

Metabotropic Glutamate Receptors (mGluRs) and Diabetic Neuropathy

Muragundla Anjaneyulu^{1,2}, Alison Berent-Spillson³ and James W. Russell^{2,1,*}

¹Department of Neurology, University of Maryland; ²Veterans Affairs Medical Center, Baltimore, Maryland, USA and ³University of Michigan, Ann Arbor, Michigan, USA

Abstract: Multiple *in vivo* and *in vitro* studies show that excessive release of glutamate, and subsequent activation of ionotropic glutamate receptors (iGluRs) and some metabotropic glutamate receptors (mGluRs) cause neuronal cell death through either necrosis or apoptosis. However, recently alternative evidence has shown that mGluRs have modulatory effects on excitotoxicity and neuronal cell death. Metabotropic glutamate receptors form a family of eight subtypes (mGluR1-8), subdivided into three groups (I-III) that initiate their biological effects by G protein-linked intracellular signal transduction. Their expression throughout the mammalian nervous system implicates these receptors as essential mediators of a cell's fate during injury to the nervous system. Activation of group-II (mGluR2 and -3) or group-III metabotropic glutamate receptors (mGluR4, -6, -7 and -8) has been established to be neuroprotective *in vitro* and *in vivo*. In contrast, group-I mGluRs (mGluR1 and -5) need to be antagonized in order to evoke protection. The pathological signaling pathways associated with diabetic neuropathy are complex and this influences development of appropriate therapies. The Group II mGluRs target several signaling pathways affected in diabetic neuropathy, prevent cellular injury in the peripheral nervous system, and may provide a novel mechanism for treatment of diabetic neuropathy. Direct or indirect activation of mGluR2/3 in animal models protects against development of diabetic neuropathy. The potential mechanisms and role of mGluRs in protection against diabetic neuropathy will be reviewed.

Key Words: Diabetic neuropathy, neuron, schwann cell, oxidative stress, glutamate receptors, neuroprotection.

1. INTRODUCTION

Glutamate is one of the primary excitatory neurotransmitters in the mammalian central nervous system (CNS), plays an important role in both physiological cellular function and cellular injury. Until the mid 1980s, the actions of glutamate in mammalian brain were thought to be mediated exclusively through the activation of glutamate-gated channels named ionotropic glutamate receptors. Subsequently, it became evident that a new class of glutamate receptors, termed metabotropic glutamate receptors (mGluRs) that are coupled to effector systems through GTP proteins (G-proteins) [1-3] affect many cellular activities in mammalian systems.

Eight subtypes of mGluRs (mGluR1-8) are presently known, and they are subdivided into three groups (I-III) based on amino acid sequence homology, signal transduction pathways, and agonist selectivity [4-7]. Group I mGluR (mGluR₁ and mGluR₅) are coupled through phosphoinositide-specific phospholipase C to phosphoinositide hydrolysis and increase the intracellular levels of inositol-3-phosphate, diacylglycerol, and calcium. Activation of Group I receptors enhance neurotoxicity either by increasing intracellular calcium levels or by enhancing N-methyl-d-aspartate (NMDA) receptor activity through activation of the diacylglycerol-protein kinase C pathway. Group II receptors (mGluR₂ and mGluR₃) and Group III receptors (mGluR₄ and mGluR₆₋₈) are negatively coupled with cyclic adenosine monophos-

phate. Activation of Group II and III receptors direct G protein-mediated inhibition of voltage-gated calcium entry and regulation of glutamate release and are neuroprotective [8]. Because of their involvement in reducing glutamate release from presynaptic terminals, Group II and III receptors are sometimes considered to function as presynaptic autoreceptors [9]. Thus, mGluR activation may contribute to both neurotoxic and neuroprotective processes depending on the receptor subtype affected.

mGluRs are expressed throughout the mammalian nervous system and are important not only for the initial development of the nervous system, but also to prevent subsequent neuronal injury [10-14]. In experimental models, activation of mGluR subtypes usually can protect cells against several types of neuronal insults [15] including traumatic brain injury, stroke [16], and NMDA excitotoxicity [17-19]. mGluR protection is also seen in other models of neuronal injury such as glucose deprivation [11], oxygen glucose deprivation [20] and oxidative stress [21,22]. However, recent research has shown that mGluR activation may be important in preventing hyperglycemic-induced neuronal injury [10, 23], and specifically in the treatment of diabetic neuropathy [24]. This review will explore the potential mechanisms of mGluR action in the nervous system and in treatment of diabetic neuropathy.

