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REVIEW ARTICLE

The Emerging Role of the Double-Edged Impact of Arachidonic Acid-Derived Eicosanoids in the Neuroinflammatory Background of Depression.

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Abstract: Eicosanoids are arachidonic acid (AA) derivatives belonging to a family of lipid signalling mediators that are engaged in both physiological and pathological processes in the brain. Recently, their implication in the prolonged inflammatory response has become a focus of particular interest because, in contrast to acute inflammation, chronic inflammatory processes within the central nervous system (CNS) are crucial for the development of brain pathologies including depression.

The synthesis of eicosanoids is catalysed primarily by cyclooxygenases (COX), which are involved in the production of pro-inflammatory AA metabolites, including prostaglandins and thromboxanes. Moreover, eicosanoid synthesis is catalysed by lipoxygenases (LOXs), which generate both leukotrienes and anti-inflammatory derivatives such as lipoxins. Thus, AA metabolites have double-edged pro-inflammatory and anti-inflammatory, pro-resolving properties, and an imbalance between these metabolites has been proposed as a contributor or even the basis for chronic neuroinflammatory effects.

This review focuses on important evidence regarding eicosanoid-related pathways (with special emphasis on prostaglandins and lipoxins) that has added a new layer of complexity to the idea of targeting the double-edged AA-derivative pathways for therapeutic benefits in depression. We also sought to explore future research directions that can support a pro-resolving response to control the balance between eicosanoids and thus to reduce the chronic neuroinflammation that underlies at least a portion of depressive disorders.

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1. INTRODUCTION

Arachidonic acid (AA, C20:4n, omega-6) 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 metabolites—-called eicosanoids—belong to a large family of lipid signalling mediators that modulate both physiological and pathological responses. Eicosanoids are involved in many processes, such as cell proliferation, metabolism, migration, and apoptosis, and they play a crucial role in the inflammatory response [2, 3]. In general, AA is transformed by two enzymes, cyclooxygenase (COX) and/or lipoxygenase (LOX). COX is primarily involved in the production of pro-inflammatory metabolites of AA, including prostaglandins and thromboxanes, whereas LOX generates both leukotrienes and anti-inflammatory derivatives such as lipoxins. Therefore, AA metabolites have double-edged activity, *i.e.*, they promote and initiate a pro-inflammatory response but contrastingly restore homeostasis *via* anti-inflammatory activity. In the latter context, particular significance is ascribed to their engagement in the resolution of inflammation (RoI), dysfunction of which has been postulated to be implicated in central nervous system (CNS) diseases. Therefore, it appears that a disturbed imbalance between AA metabolites in the CNS can be one of factors which lead to the development of CNS diseases, including depression.

In this review, we provide an update with some crucial points related to the role of AA derivatives (primarily prostaglandins and lipoxins) in the course of neuroinflammation and their modulation, and we believe that our work will pro-

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pose a potential new perspective particularly for drug-resistant depression, where the immune imbalance is a key factor limiting effective therapy.

2. ARACHIDONIC ACID: AN OVERVIEW

AA is supplied to the body *via* two main routes: by the direct consumption of food products that contain high AA levels or by synthesis from linoleic acid (LA; C18:2n, omega-6). LA is an essential fatty acid and is converted in animal cell cytosol to AA, docosatetraenoic acid (ADA; C22:4n, omega-6), and other fatty acids through a stepwise path comprising both desaturation and chain elongation. After the multistage elongation process and processing with the last desaturation reaction, AA may in turn undergo esterification with glycerol in phosphatidylethanolamine, phosphatidylcholine or phosphatidylinositide within the cell membrane. It is worth mentioning that anandamide can also be an endogenous source of AA, because fatty acid amide hydrolase (FAAH) can catalyse anandamide into AA and ethanolamine to eliminate the anandamide signal in the brain [4]. AA and docosahexaenoic acid (DHA), which is formed during α-linolenic acid (ALA) metabolism, are the main cerebral polyunsaturated fatty acids (PUFAs) [5]. Collectively, they comprise as much as 20% of brain dry weight, and are concentrated in the neuronal outer membrane and in the myelin sheath [6]. Interestingly, AA also accumulates in the immune cells of the brain, especially in microglia [7]. AA and DHA differ in their distribution within the brain, *e.g.*, in grey matter, the proportion of DHA in glycerophospholipids is higher than AA, whereas the situation is reversed in white matter [8]. These proportions in grey matter are observed in most mammals.

Although the role of AA in the brain has not been ascertained, AA ($C_{20}H_{32}O_2$) contains 20 carbon atoms with four *cis*-oriented double bonds (C20:4n, omega-6), which explains its facile binding with proteins and makes reaction with molecular oxygen possible, through which bioactive molecules including eicosanoids and isoprostanes are generated [9]. The four *cis* double bonds in AA are also responsible for membrane elasticity, liquidity, selective permeability, and signal transmission through cell membranes [10]. A role for free AA (non-esterified) as a regulator of neurotransmission has also been postulated. Among other activities, AA boosts glutamatergic neurotransmission, stimulates glutamate release, and suppresses its reuptake; its role as a retrograde trans-synaptic messenger in the long-term potentiation (LTP) mechanism has also been postulated [11]. Free AA can also induce respiratory burst associated with molecular oxygen reduction to superoxide *via* the activation of the NADPH oxidase complex [12]. This mechanism may also increase brain cell death, which is of key significance, considering that AA levels are low in cells because freely accumulated AA induces apoptotic processes connected with changes in membrane plasticity and oxidative stress [13]. It is also important that the beneficial and toxic effects of AA are in a "hazy" balance, and some studies have shown that apoptosis-inducing and physiological levels overlap. Importantly, these processes are induced by AA but not by its metabolites.

The prevailing recent opinion is that AA, by influencing ion-dependent channels, apoptosis, and necrosis, and by modulating neurotransmission and enzyme activities, is a very important PUFA in the brain, which fulfils an essential role in neurodevelopmental processes, but its deficiency can lead to CNS diseases, including depression. For this reason, in some cases, the World Health Organization (WHO) suggests AA supplementation in the perinatal period to eliminate neonatal morbidities, improve cognitive development [14], increase the proliferation of neural stem/progenitor cells, and stimulate newborn neuron and hippocampal neurogenesis [15]. In the context of depression and immune system activation in the brain, the regulatory effect of AA on endocrine activity of the HPA axis [16] should also be taken into consideration.

3. EICOSANOIDS AS AA DERIVATIVES

Arachidonic acid is a PUFA that acts as a second messenger. After the release of AA from the stereospecific sn-2 position of the membrane phospholipids by the enzyme cytosolic phospholipase A2 (PLA2), which is activated in response to various cellular activation signals from receptor-dependent events requiring G protein-coupled transducing proteins, such as toll-like receptor 4 (TLR4), purinergic receptors, and inflammatory stimulation (*e.g.*, tumour necrosis factor α (TNF-α)), AA is either transformed by beta-oxidation to eicosanoids and other metabolites or is incorporated into the membrane phospholipids [17, 18] (Fig. **1**).

Eicosanoids acting as local hormones and other signalling molecules regulate a wide range of cellular processes, including cell proliferation and migration, apoptosis, and metabolism. They also play a crucial role in the resolution of inflammatory processes in the brain [8, 19].

