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Review Article

THE ROLE OF EXCITATORY NEUROTRANSMITTER GLUTAMATE IN BRAIN PHYSIOLOGY AND PATHOLOGY

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ABSTRACT

Glutamate is the principal excitatory amino acid neurotransmitter abundantly present in the brain of mammals, as well as in dietary protein, released by an estimated 40% of all synapses and its interaction and participation with specific membrane receptors in plastic changes in the efficacy of synaptic transmission are responsible for many neurological functions, including cognition, memory, behavior, movement, sensation and in the formation of neural network during development. Our knowledge of the glutamatergic synapse has advanced enormously in the last 10 years, primarily through application of molecular biological techniques to the study of glutamate receptors (GluRs) and transporters. In addition, excitatory neurotransmitters are important in influencing the developmental plasticity of synaptic connections in the nervous system. However, in a variety of pathologic conditions, including stroke and various neurodegenerative disorders, excessive activation of GluRs (Ionotropic and metabotropic) may mediate neuronal injury of death. There is an increased release of glutamate after cerebral ischemia or hypoxia which could cause over stimulation of its receptors leading to an increase in the intracellular Ca^{2+} concentration (i[Ca^{2+}]). Sustained elevation in i[Ca^{2+}] is assumed to set various pathological processes into motion which could degenerate neurons by activating proteases, lipases, endonucleases and nitric oxide synthases and by promoting the formation of free oxygen radicals. Drugs capable of inhibiting the increase in i[Ca^{2+}] such as calcium antagonists, N-methyl-D-aspartate (NMDA) and α-amino-2-hydroxy-4-methyl-3-isoxazolepropionate (AMPA) antagonists protect neurons against damage.

Key words: Glutamate, excitotoxicity, neurodegeneration, excitatory amino acid, excitotoxicity, oxidative stress, reactive oxygen species.

INTRODUCTION

The excitatory action of amino acid L-glutamate in the mammalian brain and spinal cord has been known since the 1950s[1,2]. It is a paradox that glutamate is indispensable as a major excitatory amino acid (EAA) neurotransmitter probably involved in most aspects of normal brain function including cognition, memory and learning and, highly toxic as an endogenous excitotoxin[3-6]. Glutamate also plays major roles in the development of the central nervous system (CNS), including synapse induction and elimination, and cell migration, differentiation and death. Most neurons and even glial cells have glutamate receptors in their plasma membranes[7-11]. Further, glutamate plays a signaling role also in peripheral organs and tissues as well as in endocrine cells[12].

In spite of its ubiquitous role as a neurotransmitter, glutamate is highly toxic to neurons, a phenomenon dubbed 'excitotoxicity'[13]. It should be noted that the distribution of glutamate is in a dynamic equilibrium which is highly sensitive to changes in the energy supply. Firstly, glutamate will leak out of the cells if the cells run out of energy. Secondly, there is a rapid turnover of glutamate. Glutamate is continuously being released from cells and is continuously being removed from the extracellular fluid.

