Translational Neurodegeneration

REVIEW

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Update on the pathological roles of prostaglandin E_2 in neurodegeneration in amyotrophic lateral sclerosis

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Abstract

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by selective degeneration of upper and lower motor neurons. The pathogenesis of ALS remains largely unknown; however, inflammation of the spinal cord is a focus of ALS research and an important pathogenic process in ALS. Prostaglandin E_2 (PGE_2) is a major lipid mediator generated by the arachidonic-acid cascade and is abundant at inflammatory sites. PGE_2 levels are increased in the postmortem spinal cords of ALS patients and in ALS model mice. Beneficial therapeutic effects have been obtained in ALS model mice using cyclooxygenase-2 inhibitors to inhibit the biosynthesis of PGE_2, but the usefulness of this inhibitor has not yet been proven in clinical trials. In this review, we present current evidence on the involvement of PGE_2 in the progression of ALS and discuss the potential of microsomal prostaglandin E synthase (mPGES) and the prostaglandin receptor E-prostanoid (EP) 2 as therapeutic targets for ALS. Signaling pathways involving prostaglandin receptors mediate toxic effects in the central nervous system. In some situations, however, the receptors mediate neuroprotective effects. Our recent studies demonstrated that levels of mPGES-1, which catalyzes the final step of PGE_2 biosynthesis, are increased at the early-symptomatic stage in the spinal cords of transgenic ALS model mice carrying the G93A variant of superoxide dismutase-1. In addition, in an experimental motor-neuron model used in studies of ALS, PGE_2 induces the production of reactive oxygen species and subsequent caspase-3-dependent cytotoxicity through activation of the EP2 receptor. Moreover, this PGE_2-induced EP2 up-regulation in motor neurons plays a role in the death of motor neurons in ALS model mice. Further understanding of the pathophysiological role of PGE_2 in neurodegeneration may provide new insights to guide the development of novel therapies for ALS.

Keywords Prostaglandin E_2, Amyotrophic lateral sclerosis, Motor neuron death, E-prostanoid receptor, Microsomal prostaglandin E synthetase-1

Background

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a devastating neurodegenerative disease characterized by the selective degeneration of upper and lower motor neurons. It causes progressive paralysis and muscle atrophy for which no effective treatment exists, leading to eventual death, usually within 1 to 5 years of onset [1]. Most cases of ALS are sporadic, and the cause of sporadic ALS remains largely unknown. Familial ALS (fALS) accounts for approximately 10% of all cases, and its causative gene defects have been

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identified, including mutations in genes encoding superoxide dismutase 1 (SOD1), fused in sarcoma, TAR DNA-binding protein-43 (TDP-43), optineurin, and C9ORF72 [2]. Among these etiologies, the best characterized fALS cases are caused by a mutation in the gene encoding SOD1, which accounts for about 20% of fALS cases [3, 4]. The human *SOD1* gene with the G93A point mutation (alanine substitution for glycine at position 93) was the first experimental molecular defect to result in a progressive paralytic disease in transgenic mice with clinical features similar to human ALS [5]. Thus, G93A mice are widely used as a laboratory model to study the pathogenesis and treatment of ALS. Although multiple processes have been implicated in the pathogenesis of ALS, such as RNA processing errors, misfolded proteins, oxidative stress, mitochondrial dysfunction, and glutamate excitotoxicity [4], the mechanism of motor neuron degeneration in ALS remains largely unknown.

The role of spinal-cord inflammation in the progression of ALS is well recognized, and is reflected by the presence of elevated levels of proteins associated with inflammatory states such as phospholipase A_2 (PLA_2), cyclooxygenase (COX)-1 and COX-2 [6], and pro-inflammatory cytokines such as interleukin (IL)-6 [7], IL-8 [8], IL-18 [9], and tumor necrosis factor (TNF)-α, in the spinal cord [10]. In particular, growing evidence indicates that the numbers of activated microglia [11] and reactive astrocytes [12] increase in the spinal cords of ALS patients and model mice, indicating that inflammation plays an important role in a vicious cycle of motor neuron degeneration, implicating not only the motor neurons but also the neighboring non-motor neuron cells, especially microglia and astrocytes [13, 14]. Indeed, exogenous $SOD1^{G93A}$ has no direct neurotoxicity to primary motor neurons of mice, and is toxic only when the motor neurons are co-cultured with primary mouse microglia [15]. $SOD1^{G93A}$-activated microglia produce TNF-α, IL-1β, and superoxide [15]. IL-1α, TNF-α, and C1q released from activated microglia contribute to astrocyte activation [16], and a triple deletion of genes for these factors improves motor function and longevity in G93A mice [17]. In addition, increased astrocyte-specific expression of interferon (IFN)-stimulated gene 15 is observed in the spinal cords of G93A mice and ALS patients, and knockdown or knockout of IFN-α receptor 1 prolongs the lifespan of G93A mice [18]. These findings support the hypothesis that inflammation is associated with activation of microglia and astrocytes, and this plays an important role in the progression of ALS. By contrast, single knockout of IL-1β [19], IL-6 [20], or TNF receptor 2 [21] does not affect disease progression in G93A mice, suggesting compensatory mechanisms among these cytokines in ALS progression. An alternative interpretation suggests that the cooperative role of IL-1β, IL-6, and TNF receptor 2 should be important in the progression of ALS, similar to the significance observed with the triple genetic deletion of IL-1α, TNF-α, and C1q [17]. Furthermore, it should be noted that disease progression correlates with increases of different cytokines in cases with different ALS genetic variants [22]. Thus, the inflammatory response in ALS is very complex, and a deeper understanding is required to elucidate the pathogenesis of ALS.

Prostaglandin E_2 (PGE_2) is an eicosanoid lipid metabolite generated by the arachidonic acid cascade via multiple enzymatic reactions [23]. It is increased in postmortem brain tissues, cerebrospinal fluids (CSF), and sera from patients with sporadic ALS [24, 25], and in both the cerebral cortex and spinal cord of G93A mice [26, 27]. PGE_2 synthesis occurs when arachidonic acid is released from the cell membrane specifically by cytosolic PLA_2 ($cPLA_2$) and is metabolized by COX-1 and COX-2 to produce prostaglandin H_2 (PGH_2) [28]. Subsequently, PGH_2 is converted to PGE_2 by prostaglandin E synthase (PGES) [29, 30]. At least three distinct types of PGESs have been identified and characterized, namely, cytosolic PGES (cPGES) [31], microsomal PGES (mPGES)-1 [32], and mPGES-2 [33]. cPGES and mPGES-2 are constitutively expressed and involved in the physiological production of PGE_2, while mPGES-1 is inducible under inflammatory conditions and is functionally coupled to COX-2 [34]. The newly synthesized PGE_2 binds to specific G-protein-coupled receptors (i.e., E-prostanoid receptors [EP] 1 to 4) at the cell-surface membrane, where it exerts its physiological functions [29, 30]. Functionally, EP1 increases intracellular Ca^{2+} levels via $G_{\alpha q}$-dependent activation of phospholipase C; EP2 and EP4 increase intracellular levels of cyclic adenosine monophosphate (cAMP) via $G_{\alpha s}$-dependent activation of adenylyl cyclase; and EP3 increases or decreases intracellular cAMP via $G_{\alpha s}$ or $G_{\alpha i}$, respectively [35]. The binding affinities of PGE_2 to the EPs are as follows: EP3 ($K_i = 0.9$ nM) > EP4 ($K_i = 1.9$ nM) > EP2 ($K_i = 12$ nM) > EP1 ($K_i = 20$ nM) [36]. Free PGE_2 is rapidly oxidized to 15-ketoPGE_2 by 15-hydroxyprostaglandin dehydrogenase (15-PGDH), followed by reduction of the Δ^{13} double bond by Δ^{13}-15-keto prostaglandin reductase and β-oxidation, resulting in biological inactivation [37, 38]. 15-PGDH is the key enzyme in the biological inactivation of PGE_2, catalyzing the first step. To date, there are two known isoforms of 15-PGDH: NAD^+-dependent (type-I) and $NADP^+$-dependent (type-II) [39]. Type I has a *K*m value of 8.60, whereas type II has a *K*m value of 81.1 [40], suggesting that the type I 15-PGDH plays a major role in the catabolism of PGE_2. Figure 1 shows the major biosynthetic and metabolic pathways of PGE_2. To date, accumulatig evidence demonstrates that PGE_2 can

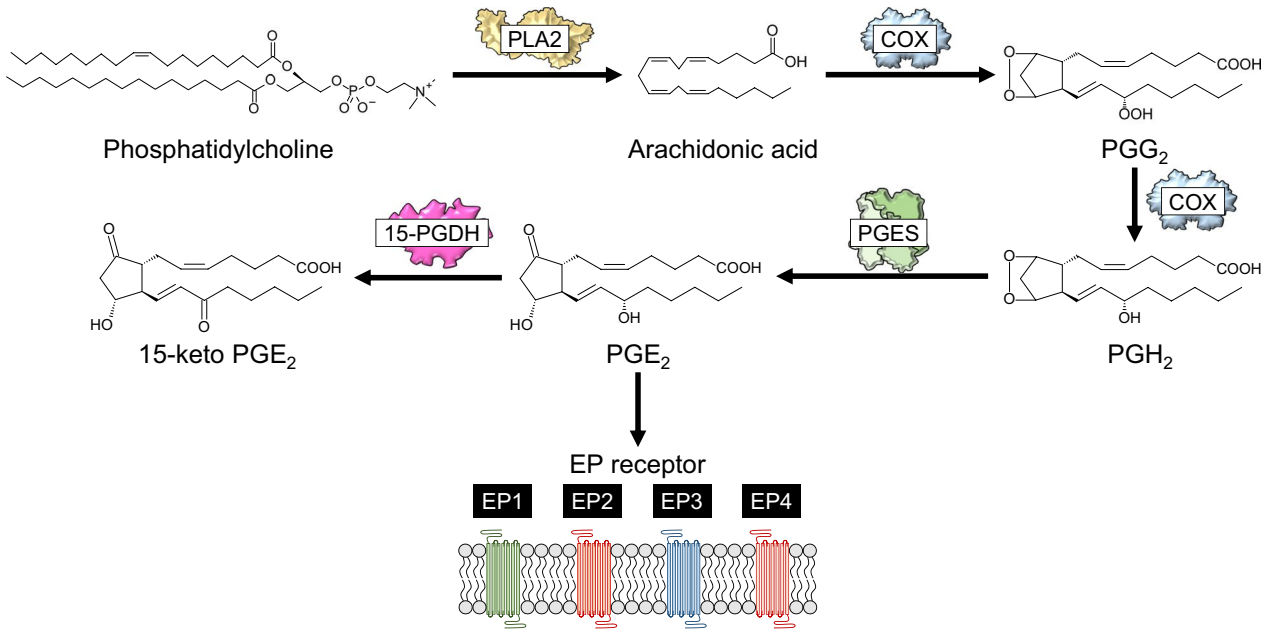

Fig. 1 The biosynthetic and metabolic pathways of PGE_2. COX, cyclooxygenase; EP1-4, E-prostanoid receptor 1–4; 15-PGDH, 15-hydroxyprostaglandin dehydrogenase; PGE_2, prostaglandin E_2; PGES, prostaglandin E synthase; PGG_2, prostaglandin G_2; PGH_2, prostaglandin H_2; PLA_2, phospholipase A_2

have opposite effects on neurons, either contributing to neuroprotection or enhancing neuroinflammatory and neurodegenerative processes [41]. Understanding the pathological function of PGE_2 in ALS will allow development of new therapies.

