

Review

Therapeutic promise and principles

Metabotropic glutamate receptors

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For a number of disease entities, oxidative stress becomes a significant factor in the etiology and progression of cell dysfunction and injury. Therapeutic strategies that can identify novel signal transduction pathways to ameliorate the toxic effects of oxidative stress may lead to new avenues of treatment for a spectrum of disorders that include diabetes, Alzheimer's disease, Parkinson's disease and immune system dysfunction. In this respect, metabotropic glutamate receptors (mGluRs) may offer exciting prospects for several disorders since these receptors can limit or prevent apoptotic cell injury as well as impact upon cellular development and function. Yet the role of mGluRs is complex in nature and may require specific mGluR modulation for a particular disease entity to maximize clinical efficacy and limit potential disability. Here we discuss the potential clinical translation of mGluRs and highlight the role of novel signal transduction pathways in the metabotropic glutamate system that may be vital for the clinical utility of mGluRs.

Oxidative Stress and Apoptotic Cell Injury

A number of mechanisms can account for the degeneration of cells in the body, but the generation of cellular oxidative stress represents a significant component for cell loss in several diseases. Oxidative stress occurs as a result of the development of reactive oxygen species (ROS) that consist of oxygen free radicals and other chemical entities. Oxygen consumption in organisms, or at least the rate of oxygen consumption in organisms, has intrigued a host of investigators and may have had some of its original origins with the work of Pearl. Pearl proposed that increased exposure to oxygen through an increased metabolic rate could lead to a shortened life span.¹ Subsequent work by multiple investigators has furthered this hypothesis by demonstrating that increased metabolic rates could be detrimental to animals in an elevated oxygen environment.² With current work, oxygen free radicals and mitochondrial DNA

mutations have become associated with oxidative stress injury, aging mechanisms, and accumulated toxicity for an organism.³

Oxidative stress is a result of the release of ROS that include superoxide free radicals, hydrogen peroxide, singlet oxygen, nitric oxide, and peroxynitrite.⁴ Oxygen free radicals and mitochondrial DNA mutations have become associated with tissue injury, aging, and accumulated toxicity for an organism.^{5,6} Most ROS are produced at low levels during normal physiological conditions and are scavenged by endogenous antioxidant systems that include superoxide dismutase, glutathione peroxidase, catalase, and small molecule substances, such as vitamins C, E, D₃⁷ and nicotinamide, the amide form of niacin or vitamin B₃.⁶⁰⁻⁶³

Oxidative stress represents a significant mechanism for the destruction of cells that can involve apoptotic cell injury.⁸⁻¹⁰ It has recently been shown that genes involved in the apoptotic process are replicated early during processes that involve cell replication and transcription, suggesting a much broader role for these genes than originally anticipated.¹¹ Apoptotic induced oxidative stress in conjunction with processes of mitochondrial dysfunction can contribute to a variety of disease states such as diabetes, ischemia, general cognitive loss, Alzheimer's disease, and trauma.¹²⁻¹⁶ Oxidative stress can lead to apoptosis in a variety of cell types that involve neurons, endothelial cells (ECs), cardiomyocytes, and smooth muscle cells through multiple cellular pathways.^{14,17-21}

Membrane phosphatidylserine (PS) externalization is an early event during cell apoptosis^{22,23} and can become a signal for the phagocytosis of cells.^{10,24,25} The loss of membrane phospholipid asymmetry leads to the externalization of membrane PS residues and assists microglia to target cells for phagocytosis.^{19,26-29} This process occurs with the expression of the phosphatidylserine receptor (PSR) on microglia during oxidative stress,^{5,30} since blockade of PSR function in microglia prevents the activation of microglia.^{27,31} As an example, externalization of membrane PS residues occur in neurons during anoxia,³²⁻³⁴ nitric oxide exposure,^{35,36} and during the administration of agents that induce the production of reactive oxygen species, such as 6-hydroxydopamine.³⁷ Membrane PS externalization on platelets also has been associated with clot formation in the vascular system.³⁸

The cleavage of genomic DNA into fragments³⁹⁻⁴¹ is considered to be a later event during apoptotic injury.⁴² Several enzymes responsible for DNA degradation have been differentiated and include the

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acidic, cation independent endonuclease (DNase II), cyclophilins, and the 97 kDa magnesium-dependent endonuclease.^{4,12} Three separate endonuclease activities are present in neurons that include a constitutive acidic cation-independent endonuclease, a constitutive calcium/magnesium-dependent endonuclease, and an inducible magnesium dependent endonuclease.^{43,44}

During oxidative stress, mitochondrial membrane transition pore permeability also is increased,^{19,45-47} a significant loss of mitochondrial NAD⁺ stores occurs, and further generation of superoxide radicals leads to cell injury.^{28,48} In addition, mitochondria are a significant source of superoxide radicals that are associated with oxidative stress.^{12,49} Blockade of the electron transfer chain at the flavin mononucleotide group of complex I or at the ubiquinone site of complex III results in the active generation of free radicals which can impair mitochondrial electron transport and enhance free radical production.^{4,30} Furthermore, mutations in the mitochondrial genome have been associated with the potential development of a host of disorders, such as hypertension, hypercholesterolemia, and hypomagnesemia.^{50,51} Reactive oxygen species also may lead to the induction of acidosis-induced cellular toxicity and subsequent mitochondrial failure.¹³ Disorders, such as hypoxia,⁵² diabetes^{53,54} and excessive free radical production^{44,55,56} can result in the disturbance of intracellular pH.

Metabotropic Glutamate Receptors (mGluRs) Structure and Functional Role

Glutamate, an excitatory neurotransmitter, plays an important role during both cellular function and cellular injury in the mammalian central nervous system (CNS). Until the mid 1980s, the actions of glutamate in the brain were believed to occur through the activation of glutamate-gated channels termed ionotropic glutamate receptors. Yet, further studies provided evidence for the existence of another family of glutamate receptors that was directly coupled to GTP-binding regulatory proteins. Initial work, such as the observation of glutamate induced phospholipase C generation in neurons, indicated that glutamate had more complex roles that could not be accounted for by only N-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), or kainate receptor families.⁵⁷ Subsequently, it became evident that a new class of glutamate receptors, termed metabotropic glutamate receptors (mGluRs), was coupled to effector systems through GTP-proteins (G-proteins).⁵⁸⁻⁶⁰

