Neurosci Bull February 1, 2010, 26(1): 77-84. http://www.neurosci.cn
DOI: 10.1007/s12264-010-0703-z

·Minireview·

Roles of the prostaglandin E_2 receptors EP subtypes in Alzheimer's disease

Li-Li WEI[1,*], Yue-Di SHEN[2,*], Ying-Chun ZHANG[1], Xing-Yue HU[3], Pei-Ling LU[3], Li WANG[3], Wei CHEN[1]

[1]*Department of Mental Health, Sir Run Run Shaw Hospital, Zhejiang University Medical School, Hangzhou 310016*
[2]*Department of Diagnostics, Affiliated Hospital, Hangzhou Normal University Medical School, Hangzhou 310015*
[3]*Department of Neurology, Sir Run Run Shaw Hospital, Zhejiang University Medical School, Hangzhou 310016*

Abstract: Neuroinflammation has always been of concern in the pathogenesis of Alzheimer's disease (AD). As a major inflammatory mediator, prostaglandin E_2 (PGE_2) plays an important role in the inflammatory process of AD. Up to now, there is still controversy on the neuroprotective or neurotoxic role of PGE_2. However, the role of PGE_2 in neurodegeneration may be far more complex, due to the 4 EP receptor subtypes. This article aims to summarize the relationship between PGE_2 receptor EP subtypes and AD. It is believed that a better understanding of the PGE_2 receptor EP subtypes may help to clarify the relation between inflammation and AD, and to develop novel therapeutic strategies targeting specific EP receptor for AD treatment.

Keywords: inflammation; Alzheimer's disease; prostaglandin E_2; prostaglandin E_2 receptors

1 Introduction

Neuroinflammation has always been of concern in the pathogenesis of Alzheimer's disease (AD)[1]. Epidemiological studies have demonstrated that long-term intake of non-steroidal anti-inflammatory drugs (NSAIDs) during normal aging reduces the risk of AD and delays the onset of the disease[2-5]. This preventive effect has been demonstrated in transgenic mice models, where NSAIDs significantly reduce amyloid β (Aβ) deposition[6-8]. Although it is assumed that the progress of AD can be delayed by NSAIDs treatment, recent clinical studies find that NSAIDs could not reduce Aβ content in AD patients[9]. Besides, there is no advantage of long-term usage of NSAIDs for significant improvement in AD pathology[10]. These conflicting results make the research of NSAIDs downstream signaling pathway very necessary. NSAIDs exert anti-inflammatory effects dependent or independent of cyclooxygenase (COX) (Fig. 1)[11], and the anti-inflammatory effect is mainly due to the inhibition of COX.

NSAIDs inhibit the enzymatic activities of COX-1 and inducible COX-2, which catalyze the first committed step in the synthesis of prostaglandin E_2 (PGE_2), and then reduce the synthesis of $A\beta_{1\text{-}42,}$ inhibiting the occurrence of inflammation[8,12]. On one hand, PGE_2 can increase the generation of Aβ[13,14] and induce the apoptosis of hippocampal neurons[15]. On the other hand, PGE_2 can also play a protective role by reducing the toxicity of Aβ to the neurons[16]. In view of these seemingly contradictory research findings, this article aims to summarize the relationship between PGE_2 receptor EP subtypes and AD, to explain this paradox from the perspective of EP, and to clarify the roles of EP in the pathogenesis of AD, providing a new target for AD treatment.

2 Distribution and signal transduction pathways of EP subtypes

* These authors contributed equally to this work.
Corresponding author: Wei CHEN
Tel: +86-571-86006860; Fax: +86-571-86044817
E-mail: srrcw@zju.edu.cn
Article ID: 1673-7067(2010)01-0077-08
Received date: 2009-07-03; Accepted date: 2009-09-22