2. STRUCTURE OF mGluRs

The mGluRs possess a 7-transmembrane domain motif, and the agonist binds in the large amino-terminal domain [25] (Fig. 1). The putative mGluR topology includes a large N-terminal extracellular domain, three extracellular and three

*Address correspondence to this author at the Department of Neurology, University of Maryland, School of Medicine, 22 South Greene Street, Box 175, Baltimore, MD 21201-1595, USA; Tel: 410-706-6689; Fax: 410-706-4949; E-mail: JRussell@som.umaryland.edu

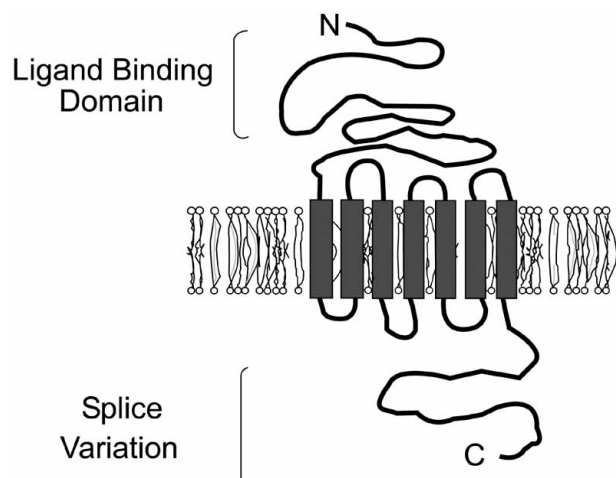


Fig. (1). mGluRs are G-protein-coupled receptors with seven transmembrane domains, an extracellular N terminus, and an intracellular C terminus. The N-terminal tail contains the ligand binding domain, while the C terminus is the site of splice variation.

intracellular loops, and a cytoplasmic C-terminal tail, separated by seven highly hydrophobic regions thought to span the lipid bilayer [26]. The N-terminal portion of the receptor contains the glutamate-binding site [27-29], whereas the intracellular domains physically interact with the G-proteins to initiate signal transduction events [30,31]. The X-ray crystal structure of the amino-terminal domain shows that glutamate complexes with the domain using a “clamshell” like structure [32]. Unlike the classical G-protein coupled receptors, the amino terminal domain of mGluRs is uniquely long, and contains the agonist binding site within a Leucine/Isoleucine/Valine Binding Protein (LIVBP)-like domain [25,33]. Studies using point mutations have shown that agonist affinity is determined by the amino acid sequence in the extracellular amino terminal, while the intracellular loops and carboxy terminal tail mediate G protein coupling [34]. The carboxy terminal in particular can have dramatic differences between subtypes, including splice variants, and determines interaction with specific binding, scaffolding, and signaling proteins [35,36].

3. mGluR SIGNAL TRANSDUCTION PATHWAYS

The 8 mGluRs are sorted into 3 distinct groups based on structure, function, and 2nd messenger association. Group I consists of mGluRs 1 and 5, and is positively coupled to phosphoinositide hydrolysis *via* G_q/G_{11} . Group II, consisting of mGluRs 2 and 3, and Group III, composed of mGluRs 4, 6, 7, and 8, are both negatively coupled *via* G_i to adenylate-cyclase activity. Alternative splice variants are also found for each mGluR, and pharmacological agents act with varying specificity at each receptor subtype [37-39].

A suggested mechanism of mGluR protection is activation of downstream signaling pathways (Fig. 2). Growth factors released from glia, for example Schwann cells, stimulate activation of mitogen activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI 3-K) signaling pathways in neurons, which in turn provides neuroprotection *via* down-

stream signaling components such as protein kinase B (Akt) that block induction of cell death [40,41]. It is most likely that protection at the level of signal transduction occurs in the neuron rather than glia. Several studies show that medium collected from glial cultures after exposure to mGluR agonists is itself protective of pure or mixed neuronal cultures [42,43], indicating that receptor stimulation induces neuroprotective factor release from glia, potentially through the signaling pathways shown in Fig. (2).

4. LOCALIZATION IN THE NERVOUS SYSTEM

4.1. Regional and Cellular Localization of mGluRs in Neurons

In situ hybridization and immunohistochemical studies have revealed distinct although partially overlapping patterns of the distribution of mRNA and immunoreactivity for the eight mGluR subtypes in neurons not only in rodents, but also in primates [44-46]. Striking differences in the regional and cellular distribution between splice variants of mGluR1 and mGluR7 have also been reported [47-49]. The distribution of mGluR1, mGluR3, mGluR5 and mGluR7 is extensive throughout the brain, spinal cord and peripheral neurons. In contrast, the distribution of mGluR2, mGluR4 and mGluR8 is more restricted to specific brain regions. Expression of mGluR6 has been found in the retina, but not in the brain or spinal cord [50]. The location of mGluR1 and mGluR5 in the post-synaptic membrane is highly specific. It is found surrounding, but not within the post-synaptic density. This very precise localization is due to regulatory proteins which bind to the intracellular portions of the receptors. In neurons, mGluR2 and mGluR3 are detectable in presynaptic and post-synaptic elements [51]. Table 1 illustrates expression of mGluRs in the nervous system, their signal transduction and specific agonists.

