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Prostaglandin J2: a potential target for halting inflammation-induced neurodegeneration

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Abstract

Prostaglandins are produced via cyclooxygenases, which are enzymes that play a major role in neuroinflammation. Epidemiological studies show that chronic treatment with low levels of cyclooxygenase inhibitors (NSAIDs) lowers the risk for Alzheimer's (AD) and Parkinson's (PD) diseases by as much as 50%. Unfortunately, inhibiting cyclooxygenases with NSAIDs blocks the synthesis of downstream neuroprotective and neurotoxic prostaglandins, thus producing adverse side effects. We focus on prostaglandin J2 (PGJ2) because it is highly neurotoxic compared to PGA1, D2, and E2. Unlike other prostaglandins, PGJ2 and its metabolites have a cyclopentenone ring with reactive α,β -unsaturated carbonyl groups that form covalent Michael adducts with key cysteines in proteins and GSH. Cysteine-binding electrophiles such as PGJ2 are considered to play an important role in determining whether neurons will live or die. We discuss *in vitro* and *in vivo* studies showing that PGJ2 induces pathological processes relevant to neurodegenerative disorders such as AD and PD. Furthermore, we found that increasing intracellular cAMP with the lipophilic peptide PACAP27 counteracts some of the PGJ2-induced detrimental effects. In conclusion, new therapeutic strategies that neutralize the effects of specific neurotoxic prostaglandins downstream from cyclooxygenases could have a significant impact on the treatment of chronic neurodegenerative disorders with fewer adverse side effects.

Keywords

prostaglandin J2; NSAID; Michael adducts; cyclooxygenases; chronic inflammation; Alzheimer's and Parkinson's diseases

One of the critical factors that contributes to neurodegeneration and its progression in neurodegenerative disorders such as Alzheimer's (AD) and Parkinson's diseases (PD) is neuroinflammation.^{1–3} An important aspect of neuroinflammation is the cyclooxygenase pathway that includes the constitutive cyclooxygenase I (COX-1) and the inducible cyclooxygenase II (COX-2).⁴ Cyclooxygenases generate a range of prostaglandins, the

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biosynthesis of which is blocked by nonsteroidal anti-inflammatory drugs (NSAIDs). Based on epidemiological studies, NSAIDs are the only currently available drugs known to decrease the risk and/or delay the onset of these disorders and other neurodegenerative conditions.⁵ However, the causal relationship between the prostaglandin products of cyclooxygenases and neurodegeneration has been poorly investigated to date.

Neurodegeneration and Neuroinflammation

AD and PD are chronic neurodegenerative disorders that develop over time and worsen with aging. Neuroinflammation is a common hallmark of these disorders and is considered to be one of their drivers and not just a consequence of the ongoing neurodegeneration.^{6–8} Postmortem, genetic, and epidemiological studies confirm that neuroinflammation plays a critical role in the neuropathology and progression of AD and PD. First, activated microglia, peripheral macrophages, and T lymphocytes are detected postmortem in the affected areas of AD and PD patients, in concert with increased levels of COX-2 and other proinflammatory mediators.^{1,3,9–12} Second, a spectrum of AD- and PD-associated genes were shown to be linked to neuroinflammation. For example, mutations in the amyloid precursor protein (APP) linked to early onset AD affect the generation and/or aggregation of the amyloid β (A β) peptide.⁸ Soluble, oligomeric, and fibril forms of A β bind to and activate microglia.² PD-associated mutations in the genes encoding LRRK2, Parkin, and α -synuclein are also related to inflammation.¹³ Moreover, genome-wide association studies (GWAS) reported that variations in loci encoding immune-related genes are genetic risk factors for AD, such as triggering receptor expressed on myeloid cells 2 (TREM2)^{14,15} and CD33^{16,17}, as well as for PD, such as human leukocyte antigen (HLA), bone marrow stromal cell antigen 1 (BST1), and TREM2.^{13,18} Lastly, epidemiological studies show an inverse relation between the use of some NSAIDs such as aspirin, ibuprofen, and naproxen, and the risk of developing AD and PD,^{19,20} with the risk reduction being as much as 50%.⁵ Although there are conflicting results,^{1,5} the link is most evident for the use of ibuprofen.^{21,22} Clinical studies with NSAIDs have not showed a similar trend.^{1,23} It has been postulated that the chronic use of NSAIDs is beneficial only in the early stages of AD or PD and that it may be too late to target inflammation with these drugs once clinical symptoms are apparent.^{5,24} A better understanding of the shared and diverse mechanism of action of these drugs, including cyclooxygenase inhibition and decreased prostaglandin production, is required to more effectively modulate the neurotoxic outcomes of neuroinflammation with fewer side effects.¹