The first mGluR, now generally termed mGluR1a, was cloned in 1991 by a functional expression screening procedure.^{60,61} Since molecular cloning has preceded pharmacological characterization in the identification of novel mGluRs, the mGluRs are numbered following the order in which their cDNAs have been cloned. G-proteins consist of heterotrimeric proteins that contain three subunits termed α , β and γ . At least forty-six G-proteins have been identified with twenty-seven classified as $G\alpha$, five classified as $G\beta$, and fourteen classified as the $G\gamma$. A variety of heterotrimeric combinations can be formed that may produce a broad spectrum of G-protein signaling.⁶² Activation of G-protein-coupled receptors results in the dissociation of the heterotrimer of the G-protein into its α and $\beta\gamma$ subunits, which can then bind to a variety of effector molecules. A particular G-protein may be responsible for the modulation of a series of signal transduction pathways. The G-protein $\beta\gamma$

has been associated with many effector molecules including adenylate cyclase (AC), phospholipase C- β (PLC- β), mitogen-activated protein kinases (MAPKs), and phosphoinositide 3 kinase (PI 3-K).⁶³

G-protein-coupled receptors can be divided into three major subfamilies based on nucleotide and amino acid sequence similarity. Family A consists of the rhodopsin/adrenergic receptors and is characterized by the presence of a restricted number of conserved residues (Asp-Arg-Tyr). Family B consists of peptide hormone and neuropeptide receptors that are characterized by a large extracellular NH₂ terminus containing six cysteine residues. Metabotropic glutamate receptors share a common molecular morphology with other G protein-linked receptors. The mGluRs are part of family C of G-protein-coupled receptors, which also includes gamma aminobutyric acid (GABA) receptors and ionotropic calcium receptor transmission. Unlike the other G-protein-coupled receptors families, mGluRs contain a long NH₂ terminal chain and couple to G-proteins through their second intracellular loop rather than the third intracellular loop of the receptor.

The mGluRs also are classified into three major groups based on sequence homology, G-protein coupling specificity, and agonist selectivity. Group I mGluRs (including mGluR1 and mGluR5) couple preferentially to G_q to stimulate PLC- β . Activation of PLC- β results in the generation of two second messengers, inositol-1, 4, 5-triphosphate (IP₃) and diacylglycerol (DAG), to mobilize intracellular calcium and activate protein kinase C (PKC). Group I mGluRs also can activate AC via coupling to G_s to result in an increase in cAMP.⁶⁴ In contrast to group I mGluRs, group II mGluRs (including mGluR2 and 3) and group III mGluRs (including mGluR4, 6, 7, and 8) are negatively coupled to AC to reduce the amount of intracellular cAMP. In addition, activation of group II/III can modulate activity of extracellular signal-regulated protein kinases (ERKs) and PI 3-K (Fig. 1).⁶⁵ Yet, different subgroups of the mGluR system may employ pathways of ERKs. For example, group I mGluRs can increase the phosphorylation of ERK2 through PKC.⁶⁶ In addition, ERKs may employ phosphorylation of the pro-apoptotic protein Bad and induction of pro-survival gene expression via the cAMP responsive element-binding (CREB) protein dependent pathway to lead to cellular protection.⁶⁷ It is not entirely evident whether the protective mechanisms utilized by mGluRs also involve the cellular pathways of the MAP-kinases, since activation of mGluRs does not alter the activity of either p38 or c-Jun N-terminal kinase (JNK), suggesting that protection by mGluRs is independent or below the level of p38 activation.^{10,68}

The G-protein-coupled receptor family is the largest family of cell-surface molecules. These receptors are activated by a wide variety of stimuli, including neurotransmitters, peptides, hormones, growth factors, ions, lipids and light. The mGluR system is one of the principal members in this receptor family and provides an important function as presynaptic auto-receptors that mediate feedback inhibition of glutamate release in a wide variety of brain regions. One of the mechanisms of glutamate inhibition is thought to result from the down-regulation of voltage-activated calcium channels which are necessary for synaptic vesicle exocytosis.⁶⁹ The mGluR system also is a critical mediator for the modulation of intracellular signal cascades and physiological function. Interaction among each G-protein subunit, such as $-\alpha$, $-\beta$ and $-\gamma$ subunits, can stimulate effector molecules including adenylyl/guanylyl cyclases,