4.2. Regional and Cellular Localization of mGluRs in Glia

In the adult rat, mGluRs are mainly expressed in neuronal cells with the exception of mGluR3, which is also extensively expressed in glial cells throughout the central and peripheral nervous system [23,52-54]. Furthermore, the expression of mGlu3 and of mGlu5 has been found to be up-regulated in reactive astrocytes [55,56]. Cultured astrocytes express mGluR4 in addition to mGluR3 and mGluR5 [57, 58], whereas cultured microglia appear to express mGluR2, mGluR4, mGluR5, mGluR6 and mGluR8 [59,60].

5. NORMAL PHYSIOLOGICAL FUNCTION OF mGluRs

mGluRs have been implicated in a variety of physiological functions, including neurotransmission, long-term potentiation, and reciprocal interactions with ionotropic glutamate receptors. mGluRs play multiple roles in synaptic plasticity: they function as a molecular switch in long-term potentiation induction and activation of NMDA receptor activity in CA1 neurons, and also in hippocampal N-methyl-D-aspartate (NMDA) receptor-dependent long-term depression thought to underlie learning and memory [29,37,38]. During the development of the nervous system, mGluRs serve to modulate neuronal transmission at excitatory and inhibitory synapses.

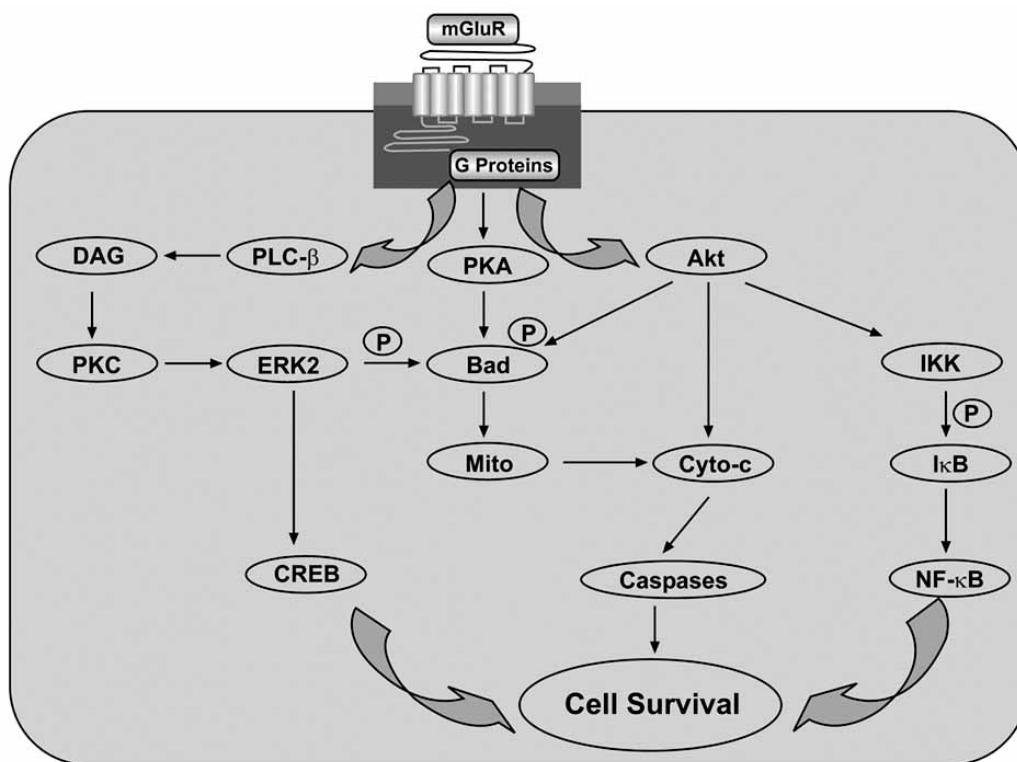


Fig. (2). Potential signal transduction pathways of metabotropic glutamate receptors (mGluRs) that may foster cellular protection. mGluRs employ G-proteins to activate phospholipase β (PLC-β), diacylglycerol (DAG), and phosphoinositide 3 kinase (PI 3-K). These pathways lead to the activation of protein kinases A (PKA), B (Akt), and C (PKC). PKA has been shown to phosphorylate (p) Bad, a member of Bcl-2 protein family, which can prevent the induction of cell injury. Akt provides an anti-apoptotic survival signal through the phosphorylation and inactivation of Bad and stimulation of NF-kappaB (NF-κB) activity. Akt can activate IκB kinase (IKK) that can precipitate the phosphorylation (p) and degradation of IκB. This is followed by liberation of free NF-κB to promote cell survival. In regards to PKC, mGluRs can activate ERK2 through PKC. ERKs also may employ phosphorylation (p) of the proapoptotic protein Bad and induction of pro-survival gene expression *via* the cAMP responsive element-binding (CREB) protein dependent pathway to lead to cellular protection. mGluRs also preserve mitochondrial membrane potential (Mito) to block cytochrome c (Cyto-c) release and caspase activation that ultimately will lead to cellular injury.