Parenteral administrations of EAA agonists in experimental animals provide informative *in vivo* models for study of the cellular and molecular mechanisms of EAA-mediated neuronal injury, developmental stage-specific features of excitotoxicity, and efficacy of neuroprotective interventions. Such models can provide important insights about the pathophysiology of a range of acute and chronic neurological disorders that are mediated, at least in part, by EAA receptor overactivation[14]. Although glutamate-induced cell death is associated with both apoptic and necrotic changes[15], the mechanism of cell death remains to be established. Many studies have reported that acute form of glutamate neurotoxicity is cellular selective and different EAAs produce distinctive degenerative patterns in the presence of agonists[16]; it is predominantly mediated by ionotropic glutamate receptors (iGluRs)[17]. The two deleterious processes can be distinguished by differences in time-dependence and ionic characteristics[18]. The acute form of neurotoxicity is characterized by excessive activation of iGluRs leading to massive influx of Na^+ followed by passive entry of Cl^- and efflux of K^+ ions which are responsible for further influx of water causing neuronal swelling, osmotic lysis and neuronal necrosis followed by massive influx of Ca^{2+}, leading to detrimental effects on the brain and can be prevented by eliminating from the culture medium, sodium or chloride, two ions responsible for the massive influx of water when glutamate-gated cation channels are open. Swelling occurs within minutes of glutamate exposure and is critically dependent on the extracellular concentrations of Na^+ and Cl^- ions[19]. In contrast, delayed neuronal degeneration caused by N-methyl-D-aspartate (NMDA) and in most cases, kainic acid (KA) agonists is Ca^{2+} ion-dependent and transpires over several hours after a brief exposure to a high concentration of agonist or prolonged exposure to a low concentration of agonist. The sustained elevation in intracellular Ca^{2+} (i[Ca^{2+}]), subsequent to Na^+, or both, is assumed to set various cascades of pathobiochemical processes in motion leading to neuronal degeneration involving a number of different pathways that cause oxidative stress and degeneration[18-20].

GLUTAMATE RELEASE

Glutamate is released from vesicles in presynaptic terminals by a Ca^{2+} dependent mechanism that involves N- and P/Q-type voltage-dependent Ca^{2+} channels[21] that appear to be closely linked to vesicle docking sites. The glutamate concentration within the vesicle is thought to be ~100 mmol/L; release of a single vesicle produces an excitatory postsynaptic potential (EPSP) that is related primarily to α-amino-2-hydroxy-4-methyl-3-isoxazolepropionate (AMPA) receptor activation. Glutamate may also be "released" by reverse operation of the glutamate transporters. This will occur when the Na^+ and K^+ gradient across the membrane is reduced during cerebral ischemia[22-23]. The synaptic release of glutamate is controlled by a wide range of presynaptic receptors. These include not only the Group II and Group III glutamate metabotropic receptors but also cholinergic (nicotinic and muscarinic) receptors, adenosine (A1), kappa opioid, γ-aminobutyric acid $(GABA)_B$, cholecystokinin and neuropeptide Y (Y2) receptors[24]. The mechanism by which this occurs leading to cell death is depicted in fig 1[25].