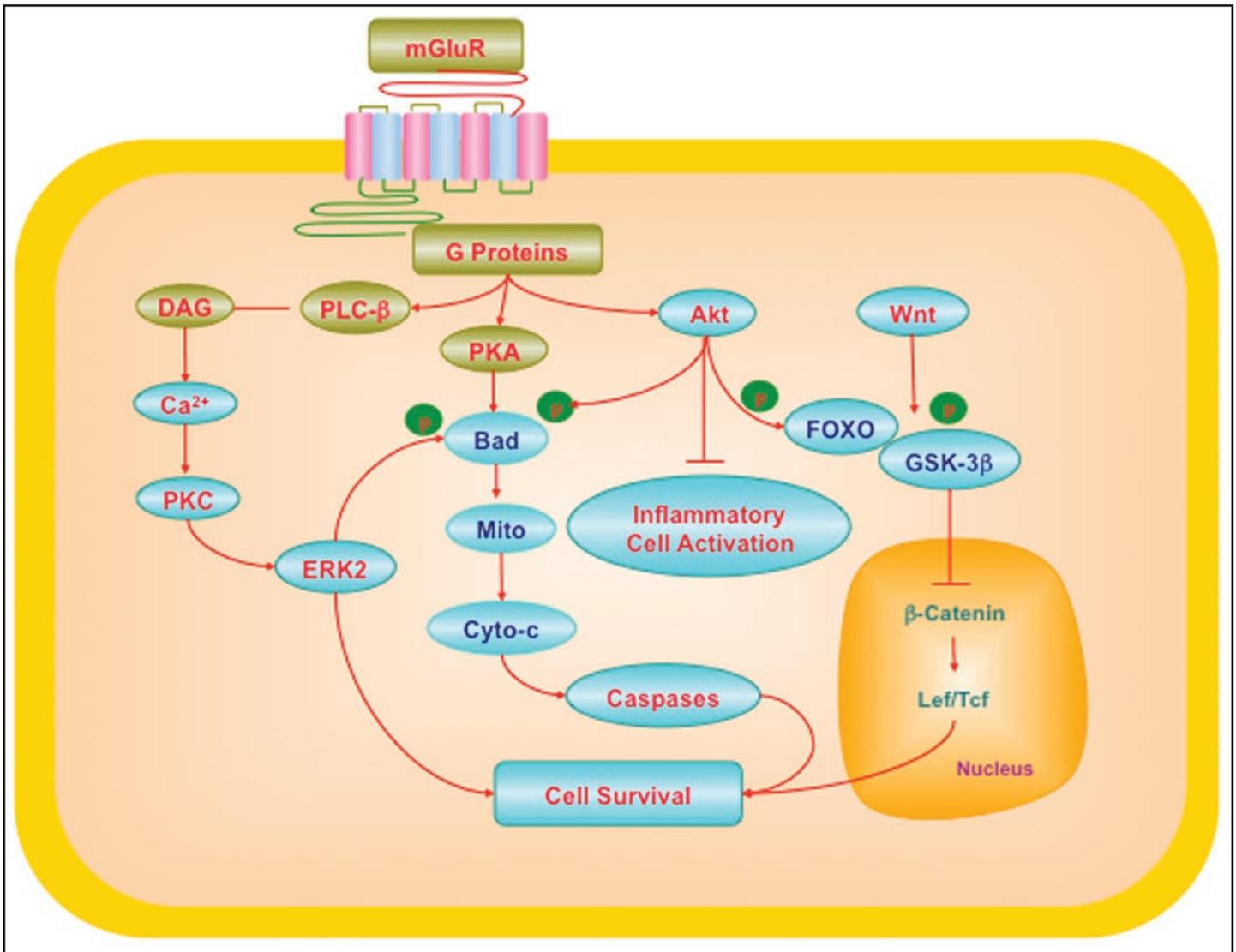


Figure 1. Cytoprotection through mGluRs may require the regulation of multiple cellular pathways. G-protein $\beta\gamma$ in the mGluR system activates phospholipase β (PLC- β), diacylglycerol (DAG), and phosphoinositide 3 kinase (PI 3-K). These pathways lead to the activation of protein kinases A (PKA), B (Akt) and C (PKC) that can involve intracellular calcium (Ca^{2+}). mGluRs can activate ERK2 through PKC. PKA can phosphorylate (p) Bad, a member of Bcl-2 protein family, which can prevent apoptotic cell injury. Akt provides an anti-apoptotic survival signal through the phosphorylation and inactivation of Bad and also interfaces with the Wnt and forkhead pathways. Wnt signaling can inhibit glycogen synthase kinase (GSK-3 β). Inhibition of GSK-3 β prevents phosphorylation (p) of β -catenin and leads to the accumulation of β -catenin. β -catenin subsequently translocates to the cell nucleus and contributes to the formation of Lef/Tcf lymphocyte enhancer factor/T cell factor (Lef/Tcf) and β -catenin complex that may cooperate with factors to target nuclear gene transcription and prevent cell injury. Interconnected pathways with Akt and Wnt involve the forkhead family members (FOXO), mitochondrial (Mito) membrane potential ($\Delta\Psi_m$), cytochrome c (Cyto-c), and caspases. If left unabated, these pathways converge to lead to apoptotic cell injury.

phosphodiesterases, phospholipases, and phosphoinositide 3-kinase (PI3-K) resulting in the modulation of other second messengers. Several second messenger systems, such as cAMP, cGMP, inositol (3,4,5)-trisphosphate (Ins(1,4,5)P3), arachidonic acid, phosphatidic acid, and calcium are active participants in these signal transduction cascades.⁷⁰

Electrophysiological studies of mGluRs have shown that activation of mGluRs may lead to a range of cellular changes such as the inhibition of calcium and potassium currents, mediation of slow excitatory postsynaptic potential, and the presynaptic inhibition of transmitter release.^{69,71,72} In particular, activation of group I mGluRs can contribute to slow-onset potentiation in the hippocampal region of CA1.⁷³ Activation of postsynaptic group I mGluRs also suppresses

transmission at excitatory synapses onto CA1 pyramidal cells.⁷⁴ In addition, group I mGluRs have been shown to alter calcium homeostasis and trigger calcium-sensitive gene transcription in striatal neurons.⁷⁵ Group II mGluRs have a significant role in the modulation of GABA afferent inhibition in the ventrobasal thalamus that controls functions of sleep, arousal, and sensation.⁷⁶ Both group I and II receptors may be required for the activity-dependent regulation of ribosomes during auditory function.⁷⁷ High-frequency stimulation appears to be particularly dependent upon group I and group II metabotropic glutamate receptors.⁷⁸ Group III mGluRs have a greater role in motor function through the inhibition of GABA and glutamate transmission in the substantia nigra, pars reticulata,⁷⁹ and the periaqueductal grey area.⁸⁰

The ubiquitous distribution of glutamatergic synapses in the nervous system offers a great potential for mGluRs to modulate global CNS function. In the spinal cord, Group I mGluRs can regulate slow excitatory synaptic transmission.⁸¹ In addition, behavioral and physiological studies have demonstrated that mGluRs can regulate fast synaptic transmission, changes in synaptic plasticity, and the modification of the calcium currents.^{39,82} During memory imprinting, group I mGluRs which are juxtaposition to NMDA receptors can modulate the potentiation of NMDA receptor activity to influence both long-term potentiation and long-term depression.^{73,83} Yet, multiple members of the mGluR system may be required for memory formation⁸⁴ or memory restoration following an ischemic insult.⁸⁵ Activation of mGluRs also can lead to depolarization-induced synapsin I phosphorylation, a process that may be involved in synaptic vesicle exocytosis in visceral sensory neurons.⁸⁶ Furthermore, cognitive impairment and psychiatric disease such as with schizophrenia may be tied to mGluR expression and activation.⁸⁷

mGluRs Expression, Progenitor Cell Differentiation and Cell Development

Metabotropic glutamate receptors are expressed throughout the mammalian CNS. In neuronal populations, the mGluR system participates in the processing of cognition, sensory, motor and olfactory information. For example, mGluRs are present in the cerebral cortex,⁸⁸ cerebellar neurons,⁸⁹ striatal neurons and in the spinal cord.⁹⁰ In the hippocampus, a more restricted expression of the receptor subtypes mGluR1b, mGluR2/3, mGluR4a and mGluR5 has been demonstrated.⁹¹ The receptor subtype mGluR4 also has a distinct distribution in the thalamus, hypothalamus, and caudate nucleus.⁹² In the retina, mGluR6 is expressed.⁹³ In contrast, mGluR3 is expressed throughout the brain with dense expression in neurons of the cerebral cortex, caudate-putamen, thalamus, and cerebellum.⁹⁴

