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REVIEW ARTICLE

Excitotoxic and Excitoprotective Mechanisms

Abundant Targets for the Prevention and Treatment of Neurodegenerative Disorders

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Abstract

Activation of glutamate receptors can trigger the death of neurons and some types of glial cells, particularly when the cells are coincidentally subjected to adverse conditions such as reduced levels of oxygen or glucose, increased levels of oxidative stress, exposure to toxins or other pathogenic agents, or a disease-causing genetic mutation. Such excitotoxic cell death involves excessive calcium influx and release from internal organelles, oxyradical production, and engagement of programmed cell death (apoptosis) cascades. Apoptotic proteins such as p53, Bax, and Par-4 induce mitochondrial membrane permeability changes resulting in the release of cytochrome c and the activation of proteases, such as caspase-3. Events occurring at several subcellular sites, including the plasma membrane, endoplasmic reticulum, mitochondria and nucleus play important roles in excitotoxicity. Excitotoxic cascades are initiated in postsynaptic dendrites and may either cause local degeneration or plasticity of those synapses, or may propagate the signals to the cell body resulting in cell death. Cells possess an array of anti-excitotoxic mechanisms including neurotrophic signaling pathways, intrinsic stress-response pathways, and survival proteins such as protein chaperones, calcium-binding proteins, and inhibitor of apoptosis proteins. Considerable evidence supports roles for excitotoxicity in acute disorders such as epileptic seizures, stroke and traumatic brain and spinal cord injury, as well as in chronic age-related disorders such as Alzheimer's, Parkinson's, and Huntington's disease and amyotrophic lateral sclerosis. A better understanding of the excitotoxic process is not only leading to the development of novel therapeutic approaches for neurodegenerative disorders, but also to unexpected insight into mechanisms of synaptic plasticity.

Index Entries: Alzheimer's disease; apoptosis; calcium; glutamate; Huntington's disease; mitochondria; neurotrophic factor; oxidative stress; Parkinson's disease; stroke.

Introduction

The purpose of this article is: 1) to provide a brief review of the current understanding of how, in certain physiological and pathological settings, excessive activation of glutamate receptors causes the death of neurons; 2) to describe several different anti-excitotoxic mechanisms that cells in the nervous system are capable of deploying; 3) to consider the evidence supporting a major role for excitotoxic cascades in the pathogenesis of acute and chronic neurodegenerative disorders; and 4) to consider different approaches for preventing excitotoxicity without compromising the normal functions of glutamatergic neuronal circuits. This article is not intended to be comprehensive and often draws upon findings from my own laboratory to illustrate a particular point.

The process of glutamate-mediated neuronal death, now called excitotoxicity, was discovered more than three decades ago (Olney, 1969). Cell culture studies have shown that glutamate can kill many different types of mammalian central nervous system (CNS) neurons in a concentration-dependent, receptor-mediated manner. The identification of natural excitotoxins such as kainic acid and domoic acid, and the development of analogs of glutamate that act as either agonists (e.g., NMDA and AMPA) or antagonists (e.g., APV and CNQX) of specific subtypes of glutamate receptor provided tools that have been used to demonstrate roles for activation of glutamate receptors in various models of neurodegenerative disorders including stroke (Dirnagl et al., 1999), traumatic brain and spinal cord injury (Hayes et al., 1992), Alzheimer's disease (AD) (Mattson, 1997), Parkinson's disease (PD) (Sonsalla et al., 1998), Huntington's disease (HD) (Sieradzan and Mann, 2001), and amyotrophic lateral sclerosis (ALS) (Ludolph et al., 2000). The cloning and molecular characterization of the various types of glutamate receptor proteins (Michaelis, 1998), combined with advances in technologies for electrophysiological evaluation of ion channel functions (Sommer et al., 1992) and measurements of intracellular calcium levels (Lipscombe et al., 1988; Mattson et al., 1989) and reactive oxygen species (ROS) (Cheng and Mattson, 1995; Dugan et al., 1995), has led to major advances in our understanding of mechanisms by which glutamate regulates developmental (Mattson et al., 1988) and synaptic (Kullman et al., 2000) plasticity, as well its roles in the pathogenesis of an array of neurological disorders (Doble, 1999).

Excitotoxic Cascades

As studies of excitotoxic cell death have progressed, the molecular complexity of the process has become apparent. The cascades of events triggered by glutamate receptor activation, that ultimately result in cell death, involve changes in different subcellular compartments including the cytosol, mitochondria, endoplasmic reticulum (ER), and nucleus. I have organized the description of the excitotoxic process that follows into events that have clearly been shown to be pivotal in the cell death process.

Calcium

The opening of ionotropic glutamate receptors, and the consequent influx of Na^+ and Ca^{2+}, are the first steps in the excitotoxic process. Activation of glutamate receptors results in an increase in the concentration of cytoplasmic Ca^{2+} as the result of Ca^{2+} influx through α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate (AMPA) and *N*-methyl-D-aspartate (NMDA) receptor channels, and through voltage-dependent Ca^{2+} channels (VDCC) (Fig. 1). In addition, activation of metabotropic glutamate receptors stimulates the release of Ca^{2+} from the ER. Depending upon the particular type of neuron, its developmental stage, and various environmental factors, AMPA/kainate and NMDA receptors may mediate calcium influx and excitotoxicity. For example, NMDA receptor antagonists are very effective in protecting cultured rat hippocampal neurons against excitotoxciity (Wang et al., 1994; Mattson et al., 1995), but are less effective in protecting motor neurons in organotypic spinal cord cultures (Saroff et al., 2000). By buffering intracellular Ca^{2+} loads, calcium-binding proteins such as calbindin may serve as endogenous anti-exctitoxic proteins (Mattson et al., 1991). Antagonists of voltage-dependent Ca^{2+} channels are reported to have been effective in protecting several different types of neurons against excitotoxicity, including hippocampal pyramidal and cortical neurons (Weiss et al., 1990; Blanc et al., 1998). An important role for Ca^{2+} release from the ER in excitotoxicity has been demonstrated in studies showing that blockers of the two different types

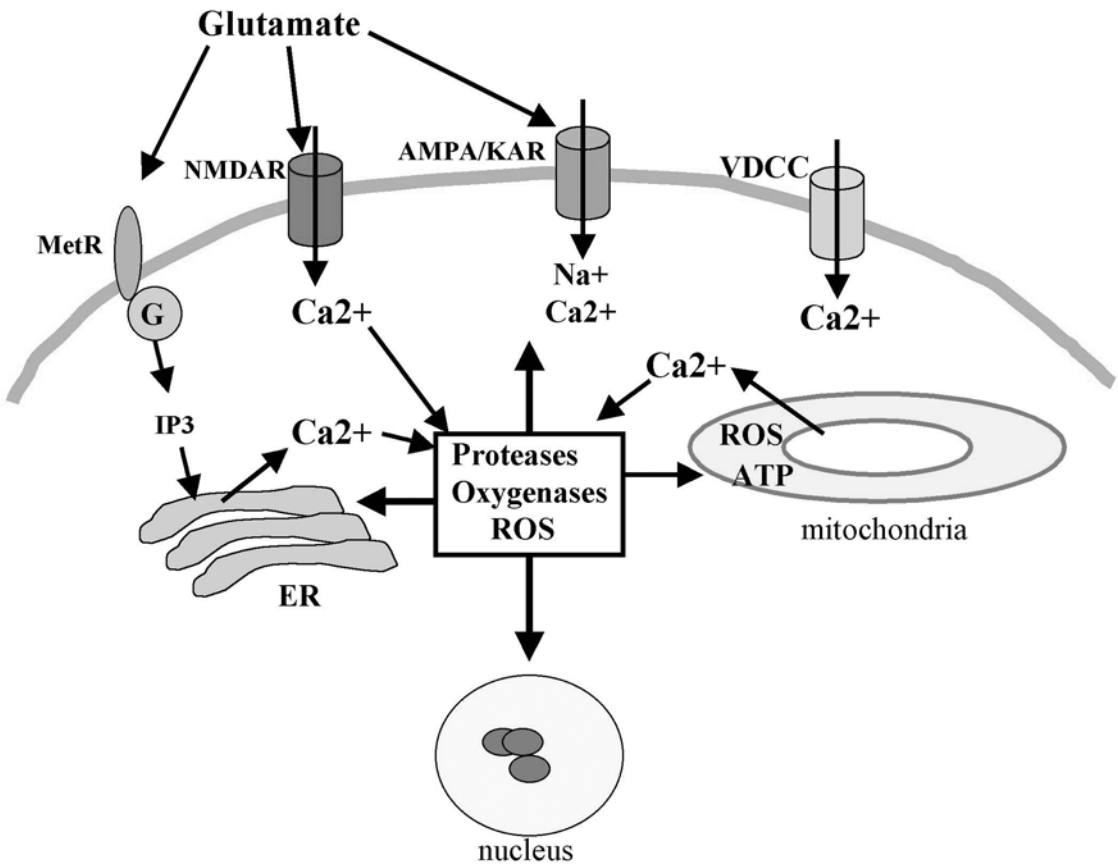

Fig. 1. Mechanisms whereby glutamate increases cytoplasmic Ca^{2+} concentrations, and modulation by endoplasmic reticulum (ER) and mitochondria. Binding of glutamate to AMPA receptors and kainate receptors (KAR) opens the receptor channels resulting in Na^{+} influx and consequent membrane depolarization and opening of voltage-dependent Ca^{2+} channels (VDCC). Some forms of AMPA receptor are also permeable to Ca^{2+}. Binding of glutamate to NMDA receptors under depolarizing conditions opens the NMDA receptor channel resulting in large amounts of Ca^{2+} influx. Activation of metabotropic glutamate receptors (MetR) induces IP3 production and activation of IP3 receptor channels in the ER membrane resulting in release of Ca^{2+} from the ER into the cytoplasm. The increases in cytoplasmic Ca^{2+} levels in response to glutamate receptor activation can induce Ca^{2+} uptake into the mitochondria which, if excessive, can induce the production of reactive oxygen species (ROS) and inhibit ATP production. By activating proteases and inducing oxidative stress, Ca^{2+} is a key mediator of excitotoxic cell death.

of ER Ca^{2+} channels, IP_3 receptors and ryanodine receptors, can protect neurons against excitotoxic injury (Frandsen and Schousboe, 1991; Mattson et al., 2000). Finally, it is now well-established that mitochondria play important roles in the regulation of neuronal calcium homeostasis (Werth and Thayer, 1994), and it has been shown that genetic and pharmacological manipulations that enhance mitochondrial calcium sequestration can protect neurons against excitotoxicity (Bruce-Keller et al., 1998; Nicholls et al., 1999; Duchen, 2000).