Generally, eicosanoids are formed from free AA *via* non-enzymatic or enzymatic pathways, including cyclooxygenase, lipoxygenase, cytochrome 450, and anandamide pathways. For the cyclooxygenase (COX) pathway, the two main isoforms COX-1 and COX-2, or prostaglandin G/H synthases, must be considered. These enzymes react with free AA to catalyse the formation of prostanoids, which include not only prostaglandins but also thromboxane products. Between these enzymes, COX-1 is constitutively expressed in all tissues and induces an acute inflammatory response upon short exposure to immune stimulation, *e.g.*, *via* bacterial endotoxin. In contrast, COX-2 is an inducible isoform that is also present in the brain, while the induction of this isoform requires a longer stimulation with immunogens, hormones, or growth factors. Interestingly, the role of a new isoform, COX-3, which is an enzymatically active splice variant of COX-1 that is, expressed mostly in the brain, is ambiguous and a subject of ongoing studies [20]. It is worth mentioning that COX isoforms show varied expression in the CNS. *COX-1* expression is highest in the telencephalon and diencephalon, *COX-2* expression is highest in the prosencephalon and spinal cord, and *COX-3* expression is highest in the hypothalamus and spinal cord. Among studies into the biological role of cyclooxygenases, COX knockout mice are

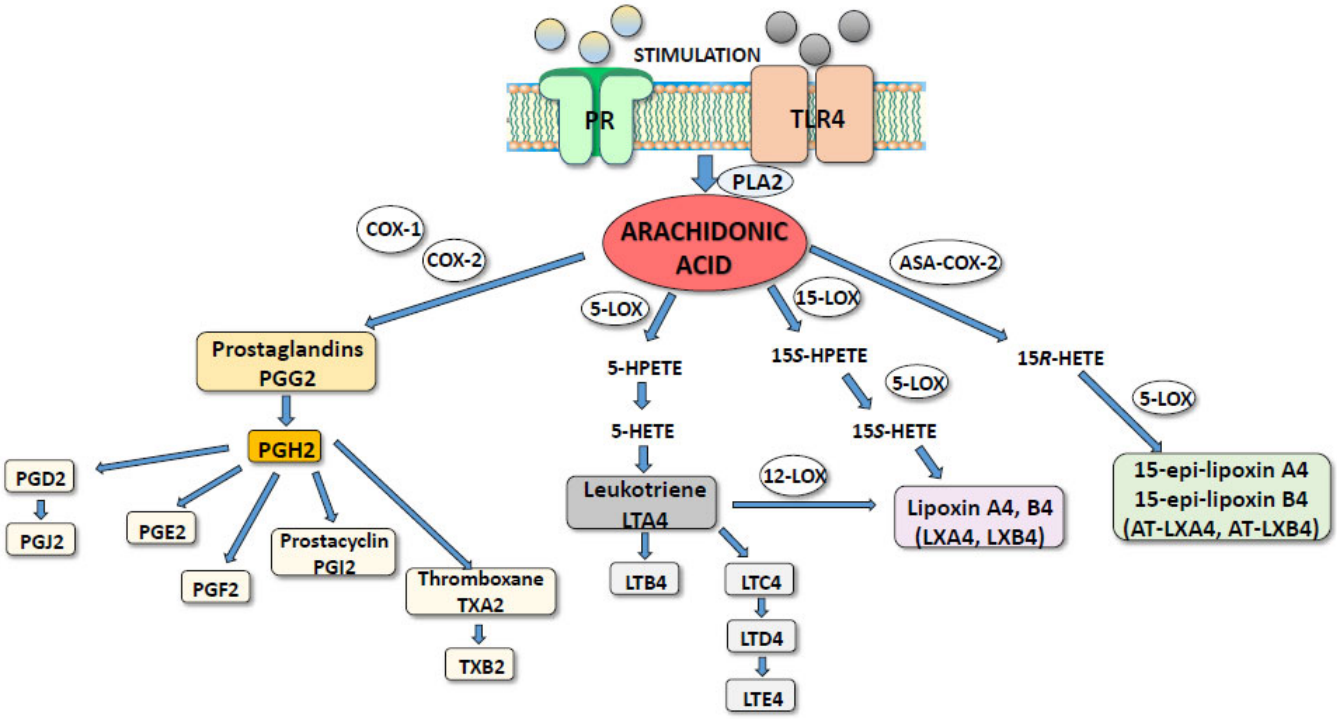

Fig. (1). Biosynthetic pathways of lipid mediators derived from arachidonic acid (AA). AA is released from membrane phospholipids by phospholipase A2 (PLA2) after the stimulation of purinergic receptors (PR) and/or Toll-like receptor 4 (TLR4). The AA is transformed by cyclooxygenases (COX-1, COX-2) or acetylated cyclooxygenase (ASA-COX-2) and lipoxygenases (5-LOX, 12-LOX, 15-LOX) to eicosanoids, including prostaglandins (PGG2, PGH2, PGD2, PGJ2, PGE2, PGF2), prostacyclin (PGI2), thromboxane (TXA2, TXB2), leukotriene (LTA4, LTB4, LTC4, LTD4, LTD4), lipoxins (LXA4, LXB4), and 15-epi-lipoxins (AT-LXA4, AT-LXB4). Other AA metabolites include 5-hydroperoxyeicosatetraenoic acid (5-HPETE), 5-hydroxyeicosatetraenoic acid (5-HETE), 15S-hydroperoxyeicosatetraenoic acid (15S-HPETE), 15-hydroxyeicosatetraenoic acid (15-HETE) and 15R-hydroxyeicosatetraenoic acid (15R-HETE). *(A higher resolution / colour version of this figure is available in the electronic copy of the article*).

of particular significance, despite some limitations [21]. These studies highlight that COX-2, but not COX-1, is implicated in the regulation of lipopolysaccharide (LPS)-induced "sickness behaviour" syndrome through the induction of PGE2 synthesis and fever, whereas COX-2 is engaged in neurodegenerative processes and inflammatory-based CNS diseases [22].

The lipoxygenase (LOX) pathway includes 5-LOX, 8-LOX, 12-LOX, and 15-LOX enzymes and their products, leukotrienes (LTA4 and LTB4, LTC4, LTD4, and LTE4, which are intermediate products) and lipoxins (LXA4 and LXB4 formed by the degradation of LXA4). The classic biosynthesis of lipoxins involves a double transcellular oxidation of AA catalysed by lipoxygenases, which leads to the production of the unstable compounds 15S-hydroperoxyeicosatetraenoic acid (15S-HPETE) and 15-hydroxyeicosatetraenoic acid (15-HETE) and derivatives called lipoxins. Generally, two lipoxins have been distinguished: LXA4 (5*S*,6*R*,15*S*-trihydroxy-7,9,13-*trans*-11-*cis*-eicosatetraenoic acid) and LXB4 (5*S*,14*R*,15*S*-trihydroxy-6,10,12-*trans*-8-*cis*-eicosatetraenoic acid).

Interestingly, in the second lipoxin synthesis pathway, AA is transformed by acetylated cyclooxygenase (ASA-COX2) into 15R-hydroxyeicosatetraenoic acid (15R-HETE), which is a precursor of epimers of lipoxins, 15-epi-LXA4 and 15-epi-LXB4, also known as AT-LXA4 and AT-LXB4, *i.e.*, aspirin-triggered lipoxins. Importantly, the generation of aspirin-triggered lipoxins usually leads to COX-2 inhibition [23].

Therefore, it can be inferred that metabolites produced during AA metabolism and the enzymes engaged in their generation are interdependent and mutually regulated, and dysfunctions of these mechanisms may be the basis for disrupted inflammatory processes, implicating eicosanoids.