The mGluR receptors are distributed in specific subcellular regions and alter their expression during development of the nervous system. During embryonic development, group III mGluRs may prevent the self-renewal of undifferentiated neocortical progenitor cells⁹⁵ while group I mGluRs can promote neuroblast proliferation.⁹⁶ Group I mGluRs including mGluR1a and mGluR5 predominantly exist on the post-synaptic membranes of the glutamatergic synapse junctions.⁹⁷ Yet, in the initial postnatal period, mGluR1a and mGluR5 can be found in proximal dendrites and the cell somata. With age, these receptors become densely distributed in the distal part of dendrites to participate in synaptic function.⁹⁸ Group II mGluRs (mGluR2/3) are present primarily in astrocytes surrounding the neuronal somata and synapses. A less dense population of group II mGluRs is also located in presynaptic axon terminals. The distribution pattern of mGluR2/3 is believed to be consistently maintained during postnatal development.⁹⁸ Of the group III mGluRs, mGluR6 is initially distributed in both the neuronal soma and dendrites in rat retinal bipolar cells, but later redistributes to postsynaptic sites.⁹⁹ Presynaptic expression is more common for the mGluR7 subtypes.¹⁰⁰ In group III mGluRs, mGluR4, mGluR6, and mGluR8 also have been identified in microglia and astrocytes.¹⁰¹ The presence of these receptors in a variety of cell types may be responsible for protection of neuronal cell populations.¹⁰² Redistribution of the expression of mGluRs appears to be necessary for proper nervous

system development. For example, redistribution of mGluR6 in rat retinal bipolar cells occurs from somatic and dendritic sites to restricted localization at postsynaptic sites.⁹⁹ In the mouse thalamus, subcellular relocalization of group I mGluRs also occurs during postnatal development.⁹⁸ In addition to redistribution of receptors, functional changes in the mGluR system also may occur during development. The generation of second messengers, such as cAMP, has been reported to vary under mGluR control during critical periods of ocular dominance and plasticity.¹⁰³

Less information is available for the role of the mGluR system in the vascular system, but new investigations are beginning to provide evidence for a vital function for the mGluR system in brain endothelial cells. Initial work has outlined the expression of mGluRs in cultured rat cerebrovascular ECs¹⁰⁴ and in cardiac cells.¹⁰⁵ Further studies have now demonstrated not only the expression of specific group I mGluRs in cerebral endothelial cells, but also the potential for the mGluR system to protect against apoptotic injury.^{26,28,106} In addition, mGluR1, mGluR2/3, mGluR4a, mGluR5 and mGluR7 have been demonstrated in the meningeal microvasculature.¹⁰⁷ Interestingly, agents such as nicotine can inhibit the expression of mGluRs in cardiac tissue.¹⁰⁸ More recent studies suggest that activation of mGluRs may control vascular tone.¹⁰⁹

mGluRs and Disorders of the Nervous and Vascular Systems

mGluRs may be involved in diseases such as diabetes mellitus (DM) which is a significant health concern.^{110,111} Approximately 16 million individuals in the United States and more than 165 million individuals worldwide suffer from DM. By the year 2030, it is predicted that more than 360 million individuals will be afflicted with DM and its debilitating conditions.¹¹² Type 2 DM represents at least 80% of all diabetics and is dramatically increasing in incidence as a result of changes in human behavior and increased body mass index.¹¹³ Type 1 insulin-dependent DM is present in 5–10% of all diabetics,¹¹¹ but is increasing in adolescent minority groups.¹¹⁴ Furthermore, the incidence of undiagnosed diabetes, impaired glucose tolerance, and fluctuations in serum glucose in the young raises additional concerns.¹¹⁵ Patients with DM can develop severe neurological and vascular disease^{116,117} that can lead to an increased risk for cognitive decline.^{12,30,118} As a result, the development of insulin resistance and the complications of DM in the nervous and vascular systems are believed to be, at least in part, a result of cellular oxidative stress.^{110,111} Hyperglycemia can lead to increased production of ROS in endothelial cells, liver and pancreatic β -cells.¹¹⁹⁻¹²² Recent clinical correlates support these experimental studies to show that elevated levels of ceruloplasmin are suggestive of increased ROS.¹²³ Furthermore, acute glucose swings in addition to chronic hyperglycemia can trigger oxidative stress mechanisms, illustrating the importance for therapeutic interventions during acute and sustained hyperglycemic episodes.¹²⁴

Several studies highlight the role of mGluRs during cellular metabolism and DM. In animal models of DM, the expression of mGluR1 and mGluR5 messenger RNA are significantly increased in all layers of the dorsal horn of the spinal cord, suggesting that mGluR expression and activity may be associated with the development of diabetic neuropathy.¹²⁵ In addition, mGluRs are expressed in pancreatic islet cells and can impact upon the release of glucagon release. For example, the mGlu8 receptor is present in glucagon-secreting

α -cells and intrapancreatic neurons and functions to inhibit glucagon release.¹²⁶ Additional work has shown that mGluR3 activation can protect neurons from glucose related oxidative stress¹²⁷ as well as prevent apoptotic injury in vascular cells.¹⁰

In regards to other disorders, the modulation of the mGluR system has been proposed for the treatment of bipolar disease since these receptors may modulate signal transduction during affective disorders.¹²⁸ Furthermore, more recent work in animal models suggests that Group III mGluRs may be beneficial for the treatment of psychosis.¹²⁹ For diseases such as trisomy 21, a congenital disorder with mental impairment, enhanced expression of the mGluR subtype 5 has been reported.¹³⁰ Furthermore, dysfunctional signaling in the Group I mGluR system may be responsible for other types of abnormal cognitive development found in disorders such as fragile X mental retardation caused by the lack of fragile X mental retardation protein (FMRP).¹³¹

In progressive disorders such as amyotrophic lateral sclerosis (ALS), the mGluR1a receptor may be offer endogenous cellular protection, since surviving motor neurons from the spinal cord of ALS patients maintain mGluR1a at levels comparable to that from controls.¹³² Yet, other work indicates that mGluR inhibition may be required to protect neurons during ALS.¹³³ In epilepsy, group I mGluR activation can lead to prolonged epileptiform discharges¹³⁴ and enhanced expression of group II and III metabotropic receptors in the hippocampus of patients with epilepsy has been observed,^{135,136} However, some work supports a protective role for mGluRs in epilepsy, since activation of group II mGluRs has been shown to prevent seizures in experimental animal models.¹³⁷ Furthermore, recent work illustrates that disruption between the mGluR7a receptor and its PDZ-interacting protein, protein interacting with C kinase 1 (PICK1), can result in behavioral changes and EEG recordings consistent with absence epilepsy, suggesting that maintenance of mGluR function can protect against epileptic disorders in some scenarios.¹³⁸ Reported abnormal expression of mGluR1 also has been reported in Pick's disease.¹³⁹ Modulation of synaptic and receptor activity by mGluRs during other chronic neuronal disorders, such as in Huntington's disease, has recently been suggested to alter cellular susceptibility to injury.¹⁴⁰ In particular, huntingtin protein, which is associated with excitotoxic death of striatal neurons, can lead to the desensitization of mGluR1 that may promote cell death.¹⁴¹ Changes in expression patterns of group III mGluRs also have been observed during inflammatory disorders, such as multiple sclerosis,^{101,142} and during acute central¹⁴³ or peripheral nerve trauma.¹⁴⁴

mGluRs also appear to have a role in Parkinson's disease (PD). For example, mGluRs have been associated with the basal ganglia synaptic transmission through several mechanisms. Increased binding of mGluR5 in the striatum of parkinsonian primates has been demonstrated with PET scanning.¹⁴⁵ Activation of group I mGluRs can invoke excitatory postsynaptic current in dopaminergic neurons,¹⁴⁶ facilitate dopamine release from nigrostriatal terminals^{147,148} and modulate GABA release.¹⁴⁹ In addition, group I mGluR activation can prevent amphetamine-induced rotational behavior in the unilateral 6-hydroxydopamine (6-OHDA) lesion rat model of PD.¹⁵⁰ These results suggest that group I mGluRs agonists may have a therapeutic potential in PD. Yet, group I mGluRs in the subthalamic nucleus appear also to increase the excitation output in

the basal ganglia. Group I mGluRs (mGluR5) can lead to an excitatory drive in subthalamic nucleus neurons.¹⁵¹ More specifically, stimulation of striatal group I mGluRs inhibits striatal projection neuronal activity, while stimulation of subthalamic metabotropic glutamate receptors increases subthalamic nucleus activity.