How does Ca^{2+} kill neurons? Considerable evidence for several different, cross-amplifying, cascades has been obtained (Fig. 1). First, Ca^{2+} activates cysteine proteases called calpains that degrade a variety of substrates including cytoskeletal proteins, membrane receptors, and metabolic enzymes (Bi et al., 1996; Caba et al., 2002; Guttmann et al., 2002). Calpains may also play an important role in the triggering of apoptotic cascades by virtue of their ability to activate caspases (Leist et al., 1997; Volbracht et al., 2001). Second, Ca^{2+} induces oxidative stress.

This occurs through several different mechanisms, including activation oxygenases such as those in the arachidonic acid metabolism cascade (Goodman et al., 1994), perturbation of mitochondrial calcium and energy metabolism (Sengpiel et al., 1998), and induction of membrane lipid peroxidation (Goodman et al., 1996). The reactive oxygen species (ROS) generated in response to glutamate-induced Ca^{2+} influx include superoxide anion radical, hydrogen peroxide, hydroxyl radical, and peroxynitrite (Culcasi et al., 1994; Mattson et al., 1995; Dawson and Dawson, 1998; Sengpiel et al., 1998; Yu et al., 1998). Third, Ca^{2+} triggers apoptosis, a form of programmed cell death (Ankarcrona, 1998). This might occur by Ca^{2+}-mediated induction/activation of pro-apoptotic proteins such as Bax, Par-4, and p53 leading to mitochondrial membrane permeability changes, release of cytochrome c and caspase activation (Duan et al., 1999; Culmsee et al., 2001; Dargusch et al., 2001).

Oxidative Stress

Numerous studies have documented increased oxidative stress in neurons subjected to excitotoxic insults in various in vitro and in vivo models. For example, cultured hippocampal, cortical, and cerebellar neurons exhibit increased levels of superoxide and hydrogen peroxide when exposed to excitotoxic concentrations of glutamate or NMDA (Lafon-Cazal et al., 1993; Gunasekar et al., 1995; Mattson et al., 1995; Vergun et al., 2001). Hydrogen peroxide can be converted to hydroxyl radical in the Fenton reaction upon interaction with Fe^{2+} or Cu^{+}; hydroxyl radical is a highly reactive free radical and potent inducer of membrane lipid peroxidation (Fig. 2). Microglial cells and some neurons produce nitric oxide in response to glutamate receptor activation; nitric oxide can react with superoxide to produce peroxynitrite which can damage membranes and proteins (Fig. 2). ROS can also damage DNA and RNA, and may thereby impair gene expression and, if severe enough, trigger apoptosis.

While oxidative stress may contribute to the excitotoxic process downstream of glutamate receptor activation, it can also render neurons vulnerable to excitotoxicity. Many studies have shown that neurons are more readily killed by glutamate when they are under conditions of increased oxidative stress. Oxidative stress, and membrane lipid peroxidation in particular, impairs the function of key proteins involved in the maintenance of cellular calcium homeostasis. For example, membrane lipid peroxidation resulting from exposure to Fe^{2+} or amyloid β-peptide impairs the activities of the plasma membrane Na^{+}/K^{+}-ATPase, Ca^{2+}-ATPase, and glucose transporter (Mark et al., 1995a, 1997a, 1997b). The latter effects of membrane lipid peroxidation result in a destabilization of Ca^{2+} homeostasis resulting in large, sustained increases of the intracellular Ca^{2+} concentration following activation of glutamate receptors. Impairment of the Na^{+}/K^{+}-ATPase results in membrane depolarization and enhanced opening of NMDA receptors. The pro-excitotoxic effects of oxidative stress are particularly pronounced in synaptic terminals (Keller et al., 1997). In addition to disrupting membrane transporter functions in neurons, oxidative stress can impair glutamate transporter function in astrocytes (Blanc et al., 1998), which would promote excitotoxicity as a result of increased concentrations of extracellular glutamate. Data suggest that the mechanism whereby lipid peroxidation promotes excitotoxicity involves the nonenzymatic production of a lipid-derived aldehyde called 4-hydroxynonenal. By covalently modifying transporter proteins on cysteine, lysine and/or histidine residues, 4-hydroxynonenal may directly compromise protein function and can also cause protein cross-linking (Mark et al., 1997a, 1997b; Blanc et al., 1998). 4-hydroxynonenal may also exacerbate Ca^{2+} influx through voltage-dependent channels, apparently by an indirect mechanism involving inhibition of a protein phosphatase and a consequent increase in the phosphorylation of Ca^{2+} channel proteins (Lu et al., 2002). Nitric oxide and other ROS may also disrupt neuronal calcium homeostasis independent of lipid peroxidation (Brorson et al., 1997). Because most neurodegenerative disorders are associated with increased oxidative stress due to age-related processes or tissue damage, it is likely that overactivation of glutamate receptors contributes to the deaths of many neurons in these disorders.

A critical role for oxidative stress in excitotoxicity has been demonstrated in various cell culture and in vivo models. Treatment of cultured neurons with antioxidants such as vitamin E, estrogens, lipoic acid, and cell-permeant forms of glutathione protects them against glutamate toxicity and ischemia-like conditions (Goodman et al., 1996; Muller and Krieglstein, 1995; Wolz and Krieglstein, 1996; Mark

