Chapter 1
Molecular Architecture of Glutamate Signaling Pathway in Glaucomatous Optic Neuropathy

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Abstract Glutamate is the predominant excitatory neurotransmitter in the central nervous system. Excessive concentrations of glutamate have been reported in various neurological diseases, including glaucomatous optic neuropathy (GON). Glutamate excitotoxicity triggered by overstimulation of *N*-methyl-D-aspartate (NMDA)-type glutamate receptors may contribute to retinal ganglion cell (RGC) degeneration in glaucoma and other retinal neuronal cell death in ischemic insult including diabetic retinopathy. Neuroprotective effects with the blockage of overstimulated NMDA receptors were found in several previous studies in RGC degeneration models, such as the axotomy, ischemia, and laser-induced high intraocular pressure models. Although there is a great deal of evidence for elevated glutamate in GON, a clinical trial of memantine, an NMDA receptor antagonist, was unsuccessful. Thus, excitotoxicity is not recognized as a primary factor in GON, although glutamate leaking from dying/dead RGCs or compromised glia may contribute to the secondary death of neighboring RGCs via excessive activation of NMDA receptors during the development of glaucoma. Therefore, appropriate modulation of NMDA receptor-mediated retinal excitotoxicity remains to be elucidated and may become a possible therapeutic target.

Keywords Excitotoxicity • Glutamate • Retina • Retinal ganglion cell

1.1 Introduction

Glutamate is an excitatory neurotransmitter in the central nervous system (CNS). Neurotoxicity in the retina caused by elevated glutamate levels was first reported by Lucas and Newhouse in 1957 [1]. This phenomenon is referred to as excitotoxicity

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and it induces neuronal degeneration. Glutamate stored within cells is not harmful. Currently, excitotoxicity is known to play a role in various neurological disorders, including acute insult and chronic stress [2]. After the original report of Lucas and Newhouse, numerous studies focusing on excitotoxicity have been performed in neurodegenerative diseases including glaucomatous optic neuropathy (GON) [3, 4]. One contested study found higher levels of glutamate in the vitreous of glaucomatous patients than in controls [5, 6]. Therefore, it appears reasonable to suggest that if ganglion cell death in glaucoma is caused by excessive activation of *N*-methyl-D-aspartate (NMDA) receptors, then the NMDA receptor antagonist memantine would be worth exploring as a potential neuroprotective agent. Based on this reasoning, a clinical trial was conducted to determine the efficacy of memantine as a neuroprotectant against glaucoma. However, that trial was unsuccessful. Unfortunately, one of the authors associated with the reports by Dreyer et al. and Brooks et al. was later discredited, and attempts by others to reproduce some of those findings were not successful [5–8]. As a result, reliance on these data as a basis for undertaking further trials is difficult to justify. However, after those reports, elevated glutamate levels in animal experimental glaucoma models were reported [9, 10]. Furthermore, ectopic vesicular glutamate release at the optic nerve head was observed 2 days after intraocular pressure (IOP) elevation and caused subsequent axonal degeneration and RGC loss [11]. Although the memantine trial failed, understanding RGC degeneration with elevated glutamate levels may be important. This chapter discusses mechanistic insights into excitotoxicity and how excitotoxicity can contribute to GON.

1.1.1 Physiology

Glutamate is the most abundant excitatory neurotransmitter in the CNS. Nerve impulses trigger the release of glutamate from presynaptic cells [12]. In the opposing postsynaptic cells, glutamate receptors, such as the NMDA receptor, bind glutamate and are activated [13]. Because of its role in synaptic plasticity, glutamate is involved in cognitive functions in the CNS. The form of plasticity known as long-term potentiation occurs at glutamatergic synapses in the brain and retina [14, 15]. Glutamate functions not only as a point-to-point transmitter but also through spillover synaptic cross talk between synapses in which glutamate released from a neighboring synapse creates extrasynaptic signaling/volume transmission. In addition, glutamate plays important roles in the regulation of growth cones and synaptogenesis during development [16, 17].