Table 1. Localization in Mammalian Brains and Signal Transduction of mGluRs

Group	Subtype	Tissue Expression	Cellular Expression	Signal Transduction	Agonists
Group I	mGluR1	Cerebral cortex, striatum, medulla oblongata, basal ganglia, substantia nigra, hippocampus, thalamus, cerebellum	Neurons Microglia		DHPG
	mGluR5	Striatum, medulla oblongata, basal ganglia, substantia nigra, hippocampus, thalamus, cerebellum.	Astrocytes Endothelial cell	↑PLC ↓ERK	
Group II	mGluR2	Cerebral cortex, striatum, medulla oblongata, olfactory bulb, corpus striatum, basal ganglia, substantia nigra, hippocampus, thalamus, cerebellum, hippocampus, spinal cord, dorsal root ganglion neurons.	Neurons	↓AC	APDC DCG-IV LY354740 LY379268
	mGluR3		Microglia Astrocytes	↑GIRK ↓VGCC	
Group III	mGluR4	Cerebral cortex, striatum, basal ganglia, hippocampus, thalamus, cerebellum, spinal cord.	Neurons Microglia Astrocytes	↓AC ↑GIRK ↓VGCC	L-AP4 I-SOP RS-PPG DCPG
	mGluR6	Retina			
	mGluR7	Medulla oblongata, thalamus, cerebellum			
	mGluR8	Olfactory bulb, pontine grey, thalamus, piriform cortex, Cerebral cortex, hippocampus, cerebellum, mammillary body			

In addition, the mGluR system is required for the modulation of intracellular calcium homeostasis that is necessary to facilitate neuronal survival, synapse formation, dendrite growth, and other cellular functions [61,62]. Group I mGluR1 facilitates L-type voltage-dependent calcium channel currents through PKC [63] and group II mGluRs can control calcium flux in the suprachiasmatic nucleus that may oversee circadian function [64]. Group II mGluRs have a significant role in the modulation of GABA afferent inhibition in the ventrobasal thalamus that controls sleep, arousal, and sensation [65]. Behavioral and physiological studies have demonstrated that mGluRs can regulate fast synaptic transmission and changes in synaptic plasticity [66,67]. 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 [68].

6. mGluRs PROTECT NEURONS AND SCHWANN CELLS FROM OXIDATIVE STRESS

Decades of research elucidating the pathophysiology of diabetic neuropathy have failed, thus far, to produce a treatment that prevents or reverses the development and progression of diabetic peripheral neuropathy. Despite the significant pathology associated with nerve degeneration, the etiology of neuropathy is still unclear. One potential mechanism for development of neuropathy is the presence of oxidative stress [69-71] and mitochondrial dysfunction [70,72,73]. Mitochondria are the main source of cellular ATP, and are also important regulators of redox balance. The mitochondrial matrix is the site of the electron transport chain and the adenine nucleotide transporter (ANT), which mediates exchange of ADP/ATP across the inner mitochondrial membrane. As electrons are passed through the electron transport chain, protons are pumped from the inner matrix. The inner mitochondrial membrane potential ($\Delta\Psi_M$) is maintained by a proton gradient and the membrane is impermeable to passage of ions unless the proton gradient is lost through channel opening or rupture. This can occur in situations of metabolic flux, such as the elevated and fluctuating glucose concentrations that can exist in diabetes [74,75]. Opening of the permeability transition pore complex, consisting of the ANT as well as the voltage-dependent anion channel (VDAC) of the outer mitochondrial membrane, is a key event in the initiation of cellular injury, and results in mitochondrial membrane depolarization, uncoupling of the electron transport chain, proton influx, loss of the inner mitochondrial membrane potential, swelling of the mitochondrial matrix, and eventual rupture of the outer mitochondrial membrane. In contrast, mGluRs and in particular Group II mGluRs can prevent this oxidative injury cascade (Figs. 3 and 4).

Redox balance is maintained by antioxidant systems, and in a stable system, ROS production is balanced by free radical scavengers. Endogenous antioxidants include distinct enzymatic and nonenzymatic groups, although the systems interact with each other. The enzymatic antioxidants include superoxide dismutase (SOD), catalase, and glutathione peroxidase, which catalyze the conversion of $O_2^{\cdot -}$ to H_2O_2 and water, and of H_2O_2 to water and oxygen.