In this paper, we summarize the roles of PGE_2-related enzymes and receptors in ALS and the effects of PGE_2 on motor-neuron death, and discuss the potential of PGE_2 as a target for therapeutic regeneration in ALS.

Roles of the mPGES-1-dependent synthetic pathway and the 15-PGDH-dependent catabolic system in ALS

The expressions of $cPLA_2$ and COX-2 are up-regulated in the spinal cords of ALS patients and ALS model mice [6, 42–44]. Nimesulide, a COX-2-selective inhibitor, suppresses PGE_2 elevation in the spinal cord, delays the onset of motor deficits, and tends to prolong the survival of G93A mice [45]. Furthermore, inhibition of COX-2 in G93A mice by celecoxib or rofecoxib, which are more selective than nimesulide, reduces the production of PGE_2, delays the onset of weight loss, ameliorates motor performance degeneration, extends survival, and protects against depletion of motor neurons in the spinal cord [26, 46]. We previously discovered that the protein level of mPGES-1 in the spinal cord was significantly increased after 15 weeks of age, which represents the early symptomatic stage, while the levels of cPGES and mPGES-2 remained constant with age [47]. Similar to the increased expression of mPGES-1, we found that the protein level of Iba1, a microglial marker, was also significantly increased in the G93A mice after 15 weeks of age. Surprisingly, our immunofluorescence staining assay demonstrated that mPGES-1 was co-localized with motor neurons both at 11 weeks (a pre-symptomatic stage) and at 15 weeks of age in these mice. On the contrary, co-localization of mPGES-1 with Iba1-positive microglia was detected in the spinal cords of G93A mice only at 15 weeks. Unlike the microglial marker Iba1, expression of the astrocytic marker glial fibrillary acidic protein (GFAP) was increased at 17 and 19 weeks of age (the symptomatic and end stage, respectively), with little co-localization with mPGES-1. These results suggest that, at the early symptomatic stage, mPGES-1, but not cPGES or mPGES-2, contributes to the PGE_2 increase in activated microglia in the spinal cord and to the progression of motor neuron degeneration in ALS.

Interestingly, AAD-2004, a dual-function drug derived from 5-aminosalicylate and sulfasalazine, has been reported to prevent PGE_2 production, microglial activation, and motor neuron degeneration through blockade of both mPGES-1 and free-radical production in G93A mice, resulting in amelioration of motor function and prolonged survival [48]. Moreover, the therapeutic effect of AAD-2004 is superior to that of ibuprofen, a type of non-steroidal anti-inflammatory drug (NSAID) [48]. While these results seem to support ours, it should

be noted that the therapeutic effect of AAD-2004 is not only dependent on the inhibition of mPGES-1, but also requires direct free-radical scavenging. Deletion of mPGES-1 has been reported to suppress oxidative stress in angiotensin II-treated hyperlipidemic mice [49] and in 6-hydroxydopamine (6-OHDA)-treated mice [50]. These reports make it difficult to determine the degree to which free-radical scavenging contributes to the therapeutic efficacy of AAD-2004, and thus it is worth investigating the therapeutic effects of mPGES-1 inhibitors without direct free-radical scavenging activity in ALS, in comparison with the effects of combination of NSAIDs and antioxidants. In addition, AAD-2004 lowers PGE_2 levels without affecting the production of prostacyclin (PGI_2) in the lumbar spinal cord of G93A mice [48]. Considering that a sustained-release PGI_2 receptor agonist, ONO-1301-MS, improves motor function and prevents loss of motor neurons in G93A mice [51], the selective inhibition of PGE_2 production by mPGES-1 is more beneficial for the treatment of ALS than the non-selective inhibition of PG production by COX-2.

Our study described above revealed the involvement of synthetic steps of PGE_2 in ALS [47]. With regard to the degradation process of PGE_2, our previous study [27] detected a band immunoreactive for 15-PGDH in the spinal cord of G93A mice starting at 15 weeks (the early symptomatic stage), and its expression was significantly increased at 17 weeks and older. Immunohistochemical analysis showed that 15-PGDH was co-localized with GFAP-positive astrocytes at 19 weeks. Unlike mPGES-1, 15-PGDH did not co-localize with NeuN-positive motor neurons or Iba-1-positive microglia in the spinal cord of G93A mice. Surprisingly, despite an increase in 15-PGDH in astrocytes, PGE_2 levels in the lumbar spinal cord were increased in an age-dependent manner, with a significant increase at 19 weeks. These results suggest that the production of PGE_2 overwhelms the increase of 15-PGDH and its activity in astrocytes at the end stage of ALS. An in vitro study reported that the uptake of PGE_2 via the prostaglandin transporter, an organic anion transporter, as well as 15-PGDH, is required for PGE_2 catabolism [52]. Although further studies are required to determine the expression of the prostaglandin transporter in spinal astrocytes in G93A mice, these results suggest that astrocytes expressing 15-PGDH internalize PGE_2 synthesized by mPGES-1-expressing motor neurons and microglia to maintain PGE_2 homeostasis.

Combining these results with those of our studies [27, 47], we offer a new concept that a significant increase of PGE_2 level is attributable to an imbalance between the mPGES-1-dependent synthetic pathway and the 15-PGDH-dependent scavenging system in ALS model mice (Fig. 2). Unlike our results from G93A mice, a decrease in the expression or activity of 15-PGDH correlates with an increase of PGE_2 in the hypothalamus of a rat model of chronic unpredictable mild stress [53] and in ischemic regions including cortex, striatum, and hippocampus in a rat stroke model (middle cerebral artery occlusion-reperfusion) [54]. Therefore, an imbalance in the synthesis and catabolism of PGE_2, despite an increase in 15-PGDH, may be the pathogenic mechanism of the transition from the early-symptomatic stage of ALS or motor-neuron disease. However, currently there have been no reports on the role of mPGES-1 and 15-PGDH in ALS patients, even in patients with other neurodegenerative diseases. Therefore, further investigation of their clinical significance is warranted.

The pathophysiological role of EPs in motor neurons in ALS

PGE_2 exerts its physiological functions by binding to the EPs. The activation of EP1 contributes to neurotoxicity in cultured rat mesencephalic neurons [55]. EP2 has been shown to induce caspase-3–dependent cell death in cultured rat cortical and hippocampal neurons [56, 57]. EP3 activation mediates the glutamate-induced excitotoxicity in cultured rat hippocampal slices [58]. In contrast, EP2 protects against glutamate cytotoxicity in cultured rat hippocampal neurons [59]. Furthermore, EP2 and EP3 have a protective effect against glutamate cytotoxicity induced by glutamate transporter inhibition in rat organotypic spinal cord slice cultures [60]. The EP4 receptor agonist ONO-AE1-329 attenuates injury in the brain in an acute murine model of the *N*-methyl-*D*-aspartate-induced excitotoxicity [61]. These studies suggest that PGE_2 exerts protective or pathogenic effects against neurotoxicity, depending on the subtype or the cell target of the activated EP. The NSC-34 cell line is the most studied motor-neuron cell line, and is produced by the fusion of mouse neuroblastoma cells with motor neurons taken from embryonic spinal cords [62]. Differentiated NSC-34 cells are reported to exhibit the unique morphological and physiological characteristics of primary motor neurons [62, 63]. Our group was the first to identify the distribution of EP subtypes and their effects on the PGE_2-induced cell death in differentiated NSC-34 cells [64]. EP2 and EP3 were highly expressed in mouse spinal cord motor neurons and in differentiated NSC-34 cells. Exposure of NSC-34 cells to exogenous PGE_2 and butaprost, an EP2-selective agonist, resulted in decreased cell viability in a concentration-dependent manner, whereas exposure to sulprostone, an EP1 and EP3 agonist, did not. These results suggest that activation of EP2, but not EP3, contributes to the PGE_2-induced motor-neuron death.