1.1.2 Glutamate Transporters

In the retina, glutamate transporters that rapidly remove excess glutamate from the extracellular space are found in neuronal and glial membranes. In retinal injury or disease, they can work in reverse, and excess glutamate can accumulate outside cells. It was reported that five distinct excitatory amino acid transporters (EAATs) that transport glutamate have been cloned: the glutamate/aspartate transporter (GLAST) [18], glial glutamate transporter (GLT)-1 [19], excitatory amino acid carrier (EAAC)-1 [20], excitatory amino acid transporter (EAAT)-4 [21], and excitatory amino acid transporter (EAAT)-5 [22]. GLAST and GLT-1, which are exclusively located in glial cells in the brain [23–25], are also present in the retina. In the retina, GLAST is considered to be the major glutamate transporter and is expressed in Müller cells [26–28], while GLT-1, which is known to be responsible for up to 90 % of all glutamate transport in the forebrain region [29], is found in retinal neurons, such as cone photoreceptors and certain types of cone bipolar cell [30].

Little is known concerning the functional significance of GLT-1 expression in these retinal neurons. The elimination of excessive glutamate in the retina and vitreous is also important in slowing retinal neurodegenerative disease. The glutamate transporter is the only mechanism for the removal of glutamate from the extracellular fluid in the retina [31]. Increased glutamate levels may result from a failure of glutamate transporters adjacent to RGCs. Mice deficient in the glutamate transporters GLAST and EAAC-1, which are glutamate transporters, demonstrate spontaneous RGC death and optic nerve degeneration without IOP elevation, suggesting that glutamate transporters are necessary to prevent excitotoxic retinal damage [32, 33]. GLAST immunoreactivity is present throughout the retina and can be double-labeled with glutamine synthetase, a specific marker of Müller glial cells. These observations indicate that the intracellular glutamate concentration is dependent on glutamate uptake via GLAST in Müller glial cells.

1.1.3 Glutamate Receptors

Glutamate receptors are categorized into two main classes: ionotropic and metabotropic. The ionotropic glutamate receptors, which are all nonselective cation channels, are described as either NMDA or non-NMDA subtypes. NMDA receptors are characterized by a high permeability to Ca^{2+}, voltage-dependent blockage by Mg^{2+}, and slow gating kinetics. These receptors are known to be involved in a variety of physiological processes in the CNS [34–36]. Cloning experiments have demonstrated that there are at least five NMDA receptor subunits: NR1 and NR2A through NR2D [37].

Most recently, the novel subunits NR3A and NR3B have been cloned [38–40]. NR3A and NR3B assemble as heterotetramers in the endoplasmic reticulum to form functional channels through distinct combinations, producing various

postsynaptic responses. In the mature nervous system, NMDA receptors are composed primarily of NR1 and NR2A through NR2C [41]. The receptor in some neurons may contain only NR1 combined with either NR2A or NR2B. The NR1 subunit in rats has at least eight splice variant forms [42, 43], and splice variants are also found in the NR2B-D and NR3A subunits [44]. On the other hand, unique genes code for each NR2 subunit [45] and for NR3A [46, 47]. NR1 serves a fundamental subunit of the NMDA receptor, without which the receptor cannot function, whereas NR2A through NR2D can be regarded as modulatory subunits [48, 49]. The NMDA receptor channel is highly permeable to Ca^{2+} [50, 51]. The increase in intracellular calcium levels ($[Ca^{2+}]i$) in neuronal cells resulting from the activation of the NMDA receptor channel has been shown to be responsible for modulating neuronal activity and producing neurotoxicity [52, 53]. There is recent evidence that the inclusion of an NR3A subunit attenuates the calcium current [54]. A unique feature of the NMDA receptor channel is the voltage dependence of the receptor-mediated inward ionic currents. This is because the channel becomes clogged by Mg^{2+} at negative membrane potentials and Mg^{2+} is driven out of the channel pore when the membrane is depolarized. The NMDA receptor-mediated inward current is maximal between −20 and −30 mV in external medium containing physiological concentrations of Mg^{2+} (approximately 1 mM), is reduced at more hyperpolarized potentials, and becomes negligible at −80 mV [55]. Therefore, at the resting membrane potentials of most spiking neurons (−70 to −90 mV), NMDA receptors undergo significant channel blockage by Mg^{2+}, and the blockage is relieved in a voltage-dependent manner when the neurons are depolarized by the activation of co-localized postsynaptic non-NMDA receptors. In other words, the NMDA receptor could serve as a molecular apparatus for detecting presynaptic signals occurring along postsynaptic depolarization at the synapse. This voltage dependence is important for synaptic integration in the CNS.