Neuroinflammation is a localized response of the CNS to brain injury induced by infection and toxic metabolites, as well as conditions such as traumatic brain injury and stroke. Neuroinflammation is also a nonspecific response, as it always results in microglia activation independent of the initiating stimulus. Acute inflammation is resolved immediately after the injured site is healed. However, neuroinflammation is widely regarded as chronic inflammation of the CNS that extends beyond the original site and spreads to healthy areas.

Neuroinflammation involves sustained activation of glial cells (microglia and astrocytes) and other immune cells recruited into the brain by crossing a compromised blood–brain

barrier, thus perpetuating the immune response. Upon activation, both microglia and astrocytes undergo morphological changes. In addition, activated microglia release a spectrum of inflammatory mediators that include prostaglandins, cytokines, chemokines, reactive free radicals, and proteases. Some of these mediators are neuroprotective while others are neurotoxic, supporting the notion that neuroinflammation is a double-edged sword playing both detrimental and beneficial roles depending on the circumstances.^{25,26}

Prostaglandins in AD and PD

Prostaglandins (PGs) are a family of 20-carbon unsaturated fatty acids produced via the cyclooxygenase pathway in response to extrinsic and intrinsic stimuli (reviewed in Ref. 27). The initial step in prostaglandin synthesis involves the hydrolysis of membrane sn-2 glycerophospholipids (phosphatidylcholine, phosphatidylethanolamine, and phosphatidylinositol) by the cytoplasmic phospholipase A2 (PLA2 group IVA) to release arachidonic acid.^{28–30} PLA2 is activated by increased calcium levels and phosphorylation. Once activated, PLA2 translocates from the cytoplasm to intracellular membranes, including the endoplasmic reticulum and nuclear envelope, where it has access to arachidonic acid-containing phospholipid substrates.³¹ Cyclooxygenases, which are bifunctional enzymes inserted into the ER and nuclear membranes, will then catalyze the cyclooxygenation of arachidonic acid to PGG2, followed by hydroperoxidation of PGG2 to PGH2.^{32–34} PGH2 diffuses from the ER lumen through its membrane to the cytoplasm to be converted to more polar prostanoids, via prostaglandin-specific synthases localized on the cytoplasmic face of the ER.³⁵ The coupling of PGH2 synthesis with the respective downstream prostaglandin synthases that produce different types of prostaglandins is intricately orchestrated in a tissue- and/or cell-specific manner.³⁶

Cyclooxygenases COX-1 and COX-2 function as homodimers.²⁹ Although the brain expresses COX-1 and COX-2 under normal physiological conditions, it is clear that cyclooxygenases are implicated in neurodegeneration.^{11,37} COX-1 is constitutively expressed and is generally viewed as being the homeostatic isoform, but studies suggest that it is actively involved in some forms of brain injury.^{38,39} The expression and activity of COX-2 are largely responsive to adverse stimuli and physiologic imbalances.⁴⁰ COX-2 upregulation following CNS injury is not restricted to neurons, since COX-2 induction is also apparent in glia.⁴¹ Although many studies support the notion that COX-1 and COX-2 are involved in neurodegeneration, the contribution of their prostaglandin products to the neurodegenerative process remains poorly defined.³⁸ NSAIDs' therapeutic effectiveness could be compromised, as these drugs block the generation of all prostaglandin products of cyclooxygenases, including those that are neuroprotective and those that are neurotoxic.