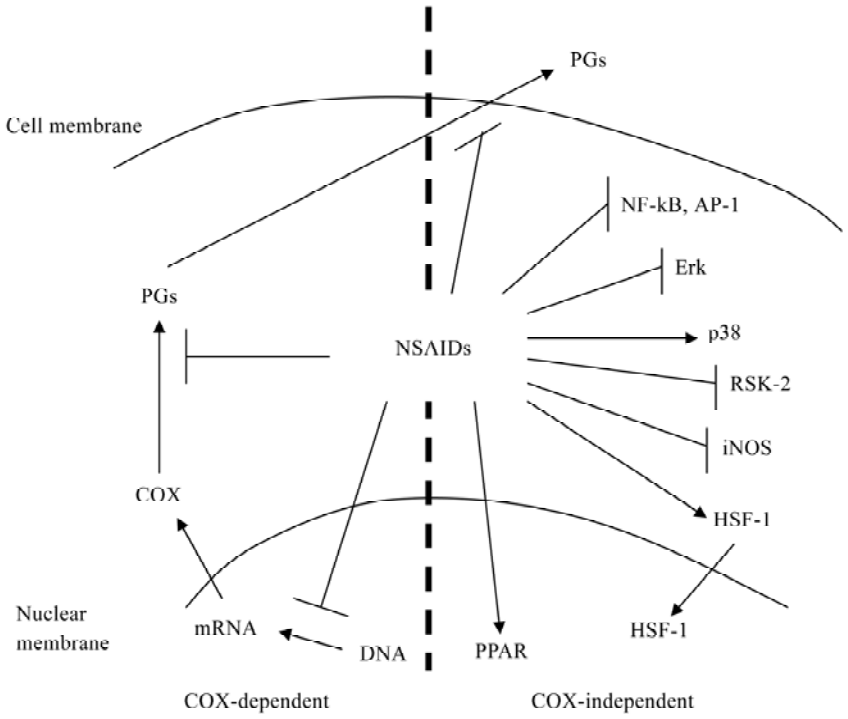

Fig. 1 Anti-inflammatory mechanisms of NSAIDs[11]. →: activation, ⊣ : inhibition by NSAIDs. AP-1: activator protein 1; COX: cyclooxygenase; Erk: extracellular signial-regulated kinase; HSF-1: heat shock transcription factor 1; iNOS: inducible nitric oxide synthase; NF-κB: muclear factor-κB; NSAIDs: non-steroidal anti-inflammatory drugs; PGs: prostaglandins; PPAR: peroxisome proliferators-activated receptor; RSK-2: ribosomal S6 kinase 2.

PGE_2, a product derived from arachidonic acid by COX and specific synthases, exerts its diverse effects by binding to G-protein-coupled receptors. There are 4 different EP receptor subtypes, namely EP1–EP4, expressed in rodent brain. EP1 and EP2 are expressed on glia and neurons, while EP3 is predominantly expressed on neurons, and on glia in an acute model of excitotoxicity in the rat striatum[17]. EP4 expression is highly restricted to some hypothalamic nuclei[18]. Among the 4 EP receptors, EP2 and EP3 receptors are enriched in hippocampus and cerebral cortex[19,20], structures of which are affected significantly in AD. EP1 and EP4 are expressed in thalamic and hypothalamic structures[20].

Besides the regional and cell-specific differences in expression and activity, the EP receptors are involved in different intracellular signal transduction pathways. EP1 receptor couples to Gq protein, but regulates Ca^{2+} channel gating via an unidentified G protein. EP3 receptor couples to Gi protein and mediates the decrease in cAMP concentration through inhibition of adenylate cyclase, while stimulation of EP2 and EP4 receptors leads to the elevation of cAMP level via Gs protein[21,22]. Furthermore, the subtype of EP2 receptor participates in a classic cAMP signaling pathway involving a marked stimulation of intracellular cAMP formation and activation of protein kinase A (PKA). The EP4 receptor can activate not only the cAMP/PKA pathway, but also the phosphatidylinositol 3-kinase (PI3K) and the extracellular signal-regulated kinases (ERKs) signaling pathways via Gi protein[23,24].

Due to the complexity mentioned above, the activation of different EP receptors could lead to opposite functions. For example, activation of EP2 and EP4 receptors can increase the intracellular cAMP level while the activation of EP3 subtype reduces it. So it is easy to understand the controversy on whether PGE_2 mediates neurotoxicity or neuroprotective effects in the pathogenesis of AD.

Despite the diversities in PGE_2 EP receptors and the com-

plex signal transduction pathways, the research development on specific agonists and antagonists provides further insights into the functions of different EP receptors and the relevant signal pathways. The widely used specific agonists and antagonists of EP receptors are summarized in Table 1.