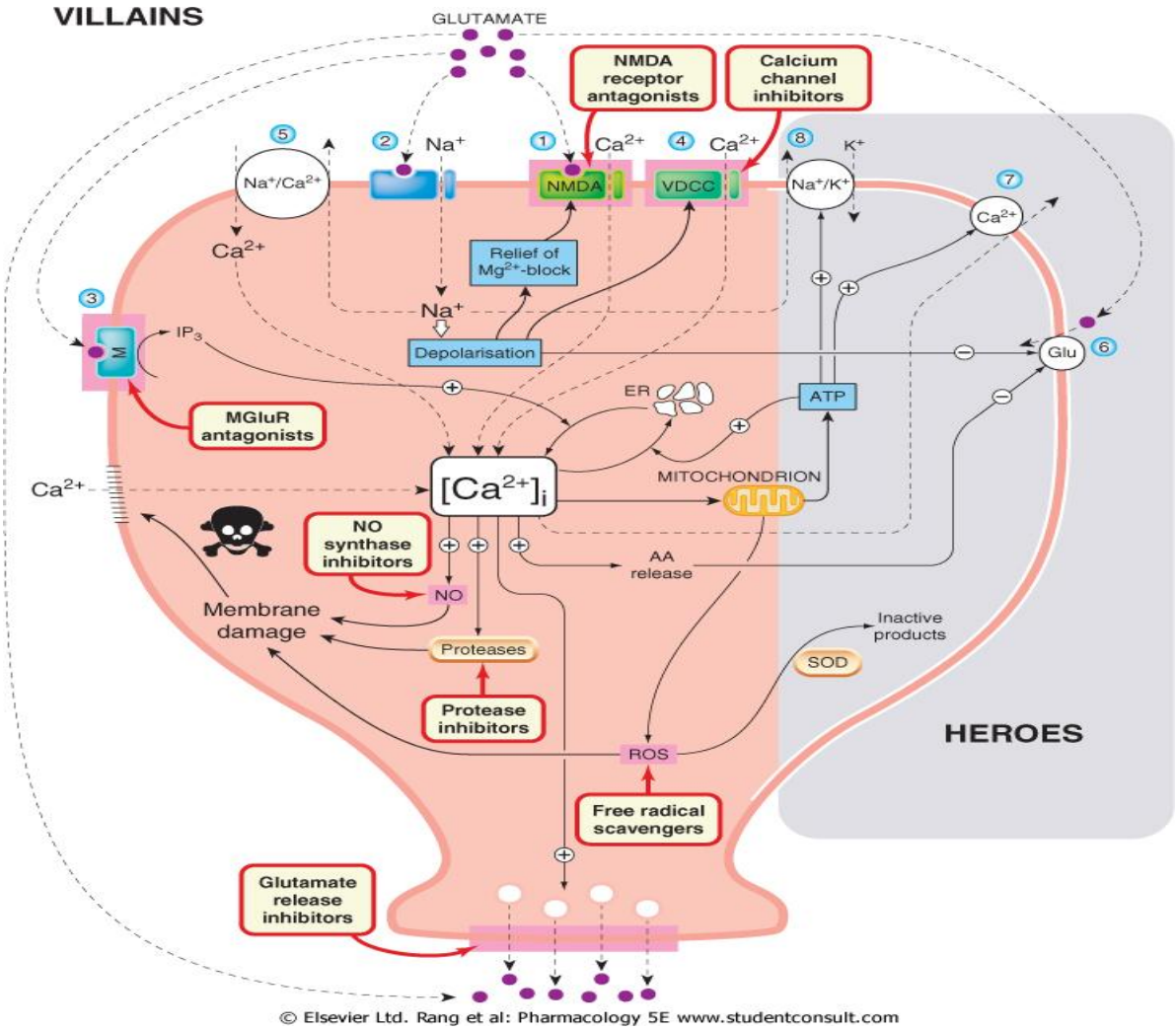

Fig 1. The physiological and pathological consequences of excitatory amino acid glutamate in mammalian brain.

GLUTAMATE RECEPTORS AND TRANSPORTERS

GluRs mediate most of the excitatory neurotransmission in the mammalian CNS and are intimately involved in both the physiology and pathology of brain functions. Excessive activation of GluRs during stress to the brain, such as ischemia, head trauma and epileptic seizures leads to the death of central neurons. The glutamate neurotoxicity may also be involved in the geneses of various neurodegenerative diseases[18,26-28]. For years the central effects of glutamate were thought to be exclusively mediated by ion channel mechanisms, however, glutamate receptors can now be categorized into two groups: ionotropic [i(GluR)] activated by glutamate and aspartate; and metabotropic [m(GluR)]. The i(GluR)s are ligand-gated ion channels, mainly localized postsynaptically, characterized by their selective affinity for the specific agonists: NMDA, AMPA and KA. The second group is that of mGluR, which are frequently present in the presynaptic membrane and do not form ion channels but are associated to G proteins and coupled to the production of second intracellular messengers[29-31]. They are subdivided into 3 types by amino acid sequence, agonist sensitivity and signal transduction mechanisms. Group I (mGluR1-5) are coupled to phospholipase C-mediated (PLC) polyphosphoinositide hydrolysis, while group II (mGluR2 and 3) and group III (mGluR4,6,7 and 8) are either negatively coupled to adenyl cyclase or linked to ion channels[32-22].

