

Prostaglandins as the Agents That Modulate the Course of Brain Disorders

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Abstract: Neurologic and neuropsychiatric diseases are associated with great morbidity and mortality. Prostaglandins (PGs) are formed by sequential oxygenation of arachidonic acid in physiologic and pathologic conditions. For the production of PGs cyclooxygenase is a necessary enzyme that has two isoforms, that are named COX-1 and COX-2. COX-1 produces type 1 prostaglandins and on the other hand, COX-2 produces type 2 prostaglandins. Recent studies suggest PGs abnormalities are present in a variety of neurologic and psychiatric disorders. In a disease state, type 2 prostaglandins are mostly responsible and type 1 PGs are not so important in the disease state. In this review, the importance of prostaglandins especially type 2 in brain diseases has been discussed and their possible role in the initiation and outcome of brain diseases has been assessed. Overall the studies suggest prostaglandins are the agents that modulate the course of brain diseases in a positive or negative manner. Here in this review article, the various aspects of PGs in the disease state have discussed. It appears more studies must be done to understand the exact role of these agents in the pathophysiology of brain diseases. However, the suppression of prostaglandin production may confer the alleviation of some brain diseases.

Keywords: prostaglandins, depression, Alzheimer, addiction, Parkinson and multiple sclerosis

Introduction

Neuropsychiatric diseases have a wide array of symptoms and related behaviors that have a high prevalence in human societies.¹ A great fraction of them occurs in a subset of people that are suffering from other medical diseases.²⁻⁵ Many studies have been performed to confirm the basic mechanisms that produce such diseases. Prostaglandins are lipid-derived small molecules that are produced from arachidonic acid by sequential enzymatic reactions.⁶ Recently it has been given great importance to these small molecules in the occurrence of neuropsychiatric disorders.⁷ Recently it has been proposed that other than physiologic functions, certain prostaglandins are associated with neuropsychiatric and neurologic disorders.⁸ New studies aim to establish a relationship between certain types of prostaglandins with a specific disease. Here in this review article, we are going to discuss the important aspects of prostaglandins in the occurrence of brain diseases.

Prostaglandins

Prostaglandins are lipid derives molecules that have important functions in our body. All prostaglandins have 20 carbons but they have different structures that account for

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diverse physiologic functions.⁹ The difference in the receptor is responsible for the diverse functions of one prostaglandin that can be inhibitory or stimulatory.¹⁰ The synthesis of prostaglandins is a multistep process that begins with the formation of arachidonic acid from diacylglycerol and phospholipase A₂. Arachidonic acid can choose the cyclooxygenase pathway or lipoxygenase pathways.¹¹ Prostaglandins are formed by sequential oxygenation of arachidonic acid. Cyclooxygenase has two isoforms COX-1 and COX-2. Recently it has been suggested that a variant of COX-1 can be considered as COX-3.¹² Constant production of COX-1 that results in the production of type 1 prostaglandins. On the other hand, COX-2 is activated in certain conditions such as inflammation and growth.¹³

Prostaglandins Receptors

Eight subtypes of membrane prostanoid receptors have already been discovered: the PGD receptor (DP), four subtypes of the PGE receptor (EP1, EP2, EP3, and EP4), the PGF receptor (FP), the PGI receptor (IP), and the TxA receptor (TP)¹⁴ (Table 1). All are G protein-coupled rhodopsin-type receptors with seven transmembrane domains, and each domain is encoded by a different gene. In Table 1 we have summarized the various prostaglandin receptors that are present in the body.¹⁵ Cyclooxygenase enzyme releases prostaglandins from arachidonic acid in membrane lipids (Figure 1). There are multiple steps that eventually all types of prostaglandins are produced. The structural difference is to account for their different

biological properties. Also different kind of receptors also may account for such differences. One prostaglandin may have a stimulatory effect in a given context and in another context have an inhibitory function. They act as paracrine substances and usually targeted tissue in the vicinity of the site of their production.

