noradrenaline and 5-HT output [53]. Thus, the clinical utility of combined treatment with antidepressants in refractory depression may be evident [53]. A previous study

reported the case of an elderly depressed woman with acute cognitive deficit who was refractory to multiple antidepressants but only responsive to celecoxib in acute treatment and sustaining remission for a 5-year treatment course [54]. Depressed patients showed lower production of cytokine responses, indicating that their immune cells are in a refractory phase, induced by a pre-existing pro-inflammatory state [55]. Thus, a drug effect could only be shown for imipramine and celecoxib, which were beneficial in terms of re-balancing the immune function [55].

While, in another previous clinical study in 1,245 individuals (mean \pm SD age, 53 \pm 15.3 years old) who remained depressed despite two or more antidepressant treatments, treatment outcomes with anti-inflammatory drugs (e.g., cytokines) was associated with a greater likelihood of depression classified as treatment resistant depression [56]. This association was apparent in the anti-inflammatory drug group but not in those using other agents with NSAID-like mechanisms such as COX-2 inhibitors [56]. With regard to no effects of COX-2 inhibitors, the authors suggested that general medical comorbidity and painful symptoms seems to be associated with poorer outcomes [56].

2.4.3. The Efficacy of COX -2 Inhibitors in Bipolar Depression

There are few studies on clinical effects of COX-2 inhibitors in bipolar depression. A previous double-blind placebo-controlled trial examined efficacy of celecoxib (400 mg/day) for 6 weeks in 28 patient with DSM-IV bipolar depression I and II [57]. In this trial, 28 patients were included if they were experiencing a major depression or mixed episode, with a Hamilton score > 18 and if they had previously been on therapeutic and regular doses of a mood stabilizer or atypical antipsychotic for at least 1 month [57]. The 14 celecoxib treated patients (mean \pm SD age, 42.3 \pm 10.4 years old) showed significant decreased score in the Hamilton Depression Rating Scale in the first week of treatment as compared to 14 placebo-controlled patients (mean \pm SD age, 41.1 \pm 9.5 years old). The two groups did not differ significantly on depressive or manic symptoms at

any later week [57]. These findings suggest that adjunctive treatment with celecoxib may produce a rapid-onset antidepressant effect in patients with bipolar depression [57].

A previous systemic review of the literature summarized the effects of COX-2 inhibitors on bipolar depression based on articles published from 1950 to April 2008 [58] reported that celecoxib may offer antidepressant effects because inflammation is closely linked with behavioral parameters such as exercise, sleep, alcohol abuse, and smoking, as well as with medical comorbidities including coronary artery disease, obesity and insulin resistance, osteoporosis, and pain [58]. However, methodological limitations precluding definitive conclusions are heterogeneity in sample composition, cytokine assessment procedures, and treatment regimens [58].

2.5. Eicosanoids in Alzheimer's Disease

2.5.1. The Role of COX in Alzheimer's Disease

AD is a neurodegenerative disorder characterized by a progressive decline of memory and cognition. The subtlety and variability of the earliest amnesic symptoms, occurring in the absence of any other clinical signs of brain injury, suggest that something is discretely, perhaps intermittently, interrupts the function of synapses that help encode new declarative memories [59]. Although the most common form of dementia, characterized by the excessive accumulation of amyloid- β peptide leads to neurofibrillary tangles composed of aggregated hyperphosphorylated tau, several epidemiological and preclinical studies indicated the pathological role of COX based on the neuroinflammation theory. In this regard, elevated levels of several proinflammatory factors including cytokines and peroxidants in the central nervous system have been detected in patients with AD [60]. These proinflammatory factors act as potent stimuli in brain inflammation through upregulation of cytosolic PLA2 and COX-2 [60]. Moreover, the mechanisms underlying the intracellular signaling pathways may be involved in the expression of several inflammatory proteins induced by proinflammatory factors in AD [60].

In an early stage of AD pathology, when low-fibrillar A β deposits are present and only very few neurofibrillary tangles are observed in the cortical areas, COX-2 expression is increased in neurons. COX-1 is primarily expressed in microglia, and associated with fibrillar A β deposits. Thus, COX-1 and COX-2 are involved in inflammatory and regenerating pathways respectively in AD pathology [61]