In support of our results [64], genetic deletion of EP2 has been reported to down-regulate the

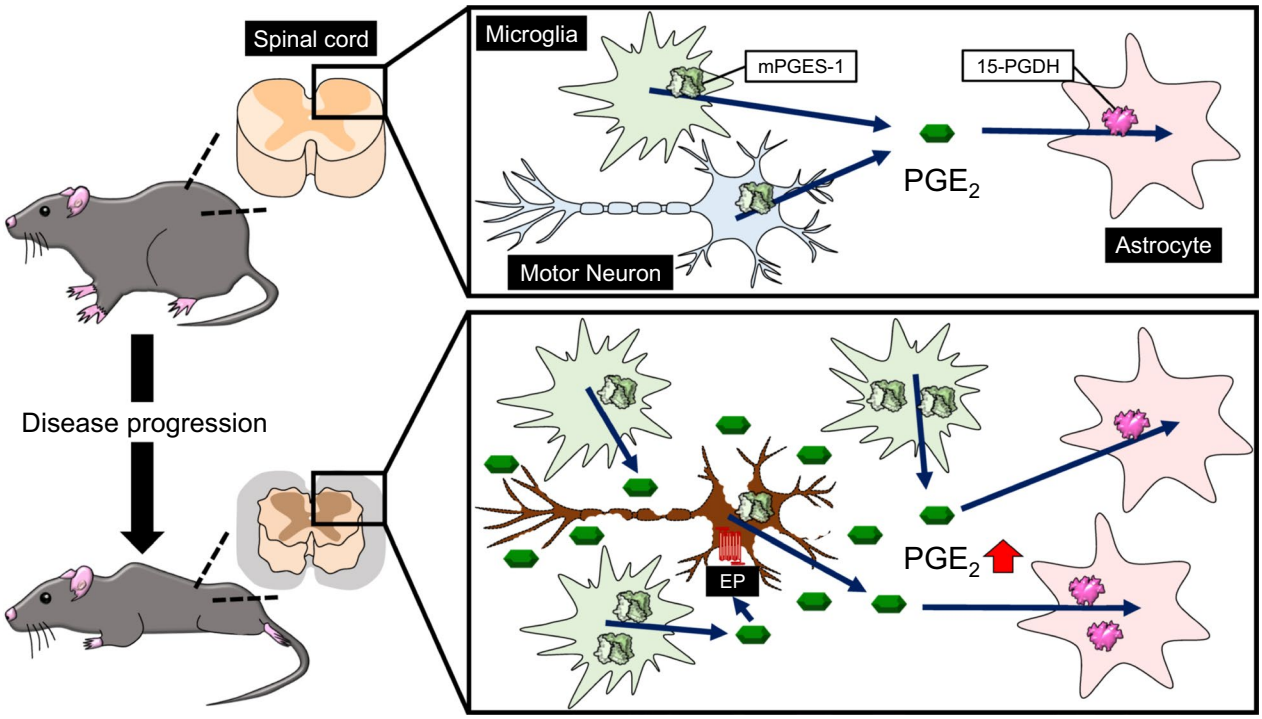

Fig. 2 Changes in PGE_2 synthesis and metabolism during disease progression in G93A model mice. EP, E-prostanoid receptor; mPGES-1, microsomal prostaglandin E synthase-1; 15-PGDH, 15-hydroxyprostaglandin dehydrogenase; PGE_2, prostaglandin E_2

pro-inflammatory process, improve motor strength and extend survival of G93A mice [65], suggesting that the PGE_2–EP2 axis plays an important role in ALS neurodegeneration. Liang et al. also revealed that the expression of EP2 was increased in GFAP-positive astrocytes and Iba1-positive microglia of spinal cord [65]. We demonstrated that the EP2 immunoreactivity that co-localized with motor neurons in G93A mice at 15 weeks (the early symptomatic stage) was significantly more intense than that in age-matched wild-type mice and than that at 11 weeks (the pre-symptomatic stage) [66]. An in vitro study using differentiated NSC-34 cells showed that PGE_2 up-regulated the expression of EP2. The cells with an increased level of EP2 resulting from pre-treatment with PGE_2 were significantly more vulnerable to the PGE_2-induced cell death. Consistently, PGE_2 is involved in the up-regulation of EP1 and EP4 in dorsal root ganglion neurons from partial sciatic nerve-ligated rats [67] and in the up-regulation of EP1 and EP2 in primary rat hepatocytes [68]. Although the mechanism underlying the positive-feedback regulation of EP2 in vivo has yet to be clarified, these results suggest that PGE_2 increases the expression of EP2 in motor neurons during the early symptomatic stage of ALS, and that its increased expression directly drives neurodegeneration in ALS.

A growing body of evidence implicates the dysfunction of cellular reduction/oxidation, termed oxidative stress, in the pathogenesis of ALS [69]. Indeed, edaravone, a free-radical scavenger, was approved as a therapeutic drug for ALS in 2015 in Japan and South Korea, and in 2017 in the United States [70]. The most important point is that oxidative stress causes inflammatory responses, and conversely, uncontrolled inflammation leads to cellular accumulation of reactive oxygen species (ROS), which are involved in oxidative stress [71, 72]. ROS activate a wide range of signaling pathways, such as nuclear factor κB, activator protein-1, and CBP/p300, and thus have been implicated in the induction of expression of $cPLA_2$, COX-2, and mPGES-1 [73]. IL-1β induces the up-regulation of PGE_2 through ROS production in primary human synovial fibroblasts, a process mediated by $cPLA_2$ [74]. Induction of COX-2 expression by IL-1, TNF-α, and lipopolysaccharide (LPS) also mediates ROS accumulation in rat mesangial cells [75]. By contrast, genetic deletion of mPGES-1 has been found to prevent the 6-OHDA-induced production of PGE_2 and oxidative stress-mediated neurotoxicity in dopaminergic neurons of the substantia nigra of mice, and that exogenous application of PGE_2 to mPGES-1-knockout neurons reverses the 6-OHDA-induced production of PGE_2 and neurotoxicity [50]. This suggests that PGE_2 plays an important role

in ROS induction in oxidative stress-mediated neuronal death. Consistent with this report, our recent study demonstrated that exposure of differentiated NSC-34 cells to PGE_2 resulted in a significant increase in intracellular ROS levels [76]. Pre-treatment with *N*-acetyl-*L*-cysteine (NAC), which is widely used as a pharmacological antioxidant, prevented the PGE_2-induced increases in intracellular ROS production and cleaved caspase-3, resulting in increased cell viability. Furthermore, similar to the results with PGE_2, butaprost, an EP2-selective agonist, induced an increase in the generation of intracellular ROS and cleaved caspase-3, and these effects were inhibited by NAC. By contrast, sulprostone, an EP1 and EP3 agonist, transiently decreased the level of intracellular ROS. We also showed that PF-04418948, an EP2-selective antagonist, suppressed the PGE_2-induced generation of intracellular ROS. Moreover, dibutyryl-cAMP, a cell-permeable cAMP analog, partially mimicked the PGE_2- and butaprost-induced stimulation of intracellular ROS and neurotoxicity in differentiated NSC-34 cells [76]. Based on these results, we conclude that in differentiated NSC-34 cells, PGE_2 activates EP2 to induce caspase-3-dependent apoptosis by the production of intracellular ROS, and that an increase in intracellular cAMP is at least partly involved as a downstream effect of the PGE_2–EP2 pathway. In support of our results, deletion of EP2 results in a significant decrease in F4-neuroprostanes, specific markers of oxidative injury to neuronal elements, in APP-Swe/PSEN1dE9 mice [77] and G93A mice [65]. Moreover, the cAMP-dependent protein kinase A signaling pathway is reported to be activated under hypoxic conditions and exacerbate hypoxia-induced ROS formation in PC12 cells [78]. However, another study demonstrated that butaprost is protective against 6-OHDA-mediated oxidative stress through cAMP-dependent protein kinase A activity in cultured primary dopaminergic neurons prepared from embryonic rat midbrain [79]. Although further studies are required to identify the downstream mechanisms of the EP2–cAMP axis responsible for ROS production by PGE_2, our studies demonstrated that PGE_2 has the ability to induce direct neurotoxicity via the EP2–cAMP–ROS axis in motor neuron-like NSC-34 cells. The mechanism of the PGE_2-induced cell death in differentiated NSC-34 cells is summarized in Fig. 3.

Mouse EP3 has three distinct splicing variants: the EP3α and the EP3β isoforms are coupled to $G_{\alpha i}$ and the EP3γ isoform is coupled to both $G_{\alpha s}$ and $G_{\alpha i}$ [80]. In our previous study, the expression of EP3α and EP3γ, but not EP3β, was detected in the spinal cords of wild-type and G93A mice [81], and the expression was not significantly different between wild-type and G93A mice. Next, laser-capture microdissection was performed to dissect out motor neurons from samples of lumbar spinal cord. In the motor neurons, EP3γ mRNA expression

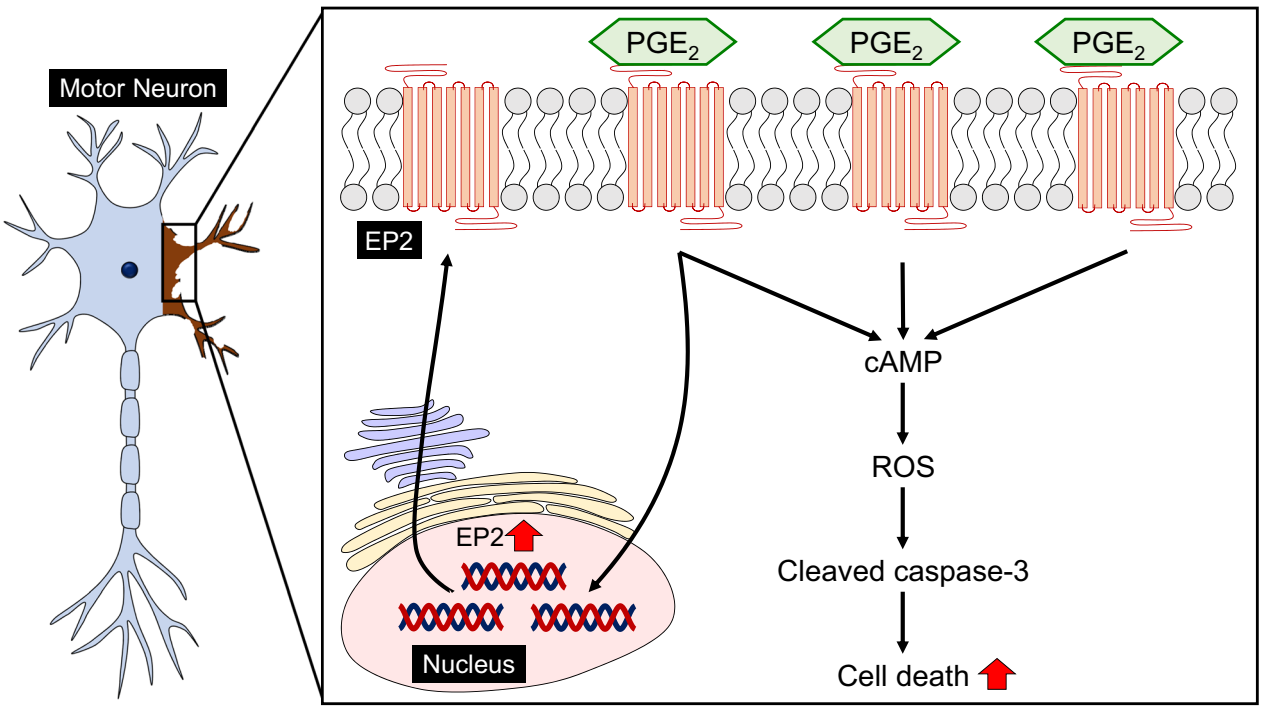

Fig. 3 A proposed mechanism underlying the PGE_2-induced motor neuron degeneration. cAMP, cyclic adenosine monophosphate; EP2, E-prostanoid receptor-2; PGE_2, prostaglandin E_2; ROS, reactive oxygen species

was predominant in both wild-type and G93A mice, whereas EP3α and EP3β mRNAs were not detected. Similar to the results in spinal cords, the expression level of EP3γ in motor neurons did not differ between G93A and wild-type mice [81]. Furthermore, EP3γ has predominant mRNA expression in differentiated NSC-34 cells [76]. Our previous studies showed that activation of EP3, unlike EP2, failed to contribute to PGE_2-induced cell death in motor neurons [64, 66, 76]. However, another study using rat organotypic spinal cord slice cultures showed that sulprostone had a protective effect against glutamate neurotoxicity [60]. Therefore, further investigations are warranted to determine the effect of EP3 on neuronal cell death induced by species other than PGE_2 and associated with the progression of ALS.