Prostaglandins and Cytokines

Cytokines are small protein molecules released by different inflammatory cell types. Based on the cell type that secretes cytokines, cytokines can be assigned different names such as lymphokines that secretes from lymphocytes and monokines that release from monocytes. Also, they have other names based on their specific activities such as chemokines (chemotactic activities) and interleukins (cytokines that interact with other leukocytes). Cytokines can act as autocrine, paracrine and endocrine. They can mediate inflammatory or anti-inflammatory processes and therefore that can be harmful or not harmful.¹⁶ Different cell types produce cytokines but mainly T cells and macrophages secrete cytokines. Pieces of evidence support the role of prostaglandins such as PGEs in the production of certain cytokines.¹⁷ The produced cytokines can be inflammatory or anti-inflammatory. However, most studies support the theory that prostaglandins promote cytokine production and the produced cytokines are harmful to neurons.¹⁸ In other diseases such as diabetes¹⁹ and atopic dermatitis²⁰ also it has been documented the inflammatory role of prostaglandins and increased production of cytokines. In a recent article, the role of

Table 1 Different Prostaglandin Receptors and Their Potencies for a Specific Type

Name of Related Prostaglandin	The Potency of Related Prostaglandin to Activate the Related Receptor	G Protein Linkage	Signaling Pathway
Prostaglandin DP1 receptor	PGD ₂ >>PGE ₂ >PGF _{2α} >PGI ₂ =TXA ₂	Gs alpha subunit	Activates AC, increases cAMP, raises Ca ²⁺
Prostaglandin DP2 receptor	PGD ₂ >>PGF _{2α} =PGE ₂ >PGI ₂ =TXA ₂	Gi alpha subunit	Inhibits AC to depress cAMP levels
Prostaglandin EP1 receptor	PGE ₂ >PGF _{2α} =PGI ₂ >PGD ₂ =TXA ₂	Gq alpha subunit	Stimulates PLC, IP3, PKC, ERK, p38 Mpk, and CREB
Prostaglandin EP2 receptor	PGE ₂ >PGF _{2α} =PGI ₂ >PGD ₂ =TXA ₂	Gs alpha subunit	Stimulates AC, raises cAMP, stimulates beta-catenin and Glycogen synthase kinase 3
Prostaglandin EP3 receptor	PGE ₂ >PGF _{2α} ,PGI ₂ >PGD ₂ =TXA ₂	Gi & G12 subunit	Inhibits AC, decreases cAMP, stimulates PLC & IP3, raises Ca ²⁺
Prostaglandin EP4 receptor	PGE ₂ >PGF _{2α} =PGI ₂ >PGD ₂ =TXA ₂	Gs alpha subunit	Stimulates AC, PKA, PI3K, AKT, ERK, p38 Mpk, & CREB; raises cAMP
Prostaglandin F2α receptor	PGF _{2α} >PGD ₂ >PGE ₂ >PGI ₂ =TXA ₂	Gq alpha subunit	Stimulates PLC, IP3, & PKC; raises Ca ²⁺
Prostacyclin I2 receptor	PGI ₂ >>PGD ₂ =PGE ₂ =PGF _{2α} >TXA ₂	Gs alpha subunit	Stimulates AC & PKA; raises cAMP
Thromboxane A2 receptor	TXA=PGH ₂ >>PGD ₂ =PGE ₂ =PGF _{2α} =PGI ₂	Gq alpha subunit	Stimulates PLC & IP3; raises Ca ²⁺

Note: It can be seen that every prostaglandin has its own receptors. However, one prostaglandin may react with other types of receptors. The difference in subtypes of receptors may account for the different effects of prostaglandins in a different situation. They generally act through G-proteins. The G-proteins may be stimulatory or inhibitory, but prostaglandins usually act through stimulatory G-proteins. Recently for one new receptor for F2a and I2 have been introduced and more research should be done to be included in the table but in the text, some information has been given.