A distinctive feature of the NMDA receptor is its voltage-sensitive block by Mg^{2+}. This is operative under normal circumstances but is overcome by partial depolarization of the resting membrane potential. A further specific feature is the need for glycine as a coagonist. Each receptor unit appears to have two glycine and two glutamate binding sites[34]. Ionotropic receptors have functional properties beyond that of opening ion channels. These are provided by the capacity of the intracellular carboxy terminal to interact with a variety of intracellular proteins. These include proteins involved in the spatial and functional organization of postsynaptic densities, but also proteins involved in signal transduction[35]. These receptors share a common molecular morphology with other G protein–linked metabotropic receptors, i.e., they are presumed to have seven *trans*-membrane domains with an extracellular N-terminal and intracellular COOH terminal. They have little sequence homology with other metabotropic receptors, except for a modest resemblance to $GABA_B$ receptors. Group I receptors activate PLC, producing diacylglycerol and inositol triphosphate as second messengers. Groups II and III are negatively coupled to adenylyl cyclase. Studies using oocyte or human embryonic kidney cells expressing specific mGluR show marked variation in the sensitivity of the receptors to glutamate, with mGluR7 being remarkably insensitive. The sensitivity to glutamate has to be considered in relation to the location of the receptor on the cell membrane relative to the synaptic cleft. Immunochemistry at the electron microscopy (EM) level reveals a highly selective expression of mGluR[36-38], with some occurring presynaptically in close relationship to the presynaptic density (mGluR7, mGluR8) and some occurring on the presynaptic axon, relatively distant from the synaptic cleft (mGluR2, mGluR3).

Five glutamate transporters have been cloned from the mammalian CNS. Two are expressed predominantly in glia [glial glutamate and aspartate transporter (GLAST) and glial glutamate transporter (GLT)] and three in neurons [EAAC1, excitatory amino acid transporter (EAAT)4 and EAAT5] (in humans, these are referred to as EAAT1–5, respectively)[39]. They are all Na^+ dependent; in fact, the

transmembrane gradients of Na^+ and K^+ provide the driving force for the transport. The suggested stoichiometry (for GLT) is one molecule of glutamate coupled to the co-transport of three Na^+ and one H^+ and the counter transport of one K^+ [22]. Interestingly, the neuronal transporters seem to be linked to a Cl^- channel, which opens when glutamate binds, thereby tending to hyperpolarize the postsynaptic membrane and diminish synaptic activity. This phenomenon is thought to be functionally significant in Purkinje cells EAAT4 prominently[40]. The glial glutamate transporters (GLT) have a marked differential regional distribution; GLT is predominant in the rat hippocampus, whereas GLAST is predominant in the cerebellum[41]. There are also differences in the proximity of astrocytic processes to glutamatergic synapses, such that synaptic cross-talk may be possible at certain sites in the hippocampus. The rat neuronal transporter EAAC (equivalent to the human EAAT3 transporter) is highly expressed in the postsynaptic neuronal membrane (with up to 15 times the density of AMPA receptors); glutamate binding to this transporter contributes to termination of the excitatory postsynaptic current.

GLUTAMATE AND NEURODEVELOPMENT

Glutamate clearly plays an important role in neuronal differentiation, migration and survival in the developing brain. This is largely through facilitating the entry of Calcium[42-43]. Blockade of NMDA receptors during the prenatal period as by dizocilpine (MK-801), phencyclidine or ethanol] can induce apoptosis in vulnerable neurons (the selectivity of the vulnerability depending on developmental stage)[44]. Recent studies have shown that glutamate plays a vital role in the development of the nervous system, especially as regards neuronal survival, growth and differentiation, development of circuits and cytoarchitecture[45]. For example, it is known that deficiencies of glutamate in the brain during neurogenesis can result in maldevelopment of the visual cortices and may play a role in the development of schizophrenia[46]. Likewise, excess glutamate can cause neural pathways to produce improper connections, a process called "miswiring of the brain". Excess glutamate during embryogenesis has been shown to reduce dendritic length and suppress axonal outgrowth in hippocampal neurons. It is interesting to note that glutamate can produce classic toxicity in the immature brain even before the glutamate receptors develop. High glutamate levels can also affect astroglial proliferation as well as neuronal differentiation. It appears to act via the phosphoinositide protein kinase C (PKC) pathway.