4. BASIC PRINCIPLES OF INFLAMMATION

The inflammatory process, which induces an active defence reaction against insults to the body, is one of the main processes in which eicosanoids play a key role. Several phases of inflammation, including initiation, propagation, and resolution, have been described. Interestingly, it is now believed that these phases do not develop sequentially but rather overlap; in other words, both inflammatory activation and resolution can occur simultaneously [24]. Among the processes of inflammatory origin, acute inflammation is a rapid and self-limiting process that disappears after the re-

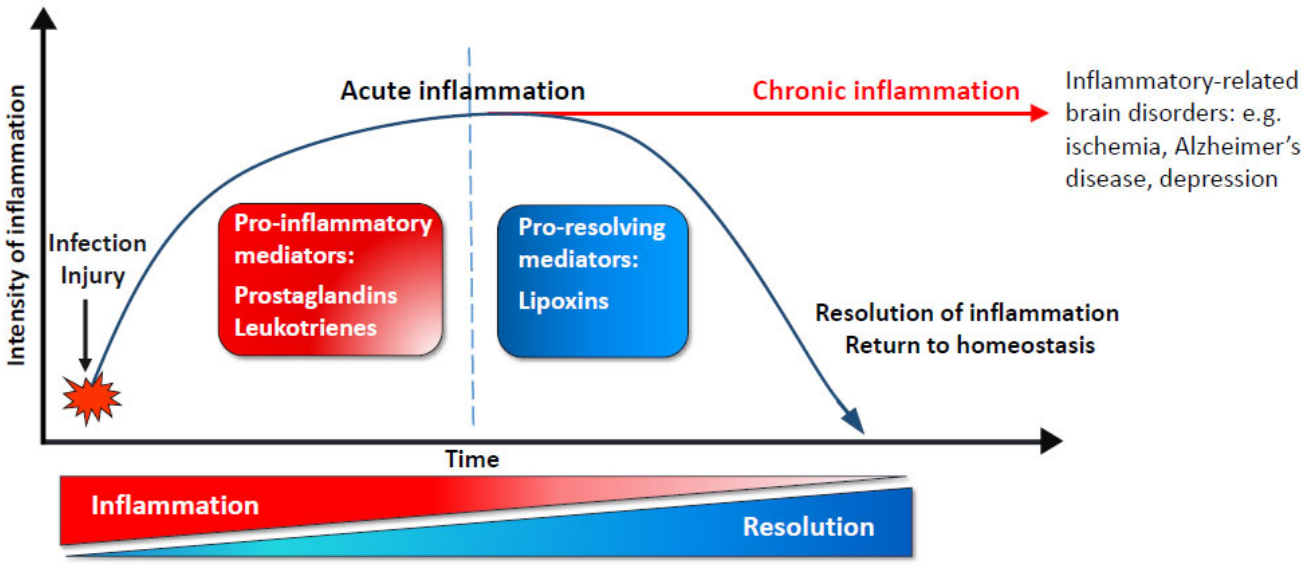

Fig. (2). Diagram of the course of the inflammatory process. The inflammatory response to injury or infection is quickly initiated by releasing endogenous pro-inflammatory AA derivatives (*e.g.*, prostaglandins and leukotrienes), leading to the acute phase of the inflammatory response, which in turn may be terminated by anti-inflammatory AA-derivatives molecules (*e.g.*, lipoxins), leading to the resolution of inflammation (RoI) and a return to homeostasis. Recent data suggest that both inflammatory activation and RoI can occur simultaneously. Importantly, the impairment of RoI leads to chronic inflammation, which is one of the main factor in the onset of the inflammatory-related brain diseases. *(A higher resolution / colour version of this figure is available in the electronic copy of the article*).

moval of the insult in the absence of major damage to the body. Therefore, when properly controlled, inflammation is a beneficial process leading to protection against the spread of infection or damage, and this is followed by the resolution phase [25, 26]. However, when the mechanisms controlling this complex reaction, triggered by several factors including proteins, lipids, and stimulatory signals derived from injured cells or by pro- and anti-inflammatory mediators (*e.g.*, chemokines, cytokines) fail, the process becomes chronic and leads to long-term pro-inflammatory activation which may be crucial in the origin of many brain diseases (Fig. **2**).

In the brain, the course of inflammatory response is slightly different due to the collective interaction of various brain cells (microglia, astrocytes, oligodendrocytes, and NG2 glia) and, in some cases, peripheral immune cells. Deleterious molecules, such as cytokines, chemokines, toxic oxygen radicals, and lipid mediators including eicosanoids which are produced in the course of neuroinflammation as specific mediators impair neuronal survival and promote brain neurodegeneration. Astrocytes respond to pro-inflammatory cytokines with increased proliferation, the expression of astrocyte markers (*e.g.*, GFAP, S100B), release of mediators (*e.g.*, TNF-α, IL-1β, nitric oxide and AA metabolites), cell hypertrophy [27] as well as the formation of glial scarring. On the other hand, reactive astrocytes produce various neurotrophic factors and cytokines to induce neuronal recovery and promote neurite outgrowth. The role of microglia as the major resident immune cells in the brain is unquestioned. In response to brain injury, microglia become activated, which entails changes in their phenotype and in the panel of the synthesized pro-inflammatory and neurotoxic molecules. It should be mentioned that some data demonstrate protective properties of activated microglia, including phagocytic activity [28].

Nevertheless, although glial cells play a dual role in the course of inflammation depending on the inflammatory environment, it is commonly accepted that prolonged chronic neuroinflammation is a prominent feature of progressive neurodegeneration. The double-edged nature of neuroinflammation suggests that proper control of the course of this process is crucial for returning to or maintaining brain homeostasis.

5. INFLAMMATORY RESPONSE IN DEPRESSION

Mood disorders including depression are among the most common diseases of the CNS [29]. The pathogenesis of depression is complex and includes changes in certain neurotransmitters (*e.g.*, serotonin) and dysfunction of the endocrine system and inflammatory responses [30, 31]. The first reports that revealed the role of inflammatory processes in the pathogenesis of depression were published by Maes *et al.* (1995, 2009), who found increased levels of inflammatory factors, such as IL-1β, IL-6, TNF-α, interleukin-1 receptor antagonist (IL-1ra), and interferon-γ (IFN-γ), in depressed patients [32, 33]. Studies showed enhanced levels of IL-6, TNF-α, and C-reactive protein (CRP) in blood samples from depressed patients [34, 35]. Moreover, clinical data confirmed that in patients suffering from depression, plasma

and cerebrospinal fluid (CSF) levels of IL-1β are elevated and that there is a positive correlation between its serum concentration and depression severity [36]. A recent meta-analysis revealed elevations in the concentrations of IL-6, TNF-α, a soluble IL-2 receptor, C-C chemokine ligand 2, IL-13, IL-18, IL-12, and IL-1 Ra in patients suffering from depression [37]. In contrast, the levels of IL-4, TGF-β [38], and IL-10 were reduced [39], which suggests the malfunction of the anti-inflammatory response or immune system dysregulation. Moreover, Torres-Platas *et al.* provided the first evidence of increased microglial activation in *post-mortem* brain samples from middle-aged people with depression who committed suicide [40]. Positron emission tomography (PET) studies provided evidence for increased translocator protein binding, which was interpreted as a marker of microglial activation, in the prefrontal cortex and anterior cingulate cortex of patients with MDD [41]. Crosstalk between peripheral immune cells and microglia can potentiate inflammation both in the periphery and the brain [42].

Additionally, investigations with animal models of depression showed alterations in the immune system function in the periphery and in the brain of experimental animals. For instance, in rats exposed to repeated intermittent LPS injections (a commonly accepted model of depression), the thymus weight and proliferative activity of lymphocytes were significantly reduced, and these changes were accompanied by changes in IFN-γ and IL-10 synthesis in the periphery [43]. Data obtained in a mouse model of restraint stress revealed the increased expression of IL-1β and TNF-α in the hippocampus, which is a key structure in the pathogenesis of depression [44]. Correspondingly, in an animal model of depression based on chronic mild stress (CMS), in which adult animals are exposed to stress, the levels of IL-1β and IL-6 in the brain and IL-6 and TNF-α in the serum were upregulated [45]. Likewise, in our studies in a prenatal stress model, we revealed enhanced microglial activity; the increased expression of neurotoxic factors, including pro-inflammatory cytokines and chemokines (IL-1β, TNF-α, IFN-γ, and CCL2); and deficits in the neuron-glial interaction (*e.g.*, CX3CL1-CX3CR1 and CXCL12-CCR4) in adult rats [46]. It is crucial to note that the changes in the immune response indicative of neuroinflammation are long-lasting and present both in young and adult animals and precede the manifestation of depressive behavioural deficits.