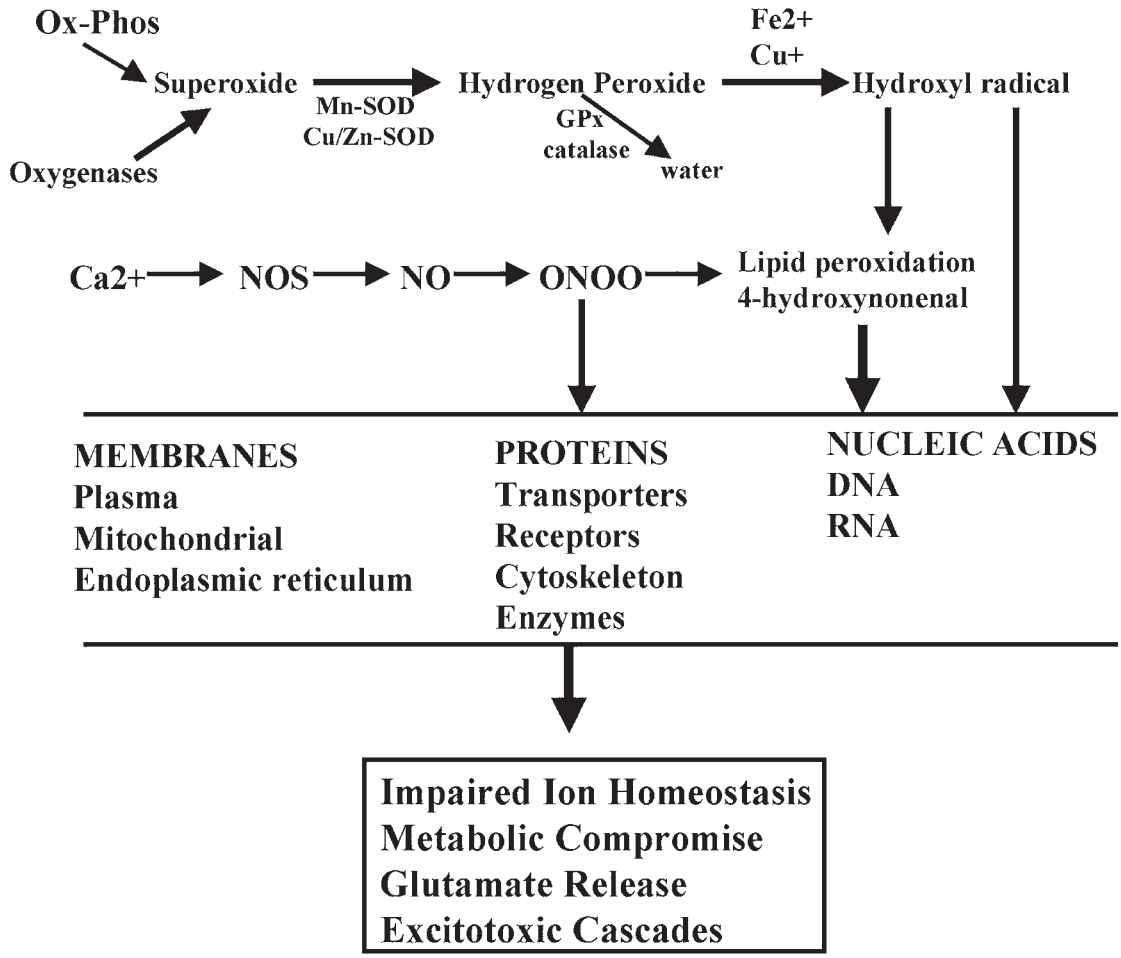

Fig. 2. Roles of oxidative stress in excitotoxicity. A major source of reactive oxygen species includes mitochondrial oxidative phosphorylation (Ox-Phos) which generates superoxide. By activating certain oxygenases Ca^{2+} can induce superoxide production. Superoxide is converted to hydrogen peroxide by the action of Mn- and Cu/Zn-superoxide dismutases (SOD). In the presence of Fe^{2+} and Cu^{+}, hydrogen peroxide is converted to hydroxyl radical, a potent inducer of membrane lipid peroxidation. Ca^{2+} can also promote ROS production by activating nitric oxide synthase (NOS) resulting in the production of nitric oxide (NO); NO interacts with superoxide to generate peroxynitrite (ONOO), a potent inducer of lipid peroxidation. Lipid peroxidation generates the cytotoxic aldehyde 4-hydroxynonenal, which covalently modifies and thereby impairs the function of membrane ion-motive ATPases, and glutamate and glucose transporters. ROS, particularly hydroxyl radical and peroxynitrite, can also directly damage proteins, lipids, and nucleic acids resulting in impairment of the functions of those molecules, thus executing the excitotoxic process.

et al., 1997a). Manipulations of the expression of genes that encode antioxidant enzymes or proteins involved in the generation of ROS have provided strong evidence that oxidative stress is involved in excitotoxic injury in vivo. Neurons in the brains of mice lacking inducible nitric oxide synthase exhibit increased resistance to ischemic and excitotoxic injury (Dawson et al., 1996). Overexpression of Cu/Zn (Chan et al., 1990) and manganese (Keller et al., 1998) superoxide dismutases in transgenic mice increases the resistance of hippocampal and cortical neurons to ischemic/excitotoxic death.

While oxidative stress can increase the vulnerability of neurons to excitotoxicity by the mechanisms described above, certain actions of ROS may be excitoprotective. For example, data suggest that NMDA receptors possess a redox modulatory site which, when oxidized, reduces channel activity (Aizenman et al., 1990; Lipton et al., 1993). Moreover, low levels of oxidative stress can stimulate the expression of genes encoding cytoprotective proteins including antioxidant enzymes, heat-shock proteins, and proteins such as Bcl-2, and inhibitor of apoptosis proteins (IAPs) that antagonize apoptotic cascades. More information on such "preconditioning" anti-excitotoxic mechanisms can be found in the section on excitoprotective mechanisms below.

Metabolic Compromise

Large amounts of ATP are required for the function of ion-motive ATPases that maintain transmembrane ion gradients under resting conditions and restore the gradients following activation of glutamate receptors. These ATPases are a major energy drain in neurons, and overactivation of glutamate receptors can therefore deplete energy reserves in neurons (Khodorov et al., 1996). In addition to the increased energy demands resulting from glutamate receptor activation, the excitotoxic process is characterized by impairment of mitochondrial function which manifests as membrane depolarization, calcium uptake, and reduced ATP production (Mattson et al., 1995). Neurons are exquisitely sensitive to excitotoxicity when they are subjected to conditions of reduced energy availability such as hypoglycemia and ischemia (Novelli et al., 1988). Indeed, glutamate receptor antagonists can prevent the death of neurons under such conditions of reduced energy availability (Nellgard and Wieloch, 1992). Certain pharmacological agents that promote the maintenance of ATP levels can protect neurons against excitotoxicity, with creatine being a prototypical example (Brustovetsky et al., 2001).

DNA Damage

DNA damage, such as occurs under conditions of oxidative stress or exposure to genotoxic agents, can render neurons vulnerable to excitotoxicity. DNA damage can stimulate the activation of poly (ADP-ribose) polymerase (PARP) which normally plays a role in the DNA repair process (Decker and Muller, 2002). However, PARP activity may lead to the depletion of nicotine adenine dinucleotide (NAD) and hence ATP depletion, thereby increasing the vulnerability of neuron to excitotoxicity. Overactivation of glutamate receptors may itself cause DNA damage, which likely results from calcium influx and oxyradical production (Didier et al., 1996). DNA damage can, in turn, induce the production and activation of a protein called p53 which can trigger apoptosis (Chen and Chuang, 1999; Kruman et al., 2000).

Apoptosis

The programmed death of neurons during development of the nervous system involves a regulated process called apoptosis. Cells undergoing apoptosis exhibit characteristic morphological changes including cell body shrinkage, the formation of cell surface membrane blebs, and nuclear chromatin condensation and fragmentation. During the process of apoptosis, the plasma and organellar membranes retain their integrity; this contrasts with a form of death called necrosis in which the cells swell and membranes lyse. Early evidence that excitotoxic neuronal death may occur by apoptosis was based upon characteristic morphological evidence (Ankarcrona et al., 1995). Studies in an array of organisms and cell types have revealed several key steps in apoptosis. In most cases of apoptosis, the death process involves pivotal mitochondrial changes (Kroemer et al., 1997), including increased membrane permeability and release of cytochrome c (Fig. 3). The mitochondrial changes are triggered by the actions of several different proteins such as Bax and Par-4 which can cause mitochondrial membrane permeability by directly interacting with the membrane or by indirect actions (Guo et al., 1998; Duan et al., 1999). Changes downstream of the mitochondrial changes that are believed to execute the cell death process include the formation of a protein complex called the apoptosome which consists of cytochrome c, Apaf-1, and caspase-9. Caspase-9 is activated, and in turn, cleaves and activates caspase-3, the latter caspase being a key player in the excitotoxic cell death process in many cases (Du et al., 1997; Mattson et al., 1998).

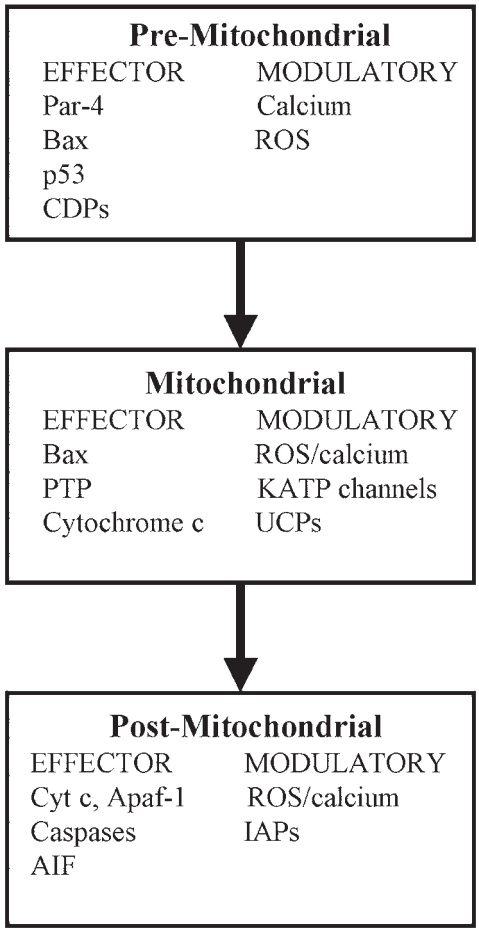

Fig. 3. Three key phases in the process of excitotoxic apoptosis. Overactivation of glutamate receptors triggers the production and/or activation of pro-apoptotic proteins including prostate apoptosis response-4 (Par-4), p53, Bax, and calcium-dependent proteases (CDPs). Such proteins promote mitochondrial membrane permeability changes resulting in the opening of permeability transition pores (PTP) and the release of cytochrome c. Mitochondrial apoptotic changes can be facilitated or inhibited by calcium, ROS, ATP-sensitive K^+ channels (KATP), and uncoupling proteins (UCP). Cytochrome c is released from mitochondria and forms a complex with Apaf-1 and caspase-9 resulting in the activation of caspase-3. In addition, apoptosis-inducing factor (AIF) may be released from mitochondria and then translocates to the nucleus where it induces nuclear chromatin condensation and fragmentation. Postmitochondrial apoptotic events can be modulated by ROS which facilitate the effector phase of cell death, and by inhibitor of apoptosis proteins (IAPs) which directly inhibit caspases.

Synaptic and Dendritic Pruning

Because glutamate receptors are concentrated in dendrites and are present at lower levels or absent from the cell body and axon, excitotoxic neuronal death is characterized by degeneration of dendrites with relative sparing of axons (Swann et al., 2000). This compartmentalization of the excitotoxic injury is manifest in neurons dying in several different neurodegenerative disorders including severe epileptic seizures, ischemic stroke, and AD (Scheibel, 1979).

Because glutamatergic synapses play fundamental roles in the processes of learning and memory, there has been intense interest in understanding the cellular and molecular events that occur in synaptic terminals which are responsible for long-term changes in synaptic strength. Several of the same changes responsible for excitotoxic cell death are known to mediate synaptic plasticity. These include calcium influx and activation of protein kinases and proteases.

