Chapter 21

Excitotoxicity and Glaucoma

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http://dx.doi.org/10.5772/57605

1. Introduction

Glutamate is a major excitatory neurotransmitter in the visual perception pathway. In the retina, rod and cone photoreceptor cells continuously release glutamate and partially depolarized in darkness, and light decreases the glutamate release in a graded manner. The photoreceptor signals are transmitted to bipolar cells and horizontal cells. The two-types of bipolar cells, ON-and OFF-bipolar cells, continuously release glutamate in lightness and in darkness, respectively [1,2]. Bipolar cells respond to light with sustained and graded potential as photoreceptor cells do. Bipolar cell signals are then transmitted to ganglion cells, which produce action potentials as a signal transduction to the brain via the axon of the ganglion cell.

Glutamate released from the presynaptic terminals diffuse to bind to the glutamate receptors on the postsynaptic membrane via the synaptic cleft. Retinal glutamate receptors are mainly located in the outer plexiform layer where glutamatergic synapses connect photoreceptors to bipolar and horizontal cells; and also in the inner plexiform layer which contains the bulk of glutamatergic synapses from bipolar cells to ganglion cells and amacrine cells [3-6].

Multiple glutamate receptor types have been identified. Though glutamate will bind onto all glutamate receptors, each receptor is characterized by its sensitivity to specific glutamate analogues and by the features of the glutamate-elicited current. Glutamate receptors are divided into three groups, N-methyl-D-aspartate (NMDA) receptors, AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate)/kainic acid receptors (non-NMDA receptors), and metabotropic receptors. NMDA and non-NMDA receptors are called ionotropic glutamate receptors, and form ion channel pores for ion influx and efflux, when glutamate binds to the receptor [7-9].

When glutamate is in excess, glutamate binds to cell surface ionotropic glutamate receptors, triggering massive Ca^{2+}influx and activation of pro-apoptotic signaling cascades. It can become

toxic to the retinal neurons [10-13]. Olney (1969)coined the term excitotoxicity to describe the process of neuronal death caused by excessive or prolonged activation of receptors for excitatory amino acid neurotransmitters [14]. Like excitotoxicity has been considered as an important contributor to the retinal ganglion cell death in ischemic retinal diseases such as vascular occlusions [15] or diabetic retinopathy [16-18] excitotoxicity may be involved in ganglion cell death in glaucoma [19].

Although massive glutamate release is characteristic for the ischemic retinal diseases [20-22], this is not necessarily required for pathogenesis of glaucoma. In fact, several studies were unable to detect the elevation of extracellular concentration of glutamate in vitreous humor samples from experimental animals with ocular hypertension, and in human glaucoma [23-27]. Correspondingly, it has been revealed that retinal glial cells play critical roles in the prevention of excitotoxocity. For example, Müller cells are responsible for the uptake of excess glutamate via GLAST (Glutamate Aspartate Transporter) [28.29], which is essential to maintain physiological concentrations of glutamate. Glutamate at physiological levels can be neurotoxic, if glutamate metabolism is impaired. Therefore, it is considered that impaired metabolism of glutamate more likely contributes to the excitotoxic injury even if glutamate is not in excess.

This review summarizes the present knowledge regarding the glutamate metabolism in glaucoma and the possible neuroprotective therapy of glaucoma.

2. Glutamate uptake and glaucoma

Glutamate released from the presynaptic terminals reaches the receptor molecules of the postsynaptic plasma membrane; but majority of glutamate are taken up by Müller glia or by retinal neurons via glutamate transporters. Glutamate transported into Müller glia is amidated to glutamine by a glutamate degrading enzyme, glutamine synthetase [30-33] (Figure 1).