Thus, it can be postulated that the abrogation or distortion of endogenous schemes regulating the mechanisms of neuroinflammation, can be responsible for the development of prolonged inflammation, which, in consequence, can lie at the origin of dysfunctions observed in depression.

6. THE ROLE OF EICOSANOIDS IN THE REGULATION OF INFLAMMATORY RESPONSE

Many studies have indicated that inflammatory processes are regulated at every stage in a very complex manner [47]. In general, proper signal transduction and cellular response require the activation of many processes.

In this context, eicosanoids play a crucial role. In fact, inflammation activates AA release from membrane phospholipids and stimulates pro-inflammatory eicosanoid synthesis. During the initiation phase, key significance is ascribed to biosynthetic pathways involving 5-lipoxygenase (5-LOX) and cyclooxygenase (COX), which release the pro-inflammatory prostaglandins E2 or D2 (PGE2, PGD2) and leukotrienes B4 or C4 (LTB4, LTC4). Among these molecules, LTB4 promotes the recruitment of neutrophils to the inflamed tissue, whereas PGD2 and PGE2 accelerate the inflammatory response [48]. This process is accompanied by a surge of pro-inflammatory mediators (*e.g.*, TNF-α, IL-1β, IL-6, IL-8, CCL-2, and prostaglandins) and the activation of various transcription factors including NF-κB [49]. This phase of inflammation is also characterized by the synthesis of reactive oxygen species, an excess of which may increase the non-enzymatic peroxidation of cell membrane lipids to form toxic and inflammation-stimulating aldehydes, such as 4-hydroxynonenal (4-HNE). Prostaglandins also activate the translation of mRNAs encoding enzymes that are needed for the production of specialized pro-resolving mediators (SPMs), which are primarily lipoxins but also include resolvins and protectins, during the resolution phase. As a consequence, the profile of the synthesized eicosanoids changes from strongly pro-inflammatory prostaglandins and leukotrienes to anti-inflammatory molecules such as lipoxins. Therefore, these data indicate that the resolution of inflammatory response is a multistage and active process [50], and the failure of one or more steps may be involved in the prolonged inflammation and the pathogenesis of chronic inflammatory diseases due to constant stimulation of the immune system, increased pro-inflammatory mediator release, oxidative stress, the destruction of tissues at the site of the inflammatory process, and an impaired return to homeostasis [51-54].

7. DOUBLE-EDGED PROSTAGLANDIN ACTIVITY IN THE DEPRESSION-RELATED INFLAMMATORY RESPONSE

Prostaglandins (PG) are distinguished among eicosanoids influencing the course of inflammation by high biological activity, however, their half-life is short, which affects the dynamics of inflammation. In general, PGs act by binding to specific transmembrane G-protein coupled receptors while the nature of this activity depends not only on the stage of reaction they mediate but also on the interaction of ligands with specific receptors.

Prostaglandin D2 (PGD2) is the most abundant eicosanoid in the brain [55], and it shows the greatest elevation under pathological conditions. PGD2 is synthesized from prostaglandin H2 (PGH2), the precursor for all prostanoids and thromboxanes, through the enzymatic activity of prostaglandin D synthase (HPGDS) and the lipocalin-type prostaglandin D synthase (Fig. **1**). Two main receptors for this prostanoid have been identified: DP1 and DP2, which are expressed in the brain on microglial cells and astrocytes [56]. Interestingly, their activation produces opposite effects; at physiological PGD2 concentrations, the activation

of DP1 receptors rescues neurons from glutamate toxicity, whereas DP2 activation aggravates the inflammatory response and enhances neuronal loss. However, these observations require further studies, because it has also been postulated that the opposite effects of DP1/DP2 stimulation are dependent on the activation of other receptors, including TLR2.

Importantly, the PGD2 activity in the brain seems to be associated with some of the symptoms exhibited by patients with major depressive disorder. Previous studies indicated that PGD2 synthase is decreased in the cerebrospinal fluid of major depressive disorder patients. Studies by Chu C. *et al.* revealed that the decreased PGD2 levels were associated with depression-like behaviours. Accordingly, investigations in an animal model of depression (chronic unpredictable mild stress) showed that depression-like behaviours, as indicated by reduced sucrose preference and increased immobility time in the forced swimming test, were accompanied by reduced PGD2 levels both in the plasma and brains of these mice [57]. Furthermore, the inhibition of PGD2 production in mice resulted in an increased immobility time and thus the exacerbation of depressive behaviours. There are several reports indicating the role of PGD2 in stress-induced depressive-like behaviour. For example, CRTH2, which is a PGD2 receptor, is crucial for the development of depressive-like behaviours induced by chronic corticosterone treatment [58]. However, there are also contrasting reports indicating that the pharmacological inhibition of PGD2 production in mice increased depressive-like behaviour in the forced swim test. Thus, PGD2 could be either pro-depressive or anti-depressive, perhaps depending on the pathology of depression or disease context, which undoubtedly calls for further investigations [57].

In the context of depressive disturbances, which are often associated with sleep disorders, it is interesting to note that PGD2 exhibits circadian fluctuations, and its release in the brain increases in an attempt to induce sleep during sleep deprivation. Moreover, animal studies demonstrated a relationship between PGD2 concentration and sleep duration [59], and the pharmacological inhibition of PGD2 production led to sleep disturbances in NREM and REM phase. It is also worth mentioning that eicosanoids participate in the formation of memory traces and synaptic plasticity regulation, and special relationships are observed between prostaglandins and BDNF (brain-derived neurotrophic factor). Thus, it has been postulated that BDNF deficits observed in the course of depression are associated with the disturbance of memory processes, which is linked with changes in PGD2 concentration or its bioavailability in the brain and with an imbalance in the brain eicosanoid network [60].

The spontaneous dehydration of PGD2 leads to the formation of prostaglandin J2 (PGJ2), which is unstable and may undergo further non-enzymatic dehydration to 15d-PGJ2. It is believed that prostaglandins of the J2 series are the most potent agents within the PGD2 degradation pathway, and their effects on neurons are complex and appear to be mediated primarily through receptor-independent mechanisms. PGJ2 may be pro-inflammatory and associated with the accumulation of ubiquitinated proteins and neurotoxic compounds [61] and caspase cleavage activation. For this reason, it is thought that the neurotoxic activity of PGD2 is largely dependent on the toxic effects of its metabolites. In contrast to the pro-inflammatory nature of the J2 series, 15d-PGJ2 produces anti-inflammatory effects because it is a ligand for peroxisome proliferator-activated receptor (PPAR) gamma. This receptor participates in many processes in the brain, including the regulation of glucose metabolism and lipid homeostasis. Interestingly, the administration of PPAR gamma agonists suppresses several genes involved in neural inflammation (TNF-α, NO) *via* the NF-κB pathway, thereby suppressing COX-2 expression and coexistent prostaglandin synthesis. In parallel, it leads to the alleviation of behavioural deficits in experimental models of disease, especially those of neurodegenerative origin [62].

Prostaglandin E2 (PGE2), one of the most abundant prostaglandins in the body, is also crucial. PGE2-mediates the emergence of all classical signs of inflammation (redness, swelling, and pain). PGE2 acts locally *via* four receptor types (EP1-EP4), of which EP3 and EP4 show the highest affinity for PGE2 and are widely distributed in almost all tissues. It was documented that the biological effects of PGE2 depend on its receptor and can range from pro- to anti-inflammatory. For instance, EP1 stimulation leads to the elevation of Ca^{2+} in the cell, the inhibition of pro-survival protein kinase AKT, and neuronal death [63]. In contrast, the modulation of microglia activation and function by EP2 stimulation suppresses toxic inflammation and increases insulin--like growth factor-1 (IGF-1) synthesis [64]. Accordingly, studies on organotypic cultures revealed that the application of an EP2 receptor agonist (butaprost) reduced inflammatory mediator release induced by immunogen stimulation, and this mechanism was related to mitogen-activated protein kinase (MAPK) pathway inhibition [65], which clearly indicates the anti-inflammatory role of EP2 receptor activation. Although the effect of EP3 activation is uncertain because studies are complicated by the presence of isoforms (EP3-I to EP3-IV) that are all expressed in brain tissue, EP4 is unanimously thought to mediate pro-survival and anti-inflammatory functions of PGE2, which are associated with changes in EP4 expression in microglia cells. Interestingly, it was recently demonstrated that PGE2–EP1 signalling is involved in depressive-like behaviour induced by repeated social defeat, which was proposed as a mouse model of depression. EP1 knockout mice did not show depressive-like and anxiety-like behaviours induced by repeated social defeat stress. Thus, PGE2–EP1 signalling seems to be crucial for the long-term behavioural consequences of repeated social defeat stress [66].