Work in my laboratory has shown that apoptotic biochemical cascades can be activated in synaptic terminals and dendrites in response to glutamate receptor activation. The following apoptotic changes have been documented in synaptosome preparations and cultured hippocampal neurons: induction of Par-4 (Duan et al., 1999), mitochondrial membrane depolarization and oxyradical production (Mattson et al., 1998), and activation of caspase-3 and the release from mitochondria of a factor(s) capable of inducing nuclear chromatin condensation and fragmentation (Mattson et al., 1998). Initiation of apoptotic pathways in postsynaptic dendritic spines may propagate to more proximal regions of dendrites and the cell body, resulting in cell death (Mattson et al., 1998). Interestingly, however, apoptotic cascades can be activated reversibly and in synapses and dendrites without the neurons dying (Glazner et al., 2000). The latter findings have led us to propose that apoptotic pathways play important roles in structural remodeling and functional plasticity of synapses (Gilman and Mattson, 2002).

How might apoptotic pathways influence synaptic function? In searching for mechanisms whereby apoptotic cascades might regulate synaptic plasticity, we discovered that two subunits of the AMPA receptor are substrates of caspase-3 (Chan et al.,

1999; Glazner et al., 2000; Lu et al., 2002). Whole-cell patch-clamp analyses and calcium-imaging studies established that cleavage of the AMPA receptor subunits results in decreased ion current flow through the AMPA receptors, and a decreased calcium response to glutamate. Reversible activation of caspases in dendritic spines, in response to stimulation of glutamate receptors, would be expected to transiently reduce postsynaptic responsivity at that synapse. With respect to a possible function of caspase-mediated AMPA receptor cleavage in excitotoxic cell death, our data suggest that this action of caspases can prevent excitoxic necrosis and thereby ensure that the cell dies by apoptosis (Glazner et al., 2000; Lu et al., 2001).

Glial Cells and Excitotoxicity

Neurons are not the only cells in the nervous system that express glutamate receptors. Indeed, each of three major types of glial cells: astrocytes, oligodendrocytes, and microglia express one or more types of glutamate receptor.

Astrocytes

Astrocytes exhibit calcium response to glutamate and, interestingly, can propagate intercellular calcium waves in response to glutamate receptor activation (Haydon, 2001). Non-NMDA ionotropic (AMPA/kainate) receptors and metabotropic receptors are expressed in astrocytes, and mediate Ca^{2+} influx and release from ER, respectively (Gallo and Russell, 1995). Astrocytes are very resistant to glutamate-induced cell death (Mattson and Rychlik, 1990), but can be killed by activation of AMPA/kainate receptors under certain conditions (David et al., 1996).

Astrocytes play important roles in modifying the excitotoxic process in neurons. Several studies have shown that astrocytes can protect neurons against excitotoxicity (Rosenberg and Aizenman, 1989; Mattson and Rychlik, 1990). Astrocytes express high levels of glutamate transporter proteins and are therefore very effective in removing glutamate from extracellular compartments, including synaptic regions (Bezzi et al., 2001). In addition, astrocytes produce several different neurotrophic factors and cytokines that have been shown to affect neuronal vulnerability to excitotoxicity, including bFGF (Mattson and Rychlik, 1990) and type 1 plasminogen activator (Gabriel et al., 2003). Astrocytes are typically connected to each other by gap junctions which are channels that permit the passage of Ca^{2+}, nucleotides, and even small peptides. Studies in which gap junctional communication in astrocytes is manipulated have provided evidence that these intercellular channels can modify neuronal vulnerability to different insults (Blanc et al., 1998), although the underlying mechanism remains to be established. Although astrocytes have been shown to protect neurons against excitotoxicity, they can also release glutamate and oxyradicals that can promote excitotoxicity (McNaught and Jenner, 2000).

Oligodendrocytes

Oligodendrocytes, the myelinating cell in the central nervous system are located in white matter. Studies showed that cells in white matter are damaged in animals subjected to severe epileptic seizures (Sperk et al., 1983). Subsequent studies of cultured oligodendrocytes revealed that this type of glial cell is especially sensitive to being killed by glutamate. Glutamate kills oligodendrocytes by activating AMPA receptors resulting in excessive calcium influx (Yoshioka et al., 1996; McDonald et al., 1998; Matute et al., 2001). The damage to oligodendrocytes that occurs in AD most likely involves a glutamate receptor activation because oligodendrocytes are vulnerable to amyloid β-peptide toxicity, and because mutations in presenilin-1 that cause early-onset inherited AD increase the vulnerability of oligodendrocytes to excitotoxic death (Pak et al., 2003). It is not known whether oligodendrocytes modify the vulnerability of neurons to excitotoxicity. Because of their location in white matter, one might expect that oligodendrocytes are not in a position to modify activation of glutamate receptors which are located on dendrites of neurons. However, oligodendrocytes do produce several trophic factors that are known to modify neuronal vulnerability to excitotoxicity, including transforming growth factor-β and basic fibroblast growth factor (bFGF) (Du and Dreyfus, 2002).

Microglia

Microglia are similar, if not identical, to peripheral macrophages. They respond to tissue injury by moving to the sites of cellular damage where they produce several cytotoxic substances and can phago-

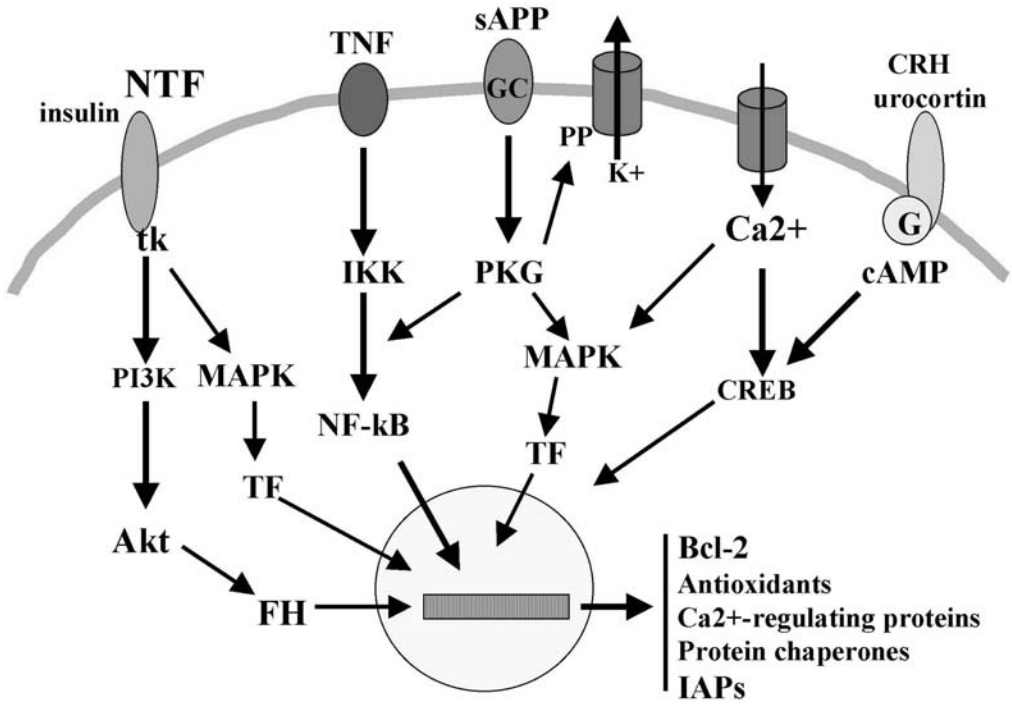

Fig. 4. Examples of excitoprotective signaling pathways. Neurotrophic factors (NTF) and hormones such as insulin activate receptor tyrosine kinases (tk) resulting in the activation of the phosphatidylinositol-3 kinase (PI3K)–Akt kinase, and mitogen-activated protein kinase (MAPK), pathways. Tumor necrosis factor (TNF) stimulates receptors coupled to the activation of IκB kinases (IKK) which, in turn, activates the transcription factor NF-κB. Secreted forms of APP (sAPP) stimulate receptors coupled to the production of cyclic GMP and the activation of cyclic GMP-dependent protein kinase (PKG). PKG phosphorylates a protein phosphatase (PP) resulting in the dephosphorylation and activation of plasma membrane K^+ channels, and a consequent membrane hyperpolarization. PKG can also induce the activation of NF-κB and MAPK. Corticotropin releasing hormone (CRH) and urocortin activate receptors coupled to adenylate cyclase and the production of cyclic AMP. Cyclic AMP can then activate the cyclic AMP-response element binding protein (CREB). Increases in the intracellular Ca^{2+} concentration can also activate, or enhance, the activation of several of these pathways including the MAPK, NF-κB, and CREB pathways. Excitoprotective genes are induced by transcription factors (TF); examples include anti-apoptotic proteins of the Bcl-2 and IAP families, antioxidant enzymes such as glutathione peroxidase and superoxide dismutases, Ca^{2+}-regulating proteins, and protein chaperones such as heat-shock proteins and glucose-regulated proteins.

cytose apoptotic cells (Stoll et al., 1998). Microglia produce ROS, including nitric oxide and superoxide (Liu et al., 2002). Data also suggests that microglia produce excitotoxins such as quinolinic acid (Espey et al., 1997). In addition to promoting excitotoxic neuronal death, microglia may promote excitotoxic death of oligodendrocytes (Tahraoui et al., 2001).

Excitoprotective Mechanisms

While neurons may undergo excitotoxic death in pathological conditions such as cerebral ischemia and epilepsy, they normally resist the calcium, oxidative, and metabolic loads induced by glutamate receptor activation. Indeed, it has become very clear that there are several different intercellular and intracellular signaling pathways that serve the function of protecting neurons against excitotoxicity (Fig. 4).