It has been shown that during brain development there is an overgrowth of neuronal connections and cellularity, and that at this stage there is a peak in brain glutamate levels whose function it is to remove excess connections and neuronal over expression. This has been referred to as "pruning". Importantly, glutamate excess during synaptogenesis and pathway development has been shown to cause abnormal connections in the hypothalamus that can lead to later endocrinopathies[47]. In general, toxicological injury in the developing fetus carries the greatest risk during the first two trimesters. But, this is not so for the brain, which undergoes a spurt of growth that begins during the third trimester and continues at least two years after birth. Dendritic growth is maximal in the late fetal period to one year of age, but may continue at a slower pace for several more years. Neurotransmitter development also begins during the late fetal period but continues for as long as four years after birth. This means that alterations in dietary glutamate and aspartate are especially dangerous to the fetus during pregnancy and for several years after birth. The developing brain's susceptibility to excitotoxicity varies, since each brain region has a distinct developmental profile. The type of excitotoxin also appears to matter. For example, kainate is non-toxic to the immature brain but extremely toxic to the mature brain. The glutamate agonist, NMDA, is especially toxic up to postnatal day seven while quisqualate and AMPA have peak toxicity from postnatal day seven through fourteen. L-cysteine is a powerful excitotoxin on the immature brain.

Myelination can also be affected by neurotoxins. In general, excitotoxic substances affect dendrites and neurons more than axons but axon demyelination has been demonstrated. During the myelination process, each fiber tract has its own spatiotemporal pattern of development, accompanied by significant biochemical changes, especially in lipid metabolism. More recent studies have shown an even more complicated pattern of CNS myelination than previously thought. This is of importance especially as regards the widespread use of aspartame, because of this triple toxin's effects on neuronal proteins and DNA. Of special concern is aspartame's methanol component and its breakdown product, formaldehyde[48]. Also, it is known that the aspartate moiety undergoes spontaneous racemization in hot liquids to form D-aspartate, which has been associated with tau proteins in Alzheimer's disease (AD)[49-50]. The development of the brain is a very complex process that occurs in a spatial and temporal sequence that is carefully controlled by biochemical, structural, as well as neurophysiological events. Even subtle changes in these parameters can produce ultimate changes in brain function that may vary from subtle alteration in behavior and learning to autism, attention deficit disorder and violence dyscontrol[51-53]. Experiments in which infant animals were exposed to monosodium glutamate (MSG), have demonstrated significant neurobehavioral deficits[54-55]. Other studies have shown that when pregnant female animals were fed MSG, their offspring demonstrated normal simple learning but showed significant deficits in complex learning, accompanied by profound reductions in several forebrain neurotransmitters[56-57]. In human this would mean that during infancy and early adolescence learning would appear normal, but with entry into a more advance education level, learning would be significantly impaired. Kubo and co-workers found that neonatal glutamate could severely injure hippocampal CA1 and CA3 neurons and dendrites and, as a result, impair discriminative learning in rats[58]. It is also important to note that neonatal exposure to MSG has been shown to cause significant alterations in neuroendocrine function that can be prolonged[59-60]. By acting on the hypothalamus and its connections to the remainder of the limbic connections, excitotoxins can profoundly affect behavior.