Results of the presented studies indicate that the biological profile of prostaglandins may be double-edged and highly dependent on receptor activation. This picture is undoubtedly complicated by networks of mutual regulation. For instance, PGE2 and PGD2 show favourable cooperative effects on nerve growth factor (NGF) synthesis by astrocytes [67]. Although the biological activity of eicosanoids in the brain

is primarily mediated by microglia and the activation of these cells enhances PGE2 *via* the COX-2 pathway, PLA2 also augments prostaglandin synthesis by expansion of the available AA pool *via* COX-2 pathway activation in astrocytes [1], thereby increasing PGE2 release in some brain areas (*e.g.*, in the hypothalamus). For this reason, the significance of proper signalling between brain cells to initiate eicosanoid synthesis has been highlighted [20] as a particularly important process in the course of chronic neuroinflammation.

In contrast, the significance of prostacyclin (PGI2), which is engaged in neuronal survival in the brain in the pathogenesis of depression, is less known. PGI2 has been observed to be localized in blood vessels throughout the brain and in oligodendrocytes and microglia, with particularly high expression in the frontal cortex and hippocampus. Generally, PGI2 inhibits the activation of astrocytes and thus shows anti-inflammatory activity. Complementary studies confirm that this prostaglandin has a pivotal role in acute inflammation and that most acute inflammatory symptoms are associated with the expression of this prostaglandin.

At present, only scarce data exist for thromboxane A2 (TXA2), which is synthesized from PGH2 by thromboxane A synthase. TXA2 is known to be quite unlike PGI2. Its expression was detected in glia cells, macrophages, the periphery in immunocompetent cells and the lung. TXA2 is very unstable under physiological conditions and is hydrolysed to stable but biologically inactive TXB2. There are two forms of TXA2 receptors (TP α and TP β), which are expressed on neurons and activated microglia and macrophages [68]. The use of antagonists of these receptors demonstrated their modulatory role in the secretion of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) and in cyclic AMP-response element binding protein (CREB) activation. The role of thromboxane A2 and its receptors is even less known in the context of mental diseases; however, it appears that they can play a role in diseases of neurodegenerative origin.

8. INHIBITION OF CYCLOOXYGENASE PATHWAYS AS A COMPLEMENTARY TOOL IN THE THERAPY OF DEPRESSION

Cyclooxygenases are key enzymes in prostaglandin synthesis; therefore, the activity of prostaglandins and their involvement in inflammatory processes can be regulated *via* modification of this enzyme's activity. To date, many studies have been dedicated to this topic, including recently published review articles [37, 69, 70]. Therefore, in this section, we will present only some selected examples demonstrating a new direction for COX modulation and its therapeutic potential in depression.

Although it is commonly accepted that COX-1 and COX-2 are necessary for the synthesis of prostaglandins involved in inflammation, some studies [71] have shown that COX-2 may act as a pro-inflammatory mediator at the early stage of an inflammatory reaction but become an anti-inflammatory factor through the generation of anti-inflammatory PGs (such as PGD2 and PGJ2). Nevertheless, these findings demonstrate that COX activity manipulation may provide a potent strategy for altering the course of inflammation, which often accompanies depression and limits the therapeutic efficacy of its treatment. In fact, COX inhibition exerts neuroprotective effects in the dentate gyrus regions, including the diminution of the inflammatory response, oxidative stress, and neuronal apoptosis, which are critical risk factors for neuronal injury and the pathophysiology of depression [72, 73]. Moreover, the beneficial impact of COX-2 inhibition *via* the suppression of glial activation has been postulated [72]. Among other effects, it was demonstrated that celecoxib decreased the expression of pro-inflammatory markers IL-1β, and TNF-α in the rat hippocampus, and this inhibition was shown to prevent clinical symptoms, such as anxiety and cognitive disturbances [74]. Interestingly, celecoxib administration also prevented dysregulation in the hypothalamic-pituitary-adrenal (HPA) axis and glucocorticoid receptor (GR) function. These effects may have been related to the downregulation of IL-6 production [74-76], because its elevation results in reduced BDNF function, which may lead to imbalanced neurogenesis and result in neural circuitry dysfunction and depressive symptoms [77]. Furthermore, celecoxib administration in rats was associated with reductions in PGE2 levels and the alleviation of stress-induced depressive-like behaviours. PGE2 has been shown to contribute to monoamine imbalance with decreased central neuronal norepinephrine release and dysregulation of the HPA axis, which alters cortisol synthesis and subsequently suppresses serotonin action. Consistent with this, experiments in animal models of depression demonstrated that celecoxib independently boosted serotonin release in the brain of rats [37].

Interestingly, COX-2 inhibitors not only have direct effects on the CNS serotonergic system but can also affect neurotransmission indirectly *via* immune processes in the brain. Higher serotonin levels were observed after the administration of rofecoxib, a selective COX-2 modulator, both in the frontal and temporoparietal cortices of rats [78]. Likewise, in other models of depression (including the olfactory bulbectomy model), the chronic administration of the COX-2 inhibitor celecoxib decreased cytokine levels and normalized depressive behaviour in animals [79]. For this reason, the existing observations support the idea of a reciprocal relationship between COX-2 modulation and neuroinflammatory responses, which may, in part contribute to the behavioural alterations underlying depression. At the same time, the above examples indicate that activation of the COX-2/PGE2-mediated inflammatory pathway may represent a significant component in the pathophysiology of depression.

Data from clinical trials appear to confirm suggestions based on animal models, especially in the context of the combined administration of COX inhibitors and antidepressant drugs. In particular, celecoxib was shown to produce a significant antidepressant effect in major depression patients treated jointly with reboxetine (vs. reboxetine plus placebo) [80, 81]. Similar therapeutic effects were observed for combined treatment with fluoxetine and celecoxib compared with fluoxetine alone [82]. Additionally, patients treated with sertraline and celecoxib in combination showed reduced serum

IL-6, which was correlated with a decreased depression rating score. In general, meta-analyses have suggested that treatment with anti-inflammatory agents, particularly celecoxib, can ameliorate the symptoms of depression [37, 83]. However, celecoxib did not mitigate depressive symptoms in healthy individuals aged 70 years or older [84], pointing that COX pathway activation may not be the only mechanism underlying the onset of depressive symptoms in adults.

The role of aspirin, which is an irreversible inhibitor of both COX-1 and COX-2, has been considered, because it is known to stimulate the endogenous production of anti-inflammatory molecules, including lipoxins, which diminish the inflammatory response and reduce the levels of inflammatory biomarkers, including CRP, TNF-α, and IL–6. Aspirin may also reduce oxidative stress and protect cells against oxidative damage [85]. In the context of monotherapy with another non-selective COX-inhibitor, the use of naproxen was also suggested, but the existing studies show contradictory results (naproxen produced beneficial effects on depressive symptoms in patients with active osteoarthritis [86], but it did not relieve depressive symptoms in healthy subjects [84]). It should also be mentioned that there are ongoing experimental animal studies on the effects of other selective COX-2 inhibitors, specifically NS-398 and diclofenac. NS398 reversed the functional effects of IL-1β in the brain of rats, such as sickness behaviour, whereas diclofenac alleviated LPS-induced reductions in anhedonia [87].