3 EP2/EP4 and AD

3.1 Neurotoxic effect Aβ plays an important role in the pathogenesis of AD. It is generated by proteolysis of the β-amyloid precursor protein (APP) by β- and γ-secretases. Studies have reported that PGE_2 could significantly increase the expression of APP protein by activating EP2/EP4 receptors, and then lead to the accumulation of Aβ by activating γ-secretase[13,28]. Pooler *et al.*[28] investigated the effects of PGE_2 on APP expression in cultured rat microglia. Results have shown that PGE_2 or EP2 receptor agonist could increase the level of APP holoprotein, whereas co-incubation with PGE_2 and EP2 receptor antagonists decreases the APP expression. These data indicate that PGE_2 regulates the expression of APP through the EP2 receptor. Moreover, Hoshino *et al.*[13] show that PGE_2 could stimulate the production of Aβ in cultured human embryonic kidney (HEK) 293 or human neuroblastoma (SH-SY5Y) cells, both of which express a mutant type of APP. Using subtype-specific agonists and antagonists of the EP1-4 receptors, they demonstrate that EP4 receptor alone or co-treatment of EP2 and EP4 receptors are responsible for this PGE_2-stimulated production of Aβ. Immunoblotting experiments and direct measurement of γ-secretase activity suggest that PGE_2-stimulated production of Aβ is mediated by activation of γ-secretase. Similarly, when the transgenic mice expressing the mutant type of APP were crossed with mice lacking either EP2 or EP4 receptors, the new-born mice showed a lower level of Aβ in the brain[13]. These *in vivo* and *in vitro* experiments demonstrate that EP2 and EP4 receptors are involved in Aβ production and AD pathogenesis.

The co-occurrence of cerebral oxidative damage and elevation of PGE_2 level is a characteristic of several degenerative and destructive diseases of brain including AD. Montine *et al.*[35] have tested the hypothesis that cerebral oxidative damage resulting from activation of innate immunity with intracerebroventricular lipopolysaccharide (LPS) is dependent on PGE_2-mediated signaling. They quantified 2 biomarkers of lipid peroxidation, F2-isoprostanes (IsoPs) and F4-neuroprostanes (NeuroPs). Results show that LPS-stimulated delayed elevations in cerebral F2-IsoPs and F4-NeuroPs could be completely suppressed by pre-treatment of NSAIDs. Besides, LPS-induced cerebral oxidative damage could be abolished by disruption of PGE_2 subtype receptor EP2. Liang *et al.*[14] have reported that deletion of the PGE_2 EP2 receptor in the APPSwe-PS1ΔE9 model of familial AD results in a marked reduction in lipid peroxidation in aging mice. Meanwhile, the levels of $A\beta_{40}$ and $A\beta_{42}$, and the activity of β-secretase are decreased significantly. These results indicate a positive reinforcing loop that PGE_2 promotes its formation via EP2 activation and increases expressions of inducible nitric oxide synthase (iNOS) and COX-2. The subsequent increase in PGE_2 production enhances the oxidative damage and Aβ deposition via EP2 activation.

Microglia acts as a phagocyte in the central nervous system, and can be neuroprotective by phagocytosing Aβ. On the other side, innate immunity could be activated during phagocytosis of Aβ, causing paracrine damage to neurons (i.e., activating complement, increasing secretion of several cytokines and chemokines, and increasing the productions of reactive oxygen and nitrogen species, combinations of

Table 1. Agonists and antagonists of EP receptors and relevant signal pathways

	EP1	EP2	EP3	EP4	PKA	PKC	PI3K
Agonists	PTPE2[25], ONO-DI-004[26]	Butaprost[15, 19, 20, 27, 28]	sulprostone[15, 27, 29]	PGE-OH[30]	forskolin[25, 27, 28]	phorbol esters [31]	insulin [32]
Antagonists	SC51089[25], ONO-8713[26]	AH-6809[28]	ONO-AE3-240[33]	ONO-AE3-208 [34]	H89[19, 25, 28], KT5720[19]	BIM[25], GF109203X [30]	LY294002 [30, 32]

