MINIREVIEW

Does the Insulin-Like Growth Factor System Interact with Prostaglandins and Proinflammatory Cytokines During Neurodegeneration? (44509)

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Abstract. **Prostaglandins and proinflammatory cytokines are implicated in the etiology of neurodegenerative diseases, such as Alzheimer's disease. Signaling cascades initiated by these factors may result in reactive oxygen species generation and cell death. The insulin-like growth factors (IGF) are ubiquitous polypeptides involved in all aspects of growth and development. Additionally, the IGF are regarded as survival factors that display potent antiapoptotic activity. Interfering with IGF production, distribution, or signaling may result in greater susceptibility to apoptotic stimuli. In neurodegenerative conditions, the IGF appear to be antagonized by prostaglandins and proinflammatory cytokines. In this review, the relationship among specific prostaglandins, the proinflammatory factors, tumor necrosis factor, interleukin-1, and interleukin-6, and the IGF system will be investigated.** [P.S.E.B.M. 2000, Vol 224:20–27]

Free radical–induced cascades initiated by prostaglandins (PG) and proinflammatory cytokines (PIC) may contribute to neurodegenerative diseases such as Parkinson's and Alzheimer's disease (AD) (1, 2). Oxidative stress contributes to AD by depleting intracellular glutathione, disrupting calcium homeostasis, and contributing to abnormal processing of the amyloid precursor protein (APP), resulting in cell death (3–5). Studies suggest that PG and PIC may participate in amyloid-beta (Aß) plaque formation (4–14). Maintenance of calcium homeostasis and protection from oxidative stress and apoptotic stimuli are actions mediated by the IGF system (15, 16). Through antagonization and modulation of IGF action, PG and PIC may accelerate neurodegeneration. Please see Table I for a list of abbreviations used in this article.

Prostaglandins

PGs are synthesized by two different isoforms of cyclooxygenase (Cox), designated Cox-1 and Cox-2 (17). Cox-1 is a constitutive isoform present in most tissues; Cox-2 is induced by cytokines, growth factors, oncogenes, and tumor promoters (17). The Cox-2 gene contains numerous cis-acting promoter elements including a nuclear factor-kappa B (NF-κB) site (17). Inflammation increases the synthesis of PG due in part to upregulation of Cox-2 (17). PG and PG-induced cytokines, such as interleukin (IL)-1 and IL-6, have been implicated in various inflammatory and degenerative disorders, including AD and prion diseases

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Table I. List of Abbreviations

Aβ	amyloid-beta
ACT	alpha-1-antichymotrypsin
ACTH	adrenocorticotropic hormone
AD	Alzheimer's Disease
APP	amyloid precursor protein
BBB	blood-brain-barrier
CNS	central nervous system
Cox	cyclooxygenase
CRH	corticotropin-releasing hormone
DS	Down Syndrome
EAE	experimental autoimmune encephalomyelitis
GH	growth hormone
HPA	hypothalamic-pituitary-adrenal
IGF	insulin-like growth factor(s)
IGFBP	IGF binding protein(s)
IL	interleukin
IRS	insulin receptor substrate
NF-κB	nuclear factor-κB
NMDA	N-methyl-D-aspartate
NSAID	nonsteroidal anti-inflammatory drug
PG	prostaglandin(s)
PIC	proinflammatory cytokines
RA	rheumatoid arthritis
ROS	reactive oxygen species
TNF	tumor necrosis factor

(10–13). In astrocytoma cells, PGE_1 and PGE_2 increased expression of IL-6, and, in addition, PGE_2 increased IL-1-stimulated IL-6 production (18). Corroborating evidence is provided by reported elevations of Cox-2 in the frontal cortex of AD patients and Aß-induced increases in Cox-2 in SH-SY5Y neuroblastoma cells (12). Neurofibrillary tangle formation has been associated with Cox-2 in neurons from individuals with Fukuyama-type congenital muscular dystrophy (19). Additionally, in differentiated murine neuroblastoma cells and fetal rat hippocampal cells, PGA_1 and PGE_1 were reported to increase Aß levels (13). In primary cultures of cortical astrocytes, PGE_2 stimulated APP expression (20).

PGE_2 may also contribute to neurodegeneration in AD by increasing levels of inactive α-1-antichymotrypsin (ACT) in serum and cerebrospinal fluid (21). Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit Cox-1 and Cox-2 by competing with arachidonate for the cyclooxygenase binding site. PG and leukotrienes, implicated in the excitatoxic death of N-methyl-D-aspartate (NMDA) neurons, may also be involved in abnormal APP processing. Cyclooxygenase inhibitors such as NSAIDs may benefit AD patients by decreasing the inflammatory response that generates free radicals and other cytotoxins (10–14).