GLUTAMATE AND NEURODEGENERATION

Glutamate is of particular interest to neurologists because of its possible involvement in acute or chronic neurodegenerative processes. A low concentration of glutamate applied to neurons in culture kills the cells and the finding in the 1970s that glutamate given orally produces neurodegeneration *in vivo* caused considerable alarm, because of the widespread use of glutamate as a 'taste-enhancing' food additive. The 'Chinese restaurant syndrome'- an acute attack of neck stiffness and chest pain is well known, but so far the possibility of more serious neurotoxicity from dietary glutamate is only hypothetical. Local injection of KA is used experimentally to produce neurotoxic lesions. It acts by excitation of local glutamate-releasing neurons and the release of glutamate, acting on NMDA and also mGluRs leading to neuronal death. Ca^{2+} overload is the essential factor in excitotoxicity. Glutamate and Ca^{2+} are arguably the two most ubiquitous chemical signals, extracellular and intracellular respectively, underlying brain function, so it is disconcerting that such cytotoxic mayhem can be unleashed when they get out of control. Both are stored in dangerous amounts in subcellular organelles, like hand-grenades in an ammunition store. Defense against excitotoxicity is clearly essential if our brains are to have any chance of staying alive. Mitochondrial energy metabolism provides one line of defense, and impaired mitochondrial function, by rendering neurons vulnerable to excitotoxic damage, may be a factor in various neurodegenerative conditions, including Parkinson's disease (PD). The role of excitotoxicity in ischemic brain damage is well established, and it is also believed to be a factor in other neurodegenerative diseases[61].

Ironically, glutamate and related EAAs are toxic to central neurons. Excessive activation of GluRs during stress to the brain, such as ischemia, head trauma and epileptic seizures leads to the death of central neurons. The glutamate neurotoxicity may also be involved in the geneses of various neurodegenerative diseases[18,26-28]. Thus, the GluRs are intimately involved in both the physiology and pathology of brain functions. Glutamate can be neurotoxic through an agonist effect on NMDA, AMPA, KA or Group I metabotropic receptors. The relative contribution of these different classes of receptor varies according to the neurons involved and a variety of

other circumstances. Selective neuronal death subsequent to status epilepticus appears to be highly dependent on NMDA receptor activation. Acute neuronal degeneration after transient global or focal cerebral ischemia seems to be dependent on both NMDA and AMPA receptors.

ENDOGENOUS GLUTAMATE AND ACUTE NEUROTOXICITY

Although glutamate-induced cell death is associated with both apoptic and necrotic changes, the mechanism of cell death remains to be established. Two distinct pathways for glutamate-induced cell death have been described: the excitotoxic pathway and the oxidative pathway. The excitotoxic pathway involves the over activation of GluRs that leads to both acute and delayed forms cytotoxic events[18-20]. NMDAR activation or neuronal increases in Ca^{2+} subsequent to sodium, or both can activate a series of enzymes, including PKC, Phopholipases (PLs), proteases, protein phosphatases, and nitric oxide synthase (NOS)[13,62,63] that may be detrimental to cell viability. The acute form of neurotoxicity is characterized by neuronal swelling in the presence of agonist, which leads to osmotic lysis of the neurons, and can be prevented by eliminating from the culture medium sodium or chloride ions, two ions responsible for the massive influx of water when glutamate-gated cation channels are open.

Glutamate acting on AMPA, NMDA and probably also mGluR1 receptors is thought to play an important role in cell death subsequent to status epilepticus, cerebral ischemia, perinatal asphyxia and traumatic brain injury. When the stress is severe, it leads to necrotic cell death; when it is less severe, apoptosis may be the consequence. The primary mechanism involved is ionic disequilibrium related to the excessive entry of Na^{+} and Ca^{2+} through ligand-gated and voltage-sensitive channels. Raised i[Ca^{2+}] activates various enzymes (e.g., proteases, PLs, NOS or endonucleases) that contribute to cell death by various mechanisms[28]. There is a complex interaction between the ionic changes, altered energy metabolism with poisoning of mitochondria and oxidative or free radical–mediated damage[64]. The role of the ligand-gated channels can be shown by using selective antagonists; thus NMDA receptor antagonists of all types (glutamate receptor competitive antagonists, glycine site competitive antagonists, open channel blockers and selective antagonists acting preferentially on a polyamine site or on the NR2B subunit of the NMDA receptor) protect against ischemic brain damage[65]. NMDA receptors have different subunit composition according to their site of expression. Receptors with NR2B subunits are expressed particularly on GABAergic interneurons, so that antagonists acting selectively on these NMDA receptors may have effects differing from those of antagonists acting on NMDAI/NR2A receptors.