Another consideration for PD is the involvement of group II mGluRs. Group II mGluRs are presynaptically localized on subthalamic nucleus terminals. Activation of these receptors inhibits excitatory transmission at subthalamic nucleus synapses.¹⁵² As a result, selective agonists of group II mGluRs can reduce excitatory drive through an indirect pathway, which is enhanced in PD, and provide a different approach to the treatment of PD. For example, in a haloperidol-induced rat model of PD, a selective agonist of group II mGluRs, LY354740 ((+)-2-aminobicyclo[3.1.0.]hexane-2,6,-dicarboxylic acid), has been demonstrated to reverse parkinsonian muscle rigidity and catalepsy.^{152,153} In another model of PD through application of reserpine in rats, the parkinsonian akinesia was relieved by injection of the group II mGluR receptor agonist, (2S,2'R,3'R)-2-(2',3'-dicarboxycyclopropyl)glycine.¹⁵⁴ In addition, group II mGluR receptor agonists may protect through the release of trophic factors¹⁵⁵ or potentially modulate extracellular glutamate uptake.¹⁵⁶ Taken together, agonists for group II mGluRs may be promising agents in the management of PD.

Group III mGluRs also play an important role in synaptic transmission in basal ganglia circuits. Of these, mGluR7 is presynaptically localized in the striatum, the globus pallidus, and the substantia nigra pars reticulata (Kosinski et al., 1999) and modulates synaptic transmission through direct and indirect pathways. Activation of mGluR7 inhibits GABA as well as glutamate transmission in the substantia nigra pars reticulata.⁷⁹ As a result, modulation of excitatory and inhibitory synaptic transmission by mGluR7 may yield no alteration in the output of the substantia nigra pars reticulata. In contrast to mGluR7, mGluR4 appears to be more selectively localized in striato-pallidal synapses and inhibits synaptic activity.¹⁵⁷ Consequently, the selective agonists for mGluR4 may provide an alternate therapy for the treatment of PD.

In addition to PD, other neurodegenerative disorders such as Alzheimer's disease (AD) have been linked to mGluRs. AD is characterized by two pathologic hallmarks that consist of extracellular plaques of amyloid- β peptide aggregates and intracellular neurofibrillary tangles composed of hyperphosphorylated microtubular protein tau.^{12,13} The β -amyloid deposition that constitutes the plaques is composed of a 39-42 amino acid peptide (A β), which is the proteolytic product of the amyloid precursor protein (APP).¹³ Large soluble fragments (APPs) that are the result from the cleavage of APP within its A β domain are secreted into the extracellular medium. Overexpression of APP can accelerate A β secretion which can form insoluble amyloid aggregates contributing to the development of AD. In AD, a downregulation of mGluR binding sites occurs.¹⁵⁸ In addition, group I mGluRs are desensitized in the frontal cortex in AD patients and these modifications have been correlated with the progression of AD.¹⁵⁹ Other work has shown that mGluR antagonists may control A β synaptic transmission.¹⁶⁰ Interestingly, postsynaptic FMRP binds to and regulates the translation of amyloid precursor protein (APP) mRNA through metabotropic glutamate receptor activation to suggest a link between fragile X syndrome and AD.¹⁶¹

Metabotropic receptors also have been coupled to the acceleration of APP processing. Activation of mGluR1 in human glioma and neuroblastoma cells favors the processing of APP into nonamyloidogenic APPs resulting in the reduction of A β formation¹⁶² and an alteration in APP secretion.¹⁶³ In hippocampal neurons, the release of APPs also is accelerated by stimulation of mGluRs, but not with ionotropic glutamate receptors.¹⁶² In brain cortical and hippocampal slices, the stimulation of group I and group II mGluRs by trans-(1S,3R)-1-amino-1,3-cyclopentane dicarboxylic acid (ACPD) can increase the release of APPs. The process can be blocked by the administration of (\pm)- α -methyl-4-carboxyphenylglycine, a non-selective antagonist of group I and group II mGluRs.¹⁶⁴

The regulation of APP processing by mGluRs also appears to be dependent on the activation of protein kinase C (PKC). PKC consists of a family of serine-threonine kinases that are physiologically activated by a number of lipid cofactors and are considered to be important transducers in several agonist-induced signaling cascades. In the PKC family, at least 12 distinct serine/threonine kinase isoenzymes that have important actions in transmembrane signal transduction pathways regulating cell proliferation, differentiation, cytoskeletal functions, gene transcription, apoptosis, and drug resistance exist.¹⁶⁵ Activation of PKC may be either pro-apoptotic or anti-apoptotic depending on the cell type.¹⁶⁶⁻¹⁶⁸ Studies have begun to define isoform-specific functions of PKC in the apoptotic pathway and the alterations of specific PKC isoforms during injury.^{33,167-170} For example, PKC isoforms that appear to be anti-apoptotic include PKC- α , PKC- β II, and PKC- ϵ and the atypical isoforms PKC- λ and PKC- ζ .¹⁷¹ During free radical exposure or anoxia, activation of mGluRs has been shown to protect neurons through pathways that can modulate PKC. Neuroprotection by the subtypes mGluR1a, mGluR2, and mGluR5 appears to be dependent on the direct modulation of PKC activity (Fig. 1).¹⁶⁷ Furthermore, PKC may be able to phosphorylate mGluRs and lessen activation of these receptors.¹⁷² In regards to AD, inhibition of PKC activity can block alterations in secretion of APPs in response to the activation of mGluRs.^{162,164}

Of equal importance to the functional preservation of cells during neurodegenerative processes is the role of mGluRs during cellular inflammation. In particular, one can consider the role of microglia in the brain that can lead to the phagocytic removal of both neurons and vascular cells.^{17,19,24} During inflammation, microglial cells require the activation of intracellular cytoprotective pathways^{18,25} to proliferate and remove injured cells.^{29,173} Subsequently, microglia can form a barrier for the removal of foreign microorganisms from the CNS and promote tissue repair during neuronal and vascular cell injury.^{18,174} Yet, microglia also may lead to cellular damage through the generation of reactive oxygen species^{49,175} and through the production of cytokines.^{176,177} Furthermore, microglial activation has been correlated with several neurodegenerative disorders that include AD with the co-localization of microglia and amyloid plaque development.¹⁷⁸

