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Glutamate and Neurotrophic Factors in Neuronal Plasticity and Disease

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Abstract

Glutamate's role as a neurotransmitter at synapses has been known for 40 years, but glutamate has since been shown to regulate neurogenesis, neurite outgrowth, synaptogenesis and neuron survival in the developing and adult mammalian nervous system. Cell surface glutamate receptors are coupled to Ca^{2+} influx and release from endoplasmic reticulum stores which causes rapid (kinase- and protease-mediated) and delayed (transcription-dependent) responses that change the structure and function of neurons. Neurotrophic factors and glutamate interact to regulate developmental and adult neuroplasticity. For example, glutamate stimulates the production of brain-derived neurotrophic factor (BDNF) which, in turn, modifies neuronal glutamate sensitivity, Ca^{2+} homeostasis and plasticity. Neurotrophic factors may modify glutamate signalling directly, by changing the expression of glutamate receptor subunits and Ca^{2+}-regulating proteins, and also indirectly by inducing the production of antioxidant enzymes, energy-regulating proteins and anti-apoptotic Bcl2 family members. Excessive activation of glutamate receptors, under conditions of oxidative and metabolic stress, may contribute to neuronal dysfunction and degeneration in diseases ranging from stroke and Alzheimer's disease to psychiatric disorders. By enhancing neurotrophic factor signalling, environmental factors such as exercise and dietary energy restriction, and chemicals such as antidepressants may optimize glutamatergic signalling and protect against neurological disorders.

Keywords

Alzheimer's disease; AMPA receptors; BDNF; calcium homeostasis; GDNF; Huntington's disease; NMDA; Parkinson's disease

Introduction

Glutamate functions as a neurotransmitter in organisms as diverse as insects, worms, amphibians and mammals[1]. It is the major excitatory neurotransmitter in the central nervous system (CNS) of mammals, and is therefore essential for all of our behaviours[2]. Although best known for its role at synapses in the mature nervous system, glutamate is also of vital importance during development where it regulates neurogenesis, neurite outgrowth, synaptogenesis and programmed cell death (apoptosis)[3]. Because of the well-established functions of neurotrophic factors in nervous system development, interactions between glutamate and neurotrophic factors have been sought, and found. Indeed, a delicate interplay between glutamate and neurotrophic factor signalling systems is at the heart of activity-dependent neuroplasticity during development and in the adult[4]. Because of the large scope of this topic, the present article will focus primarily on glutamate – neurotrophic factor

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interactions in the hippocampus, a region of the CNS that provides a tractable model of developmental and adult neuroplasticity[5], and is a focus of several major neurological disorders in humans including epilepsy, depression and Alzheimer's disease (AD)[6]. This article is not intended to be a comprehensive review of the topic; instead, I provide examples from some of our own studies, and related findings from other laboratories. Only a few of the many neurotrophic factors that have been shown to influence, or be influenced by, glutamate signalling will be discussed in any detail; they include brain-derived neurotrophic factor (BDNF), basic fibroblast growth factor (bFGF), insulin-like growth factor 1 (IGF1) and nerve growth factor (NGF) and glial cell line-derived neurotrophic factor (GDNF). The importance of a tightly-regulated interplay between glutamate and neurotrophic factor signalling for hippocampal plasticity, and the pathological consequences of dysregulation of these systems is emphasized.

Glutamate Receptors and Signal Transduction

There are two major types of ionotropic glutamate receptors; alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors flux mainly Na^+ and some Ca^{2+}, whereas N-methyl-D-aspartate (NMDA) receptors flux Ca^{2+} in large amounts[7]. Activation of AMPA receptors depolarizes the membrane resulting in the opening of voltage-dependent Ca^{2+} channels and NMDA receptor channels. A different type of glutamate receptor, so called-metabotropic receptors, are coupled to the GTP-binding protein Gq11 which, in turn activates phospholipase C resulting in production of inositol triphosphate (IP_3) which induces Ca^{2+} release from endoplasmic reticulum stores, and the activation of protein kinase C[8]. Glutamate-induced elevation of cytosolic Ca^{2+} levels activates: protein kinases such as calcium/calmodulin-dependent protein kinase II and PKC; proteases such as calpains; and transcription factors such as cyclic AMP response element-binding protein (CREB) and NF-κB[9–11]. In these ways, glutamate elicits rapid local (dendritic) changes in membrane excitability and cytoskeletal architecture, and delayed transcriptional changes in a variety of genes involved in plasticity including those encoding neurotrophic factors.