Neurotrophic Factor Signaling

Although initially discovered based on their ability to prevent developmental neuronal death (Conover and Yancopoulos, 1997), subsequent stud-

ies have shown that neurotrophic factors can also protect neurons against pathological death (Mattson, 1997). The first neurotrophic factor shown to protect neurons against excitotoxicity was bFGF (Mattson et al., 1989). Additional studies demonstrated the abilities of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-4/5, insulin-like growth factors, and platelet-derived growth factors to protect neurons against excitotoxic, metabolic, and excitotoxic insults (Cheng and Mattson, 1991, 1992, 1994, 1995; Cheng et al., 1994a). Certain cytokines can also protect neurons against excitotoxicity, including tumor necrosis factor (TNF) and TGFβ (Cheng et al., 1994b; Bruce et al., 1996; Gary et al., 1998). In addition, novel excitoprotective factors have been discovered including secreted forms of β-amyloid precursor protein (sAPP) (Mattson et al., 1993; Furukawa et al., 1996) and activity-dependent neurotrophic factor (Glazner and Mattson, 1999). Activation of integrin receptors by extracellular cell adhesion molecules can protect neurons against excitotoxicity by a mechanism involving integrin-linked kinase and Akt kinase (Gary and Mattson, 2001; Gary et al., 2003). In several instances in vivo studies have confirmed excitoprotective actions of specific ligands. For example, administration of bFGF, TGFβ, and sAPP reduced ischemic neuronal death in rodent stroke models (Prehn et al., 1993; Koketsu et al., 1994; Smith-Swintosky et al., 1994). Traumatic spinal cord injury was reduced and functional outcome improved in rats administered bFGF (Rabchevsky et al., 2000).

Where studied, each of the excitoprotective factors stabilized cellular Ca^{2+} homeostasis such that glutamate-induced elevation of intracellular Ca^{2+} concentration was reduced (Mattson et al., 1989; Cheng and Mattson, 1991, 1992; Mattson et al., 1993; Cheng et al., 1995). Excitoprotective factors may also suppress oxidative stress and preserve mitochondrial function (Mattson et al., 1993). In several cases, the signal transduction pathways that mediate excitoprotection have been identified (Fig. 4). Activation of bFGF receptors results in tyrosine phosphorylation of the receptors and activation of kinases such as mitogen-activated protein (MAP) kinases that phosphorylate transcription factors. Some of the genes known to be regulated by bFGF that are likely to contribute to its anti-excitotoxic action are NMDA and AMPA receptor subunits (Mattson et al., 1993; Cheng et al., 1995), antioxidant enzymes (Mattson et al., 1995), and calcium-binding proteins (Pappas and Parnavelas, 1997). In the case of BDNF, it activates receptors coupled to the phosphatidylinositol-3-kinase–Akt kinase pathway which stimulates the expression of antioxidant enzymes and anti-apoptotic Bcl-2 family members (Allsopp et al., 1995; Mattson et al., 1995). A different excitoprotective mechanism is employed by TNF. The latter cytokine activates receptors coupled to transduction proteins that activate the transcription factor NF-κB which stimulates the transcription of genes encoding several different neuroprotective proteins, including manganese superoxide dismutase, the calcium-binding protein calbindin, and Bcl-2 (Mattson and Camandola, 2001). NF-κB may also regulate the expression of certain NMDA and AMPA receptor subunits (Furukawa et al., 1998). Studies of the excitoprotective mechanism of sAPP have revealed a novel pathway involving a presumptive membrane receptor guanylate cyclase which catalyzes the production of cyclic GMP. Cyclic GMP then activates kinases and phosphatases resulting in the activation of high-conductance K^+ channels and membrane hyperpolarization (Furukawa et al., 1996). In addition, activation of the cyclic GMP pathway by sAPP results in activation of NF-κB and induction of the same neuroprotective genes induced by TNF (Barger and Mattson, 1996).

Stress Response Pathways

Pretreatment of cultured neurons with a subtoxic level of glutamate or NMDA can protect those neurons against death when subsequently exposed to an otherwise neurotoxic concentration of NMDA (Marini and Paul, 1992). A variety of other types of mild stress can also protect neurons against excitotoxic death including heat stress (Lowenstein et al., 1991), metabolic stress (Gorgias et al., 1996), and even intermittent fasting, a diet-induced stress (Bruce-Keller et al., 1999). Several different, and presumably complementary, stress-response pathways that mediate such excitoprotective "preconditioning" have been identified. NMDA-induced preconditioning in cerebellar cells has been shown to involve stimulation of BDNF production and activation of NF-κB (Marini et al., 1998; Lipsky et al., 2001). Several different stress-responsive protein chaperones have been shown to be upregulated in

neurons subjected to mild neuroprotective stressors, including heat-shock protein 70 and glucose-regulated protein 78. Studies in which levels of these protein chaperones are manipulated suggest that they play key roles in excitoprotection (Yu et al., 1999). Interestingly, increased production of BDNF and protein chaperones also play important roles in the neuroprotective effect of dietary restriction (Duan and Mattson, 1999; Yu and Mattson, 1999; Duan et al., 2001; Lee et al., 2002).

Cytoskeleton-Mediated Neuroprotection

Activation of glutamate receptors results in structural changes in the cytoskeleton of neurons. These changes include depolymerization of actin filaments and microtubules, and reorganization of dendritic spines. While such structural changes are thought to be important for adaptive modifications in the structure of neuronal circuits, they may also influence the vulnerability of neurons to excitotoxicity. Electrophysiological recordings of glutamate-induced currents and Ca^{2+} currents in cultured hippocampal neurons exposed to agents that effect the polymerization states of actin and tubulin have demonstrated roles for these cytoskeletal polymers in regulating activity of NMDA receptor channels and voltage-dependent Ca^{2+} channels (Rosenmund and Westbrook, 1993; Furukawa et al., 1995). The actin-depolymerizing agent cytochalasin D reduces currents through NMDA receptor channels and voltage-dependent Ca^{2+} channels by enhancing channel rundown, and conversely, stabilization of actin filaments with jasplakinolide reduces channel rundown (Furukawa et al., 1995). Because Ca^{2+} influx induces actin depolymerization, the latter studies suggested that actin depolymerization serves as part of an excitoprotective feedback pathway. Gelsolin is a Ca^{2+}-activated actin-severing protein. Studies of gelsolin-deficient mice have demonstrated an excitoprotective role for gelsolin, and have solidified the evidence that actin filaments regulate NMDA receptor channels and voltage-dependent Ca^{2+} channels (Furukawa et al., 1997). Not only do actin filaments regulate Ca^{2+} influx through plasma membrane channels, they regulate Ca^{2+} release from ER stores. When actin filaments in cultured hippocampal neurons are depolymerized using cytochalasin D, Ca^{2+} release from IP_3-sensitive stores is reduced (Wang et al., 2002). The molecular interactions responsible for modulation of NMDA receptors, VDCC, and IP_3 receptors by actin have not been established. Actin might directly interact with channel proteins, but it is more likely that there are actin-binding proteins that mediate the effects of actin filaments on the channels.

As for microtubules, they also modulate neuronal Ca^{2+} homeostasis and responsivity to glutamate. Calcium responses to glutamate are increased in cultured hippocampal neurons that are treated with the microtubule-depolymerizing agent colchicines (Furukawa and Mattson, 1995). Conversely, stabilization of microtubules with taxol suppresses glutamate-induced Ca^{2+} influx and protects neurons against excitotoxicity (Furukawa and Mattson, 1995). The microtubule-associated protein tau regulates microtubule polymerization. Abnormalities in tau, including hyperphosphorylation and aggregation, occur in AD and other dementing disorders. Calcium-imaging studies of cultured human neuroblastoma cells overexpressing either wild-type tau or a mutant form of tau that causes inherited fronto–temporal lobe dementia and Parkinsonism linked to chromosome 17 suggest roles for tau and microtubule polymerization state in modulating VDCC (Furukawa et al., 2003). The latter study demonstrates that mutant tau enhances Ca^{2+} influx through VDCC by a mechanism involving enhanced microtubule depolymerization.

Excitotoxicity and Neurological Disease

This section describes some of the evidence supporting a role for excitotoxicity in the pathogenesis of major neurological disorders. More in-depth information on the cellular and molecular mechanisms involved in each disorder can be found in the references cited. A general conclusion that is reached from analyses of studies of the pathogenesis of acute and chronic neurodegenerative disorders is that excitotoxicity is a convergence point in the neurodegenerative cascade of each disorder (Fig. 5).