which can be neurotoxic). Thus microglia has been proposed to play both neuroprotective and neuotoxic roles in AD pathogenesis. So it may work better by enhancing microglial Aβ phagocytosis while suppressing microglia-mediated neurotoxicity. Shie *et al.*[25] have observed enhanced phagocytosis to synthetic $A\beta_{1-42}$ of primary cultures of microglia from $EP2^{-/-}$ mouse cerebrum, and increased *ex vivo* clearance of $A\beta_{1-40}$ and $A\beta_{1-42}$ in hippocampal slices of patients who died of AD. Meanwhile, lack of EP2 could completely suppress Aβ-activated microglia-mediated paracrine neurotoxicity. The enhanced phagocytosis is PKC-dependent and associated with elevated microglial secretions of chemokines, macrophage inflammatory protein-1α and macrophage chemoattractant protein-1, which suggests that microglial activation is negatively regulated by EP2 signaling through suppression of prophagocytic cytokine secretion. These data unexpectedly demonstrate that blockade of microglial EP2 is a highly desirable strategy for AD treatment, since it can maximize the neuroprotective actions and minimize the side effects in neurons. In another study using intracere-broventricular (i.c.v) injection of LPS, Shie *et al.*[36] have also found that levels of iNOS and COX-2 are decreased in $EP2^{-/-}$ mice, and the neurotoxicity is abolished. By co-culturing murine microglia and neurons, they further prove that microglial EP2 is required for paracrine neurotoxicity following activation of innate immunity. Similarly, Jin *et al.*[37] investigated the role of EP2 in α-synuclein aggregation-induced microglial activation using *ex vivo*, *in vivo* and *in vitro* experimental systems. Results have demonstrated that ablation of EP2 significantly enhances microglia-mediated clearance of α-synuclein aggregates and attenuates the neurotoxicity. Therefore, ablation of microglial EP2 can not only enhance Aβ phagocytosis, but also completely suppress the damage to neurons, maximizing beneficial effects while minimizing deleterious effects in AD brain.

Moreover, the effect of PGE_2 on cell viability has also been examined in hippocampal cells. PGE_2 can induce apoptosis in a dose-dependent manner, which is characterized by cell shrinkage, nuclear condensation or fragmentation, *etc*. In addition, PGE_2 activates caspase-3 in a dose-dependent manner, and the caspase-3 inhibitor could prevent the PGE_2-induced apoptosis. Further studies using the selective EP agonists have revealed that the direct effects of PGE_2 on hippocampal neurons are mediated by activation of EP2 receptors, followed by elevation of the intracellular cAMP level[15].

Besides the above models, the model of cerebral ischemia has been used to investigate the neurotoxic effect of EP2 receptor. The up-regulation of COX-2 and PGE_2 has been detected after cerebral ischemic insult. Cerebral ischemia then induces neuron death, during which the glutamate receptors, particularly the over-activation of *N*-methyl-*D*-aspartate (NMDA) receptors, are involved. Takadera *et al.*[27] investigated whether PGE_2 would affect glutamate receptor-mediated cell death in cultured rat cortical cells. Results show that PGE_2 could augment NMDA-mediated cell death, and further research reveals that this neurotoxicity is mediated through EP2 receptor.

All these studies indicate that PGE_2 can induce neurotoxicity through the activation of EP2 and EP4 receptors. Ablation of these receptors, especially the EP2 subtype, will exert a neuroprotective effect.

3.2 Neuroprotective effect Meanwhile, recent studies also suggest neuroprotective roles of PGE_2 and its receptors EP2 and EP4, in multiple neuronal injury models.

Recent studies have reported that PGE_2 regulates membrane excitability and long-term synaptic plasticity in hippocampal perforant path-dentate gyrus synapses[38], and can also rescue cortical neurons from Aβ-induced apoptosis[39]. Importantly, some studies declare that the protective effect of NSAIDs may be independent of the inhibition of COX activity[40,41]. These observations strongly suggest a possible neuroprotective role of PGE_2 in early progression of AD. To elucidate the molecular mechanisms by which PGE_2 participates in neuronal cell signaling, Lee *et al.*[30] investigated the direct effect of PGE_2 on cell viability in SH-SY5Y neuronal cells treated with tumor necrosis factor-alpha (TNF-α), a main mediator of inflammatory neurotoxicity in AD. Results have shown that PGE_2 does not promote neurotoxicity, but rather exerts a strong protective effect by ameliorating TNF-α-induced apoptosis. Pharmacological studies provide further evidence supporting that the stimulation of cAMP/

PKA signaling through EP1-, EP2-, and EP4-mediated increases of intracellular β-catenin level, is involved in PGE_2-mediated neuroprotection against TNF-α.

Using primary cultures of postnatal mouse cortical neurons, Echeverria *et al.*[16] investigate *in vitro* whether PGE_2 would alter neuron susceptibility to $A\beta_{1-42}$ toxicity, by acting on EP1-4 receptors. They find that at nanomolar concentrations, PGE_2 could significantly protect neurons from $A\beta_{1-42}$ toxicity. Application of EP receptor agonists has further revealed that PGE_2-induced neuroprotection is mediated by activation of EP2 and EP4 receptors. Besides, the subsequent increase in cAMP level is likely to be involved in the neuroprotection, which also results in significant attenuation of the production of free radicals after $A\beta_{1-42}$ exposure. These results demonstrate that PGE_2, by acting on EP2 and EP4 receptors, can decrease $A\beta_{1-42}$ neurotoxicity and reduce the reactive oxygen species (ROS) level, to protect the neurons.