Upon neuronal injury, activated microglia produce large quantities of prostaglandins, such as PGD2 and PGE2,⁴² as well as PGJ2,⁴³ which act as potent local regulators of physiologic and pathologic pathways linked to neuroinflammation. For example, PGE2 induces neuroprotection or neurotoxicity depending on the cell type and the receptor that it activates. Binding of PGE2 to its EP4 receptor in neurons is highly protective in a mouse model of cerebral ischemia.⁴⁴ However, preventing PGE2 binding to its EP2 receptor in microglia

restores beneficial microglial function and prevents the progression of AD pathology in animal models.⁴⁵

PGD2 is the most abundant prostaglandin in the brain^{4,46–48} and the one that becomes the most elevated under pathological conditions.⁴⁹ PGD2 levels are also significantly increased in the frontal cortex of AD patients compared to age-matched controls.⁵⁰ PGD2 is produced by two distinct types of prostaglandin D2 synthases (PGDS): (1) the lipocalin enzyme (L-PGDS) that is present in the brain and is regulated by estradiol,⁵¹ and (2) the hematopoietic enzyme (H-PGDS) that is mostly active in the immune system and mast cells.⁵² In addition, PGD2 binds to the G protein–coupled receptors (GPCRs) DP1 and DP2.⁵² In AD patients and in Tg2576 mice, a well-established AD model, the levels of H-PGDS and DP1 were found to be selectively upregulated in microglia and astrocytes within senile plaques.⁵³ These results indicate that PGD2 acts as a mediator of plaque-associated inflammation in the AD brain.⁵³ Similarly, L-PGDS, which is one of the most abundant CSF proteins produced in the brain, was detected in amyloid plaques in both AD patients and Tg2576 mice.⁵⁴ Secreted L-PGDS in the CSF has a dual function: it increases CSF-PGD2 levels⁵⁵ and also acts as a lipophilic-ligand carrier.⁵⁶ L-PGDS was found to bind A β monomers and prevent A β aggregation, suggesting that L-PGDS is a major A β chaperone, and disruption of this function could be related to the onset and progression of AD.⁵⁴

Investigations on the role of PGD2 in PD are more recent and therefore less extensive.⁵⁷ Nevertheless, there are a few studies supporting the role of PGD2 in PD. For example, significant changes in L-PGDS isoforms were detected in the CSF of at least 20 idiopathic PD patients compared to 100 controls.⁵⁸ These alterations reflected up/downregulation of L-PGDS isoforms likely to represent pathology at the cellular level, to affect prostaglandin production, and to correlate with disease symptoms.⁵⁸ It was speculated that these altered isoforms could be candidate diagnostic biomarkers of PD, and they may have predictive value.⁵⁸

Why investigate the role of PGJ2?

PGD2 is highly unstable (estimated brain half-life of 1.1 min) and readily undergoes spontaneous dehydration to generate the biologically active cyclopentenone J2 prostaglandins, which include PGJ2, 12-PGJ2 and 15-deoxy- 12,14-PGJ2 (15d-PGJ2) (Fig. 1).⁵⁹ The neurotoxic effects of PGD2 were shown to be mediated by the bioactive J2 prostaglandins.⁵⁹ Formation of cyclopentenone eicosanoids in the brain, such as PGJ2, is a novel pathogenic mechanism that potentially contributes to many neurodegenerative conditions, including AD and PD.⁶⁰ Upon stroke and TBI, the *in vivo* concentration of free PGJ2 in the rodent brain increases from almost undetectable to an average of 100 nM.^{61,62} Since PGJ2 binds covalently to proteins, local cellular and intracellular concentrations of PGJ2 are potentially even higher.⁵⁹ Stroke and TBI increase the long-term risk for AD⁶³ and PD,^{64;65} thus strongly supporting the idea that PGJ2 contributes to the pathogenesis of these disorders. PGJ2 was also shown to accumulate in the spinal cord of sporadic amyotrophic lateral sclerosis (ALS) patients.⁶⁶