2.1. Physiology of glutamate transporters

Glutamate uptake is mediated by five distinct glutamate transporters (EAAT1-5): GLAST (EAAT1) [34], GLT-1 (EAAT2) [35], EAAC1 (EAAT3) [36], EAAT4 [37] and EAAT5 [38]. In five EAATs, GLAST (EAAT1) and GLT-1 (EAAT2) are the major glutamate transporters in the retina. GLAST is mainly expressed in the Müller cells, whereas GLT1 and EAAC1 are in retinal neurons. We describe the physiological roles of GLAST and GLT-1, respectively.

a. GLAST

GLAST is the prominent glutamate transporter in the retina, and mainly expressed in the Müller cells [10, 31-33, 39, 40]. Müller cells remove the majority of glutamate from extracellular sites [41-47]. When Müller glial uptake is pharmacologically blocked, extracellular glutamate concentration increase [48], and severe excitotoxicity is induced [48, 49]. In GLAST KO mice, the Vmax for Müller glial glutamate transport is suppressed by 50%, suggesting that approximately 50% of glutamate is taken up via GLAST, another 40% through electroneutral, sodium-dependent (presently undefined) glutamate transporters, and 10% via sodium-independent

http://dx.doi.org/10.5772/57605

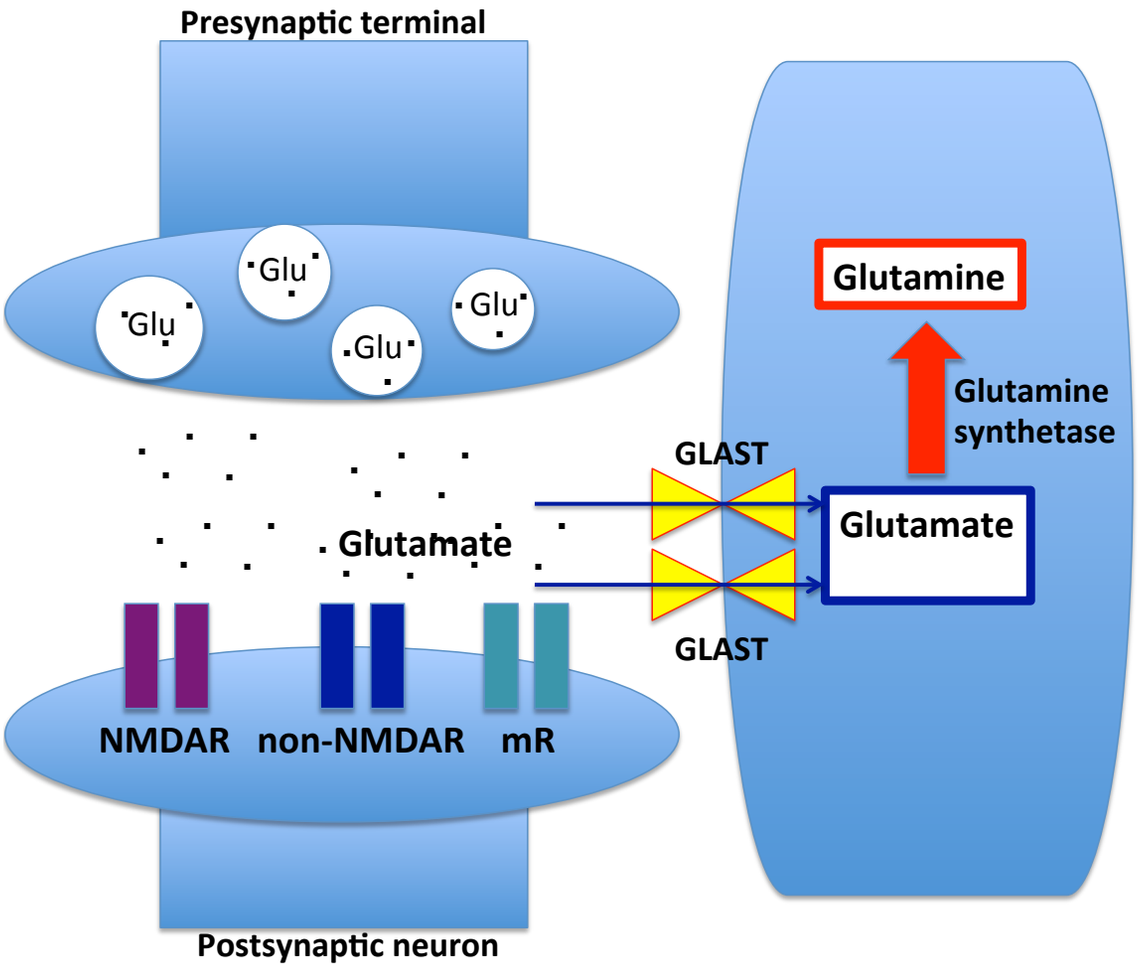

Figure 1. After release from the presynaptic terminal, glutamate binds to the post-synaptic glutamate receptors.Then, excess of glutamate is transported into the Mullller glia via glial glutamate transporter, GLAST, and catalyzed by glutamine synthetase to the nontoxic amino acid glutamine. Glutamate is also transported into retinal neurons via neuronal glutamate transporter, GLT-1.

transporters or exchangers [50]. Although antisense GLAST fails to induce apparent excitotoxicity [51], antisense suppresses the b-wave and oscillatory potentials of electrocardiogram [46, 51], and doubles total glutamate levels in the retina [50]. These results indicate that GLAST is essential to maintain the homeostasis of glutamate metabolism and physiological neural functions. In support of this, it has been shown that retinas from mice with targeted deletions of GLAST are extremely sensitive to ischemic insults [46].

b. GLT-1

GLT-1 (EAAT2) is the neuronal glutamate transporter, and exists in several distinct forms, including the originally described form (GLT-1, also referred as GLT-1a), along with GLT-1b (also called GLT1v) and GLT1c [48]. GLT-1a appears to be associated mainly with a population of amacrine cells and bipolor cells, whereas GLT-1b is associated with cone photoreceptors and subpopulations of bipolar cells [52,53]. GLT-1c is normally only expressed by the photoreceptors in the mammalian retina [54]. GLT1 knockout mice appear to exhibit minimal