Neurotrophic Factor Receptors and Signal Transduction

Many of the major neurotrophic factors, including BDNF, NGF, bFGF and IGF1 activate receptors that possess intrinsic tyrosine kinase activity[12,13]. Binding of each of the latter four ligands to their receptors results in receptor dimerization and trans-autophosphorylation of tyrosine residues in the cytoplasmic domains of the receptors. Specific adaptor proteins and kinases then associate with the activated growth factor receptors to form a signalling complex. Major downstream pathways activated by neurotrophic factors include the phosphatidylinositol-3-kinase – Akt pathway, PKC, and the mitogen-activated protein kinase pathway[14]. These kinase pathways activate one or more transcription factors including AP1, NF-κB and FOXOs. Some of the genes induced by neurotrophic factors include those encoding anti-apoptotic proteins, antioxidant enzymes, and proteins involved in energy metabolism and ion homeostasis. For example, bFGF regulates the expression of NMDA and AMPA receptor subunits in cultured embryonic hippocampal neurons, and thereby modifies the sensitivity of the neurons to glutamate[15,16]. Neurotrophic factors may also exert local transcription-independent effects on neural cells. For example, BDNF can induce local influx of Ca^{2+} in neurites of cultured neurons[17], and bFGF and NGF can act directly on synaptic terminals in ways that stabilize mitochondrial function[18].

Neurogenesis

Neurons and glial cells are produced by asymmetric divisions of self-renewing neural progenitor cells (NPC) (Fig. 1). Many different signalling pathways are involved in determining the fate of NPC including those activated by extracellular matrix and cell adhesion

molecules, growth factors, cytokines and neurotransmitters. Glutamate may influence NPC either directly or indirectly by stimulating the production of neurotrophic factors and other signalling molecules in neurons. An example of evidence supporting a direct action of glutamate on NPC comes from studies of cultured human NPC which respond to glutamate by increasing their proliferation rate, and by increasing their potential for neurogenesis[19]. Glutamate can also stimulate neurogenesis indirectly by inducing the production of growth factors, cytokines and other intercellular messengers in neurons and glial cells. Glutamate stimulates the production of BDNF in neurons, and BDNF promotes neurogenesis[20,21]. Interestingly, as neurons differentiate from NPC they express nitric oxide synthase, and the nitric oxide they produce acts on adjacent NPC to inhibit their proliferation and promote their differentiation into neurons[22]. Because activation of glutamate receptors stimulates nitric oxide production, a Ca^{2+}-mediated process, it is likely that nitric oxide mediates, at least in part, activity-dependent neurogenesis in the adult brain.

Numerous growth factors have been identified that influence the fate of NPC. bFGF and EGF promote the self-renewal (proliferation) of NPC in the developing and adult brain[23]. BDNF and IGF-1 promote the differentiation of NPC into neurons, and promote the survival of newly-generated neurons[24,25]. BDNF is particularly noteworthy for its apparent role as a mediator of the effects of environmental factors on hippocampal neurogenesis. Levels of BDNF are increased in the hippocampus in response to exercise[26], dietary energy restriction[21], and cognitive stimulation[27], all of which stimulate neurogenesis. Studies of rodents in which BDNF levels or signalling are reduced have provided evidence for a pivotal role for BDNF in basal and stimulated hippocampal neurogenesis[21,28]. Conversely, reductions in BDNF production may contribute to the impaired hippocampal neurogenesis associated with diabetes and clinical depression[29,30].

Neurite outgrowth and Synaptogenesis

Glutamate, released from growth cones in an activity-dependent manner, can act on the growing dendrites of adjacent cells to alter their outgrowth and promote synaptogenesis (Fig. 1). In cultured embryonic hippocampal neurons glutamate selectively inhibits the outgrowth of dendritic (but not axonal) growth cones[31]. The latter study showed that glutamate-induced inhibition of dendrite outgrowth is mediated by Ca^{2+} influx in the dendrites. Glutamate released from the axons of entorhinal cortex neurons inhibits dendrite outgrowth of, and promotes synaptogenesis with, target hippocampal neurons[32]. Similar roles for glutamate in regulating synaptogenesis in the developing visual system have been reported[33]. Glutamate regulates neurite outgrowth by affecting cytoskeletal dynamics in the growth cone and neurite shaft. Glutamate-induced Ca^{2+} influx may cause a rapid local polymerization of actin to form filopodial extensions of growth cones, while inhibiting tubulin polymerization and hence neurite elongation[34]. Sustained elevation of intracellular Ca^{2+} in response to glutamate receptor activation can result in depolymerisation of microfilaments and microtubules resulting in dendrite outgrowth cessation and regression.

Neurotrophic factors typically enhance the outgrowth of axons and dendrites. For example, in embryonic hippocampal neurons, bFGF increases the outgrowth rate of axons and dendrites, and may also increase the complexity (branching) of the neurites[35]. The neurite outgrowth-promoting effects of neurotrophic factors are likely mediated by both transcription-independent and dependent mechanisms. Thus, the growth factors may influence local cytoskeletal dynamics through Ca^{2+} and kinase-mediated mechanisms, but also induce the expression of genes that encode cytoskeletal proteins and cell adhesion molecules, for example. Growth factors can override inhibitory effects of glutamate on dendrite outgrowth by modifying glutamate-induced Ca^{2+} responses. Importantly, glutamate and neurotrophic factors interact in processes of activity-dependent control of neurite outgrowth and synaptogenesis.