ENDOGENOUS GLUTAMATE AND CHRONIC NEURODEGENERATION

In contrast, delayed neuronal degeneration caused by NMDA and in most cases, KA agonists is Ca^{2+}-dependent and transpires over several hours after a brief exposure to a high concentration of agonist or prolonged exposure to a low concentration of agonist. The GluR-mediated sustained elevation in i[Ca^{2+}] is assumed to set various cascades of pathobiochemical processes in motion leading to neuronal degeneration involving a number of different pathways that cause oxidative stress and degeneration[18-20]. The oxidative pathway involves breakdown of the glutamate-cystine antiporter and a drop in glutathione levels which allows for aberrant formation of neurotoxic reactive oxygen species (ROS). With a diminishing supply of GSH, there is an accumulation of excessive amounts of ROS and ultimately cell death. Understanding the relationship between glutathione (GSH) depletion and ROS production should lead to a better understanding of all forms of programmed cell death in which ROS play a central role. PLs capable of breaking down the cell membrane and liberating arachidonic acid (AA) are activated by glutamate[32]. AA metabolism, by cellular oxidases, generates ROS, resulting in the degradation of lipid membranes[66]. The influx of extracellular Ca^{2+}, augmented by release from intracellular i[Ca^{2+}] stores, may act via a positive feedback mechanism to enhance synaptic efficacy and neuronal excitability, causing further release of glutamate[67]. It has been proposed that neurodegeneration in a variety of late onset neurological disorders are at least partially dependent on endogenous glutamate activating NMDA or AMPA receptors. These include motor neuron disease, Huntington's disease, PD and AD.

The evidence that AMPA receptors on spinal motorneurons are involved in motor neuron disease (amyotrophic lateral sclerosis)[68-69]. There appears to be a reduction in the expression of GLT-1, a glial glutamate transporter, in the spinal cord and brain regions showing loss of motoneurons[70]. In organotypic cultures of spinal cord, glutamate transport inhibitors cause degeneration of motorneurons. This can be prevented by AMPA receptor antagonists such as GYKI 52466[71-72]. Huntington's disease (HD) may involve a primary metabolic or mitochondrial defect that causes striatal neurons to become vulnerable to excitotoxic effects of NMDA receptor activation.

THE FREE RADICAL CONNECTION

Glutamate toxicity is a major contributor to pathological cell death within the nervous system and appears to be mediated by ROS[16]. There are two forms of glutamate toxicity: receptor-initiated excitotoxicity[18] and non-receptor-mediated oxidative glutamate toxicity[73]. Oxidative glutamate toxicity is initiated by high concentration of extracellular glutamate that prevent cystine uptake into the cells, followed by the depletion of intracellular cystine and the loss of GSH. With a diminishing supply of GSH, there is an accumulation of excessive amounts of ROS and ultimately cell death. Understanding the relationship between GSH depletion and ROS production should lead to a better understanding of all forms of programmed cell death in which ROS play a central role. Oxidative glutamate toxicity has been observed in primary neuronal cell cultures[73-74] and tissue slices[75] and has been studied recently in the immortalized mouse hippocampal cell line, HT22[76]. In HT22 cells, glutamate induces a form of programmed cell death with characteristics of both apoptosis and necrosis. The exposure of HT22 cells, cortical neurons and neuroblastoma cells to glutamate results in the rapid depletion of GSH followed by an increase in ROS. The assumption has been that the increase in ROS is a direct result of this GSH depletion, but the functional relationship between the two has not been defined. There are two phases of ROS formation after exposure to glutamate: an early 5-10 fold increase coupled to GSH depletion and a later 200-400 fold increase derived from mitochondria[77]. Early gene activation and caspase activity are required for both maximal ROS production a subsequent cell death.