compromise of retinal function, suggesting that GLAST is essential for the maintenance of normal synaptic transmission [46, 49]. However, it is still controversial because other researchers reported that treatment with antisense oligonucleotides against GLT-1 induced the excitotoxic ganglion cell death in the rat retina [42].

2.2. Impairment of glutamate removal in glaucoma

a. GLAST

Some studies have shown that GLAST expression diminishes [55-57] or remains stable [58] in experimental glaucoma, whereas others have reported increased expression [59]. Thus, it remains unclear whether elevated intraocular pressure (IOP) alters glutamate uptake by modulating GLAST. After experimental IOP elevation in rats, Holcombe et al. (2008) [47] immunohistochemically determined the glutamate transport activity as aspartate uptake into Müller glia, and found that Müller glial uptake is normal even IOP is as high as 70 mmHg but compromised at 80 mmHg or higher. These results suggest that GLAST is functional as long as retinal perfusion is maintained.

We [60] used a rat *ex vivo* model incubating rat eye cups under hydrostatic pressure at the bottom of a deep cylinder. Such acute high pressures can induce retinal ischemia clinically and in *in vivo* glaucoma models [61-63] but not in this *ex vivo* model. The advantages of *ex vivo* hydrostatic pressure model include better preservation of eyecup samples without ischemia, making it possible to investigate direct effects of pressure-induced retinal injury on glutamate metabolism. In this acute *ex vivo* model, axonal damage of the retinal ganglion cells were prominent, and Western blot and real-time RT-PCR analyses revealed that 75 mm Hg pressure depressed GLAST expression [64]. Administration of glutamate receptor blockers prevented axonal damages, indicating that IOP elevation induces excitotoxicity via depression of GLAST. It should be also noticed that IOP elevation can depress GLAST activity even if retinal perfusion is preserved.

Harada et al. (2007) [65] show that GLAST-deficient mice demonstrate spontaneous RGC loss and optic nerve degeneration in spite of normal IOP. In GLAST-deficient mice, administration of glutamate receptor blockers prevented RGC loss.