In vitro studies in dispersed neurons and organotypic hippocampal slice models demonstrate that activation of the EP2 receptor is neuroprotective against NMDA toxicity and oxygen glucose deprivation (OGD)[19]. In the middle cerebral artery occlusion–reperfusion (MCAO-RP) model of transient forebrain ischemia, genetic deletion of EP2 receptor could significantly aggravate cerebral infarction in cerebral cortex and subcortical structures[19]. Similarly, Liu *et al.*[20] point that after excitotoxicity in an organotypic hippocampal model receiving NMDA challenge for up to 3 h, activation of EP2 could still lead to significant neuroprotection in hippocampal slices. Moreover, in a mouse model of permanent focal forebrain ischemia, genetic deletion of EP2 results in a marked increase in stroke volume. These studies at the cellular, organotypic and animal levels indicate that activation of the PGE_2 EP2 receptor can protect against excitotoxic and anoxic injury.

Furthermore, a recent study demonstrates that misoprostol, a PGE_2 receptor agonist, plays a neuroprotective role in the MCAO-RP model[42]. Administration of misoprostol, at the time of MCAO or 2 h after MCAO, could result in a significant rescue of infarct volume at 24 h and 72 h, respectively. Immunocytochemistry method has revealed dynamic regulation of EP2 and EP4 receptors during reperfusion in neurons and endothelial cells of cerebral cortex and striatum, with limited expression of EP3 receptor. Moreover, administration of misoprostol in $EP3^{+/+}$ and $EP3^{-/-}$ mice showed similar levels of infarct rescue, indicating that misoprostol protection in cerebral ischemia is mediated probably through EP2 and/or EP4 receptors.

4 EP1/EP3 and AD

Up to now, EP1 receptor has been indicated to play a neurotoxic role while the EP3 receptor is considered to exert neuroprotective effects. To confirm the neurotoxicity of EP1 receptor, Ahmad *et al.*[26] pretreated C57BL/6 wild type mice with EP1 receptor specific agonist and antagonist, followed by striatal unilateral NMDA injection. Results reveal that agonist could increase NMDA-induced lesion volume, while antagonist could significantly decrease the lesion volume as compared to the NMDA-control group. Similarly, NMDA- and MCAO-induced lesion volume decreased remarkably in $EP1^{-/-}$ mice, compared to those in wide type controls. All together, these data show that EP1 receptor activation promotes neurotoxicity, while blockade of it promotes neuroprotection. It is known that the characteristic of excitotoxic injury is the excessive intracellular accumulation of Ca^{2+}. Studies using the models of excitotoxicity, OGD and MCAO find that PGE_2 EP1 receptors are essential for the neurotoxicity mediated by COX-2-derived PGE_2. EP1 receptors disrupt Ca^{2+} homeostasis by impairing Na^+-Ca^{2+} exchange; on the other hand, pharmacological inhibition or gene inactivation of EP1 receptors ameliorates brain injury[43]. Thus, EP1 receptors induce neurotoxicity by augmenting the Ca^{2+} dysregulation underlying the excitotoxic neuronal death.

Previous pharmacological examinations have shown neuroprotective effects of EP3 in spinal cord slices with chronic glutamate toxicity from blockade of astrocytic glutamate transporters[44] and in organotypic hippocampal slices with acute NMDA toxicity[29]. The EP3-mediated neuroprotection is associated with an increase in the level of pro-survival phospho-AKT[44]. In the former model, chronic glutamate toxicity was induced by treatment of glutamate transporter inhibitors in organotypic spinal cord slices, resulting in motor neuron loss after several weeks of treatment[44].

However, activation of EP3 receptor with sulprostone could significantly rescue this motor neuron loss. To further characterize the EP3-mediated neuroprotective pathway, Bilak *et al.*[44] measured the level of the prosurvival phophorylated form of AKT in spinal cord slices stimulated with sulprostone. Results demonstrate a time-dependent increase in phospho-AKT level after EP3 activation, indicating that EP3 mediates neuroprotection through phosphorylation of AKT[45]. In another study of Wu *et al.*[29], the hippocampal slices from Sprague Dawley rats or C57BL/6 mice were treated with NMDA, and stimulation of EP3 receptor by picomolar concentrations of agonist sulprostone resulted in a significant rescue of CA1 pyramidal neurons. This finding is consistent with previous studies in spinal cord slices, where EP3 activation rescues motor neurons subjected to chronic glutamate toxicity.