1.1.4 Downstream Signaling Cascade After Stimulation of NMDA Receptors

Stimulation of NMDA receptors is observed in the retina in various animal models of neurodegeneration, such as experimental glaucoma, axotomy, ischemia-reperfusion, and NMDA injection [56–59]. Intravitreal injection of NMDA causes relatively acute neuronal death, especially in the inner retina, through several molecular pathways (Fig. 1.1). The increase in Ca^{2+}[i] influx is the initial key molecular event in NMDA receptor-mediated cell death [60]. Ca^{2+}[i] overload activates Ca^{2+}-dependent enzyme systems such as calpain- and calcium-/calmodulin-dependent kinase 2 (CaMK2) [61, 62]. Calpain is localized in TUNEL-positive apoptotic cells in the inner retina after NMDA injection, and the inhibition of calpain results in less NMDA-induced neuronal cell death, suggesting a proapoptotic role of calpain in NMDA-induced neurotoxicity. In contrast, phosphorylation of CaMK2

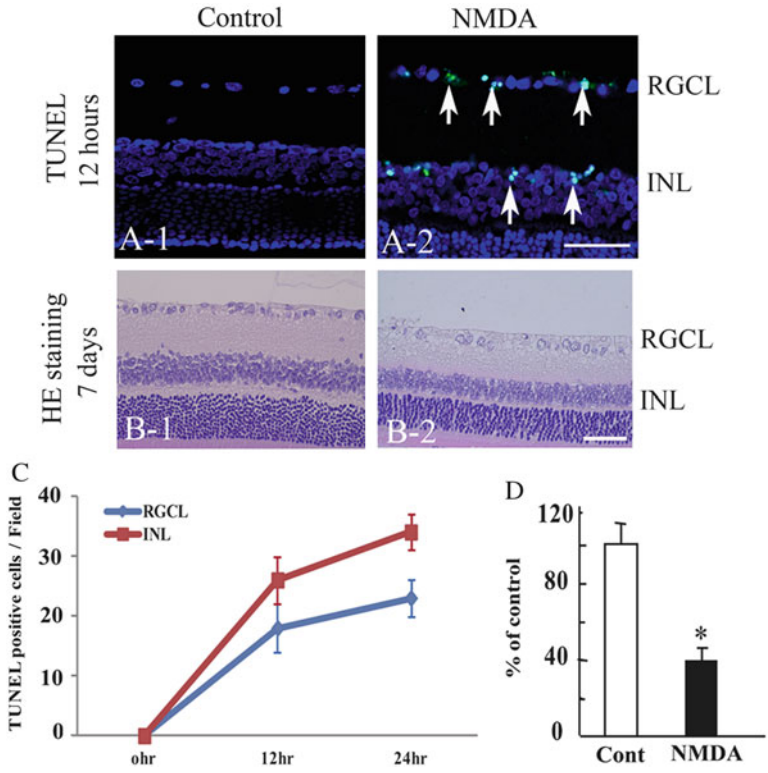

Fig. 1.1 TUNEL staining after NMDA injection (**A**-1, 2). Hematoxylin and eosin staining (**B**-1, 2). TUNEL-positive cells were observed in the inner retina after NMDA injection. There are no TUNEL-positive cells in the control retina. *Arrows* are TUNEL-positive apoptotic cells. Time course of TUNEL-positive cells in the inner retina (**C**). Intravitreal injection of 20 nmol NMDA induced neurotoxicity in the inner retina. Approximately 60 % neuronal cell loss was observed in the RGCL after NMDA injection (**D**). Scale bar = 50 μm

is observed in the retina relatively early after NMDA injection, and inhibition of CaMK2 synthesis accelerates NMDA-induced RGC loss, indicating an antiapoptotic role of CaMK2 [62]. Ca^{2+}[i] influx also affects mitochondrial activity, such as the release of cytochrome C and reactive oxygen species, and results in the activation of several apoptotic pathways. Apoptosis-inducing factor is one key factor released from mitochondria and also contributes to DNA damage with overactivation of NMDA receptors [63]. PARP-1 activation occurs in the retina after NMDA injection in the vitreous and is accompanied by a decrease in ATP levels [64]. Conversely, a PARP inhibitor protects RGCs from NMDA-induced excitotoxicity. Our previous studies on the downstream Ca^{2+}[i] influx led us to propose that the activation of proapoptotic molecules, such as nuclear factor-κB p65 and p38, c-Jun *N*-terminal kinase, and c-Jun, plays a role in NMDA-induced neurotoxicity [65–68] (Fig. 1.2). An inflammatory response, i.e., the upregulation of interleukin-1β, is also observed in the glia and RGCs after NMDA administration,