These findings suggest that glutamate transporters are necessary to prevent glaucomatous excitotoxic retinal damages.

b. GLT-1

GLT-1, the main neuronal glutamate transporter in the retinal neurons, is reported to be down-regulated in glaucomatous eyes in rats [58, 66] and mice [57]. By contrast, Park et al. [58] reported that the expression of GLT-1 was expressed in cone photoreceptors and the level of expression in some cone bipolar cells was significantly increased in *in vivo* glaucoma model. They also demonstrated that GLAST expression in Müller cells remained stable during the experimental period. These results suggest that integrity of GLT-1 may be a prerequisite for the maintenance of glutamate homeostasis in the retina undergoing glaucoma [67].

Sullivan et al. (2006) [68] reported the expressional changes of the splice variant of GLT-1 (GLT-1c) in the glaucoma eyes. In normal eyes of humans and rats, GLT-1c is expressed only in photoreceptors. In glaucoma, additional robust expression of GLT-1c is detected in retinal ganglion cells, including occasional displaced ganglion cells [106]. The new induction of GLT-1c expression by retinal ganglion cells may imply abnormalities in glutamate homeostasis in glaucomatous RGCs. The same authors said that GLT-1c may be a useful indicator of the extent of stress of the RGCs and thus a tool for examining outcomes of potential therapeutic and experimental interventions.

2.3. Neuroprotection by upregulation of glutamate transporters

Several studies [56, 64] revealed that the expression of the major glutamate transporter, GLAST, decreases after pressure loading. Therefore, agents that effectively enhance glutamate transporter function may serve as potential therapeutics against the pressure-induced injury. Enhancement of glutamate transport is developing into a new strategy for reducing excitotoxicity also in brain injury and neurodegenerative disease [69-71]. Lee et al. (2009) [72] reported that tamoxifen, estrogen modulator, possessed neuroprotective properties against excitotoxicity by the up-regulation of GLAST at protein and mRNA levels in the mannganese-induced excitotoxicity. Estradiol and its derivative also reported to increase GLAST expression, though these drugs have not been applied to glaucoma patients.

Recently, the daily treatment with 17β-estradiol (E2) eye drops resulted in significant E2 concentration in the retina with concomitant profound neuroprotective therapeutic benefits, even in the presence of continually elevated IOP [73]. However, E2 eye drop induces the adverse effect to other organs induced by stimulation of estrogen receptors. It seems safe to apply E2 eye drops to postmenopausal women. Taking all above into consideration, there is a long way to go before topical estrogen drops becomes a new therapeutics of glaucoma.

3. Enzymatic degradation of glutamate and glaucoma

In the Müller cells, glutamate is rapidly converted into glutamine by the glia-specific enzyme, glutamine synthetase [33]. Glutamine synthetase is specifically localized in the cytosol of Müller cells [74].Glutamine synthetase catalyzes the following reaction,

$$\text{Glutamate} + NH^{4+} + ATP \rightarrow \text{glutamine} + ADP + P_i + H^{+},$$

in the presence of Mn^{2+}or Mg^{2+}.

The activity of the glutamine synthetase influences the rate of the glutamate uptake by the Müller cells [41]. The rapid metabolization of glutamate to glutamine causes a stronger driving force for the glutamate uptake in the Müller cells than in neurons, which have intracellular free glutamate concentrations two orders of magnitude higher than the Müller cells [75]. A prerequisite for an effective glutamate-glutamine cycle in Müller cells would be the regulated coordination between glutamate uptake and glutamate degradation [39].

The activity of glutamine synthetase is stimulated by glucocorticoids [76,77]. In chick embryo retinas the stimulated glutamine synthetase by glucocorticoids is correlated with amounts of released glutamine from Müller glia, suggesting that the activity of glutamine synthetase influences glutamate uptake [78]. Conversely, it is also reported that basic fibrogrowth factor (bFGF) suppresses the activity of glutamine synthetase presumably through inhibition of glucocorticoid actions [79].

Glutamine, synthesized from glutamate in Müller glia, is the major source of glutamate found in retinal neurons. MSO, an inhibitor of glutamine synthetase, rapidly abolish free glutamate from bipolar cells and retinal ganglion cells [80]. Therefore, glutamine synthetase is a key enzyme in glutamate-glutamine cycle.