Nonenzymatic antioxidants include glutathione (GSH), the reduced form of the tripeptide γ -glutamylcysteinylglycine. GSH is a powerful antioxidant with a large electron-

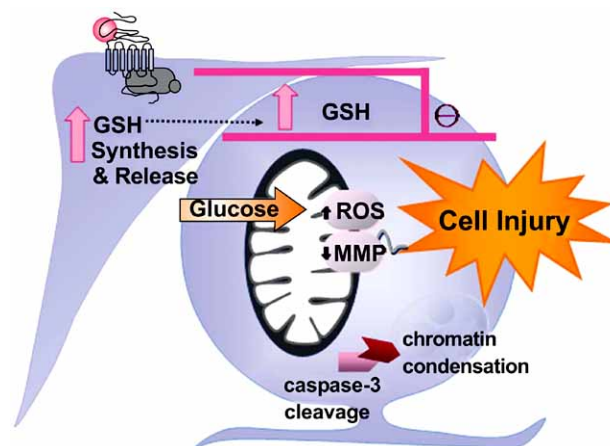


Fig. (3). Mechanism of mGluR3-mediated neuroprotection: mGluR3 activation prevents glucose-induced oxidative damage in DRG neurons co-cultured with Schwann cells, preventing ROS accumulation, mitochondrial membrane depolarization, and PCD. Activating mGluR3, which is preferentially located on Schwann cells, increases GSH concentration in neurons and Schwann cells, likely through increased GSH synthesis and release from Schwann cells. Increased GSH antioxidant response is able to counter increased free radical production and prevent glucose-induced oxidative damage to neurons.

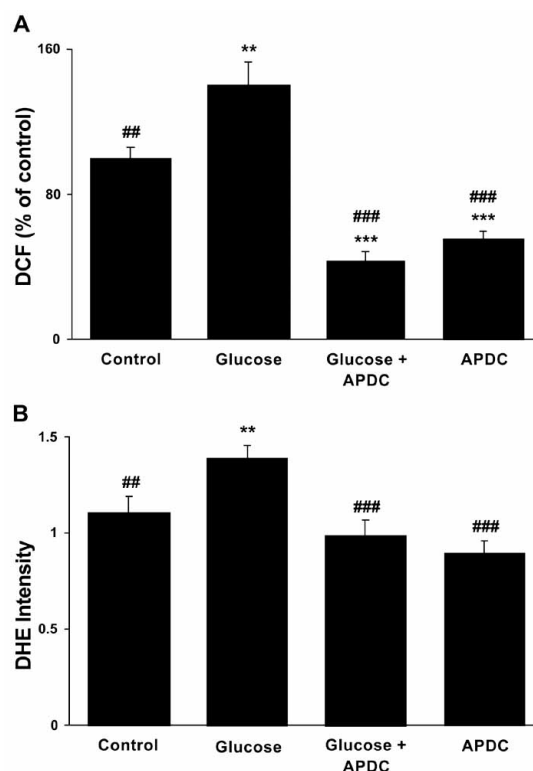


Fig. (4). The mGluR3 agonist APDC prevents glucose-induced oxidative injury. DRG neurons were co-cultured with endogenous SC for 24 hours \pm 20 mM added glucose \pm 100 μ M APDC, then assessed for ROS expression determined by DCF or DHE. Data are expressed as mean \pm SEM. * P < 0.05; ** P < 0.01; *** P < 0.001 versus control; # P < 0.05; ## P < 0.01; ### P < 0.001 versus 20 mM added glucose. Adapted from [23], Wiley-Blackwell Publishing Ltd., Oxford, U.K.

donating capacity, and is present at high concentrations in most cell types. Regulation of GSH turns out to be critically important in preventing glucose-induced injury in neurons and Schwann cells. Depleting GSH increases vulnerability to oxidative stress and cell death. Loss of GSH may be an underlying factor in many neurodegenerative disorders [76]. Thus, mGluR2/3 agonists are able to regulate oxidative stress in neurons exposed to a high glucose load primarily by regulating glutathione. These effects are blocked by the GSH synthesis inhibitor buthionine sulfoximine (BSO) [23].

GSH homeostasis is normally maintained by oxidation-reduction pathways that recycle reduced GSH from oxidized glutathione disulfide (GSSG), as well as through synthesis by the γ -glutamyl cycle (Fig. 5). The disulfide cysteine, and subsequent formation of reaction intermediate γ -glutamylcysteine, is the rate-limiting step of the GSH synthesis reaction. Cystine uptake – and subsequently cysteine formation – is often linked to glutamate transporters, and the sodium-independent cystine-glutamate antiporter system (X_C^-) transports one cystine molecule in for each glutamate molecule out. At least some glial cystine uptake occurs through this system, and formation of cysteine is thus linked to glutamate transport and release [77-81]. Despite the ability to transport cysteine, there is ample evidence that neurons require assistance in synthesizing GSH, and may depend on neighboring glia to synthesize GSH or provide critical reaction precursors. Experimental evidence suggests that GSH that is synthesized and released from glia may be extracellularly degraded into precursors for uptake and synthesis in neurons. Neurons co-cultured with astrocytes have higher GSH concentration, and are less susceptible to oxidant injury, than are pure-cultured neurons. Conditioned media from cultured astrocytes has a similar effect as co-culture on neuronal GSH concentration and antioxidant protection [81-84], and neurons co-cultured with GSH-deficient astrocytes are more vulnerable to oxidative stress than those cultured with control astrocytes [85]. Neurons are also able to use exoge-