IGF and Prostaglandins

Interactions between the IGF and PG are diverse and regulated in a tissue-specific manner, for example, in cartilage, PGE_2 increases IGF-1 *via* an autocrine loop and also increases IGF binding protein (IGFBP)-1 production (Table II) (22–24). In osteoblasts, IGF-1 is capable of decreasing Cox-2 expression (22). Whether downregulation of Cox-2 in the central nervous system (CNS) contributes to the neuroprotective actions of the IGF has yet to be determined. However, PG and IGF antagonism has been described in the CNS. In C6 glioma cells, cyclopentenone PG (PGA and PGJ) decrease IGF-1 gene expression, an action that was attenuated by the glutathione-repleting agent, N-acetylcysteine (25). PGA_2 in these cells decreases cyclin D1 expression, an action that is reversed by IGF-1 (25).

Cerebrospinal fluid levels of PG-like F2-isoprostanes, stable products of arachidonate peroxidation, are increased in AD (26). IGF attenuated carbon tetrachloride-induced peroxidative damage of rat liver, an effect that may also extend to brain (27).

Table II. Actions of Prostaglandins and Proinflammatory Cytokines in Neurodegenerative Disease and Interactions with IGF System

Factor	Action	Interaction
Prostaglandins	1. Increase Aβ levels 2. PG and PG-induced cytokines, IL-1 and IL-6, implicated in AD	1. PG decrease IGF-1 and cyclin D1 2. IGF may decrease PG production
IL-1	1. Promotes neuritic plaque formation 2. Production/processing of APP 3. Increases levels of ACT 4. HPA hyperactivity	1. Decreases GH receptor mRNA 2. Decreases IGF-1 mRNA/protein 3. Inhibits GH stimulation of IGF-1 4. Alters responsiveness to IGF-1
TNF	1. Stimulates ACT production 2. Increases production of PGE_2 3. Induces expression of IL 4. Accentuates Aβ toxicity 5. Alters BBB permeability	1. Inhibits GH stimulation of IGF-1 2. Stimulates IGFBP-1 production 3. Alters responsiveness to IGF-1 4. Decreases IGF-1 levels
IL-6	1. Contributes to AD pathology 2. Correlated with neuropathological changes 3. HPA hyperactivity 4. Alters BBB permeability	1. Stimulates IGFBP-1 production 2. Decreases IGF-1 concentrations 3. Antagonizes IGF action

Interleukins and Tumor Necrosis Factor

Immune dysregulation involving the PIC, IL-1, tumor necrosis factor (TNF), and IL-6 has been implicated in neurodegenerative conditions and AD pathophysiology (4–10, 28–30). IL-1 involvement in AD has been reported to include promotion of neuritic plaque formation and induction of chronic inflammatory cascades leading to cell dysfunction and death. Overexpression of IL-1 in AD may contribute to neuritic plaque development by enhancing production and processing of APP and increasing levels of ACT (31). Both IL-1 and TNF stimulated ACT production *via* activation of NF-κB in astrocytoma cells (31, 32).

Reciprocally, Aß is capable of elevating release of functional IL-1β from macrophages/microglia that may then stimulate TNF production. The inflammatory cascade can be continued by IL-1 and TNF stimulation of PGE_2 production *via* increased Cox-2 expression and histamine (4–10, 33–40). Indeed, elevated concentrations of histamine and IL-1 have been reported in AD patients (32, 34). IL-1 is increased during neurodegenerative conditions and is elevated in hippocampi of aged rats. Chronic exposure to IL-1 may promote lipid peroxidation and associated cell dysfunction *via* free radical cascades. Hippocampal IL-1 expression is associated with stress and age-induced derangements in long-term potentiation (4, 32, 33). IL-1 and TNF may also potentiate ischemic brain damage (33–40).