5 Conclusion

PGE_2, as a product of COX, is a major inflammatory mediator and plays an important role in the inflammatory process of AD. However, there is still disagreement on the neuroprotective or neurotoxic role of PGE_2. In a recent study, Chen *et al.*[46] find that the expressions of COX-2 and PGE_2 in PC-12 cells could be up-regulated by LPS. And application of triptolide could then inhibit this increase, while having no effect on the proliferation of PC-12 cells. So the role of PGE_2 in neurodegeneration may be far more complex due to the presence of 4 EP receptor subtypes.

Due to the different distribution and expression styles of the PGE_2 receptor EP subtypes, the specificity and complexity of the EP receptor downstream signaling pathways, and the different experimental models, PGE_2/EP receptors have been conflictingly reported to mediate neurotoxicity and to be neuroprotective both *in vitro* and *in vivo*. So before identifying the roles of EP receptors in AD, we should first ascertain the distribution and expression of EP. Fortunately, the specific agonists and antagonists make the functions of different EP receptors clear. In addition, the application of gene knockout technology makes it possible to clarify the EP effects in AD. It is believed that a better understanding of the PGE_2 receptor EP subtypes may help to clarify the relation between inflammation and AD, and meanwhile to develop novel therapeutic strategies in AD treatment.

Acknowledgement: This work was supported by grants from the Natural Science Foundation of Zhejiang Province (No. Y206153), the Science and Technology Major Projects of Zhejiang Province (No. 2007C13053, 2008F80009), and the Science and Technology Programme of Hangzhou Municipality (No. 20051323B45).

References:

[1] Wan Y, Wang G, Chen SD. Genetic predisposition to inflammation: a new risk factor of Alzheimer's disease. Neurosci Bull 2008, 24: 314-322.

[2] Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, *et al.* Inflammation and Alzheimer's disease. Neurobiol Aging 2000, 21: 383-421.

[3] Etminan M, Gill S, Samii A. Effect of non-steroidal anti-inflammatory drugs on risk of Alzheimer's disease: systematic review and meta-analysis of observational studies. BMJ 2003, 327: 128.

[4] in t' Veld BA, Ruitenberg A, Hofman A, Launer LJ, van Duijn CM, Stijnen T, *et al.* Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease. N Engl J Med 2001, 345: 1515-1521.

[5] Szekely CA, Thorne JE, Zandi PP, Ek M, Messias E, Breitner JC, *et al.* Nonsteroidal anti-inflammatory drugs for the prevention of Alzheimer's disease: a systematic review. Neuroepidemiology 2004, 23: 159-169.

[6] Jantzen PT, Connor KE, DiCarlo G, Wenk GL, Wallace JL, Rojiani AM, *et al.* Microglial activation and beta-amyloid deposit reduction caused by a nitric oxide-releasing nonsteroidal anti-inflammatory drug in amyloid precursor protein plus presenilin-1 transgenic mice. J Neurosci 2002, 22: 2246-2254.

[7] Lim GP, Yang F, Chu T, Chen P, Beech W, Teter B, *et al.* Ibuprofen suppresses plaque pathology and inflammation in a mouse model for Alzheimer's disease. J Neurosci 2000, 20: 5709-5714.

[8] Yan Q, Zhang J, Liu H, Babu-Khan S, Vassar R, Biere AL, *et al.* Anti-inflammatory drug therapy alters beta-amyloid processing and deposition in an animal model of Alzheimer's disease. J Neurosci 2003, 23: 7504-7509.

[9] Szekely CA, Green RC, Breitner JC, Ostbye T, Beiser AS, Corrada MM, *et al.* No advantage of A beta 42-lowering NSAIDs for prevention of Alzheimer dementia in six pooled cohort studies.

Neurology 2008, 70: 2291-2298.

[10] Arvanitakis Z, Grodstein F, Bienias JL, Schneider JA, Wilson RS, Kelly JF, *et al.* Relation of NSAIDs to incident AD, change in cognitive function, and AD pathology. Neurology 2008, 70: 2219-2225.

[11] Zhang B, Du GH. Anti-inflammatory mechanism of non-steroidal anti-inflammatory drugs. Chin Pharm Bull 2005, 21: 905-910.