Given the impact that inflammatory cells may have upon the progression or resolution of degenerative insults throughout the body, it becomes essential to consider whether mGluRs can control inflammatory pathways. In regards to mGluRs, activation of group I mGluRs can prevent neuronal membrane PS exposure and inhibit microglial activation by decreasing the expression of proliferating cell nuclear antigen (PCNA) and uptake of bromodeoxyuridine (BrdU)

in microglia. Activation of group I mGluRs can block neuronal PS exposure and prevented subsequent neuronal cell engulfment by microglia seeking neurons with PS externalization.²⁴ However, other subgroups of mGluRs may invoke a different response with microglial activation during cell injury. For example, during ischemic stroke in an animal model, activation of group II mGluRs may lead to microglial release of tumor necrosis factor- α (TNF- α) that can be toxic to neurons.¹⁷⁹

mGluRs and Novel Signal Transduction Pathways

Protein kinases. Several cellular signal transduction pathways may impact upon the ultimate biological function of mGluRs. For example, the phosphatidylinositol 3-kinase (PI 3-K) pathway through protein kinase B (Akt) can determine cytoprotection through mGluRs.¹⁸⁰ Phosphorylation of Akt by mGluRs leads to its activation and protects against genomic DNA degradation and membrane PS exposure.^{24,180,181} Upregulation of Akt activity during multiple injury paradigms, such as with matrix detachment,¹⁸² neuronal axotomy,¹⁸³ N-methyl-D-aspartate toxicity,¹⁸⁴ hypoxia,^{185,186} β -amyloid toxicity,^{187,188} and oxidative stress^{17,19,27} increases cell survival. Akt also can directly control microglial activation through the prevention of Bcl-x_L degradation¹⁷ and the inhibition of caspase 1-, 3-, and 9-like activities.^{19,24,27} Activation of Akt by mGluRs also may contribute to new dendritic cell growth and protein synthesis in neurons.¹⁸⁹ These observations are thought provoking since Akt is closely associated with a number of trophic factors such as erythropoietin (EPO).¹⁹⁰⁻¹⁹⁴ The ability of EPO to enhance cell survival during injury can depend upon the PI 3-K pathway through protein kinase B (Akt). Akt may be an essential component for EPO protection especially during disease processes such as diabetes, since inhibition of Akt activity blocks cellular protection and anti-inflammatory mechanisms by EPO.^{31,46,195} EPO has been shown to employ the PI 3-K/Akt pathway in a variety of experimental models of injury.^{25,31,185,195-203} Cytoprotection in these models can involve transcription factor regulation,¹⁹⁷ maintenance of $\Delta\Psi_m$, prevention of cytochrome c release^{31,46,195} and blockade of caspase activity.^{31,46,185}

Experimental studies have demonstrated that mGluRs can increase cellular survival during injury paradigms through the activation of the PI 3-K/Akt pathways²⁶ (Fig. 1). In rat hippocampal neuronal cultures, application of the group I mGluR agonists prevent neuronal injury during oxidative stress through increased Akt activity.^{24,181} In addition, Akt activation through mGluRs may protect against amyloid toxicity.²⁰⁴ This enhancement of Akt activity by mGluR1 may proceed through the formation of a complex that includes Homer, an adaptor protein, and PI 3-K to prevent neuronal apoptosis.²⁰⁵ As a second possible protective mechanism, mGluR inhibition of caspase 3-like activity may serve to prevent the caspase 3 mediated cleavage of Akt and foster increased cellular survival through a prolonged half-life of Akt (Fig. 1).^{10,68,206} Furthermore, regulation of Akt activity appears closely linked to memory formation that involves mGluRs.^{207,208} Interestingly, mGluRs, such as mGluR1 α , can lose the ability to be cytoprotective and activate Akt during NMDA receptor activation that may lead to the calpain-mediated truncation of mGluR1 α .²⁰⁹

In addition to Akt and PKC that have been previously discussed, protein kinase A (PKA) is another potential pathway that may offer

control of synaptic plasticity as well as cytoprotection through the mGluR system (Fig. 1).^{168,210} The mGluR system employs PKA activation for the regulation of memory retrieval^{211,212} and long-term depression.²¹³ In addition, postsynaptic depolarization of Purkinje neurons in the rat cerebellar cortex that leads to long-term potentiation of GABA receptor responsiveness termed rebound potentiation requires both mGluR1 and PKA.²¹⁴ During paradigms of cellular injury, activation of PKA can prevent apoptosis in a number of cell types, including neurons, neutrophils, and smooth muscle cells.^{168,215,216} In addition, loss of PKA activity during toxic insults can lead to cell injury.^{168,217,218} Protection by PKA is believed to reside upstream from the inhibition of caspase 3-like activity.²¹⁹ Furthermore, PKA has been shown to phosphorylate Bad, a member of Bcl-2 protein family, which can prevent the induction of cell injury.²²⁰ In the mGluR system, the subtype mGluR4 requires the activation of PKA to prevent cellular injury following acute neurodegenerative insults.¹⁶⁷

Forkhead transcription factors. Several other novel pathways that may determine the cytoprotective capacity of mGluRs during oxidative stress are linked to Akt. For example, Akt is a central regulatory element for the mammalian forkhead transcription factor family that oversees processes that can involve cell metabolism, cell development, and apoptosis.^{117,221,222} Over one hundred forkhead genes and 19 human subgroups that range from FOXA to FOXS are now known to exist since the initial discovery of the fly *Drosophila melanogaster* gene *forkhead*.²²³ In particular, members of the mammalian forkhead transcription factors of the O class (FoxOs), FoxO1, FoxO3, FoxO4 and FoxO6, have emerged as important targets in the neuronal and vascular systems since they can modulate processes associated with angiogenesis, stem cell proliferation, cardiovascular injury, tumorigenesis, and vascular cell longevity. Forkhead proteins function as transcription factors to either inhibit or activate target gene expression. These proteins bind to DNA through the forkhead domain that relies upon fourteen protein-DNA contacts. Post-translational modification of forkhead proteins, such as phosphorylation or acetylation, alters the binding to DNA to prevent transcriptional activity. However, other mechanisms may influence DNA binding of forkhead proteins, such as variations in the N-terminal region of the DNA recognition helix, changes in electrostatic distribution, and the ability of forkhead proteins to be shuttled to the cell nucleus.^{222,224}