TNF signaling pathways involve activation of NF-κB and phospholipase A2 and production of arachidonic acid leading to PG and leukotriene formation and the generation of free radicals (37–40). TNF is able to induce apoptosis in neurons and oligodendrocytes *via* pathways involving free radical formation (37–40). TNF and IL-1 stimulate reactive oxygen species (ROS) generation in many cell lines (37–40). In astrocytoma cells, NF-κB was shown to mediate the effects of TNF and IL-1 (31). Activation of NF-κB can be prevented by antioxidants suggesting that dietary intervention should be considered in AD prevention and treatment (10–14). TNF induces the expression of IL-6, IL-8, and other proinflammatory chemicals, potentiates glutamate neurotoxicity in cell culture, and accentuates Aß toxicity in thyroid, kidney, neuroblastoma, and prostate cancer cell lines (37–40). Overexpression of TNF in brains of transgenic mice decreased nerve growth factor and choline acetyltransferase in the hippocampus (41). TNF is also capable of completing a positive feedback cycle by stimulating release of IL-1 and IL-6 that may be potentiated by histamine (35–37). Adrenal function has also been reported to be altered in AD (42–50). Hypothalamic-pituitary-adrenal (HPA) dysfunction as measured by postdexamethasone cortisol concentrations was correlated with hippocampal atrophy in individuals with AD (46). Glucocorticoids impair glucose transport and glutamate uptake in hipppocampal astrocytes and may contribute to AD progression (43). By decreasing cholinergic transmitter synthesis, TNF may increase HPA hyperactivity (47).

Additional mechanisms also contribute to PIC stimulation of the HPA axis (Fig. 1) (51–56). IL-1 administered systemically in rats increases adrenocorticotropic hormone (ACTH) concentrations and stimulates corticotropin-releasing hormone (CRH) neurons (53). TNF and IL-6 also stimulate CRH, ACTH, and corticosterone production (54–56). In rats, IL-1 more acutely stimulated the HPA axis than TNF or IL-6. However, combinations of the cytokines also resulted in dose-dependent increases in corticosterone (53).

IL-6 appears to be involved in neurodegenerative conditions; elevated levels of IL-6 are observed in the CNS in AIDS dementia, AD, multiple sclerosis, and trauma (57). IL-6 immunoreactivity has been consistently detected in the brains of AD patients (58–60). Interestingly, a polymorphism in IL-6 gene delayed onset and reduced risk of AD (61). IL-6 expression may be a harbinger of neuritic changes, as IL-6 increases neuronal APP mRNA expression (62–65). Suppression of IL-6 synthesis may therefore be of therapeutic value in treatment of AD (62–69). Tenidap, naproxen, and meloxicam inhibit, whereas ibuprofen, piroxicam, diclofenac, and indomethacin do not affect IL-1β-induced synthesis of IL-6 (8, 10, 66). Tenidap strongly inhibits IL-6 protein synthesis and also decreases IL-6 mRNA levels. NSAIDs, and particularly tenidap, may be useful for treatment of inflammatory processes associated with AD (8, 66).

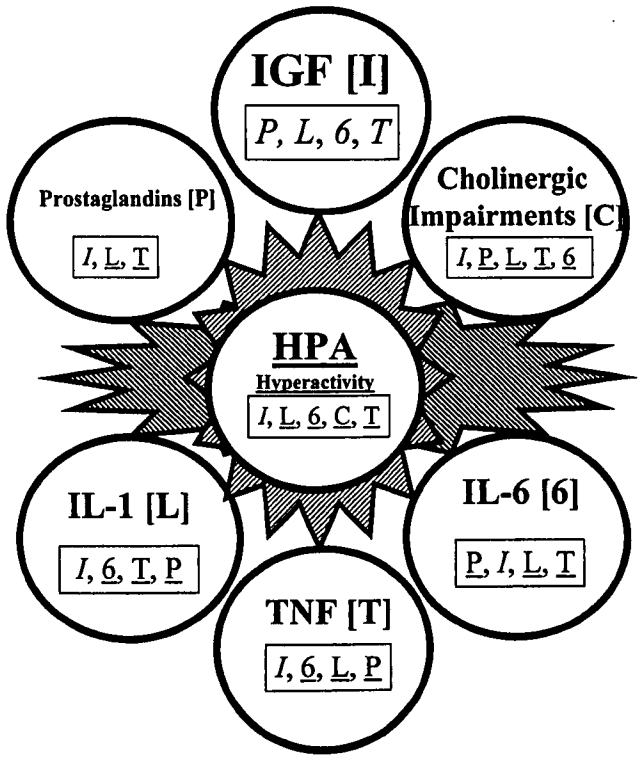

Figure 1. Relationships between factors involved in HPA hyperactivity. Each factor is given an initial or number in brackets: IGF [I], prostaglandins [P], IL-1 [I], IL-6 [6], TNF [T], and cholinergic impairments [C]. Negative relationships are italicized whereas positive relationships are underlined. For example, IGF abbreviated [I] is negatively associated with TNF, and therefore *I* is indicated in the TNF circle.