nously supplied precursors in GSH synthesis reactions, including γ -glutamylcysteine, cysteinylglycine, N-acetylcysteine, and cysteine, and increasing the availability of these GSH precursors protects neurons from oxidative stressors. However neurons do not efficiently synthesize cysteine from cystine, and increasing extracellular cystine concentration does not enhance neuronal GSH synthesis. [83,84,86-88]. In neurons and Schwann cells, mGluR3 receptor activation is positively correlated with increasing GSH concentration, consistent with an increase in GSH synthesis [23] (Fig. 6).

7. mGluR3 AND SCHWANN CELLS

One critical factor in mGluR peripheral neuroprotection is the role of the Schwann cell. In general, glia are necessary for mGluR3 activation to be neuroprotective to neurons [42,89,90]. In models of glucose-induced neuronal injury, mGluR3-mediated neuroprotection requires the presence of Schwann cells, indicating a need for glial-neuronal interactions [10]. This is likely due to the presence of mGluR2/3 on glia rather than neurons. Similar to previous findings [91], it is hypothesized that mGluR3 activation induces the release of neuroprotective growth factors from the glia and indirectly protects neurons from cellular injury. Recent studies also show that activating mGluR3 increases GSH concentration in Schwann cells and in neurons co-cultured with Schwann cells, but does not affect GSH concentration in neurons cultured without Schwann cells [23]. This supports the hypothesis that activating mGluR3 located on Schwann cells increases neuronal GSH, through increased GSH synthesis in Schwann cells and transport of GSH or GSH synthesis precursors to neurons.

8. mGluRs AND NEUROPATHY

Both direct activation of mGluR3 or indirect activation of the mGluR3 receptor by inhibition of glutamate carboxypeptidase II (GCPII) is protective against glucose induced neuronal and axonal injury [10,92,93]. The GCP II inhibitor 2-

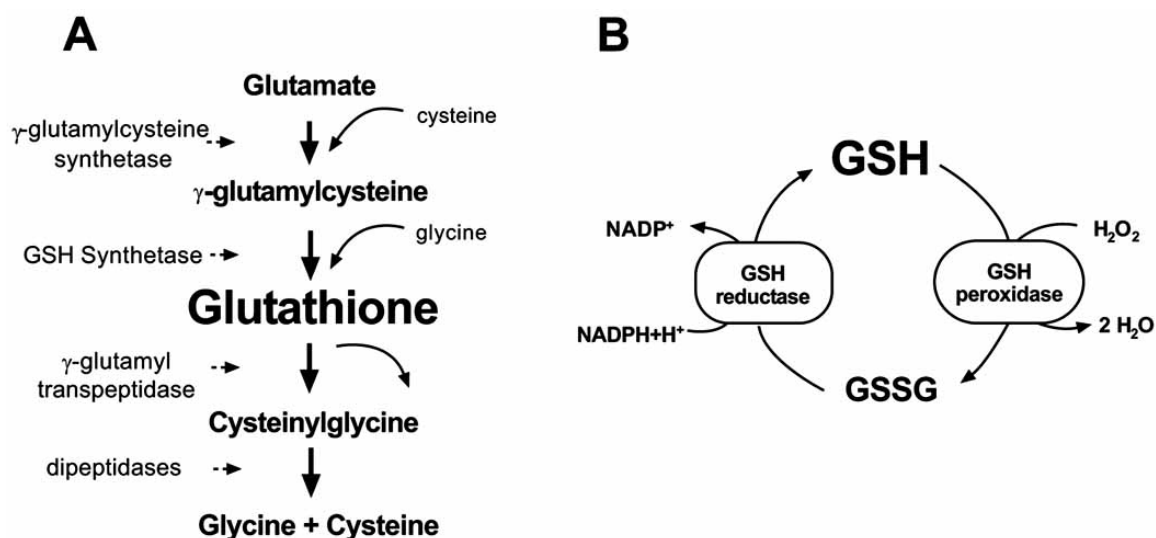


Fig. (5). GSH is maintained through the γ -glutamyl cycle & by recycling from GSSG. In the γ -glutamyl cycle (A), the rate-limiting GSH synthesis intermediate γ -glutamylcysteine is formed from glutamate + cysteine, and catalyzed by γ -glutamylcysteine synthetase. With the addition of glycine, GSH synthetase catalyzes formation of GSH. Degradation yields cysteinylglycine and the substrate amino acids, glutamate, glycine, & cysteine. GSH:GSSG recycling (B) is catalyzed by GSH reductase & peroxidase, and requires NADPH + H^+ .