Akt can phosphorylate and inactivate FoxO1, FoxO3a and FoxO4.^{221,222} During oxidative stress, Akt can prevent cellular apoptosis through the phosphorylation of FoxO proteins.^{225,226} Post-translational phosphorylation of FoxO proteins maintain FoxO transcription factors in the cytoplasm²²⁷ by association with 14-3-3 proteins and prevent the transcription of pro-apoptotic target genes.^{194,197} An exception in regards to the subcellular trafficking of FoxO proteins involves FoxO6. This FoxO protein usually resides in the nucleus of cells and is phosphorylated by Akt in the nucleus.²²² Activation of Akt also controls the apoptotic pathways of the caspase family that may offer an alternative mechanism to regulate FoxO proteins.^{4,17} The caspases 1 and 3 have each been linked to the apoptotic pathways of genomic DNA cleavage, cellular membrane PS exposure, and activation of inflammatory cells.^{31,42,46} Caspase pathways may be tied to the forkhead transcription factor FoxO3a since increased activity of FoxO3a can result in cytochrome c release and caspase-induced apoptotic death.^{181,197,228,229} Pathways that

can inhibit caspase 3 activity appear to offer a unique regulatory mechanism. For example, caspase 3 cleavage of FoxO3a can lead to pro-apoptotic amino-terminal (Nt) fragments that can lead to cell death. However, during caspase 3 inhibition, inactive phosphorylated FoxO3a remains intact and does not lead to apoptotic cell injury during oxidative stress.^{181,197,228}

During periods of oxidative stress, FoxO transcription factors can lead to cell injury and apoptosis,¹⁹⁰ since forkhead transcription factors such as FoxO1 and FoxO3a must be present for oxidative stress to result in apoptotic cell injury.²³⁰ In addition, FoxO3a in conjunction with c-Jun N-terminal kinase (JNK) has been shown to modulate an apoptotic ligand activating a Fas-mediated death pathway in cultured motoneurons,²³¹ to lead to apoptosis through tumor-necrosis-factor-related apoptosis-inducing ligand (TRAIL) and BH3-only proteins Noxa and Bim in neuroblastoma cells²²⁹ and to promote pro-apoptotic activity of p53.²³² These studies correlate well with experimental work demonstrating that protein inhibition or gene knockdown of FoxO1 or FoxO3a can result in stroke reduction,²³³ enhance pancreatic β -cell or neuronal survival through NAD⁺ precursors during oxidative stress²²⁸ and provide trophic factor protection in the cardiovascular system with EPO¹⁹⁷ and neurotrophins.²³⁴ However, some studies suggest that the loss of FoxO1, FoxO3a and FoxO4 protein expression may actually lead to an increase in free radical release that can be responsible for oxidative stress.²³⁵

In relation to mGluRs, inhibition of FoxO3a activity appears to be required to mediate cellular protection during oxidative stress (Fig. 1).¹⁸¹ During oxidative stress in primary hippocampal neurons, free radical exposure can increase the phosphorylation of FoxO3a within 6 hours, but over the course of a 12 hour period the expression of phosphorylated and total FoxO3a is lost, suggesting its destruction. In contrast, activation of the mGluR1 receptors maintains inhibitory phosphorylation of FoxO3a over both a 6 and 12 hour period to block FoxO3a activation.¹⁸¹ Furthermore, prevention of phosphorylated and total FoxO3a degradation by mGluR1 activation may assist with neuronal cytoprotection by inhibiting the formation of Nt fragments. The subsequent proteolysis of phosphorylated and total FoxO3a can lead to the generation of apoptotic amino-terminal (Nt) fragments.²³⁶

The proteolytic processing of FoxO3a also is linked to the induction of caspase 3 activity. FoxO3a has been shown to be a substrate for caspase 3-like proteases at the consensus sequence DELD304A (Fig. 1).²³⁶ Blockade of caspase 3-like activity prevents the destruction of phosphorylated FoxO3a in neurons during free radical exposure.¹⁸¹ Yet, inhibition of caspase 9-like activity does not offer a similar level of prevention for the degradation of phosphorylated FoxO3a since FoxO3a has a consensus sequence specific for caspase 3. Some protection by caspase 9 inhibition against FoxO3a degradation could be expected since caspase 3 activation is dependent upon initial caspase 9 activation.²³⁷ The results correlate well with other reports that illustrate that mGluR1 receptor activation can prevent caspase 3 and caspase 9 activity^{10,22,180} and that activation of group III mGluRs prevent caspase 3 activity during amyloid toxicity,²³⁸ suggesting that the mGluR receptors are able to block the degradation of FoxO3a as a result of the inhibition of caspase activity.

β -catenin, glycogen synthase kinase-3 β and calcium pathways. FoxO proteins are associated with additional pathways that modulate

cellular survival during oxidative stress. One pathway involves proteins derived from the *Drosophila Wingless* (Wg) and the mouse *Int-1* genes. The Wnt proteins are secreted cysteine-rich glycosylated proteins that can control cell proliferation, differentiation, survival, and tumorigenesis.^{5,6} More than eighty target genes of Wnt signaling pathways have been demonstrated in human, mouse, *Drosophila*, *Xenopus* and zebrafish. These genes are present in several cellular populations, such as neurons, cardiomyocytes, endothelial cells, cancer cells and pre-adipocytes.²³⁹ At least nineteen of twenty-four Wnt genes that express Wnt proteins have been identified in the human.^{5,6,173} Wnt proteins are divided into functional classes based on their ability to induce a secondary body axis in *Xenopus* embryos and to activate certain signaling cascades that consist of the Wnt1 class and the Wnt5a class.^{6,239} One Wnt pathway involves intracellular calcium release and is termed the non-canonical or Wnt/calcium pathway consisting primarily of Wnt4, Wnt5a and Wnt11. The non-canonical system functions through non- β -catenin-dependent pathways and also includes the planar cell polarity (PCP) pathway or the Wnt-calcium-dependent pathways.^{5,6,173} A second pathway controls target gene transcription through β -catenin, generally referred to as the canonical pathway that involves Wnt1, Wnt3a and Wnt8.