Our studies focus on PGJ2 because we established in neuronal cultures that PGJ2 was by far the most neurotoxic of the four prostaglandins that we tested, including PGA1, D2, E2, and J2, with PGE2 being the least neurotoxic of the four.⁶⁷ PGJ2 is a highly toxic prostaglandin that impairs the ubiquitin/proteasome pathway (UPP) by targeting (a) the 26S proteasome, perturbing its assembly and oxidatively modifying the S6ATPase (Rpt3) subunit, and (2) deubiquitinating enzymes such as UCH-L1; thus, PGJ2 induces the accumulation/aggregation of ubiquitinated (Ub) proteins.^{61,62,67–72} PGJ2 also disrupts cytoskeletal integrity,^{68,73,74} induces oxidative stress⁷⁵ and neuronal apoptosis,⁶⁶ and inhibits mitochondrial complex 1 activity.⁷⁶ Thus, PGJ2 induces many of the pathological processes involved in AD and PD.²⁷

Receptor-dependent PGJ2 signaling

J2 prostaglandins bind to DP1 and DP2, which are GPCRs for PGD2.⁵² DP1 and DP2, like other GPCR prostaglandin receptors, are present not only at the plasma membrane⁴ but also at the nuclear membrane, thus providing for intracrine (intracellular) signaling.⁷⁷ DP1 activation is coupled to the G protein G_s, resulting in increased cAMP levels, whereas DP2 activation is coupled to G_i, thus decreasing cAMP levels and increasing intracellular calcium.⁷⁸ Moreover, DP2 activation potentiates neuronal injury in hippocampal neuronal cultures and organotypic slices, while DP1 activation is neuroprotective.^{11,49} J2 prostaglandins have a higher affinity for DP2 (by as much as 100-fold) than for DP1, and bind to DP2 with an affinity similar to PGD2 (i.e., in the nanomolar range).^{79,80}

Although controversial,⁴ the J2 prostaglandins 15d-PGJ2 and 12-PGJ2 are considered to be endogenous ligands for the nuclear peroxisomal proliferator activator receptor (PPAR γ), to which they bind with high affinity.^{81,82} PPAR γ activation in the nucleus plays a major role in the regulation of adipogenesis, glucose homeostasis, cellular differentiation, apoptosis, and inflammation.⁸³ PPAR γ agonists, such as the J2 prostaglandins, promote neuroprotection in models of stroke, AD, HD, PD, multiple sclerosis, and spinal cord injury, via anti-inflammatory– or antioxidant-dependent mechanisms.^{84–86}

Posttranslational covalent modification of proteins by PGJ2

Unlike most prostaglandins, PGJ2 and its metabolites 15d-PGJ2 and 12-PGJ2 have a cyclopentenone ring with α,β -unsaturated carbonyl groups (Fig. 2, red star). These carbonyl groups are highly reactive with free cysteine thiols in glutathione and proteins, forming covalent Michael adducts^{87,88} (Fig. 2). This highly conserved redox reaction involving cysteine thiols and PGJ2 in the brain represents a novel pathologic change and could play a critical role in neurodegeneration in AD and PD.⁸⁹

Electrophile binding (S-alkylation, Fig. 2) by endogenous compounds such as PGJ2 is currently regarded to play an important role in determining whether neurons will live or die.⁸⁸ This posttranslational protein modification seems to be highly selective, as only a specific set of cysteine residues are vulnerable to covalent modification, independent of protein thiol content.^{89,90} Of the several hundred cellular proteins with potentially reactive thiols, only ~ 10% form covalent adducts with J2 prostaglandins and are considered members of the *electrophile-responsive proteome*.^{91,92} Proteomic approaches identified 358

proteins in human aortic endothelial cells that are covalently modified by 15d-PGJ2.⁹³ J2 prostaglandins covalently bind to specific sites within the plasma membrane, as well as within the nuclear and cytosolic subcellular fractions.⁹⁴ At least 11 plasma membrane proteins were identified as binding biotinylated 15d-PGJ2, and they were distributed into three functional groups: glycolytic enzymes, molecular chaperones, and cytoskeletal proteins.⁹⁴ Furthermore, J2 prostaglandin binding alters protein catalysis, binding, structural function, and transport.^{93,95}