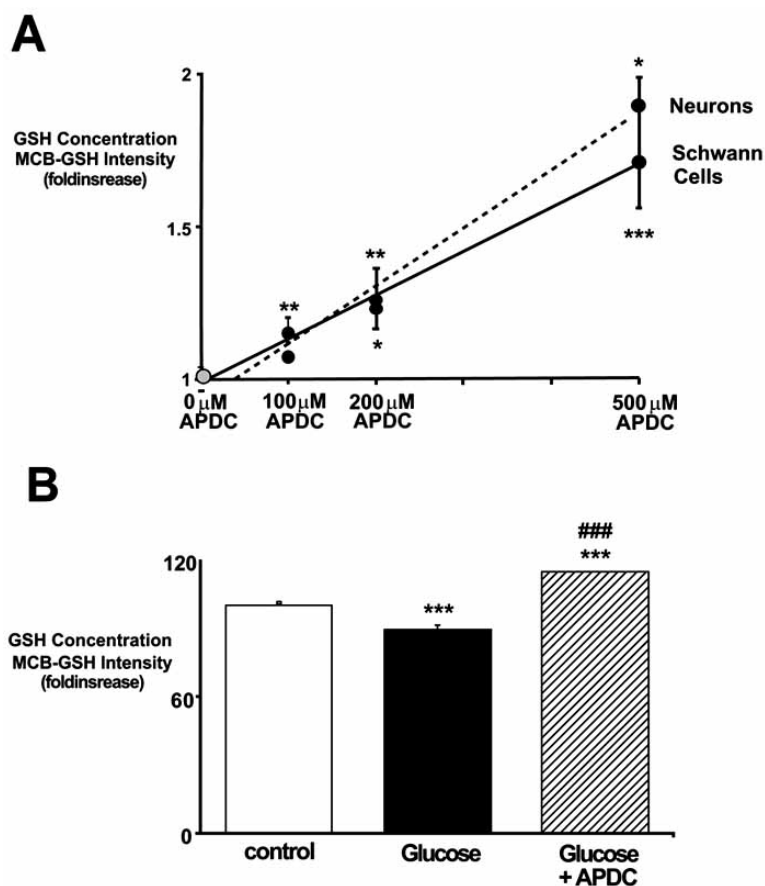


Fig. (6). (A) In DRG/SC cocultures, the mGluR3 agonist, APDC, stimulates GSH synthesis and (B) prevents glucose induced depletion of GSH in neurons. A.: co-cultures were treated with 0, 100, 200, or 500 μM APDC for 24 hours, then incubated with MCB. Relative GSH concentration was determined by fluorescent intensity of the MCB-GSH adduct using microscopy in DRG neurons and SC. Data is presented for DRG neurons and is expressed as fold increase over control (mean \pm SEM). * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ versus 0 μM APDC. The coefficient of determination (R^2) was 0.9896. In the same experiment, similar results were obtained for SC, $R^2 = 0.9762$. B.: co-cultures were treated for 24 hours \pm 20 mM added glucose \pm 100 μM APDC. *** $P < 0.001$ versus control; ### $P < 0.001$ versus 20 mM added glucose. Adapted from [23], Wiley-Blackwell Publishing Ltd., Oxford, U.K.

(phosphonomethyl) pentanedioic acid (2-PMPA) prevents glucose-induced cell injury and neurite degeneration in DRG neurons [10]. GCPII, previously called NAALADase, is a neuropeptidase, expressed primarily in glial cells, which hydrolyzes the neuropeptide N-acetyl-aspartyl-glutamate (NAAG) into NAA [94]. NAAG protects neurons by acting as an agonist primarily at mGluR3 [95-98]. Although there is no evidence of NAAG activity at mGluR2, another agonist APDC has activity at mGluR2 as well as mGluR3, and it is thus possible that mGluR2 activation is also neuroprotective. Evidence of neuroprotection is also seen in animal models of diabetic neuropathy. Inhibitors of GCPII, probably by increasing NAAG, have been shown to have a beneficial effect on hyperalgesia and neurophysiological and structural degenerative diabetic neuropathy changes in inbred type 1 diabetic BB/Wor rats [99].

Ongoing experiments indicate that treatment with the direct mGluR3 agonist, LY379268 provides significant protection against diabetic neuropathy [24]. Rats were made diabetic with streptozotocin and treated with the mGluR3 agonist LY379268 and then electrophysiological methods were used to measure changes in neuropathy from baseline.