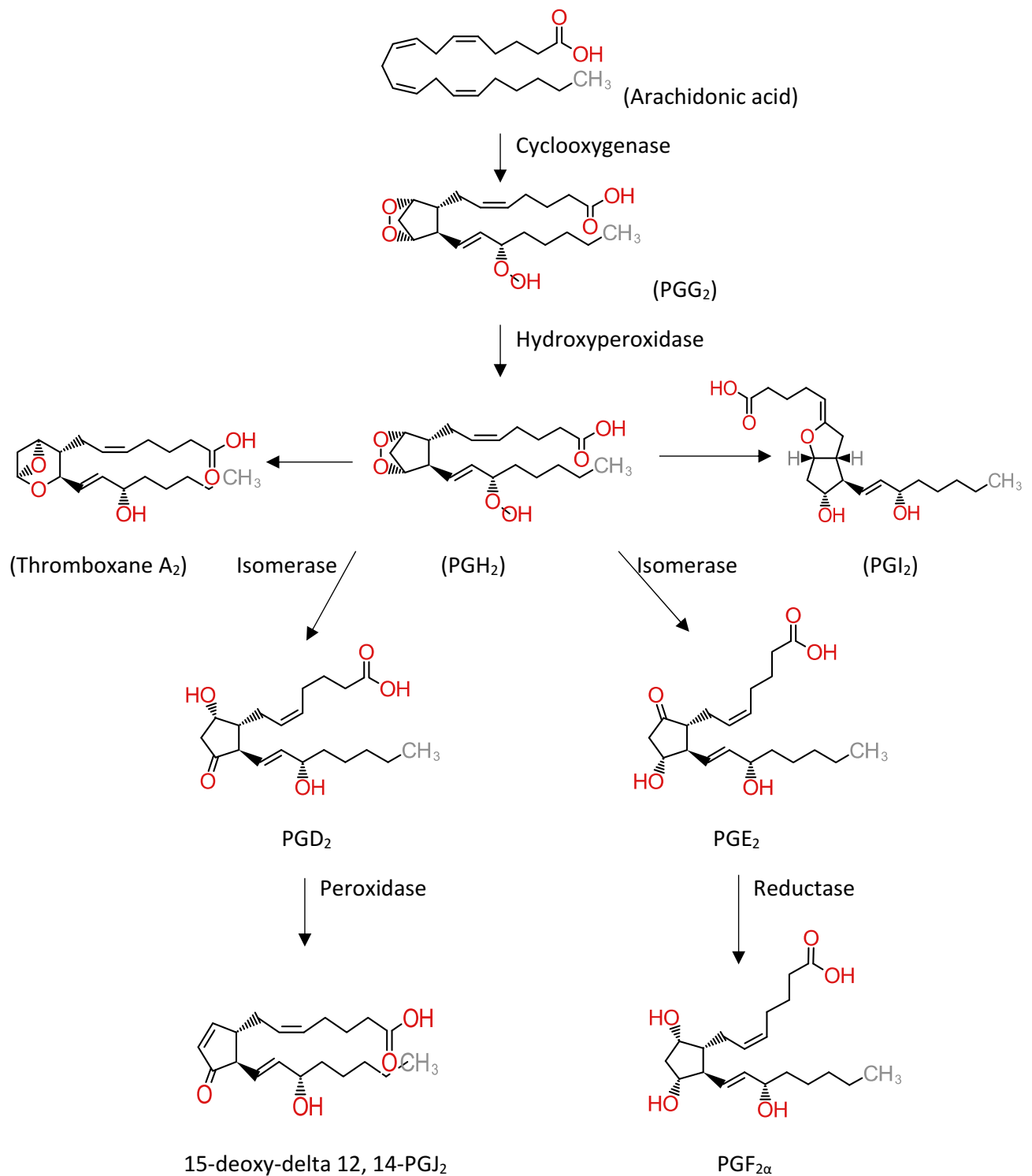


Figure 1 Metabolic cascade of the arachidonic acid pathway that leads to prostaglandin production. The cyclooxygenase pathway has been illustrated in the figure. Thromboxane A₂ and prostaglandin I₂ are synthesized by synthase enzymes.

cytokines in the production of chronic inflammation has been well discussed and these shreds of evidence support the role of prostaglandins in the pathophysiology of

neurodegenerative diseases.²¹ However other studies support the fact that prostaglandins via production of cytokines may be inflammatory or anti-inflammatory agents.²²