It is now known that glutamate acts on its receptor via a nitric oxide (NO) mechanism[78]. Overstimulation of the GluRs can produce an accumulation of reactive nitrogen species, resulting in the generation of several species of dangerous free radicals, including peroxynitrite. There is growing evidence that, at least in part, this is how excess glutamate damages nerve cells[79]. In a multitude of studies, a close link has been demonstrated between excitotoxicity and free radical generation[80-83]. Again, it should be realized that excessive glutamate stimulation triggers a chain of events that in turn sparks the generation of large numbers of free radical species, both as nitrogen and oxygen species. These free radicals have been shown to damage cellular proteins (protein carbonyl products) and DNA. The most immediate DNA damage is to the mitochondrial DNA, which controls protein expression within that particular cell and its progeny, producing rather profound changes in cellular energy production. It is suspected that at least some of the neurodegenerative diseases, PD in particular, are affected in this way[84]. Chronic free radical accumulation would result in an impaired functional reserve of antioxidant vitamins/minerals and enzymes, and thiol compounds necessary for neural protection. Chronic unrelieved stress, chronic infection, free radical generating metals and toxins, and impaired DNA repair enzymes all add to this damage[85].

CONCLUSION

As our knowledge of the pathophysiology and biochemistry of the neurodegenerative diseases increases, the connection to excitotoxicity has become stonger[94]. This is especially so with the interrelationship between excitotoxicity and free radical generation

and declining energy production with aging. Several factors of aging have been shown to magnify this process. For example, as the brain ages its iron content increases, making it more susceptible to free radical generation. Also, aging changes in the blood brain barrier, micovascular changes leading to impaired blood flow, free radical mitochondrial injury to energy generating enzymes, DNA adduct formation, alterations in glucose and glutamate transporters and free radical and lipid peroxidation induced alterations in the neuronal membranes all act to make the aging brain increasingly susceptible to excitotoxic injury. Over a lifetime of free radical injury due to chronic stress, infections, trauma, impaired blood flow, hypoglycemia, hypoxia and poor antioxidant defenses secondary to poor nutritional intake, the nervous system is significantly weakened and made more susceptible to further excitotoxic injury. We had known that a loss of neuronal energy generation is one of the early changes seen with the neurodegenerative diseases. This occurs long before clinical disease develops. But, even earlier is a loss of neuronal glutathione functional levels.

Our knowledge of this process opens up new avenues for treatment as well as prevention of excitotoxic injury to the nervous system. For example, there are many nutritional ways to improve CNS antioxidant defenses and boost neuronal energy generation, as well as improve membrane fluidity and receptor integrity. By using selective glutamate blocking drugs or nutrients, one may be able to alter some of the more devastating effects of PD. For example, there is evidence that dopamine deficiency causes a disinhibition (overactivity) of the subthalamic nucleus and that this may result in excitotoxic injury to the substantia nigra[95]. By blocking the glutamatergic neurons in this nucleus, one may be able to reduce this damage. There is also evidence that several nutrients can significantly reduce excitotoxicity. For example, combinations of coenzyme Q10 and niacinamide have been shown to protect against striatal excitotoxic lesions. Methylcobolamine, phosphotidylserine, picnogenol and acetyl L-carnitine all protect against excitotoxicity as well. Of particular concern is the toxic effect of these excitotoxic compounds on the developing brain. It is well recognized that the immature brain is four times more sensitive to the toxic effects of the EAAs as is the mature brain. This means that excitotoxic injury is of special concern from the fetal stage to adolescence. There is evidence that the placenta concentrates several of these toxic amino acids on the fetal side of the placenta. Consumption of aspartame and MSG containing products by pregnant women during this critical period of brain formation is of special concern and should be discouraged. Many of the effects, such as endocrine dysfunction and complex learning, are subtle and may not appear until the child is older. Other hypothalamic syndromes associated with early excitotoxic lesions include immune alterations and violence dyscontrol. The prospects for identifying novel therapeutic agents acting on glutamatergic transmission that are effective in the conditions described above are now exceptionally good.

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