Epileptic Seizures

Approximately 1.4 million Americans have epilepsy and the vast majority are under the age of 45 yr (http://www.epilepsyfoundation.org). In

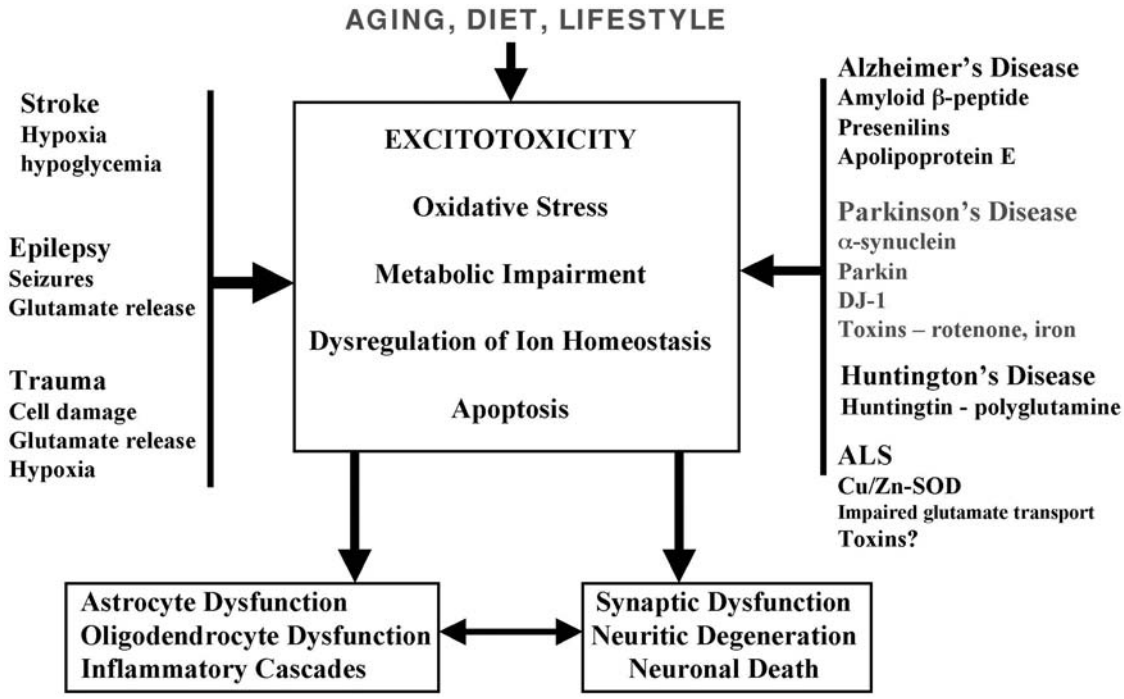

Fig. 5. Excitotoxicity is a convergence point in the neurodegenerative cascades of each of the major acute and chronic neurodegenerative disorders. The genetic and environmental factors that initiate the neurodegenerative process may differ among disorders. For example: stroke is caused by atherosclerotic occlusion of a cerebral blood vessel; Alzheimer's disease (AD) can result from mutations in the amyloid precursor protein (APP) or presenilins, or by age-related increases in oxidative and metabolic stress, resulting in increased production of neurotoxic forms of amyloid β-peptide; and Huntington's disease is caused by polyglutamine expansions in the huntingtin gene. Despite such differences in initiating factors, each disorder results in similar neurodegenerative cascades that involve increased oxidative stress, metabolic impairment, and overactivation of glutamate receptors resulting in excessive Ca^{2+} influx and excitotoxic cell-death. The aging process, dietary factors, and certain aspects of lifestyle can influence the risk of both the acute neurodegenerative conditions listed on the left and the chronic neurodegenerative disorders listed on the right.

those patients with severe and frequent seizures, degeneration of neurons occurs resulting in functional deficits that can manifest as learning and memory problems or motor dysfunction. Uncontrolled excitability of neurons, particularly those in temporal lobe structures such as the hippocampus, characterizes epilepsy. Activation of glutamate receptors is at the core of this disease, being necessary for both the seizure activity and the damage and death of neurons that occurs (for review *see* Meldrum et al., 1999; Ben-Ari and Cossart, 2000; Armijo et al., 2002). Kainate, domoate, and other kainate receptor agonists are potent inducers of seizures in rodents and humans (Cendes et al., 1995). Seizure-induced neuronal death may be exacerbated by several factors, including glucocorticoid production resulting from neuroendocrine stress responses (Elliott et al., 1993; Stein-Behrens et al., 1994). Glutamate receptor antagonists such as MK-801 and ketamine are effective in reducing seizure-induced neuronal degeneration in animal models (Sagratella, 1995; Kelsey et al., 2000). Anticonvulsant drugs that have proven effective in treating human epilepsy patients, including phenobarbital, phenytoin, and carbamazepine are effective in protecting neurons against excitotoxic injury (Fuller and Olney, 1981; Mattson and Kater, 1989), confirming the central role of glutamate receptor activation in the pathogenesis of epilepsy. In addition, by reducing Ca^{2+} influx through NMDA receptors and voltage-

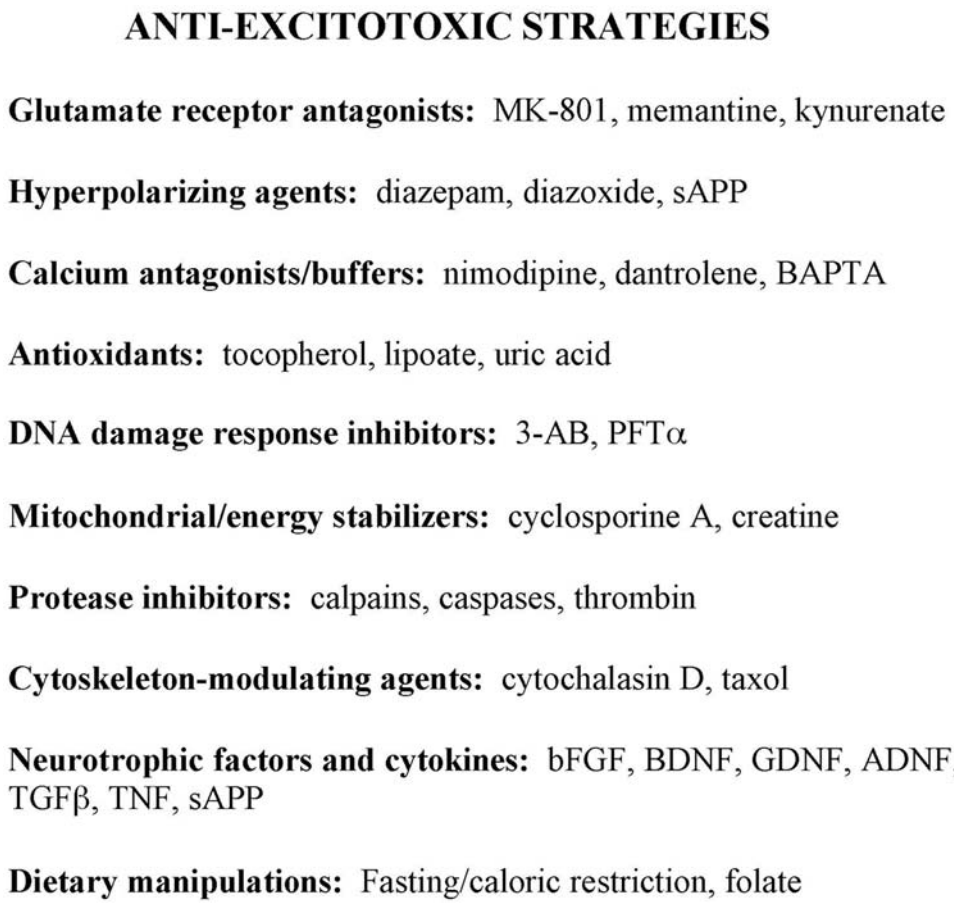

Fig. 6. Examples of anti-excitotoxic strategies.

dependent calcium channels, cytochalasin D is reported to be effective in reducing kainate-induced excitotoxic damage to hippocampal neurons in rats (Furukawa et al., 1995).

Some of the events in the excitotoxic process downstream of glutamate receptor activation, many of which are described above, have been targeted in preclinical studies (Fig. 6). Examples of approaches that have been reported to be effective in reducing excitotoxic damage in epilepsy models include: cell-permeant Ca^{2+} chelators which reduce excitotoxic and ischemic neuronal death (Tymianski et al., 1992); dantrolene, a blocker of Ca^{2+} release from the ER (Berg et al., 1995); the antioxidants vitamin E, PBN, and melatonin (Giusti et al., 1996; Milatovic et al., 2002); cyclosporine A, an inhibitor of the mitochondrial membrane permeability transition (Liu et al., 2001); FK-506, a calcineurin inhibitor and immunosuppressant (Moriwaki et al., 1998); the p53 inhibitor, PFT-α (Culmsee et al., 2001); and caspase inhibitors (Kondratyev and Gale, 2000). In addition to drugs, several dietary and behavioral manipulations have been shown to reduce seizure-induced excitotoxic damage, including an intermittent fasting dietary restriction regimen (Bruce-Keller et al., 1999), high fat ketogenic diets (Bough et al., 2002), and docosahexanoic acid (Mizota et al., 2001).

Ischemic Stroke

Stroke is the third leading cause of death with approx 200,000 stroke-related deaths per year in the United States; stroke is the leading cause of neurological disability (http://www.strokeassociation.org). The reduction in glucose and oxygen

availability to neurons supplied by the occluded/ruptured blood vessel results in a cascade of events that includes activation of glutamate receptors and Ca^{2+} influx (for review *see* Collins et al., 1989; Dirnagl et al., 1999). Blood-borne factors may also modify the ischemic/excitotoxic process (Smith-Swintosky et al., 1995). Several different glutamate receptor antagonists, including those selective for either NMDA or AMPA receptors, have been reported to be effective in reducing neuronal damage and improving functional outcome in rodent stroke models (Boxer et al., 1990; Kawasaki-Yatsugi et al., 1998; Tatlisumak et al., 1998; Akins and Atkinson, 2002). However, several clinical trials of NMDA receptor antagonists in human stroke patients failed to produce a statistically significant beneficial effect (Davis et al., 2000; Lees et al., 2000; Legos et al., 2002). While the reason(s) for the failure of glutamate receptors to show efficacy in human trials was not established, it seems unlikely that overactivation of glutamate receptors does not play a role in stroke pathogenesis in humans. Instead, it is likely that the reproducible neuroprotective effects of these drugs established in animal models wherein the ischemic insult is uniform among individuals, is not clearly seen in humans wherein the inter-individual variability is large.