Prostaglandins in Inflammation

Prostaglandins are considered as the agents that most commonly secreted in inflammation states. Here, we are going to explain the possible role of PGs in neuroinflammation that eventually leads to neurodegeneration.²³ However, it is noteworthy to remember that prostaglandins are not always considered as agents that may cause neurodegeneration and will be discussed later. Glia and neurons are in close talk with each other. Astrocyte development is associated with the development of synaptic structures. Enough level of neuroplasticity can be achieved by the proper function of astrocytes.²⁴ Also in later stages of life astrocytes play an important role in neurotransmitter metabolism.²⁵ Another important type of glial cell is microglia cells that can act in two different ways. They can be destructive to neurons and also they can help to repair neurons. In this sense activation of microglial cells after neuronal destruction can alleviate the severity of disease.²⁶ Prostaglandins as the agents that are mostly produced in inflammation state, can disturb the neuro-glial interaction and eventually disturb the neuronal network. Also, they can impair the microglial function in later stages of the disease.²⁷ The lack of studies about this subject prevents us from further discussion about this issue. However, in different studies, it has been shown that prostaglandins are the cause of inflammation. This is important because prostaglandins are the cause of many abnormalities independent of any mediators. Here we are going to discuss the important aspect of prostaglandins in this context.

Prostaglandin E₂ and Inflammation

It is one of the most abundant prostaglandins in the body. It has diverse functions but in inflammation, it mediates the emergence of all classical signs of inflammation such as redness, swelling, and pain.²⁸ The importance of PGE₂ in the inflammation process mainly comes from mPGES-1. mPGES-1 is a member of the MAPEG (membrane-associated proteins involved in eicosanoid and glutathione metabolism) superfamily that needs glutathione as a cofactor for PGE₂ production.²⁹ In mPGES-1 deficient mice, there was a reduction in severity and incident of rheumatoid arthritis (RA).^{30,31} Complementary studies revealed that mPGES-1 can cause angiogenesis and formation of granulation tissue.³¹ Other studies about pain showed similar effects.³² PGE₂ acts locally through four different receptors (EP1-EP4). EP3 and EP4 have the

highest affinity for PGE₂ and almost are found in all tissues and in contrast to EP1 are found in some restricted organs and EP2 is the least abundant.³³ EP3 and EP4 are associated with swelling that are one of the symptoms of inflammation³⁴ and EP2 and EP3 causes exudates formation.³⁵ Also, EP4 deficient mice showed an attenuated response in antibody-induced RA.³⁶ In contrast to these effects, anti-inflammatory action can be considered for this type of prostaglandins especially in allergic asthma.³⁷ More studies revealed that this prostaglandin has both inflammatory and anti-inflammatory actions and this is because of the presence of different types of receptors and different kinds of actions of PGE₂ on different cell types.³⁸⁻⁴¹ During neuroinflammation also these contrasting roles can be seen.^{42,43}

Prostaglandin I₂ and Inflammation

PGI₂ is one of the most important regulators of circulation.⁴⁴ However, besides this important role, PGI₂ also is a mediator of edema and pain that is seen in acute inflammation and also mediates extravasations of cells through vessels.^{45,46} Complementary studies about the PGI₂ receptor confirm that this prostaglandin has a pivotal role in acute inflammation and most acute inflammation signs are associated with the emergence of this prostaglandin.⁴⁷ Furthermore, PGI₂ has an important role in pain perception.⁴⁸ In other animal models of pain assessment, PGI₂ was the origin of pain perception that is a symptom of most neurologic diseases.^{49,50} This prostaglandin also has a selective role through its action on CD4-Th₂.⁵¹