Chronic overexpression of IL-6 in transgenic mice leads to significant pathophysiological changes similar to those exhibited in neurodegenerative conditions (69). Transgenic mice, chronically expressing IL-6 in astrocytes, exhibit dose- and age-related deficits in avoidance learning that correlate with neuropathological changes (67–69). Transgenic mice bearing additional copies of the *IL-6* gene under control of a brain-specific promoter develop abnormalities including altered dendritic arborization of cortical neurons (67–69). During inflammatory conditions, such as thyroiditis and rheumatoid arthritis (RA), IL-6 production is increased (28–30, 63). Lending credence to the theory of cytokine involvement in HPA hyperactivity, transgenic mice with astrocytic overexpression of IL-6 develop adrenal hypersensitivity to ACTH; IL-6 also contributes to hypercortisolemia that develops after stroke, independent of ACTH (70, 71).

Evidence for cytokine involvement in compromised blood-brain-barrier (BBB) function is provided from several reports (72–74). Transgenic mice overexpressing IL-6 had extensive BBB disruption resulting in increased neuronal degeneration and macrophage accumulation (72, 73). TNF also increases the permeability of the BBB, thereby enhancing leukocyte infiltration (72–75). By increasing BBB permeability, impairing glucose metabolism, and potentially IGF transport, these cytokines may accelerate or perpetuate neuronal insults in the cycle of cell dysfunction and death (72–75).

IGF and Proinflammatory Cytokines

An antagonistic relationship between the PIC and the IGF is generally observed during degenerative conditions (76–81). Decreased concentrations of IGF-1 in critical illness are observed despite increased or normal levels of growth hormone (GH). Many of the acute inflammatory responses in critical illness are mediated by the PIC. IL-1β decreases expression of GH receptor mRNA, IGF-1 mRNA and IGF-1 protein levels (76–81). IL-1β and TNF inhibit in a dose-dependent manner the stimulatory effects of GH on IGF-1 expression, an example of GH resistance (76–81). Both IL-1β and TNF have additive inhibitory effects on IGF-1 protein concentrations; however, IGF-1 and GH receptor mRNA levels return to normal after cytokine withdrawal (76–81).

The liver is the primary producer of circulating or endocrine IGF; however, the importance of endocrine or paracrine/autocrine IGF in aging and neurodegeneration has yet to be established. Cre/Lox deletion of *igf1* gene exclusively in the liver resulted in greatly decreased circulating or endocrine IGF-1 levels. However, growth, body, and femoral length were not different from controls (82). Endocrine IGF, as discussed above, is inhibited by IL-1 and TNF. However, in the absence of GH, IL-6 stimulated IGF expression, an effect inhibited by IL-1 (83). In the presence of GH, IL-6 did not affect IGF production by hepatocytes (83). The relationship between PIC and paracrine/autocrine IGF should be investigated. Many other factors including insulin sensitivity and nutrition also regulate IGF production and should be considered in the context of AD.

IGF action, transport, and half-life is influenced by IGFBP. The classical IGFBP consists of six proteins that may undergo post-translational modifications such as phosphorylation or glycoslyation (84). IGFBP may also have cell surface receptors or bind to cells *via* integrin recognition sites. Post-translational modifications and location (cell surface or circulating) influence whether the action of IGFBP inhibits or stimulates IGF activity (84).

The PIC directly stimulate IGFBP-1 production, suggesting that increased IGFBP-1 expression observed during catabolic conditions is mediated by PIC (76–81). Transgenic mouse lines expressing high levels of circulating IL-6 since early after birth have reduced growth rates resulting in mice 50%–70% the size of nontransgenic littermates. In these mice, IGF-1 concentrations were significantly decreased when compared with nontransgenic controls, whereas GH concentrations were not affected, another example of cytokine-induced resistance affecting the IGF system (79). Injection of IL-6 into control mice resulted in significant decreases in IGF-1 concentrations (79). Intravenous injection of IL-1β also decreased IGF-1 concentrations in plasma, liver, skeletal muscle, pituitary, and brain. These reductions in IGF-1 were associated with a greater than 2.5-fold elevation in plasma corticosterone levels, again revealing a relationship among IGF, cytokines, and HPA hyperactivity (77–81). IGF, reciprocally, may antagonize PIC activity by decreasing expression of the IL-R and *via* suppressor of cytokine signaling proteins (81, 85, 86).