Possible crosstalks between pro-inflammatory cytokines and PGE_2 in ALS

mPGES-1, 15-PGDH, and EP2 have been shown to be induced in the spinal cords in G93A mice. However, the underlying mechanism of the induction in ALS remains to be determined. One possible contributor to the induction of these expressions is pro-inflammatory cytokines. The spinal cords of mice injected with either IL-1β or TNF-α show increased expression of COX-2 [82]. TNF-α induces PGE_2 synthesis via increased expression of COX-2 and mPGES-1 in primary mixed spinal cord cells from mice [83]. Polyinosinic-polycytidylic acid increases PGE_2 production through induction of COX-2 and mPGES-1 synthesis in primary rat microglia [84]. In primary mouse astrocytes, PGE_2 expression can be induced by TNF-α [85] and IL-1β stimulation [86]. Although the mechanism of 15-PGDH expression in the nervous system is unknown, IL-4 has been reported to increase it in human lung cancer cells [87]. Furthermore, IL-1β increases the expression of EP2 and EP4 in primary rat hippocampal neurons [88], and EP3 expression in primary rat astrocytes and the U373 human astrocyte cell line [89]. However, in another study, IL-1β and TNF-α did not alter the mRNA expression of EP receptors in primary rat dorsal root ganglia cells [90], suggesting that the regulation of EP expression by proinflammatory cytokines depends on the cell type. These studies indicate that pro-inflammatory cytokines induce up-regulation of mPGES-1, 15-PGDH, and EPs under pathological conditions, and further studies are required.

Interestingly, however, PGE_2 suppresses the LPS-induced COX-2 and mPGES-1 expression and decreases TNF-α production via activation of EP2 in primary mouse mixed spinal cord cells [91]. Studies using the BV-2 mouse microglial cell line have also reported that PGE_2 suppresses the LPS-induced IL-18 expression [86] and the amyloid-β (Aβ)-induced TNF-α expression [92]. The latter may be mediated by EP4 [92]. These reports support for a protective role of PGE_2, contrary to our studies. Considering that COX-2-selective inhibitors [26, 45, 46] and a mPGES-1 inhibitor [48] suppress disease progression in G93A mice, the responsiveness to PGE_2 may differ between LPS-stimulated transient inflammatory conditions and the chronic inflammatory conditions of ALS. Most importantly, previous studies have reported that the primary astrocytes from G93A mice [85] and TDP-43–deficient microglia [93] show upregulation of COX-2 expression and PGE_2 production. G93A mouse-derived primary astrocytes have higher levels of basal TNF-α and elicit a greater increase in TNF-α expression after either a IFN-γ or a TNF-α challenge compared with those from non-transgenic mice [85]. Therefore, although further investigations are required, the chronic increase in basal levels of PGE_2 in $SOD1^{G93A}$ mice may facilitate the transition of astrocytes into a more active inflammatory state. Furthermore, TDP-43-deficient microglia induced neuronal death in a co-culture system, which was suppressed by the COX-2 inhibitor celecoxib [93], suggesting that the glial cells with genetic variant associated with ALS, not limited to $SOD1^{G93A}$, contribute to neurodegeneration in ALS through elevated basal levels of PGE_2.

Limitations due to the failure of a clinical study and the potential of PGE_2 as a differentiation factor

We here examine the role of the PGE_2-related enzymes and receptors in ALS and the cytotoxicity and interactions of PGE_2 relevant to motor neurons, and we discuss the importance of PGE_2 for the progression of ALS. This review has some limitations, but it also has some important implications for future studies.

First, even though COX-2 inhibitors improve motor function and prolong the life span of G93A mice [26, 45, 46], no anti-inflammatory drugs, including COX-2 inhibitors, have shown significant benefits in clinical studies in ALS patients [94]. The administration of celecoxib at 800 mg/day for 12 months did not improve muscle strength, vital capacity, estimated exercise units, or the ALS Functional Rating Scale-Revised, nor did it prolong survival [95]. The most notable issue is an absence of PGE_2 increase in the CSF of ALS patients, and that celecoxib did not reduce PGE_2 levels in the CSF of ALS patients [95]. However, other studies have reported increased levels of PGE_2 in the CSF of sporadic ALS patients [24, 25]. For instance, Cudkowicz et al. suggested that the failure to detect high levels of PGE_2 was due to the absence of a significant degree of inflammation at the disease stage studied, or due to the fact that PGE_2 levels in the CSF do not necessarily reflect COX-2 activity in the central nervous system [95]. This discrepancy

may be explained by the expression and localization of mPGES-1 in the spinal cord [48]. Although the measured concentrations in clinical studies refer to levels in the CSF, the local tissue concentrations are more important because PGE_2 acts as an autocrine or paracrine factor in target cells. We observed that mPGES-1 co-localizes with motor neurons and activated microglia of the spinal cord [48], suggesting that the local up-regulation of mPGES-1 under pathological conditions contributes to increased local concentrations of PGE_2 and that PGE_2 can be produced locally even under COX-2 inhibition. Thus, inhibition of mPGES-1 or antagonism of EP2 remains useful therapeutic targets. However, the local cellular concentrations of PGE_2 in the spinal cord are unknown. Furthermore, no studies have tested mPGES-1 inhibitors [96] or EP2 antagonists in ALS patients, so their usefulness in humans is unclear; further studies are required. Most recently, it has been reported that the combination of ciprofloxacin and celecoxib restores the morphological defects and abnormal neuromuscular junctions of motor neurons and improves locomotor function in SOD1 G93R transgenic zebrafish and TDP-43-mutant zebrafish, compared to treatment with each drug alone [97]. Therefore, the potential synergistic effects of COX-2 inhibitors with other pharmaceuticals are of interest.

Second, the PGE_2–EP2–cAMP signaling pathway may be involved not only in motor-neuron cell death but also in motor-neuron differentiation [98]. We previously showed that PGE_2 induces morphological differentiation through EP2 activation in undifferentiated NSC-34 cells. Moreover, the cAMP signaling axis is at least partially involved in the molecular mechanisms of these effects [99]. Furthermore, it is noteworthy that PGE_2-differentiated cells have the physiological and electrophysiological properties of mature motor neurons [100]. Previous studies have reported that the COX-2 inhibitors meloxicam and nimesulide suppress neurogenesis in the olfactory bulb in the adult mouse brain [101], and that PGE_2 promotes the neural differentiation of mouse brain-derived neuroectodermal stem cells [102], suggesting that PGE_2 plays a key role in the differentiation of endogenous neural stem/progenitor cells into neural cells. Interestingly, neural progenitor cells were reported to migrate to regions near degenerated motor neurons in the spinal cord of G93A mice during the early symptomatic and symptomatic stages and then differentiate into neurons [103]. According to discussions of mPGES-1 in the first limitation, high concentrations of PGE_2 are present near degenerated motor neurons. Although further studies using adult neural progenitor cells derived from the spinal cord are required to clarify the role of PGE_2 in the differentiation of motor neurons, these shreds of evidence suggest that PGE_2 may also play an important role in a neurogenesis process that compensates for the neurodegeneration of ALS. Taken together, these results suggest new physiological roles for PGE_2, where it can exert multiple effects depending on the stage of neurodevelopment of spinal motor neurons. This supports the hypothesis that increased PGE_2 in the spinal cord, the mechanistic focus of ALS, is induced to promote the differentiation of new motor neurons, but the net effect is toxicity to surrounding mature motor neurons, resulting in the exacerbation of ALS.

The pathophysiological roles of PGE_2 in other neurodegenerative diseases

The level of PGE_2 in the central nervous system is also increased in other neurodegenerative disorders, such as in the CSF in Alzheimer's disease (AD) [104] and in the substantia nigra in Parkinson's disease (PD) [105].

AD is the most common cause of dementia/memory loss [106], characterized by accumulation of Aβ and neuronal tau proteins in the brain, which leads to the destruction of cholinergic neurons and damage to brain tissue. In the brains of AD patients, COX-1 accumulates mainly in microglia, whereas COX-2 accumulates mainly in neurons [107]. Furthermore, immunofluorescence staining of AD brain tissues showed that the expression of mPGES-1 was increased in neurons, microglia, astrocytes, and endothelial cells [108], and that mPGES-2 was markedly increased in pyramidal neurons [109]. Clinical trials have reported that treatment with indomethacin, a nonselective COX inhibitor, ameliorates cognitive impairment in patients with AD [110], and that naproxen, a selective COX-2 inhibitor, blocks the Aβ-mediated suppression of long-term potentiation and memory function in Tg2576 AD model mice [111]. Interestingly, PGE_2 induces the production of Aβ through activation of EP2 and EP4 both in vitro and in vivo [112, 113]. Genetic deletion of EP2 prevents oxidative brain damage, reduces Aβ levels, and improves the spatial memory of AD model mice [77, 114]. Unfortunately, as of May 27, 2023, there have been no clinical trials on AD that target the enzymes or receptors associated with PGE_2 [115].