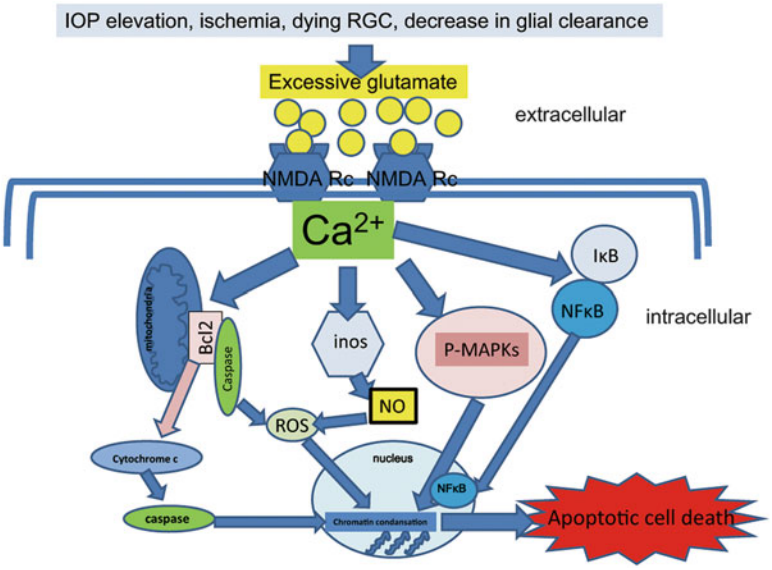

Fig. 1.2 Schema for molecular pathway for glutamate neurotoxicity

suggesting the involvement of inflammation in response to excitotoxicity [69]. Our previous study showed that axonal degeneration with neurofilament loss is evident 3 days after intravitreal injection of NMDA [70]. Although NMDA penetrates into the inner retina after intravitreal injection and induces various molecular changes in the glia and RGCs which lead to RGC apoptotic degeneration and inner retinal thinning, those changes occur after TUNEL-positive DNA fragmentation in RGCs, indicating anterograde degenerative change in NMDA-induced neurotoxicity. Furthermore, apoptotic cell body death affects axonal transport to axons through the disruption of kinesin-1 activity, an anterograde axonal motor protein related to microtubules and neurofilament. These findings indicate anterograde neurodegeneration in NMDA-induced neurotoxicity [70].

1.2 Future Perspectives

Glutamate levels in the vitreous have been measured under the premise that the vitreous represents the extracellular space of the retina. The true extracellular space is the intracellular space between retinal cells. Because of technical difficulties in measuring such glutamate concentrations in the human retina, it has not been confirmed whether glutamate levels are elevated in human patients with glaucoma. The epicenter of GON is proposed to be the optic nerve head or lamina cribrosa, where soft tissues, including RGC axons and blood vessels circulating the optic nerve head, are likely to be compressed as a result of deformation of the laminar

structure [71, 72]. Excitotoxicity may play a role in the pathophysiology of glaucoma by causing secondary RGC death because of glutamate leaking from injured cells, thereby triggering the activation of the apoptotic pathway. Harada and coworkers found that mice deficient in the glutamate transporters GLAST or EAAC-1 demonstrate spontaneous RGC and optic nerve degeneration without elevated IOP [33]. The retinas of glaucoma patients showed lower immunoreactivity of the EAAT-1 [73]. Furthermore, other studies showed that the optic nerve head is ischemic in glaucoma [74, 75]. Excitotoxicity can also contribute to the development of glaucomatous axonal degeneration because glutamate clearance by the glia decreases under ischemic conditions [76]. Although excitotoxicity is not a primary event in GON, glutamate leaking from dying/dead RGCs or compromised glia may contribute to the secondary death of neighboring RGCs via excessive activation of NMDA receptors in the development of glaucoma (Fig. 1.2). Therefore, the more appropriate therapeutic modulation of NMDA receptor-mediated retinal excitotoxicity remains to be elucidated and may become a potential therapeutic target.

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