Recently, combination therapies including COX activity modulators have been recommended particularly in treatment-resistant patients with increased levels of pro-inflammatory cytokines and PGE2 in the clinical picture [1, 88]. In these cases, the administration of COX-2 inhibitors enhanced the efficacy of both reboxetine and fluoxetine in treatment-resistant depression. Moreover, depressed patients showed decreased production of inflammatory factors induced by a pre-existing pro-inflammatory state, indicating that their immune cells are in a refractory phase [89]. Thus, the clinical utility of combined treatment with COX-2 inhibitors and antidepressants in refractory depression may be evident [88].

On the other hand, it should be stressed that the administration of COX-2 antagonists is usually accompanied by significant cardiovascular and gastrointestinal side effects; therefore, it is undoubtedly necessary to identify new targets in the neuroinflammatory system to develop effective and safe therapeutic strategies for the treatment of depression [90].

9. LIPOXYGENASES AND THEIR PRODUCTS

Lipoxygenases represent a non-haem iron-requiring class of enzymes that oxidize an array of PUFA substrates, and this pathway encompasses 5-LOX, 8-LOX, 12-LOX, and 15-LOX enzymes and their products including leukotrienes (LTA4, LTB4, LTC4, LTD4, and LTE4, which are intermediate products) and lipoxins (LXA4 and LXB4, which are formed by LXA4 degradation). Thus, lipoxygenases participate in the production of AA derivatives: eicosanoids with pro-inflammatory (leukotrienes) and anti-inflammatory (lipoxins) profiles.

Leukotrienes are classified as AA derivatives produced by 5-lipoxygenase (5-LOX) in the presence of 5-lipoxygenase activating protein (FLAP). Their biosynthetic pathway involves a sequence of stages beginning from the synthesis of 5-hydroperoxyeicosatetraenoic acid (5-HPETE), which is transformed into leukotriene A-4 (LTA-4), which is hydrolysed to leukotriene B-4 (LTB-4) or is transformed by glutathione-S transferase into leukotriene C-4 (LTC-4) and then sequentially into leukotriene D-4 (LTD-4) and leukotriene E-4 (LTE-4) [2, 91, 92] (Fig. **1**). Leukotrienes LTC4-LTE4 contain a cysteine residue at carbon-6 in their structure and thus are called cysteinyl leukotrienes (CysLTs). The mechanism of action of leukotrienes implicates the following specific receptors: BLT1 and BLT2 for leukotriene B4 and CysLT1 and CysLT2 for cysteinyl leukotrienes.

5-lipoxygenase (5-LOX) expression in the brain increases with ageing and in various forms of brain damage [93, 94]. However, the inhibition of 5-lipoxygenase activity (*e.g.*, by zileuton) [95, 96] or the blockade of CysLT1 or GPR17, which are CysLT receptors, ameliorates memory impairment and the course of neuroinflammation in aged animals [97]. Recently, it was demonstrated that chronic mild stress increased the expression of 5-lipoxygenase in the hippocampus [98], and that CysLT1 knockdown in the hippocampus reduced the expression of pro-inflammatory cytokines in the hippocampus and alleviated depressive-like behaviour induced by chronic mild stress [99]. Thus, it can be postulated that 5-lipoxygenase signalling plays an important role in depressive-like behaviour. Studies have indicated that 5-lipoxygenase and leukotriene receptors are abundant in myeloid cells, including microglia. Therefore, it appears that CysLTs may be involved in an amplifying loop for stress-induced microglial activation. It is also known that this lipoxygenase and CysLT synthesis can be activated by various inflammatory stimuli, including pro-inflammatory cytokines derived from activated microglia, which in chronic stress models can trigger the amplifying loop of CysLTs. However, a potential relationship between CysLTs and PGE2 in the brain and the use of the AA pool for synthesizing these compounds remain unexplored, although these processes seem to be significant, especially in the context of the involvement of leukotrienes in cognitive impairment processes (during ageing and diseases of neuroinflammatory and neurodegenerative origin) [99-101]. It also must be highlighted that there is a constant need for experimental verification of the role of 5-LOX in depression, particularly in light of reports on the impact of 5-LOX and related metabolites on IL-1β, and PGE2 release and on the influence of this inflammatory environment on HPA axis dysfunctions, which have been observed in some patients suffering from depression [102].

In contrast, lipoxygenases are directly or indirectly involved in the formation of anti-inflammatory eicosanoids, lipoxins. Moreover, the synthesis of lipoxin epimers can be triggered by aspirin treatment [23, 103]. Briefly, there are

three main lipoxygenases that are engaged in lipoxin synthesis: 5-LOX, 15-LOX, and 12-LOX. The first step of lipoxin synthesis involves leukotriene A4 activation by 12-LOX and its conversion to lipoxins. Moreover, AA is converted to 15 HPETE through a series of LOX (mainly 5-LOX and 15-LOX)-catalysed steps. Subsequently, 15 HPETE is converted to lipoxin A and lipoxin B. The third step is dependent on aspirin and leads to the generation of 15 epi-lipoxin A4, which is also known as aspirin-triggered lipoxin (ATL) and 15 epi-lipoxin B4.

Lipoxin A4 (LXA4) and its epimer 15-epi-LXA4 act essentially through formyl peptide receptor 2 (FPR2/ALX), which belongs to a comprehensive family of membrane G-protein-coupled receptors. This receptor is expressed in many tissues and cells, including neutrophils, monocytes, macrophages, endothelial cells, astrocytes, microglia, and neural stem cells [104]. The biological effects of FPR2/ALX stimulation are diverse and cell specific, which is particularly significant in the brain [105]. Importantly, ligand structure-dependent FPR2/ALX activation is also of pivotal importance for the mediation of pro-inflammatory or pro-silencing reactions [106]. Furthermore, LXA4 can activate other receptors, including orphan G-protein coupled receptor (GPR32), aryl hydrocarbon receptor, oestrogen receptor, and high affinity cysteinyl leukotriene receptor [107].

It is commonly accepted that lipoxins and epi-lipoxins acting *via* FPR2/ALX can exert anti-inflammatory effects. LXA4 decreases ROS, pro-inflammatory cytokine, and chemokine production [105, 108]. Lipoxins stimulate monocyte chemotaxis and adherence without causing degranulation or the release of ROS, which suggests that their effects are related to the recruitment of monocytes to sites of injury [109]. Anti-inflammatory responses related to lipoxins include the involvement of many intracellular signalling pathways, including transcription factors, such as AP-1, NF-κB, and Nrf2, the main regulator of the expression of antioxidant response element-associated genes, which are involved in the production of antioxidants and detoxification enzymes [110]. Moreover, LXA4 activates peroxisome proliferator-activated receptor (PPAR) gamma, which plays an important role in terminating the inflammatory response [111, 112].

Because of the multiple effects of FPR2/ALX receptor stimulation and the biological activity of LXA4 and the 15-epimer, lipoxins are perceived as strong endogenous anti-inflammatory agents. However, recently, the view of the role of these eicosanoids has broadened, and they have been highlighted as important specialized pro-resolving lipid mediators (SPMs) in the course of inflammatory processes in the CNS.

10. INTENSIFICATION OF RESOLUTION OF INFLAMMATION AS A NEW TOOL IN THERAPY OF DEPRESSION

A significant role of long-term inflammation in the pathogenesis of depression has been emphasized, at least in some patients. Therefore, the question arises whether the active and complex process of resolution of inflammation (RoI) might be distorted in this disease [25, 113].

Data have demonstrated that RoI requires a proper endogenous activation to induce a switch from the release of pro-inflammatory molecules towards the secretion of pro-resolving mediators, which comprise a wide variety of compounds, including SPMs and AA derivatives such as lipoxins [48]. A specific feature of SPMs is the induction of processes that reduce the expression of pro-inflammatory molecules rather than a complete blockage of signal transduction within the inflammatory cascade. Furthermore, SPMs activate cascades that lead to remodelling within sites damaged by inflammatory processes. In any case, SPMs elicit "mild to moderate effects", which, by establishing the equilibrium between pro- and anti-inflammatory response, help to strike a balance and restore homeostasis [114].