Contrasting effects of J2 prostaglandins

The role of J2 prostaglandins in inflammation is complex.^{96,97} Under certain conditions, they exert anti-inflammatory effects by inhibiting the production of proinflammatory mediators, such as iNOS, TNF α , and IL1 β ; suppressing microglia and astrocyte activation; and inducing apoptosis.^{98–100} In other circumstances, J2 prostaglandins are proinflammatory agents. They stimulate the production of proinflammatory mediators such as IL8, activate MAPK,^{101,102} and activate microglia as well as astrocytes.^{103,104} Furthermore, 15d-PGJ2 seems to play a role in the regulation of human autoimmune diseases and to inhibit inflammation in models of arthritis, ischemia–reperfusion injury, inflammatory bowel disease, lupus nephritis, and AD.¹⁰⁵

J2 prostaglandins also display both protective and destructive effects. Their biological activities include antiviral and antitumoral effects, modulation of the heat shock response, induction of oxidative stress and apoptosis,¹⁰⁶ upregulation of the death receptor 5 (DR5), sensitization to TRAIL-induced cytotoxicity, and caspase 8 activation.^{66,107–109} Although their antiproliferative and proapoptotic effects are most frequently described, J2 prostaglandins also induce the proliferation of different forms of cancer cells when used at nanomolar to low micromolar concentrations.¹¹⁰

The effects of J2 prostaglandins most likely depend on their intracellular targets and downstream pathways, which can be dose and cell type dependent.¹¹¹ J2 prostaglandins may exert some of their anti- or proinflammatory as well as anti- or prosurvival effects through PPAR γ -dependent mechanisms. However, these prostaglandins also exert their actions through PPAR γ -independent pathways, including activation of the MAPK and JNK pathways,^{112,113} stabilization of the transcription factor Nrf2 via its interaction with Keap1,^{114–116} and inhibition of the NF- κ B pathway.^{117,118} This may account for the different effects of 15d-PGJ2 compared to other PPAR γ ligands, such as pioglitazone, which do not replicate all of the effects attributed to J2 prostaglandins.⁵⁵ Identifying the mechanism by which J2 prostaglandins exert their neurotoxic effects could lead to new strategies to prevent and/or delay neurodegeneration linked to inflammation.

Potential role of PGJ2 in the transition from acute to chronic inflammation

The mechanisms underlying the transition from acute to chronic inflammation are poorly understood. It has been postulated that, besides being mediators of acute inflammation, prostaglandins also function in the transition and maintenance of chronic inflammation, thus inducing long-lasting effects.¹¹⁹ Prostaglandins accomplish this by amplifying cytokine signaling, upregulating COX-2, inducing chemokines, and recruiting inflammatory cells

such as macrophages.¹¹⁹ We and others demonstrated that PGJ2 induces COX-2 upregulation in cancer cells^{120;121} and neuronal cells.¹¹³ Thus, PGJ2 may facilitate the transition from acute to chronic inflammation (Fig. 3) via a positive feedback loop that involves COX-2 upregulation.^{113,119} A slow, steady stream-like release of J2 prostaglandins as a result of chronic neuroinflammation could be cumulative, leading overtime to accumulation of covalent PGJ2–protein adducts until they reach a toxic threshold. The covalent protein modification in the brain by highly reactive electrophiles such as J2 prostaglandins represents a novel pathologic posttranslational change¹²² that may play a critical role in progressive neurodegeneration.

Prostaglandins are largely produced by activated microglia and reactive astrocytes (less by neurons) during neuroinflammation. PGJ2 also induces microglia and astrocyte activation.^{103,104} Characterizing the self-perpetuating cycle of inflammatory processes involving PGJ2 in the brain that potentially drives the slow progression of neurodegeneration will contribute to preventing/arresting neurodegenerative disorders, such as AD and PD, that are associated with the cyclooxygenase pathway.