Prostaglandin D₂ and inflammation

PGD₂ is found in the brain and also in peripheral tissues.⁵² In the central nervous system, this prostaglandin regulates pain and also causes pain.^{53,54} PGD₂ is synthesized in the leptomeninges, choroid plexus and oligodendrocytes in the brain and secreted to cerebrospinal fluid (CSF).⁵⁴ In the peripheral tissues it is mostly secreted by mast cells and other cells also produce PGD₂.^{55,56} This prostaglandin has two types of receptor: DP1 and DP2 (CRTH2). Besides its role in inflammation especially in allergic asthma, this prostaglandin can act to inhibit inflammation.⁵⁷ However, in contrast to the proinflammatory role, PGD₂ may take a role to inhibit inflammation in other areas. This anti-inflammatory role has been reported through the DP1 receptor that is present in dendritic cells.⁵⁸⁻⁶⁰ PGD₂ as the precursor of 15d-PGJ₂, through this prostaglandin, can suppress inflammation.⁶¹⁻⁶³

Prostaglandin F_{2α} and Inflammation

This is an inflammatory prostaglandin⁶⁴ that has two receptors: FPA and FPB. This prostaglandin mainly plays an important role in the female reproductive system^{65,66} but also has a variety of roles in other parts of the body such as brain injury and pain.^{67,68}

Thromboxane and Inflammation

TXA₂ normally derived from platelet but also another cell with a half-life of the 30s.⁶⁹ It reacts mainly through TP (thromboxane/endoperoxide receptor) but also two other isoforms have been reported.⁷⁰ Besides platelet aggregation and smooth muscle contraction, they have an important role in inflammation.⁷¹ TP receptor also is activated with PGH₂ and HETEs.^{72,73} This prostaglandin has a role in inflammation because TP deficient mice will not develop full manifestation of septic shock syndrome.^{74,75}

Prostaglandins in Neuropsychiatric Disease

Neuropsychiatric disease encompasses a wide variety of diseases. Schizophrenia, depression, bipolar disorder, anxiety and addiction to drug abuse and many others are classified as neuropsychiatric disorders. Recently it has been given much interest to find a biomarker for neuropsychiatric diseases.⁷⁶ Recent studies suggest that prostaglandins can have a role in the occurrence of neuropsychiatric diseases. However because of the lack of enough studies that cover all types of neuropsychiatric disorders, here we cannot discuss all types of neuropsychiatric diseases (Table 2).

Schizophrenia

Schizophrenia is a mental health illness that globally affects about 15.23/100,000 persons of all adults.⁷⁷ Schizophrenia is a chronic, severe mental disorder that affects thinking, feelings and behavior. Schizophrenic patients often lose touch with reality.⁷⁸ Schizophrenic patients come to the clinician with different symptoms. They may have negative or positive symptoms, or have acute symptoms and maybe with exacerbation of pre-existent disease.^{79,80} The evidence that supports prostaglandins plays an important role in schizophrenia comes back to the 70s and 80s. Some studies proposed that prostaglandin deficiency is present in this disease.⁸¹ In one study replacement therapy with prostaglandins diminished negative and positive symptoms in

Table 2 Protective Roles of NSAIDs and COX Inhibitors in Brain Diseases

Postulated Prostaglandins and Related Therapies	Brain Diseases
COX-1 and COX-2 inhibitors	Schizophrenia Depression Alzheimer's disease Parkinson's disease Huntington disease
TXA ₂ inhibitors	Alzheimer's disease
PGA ₁ inhibitors	Huntington disease
PGF _{2α} inhibitors	Addiction Huntington disease
PGE ₂ inhibitors	Addiction Alzheimer's disease Parkinson's disease Huntington disease Amyotrophic lateral sclerosis (ALS)
PGD ₂ inhibitors	Multiple Sclerosis Parkinson's disease
PGJ ₂ inhibitors	Multiple Sclerosis Parkinson's disease

Note: Likewise, by application of selective prostaglandins receptor inhibitors also some certain diseases alleviate. Meanwhile, it should be noted that some prostaglandins selectively react with certain receptors in some cases.

schizophrenic patients.⁸² However, some studies support the increased activity of prostaglandins in schizophrenic patients.⁸³ Thus it can be considered that the reduction of prostaglandins can have a useful effect. Recent studies suggest that treatment with drugs that inhibit prostaglandins may have a palliative role for this disease. In recent years, antipsychotic drugs are administered along with anti-inflammatory such as aspirin to increase the efficacy of treatment in schizophrenic patients.⁸⁴ The increased inflammatory activity in the prefrontal cortex has been associated with the severity of the disease.⁸⁵