Huntington's disease (HD) is an autosomal dominant pathological disease characterized by a movement disorder and dementia [116]. Although the expression and distribution of PGE_2-related enzymes and receptors in HD are poorly understood, in vivo studies in R6/1 HD model mice showed that antagonization of EP1 by SC-51089 ameliorated memory and motor deficits [117], while activation of EP2 by misoprostol ameliorated long-term memory deficits through up-regulation of brain-derived neurotrophic factor in the hippocampus [118]. These reports suggest that EP could be a promising therapeutic target; to our knowledge, there has been no report on the

Table 1 The pathophysiological roles of PGE_2 and its related enzymes and receptors in ALS and other neurodegenerative diseases

	Enzymes				Receptors			
	PGE_2	**COX**	**PGES**	**15-PGDH**	**EP1**	**EP2**	**EP3**	**EP4**
ALS	*Increase* Model mice: cerebral cortex and spinal cord [26, 27] Patients: brain tissue, CSF, and serum [24, 25]	*Upregulation* Model mice: COX-2 in spinal cord [45]; Patients: COX-2 in spinal cord [6] *Treatment* Model mice: Nimesulide—Delay in the onset of movement disorders and tendency to prolong survival [45] Celecoxib —Delay in the onset of movement disorders and prolong survival [26, 46] Rofecoxib —Delay in the onset of movement disorders and prolong survival [26] Patients: Celecoxib —No effect [94]	*Upregulation* Model mice: mPGES-1 in motor neurons and microglia [47]	*Upregulation* Model mice: astrocytes [27]	Unknown	*Upregulation* Model mice: Astrocytes [65], microglia [65] and motor neurons [66] *Treatment* Model mice: Knockout—Prolong survival [65], and suppression of oxidative injury [65]; Model cells: Butaprost (agonist)—Caspase-3-dependent apoptosis via ROS production [76]	*No change* Model mice: Motor neurons [81]	Unknown
AD	*Increase* Patients: CSF [104]	*Upregulation* Patients: COX-1 in microglia, and COX-2 in neurons [73] *Treatment* Model mice: Naproxen—Improvement of memory function[111] Patients: Indomethacin—Improvement of cognitive impairment [110]	*Upregulation* Patients: mPGES-1 in neurons, microglia, astrocytes, and endothelial cells [108]; mPGES-2 in pyramidal neurons [109]	Unknown	Unknown	*Treatment* Model mice: Knockout – Suppression of oxidative injury [77, 114]; Model cells: AE-259 (agonist) – Enhanced Aβ production [113]	Unknown	*Treatment* Model cells: AE-329 (agonist)—Enhanced Ap production [113]
HD	Unknown	Unknown	Unknown	Unknown	*Treatment* Model mice: SC-51089 (antagonist)—Improvement of memory and motor deficits [119]	*Treatment* Model mice: Misoprostol (agonist)—Improvement of longterm memory deficits [118]	Unknown	Unknown

Table 1 (continued)

	Enzymes				Receptors			
	PGE_2	**COX**	**PGES**	**15-PGDH**	**EP1**	**EP2**	**EP3**	**EP4**
PD	*Increase* Patients: substantia nigra [105]	*Upregulation* Patients: substantia nigra [50] *Treatment* Model mice: DuP697—Inhibition of dopaminergic neurotoxicity [121] Valdecoxib—Improvement of motor deficits [122] Patients: NSAIDs other than ibuprofen—No effect [123] Ibuprofen—Lower risk of development than non-use [124]	*Upregulation* Patients: mPGES-1 in substantia nigra [120] *Treatment* Model mice: Knockout—Suppression of the 6-OHDA-induced neurodegeneration [50]	Unknown	Unknown	*Treatment* Model cells: Butaprost (agonist)—Protection against oxidative stress [79]; Knockout—Enhanced microglia-mediated α-synuclein clearance [125]	Unknown	Unknown
MS	*Increase* Model mice: cerebral cortex, cerebellum, and spinal cord [127]	*Upregulation* Model mice: COX-1 and COX-2 in cerebral cortex, cerebellum, and spinal cord [92] *Treatment* Model mice: Indomethacin—Delay in the progression [126]	*Upregulation* Model mice: mPGES-1 in macrophages in spinal cord [128] Patients: mPGES-1 in macrophages in the brain [128] *Treatment* Model mice: Knockout—Improvement of clinical score [129]	Unknown	Unknown	*Function* Model mice: Enhanced generation of T helper 1 and helper 17 cells [130]	Unknown	*Function* Model mice: Enhanced generation of T helper 1 and helper 17 cells, and prevention of BBB invasion by these cells [130]

Aβ, amyloid β; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; COX, cyclooxygenase; CSF, cerebrospinal fluid; EP, E-prostanoid receptor; HD, Huntington's disease; mPGES-1, microsomal prostaglandin E synthase-1; MS, multiple sclerosis; 6-OHDA, 6-hydroxydopamine; PD, Parkinson's disease; 15-PGDH, 15-hydroxyprostaglandin dehydrogenase; PGE_2, prostaglandin E_2; ROS, reactive oxygen species

clinical significance of PGE_2 in HD, so further investigation is warranted.

PD is characterized by abnormal α-synuclein aggregations known as Lewy bodies and Lewy neurites, resulting in bradykinesia due to massive death of the nigrostriatal dopaminergic neurons [119]. Consistent with increased PGE_2 [105], the expressions of COX-2 and mPGES-1 are up-regulated in the substantia nigra of post-mortem PD brains compared to those of healthy controls [50, 120]. Previous studies in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced mouse model of PD showed that DuP697, a selective COX-2 inhibitor, significantly reduced PGE_2 production and dopaminergic neurotoxicity [121], and that COX-2 deficiency combined with the COX-2-specific inhibitor valdecoxib attenuated the microglial activation, the loss of dopaminergic neurons, and the motor deficits [122]. However, a nested case–control study found no benefit of NSAIDs in PD [123]. Conversely, a meta-analysis by Gao et al. demonstrated that ibuprofen, unlike other NSAIDs or acetaminophen, lowers the risk of early PD progressing to PD compared to non-administration [124]; thus the neuroprotective effect of ibuprofen is noteworthy. In vitro studies reported that activation of EP1 was selectively neurotoxic to dopaminergic neurons in rat embryonic primary mesencephalic neuronal cultures [55], and that activation of EP2 by butaprost protected against the 6-OHDA-induced oxidative stress in midbrain-derived dopaminergic neurons from embryonic rats [79]. By contrast, ablation of EP2 enhanced microglia-mediated α-synuclein clearance in a co-culture of mouse microglia and mesocortical slices from patients with Lewy body disease. Ablation of EP2 also significantly reduced the level of neurotoxicity and α-synuclein aggregation in mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [125]. Because of these conflicting results [79, 125], the therapeutic effects of EP2 on PD warrant further investigation.

Multiple sclerosis (MS) is an autoimmune disease characterized by white-matter lesions attributable to loss of the myelin sheaths around the axons of neurons [126]. Although PGE_2 levels in MS patients are unknown, elevated expression of COX-1 and COX-2 and levels of PGE_2 have been observed in the cerebral cortex, cerebellum, and spinal cord of MS model mice with experimental autoimmune encephalomyelitis (EAE) [127]. In support of this, indomethacin, a non-selective COX inhibitor, attenuates the progression of EAE [128]. Furthermore, mPGES-1 upregulation occurs in macrophages in the spinal cord lesions of the EAE mouse model and in the brain tissues of MS patients [129]. mPGES-1-deficient mice have better clinical scores and suppressed responses of T helper 1 and helper 17 cells compared with non-deficient mice after EAE induction [129]. In EAE mice, PGE_2 has two opposing effects: it promotes the generation of T helper 1 and helper 17 cells through EP2 and EP4 while protecting the blood–brain-barrier via EP4 to prevent invasion of these cells into the brain [130].

Taken together, these studies indicate that PGE_2 is strongly correlated with the significant neuroinflammation characterizing the pathogenesis of neurodegenerative diseases, including ALS (Table 1).

Conclusions

Here, we summarize evidence on the pathophysiological role of PGE_2 in neurodegenerative diseases, mainly focusing on ALS. PGE_2 and its enzymes and receptors possess dual (destructive and neuroprotective) effects in multiple neurodegenerative disorders. Therefore, it should be noted that not only the local concentrations of PGE_2 present in the lesion site but also the target cells and subtypes of activated receptors of PGE_2 are involved in the disease, and further studies are required to clarify the pathophysiological role of PGE_2 in neurons. A major challenge remains in adequately and sustainably delivering PGE_2-specific inhibitors locally to target cells. This article provides new evidence on the spatiotemporal role of PGE_2 synthetic and metabolic enzymes and receptors in the mechanism of cell death in ALS. We thus provide a new insight: selective inhibition of mPGES-1 and EP2 is potentially a new therapeutic strategy for patients with ALS.

Abbreviations

15-PGDH	15-Hydroxyprostaglandin dehydrogenase
6-OHDA	6-Hydroxydopamine
AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
Aβ	Amyloid-β
cAMP	Cyclic adenosine monophosphate
COX	Cyclooxygenase
cPGES	Cytosolic PGES
$cPLA_2$	Cytosolic PLA_2
CSF	Cerebrospinal fluids
EAE	Experimental autoimmune encephalomyelitis
EP	E-prostanoid receptor
fALS	Familial ALS
GFAP	Glial fibrillary acidic protein
HD	Huntington's disease
IFN	Interferon
IL	Interleukin
LPS	Lipopolysaccharide
mPGES	Microsomal PGES
MS	Multiple sclerosis
NAC	*N*-acetyl-*L*-cysteine
NSAID	Non-steroidal anti-inflammatory drug
PD	Parkinson's disease
PGE_2	Prostaglandin E_2
PGES	Prostaglandin E synthase
PGH_2	Prostaglandin H_2
PGI_2	Prostacyclin
PLA_2	Phospholipase A_2
ROS	Reactive oxygen species
SOD1	Superoxide dismutase 1