Lipopolysaccharide (LPS)-mediated models of neurodegeneration

LPS-mediated models of neuroinflammation are often used to address the relationship between neuroinflammation and the pathogenesis of AD and PD.¹²³ LPS is a lipoglycan component of the Gram-negative bacterial outer wall that binds to CD14 on microglia membranes and elicits a strong immune reaction in animals. Single systemic administration of LPS to adult rats induced hippocampal-dependent selective impairment in context–object discrimination, but not spatial memory, mimicking, in part, AD cognitive deficits.¹²⁴ In mice, a single LPS systemic administration caused progressive dopaminergic neuronal loss.¹²⁵ Unfortunately, as microglia are present in a variety of brain regions, activation of microglia and the subsequent proinflammatory response induced by systemically administered LPS are not specific and include other regions of the brain relevant to AD or PD. To overcome this drawback, LPS is also administered intracranially into the fourth ventricle or hippocampus for AD-like models¹²⁶ or the SN, striatum, or globus pallidus for PD-like models.¹²⁷ Both AD- and PD-like models exhibit microglia activation. Intracellular A β aggregates¹²⁸ and apoptotic neuronal death¹²⁹ were detected in the AD-like models.¹²⁶ PD-like models show dopaminergic neuron loss with no damage to GABAergic or serotonergic neurons, enhanced α -synuclein nitration, increased level of proinflammatory cytokines (IL-1 β , TNF- α , IL-6, and NO), and motor deficits.¹²⁷ A significant finding is that the LPS-induced pathological changes were more severe in middle-aged (16-month-old) rats than in young (3-month-old) rats, supporting the view that aging is a critical risk factor in the development of PD.¹³⁰

One of the shortfalls of the LPS models of AD and PD is that, when injected intracranially, the LPS effect is very acute, causing, for example, nigral DA neuronal loss within 24 hours that persists at the same level over 30 days, therefore not mimicking the progressive nature of PD pathology.¹³¹ In addition, these LPS models of AD or PD address the central role of inflammation in these disorders, but they do not distinguish which of the factors produced by activated microglia and astrocytes induce neurodegeneration. This is a very important

issue since some products of inflammation are neuroprotective and others neurotoxic. The mechanisms by which neurotoxic prostaglandins target neurons remain critical missing links in the proof of a pathogenic role for the cyclooxygenase pathway in AD and PD.

Justification for PGJ2 rodent models

As far as we know, there are no models of AD or PD that include administering prostaglandin products of cyclooxygenases to mimic the pathology of these disorders. This is a critical gap, not only because COX-2 is highly induced in AD and PD brains, but also because NSAIDs, which inhibit prostaglandin biosynthesis, are the only currently established drugs that potentially decrease the risks and/or delay the onset of these disorders. Unfortunately, these drugs have serious side effects that include bleeding and ulcers. Therefore, there is an urgent need to develop more potent anti-inflammatory drugs with fewer undesirable side effects. Investigating the effects of neurotoxic prostaglandins will contribute to the development of drugs that fulfill this need.

Our recent studies focus on establishing PGJ2-induced rodent models of PD. Our previously established PGJ2 mouse model of PD addresses the potential of a specific prostaglandin to induce PD pathology or how to protect from it.^{103,104} We determined that nigral/striatal microinfusion of PGJ2 into adult (12-week-old) FVB male mice led to (a) a dose-dependent reduction in the number of dopaminergic neurons in the substantia nigra pars compacta (SNpc) with little damage to dopaminergic neurons in the ventral tegmental area (VTA) and GABAergic interneurons in the SN pars reticulata (SNpr); (2) activated microglia and astrocytes; (3) detection of neuronal Lewy-like bodies with ubiquitinated proteins; and (4) impaired gait and balance mimicking PD motor deficits. Since PGJ2 upregulates the expression and activity of COX-2,¹¹³ PGJ2 also has potential to initiate a series of deleterious cascades leading to self-sustained progressive neurodegeneration. Thus, PGJ2-based PD animal models can serve an important role in developing and evaluating possible neuroprotective or neurorestorative therapeutics for PD patients.

Our current studies (unpublished) are investigating a PGJ2-induced rat model of PD. Rat models offer many advantages over mouse models for human disease.¹³² Compared to the mouse, rat physiology is easier to monitor and closer to the human condition, and rats are more intelligent and capable of learning a broader variety of tasks.¹³² Rats are also larger than mice and thus better suited for the use of μ PET in preclinical research and drug development, due to the requirement of high spatial resolution to visualize the structures of interest and to maintain quantitative accuracy.