3.1. Impairment of glutamate metabolism and glaucoma

Several studies have shown increases in the expression of glutamine synthetase [78] after pressure elevation [81,82], whereas others have reported decreases. Thus, it remains controversial whether elevated IOP alters glial cell glutamate metabolism as a potential mechanism of retinal excitotoxicity [83].

In primary glaucoma in dogs [84], decreases in immunoreactivity of glutamine synthetase were associated with glutamate redistribution. These decreases in glutamine synthetase occurred even in mildly damaged regions of retina before retinal thinning. Reactive Müller cells were seen primarily in chronic primary glaucoma in severely damaged regions. Decreases in glutamine synthetase may potentiate ischemia-induced early glutamate redistribution and neuronal damage in canine primary glaucoma.

We (2010) [60] reported that pressure elevation induced reduction of glutamine synthetase activity compared with control pressure in an acute*ex vivo* model. The result suggests that the neural degeneration observed during pressure elevation is caused by impaired glial glutamate metabolism.

Although GLAST and the activities of glutamine synthetase are intimately intertwined [85], both are simultaneously suppressed by high pressure-loading. Thus, it is also possible that suppression of GLAST and the activities of glutamine synthetase occur separately during pressure-loading [86]. However, a series of observations using acute *ex vivo* model suggest that during pressure-loading, the impairment of GLAST expression precedes the depression of glutamine synthetase activity. Pharmacologic inhibition of glutamine synthetase activity with MSO fails to modulate GLAST expression, whereas inhibition of GLAST with TFB-TBOA substantially suppresses glutamine synthetase activity. Based on these findings, it is hypothesize that during pressure-loading, impairment of GLAST takes place first and results in downregulation of activities of glutamine synthetase as a secondary effect [62], though it is also possible that changes in the activities of glutamine synthetase influence GLAST activities [78].

3.2. Neuroprotection by upregulation of glutamine synthetase

Hydrocortisone, which is shown to increase the expression of glutamine synthetase in the Müller cells, is considered as neuroprotectve against excitotoxicity [87-89]. Upregulation of glutamine synthetase by hydrocortisone may be related to the fact that the upstream region of the glutamine synthetase gene contains a glucocorticoid response element that can bind the glucocorticoid receptor protein [53]. Glutamine synthtase was also reported upregulated by taurine supplementation in the diabetic retina [90]. These agents that effectively enhance glutamine synthetase function and expression may serve as potential therapeutics against the pressure-induced injury.

4. Glutamate receptors

The excitotoxicity is predominantly mediated by the overstimulation of NMDA receptors due to their extreme permeability to calcium ions [94]. Many researchers have concluded, therefore, that excitotoxicity occurs, in part, via NMDA receptors activation [99,100]. There is still remained a possibility that glutamate acts via non-NMDA receptors to initiate neurotoxicity [101-105]. However, the role of non-NMDA receptorsin pathogenesis of glaucoma has not been elucidated.

We describe the present knowledge concerning the molecular function of NMDA receptors and its relation to excitotoxicity.

a. NMDA receptors

Retinal ganglion cells express abundant NMDA receptors [106-109]. A number of studies demonstrated that ganglion cells are extremely vulnerable to exogenously applied NMDA, which inducesganglion cell degeneration.It has been also shown that NMDA receptor antagonists are neuroprotective in experimental glaucoma models [110-117]. NMDA receptors permit the influx of sodium ions (Na^+) and calcium ions (Ca^{2+}) and the efflux of potassium ions (K^+).