IGF-1 correlated inversely to the degree of inflammation in RA (86). Patients with RA have lower concentrations of both IGF-1 and IGF-2 than healthy controls (80, 87, 88). Stunted growth is a major complication of chronic inflammation and recurrent infections in children. Systemic juvenile RA is a chronic inflammatory disorder characterized by markedly elevated circulating levels of IL-6 (79). Furthermore, IGF-1 and IL-6 concentrations are negatively correlated in this disease, suggesting that IL-6-induced depression of IGF-1 is responsible for resulting growth impairments (79).

Depending on cell type, TNF may stimulate or inhibit IGFBP-3 production. In fibroblasts, TNF inhibited production of IGFBP-3, but in MCF-7 cells TNF stimulated production of IGFBP-3 (89, 90). The antiproliferative action of TNF in these cells was mediated by IGFBP-3. TNF may also stimulate or inhibit IGF production in a cell-specific manner. TNF decreased IGF-1 in liver, gastrocnemius muscle, and pituitary, while increasing IGF-1 in kidney and brain of rats (91). Expression does not always correlate with activity. Recently, TNF-induced resistance to IGF has been documented in the CNS (92). TNF suppressed IGF-1 induced phosphorylation of insulin receptor substrate (IRS)-2 and subsequent phosphatidylinositol 3-kinase activation in murine cerebellar granule cells (92). Reciprocally, the IGF

were able to interfere with TNF signaling *via* stress-activated protein kinase/c-*jun* N-terminal kinase (93). The antiapoptotic and proliferative actions of IGF protected oligodendrocytes from TNF-induced injury (94).

The inflammatory agent zymosan increased the plasma concentration of TNF, IL-1, and IL-6 and decreased IGF-1 concentrations in plasma, liver, heart, and brain (80, 86, 87). The relationship between cytokines and IGFBP-1 is revisited by the ability of zymosan to increase concentrations of IGFBP-1 in plasma, liver, and muscle (80). Accompanying these alterations, an unresponsiveness to IGF-1 developed in chondrocytes. Mice treated with IL-1 antibody or having an inherent deficiency in nitric oxide synthase maintained IGF-responsiveness (86, 87). Perhaps IL, like TNF, can alter the cellular responsiveness to IGF-1. If correct, then indicators of cellular responsiveness need to be identified and examined in conjunction with IGF concentrations in inflammatory and cachectic conditions.

TNF *via* its effects on cell adhesion, macrophage activation, and direct cytolysis of oligodendrocytes contributes to CNS injury and, in mice, appears to be involved in the initiation of the inflammatory response to experimental autoimmune encephalomyelitis (EAE) (56, 88). Within the CNS, baseline production of TNF is low; however, in EAE and multiple sclerosis, TNF production is increased, being produced by leukocytes, activated microglia, neurons, and astroglia (56, 88). Inhibitors of TNF prevent or attenuate the clinical course of experimental EAE (56, 88). In rats with EAE, IGF-1 decreased clinical deficits, lesion numbers, and severity as well as decreased immune cell reactivity. Additionally, IGF reduced BBB disruption, previously described to be induced by cytokines, and may be of therapeutic value in multiple sclerosis (15, 16, 95).

Concentrations of TNF in centenarians were increased compared with younger individuals and were associated with AD and atherosclerosis and IL-6 (96). Interestingly, IGF-1 levels were positively associated with mental function and inversely associated with triglyceride levels and free fatty acids in healthy centenarians (97). In familial AD, IGF-1 concentrations were decreased, whereas that of GH and prolactin were not decreased, indicating that dysregulation of IGF production is associated with AD (98).

Down's Syndrome

Individuals with Down syndrome (DS) overexpress APP, typically develop AD pathology during their third to fourth decade, and have impaired GH-IGF function (99–104). Considering the relationship among IGF, insulin, and diabetes with AD pathology, it is interesting to find that individuals with DS are at greater risk of developing diabetes (105–107). The PIC are also affected in DS; IL-6 has been associated with dementia severity in DS and overexpression of TNF, and IL-1 has also been reported in DS individuals (105–111). Although not extensively studied, similar pathophysiological mechanisms involving the IGF system may exist in DS and AD (105–111).

Summary

The answer to the question presented as the title of this review is yes. Interactions between IGF and PG in the CNS indicate that an antagonistic relationship may exist, where the IGF and PG promote survival and degeneration, respectively. Recent research indicates that impairment of survival factor production, action, or signaling may result in greater susceptibility to degenerative stimuli. In addition to interfering with IGF production and action, the PIC may also induce degenerative stimuli. Further research should focus on manipulating these relationships to benefit those with neurodegenerative conditions.

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