Several different postreceptor targeting mechanisms have proven effective in reducing brain damage and improving outcome in animal stroke models. The Ca^{2+} channel antagonist, nimodipine, reduced brain injury and improved functional outcome in rodents (Mossakowski and Gadamski, 1990; Nuglisch et al., 1990) and nonhuman primate stroke models (Hadley et al., 1989), and may improve outcome in human stroke patients (Kakarieka et al., 1994; Nag et al., 1998). Dantrolene reduced ischemic injury to neurons in mice (Mattson et al., 2000) and gerbils (Wei and Perry, 1996) suggesting an important contribution of Ca^{2+} release from ER stores in the ischemic cell death process. Nitric oxide contributes to ischemia-induced oxidative stress and neuronal death (Huang et al., 1994; Iadecola et al., 1997), and drugs that inhibit nitric oxide synthase or scavenge nitric oxide were reported to reduce neuronal damage in rodent stroke models (Kamii et al., 1996; Satoh et al., 2002). The actin depolymerizing agent, cytochalasin D, was reported effective in reducing focal ischemic brain injury in mice (Endres et al., 1999). The ability of 3-aminobenzamide to reduce ischemic brain damage in mice (Endres et al., 1997) suggests a roles for PARP in stroke pathogenesis. Further evidence for the involvement of DNA damage in triggering ischemic neuronal death comes from studies showing that a synthetic inhibitor of p53 reduces infarct size in a mouse model of focal ischemic stroke (Culmsee et al., 2001). Several antioxidants have been reported to be effective in rodent stroke models including vitamin E (Hara et al., 1990), lipoate (Wolz and Krieglstein, 1996), and uric acid (Yu et al., 1998).

Neurotrophic factors have proven effective in reducing stroke-induced brain damage, including bFGF (Nozaki et al., 1993) and sAPP (Smith-Swintosky et al., 1994). Agents that target mitochondrial apoptotic events, including inhibitors of permeability transition pores (Uchino et al., 2002), Bcl-2 (Martinou et al., 1994), and potassium channel activators and inhibitors (Liu et al., 2002, 2003) were very effective in reducing brain damage in rodent stroke models. Caspases are believed to play a central role in neuronal apoptosis after a stroke and caspase inhibitors can reduce infarct size in rodent stroke models, although they may delay rather than prevent neuronal death (Loetscher et al., 2001).

Dietary factors clearly affect the risk for stroke by virtue of their impact on the atherogenic process in cerebral blood vessels, and they may also affect outcome in those who do suffer a stroke. High fat and high calorie diets, and diets deficient in folic acid, increase the risk of stroke by promoting atherosclerosis (Gariballa, 2000). Dietary restriction (intermittent fasting) was reported to be very effective in reducing brain damage and improving functional outcome in a rat model of focal ischemic brain injury (Yu and Mattson, 1999). The neurprotective mechanism of dietary restriction may involve a cellular stress response similar to that of ischemic preconditioning. Homocysteine can increase the vulnerability of neurons to excitotoxic and oxidative insults, and dietary folic acid can reduce homocysteine levels (Kruman et al., 2000), suggesting a possible beneficial effect of dietary folic acid in improving stroke outcome.

Traumatic Brain and Spinal Cord Injuries

Traumatic injuries to the brain and spinal cord are the leading cause of long-term disability and

death of individuals less than 35 yr old (http://www.biausa.org/Pages/home.html; http://www.spinalcord.org). Levels of extracellular glutamate are increased in the traumatized brain and spinal cord, and glutamate receptor antagonists have been shown to reduce neuronal loss and improve behavioral outcome in some animal models of traumatic brain and spinal cord injury (Ikonomidou and Turski, 1996; Agrawal and Fehlings, 1997; Springer et al., 1997; Allen et al., 1999; McAdoo et al., 1999; Gaviria et al., 2000; Mills et al., 2002). Some clinical studies have revealed effectiveness of glutamate receptor antagonists in traumatic brain injury patients (Bullock et al., 1999). The cascade of events leading to neuronal death in the traumatized nervous system involves many of the same mecahnisms that occur in stroke including increased oxidative stress, metabolic impairment, calcium overload, mitochondrial dysfunction, and activation of apoptotic proteases (Azbill et al., 1997; Marion, 1998; Eldadah and Faden, 2000; Lewen et al., 2000). The targeting of each of the latter mecahnisms has been reported to reduce brain/spinal cord damage and improve functional outcome in rodent models. For example, antioxidants that inhibit membrane lipid peroxdiation are effective in rodent models of brain and spinal cord injury (Hall, 1993; Wada et al., 1999); creatine, which promotes maintenance of cellular ATP levels, protects agains traumatic brain injury in rats (Sullivan et al., 2000); cyclosporine A reduces impairment of hippocampal synaptic plasticity in a rat model of traumatic brain injury (Albensi et al., 2000); and caspase inhibitors are neuroprotective in some injury models (Yakovlev et al., 1997; Ozawa et al., 2002). Several studies have reported efficacy of neurotrophic factors in brain or spinal cord injury models (Mattson and Scheff, 1994; Dixon et al., 1997; Rabchevsky et al., 2000; Kim et al., 2001).

Alzheimer's Disease

There are currently more than 4 million Americans with AD, and the numbers are progressively increasing as people live longer (http://www.alz.org). AD is characterized by the accumulation of amyloid β-peptide (Aβ), synaptic dysfunction and degeneration, and neuronal death in brain regions involved in learning and memory processes (Hardy and Selkoe, 2002). While most cases of AD have a late age of onset and have no apparent genetic basis, some cases have an earlier age of onset and are inherited in an authosomal dominant manner. Mutations in three different genes have been linked to early-onset familial AD, namely, those encoding the amyloid precursor protein (APP), presenilin-1 and presenilin-2 (Tanzi and Bertram, 2001; Sisodia and St George-Hyslop, 2002). Studies of cultured cells and transgenic mice expressing AD-linked APP and presenilin mutations have greatly advanced understanding of the disease process. A critical event in AD is an alteration(s) in APP processing that results in increased production of Aβ, particulary a long, 42 amino acid form that has a tendency to aggregate. Aβ may damage neurons and render them vulnerable to excitotoxicity and apoptosis by inducing membrane lipid peroxidation and impairing the function of ion-motive ATPases, glucose and gluatmate transporters, and ion channels (Mattson et al., 1992; Mark et al., 1995a, 1997a, 1997b; Keller et al., 1997; Kruman et al., 1997). The altered APP processing that results in increased production of Aβ may also reduce levels of a neuroprotective secreted form of APP (Mattson et al., 1993; Furukawa et al., 1996). Studies of the pathogenic mechanisms of presenilin mutations reveals an adverse effect on ER Ca^{2+} homeostasis that results in an increased release of Ca^{2+} in cells exposed to agonists that stimulate ER Ca^{2+} release (Guo et al., 1996, 1997, 1999a). The latter effect of the presenilin mutations renders neurons vulnerable to excitotoxicity (Guo et al., 1999a).

While major efforts in AD therapeutics have targeted APP processing and Aβ metabolism with the hope of reducing the accumulation of Aβ in the brain, neuroprotective strategies downstream of Aβ are also being pursued. Evidence that targets relevant to the excitotoxic aspect of neuronal degeneration might be effective in AD prevention and/or treatment include: glutamate receptor antagonists and agents that block Ca^{2+} protect neurons against Aβ toxicity and the cell death-promoting effects of presenilin-1 mutations (Mattson et al., 1992; Weiss et al., 1994; Le et al., 1995; Mark et al., 1995b; Guo et al., 1997, 1999a); antioxidants (e.g., vitamin E, glutathione, ubiquinone, and propyl gallate) and agents that stabilize mitochondrial function and energy production (creatine, FK-506, and cyclosporine A) protect neurons against Aβ toxicity (Goodman and Mattson, 1994; Mark et al., 1995a; Brewer and Wallimann, 2000; Parks et al., 2001; Chen et al., 2002); and agents that inhibit proteins that mediate DNA

damage-induced cell death (3-aminobenzamide and pifithrin-α) protect neurons against Aβ and other insults relevant to AD (Kruman et al., 2000; Culmsee et al., 2001). Neurotrophic factors and certain cytokines can protect cultured neurons against Aβ toxicity and/or the pathogenic actions of presenilin-1 mutations (Mattson et al., 1993; Barger et al., 1995; Guo et al., 1999b). In addition, some neuropeptides that increase cyclic AMP levels in neurons, such as corticotropin-releasing hormone and urocortin, can protect hippocampal neurons against Aβ toxicity (Pedersen et al., 2001, 2002). Finally, dietary factors may affect the risk of excitotoxic neuronal degeneration in AD. Three such factors are caloric intake (Mattson et al., 2000; Luchsinger et al., 2002), cholesterol/fat intake (Refolo et al., 2000; Burns and Duff, 2002), and folate intake (Kruman et al., 2002; Seshadri et al., 2002).