According to our preliminary results, PGJ2 has a similar toxic effect on mice and rats. This is not the case for all drug-based PD models. For unknown reasons, some environmental toxin-based models are species specific. For example, rats are resistant to MPTP, and the MPTP sensitivities of different strains of mice differ widely.¹³³ On the other hand, mice and other species are resistant to rotenone under the conditions tested for the rotenone rat model.¹³³ The PGJ2 mouse and rat models will potentially show equivalent pathology.

Therapeutic interventions for AD and PD with a focus on PGJ2

J2 prostaglandins bind to the G_i -coupled DP2 receptor, resulting in a decrease in basal cAMP levels (discussed above). We confirmed this by showing that PGJ2 lowers neuronal cAMP.¹⁰⁹ On the basis of these findings, we investigated whether agents that restore and/or elevate intracellular cAMP will overcome the toxic effects of PGJ2. We focused on PACAP (pituitary adenylate cyclase-activating polypeptide), which is a lipophilic peptide that signals via activation of the G_s protein-coupled receptor PAC1R (pituitary adenylate cyclase 1 receptor).¹³⁴ PAC1R is expressed in the cerebral cortex, hippocampus, SNpc, ventral tegmental area, and other brain areas.^{135,136} Nanomolar concentrations of the two forms of PACAP, PACAP38 and the truncated form PACAP27, activate adenylate cyclase and elevate intracellular cAMP.¹³⁴ The mechanisms by which PACAP mediates neuroprotection are reviewed in Ref. 137. We and others demonstrated that PACAP treatment of neuronal cultures overcomes the decrease in cAMP levels induced by PGJ2,^{109;138} as well as neuronal death and proteasome deficits.¹⁰⁹ PACAP treatment also provides neuroprotection in several *in vivo* models of AD and PD by exerting antiapoptotic, anti-inflammatory, and antioxidant effects,¹³⁹ thus supporting the neuroprotective potential of PACAP administration.

We evaluated the neuroprotective effects of PACAP27 in the PGJ2-induced mouse model of PD.¹⁰³ PACAP27 suppressed PGJ2-induced dopaminergic neuronal loss and motor deficits but not the sustained microglia activation.¹⁰³ Our results with PACAP27 suggest that persistent microglia activation is likely to play a key role in disease progression, extending beyond the time of injury. It is clear that the PD pathology exhibited by the PGJ2-induced mouse model involves integrated signaling across neurons and microglia. There is a need to optimize candidate anti-inflammatory therapies designed to target the integrated signaling across neurons and microglia to fully benefit patients with AD or PD.

Another approach to target the adverse effects of PGJ2 is the development of pathologically activated therapeutics (PATs).¹⁴⁰ The principle of these types of drugs is that they only become active at the site of injury, thus decreasing potential severe side effects and improving drug tolerance by the treated patients. Some of these PATs are compounds, such as carnosic acid and some other types of hydroquinones, which only become electrophilic at the site of tissue injury undergoing oxidative stress.^{141,142} Once electrophilic, these PATs activate the Keap1/Nrf2/ARE (antioxidant-response element) transcription pathway, via *S*-alkylation of specific cysteines in Keap1. This results in Nrf2 stabilization and translocation to the nucleus to induce the synthesis of endogenous antioxidant phase 2 enzymes.⁸⁸ These neuroprotective PATs are weaker electrophiles than others that are neurotoxic, such as PGJ2.¹⁴⁰ Stronger electrophiles, such as PGJ2, *S*-alkylate glutathione (GSH) cysteines, depleting the intracellular reducing conditions, leading to ROS accumulation and mitochondrial dysfunction.^{143–145} The contrasting neuroprotective or neurotoxic effects of *S*-alkylating electrophiles depends in part on which cysteines they target. A precise identification of the cysteine targets of electrophiles like J2 prostaglandins is important to understand and develop improved therapeutics to combat their neurodegenerative effects.¹⁴¹