TDP-43 TAR DNA-binding protein-43
TNF Tumor necrosis factor

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References

1. Bruijn LI, Miller TM, Cleveland DW. Unraveling the mechanisms involved in motor neuron degeneration in ALS. Annu Rev Neurosci. 2004;27:723–49.
2. Ferraiuolo L, Kirby J, Grierson AJ, Sendtner M, Shaw PJ. Molecular pathways of motor neuron injury in amyotrophic lateral sclerosis. Nat Rev Neurol. 2011;7(11):616–30.
3. Rosen DR, Siddique T, Patterson D, Figlewicz DA, Sapp P, Hentati A, et al. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. Nature. 1993;362(6415):59–62.
4. Morgan S, Orrell RW. Pathogenesis of amyotrophic lateral sclerosis. Br Med Bull. 2016;119(1):87–97.
5. Gurney ME, Pu H, Chiu AY, Dal Canto MC, Polchow CY, Alexander DD, et al. Motor neuron degeneration in mice that express a human Cu. Zn superoxide dismutase mutation Science. 1994;264(5166):1772–5.
6. McGeer PL, McGeer EG. Inflammatory processes in amyotrophic lateral sclerosis. Muscle Nerve. 2002;26(4):459–70.
7. Sekizawa T, Openshaw H, Ohbo K, Sugamura K, Itoyama Y, Niland JC. Cerebrospinal fluid interleukin 6 in amyotrophic lateral sclerosis: immunological parameter and comparison with inflammatory and non-inflammatory central nervous system diseases. J Neurol Sci. 1998;154(2):194–9.
8. Mennini T, Giordano L, Mengozzi M, Ghezzi P, Tonelli R, Mantegazza R, et al. Increased IL-8 levels in the cerebrospinal fluid of patients with amyotrophic lateral sclerosis. Eur J Inflamm. 2009;7(1):39–44.
9. Italiani P, Carlesi C, Giungato P, Puxeddu I, Borroni B, Bossù P, et al. Evaluating the levels of interleukin-1 family cytokines in sporadic amyotrophic lateral sclerosis. J Neuroinflamm. 2014;11:1–7.
10. Tortarolo M, Lo Coco D, Veglianese P, Vallarola A, Giordana MT, Marcon G, et al. Amyotrophic lateral sclerosis, a multisystem pathology: insights into the role of TNFα. Mediators Inflamm. 2017;2017:2985051.
11. Lampson LA, Kushner PD, Sobel RA. Major histocompatibility complex antigen expression in the affected tissues in amyotrophic lateral sclerosis. Ann Neurol. 1990;28(3):365–72.
12. Sasaki S, Shibata N, Komori T, Iwata M. iNOS and nitrotyrosine immunoreactivity in amyotrophic lateral sclerosis. Neurosci Lett. 2000;291(1):44–8.
13. Dachet F, Liu J, Ravits J, Song F. Predicting disease specific spinal motor neurons and glia in sporadic ALS. Neurobiol Dis. 2019;130:104523.
14. Crisafulli SG, Brajkovic S, Cipolat Mis MS, Parente V, Corti S. Therapeutic strategies under development targeting inflammatory mechanisms in amyotrophic lateral sclerosis. Mol Neurobiol. 2018;55(4):2789–813.
15. Zhao W, Beers DR, Henkel JS, Zhang W, Urushitani M, Julien JP, et al. Extracellular mutant SOD1 induces microglial-mediated motoneuron injury. Glia. 2010;58(2):231–43.
16. Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, et al. Neurotoxic reactive astrocytes are induced by activated microglia. Nature. 2017;541(7638):481–7.
17. Guttenplan KA, Weigel MK, Adler DI, Couthouis J, Liddelow SA, Gitler AD, et al. Knockout of reactive astrocyte activating factors slows disease progression in an ALS mouse model. Nat Commun. 2020;11(1):1–9.
18. Wang R, Yang B, Zhang D. Activation of interferon signaling pathways in spinal cord astrocytes from an ALS mouse model. Glia. 2011;59(6):946–58.
19. Nguyen MD, Julien JP, Rivest S. Induction of proinflammatory molecules in mice with amyotrophic lateral sclerosis: no requirement for proapoptotic interleukin-1β in neurodegeneration. Ann Neurol. 2001;50(5):630–9.
20. Han Y, Ripley B, Serada S, Naka T, Fujimoto M. Interleukin-6 deficiency does not affect motor neuron disease caused by superoxide dismutase 1 mutation. PLoS ONE. 2016;11(4):1–13.
21. Tortarolo M, Vallarola A, Lidonnici D, Battaglia E, Gensano F, Spaltro G, et al. Lack of TNF-alpha receptor type 2 protects motor neurons in a cellular model of amyotrophic lateral sclerosis and in mutant SOD1 mice but does not affect disease progression. J Neurochem. 2015;135(1):109–24.
22. Olesen MN, Wuolikainen A, Nilsson AC, Wirenfeldt M, Forsberg K, Madsen JS, et al. Inflammatory profiles relate to survival in subtypes of amyotrophic lateral sclerosis. Neurol Neuroimmunol Neuroinflamm. 2020;7(3): e697.
23. Phillis JW, Horrocks LA, Farooqui AA. Cyclooxygenases, lipoxygenases, and epoxygenases in CNS: their role and involvement in neurological disorders. Brain Res Rev. 2006;52(2):201–43.
24. Almer G, Teismann P, Stevic Z, Halaschek-Wiener J, Deecke L, Kostic V, et al. Increased levels of the pro-inflammatory prostaglandin PGE2 in CSF from ALS patients. Neurology. 2002;58(8):1277–9.
25. Iłzecka J. Prostaglandin E2 is increased in amyotrophic lateral sclerosis patients. Acta Neurol Scand. 2003;108(2):125–9.
26. Klivenyi P, Kiaei M, Gardian G, Calingasan NY, Beal MF. Additive neuroprotective effects of creatine and cyclooxygenase 2 inhibitors in a transgenic mouse model of amyotrophic lateral sclerosis. J Neurochem. 2004;88(3):576–82.
27. Miyagishi H, Kosuge Y, Takano A, Endo M, Nango H, Yamagata-Murayama S, et al. Increased expression of 15-hydroxyprostaglandin dehydrogenase in spinal astrocytes during disease progression in a model of amyotrophic lateral sclerosis. Cell Mol Neurobiol. 2017;37(3):445–52.
28. Hayashi D, Mouchlis VD, Dennis EA. Omega-3 versus Omega-6 fatty acid availability is controlled by hydrophobic site geometries of phospholipase A2s. J Lipid Res. 2021;63: 100113.
29. Ricciotti E, Fitzgerald GA. Prostaglandins and inflammation. Arterioscler Thromb Vasc Biol. 2011;31(5):986–1000.
30. Peebles RS. Prostaglandins in asthma and allergic diseases. Pharmacol Ther. 2019;193:1–19.
31. Tanioka T, Nakatani Y, Semmyo N, Murakami M, Kudo I. Molecular identification of cytosolic prostaglandin E2 synthase that is functionally coupled with cyclooxygenase-1 in immediate prostaglandin E2 biosynthesis. J Biol Chem. 2000;275(42):32775–82.
32. Jakobsson PJ, Thorén S, Morgenstern R, Samuelsson B. Identification of human prostaglandin E synthase: a microsomal, glutathione-dependent, inducible enzyme, constituting a potential novel drug target. Proc Natl Acad Sci U S A. 1999;96(13):7220–5.