Parkinson's Disease

PD is a progressive and always fatal neurodegenerative disorder in which dopaminergic neurons in the substantia nigra degenerate resulting in motor dysfunction. It is estimated that there are currently 1.5 million Americans with PD (http://www.parkinson.org). Most cases of PD are sporadic and the causes are unknown. However, rare forms of PD are inherited and mutations in three different genes have been linked to some of these inherited cases, namely: α-synuclein, Parkin, and DJ-1 (Dawson and Dawson, 2003). Epidemiological and experimental findings suggest a potential role for environmental toxins such as the pesticide rotenone in the pathogenesis of PD (Betarbet et al., 2000; Lockwood, 2000). As in other age-related neurodegenerative disorders, the dopaminergic neurons that degenerate in PD express glutamate receptors and are vulnerable to excitotoxicity (Miranda et al., 1997). It is believed that mitochondrial dysfunction and associated ATP depletion and oxidative stress are pivotal, and relatively early events in the neurodegenerative process in PD (Schapira, 1999). Indeed, agents such as rotenone and MPTP that induce PD-like pathology and symptoms in rodents, monkeys, and man inhibit mitochondrial electron transport and induce oxyradical production in dopaminergic neurons (Feger et al., 2002). Symptomatic improvement is achieved in PD patients by administering L-dopa, a precursor to dopamine. However, there is as yet no treatment that has proven effective in stopping or even slowing the progression of the neurodegenerative process.

Approaches that have proven effective in protecting dopaminergic neurons in animal models of PD include, glutamate receptor antagonists such as NBQX (Turski et al., 1991), antioxidants such as ubiquinone (Beal et al., 1998), energy-enhancing agents such as creatine (Matthews et al., 1999), synthetic p53 inhibitors (Duan et al., 2002a), and neurotrophic factors such as BDNF and GDNF (Grondin et al., 2002). Dietary restriction protected, (Duan and Mattson, 1999) and dietary folate deficiency endangered (Duan et al., 2002b) dopaminergic nigrostriatal neurons in a mouse model of PD. The results of recent clinical trials of various anti-excitotoxic treatments in PD patients have yielded mixed results. In quite extensive studies there was no clear beneficial effects of vitamin E on deprenyl in PD patients (Shoulson, 1998). It was reported that administration of ubiquinone (coenzyme Q10) slowed functional decline when administered to PD patients (Shults et al., 2002). A great effort has been made to replace lost dopaminergic cells by the transplantation of embryonic dopaminergic cells or neural stem cells. Clinical trials in PD patients have, overall, demonstrated the potential of this approach (Borlongan and Sanberg, 2002). PD will therefore continue to be the leading candidate neurodegenerative disorder for stem cell-based therapy.

Huntington's Disease

HD is a genetic disorder caused by abnormal increases in the number of CAG repeats in the huntingtin gene resulting in a huntingtin protein with expanded polyglutamine repeats (Brandt et al., 1996). Approximately 30,000 Americans have HD and an additional 150,000 have a 50% risk of developing the disease (http://www.hdfoundation.org). The neurons most severely affected in HD are striatal medium spiny neurons, but the disease also involves neurons in the frontal cortex and limbic system, particularly in the latter stages of the disease (Sieradzan and Mann, 2001). Numerous studies have documented an abnormality in energy metabolism in HD; most patients are hyperglycemic and undergo progressive weight loss despite a normal or increased appetite (Podolsky et al., 1972;

Djousse et al., 2002). Studies have shown that striatal neurons are much more vulnerable to energy impairment than any other cell type in the brain, and that they die by an excitotoxic mechanism in rodents exposed to the mitochondrial toxin 3-nitropropionic acid (Brouillet et al., 1999). Huntingtin mutant transgenic mice exhibit phenotypes similar to human HD patients, including progressive degeneration of striatal and cortical neurons characterized by intracellular inclusions of mutant huntingtin protein, progressive motor dysfunction, and death (Menalled and Chesselet, 2002). They also exhibit hyperglycemia and a depletion of BDNF levels in the striatum and cortex (Hurlbert et al., 1999; Zuccato et al., 2001; Duan et al., 2003). Several interventions have been reported to reduce neuronal degeneration and increase survival in huntingtin mutant mice including creatine (Andreassen et al., 2001a), coenzyme Q (Ferrante et al., 2002), and dietary restriction (Duan et al., 2003). Dietary restriction increased brain BDNF levels and improved glucose metabolism in the huntingtin mutant mice, suggesting that impaired BDNF signaling is responsible for both the degeneration of striatal and cortical neurons and the abnormal glucose metabolism in HD (Duan et al., 2003).

Amyotrophic Lateral Sclerosis

ALS is characterized by the progressive degeneration of lower and upper motor neurons resulting in paralysis and death; it affects upwards of 30,000 Americans, most of whom die within 5 yr of diagnosis (http://www.alsa.org). Most cases of ALS are sporadic, but mutations in Cu/Zn-SOD have been shown to be the cause of ALS in some families in which the disease is inherited (Siddique and Lalani, 2002). Environmental toxins are also implicated in ALS, based mainly upon evidence that a dietary excitotoxin may cause an ALS-related syndrome on certain islands in the South Pacific (Cox and Sachs, 2002). Data from analyses of ALS patients and Cu/Zn-SOD mutant mice have provided evidence that impaired glutamate transport, and increased oxidative stress including prominent membrane lipid peroxidation, play major roles in the degeneration of motor neurons (Rothstein et al., 1995; Ferrante et al., 1997; Pedersen et al., 1998; Cutler et al., 2002). Mutant Cu/Zn-SOD renders motor neurons vulnerable to excitotoxicity (Kruman et al., 1999). Transgenic mice expressing ALS Cu/Zn-SOD mutations exhibit progressive degeneration of motor neurons, paralysis, and death. Such transgenic mice are now being used to establish the cellular and molecular mechanisms responsible for motor neuron degeneration in ALS and in preclinical studies aimed at identifying therapeutic agents. As with human patients, ALS mice exhibit increased levels of oxidative stress, as well as evidence of excitotoxicity (Cluskey and Ramsden, 2001). Alterations in calcium homeostasis, (Simpson et al., 2002) sphingolipid/ceramide, and cholesterol metabolism (Cutler et al., 2002) may also contribute to the neurodegenerative process. Several different agents have proven effective in delaying disease onset and mortality in ALS mice including the glutamate-reducing agent riluzole (Gurney et al., 1996), vitamin E (Gurney et al., 1996), lipoate (Andreassen et al., 2001b), combined treatment with the copper chelator trientine and ascorbate Nagano et al., 1999), the cyclooxygenase-2 inhibitor celecoxib (Drachman et al., 2002), and adenovirus-mediated expression of the GDNF gene (Manabe et al., 2002).

Conclusions and Implications for the Prevention and Treatment of Neurological Disorders

Glutamate is the major excitatory neurotransmitter in the mammalian CNS, with virtually all neurons expressing the different ionotropic and metabotropic receptors in varying amounts. There is often a fine line between levels of glutamate receptor activation required for synaptic transmission and plasticity, and slightly higher levels that can trigger excitotoxic cell death. In addition, levels of glutamate receptor activation that are normally innocuous become lethal under conditions of oxidative and metabolic stress. Calcium influx through ionotropic glutamate receptor channels triggers excitotoxic death be activating proteases, inducing oxidative stress, and inducing the process of apoptosis. The reason that excitotoxicity does not occur under normal circumstances is that multiple mechanisms exist that guard against it, including neurotrophic factor signaling cascades and stress response pathways. Glial cells also express glutamate receptors and, in addition, express glutamate

transporter proteins, neurotrophic factors and cytokines that can modify the vulnerability of neurons to excitotoxicity.

Excitotoxicity has been implicated in the death of neurons that occurs in virtually every acute and chronic neurodegenerative disorder including stroke, traumatic brain, and spinal cord injury, AD, PD and HD, and ALS. In each of these disorders, the neurons that degenerate express glutamate receptors, and cell culture and in vivo studies have shown that equivalent populations of neurons are susceptible to excitotoxicity. In several cases, glutamate receptor antagonists have been shown to be effective in suppressing the neurodegenerative process in animal models. Glutamate receptor antagonists can also protect appropriate populations of neurons against death in experimental models relevant to AD, PD, HD, and ALS. Because glutamate signaling is critical for the proper functioning of essentially all neuronal circuits in the CNS, chronic treatment with glutamate receptor antagonists is likely to have serious side-effects. Clinical trials of glutamate receptor antagonists in humans have therefore focused on acute neurodegenerative conditions such as stroke. However, in contrast to animal models of stroke in which the location and severity of the stroke can be tightly controlled, the inter-individual variability in human stroke subjects may mask any neuroprotective effects of glutamate receptor antagonists. Recently, excitoprotective efforts have focused on the development of drugs that block the excessive activation of glutamate receptors that underly excitotoxicity, while at the same time allowing the lower levels of glutamate receptor activation required for normal function of neuronal circuits. A leading agent arising from such studies is memantine (Kilpatrick and Tilbrook, 2002).

While glutamate receptor antagonists may eventually prove useful in the clinic, a better strategy may be to target the conditions and pathways that increase the vulnerability of neurons to excitotoxicity. As described above, oxidative stress and metabolic compromise are two such pro-excitotoxic conditions. Pharmacological interventions that target oxidative stress, energy metabolism, and apoptotic cascades are being pursued. Importantly, recent finding suggest that dietary factors, such as the amounts of calories, fats, and folic acid can influence one's risk of excitotoxic neurodegenerative disorders. It may therefore be possible to effectively prevent and treat such disorders through approaches that target excitotoxic pathways.

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