Fig. (7) shows initial sensory testing using Von Frey hairs placed on the surface of the foodpad. Trials were repeated 4 times for each hair and the hair strength (g) at the threshold recorded for each animal (Fig. 7). This shows that as expected diabetic animals have hyperalgesia at one month of diabetes. This hyperalgesia was reduced by using 3 mg/kg LY379268 in a primary intervention study. Nerve conduction data also shows that induction of diabetic neuropathy is reduced by LY379268 [24]. As in cell culture, the mGluR3 appears to regulate mitochondrial function in diabetic neurons and Schwann cells. Another potential mechanism by which mGluR3 agonist may prevent neuropathy is by antagonism of TGF- β . In diabetic DRG, TGF- β 1 and TGF- β 2 mRNA, but not TGF- β 3, is increased in diabetic animals [100]. In sciatic nerve from diabetic animals only TGF- β 3 was increased. Similar results were found using TGF- β immunohistochemistry of diabetic DRG and sciatic nerve. *In vitro*, TGF- β is increased in western blots of DRG treated with added glucose, cellular injury is increased 6 fold when glucose and TGF- β 2 are combined, and TGF- β neutralizing antibody inhibits cellular injury. Furthermore, TGF- β isoforms reduce neurite outgrowth. In contrast to injury induced

by TGF- β , the mGluR3 agonist APDC is able to reduce the glucose-induced increase in TGF- β and thus protect against TGF- β neuronal or Schwann cell injury (Fig. 8).

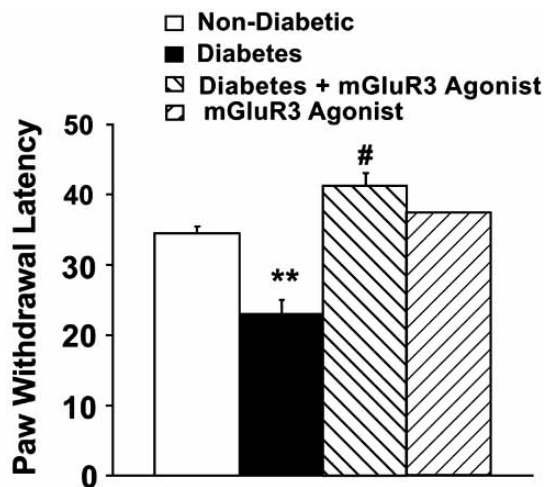


Fig. (7). The mGluR3 agonist, LY 379268 reduces plantar hyperalgesia determined using Von Frey monofilament testing in the hind limb paw. The groups are control, diabetic, diabetic+3mg/kg LY379268 and control+LY379268. Data is mean \pm SEM. ** $P < 0.01$ as compared with non-diabetic rats; # $P < 0.05$, as compared with diabetic rats.

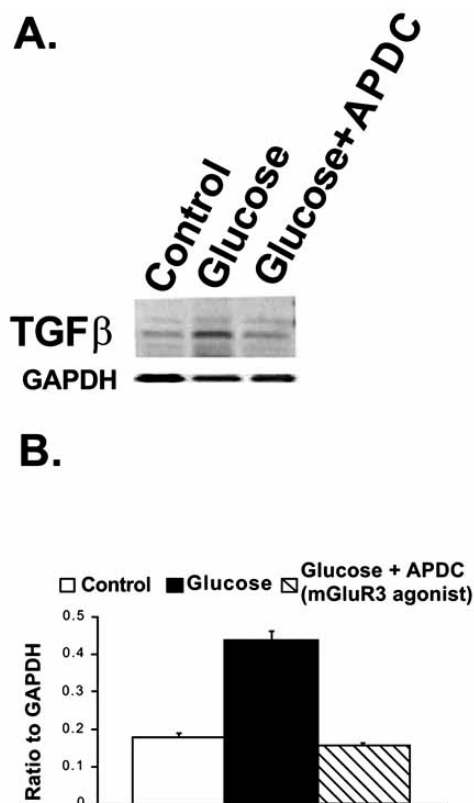


Fig. (8). High-glucose increases expression of TGF β in pure differentiated SC cultures. This effect is blocked by an mGluR3 agonist, APDC. (A) Lane 1 shows an IP with control expression of TGF β , lane 2 in the presence of 20 mM added glucose, and lane 3 expression in the presence of 100 mM APDC and added glucose. 5 μ g of protein was loaded in each lane and samples were obtained after 6 h of treatment. (B) Shows the ratio of TGF β to GAPDH.

9. CONCLUSIONS

mGluRs have proven to be protective against a wide variety of injury within the mammalian nervous system, and are thus a potential target for treatment of neurological disease. Oxidative stress is important as one mechanism leading to diabetic neuropathy. Direct or indirect activation of Group II mGluRs reduces oxidative stress and cellular injury, primarily by regulating GSH. This antioxidant effect requires a Schwann cell neuronal or axonal interaction that indicates that mGluR3 agonists primarily exert their neuroprotective effects by a direct action on Schwann cells. Furthermore, mGluR3 agonists prevent upregulation of isoforms of TGF- β that in turn are markers of cellular injury in diabetic neuropathy. In animal models of diabetes, mGluR3 agonists prevent the development of diabetic neuropathy and may prove to be a novel mechanism of neuroprotection in human diabetic neuropathy.

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