33. Tanikawa N, Ohmiya Y, Ohkubo H, Hashimoto K, Kangawa K, Kojima M, et al. Identification and characterization of a novel type of membrane-associated prostaglandin E synthase. Biochem Biophys Res Commun. 2002;291(4):884–9.
34. Samuelsson B, Morgenstern R, Jakobsson PJ. Membrane prostaglandin E synthase-1: a novel therapeutic target. Pharmacol Rev. 2007;59(3):207–24.
35. Mohan S, Ahmad AS, Glushakov AV, Chambers C, Doré S. Putative role of prostaglandin receptor in intracerebral hemorrhage. Front Neurol. 2012. https://doi.org/10.3389/fneur.2012.00145.
36. Kiriyama M, Ushikubi F, Kobayashi T, Hirata M, Sugimoto Y, Narumiya S. Ligand binding specificities of the eight types and subtypes of the mouse prostanoid receptors expressed in Chinese hamster ovary cells. Br J Pharmacol. 1997;122(2):217–24.
37. Anggard E, Oliw E. Formation and metabolism of prostaglandins in the kidney. Kidney Int. 1981;19(6):771–80.
38. Jerde TJ, Mellon WS, Fischer SM, Liebert M, Bjorling DE, Nakada SY. Suppression of 15-hydroxyprostaglandin dehydrogenase messenger RNA concentration, protein expression, and enzymatic activity during human ureteral obstruction. J Pharmacol Exp Ther. 2004;309(1):398–403.
39. Lee SC, Levine L. Prostaglandin metabolism. II. Identification of two 15-hydroxyprostaglandin dehydrogenase types. J Biol Chem. 1975;250(2):548–52.
40. Jarabak J, Fried J. Comparison of substrate specificities of the human placental NAD- and NADP-linked 15-hydroxyprostaglandin dehydrogenases. Prostaglandins. 1979;18(2):241–6.
41. Yagami T, Koma H, Yamamoto Y. Pathophysiological roles of cyclooxygenases and prostaglandins in the central nervous system. Mol Neurobiol. 2016;53(7):4754–71.
42. Almer G, Guégan C, Teismann P, Naini A, Rosoklija G, Hays AP, et al. Increased expression of the pro-inflammatory enzyme cyclooxygenase-2 in amyotrophic lateral sclerosis. Ann Neurol. 2001;49(2):176–85.
43. Yasojima K, Tourtellotte WW, McGeer EG, McGeer PL. Marked increase in cyclooxygenase-2 in ALS spinal cord: implications for therapy. Neurology. 2001;57(6):952–6.
44. Kiaei M, Kipiani K, Petri S, Choi DK, Chen J, Calingasan NY, et al. Integrative role of cPLA2 with COX-2 and the effect of non-steriodal anti-inflammatory drugs in a transgenic mouse model of amyotrophic lateral sclerosis. J Neurochem. 2005;93(2):403–11.
45. Pompl PN, Ho L, Bianchi M, McManus T, Qin W, Pasinetti GM. A therapeutic role for cyclooxygenase-2 inhibitors in a transgenic mouse model of amyotrophic lateral sclerosis. FASEB J. 2003;17(6):725–7.
46. Drachman DB, Frank K, Dykes-Hoberg M, Teismann P, Almer G, Przedborski S, et al. Cyclooxygenase 2 inhibition protects motor neurons and prolongs survival in a transgenic mouse model of ALS. Ann Neurol. 2002;52(6):771–8.
47. Miyagishi H, Kosuge Y, Ishige K, Ito Y. Expression of microsomal prostaglandin E synthase-1 in the spinal cord in a transgenic mouse model of amyotrophic lateral sclerosis. J Pharmacol Sci. 2012;118(2):225–36.
48. Shin JH, Lee YA, Lee JK, Lee YB, Cho W, Im DS, et al. Concurrent blockade of free radical and microsomal prostaglandin e synthase-1-mediated PGE 2 production improves safety and efficacy in a mouse model of amyotrophic lateral sclerosis. J Neurochem. 2012;122(5):952–61.
49. Wang M, Lee E, Song W, Ricciotti E, Rader DJ, Lawson JA, et al. Microsomal prostaglandin E synthase-1 deletion suppresses oxidative stress and angiotensin II-induced abdominal aortic aneurysm formation. Circulation. 2008;117(10):1302–9.
50. Ikeda-Matsuo Y, Miyata H, Mizoguchi T, Ohama E, Naito Y, Uematsu S, et al. Microsomal prostaglandin E synthase-1 is a critical factor in dopaminergic neurodegeneration in Parkinson's disease. Neurobiol Dis. 2018;2019(124):81–92.
51. Tada S, Okuno T, Shimizu M, Sakai Y, Sumi-Akamaru H, Kinoshita M, et al. Single injection of sustained-release prostacyclin analog ONO-1301-MS ameliorates hypoxic toxicity in the murine model of amyotrophic lateral sclerosis. Sci Rep. 2019;9(1):1–9.
52. Nomura T, Lu R, Pucci ML, Schuster VL. The two-step model of prostaglandin signal termination: in vitro reconstitution with the prostaglandin transporter and prostaglandin 15 dehydrogenase. Mol Pharmacol. 2004;65(4):973–8.
53. Guo JY, Bian H, Yao Y. Chronic unpredictable mild stress induces parallel reductions of 15-PGDH in the hypothalamus and lungs in rats. Behav Brain Res. 2015;286:278–84.
54. Xu Y, Liu Y, Li K, Miao S, Lv C, Wang C, et al. Regulation of PGE2 pathway during cerebral ischemia reperfusion injury in rat. Cell Mol Neurobiol. 2021;41(7):1483–96.
55. Carrasco E, Casper D, Werner P. PGE2 receptor EP1 renders dopaminergic neurons selectively vulnerable to low-level oxidative stress and direct PGE2 neurotoxicity. J Neurosci Res. 2007;85(14):3109–17.
56. Takadera T, Yumoto H, Tozuka Y, Ohyashiki T. Prostaglandin E2 induces caspase-dependent apoptosis in rat cortical cells. Neurosci Lett. 2002;317(2):61–4.
57. Takadera T, Shiraishi Y, Ohyashiki T. Prostaglandin E2 induced caspase-dependent apoptosis possibly through activation of EP2 receptors in cultured hippocampal neurons. Neurochem Int. 2004;45(5):713–9.
58. Ikeda-Matsuo Y, Tanji H, Ota A, Hirayama Y, Uematsu S, Akira S, et al. Microsomal prostaglandin e synthase-1 contributes to ischaemic excitotoxicity through prostaglandin E2 EP3 receptors. Br J Pharmacol. 2010;160(4):847–59.
59. McCullough L, Wu L, Haughey N, Liang X, Hand T, Wang Q, et al. Neuroprotective function of the PGE2 EP2 receptor in cerebral ischemia. J Neurosci. 2004;24(1):257–68.
60. Bilak M, Wu L, Wang Q, Haughey N, Conant K, St Hillaire C, et al. PGE2 receptors rescue motor neurons in a model of amyotrophic lateral sclerosis. Ann Neurol. 2004;56(2):240–8.
61. Ahmad AS, Ahmad M, De Brum-Fernandes AJ, Doré S. Prostaglandin EP4 receptor agonist protects against acute neurotoxicity. Brain Res. 2005;1066(1–2):71–7.
62. Cashman NR, Durham HD, Blusztajn JK, Oda K, Tabira T, Shaw IT, et al. Neuroblastoma × spinal cord (NSC) hybrid cell lines resemble developing motor neurons. Dev Dyn. 1992;194(3):209–21.
63. Maier O, Böhm J, Dahm M, Brück S, Beyer C, Johann S, et al. Differentiated NSC-34 motoneuron-like cells as experimental model for cholinergic neurodegeneration. Neurochem Int. 2013;62(8):1029–38.
64. Miyagishi H, Kosuge Y, Yoneoka Y, Ozone M, Endo M, Osada N, et al. Prostaglandin E2-Induced cell death is mediated by activation of EP2 receptors in motor neuron-like NSC-34 cells. J Pharmacol Sci. 2013;121(4):347–50.
65. Liang X, Wang Q, Shi J, Lokteva L, Breyer RM, Montine TJ, et al. The prostaglandin E2 EP2 receptor accelerates disease progression and inflammation in a model of amyotrophic lateral sclerosis. Ann Neurol. 2008;64(3):304–14.
66. Kosuge Y, Miyagishi H, Yoneoka Y, Yoneda K, Nango H, Ishige K, et al. Pathophysiological role of prostaglandin E2-induced up-regulation of the EP2 receptor in motor neuron-like NSC-34 cells and lumbar motor neurons in ALS model mice. Neurochem Int. 2018;119:132–9.
67. Ma W, Chabot JG, Vercauteren F, Quirion R. Injured nerve-derived COX2/PGE2 contributes to the maintenance of neuropathic pain in aged rats. Neurobiol Aging. 2010;31(7):1227–37.
68. Pérez S, Maldonado EN, Aspichueta P, Ochoa B, Chico Y. Differential modulation of prostaglandin receptor mRNA abundance by prostaglandins in primary cultured rat hepatocytes. Mol Cell Biochem. 2004;266(1–2):183–9.
69. Parakh S, Spencer DM, Halloran MA, Soo KY, Atkin JD. Redox regulation in amyotrophic lateral sclerosis. Oxid Med Cell Longev. 2013. https://doi.org/10.1155/2013/408681.
70. Oskarsson B, Gendron TF, Staff NP. Amyotrophic lateral sclerosis: an update for 2018. Mayo Clin Proc. 2018;93(11):1617–28.
71. Biswas SK. Does the interdependence between oxidative stress and inflammation explain the antioxidant paradox? Oxid Med Cell Longev. 2016;2016:1–9.
72. Hensley K, Mhatre M, Mou S, Pye QN, Stewart C, West M, et al. On the relation of oxidative stress to neuroinflammation: lessons learned from the G93A-SOD1 mouse model of amyotrophic lateral sclerosis. Antioxidants Redox Signal. 2006;8(11–12):2075–87.
73. Korbecki J, Baranowska-Bosiacka I, Gutowska I, Chlubek D. The effect of reactive oxygen species on the synthesis of prostanoids from arachidonic acid. J Physiol Pharmacol. 2013;64(4):409–21.
74. Chi PL, Chen YW, Hsiao LD, Chen YL, Yang CM. Heme oxygenase 1 attenuates interleukin-1β-induced cytosolic phospholipase A2