Unfortunately, despite promising results from experimental studies indicating beneficial effects from LXA4 and its derivatives, including LXA4-ATL, their use is significantly limited by very rapid enzymatic inactivation *in vivo* [115]. In fact, lipoxins are rapidly metabolized, and the major routes of degradation include dehydrogenation at C-15 and possible ω-oxidation at C-20 [103]. Because this instability precludes the use of exogenous lipoxins as anti-inflammatory drugs, stable analogues have been developed with modifications primarily at C-15, C-26, and/or C-20. Importantly, these compounds maintain the biological activity of native lipoxins and have been shown to bind to FPR2/ALX with higher affinity. The enhanced stability and improved efficacy of these analogues seem to suggest their significant therapeutic potential in some animal models of inflammation [116].

On the other hand, the abovementioned limitations in the use of endogenous ligands and their new derivatives prompted the search for new strategies based on the modulation of eicosanoid receptors [23, 113, 117, 118]. Importantly, it has been shown that the characteristics of FPRs/ALX result from their ability to interact with many structurally diverse agents that stimulate cellular responses downstream of receptor activation, thus triggering ligand-specific responses [119] (Fig. **3**). This ability is caused by FPR2/ALX biased agonist. Recently, Raabe CA. *et al.* (2019) discussed the biased perspectives on FPRs and concluded that FPR2/ALX is unique because the ligand selectively activates subsets of downstream signalling pathways coupled to the receptor while inhibiting others [120]. This capability explains why different FPR2/ALX agonists do not cause the same effects and why some shift a pro-inflammatory response into an anti-inflammatory response, thus leading to RoI.

Accordingly, Qin *et al.* performed the first study into the effects of biased agonist using two small-molecular FPR/ALX agonists, compound 43 and compound 17b, on the protective profile in myocardial infarction. Their data showed that compound 17b, unlike compound 43, decreased Ca^{2+} flux relative to that induced by ERK1/2-Akt signal transduction. Therefore, the biased agonist of compound 17b provides beneficial outcomes in *in vivo* models of myocardial infarction, because the increased intracellular Ca^{2+} con-

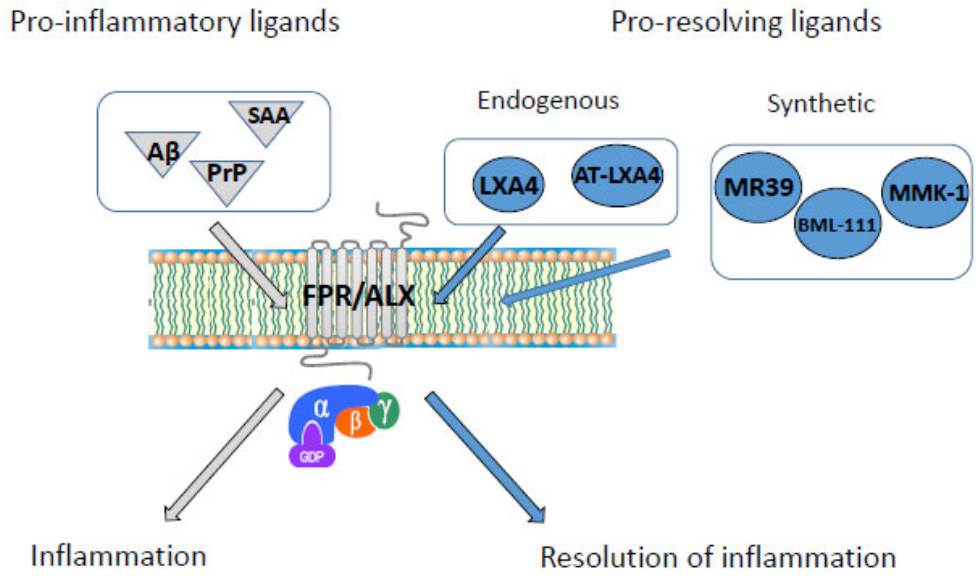

Fig. (3). The biased agonism is ligand-dependent selective activation of FPR2/ALX to interact with many structurally diverse agents. The binding of both pro-resolving ligands, including endogenous: lipoxin A4 (LXA4), 15-epi-lipoxin A4 (AT-LXA4) or new synthetic (*e.g.*, MR39, BML-111, MMK-1) as well as pro-inflammatory: serum amyloid A (SAA), amyloid β (Aβ) or prion protein (PrP) to FPR2/ALX induces contrasting effects on inflammatory pathway activation and immune response. The biased signalling can provide a new method for shifting pro-inflammatory to anti-inflammatory pathways and in this way improve efficiency of RoI. *(A higher resolution / colour version of this figure is available in the electronic copy of the article*).

tributes to cardiomyocyte damage and is an important contributor to the influx of inflammatory neutrophils and macrophages [119].

Moreover, exploiting the biased signalling can offer a new method for balancing pro-inflammatory and anti-inflammatory pathways to retain the homeostatic environment in inflammatory diseases, and this approach can also be applied to the development of drugs for psychiatric disorders. This opinion is supported by the fact that FPR2/ALX expression is confirmed in many structures, including the brain, hypoglossal nucleus neurons, choroid plexus, and epithelium. Hippocampal neurons, pyramidal cell neurons, end-plate pyramidal cells, astrocytes, Schwann cells of the peripheral nervous system, and cells in the parasympathetic system express high levels of FPRs [121]. Interestingly, in microglial cells, FPR2/ALX expression is low, but inflammatory activation (*e.g.*, by bacterial endotoxin) boosts it considerably [122, and our unpublished data]. Correspondingly, it was shown that compound BML-111 (5(S),6(R),7-trihydroxyheptanoic acid methyl ester), which activates FPR2/ALX, reduced inflammation and neutrophil infiltration while potentiating the release of anti-inflammatory factors (*e.g.*, IL-4, IL-10) in a number of inflammatory disorders [123-127]. Other compounds, including MMK-1 (LESIFRSLLFRVM), which is a potent FPR2/ALX agonist, also produce a beneficial effect. It should be mentioned that FPR2/ALX agonists have wide chemical diversity, and the analysis of these and future agonists will enhance our knowledge of ligand–FPR2/ALX interactions such as the peptide CGEN-855A, which has cardioprotective effects in rat and murine myocardial ischaemia. This study provides further evidence of a beneficial effect of the FPR2/ALX pathway in neuroinflammation.

According to this opinion in our previous studies, we identified a series of ureidopropanamide derivatives as FPR2/ALX agonists [128]. Using appropriate structural modifications, we selected compound MR39 for its favourable pharmacokinetic properties. This compound is resistant to oxidative metabolism in rat liver microsomes and displays a good passive permeability through a monolayer of h CMEC/D3 cells, immortalized human brain microvascular endothelial cells that are considered an *in vitro* model of the blood-brain barrier (BBB). Furthermore, MR39 diminished IL-1β and TNF-α expression in lipopolysaccharide-stimulated rat primary microglial cell cultures and thus showed protective and anti-inflammatory properties [128]. Interestingly, our *ex vivo* studies in a prenatal stress paradigm (animal model of depression) showed that the expression of both FPR2/ALX and pro-inflammatory cytokine genes was upregulated, but the new ureidopropanamide agonists exhibited anti-inflammatory and pro-resolving actions. However, these interesting findings require further confirmation to use them for the development of a new supportive therapeutic strategy. Altogether, keeping in mind that LXA4 is rapidly inactivated *in vivo* [129] and that there is no direct evidence that LXA4 can pass the BBB, FPR2/ALX modulation by new