2.5.2. Efficacy of COX-2 and COX-1 Inhibitors in Alzheimer's Disease

Because COX-2 is typically induced by inflammatory stimuli in the majority of tissues, it was thought to be the only isoform responsible for propagating the inflammatory response and thus, considered as the best target for anti-inflammatory drugs [62]. In this regard, deficits in spatial working memory in female but not male mice were abolished by COX-2 inhibitor celecoxib with alteration of A β peptides [63]. Another animal study found that COX-2 inhibitor NS-398 protected memory deficit in mice [64]. According to another animal study, COX-2 inhibitors such as rofecoxib (5 and 10 mg/kg, ip) or valdecoxib (5 and 10

mg/kg, ip) improved memory deficit [65]. With regard to clinical effects of COX-2 inhibitor, a 52-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients aged 50 years or older reported that at the final 52 weeks, change in Assessment Scale-Cognitive Behavior scores from baseline was not significantly different between placebo and celecoxib 200 mg treated groups (5.00 and 4.39, respectively) [66]. According to a randomized, double-blind, multicenter clinical trial of naproxen or celecoxib vs placebo (1:1:1.5 assignment ratio), which conducted between 2001 and 2004 at six U.S.-based clinics in 2528 people with age of 70 years or older, there was no significant effects of celecoxib treatment in these elder patients with AD [67]. In similar line of evidence, according to a double-blinded, multicenter trial in 692 patients with mild or moderate AD aged 50 years or older treated with 25 mg/day COX-2 inhibitor rofecoxib or placebo for 12 months, there is no significant improvement in the rofecoxib treatment group compared with placebo control group [68]. In another double-blind study to investigate whether rofecoxib could delay a diagnosis of AD in patients with mild cognitive impairment aged 65 years or older, rofecoxib 25 mg/day (n = 725) or placebo (n = 732) were treated for up to 4 years [69]. This study did not demonstrate differences between treatment groups. This study reported no consistent evidence that rofecoxib differed from placebo in post hoc analyses comparing the AD assessment scales [69]. Thus, this study did not support the hypothesis that rofecoxib would delay a diagnosis of AD [69]. In conjunction with the lack of effects observed in previous AD studies, the findings suggest that inhibition of COX-2 is not a useful therapeutic approach in AD [69]. Drawing these strands together, COX-2 inhibitors improved memory deficits in animal model of AD, however, several clinical studies did not support the hypothesis that celecoxib prevent progress of adult AD patients. Further precise clinical trial will be needed to study the clinical effects of COX-2 inhibitors.

In regard to efficacy of COX-1 inhibitors, animal studies reported preferential effects of COX-1 inhibitors, rather than COX-2 inhibitors [70, 71]. Mice with the lateral ventricle of COX-1-deficient (COX-1(-/-)) induced by injection with beta-amyloid (A β (1-42)) exhibited neurodegeneration compared to their wild-type (WT) mice, indicating that inhibition of COX-1 activity may be valid therapeutic strategy to reduce brain inflammatory response and neurodegeneration [70]. Similarly, triple transgenic AD (3 \times Tg-AD) mice treated with the COX-1 selective inhibitor SC-560 improved spatial learning and memory, and reduced amyloid deposits and tau hyperphosphorylation [71]. These findings may demonstrate that selective COX-1 inhibition reduces neuroinflammation and neuropathology, and improves cognitive function in 3 \times Tg-AD mice [71]. Thus, selective COX-1 inhibition might be a potential therapeutic approach for AD. However, there is few clinical trial with COX-1 inhibitors. Further clinical trials will be needed to demonstrate the efficacy of COX-1 inhibitors in AD.

2.5.3. Differences in Action between COX-1 and COX-2 Inhibitors in Alzheimer's Disease

The expression levels of COX-1 and COX-2 change in the different stages of AD pathology. In an early stage,

COX-2 is increased in neurons with increased neuronal COX-2 expression and with the expression of cell cycle proteins [61]. COX-2 is found in post synaptic dendrites and excitatory terminals, particularly in the cortex, hippocampus and amygdala, with both neuronal and vascular associations [62]. Moreover, COX-2 has a compartmental distribution in somatosensory cortical neurons consistent with the local neuronal synthesis of prostanoids that are involved in neurovascular coupling [72]. While, COX-1 plays anti-inflammatory role [73] and primarily expressed in microglia [61]. Thus, COX-1 and COX-2 play each role in the different stages of AD pathology [61]. Because COX-2 is typically induced by inflammatory stimuli in the majority of tissues, it was thought to be the only isoform responsible for propagating the inflammatory response and thus, considered as the best target for anti-inflammatory drugs [62].

2.6. Eicosanoids in Autism Spectrum Disorders

2.6.1. The Role of Eicosanoids in Autism Spectrum Disorders

The COX/PEG2 pathway play an important role in synaptic plasticity and also may be included in pathophysiology of ASD [12]. Accumulating evidence indicated that PGE2 signalling interacts with another crucial developmental pathway such as the Wnt (wingless-related MMTV integration site) signalling pathway [74]. The Wnt signalling also regulates neuronal connectivity by controlling axon pathfinding, axon remodelling, dendrite morphogenesis and synapse formation [75]. The canonical Wnt signaling pathway is composed of a network of proteins that modify cell communication and interaction with other cells [76]. The Wnt signaling pathway therefore may be implicated for development of ASD [76]. In most previous studies, changes in families of eicosanoids have reported alterations in antioxidant status in ASD patients [77, 78]. According to a previous study in 44 ASD children aged 3.5-12 years and 44 age-matched healthy matched-children, elevated plasma F2-isoprostane, which is significant risk for antineuronal positivity, was found in 54.5% of ASD children [77]. Families of eicosanoids such as PGE2, leukotrienes and isoprostanes have been reported to be significantly elevated levels in 20 male ASD compared to 19 age and gender-matched controls [78]. Thus, pathophysiology of ASD may be related to eicosanoid regulation [78].