Depression

Major depressive disorder (MDD), also known simply as depression, is a mental disorder characterized by at least two weeks of low mood state that is present across most situations. It is often accompanied by low self-esteem, loss of interest in normally enjoyable activities, low energy, and pain without a clear cause.⁸⁶ The lifetime prevalence of depression in the United States is about 15% to 20%.⁸⁷ This disease affects women more than

men.⁸⁸ It is the leading risk factor for suicide.⁸⁹ Recent studies suggest that prostaglandins can play a role in depression diagnosis and treatment. Overall all studies support the theory that an increase in prostaglandins and their activity are associated with depression. The existing literature is not so rich about this subject. Based on a few studies, increases in prostaglandins in salivary⁹⁰ and in serum⁹¹ have been associated with this disease. Also, treatment with cyclooxygenase-2 inhibitor celecoxib had a therapeutic effect in major depression.⁹² However, in one study treatment with ethyl-eicosapentaenoic at a dosage of 1 g/d was effective in treating depression in patients who remained depressed despite adequate standard therapy.⁹³

Addiction

Addiction to drug abuse is a devastating state that has severe harmful effects on all aspects of life from school, workplace city and families to many other areas.⁹⁴ It is mostly considered as a reward system dysfunction.^{95,96} Unrestricted abuse of a drug that is rewarding in nature is considered as addiction despite the adverse effects.⁹⁵ Preoccupation with good memories of the desired effects of the drugs is mostly responsible for relapse to drug abuse.⁹⁷ The 12-month prevalence of drug addiction in the United States is about 15% to 61%.⁹⁸ Also, alcohol addiction is another type of addiction that has a high prevalence in western countries.⁹⁹ The high rates of morbidity and mortality mandate performing different experiments to understand the basic mechanisms that help to control the uncontrolled behaviors. Alcohol consumption increases the production of prostaglandins. Animal studies propose that alcohol consumption increase brain levels of PGE, and PGF.¹⁰⁰ Blocking PG production attenuates the behavioral effects of alcohol, and it can be inferred that PGs have a role in the development of alcohol addiction.¹⁰¹ Chronic alcohol consumption also is associated with paradoxical regulation of PGE₁ and PGE₂.¹⁰² In another study overproduction of PGE₁ has been associated with cocaine abuse.¹⁰³ It has been proposed that PGE is mainly involved in the reinstatement of self-administration. It should be noted that prostaglandin receptors are found in the cerebral cortex, hippocampus, and midbrain.¹⁰⁴ The reinstatement to drug abuse is mainly mediated by the synergistic effect of the cannabinoid system and arachidonic acid by-products.¹⁰⁵ From this view, prostaglandins have an important role in drug addiction.

Prostaglandins and Neurologic Diseases

Neurological disorders are increasingly recognized as one of the most prevalent disorders with a high burden to the patients, their families, and society. Statistics showed that globally, in 2016, neurological disorders were the leading cause of DALYs (Years Lived with Disability) (276 [95% UI 247–308] million) and the second leading cause of deaths (9.0 [8.8–9.4] million). So this is very important to introduce new mechanisms that are responsible for the occurrence of these diseases and also introduce new hopes for the treatment of such disorders (Table 2).¹⁰⁶