Conclusions

J2 prostaglandins are endogenous products of the cyclooxygenase pathway that exhibit pro- and anti-inflammatory effects through receptor-mediated and receptor-independent signaling. J2 prostaglandins induce many of the pathological changes involved in AD and PD, including (1) inhibition of the proteasome and the ubiquitin hydrolase UCH-L1 and accumulation/aggregation of ubiquitinated proteins; (2) disruption of cytoskeleton integrity; (3) oxidative stress, mitochondrial complex 1 inhibition, and neuronal apoptosis; and (4) COX-2 upregulation as well as microglia and astrocyte activation, which may initiate a positive feedback loop and lead to progressive long-term effects. Drugs that are currently available to inhibit the cyclooxygenase pathway, such as NSAIDs, are effective for preventing/halting inflammation, but unfortunately produce severe side effects. Therapeutic strategies, such as the ones we discussed, that target neurotoxic factors downstream of cyclooxygenases, including J2 prostaglandins, offer great promise as a new approach that maintains the homeostatic balance offered by the cyclooxygenase pathway. This new therapeutic approach is relevant to AD, PD, and other neurodegenerative disorders in which the cyclooxygenase pathway of inflammation plays a critical role in mediating neurodegeneration.

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J2 PROSTAGLANDINS

Figure 1.

Formation of PGJ2 and its metabolites. PGJ2 is a product of spontaneous dehydration (–H₂O) of PGD2, which is the most abundant prostaglandin in the brain and the one that changes the most under pathological conditions. PGJ2 can be further metabolized into 12- and 15d-PGJ2 by reactions catalyzed by human serum albumin (HSA) or by dehydration (–H₂O), respectively. In rodents, the *in vivo* concentration of free PGJ2 in the brain upon stroke and TBI increases to neurotoxic levels. Since PGJ2 binds covalently to proteins and GSH, its cellular and intracellular concentrations in the brain are predicted to be much higher than free PGJ2. The stars indicate highly reactive a,b-unsaturated carbonyl groups.

Figure 2.

Receptor-dependent and independent actions of PGJ2. Some of the PGJ2 effects are receptor mediated. The DP2 receptor, which is a G protein–coupled receptor (GPCR) for PGD2, is coupled to G_i , thus decreasing cAMP levels and increasing intracellular calcium. DP2 activation is linked to neuronal injury. We established that the peptide PACAP, which binds to its PAC1R receptor and increases cAMP, prevents some of the adverse effects of PGJ2. The nuclear receptor PPAR γ is a transcription factor. PPAR γ activation is associated with anti-inflammatory and neuroprotective signaling. Moreover, unlike most prostaglandins, PGJ2 and its metabolites (12-PGJ2 and 15d-PGJ2) have a cyclopentenone ring with reactive α,β -unsaturated carbonyl groups (red star) that mediate their receptor-independent effects. Through S-alkylation, these groups form covalent Michael adducts with free sulfhydryls in cysteine residues in glutathione and cellular proteins. This covalent posttranslational modification by PGJ2 in the brain represents a novel pathologic change and could play a critical role in neurodegeneration in AD and PD. Pathologically activated therapeutics (PATs) are small molecules that become chemically activated at sites of tissue injury undergoing oxidative stress. These PATs are postulated to counteract the effects of electrophiles such as PGJ2, by activating the Keap1/Nrf2/ARE transcription pathway. Activation of the latter pathway induces the synthesis of endogenous antioxidant phase 2 enzymes that protect against oxidative and electrophilic stresses.

Figure 3.

PGJ2 is a potential factor in the transition from acute to chronic inflammation. Besides being mediators of acute inflammation, prostaglandins also function in the transition and maintenance of chronic inflammation, thus inducing long-lasting effects. Prostaglandins, such as PGJ2, accomplish this by amplifying cytokine signaling, upregulating COX-2, inducing chemokines, and recruiting inflammatory cells such as macrophages. Thus, therapeutically targeting prostaglandins such as PGJ2 has potential to prevent/block chronic neuroinflammation relevant to neurodegeneration in AD and PD.