[12] Weggen S, Eriksen JL, Sagi SA, Pietrzik CU, Golde TE, Koo EH. Abeta42-lowering nonsteroidal anti-inflammatory drugs preserve intramembrane cleavage of the amyloid precursor protein (APP) and ErbB-4 receptor and signaling through the APP intracellular domain. J Biol Chem 2003, 278: 30748-30754.

[13] Hoshino T, Nakaya T, Homan T, Tanaka K, Sugimoto Y, Araki W, *et al.* Involvement of prostaglandin E2 in production of amyloid-beta peptides both *in vitro* and *in vivo*. J Biol Chem 2007, 282: 32676-32688.

[14] 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: 10180-10187.

[15] 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: 713-719.

[16] Echeverria V, Clerman A, Dore S. Stimulation of PGE receptors EP2 and EP4 protects cultured neurons against oxidative stress and cell death following beta-amyloid exposure. Eur J Neurosci 2005, 22: 2199-2206.

[17] Slawik H, Volk B, Fiebich B, Hull M. Microglial expression of prostaglandin EP3 receptor in excitotoxic lesions in the rat striatum. Neurochem Int 2004, 45: 653-660.

[18] Shie FS, Montine KS, Breyer RM, Montine TJ. Microglial EP2 as a new target to increase amyloid beta phagocytosis and decrease amyloid beta-induced damage to neurons. Brain Pathol 2005, 15: 134-138.

[19] 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: 257-268.

[20] Liu D, Wu L, Breyer R, Mattson MP, Andreasson K. Neuroprotection by the PGE2 EP2 receptor in permanent focal cerebral ischemia. Ann Neurol 2005, 57: 758-761.

[21] Breyer RM, Bagdassarian CK, Myers SA, Breyer MD. Prostanoid receptors: subtypes and signaling. Annu Rev Pharmacol Toxicol 2001, 41: 661-690.

[22] Wilson RJ, Rhodes SA, Wood RL, Shield VJ, Noel LS, Gray DW, *et al.* Functional pharmacology of human prostanoid EP2 and EP4 receptors. Eur J Pharmacol 2004, 501: 49-58.

[23] Fujino H, Salvi S, Regan JW. Differential regulation of phosphorylation of the cAMP response element-binding protein after activation of EP2 and EP4 prostanoid receptors by prostaglandin E2. Mol Pharmacol 2005, 68: 251-259.

[24] Sugimoto Y, Narumiya S. Prostaglandin E receptors. J Biol Chem 2007, 282: 11613-11617.

[25] Shie FS, Breyer RM, Montine TJ. Microglia lacking E Prostanoid Receptor subtype 2 have enhanced Abeta phagocytosis yet lack Abeta-activated neurotoxicity. Am J Pathol 2005, 166: 1163-1172.

[26] Ahmad AS, Saleem S, Ahmad M, Dore S. Prostaglandin EP1 receptor contributes to excitotoxicity and focal ischemic brain damage. Toxicol Sci 2006, 89: 265-270.

[27] Takadera T, Ohyashiki T. Prostaglandin E2 deteriorates N-methyl-D-aspartate receptor-mediated cytotoxicity possibly by activating EP2 receptors in cultured cortical neurons. Life Sci 2006, 78: 1878-1883.

[28] Pooler AM, Arjona AA, Lee RK, Wurtman RJ. Prostaglandin E2 regulates amyloid precursor protein expression via the EP2 receptor in cultured rat microglia. Neurosci Lett 2004, 362: 127-130.

[29] Wu L, Wang Q, Liang X, Andreasson K. Divergent effects of prostaglandin receptor signaling on neuronal survival. Neurosci Lett 2007, 421: 253-258.

[30] Lee EO, Shin YJ, Chong YH. Mechanisms involved in prostaglandin E2-mediated neuroprotection against TNF-alpha: possible involvement of multiple signal transduction and beta-catenin/T-cell factor. J Neuroimmunol 2004, 155: 21-31.

[31] Kazanietz MG, Caloca MJ, Eroles P, Fujii T, Garcia-Bermejo ML, Reilly M, *et al.* Pharmacology of the receptors for the phorbol ester tumor promoters: multiple receptors with different biochemical properties. Biochem Pharmacol 2000, 60: 1417-1424.

[32] Hui L, Pei DS, Zhang QG, Guan QH, Zhang GY. The neuroprotection of insulin on ischemic brain injury in rat hippocampus through negative regulation of JNK signaling pathway by PI3K/Akt activation. Brain Res 2005, 1052: 1-9.