Although all NMDA receptors express the NR1 subunit [122,123,124], NR2 subunits are major determinants of the functional properties of NMDA receptor [125]. Recently, Bai et al. (2013) [126] reported the roles of the four different NR2 subtypes (NR2a, NR2b, NR2c, NR2d) in NMDA-induced retinal cell death using mice lacking specific NR2 subunits. They also evaluated the neuroprotective effect of 7-hydroxy-6-methoxy-2-methyl-1-(2-(4-(trifluoromethyl)phenyl)ethyl)-1,2,3,4-tetra-hydro-isoquinoline hydrochloride (HON0001) [127], an specific NR2b antagonist, on ganglion cell degeneration due to glutamate excitotoxicity in GLAST-deficient mice. As the results, NR2b-and NR2d-deficiency protected ganglion cells from NMDA-induced excitotoxicity. Pharmacological inhibition of the NR2b subunit by HON0001 attenuated ganglion cell loss in GLAST deficient mice. These findings suggest that NR2b-and NR2d-containing NMDA receptors play a critical role in NMDA receptor-mediated excitotoxicity in the retina. Based on these findings,inhibition of NR2b and NR2d activity is a

potential therapeutic strategy for the treatment of retinal neurodegeneration induced by excitotoxicity.

The same authors demonstrate that NR2d deficiency attenuates ganglion cell loss in GLAST-deficient mice [126]. Furthermore, Dock3, a guanine nucleotide exchange factor, binds to the NR2d C-terminal domain and reduces the expression of NR2d, thereby protects ganglion cells from excitotoxicity. These results suggest that NR2d is involved in the excitotoxic ganglion cell death, and that the interaction between NR2d and Dock3 may have a neuroprotective effect. These findings indicate the possibility that NR2d and Dock3 might be therapeutic targets for glaucoma.

b. Neuroprotection by NMDA receptor antagonists

Classical pharmacological approaches for reducing excitotoxicity have focused on antagonism of glutamate receptors. Memantine is an uncompetitive NMDA antagonist, binding near the Mg^{2+}site within the ion channel [128]. The degree of blockade of the NMDA receptors is changed according to the concentration of memantine [128]. Memantine is a neuroprotective agent that has completed phase III clinical trial in patients with glaucoma [129, 130]. The trial showed that memantine was ineffective by the primary end point, with the variable mechanisms of retinal ganglion apoptosis being offered as an explanation [131].

A recent study demonstrated that NR2c-and NR2d-containing NMDA receptors are the primary targets of memantine [132]. It has been reported that memantine prevents the loss of retinal ganglion cells in GLAST knockout mice, a model of normal tension glaucoma (NTG), suggesting that NR2d-containing receptors may be involved in ganglion cell loss in glaucoma [125, 126]. It was also demonstrated that Mg^{2+}regulates the sensitivity of NMDA receptors to memantine [133]. In a physiological concentration (1 mM) of extracellular Mg^{2+}, memantine exerts a more potent blocking effect at NR2c and NR2d subunits than at NR2a and NR2b subunits. These findings suggest that NR2c-and NR2d-containing NMDA receptors are likely to be the main targets of memantine.

5. Concluding comments

Glutamate accumulation in extracellular spaces can be potentially neurotoxic if glutamate is not removed in an appropriate manner. It should be noticed that excitotoxicity does not always due to excess of glutamate. Extracellular glutamate level duringretinal ischemia may not be sufficient to induceneuronal damage under normal conditions. This suggeststhat clearance of glutamate is essential in preventingretinal excitotoxicity. In glaucomatous models, glutamate metabolism can be impaired by inhibition of glutamate transporter and glutamine synthetase, resulting in excitotoxic glaucomatous damages of retinal ganglion cells. A series of observations using ex vivo glaucomatous model suggest that during pressure-loading, the impairment of glutamate transporter expression precedes the depression of glutamine synthetase activity. Therefore, it is also possible that changes in the activities of glutamine synthetase influence GLAST activities.Agents that effectively enhance glutamate transporter function may serve as

potential therapeutics against the pressure-induced injury. Enhancement of glutamine synthetase may be a therapeutic strategy for reducing excitotoxicity.

Acknowledgements

I thank Yoko Hayami, and Sanae Takaseki (Department of Ophthalmology Akita Graduate University School of Medicine) for instructions and suggestions. This work was supported by JSPS KAKENHI Grant Numbers 24592666 to M.I.

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