expression via a decrease in NADPH oxidase/reactive oxygen species/activator protein 1 activation in rheumatoid arthritis synovial fibroblasts. Arthritis Rheum. 2012;64(7):2114–25.
75. Feng L, Xia Y, Garcia GE, Hwang D, Wilson CB. Involvement of reactive oxygen intermediates in cyclooxygenase-2 expression induced by interleukin-1, tumor necrosis factor-α, and lipopolysaccharide. J Clin Invest. 1995;95(4):1669–75.
76. Kosuge Y, Nango H, Kasai H, Yanagi T, Mawatari T, Nishiyama K, et al. Generation of cellular reactive oxygen species by activation of the EP2 receptor contributes to prostaglandin E2-induced cytotoxicity in motor neuron-like NSC-34 cells. Oxid Med Cell Longev. 2020; 2020:6101838.
77. Liang X, Wang Q, Hand T, Wu L, Breyer RM, Montine TJ, et al. Deletion of the prostaglandin E2 EP2 receptor reduces oxidative damage and amyloid burden in a model of Alzheimer's disease. J Neurosci. 2005;25(44):10180–7.
78. Gozal E, Metz CJ, Dematteis M, Sachleben LR, Schurr A, Rane MJ. PKA activity exacerbates hypoxia-induced ROS formation and hypoxic injury in PC-12 cells. Toxicol Lett. 2017;279:107–14.
79. Carrasco E, Werner P, Casper D. Prostaglandin receptor EP2 protects dopaminergic neurons against 6-OHDA-mediated low oxidative stress. Neurosci Lett. 2008;441(1):44–9.
80. Hatae N, Sugimoto Y, Ichikawa A. Prostaglandin receptors: advances in the study of EP3 receptor signaling. J Biochem. 2002;131(6):781–4.
81. Kosuge Y, Miyagishi H, Shinomiya T, Nishiyama K, Suzuki S, Osada N, et al. Characterization of motor neuron prostaglandin E2 EP3 receptor isoform in a mouse model of amyotrophic lateral sclerosis. Biol Pharm Bull. 2015;38(12):1964–8.
82. Narita M, Shimamura M, Imai S, Kubota C, Yajima Y, Takagi T, et al. Role of interleukin-1β and tumor necrosis factor-α-dependent expression of cyclooxygenase-2 mRNA in thermal hyperalgesia induced by chronic inflammation in mice. Neuroscience. 2008;152(2):477–86.
83. Brenneis C, Maier TJ, Schmidt R, Hofacker A, Zulauf L, Jakobsson PJ, et al. Inhibition of prostaglandin E 2 synthesis by SC-560 is independent of cyclooxygenase 1 inhibition. FASEB J. 2006;20(9):1352–60.
84. de Oliveira ACP, Yousif NM, Bhatia HS, Hermanek J, Huell M, Fiebich BL. Poly(I: C) Increases the expression of mPGES-1 and COX-2 in rat primary microglia. J Neuroinflamm. 2016;13(1):1–11.
85. Hensley K, Abdel-Moaty H, Hunter J, Mhatre M, Mhou S, Nguyen K, et al. Primary glia expressing the G93A-SOD1 mutation present a neuroinflammatory phenotype and provide a cellular system for studies of glial inflammation. J Neuroinflamm. 2006;3:1–9.
86. Suk K, Yeou Kim S, Kim H. Regulation of IL-18 production by IFNγ and PGE2 in mouse microglial cells: Involvement of NF-kB pathway in the regulatory processes. Immunol Lett. 2001;77(2):79–85.
87. Chi X, Tai HH. Interleukin-4 up-regulates 15-hydroxyprostaglandin dehydrogenase (15-PGDH) in human lung cancer cells. Exp Cell Res. 2010;316(14):2251–9.
88. Zhu P, Genc A, Zhang X, Zhang J, Bazan NG, Chen C. Heterogeneous expression and regulation of hippocampal prostaglandin E2 receptors. J Neurosci Res. 2005;81(6):817–26.
89. Waschbisch A, Fiebich BL, Akundi RS, Schmitz ML, Hoozemans JJM, Candelario-Jalil E, et al. Interleukin-1 beta-induced expression of the prostaglandin E 2-receptor subtype EP3 in U373 astrocytoma cells depends on protein kinase C and nuclear factor-kappaB. J Neurochem. 2006;96(3):680–93.
90. Fehrenbacher JC, Burkey TH, Nicol GD, Vasko MR. Tumor necrosis factor α and interleukin-1β stimulate the expression of cyclooxygenase II but do not alter prostaglandin E 2 receptor mRNA levels in cultured dorsal root ganglia cells. Pain. 2005;113(1–2):113–22.
91. Brenneis C, Coste O, Altenrath K, Angioni C, Schmidt H, Schuh CD, et al. Anti-inflammatory role of microsomal prostaglandin E synthase-1 in a model of neuroinflammation. J Biol Chem. 2011;286(3):2331–42.
92. Woodling NS, Wang Q, Priyam PG, Larkin P, Shi J, Johansson JU, et al. Suppression of Alzheimer-associated inflammation by microglial prostaglandin-E2 EP4 receptor signaling. J Neurosci. 2014;34(17):5882–94.
93. Xia Q, Hu Q, Wang H, Yang H, Gao F, Ren H, et al. Induction of COX-2-PGE2 synthesis by activation of the MAPK/ERK pathway contributes to neuronal death triggered by TDP-43-depleted microglia. Cell Death Dis. 2015;6: e1702.
94. Petrov D, Mansfield C, Moussy A, Hermine O. ALS clinical trials review: 20 years of failure Are we any closer to registering a new treatment? Front Aging Neurosci. 2017;9:68.
95. Cudkowicz ME, Shefner JM, Schoenfeld DA, Zhang H, Andreasson KI, Rothstein JD, et al. Trial of celecoxib in amyotrophic lateral sclerosis. Ann Neurol. 2006;60(1):22–31.
96. Bergqvist F, Morgenstern R, Jakobsson PJ. A review on mPGES-1 inhibitors: From preclinical studies to clinical applications. Prostaglandins Other Lipid Mediat. 2020;147: 106383.
97. Goldshtein H, Muhire A, Petel Légaré V, Pushett A, Rotkopf R, Shefner JM, et al. Efficacy of ciprofloxacin/celecoxib combination in zebrafish models of amyotrophic lateral sclerosis. Ann Clin Transl Neurol. 2020;7(10):1883–97.
98. Nango H, Kosuge Y. Present state and future perspectives of prostaglandins as a differentiation factor in motor neurons. Cell Mol Neurobiol. 2022;42(7):2097–108.
99. Nango H, Kosuge Y, Miyagishi H, Sugawa K, Ito Y, Ishige K. Prostaglandin E2 facilitates neurite outgrowth in a motor neuron-like cell line, NSC-34. J Pharmacol Sci. 2017;135(2):64–71.
100. Nango H, Kosuge Y, Sato M, Shibukawa Y, Aono Y, Saigusa T, et al. Highly efficient conversion of motor neuron-like NSC-34 cells into functional motor neurons by prostaglandin E2. Cells. 2020;9(7):1741.
101. Goncalves MB, Williams EJ, Yip P, Yáñez-Muñoz RJ, Williams G, Doherty P. The COX-2 inhibitors, meloxicam and nimesulide, suppress neurogenesis in the adult mouse brain. Br J Pharmacol. 2010;159(5):1118–25.
102. Wong CT, Ussyshkin N, Ahmad E, Rai-Bhogal R, Li H, Crawford DA. Prostaglandin E2 promotes neural proliferation and differentiation and regulates Wnt target gene expression. J Neurosci Res. 2016;94(8):759–75.
103. Chi L, Ke Y, Luo C, Li B, Gozal D, Kalyanaraman B, et al. Motor neuron degeneration promotes neural progenitor cell proliferation, migration, and neurogenesis in the spinal cords of amyotrophic lateral sclerosis mice. Stem Cells. 2006;24(1):34–43.
104. Ho L, Luterman JD, Aisen PS, Pasinetti GM, Montine TJ, Morrow JD. Elevated CSF prostaglandin E2 levels in patients with probable AD. Neurology. 2000;55(2):323.
105. Mattammal MB, Strong R, Lakshmi VM, Chung HD, Stephenson AH. Prostaglandin H synthetase-mediated metabolism of dopamine: implication for Parkinson's disease. J Neurochem. 1995;64(4):1645–54.
106. Hampel H, Hardy J, Blennow K, Chen C, Perry G, Kim SH, et al. The amyloid-β pathway in Alzheimer's disease. Mol Psychiatry. 2021;26(10):5481–503.
107. Hoozemans JJ, Rozemuller AJ, Janssen I, De Groot CJ, Veerhuis R, Eikelenboom P. Cyclooxygenase expression in microglia and neurons in Alzheimer's disease and control brain. Acta Neuropathol. 2001;101(1):2–8.
108. Chaudhry UA, Zhuang H, Crain BJ, Doré S. Elevated microsomal prostaglandin-E synthase-1 in Alzheimer's disease. Alzheimers Dement. 2008;4(1):6–13.
109. Chaudhry U, Zhuang H, Doré S. Microsomal prostaglandin E synthase-2: Cellular distribution and expression in Alzheimer's disease. Exp Neurol. 2010;223(2):359–65.
110. Kirby LC, Hempelman SR, Berry DL, Mcgeer PL, Kaszniak AW, Cofield M, et al. Clinical trial of indomethacin in Alzheimer's disease. Neurology. 1993;43:1609–11.
111. Kotilinek LA, Westerman MA, Wang Q, Panizzon K, Lim GP, Simonyi A, et al. Cyclooxygenase-2 inhibition improves amyloid-β-mediated suppression of memory and synaptic plasticity. Brain. 2008;131(3):651–64.
112. Hoshino T, Namba T, Takehara M, Nakaya T, Sugimoto Y, Araki W, et al. Prostaglandin E2 stimulates the production of amyloid-β peptides through internalization of the EP4 receptor. J Biol Chem. 2009;284(27):18493–502.
113. Hoshino T, Nakaya T, Homan T, Tanaka KI, Sugimoto Y, Araki W, et al. Involvement of prostaglandin E2 in production of amyloid-β peptides both in vitro and in vivo. J Biol Chem. 2007;282(45):32676–88.
114. Savonenko A, Munoz P, Melnikova T, Wang Q, Liang X, Breyer RM, et al. Impaired cognition, sensorimotor gating, and hippocampal long-term depression in mice lacking the prostaglandin E2 EP2 receptor. Exp Neurol. 2009;217(1):63–73.

115. Cummings J, Lee G, Nahed P, Kambar MEZN, Zhong K, Fonseca J, et al. Alzheimer's disease drug development pipeline: 2022. Alzheimers Dement (N Y). 2022;8(1):e12295.
116. Tabrizi SJ, Ghosh R, Leavitt BR. Huntingtin lowering strategies for disease modification in Huntington's disease. Neuron. 2019;101(5):801–19.
117. Anglada-Huguet M, Xifró X, Giralt A, Zamora-Moratalla A, Martín ED, Alberch J. Prostaglandin E2 EP1 receptor antagonist improves motor deficits and rescues memory decline in R6/1 mouse model of Huntington's disease. Mol Neurobiol. 2014;49(2):784–95.
118. Anglada-Huguet M, Vidal-Sancho L, Giralt A, García-Díaz Barriga G, Xifró X, Alberch J. Prostaglandin E2 EP2 activation reduces memory decline in R6/1 mouse model of Huntington's disease by the induction of BDNF-dependent synaptic plasticity. Neurobiol Dis. 2016;95:22–34.
119. Bloem BR, Okun MS, Klein C. Parkinson's disease. Lancet. 2021;397(10291):2284–303.
120. Knott C, Stern G, Wilkin GP. Inflammatory regulators in Parkinson's disease: iNOS, lipocortin-1, and cyclooxygenases-1 and -2. Mol Cell Neurosci. 2000;16(6):724–39.
121. Wang T, Pei Z, Zhang W, Liu B, Langenbach R, Lee C, et al. MPP+-induced COX-2 activation and subsequent dopaminergic neurodegeneration. FASEB J. 2005;19(9):1134–6.
122. Vijitruth R, Liu M, Choi DY, Nguyen XV, Hunter RL, Bing G. Cyclooxygenase-2 mediates microglial activation and secondary dopaminergic cell death in the mouse MPTP model of Parkinson's disease. J Neuroinflamm. 2006;3:1–16.
123. Driver JA, Logroscino G, Lu L, Gaziano JM, Kurth T. Use of non-steroidal anti-inflammatory drugs and risk of Parkinson's disease: nested case-control study. BMJ. 2011;342:d198.
124. Gao X, Chen H, Schwarzschild MA, Ascherio A. Use of ibuprofen and risk of Parkinson disease. Neurology. 2011;76(10):863–9.
125. Jin J, Shie FS, Liu J, Wang Y, Davis J, Schantz AM, et al. Prostaglandin E2 receptor subtype 2 (EP2) regulates microglial activation and associated neurotoxicity induced by aggregated α-synuclein. J Neuroinflamm. 2007;4:1–10.
126. Reich DS, Lucchinetti CF, Calabresi PA. Multiple sclerosis. N Engl J Med. 2018;378(2):169–80.
127. Ayoub SS, Wood EG, Hassan SU, Bolton C. Cyclooxygenase expression and prostaglandin levels in central nervous system tissues during the course of chronic relapsing experimental autoimmune encephalomyelitis (EAE). Inflamm Res. 2011;60(10):919–28.
128. Reder AT, Thapar M, Sapugay AM, Jensen MA. Prostaglandins and inhibitors of arachidonate metabolism suppress experimental allergic encephalomyelitis. J Neuroimmunol. 1994;54(1–2):117–27.
129. Kihara Y, Matsushita T, Kita Y, Uematsu S, Akira S, Kira JI, et al. Targeted lipidomics reveals mPGES-1-PGE2 as a therapeutic target for multiple sclerosis. Proc Natl Acad Sci U S A. 2009;106(51):21807–12.
130. Esaki Y, Li Y, Sakata D, Yao C, Segi-Nishida E, Matsuoka T, et al. Dual roles of PGE2-EP4 signaling in mouse experimental autoimmune encephalomyelitis. Proc Natl Acad Sci U S A. 2010;107(27):12233–8.

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