[33] Amano H, Hayashi I, Endo H, Kitasato H, Yamashina S, Maruyama T, *et al.* Host prostaglandin E(2)-EP3 signaling regulates tumor-associated angiogenesis and tumor growth. J Exp Med 2003, 197: 221-232.

[34] Kabashima K, Saji T, Murata T, Nagamachi M, Matsuoka T, Segi E, *et al.* The prostaglandin receptor EP4 suppresses colitis, mucosal damage and CD4 cell activation in the gut. J Clin Invest 2002, 109: 883-893.

[35] Montine TJ, Milatovic D, Gupta RC, Valyi-Nagy T, Morrow JD, Breyer RM. Neuronal oxidative damage from activated innate immunity is EP2 receptor-dependent. J Neurochem 2002, 83:

463-470.

[36] Shie FS, Montine KS, Breyer RM, Montine TJ. Microglial EP2 is critical to neurotoxicity from activated cerebral innate immunity. Glia 2005, 52: 70-77.

[37] 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 alpha-synuclein. J Neuroinflammation 2007, 4: 2.

[38] Chen C, Magee JC, Bazan NG. Cyclooxygenase-2 regulates prostaglandin E2 signaling in hippocampal long-term synaptic plasticity. J Neurophysiol 2002, 87: 2851-2857.

[39] Yagami T, Nakazato H, Ueda K, Asakura K, Kuroda T, Hata S, *et al.* Prostaglandin E2 rescues cortical neurons from amyloid beta protein-induced apoptosis. Brain Res 2003, 959: 328-335.

[40] Takahashi Y, Hayashi I, Tominari Y, Rikimaru K, Morohashi Y, Kan T, *et al*. Sulindac sulfide is a noncompetitive gamma-secretase inhibitor that preferentially reduces Abeta 42 generation. J Biol Chem 2003, 278: 18664-18670.

[41] Weggen S, Eriksen JL, Sagi SA, Pietrzik CU, Ozols V, Fauq A, *et al.* Evidence that nonsteroidal anti-inflammatory drugs decrease amyloid beta 42 production by direct modulation of gamma-secretase activity. J Biol Chem 2003, 278: 31831-31837.

[42] Li J, Liang X, Wang Q, Breyer RM, McCullough L, Andreasson K. Misoprostol, an anti-ulcer agent and PGE2 receptor agonist, protects against cerebral ischemia. Neurosci Lett 2008, 438: 210-215.

[43] Kawano T, Anrather J, Zhou P, Park L, Wang G, Frys KA, *et al.* Prostaglandin E2 EP1 receptors: downstream effectors of COX-2 neurotoxicity. Nat Med 2006, 12: 225-229.

[44] 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: 240-248.

[45] Brunet A, Datta SR, Greenberg ME. Transcription-dependent and -independent control of neuronal survival by the PI3K-Akt signaling pathway. Curr Opin Neurobiol 2001, 11: 297-305.

[46] Chen W, Shen YD, Yao HP, Zhao GS. Inhibition of lipopolysaccharide-induced expression of cyclooxygenase-2 in PC-12 cells by triptolide. Chin Pharm J 2005, 40: 274-277.

前列腺素 E_2 受体 EP 亚型在阿尔茨海默病中的作用

魏丽丽[1], 沈悦娣[2], 章迎春[1], 胡兴越[3], 卢佩琳[3], 王莉[3], 陈炜[1]

[1] 浙江大学医学院附属邵逸夫医院精神卫生科，杭州 310016

[2] 杭州师范大学医学院附属医院，杭州 310015

[3] 浙江大学医学院附属邵逸夫医院神经内科，杭州 310016

摘要: 神经炎症在阿尔茨海默病(Alzheimer's disease, AD)发病机制中的作用一直备受关注。前列腺素 E_2(PGE_2)作为一个主要的炎症介质，在 AD 的炎症过程中发挥着重要的作用。然而，目前关于 PGE_2 对神经元是保护还是损害仍存有分歧。PGE_2 受体存在 EP1-4 四类亚型，因此要探讨 PGE_2 在神经元损伤中扮演的角色，我们需综合考虑下游信号通路的作用。本文旨在综述 PGE_2 受体 EP 亚型与 AD 的关系。对 PGE_2 受体 EP 亚型的进一步研究将有助于阐明炎症与 AD 的联系，为 AD 治疗找到新的靶点。

关键词: 炎症；阿尔茨海默病；前列腺素 E_2；EP 受体亚型