2.6.2. Eicosanoids and AA-Derived Signaling Mediators in Autism Spectrum disorders: Ceruloplasmin

In most previous ASD studies, changes in blood eicosanoid families such as superoxide dismutase (SOD), transferrin (Tf) and ceruloplasmin (Cp) levels indicated alterations in antioxidant status [79-81], vulnerability to oxidative stress [82, 83], and copper dyshomeostasis [84, 85] in ASD patients. It was known that iron and copper can modulates the synthesizing and catabolism of prostaglandins [86]. Furthermore, copper [87] and iron [88] mediators are closely related to AA-derived eicosanoid signaling mediators [89]. In this regard, ceruloplasmin (Cp) is a major copper transport protein in plasma in relation to neurodegenerative conditions, including Alzheimer's disease [90]. Copper supplementation (gycinat, 2 mg/day for 8 weeks) produced a 39 % mean decrease in plasma for eicosanoid family F2 α -

isoprostanes in young adult women [91]. Superoxide dismutase (SOD), which is a biomarker of copper status that plays a role in signaling [92], play a role in controlling prostaglandin F2 alpha [93]. Further, transferrin (Tf), which carries iron throughout the systemic circulation of tissues [94], may relate to alteration of eicosanoid metabolism [95]. Tf has been reported to have association with COX-2 in liver cancer [96], and COX2 invasion *via* NF-KB signaling [97]. It is therefore suggested that plasma Tf may be related to eicosanoid signaling. In this regard, a previous 16-week double-blind, randomized placebo-controlled trial examined the role of eicosanoid families estimated the efficacy of supplementation with larger doses of ARA (240 mg/day) added to DHA (240 mg/day) in individuals with ASD (n = 7) (mean age = 14.6 \pm 5.9 years) [98]. In this study, plasma Tf levels in the 7 individuals with ASD treated with this supplementation were significantly increased compared to 6 placebo treated controls [98]. There was also a trend towards significant difference (P = 0.08) in the change in plasma SOD levels [98]. The supplementation significantly improved the Aberrant Behavior Checklist-measured social withdrawal and the Social Responsiveness Scale-measured communication. Considering that mutual relationship between SOD and Tf acts as a mediator in signaling pathways [99], these findings regarding the plasma levels of TF, as well as SOD, suggest that signal transduction was upregulated in the ARA plus DHA supplementation group. Collectively, improvement of social impairment induced by supplementation with larger doses of ARA added to DHA may be related to upregulation of signal transduction [98].

SUMMARY

AA-derived eicosanoids belong to a complex family of lipid signaling mediators that regulate a wide variety of physiological responses and pathological processes, and control important cellular processes, including cell proliferation, apoptosis, metabolism and migration. Moreover, eicosanoids perform numerous regulatory functions in the brain and throughout the rest of the body. AA can be converted into biologically active compounds by COX. The COX pathway are important lipid mediators involved in numerous homeostatic and pathophysiological processes, including neuropsychiatric conditions such as schizophrenia. Celecoxib, a selective COX-2 inhibitor, has been known to have antipsychotic effects in patients with schizophrenia. The main mechanism of action the efficacy of COX-2 inhibitors in early stage of schizophrenia is inhibiting conversion of AA into active prostanoids such as PLE2, prostanoids D2, prostanoids 12 and others. This review summarized beneficial antipsychotic effects of celecoxib add-on therapy compared to atypical antipsychotics such as risperidone or amisulporide. Celecoxib can be considered as an effective add-on treatment for refractory major depression and bipolar depression. The COX/PEG2 pathway an important role in synaptic plasticity and may be included in pathophysiology of ain ASD. In this regard, plasma Tf, which is an iron mediator related to eicosanoid signaling, may be related to social impairment of ASD.

COX-1 and COX-2 are involved in inflammatory and regenerating pathways respectively in AD pathology. COX-1 is typically induced by inflammatory stimuli in the majority

of tissues, and the only isoform responsible for propagating the inflammatory response and thus, considered as the best target for AD. However, animal model studies and a few clinical trials demonstrated efficacy of COX-2 inhibitors, further precise clinical studies on efficacy of inhibitors of COX-2 as well as COX-1 are needed to show definitive efficacy of these inhibitors

CONFLICT OF INTEREST

The authors confirm that this article had no conflict of interest.

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