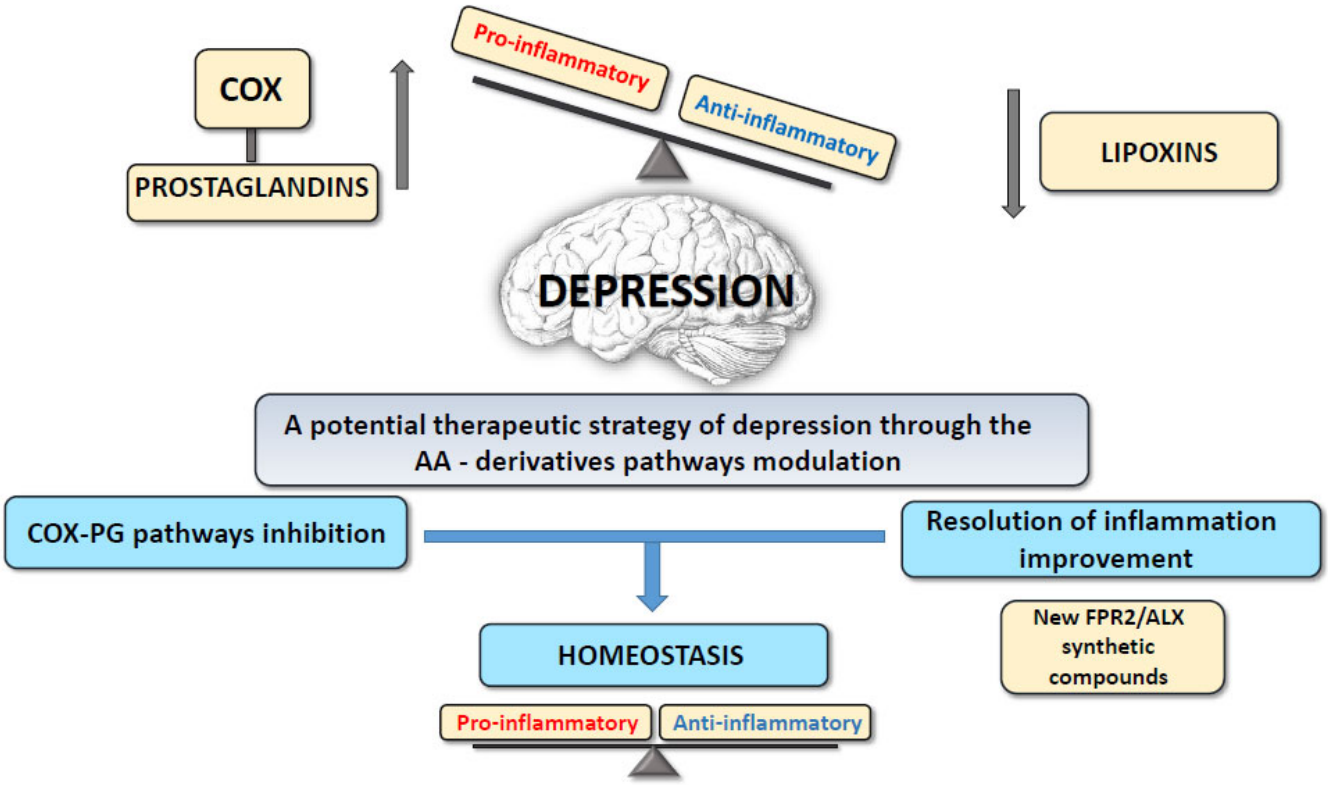

Fig. (4). Although the pathogenesis of depression is complex, the chronic inflammation may be one of the crucial risk factors. Arachidonic acid derivatives have the "double-edged" activity and are involved in the inflammatory response as well as the resolution of inflammation. In the course of depression, the pro-inflammatory to anti-inflammatory balance of eicosanoids is disturbed. The enhanced activity of prostaglandins (PG) and cyclooxygenases (COX), while diminished of lipoxins have been observed. The proposed therapeutic strategy involves simultaneous reduction of the pro-inflammatory response through COX-PG pathway inhibition as well as potentiation of the resolution of inflammation. The new FPR2/ALX synthetic ligands, based on the biased agonists, may shift the pro-inflammatory to anti-inflammatory response, thereby improves RoI and leads to the homeostasis. *(A higher resolution / colour version of this figure is available in the electronic copy of the article*).

synthetic ligands may represent a promising tool for studying the potential of FPR2/ALX as a target for the pharmacotherapy of brain diseases, including depression.

CONCLUDING REMARKS

Despite many years of studies from several research centres, the efficacy of therapeutic interventions in some CNS diseases remains unsatisfactory. This situation seems to result from the complex and multifactorial nature of the pathological basis of these diseases. In the present review, particular attention has been given to depression, because the prolonged inflammatory status undoubtedly plays a key role in its pathogenesis. It is thought that chronic inflammation hinders pharmacotherapy of depression. Therefore, a novel and innovative approach to the resolution of the inflammatory response in the course of depressive disorders is needed. Accordingly, the present article updated the current knowledge concerning the "double-edged" activity of main arachidonic acid derivatives that are induced in the inflammatory response as well as involved in the resolution of inflammation based on the selected preclinical and clinical studies in the course of depression. An attempt has been made to document that prostaglandins with commonly accepted pro-inflammatory spectrum can also show pro-resolving properties, while the inhibition of cyclooxygenases support the efficacy of antidepressant drugs. At the same time, a unique role of the relationships between pro- and anti-inflammatory eicosanoids in the regulation of the chronic neuro-inflammatory response has been highlighted. Attention has also been given to anti-inflammatory deficits in depression, including those associated with limited bioavailability and biological activity of lipoxins and to synthetic ligands of FPR2/ALX receptors as new tools, to amplify the termination of chronic inflammatory processes. It appears justifiable to conclude that new an alternative strategy in depression can involve regulation of the "double-edged" activity of eicosanoid-related pathways by simultaneous reduction of the pro-inflammatory response (*via* COX pathway inhibition) as well as potentiation of the resolution of inflammation (*via* FPR2/ALX biased agonists). The search for new pro-resolving FPR2/ALX ligands as a target to increase the efficacy of pharmacotherapy can be a highly promising strategy of particular relevance in drug-resistant depressed patients, with disturbed resolution of inflammatory response.

LIST OF ABBREVIATIONS

15-HETE	=	15-Hydroxyeicosatetraenoic Acid
15-HPETE	=	15-Hydroperoxyeicosatetraenoic Acid
4-HNE	=	4-Hydroxynonenal
AA	=	Arachidonic Acid
ADA	=	Docosatetraenoic Acid
ALA	=	α-Linolenic Acid
ASA-COX2	=	Acetylated Cyclooxygenase
ATL	=	Aspirin-Triggered Lipoxin
AT-LXA_4	=	AT-LXB_4 – Aspirin-Triggered Lipoxins
BBB	=	Blood-Brain Barrier
BDNF	=	Brain-Derived Neurotrophic Factor
CNS	=	Central Nervous System
COX	=	Cyclooxygenase
CRP	=	C-reactive Protein
CSF	=	Cerebrospinal Fluid
DHA	=	Docosahexaenoic Acid
FAAH	=	Fatty Acid Amide Hydrolase
HPA	=	Hypothalamic-Pituitary-Adrenal
IFN-γ	=	Interferon-γ
LA	=	Linoleic Acid
LOX	=	Lipoxygenase
LPS	=	Lipopolysaccharide
LTB_4	=	LTC_4 – Leukotrienes
LTP	=	Long-Term Potentiation
MAPK	=	Mitogen-Activated Protein Kinase
MDD	=	Major Depressive Disorder
NGF	=	Nerve Growth Factor
PET	=	Positron Emission Tomography
PGE_2	=	PGD_2 – Prostaglandins
PLA2	=	Phospholipase A2
PUFA	=	Polyunsaturated Fatty Acid
RoI	=	Resolution of Inflammation
SPMs	=	Specialized Pro-Resolving Mediators
TLR4	=	Toll-Like Receptor 4
TNF-α	=	Tumour Necrosis Factor α
TXA2	=	Thromboxane A2

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise.

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