Multiple Sclerosis

Multiple sclerosis (MS) is considered a disabling condition that mainly involves the brain and spinal cord.¹⁰⁷ The symptoms of the disease are different and miscellaneous such as numbness or weakness, loss of vision, pain, tremor, slurred speech, fatigue, dizziness and bowel and bladder dysfunction.¹⁰⁸ The reaction of the immune system to myelin causes the production of autoantibody and loss of myelin which in turn causes loss of the brain connection to the rest of the body. MS has four types 1) relapsing-remitting (the most common type) 2) primary progressive MS 3) secondary progressive MS 4) progressive relapsing.¹⁰⁹ Since the neuroinflammation plays an important role in this disease, new studies have been focused on the assessment of various neuroregulators that causes inflammation. Animal studies bring evidence that prostaglandins can interfere with the disease process. The evidence to support this theory comes from the alleviation of MS by systemic injection of 15d-PGJ₂ in animal studies.¹¹⁰ Other evidence support that anti-inflammatory agents such as peroxisome proliferator-activated receptor (PPAR)- γ agonists, including thiazolidinediones (TZDs) and 15-deoxy- Δ 12, 14 prostaglandin J₂ (15d-PGJ₂), have been shown to be effective in the treatment of experimental autoimmune encephalomyelitis (EAE).¹¹¹ So, it has been suggested that glial cells especially astrocytes have a vital role in controlling autoimmune encephalitis.^{112,113} 15d-PGJ₂ a metabolite of PGD₂ suppresses the immune response and it is useful for the treatment of MS. Also, the overproduction of this prostaglandin in disease states suggests that this prostaglandin is a necessary factor that controls the progression of the disease. On the other hand, prostaglandin E has a protective role by activating oligodendrocytes that produce myelin.¹¹⁴ Experiments have suggested that prostaglandins are not the

same in all types of MS. A more recent study showed that PGD₂, PGI₂ and 5-lipoxygenase pathways are suppressed in the acute phase of EAE and return to constitutive levels in the chronic phase,¹¹⁴ but in a relapsing-remitting MS, PGD₂ does not change.¹¹⁵

Alzheimer's Disease

Alzheimer's disease is a neurodegenerative disorder that is defined as the most prevalent cause of dementia (60% to 80%).¹¹⁶ Sever memory loss occurs in this disease that interferes with normal daily life.¹¹⁷ This disease is associated with the accumulation of Amyloid plaques and Tau tangles in the brain.¹¹⁸ In most cases, it begins in individuals over 65 years old. Different mechanisms have been proposed for Alzheimer's disease. The first evidence that supports the role of inflammation derives from the reduction of the occurrence of Alzheimer's disease in the subset of patients that take NSAIDs for rheumatoid arthritis.¹¹⁹ Further experiments showed the overproduction of PGE₂ in a subset of patients and NSAID therapy was useful in these patients.¹²⁰ Astrocyte and microglia interplay plays an important role in the pathophysiology of Alzheimer's disease and PGE₂ is present in some subset of patients. Indeed, PGE₂ is a necessary factor that mediates the negative consequence of amyloid-beta and glial cell interaction. Emerging data support the benefit of the application of NSAIDs rather than cox-2 selective inhibitors in controlling Alzheimer's disease.¹²¹ In the later course of Alzheimer's disease, the negative effect of amyloid-beta aggregation is mediated by PGE₂ that its receptor is present in microglial cells that play an important role in Alzheimer's pathophysiology.¹²² Recent studies suggest that suppressing prostaglandin's action on neuronal metabolism is associated with less neuronal injury and lower secretion of proinflammatory cytokines, TNF α , and IL-6.^{123,124} Also, it seems that prostaglandins may be an agent that alleviates the severity of ischemia-induced dementia.¹²⁴ The adverse effect of prostaglandins in Alzheimer's disease is mainly mediated through disturbance that occurs as the consequence of oxidative stress¹²⁵ and microglia function mediates immune clearance of unwanted by-product materials.¹²⁶ All these studies suggest that prostaglandins are the agents that may interfere with all the stages that may necessary for both progression and initiation of dementia. Based on these reasons, prostaglandins antagonist have used successfully for the alleviation of Alzheimer's disease.¹²⁷ Prostaglandins have been shown to cause the formation and disappearance of APP holoprotein that has

a toxic effect on the proteins.¹²⁸ The positive effect of this treatment is mainly mediated through the selective antagonist of the PGE₂ receptor.¹²⁹ Also, the PGE₃ receptor antagonist has a protective role in dementia that is caused by disturbed oxidative stress that eventually leads to amyloid-beta plaque formation (Ikeda-Matsuo). PGE₄ antagonist also is an effective treatment for alleviating the cognitive deficit of patients.¹³⁰ Other prostaglandins such as PGD₂ have related to Alzheimer's disease¹³¹ but about PGF_{2 α} and TXA₂ studies are not confirmatory.