The β -catenin pathway ties FoxO proteins and Wnt signaling together. For example, in relation to Alzheimer's disease, amyloid is toxic to cells^{187,240} and is associated with the phosphorylation of FoxO1 and FoxO3a that can be blocked with ROS scavengers.²⁴¹ A common denominator in the pathways linked to amyloid toxicity involves Wnt signaling through β -catenin. β -catenin may increase FoxO transcriptional activity and competitively limit β -catenin interaction with members of the lymphoid enhancer factor/T cell factor family²⁴² and β -catenin also has been demonstrated to be necessary for protection against amyloid toxicity in neuronal cells.²⁴⁰ With the mGluR system, activation of group I mGluRs can modulate the phosphorylation of β -catenin and its intracellular translocation from the cytoplasm to the cell nucleus (Fig. 1). During oxidative stress, phosphorylation of β -catenin is increased that can lead to its degradation and subsequent cell injury, but group I mGluR activation blocks phosphorylation of β -catenin within 6 hours following free radical exposure.¹⁸¹ The blockade of β -catenin phosphorylation is associated with its translocation from the cytoplasm to the nucleus to allow it to assist with known cytoprotective pathways. In addition, the ability of mGluR activation to control the phosphorylation and activity of β -catenin has been shown to be dependent upon Akt1, since gene silencing of Akt1 expression leads to phosphorylation of β -catenin during oxidative stress.¹⁸¹

Glycogen synthase kinase-3 β (GSK-3 β) also plays a role in these pathways, since Wnt binds to its receptors and the co-receptor low-density lipoprotein receptor-related protein 5/6 (LRP-5/6) to inhibit GSK-3 β . Pathways that block GSK-3 β activity such as through Wnt appear to be critical for neuronal protection. For example, the neuroprotective attributes of Wnt1 against β -amyloid toxicity are lost during gene silencing of Wnt1 protein expression. More importantly, Wnt 1 protection is dependent upon Akt activity and the inhibition of GSK-3 β with the cellular translocation β -catenin to the nucleus.²⁴⁰ Modulation of GSK-3 β activity also can regulate progenitor cell proliferation and differentiation,^{243,244} promote midbrain differentiation,²⁴⁵ control cardiac hypertrophy^{246,247} and increase cell survival during oxidative stress, such as during

neurofibrillary pathology²⁴⁸ and cardiac injury.²⁴⁹ GSK-3 β activity also can influence inflammatory cell survival and activation.^{25,240,250} As a result, GSK-3 β is considered to be an important treatment strategy for several degenerative disorders.^{12,18,251,252} Recently, additional work has shown that mGluR activation blocks GSK-3 β activity to promote translocation of β -catenin to the nucleus through an Akt dependent mechanism (Fig. 1).²⁵³

Other Wnt pathways also pertain to the control of intracellular calcium (Ca²⁺) release. These involve the non-canonical or Wnt/Ca²⁺ pathway consisting primarily of Wnt4, Wnt5a and Wnt11 that functions through non- β -catenin-dependent pathways and also include the planar cell polarity (PCP) pathway²⁵⁴ and the Wnt-Ca²⁺-dependent pathways.^{254,255} In the Wnt-Ca²⁺-dependent pathways, calcium dependent kinases are activated through G-protein signaling that leads to elevations in intracellular Ca²⁺ either through cGMP or phospholipase activation.²⁵⁵⁻²⁵⁷

Interestingly during the development of the nervous system, G-protein signaling with the mGluR system is required for the modulation of intracellular calcium homeostasis. Immature and developing neurons require higher intracellular calcium concentrations than their mature counterparts to facilitate neuronal survival, synapse formation, dendrite growth, and other cellular functions.²⁵⁸ As a result, the modulation of intracellular calcium by the mGluR system has proven to be necessary for neuronal development, such in the cochlear nucleus magnocellular neurons²⁵⁹ and in maturing hippocampal neurons.³⁹ Furthermore, group I mGluR1 facilitates L-type voltage-dependent calcium channels currents through PKC 260 and group II mGluRs can control calcium flux in the suprachiasmatic nucleus that may oversee circadian function.²⁶¹ In astrocytes, both group I and group II mGluRs have been associated with the generation of calcium oscillations.²⁶²

Modulation of intracellular calcium by the mGluR system also may be vital for cytoprotection (Fig. 1). For example, preservation of cellular energy reserves during oxidative stress is dependent upon the maintenance of mitochondrial integrity.²⁶³ Group I mGluRs can preserve mitochondrial membrane potential in endothelial cells^{10,26} and neurons^{181,264} to prevent cell injury during oxidative stress. The precise mechanisms by which the mGluRs employ to preserve mitochondrial integrity are not clear, but may involve the modulation of intracellular calcium stores and intracellular pH. Reduction in mitochondrial intracellular calcium stores and free radical generation has been suggested to promote the maintenance of mitochondrial membrane potential and integrity.²⁶⁵ Activation of group I mGluRs can regulate the release of intracellular calcium from both Ins (1,4,5) P₃-sensitive and ryanodine-sensitive calcium stores.³⁹ In addition, group I mGluRs can modulate free radical signal transduction cascades in both neuronal and endothelial cell populations.^{10,22,266} Furthermore, intracellular acid-base levels may be involved in these protective mechanisms since calcium as well as pH control cellular endonuclease activity. For example, activation of mGluRs prevents cellular injury through the modulation of endonuclease activity that is linked to changes in intracellular pH.⁴⁴

Considerations for the Future

As members of the broad G-protein receptor family, mGluRs play a diverse role in multiple processes that include cell development, cell signaling, and cell survival. Effective treatment for a

number of disease entities such as amyotrophic lateral sclerosis, psychiatric disease, Parkinson's disease, and Alzheimer's disease may ultimately rely upon mGluR modulation and targeting novel signal transduction pathways of metabotropic receptors during oxidative stress. In particular, pathways tied to Akt, forkhead transcription factors, β -catenin, and intracellular calcium release may prove to be vital for the development of new therapeutic strategies.

Yet, the role of the mGluR activation during cell injury is not always clear and can differ among cell systems. In models of demyelinating disease, only activation of specific mGluRs has the capacity to protect oligodendrocyte progenitor cells.²⁶⁷ mGluRs also can have adverse consequences or ineffective results.²⁶⁸ In rat cerebellar granule cells and mouse cortical neurons, trophic deprivation can result in increased mGluR1 expression that is correlated with eventual cell death.²⁶⁹ In other scenarios, activation of the mGluR system may potentiate activity of the capsaicin receptor and contribute to hyperalgesia.²⁷⁰ However, downregulation of the mGluR system has been suggested to lead to the generation of post-injury pain following spinal cord injury during both pharmacological²⁷¹ and in knockdown studies.²⁷²

Some studies also suggest that antagonism of mGluRs may be beneficial. For example, inhibition of mGluR activity during the progression of a toxic insult in some experimental models may subsequently improve neuronal survival.^{273,274} Acute versus chronic application of mGluR antagonists also may generate different therapeutic efficacy. In a rat model of PD, it is chronic rather than acute treatment with a mGluR5 antagonist that can reverse akinetic deficits.²⁷⁵ Furthermore, changes in the cellular environment, such as decreased intracellular calcium release, may allow antagonism of the mGluR system to exert cytoprotection.³⁹ In addition, the nature and extent of the cellular injury may determine whether activation or inhibition of the mGluR system is ultimately required for cellular protection. Since the role mGluRs play in the body is not straightforward, future investigations are necessary to further define the unique signal transduction pathways controlled by the metabotropic system for the effective translation of mGluRs into new therapeutic avenues.

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