Parkinson's Disease

Parkinson's disease is a long-term progressive brain disease that affects movements. The disease usually progresses over time.¹³² The most prevalent symptoms at the onset of the disease are shaking, rigidity, slowness of movement and difficulty in walking.¹³³ Destruction of dopaminergic neurons in substantial nigra is necessary for the occurrence of the symptoms of the disease. Different treatments have been proposed for this disease.¹³⁴ An experiment that supports inflammation has a role in this disease is derived from microglial activation. However, prostaglandins in this disease have a negative role. Dopamine is the main target for the treatment of Parkinson's disease can be considered for prostaglandin-related treatment. A recent study suggests that prostaglandins can cause unfolding and aggregation of Parkinson's disease associated with UCHL₁.¹³⁵ Also, COX-2 overproduction can cause PGE₂ overexpression that results in the death of dopaminergic neurons.¹³⁶ COX-2 overproduction has been confirmed in another study in this disease.¹³⁷ NSAID (nonsteroidal anti-inflammatory drugs) intake has been well substantially reduced the severity of Parkinson's disease by increasing the survival of dopaminergic neurons.¹³⁸ However, in some studies, this positive effect did not observe. In different experiments, PGE has been shown that is the most putative prostaglandin that interferes with Parkinson's disease.¹³⁹ Other prostaglandins such as PGD₂ and PGJ₂ have been shown to interfere with normal protein metabolism but strong evidence that supports the involvement of such prostaglandins in Parkinson disease is not confirmatory.¹⁴⁰

Huntington's Disease

Huntington's disease is a progressive brain disease that mainly affects individuals in their thirties and forties. It manifests itself through uncontrolled movements, emotional problems, and loss of cognition.¹⁴¹ Many people

with Huntington's disease develop involuntary jerking or twitching movements known as chorea. Also, juvenile Huntington's disease that is less common than adult-onset tends to progress more quickly than adult form.¹⁴² Huntington's disease affects an estimated 3 to 7 per 100,000 people. Mutations with an autosomal dominant pattern in the HTT gene cause Huntington's disease.¹⁴³ COX-2 inhibitors overall improved the outcome of motor function in Huntington's diseases.^{144–146} This positive effect was not observed in transgenic animals.¹⁴⁷ Enhancement of prostaglandin levels such as PGE₂, PGF_{2α} by injection has a negative effect of motor function and neuronal markers and restoration of the normal level of prostaglandins by COX-2 inhibitors had a positive outcome in the treatment of Huntington's disease.^{148,149} PGA₁ has also suggested having a role in Huntington Disease but further experiments are needed to establish its role.¹⁵⁰

Amyotrophic Lateral Sclerosis (ALS)

ALS is a rare neurologic disorder that is characterized by the loss of neurons that are necessary for voluntary movements.¹⁵¹ ALS manifests by stiff muscles, muscle twitching, and muscle weakening. In 90% to 95% of the case, no definite cause is identified.¹⁵² The patient has difficulty in all actions that movement of voluntary muscles is necessary such as walking, swallowing and finally breathing. In this disease, prostaglandin alternations also have been observed. In ALS prostaglandins are elevated and have a negative effect on neuronal function. Elevated prostaglandins especially PGE₂ has been associated with an increased rate of neuronal death and disability.¹⁵³ Also, another study confirms that prostaglandin production can cause the disease to progress.¹⁵⁴ For this reason, NSAID therapy has been proposed for the alleviation of this disease.^{155,156}

Conclusion

In this review article, the importance of prostaglandins in brain diseases was discussed. Prostaglandins in some diseases act as a protective role and in some diseases act in a negative manner. So NSAID therapy is not recommended in all patients. So, more studies should be done to understand the precise pathophysiology that is responsible for the initiation and progression of brain diseases. Overall these studies suggest prostaglandins are the agents that have an important role in brain disorders' pathophysiology and these agents modulate the course of the diseases.

Disclosure

The authors report no conflicts of interest in this work.

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