Thus, glutamate stimulates the production of neurotrophic factors such as BDNF which, in turn promotes neurite outgrowth and synaptogenesis.

Activity-Dependent Neuron Survival

During development of the nervous system many more neurons are produced than ultimately integrate into neuronal circuits and survive. The programmed cell death of neurons during development is activity-dependent – neurons that are stimulated (by glutamate or other excitatory transmitters) survive, whereas those that do not receive stimulation may die[36]. As synapses form the local activation of glutamate receptors induces the production of neurotrophic factors (BDNF and NGF, for example) in the postsynaptic neuron[37,38]. The neurotrophic factor is then released locally at the active synapses and activates receptors in the presynaptic neuron, resulting in upregulation of genes that encode proteins critical for cell survival including Bcl-2 and antioxidant enzymes[39, 40]. In the adult hippocampus, the production of neurotrophic factors is also increased in response to glutamate receptor-mediated activity in neuronal circuits[4, 41], and so survival of many neurons in the adult may also depend upon activity in neuronal circuits. For example, an episode of synaptic activity can promote the survival of neurons in the hippocampus by a mechanism involving both CREB-independent and CREB-dependent pathways[42]. An activity-dependent survival mechanism is believed to underlie the ability of exercise and intermittent fasting to prevent the death of neurons in experimental models of stroke[43,44]. However, exercise and environmental enrichment did not protect hippocampal neurons against seizure-induced death despite a stimulation of BDNF production[45].

During the process of neurogenesis in the adult hippocampus, many of the newly-generated neurons undergo apoptosis[46] (Fig. 1). Neuronal activity-dependent upregulation of BDNF signalling may mediate the increased survival of newly-generated neurons in the hippocampus of rodents maintained on exercise or dietary energy restriction regimens, compared to sedentary overfed control rodents[21,27–29]. Although the mechanisms that determine whether or not newly-generated neurons live or die in the adult hippocampus have not been established, it has been reported that newly-generated neurons are particularly susceptible to apoptosis. For example, compared to NPC and mature neurons, newly-generated neurons are hypersensitive to DNA and telomere damage[47]. Although not yet established, it is reasonable to consider that glutamate and neurotrophic factors influence the survival of newly-generated neurons by modifying regulatory systems involved in the protection against DNA damage and maintenance of telomeres.

Synaptic Plasticity

There has been intense interest in elucidating the molecular mechanisms that mediate the strengthening (or weakening) of synaptic strength that occurs in response to various behavioural and environmental changes. Studies of hippocampal synaptic transmission have been particularly informative in revealing roles for glutamate and neurotrophic factors in synaptic plasticity. Both AMPA and NMDA receptors are of fundamental importance for activity-induced strengthening of synaptic strength, a process called long-term potentiation (LTP)[48]. Ca^{2+} influx activates kinases and phosphatases that act on a variety of substrates including ion channels and cytoskeletal proteins that mediate local remodelling of postsynaptic spines, and transcription factors which translocate to the nucleus and induce the expression of genes that promote neuronal survival and plasticity, including neurotrophic factors (Fig. 1). Stimulus paradigms that induce LTP also induce the expression of BDNF and other neurotrophic factors including neurotrophin-3 in the hippocampus[49]. However, LTP is only induced when glutamatergic synapses are activated within a narrow range of frequencies and

amplitudes. Lower levels of stimulation may result in long-term depression of the synapses[50], whereas sustained overstimulation can cause degeneration of the synapses[51].

Critical roles for neurotrophic factors in LTP and learning and memory are suggested from numerous studies in rodents. Hippocampal LTP is impaired in mice lacking BDNF in their neurons[52], and BDNF enhances LTP in the hippocampus[53] and visual cortex[54]. Interestingly, BDNF released from neurons during LTP may be recycled and used for LTP maintenance[55]. In addition to BDNF, several other neurotrophic factors are believed to play roles in synaptic plasticity. For example, NGF is involved in LTP in the hippocampal dentate gyrus[56], bFGF receptors are required for hippocampal LTP and memory consolidation[57], and a secreted form of amyloid precursor protein enhances LTP at hippocampal CA1 synapses[58]. Consistent with important roles for neurotrophic factors in LTP and learning and memory are data showing that environmental manipulations that enhance LTP and cognition also increase production of one or more neurotrophic factors. For example, dietary energy restriction (which enhances synaptic plasticity) increases the production of BDNF and glial cell line-derived neurotrophic factor[21,59], while depression, diabetes and chronic psychosocial stress (which impair learning and memory) decrease the production of BDNF[60–62].

Excitotoxicity and Epilepsy

Excessive sustained activation of glutamate receptors can kill neurons, particularly under conditions of reduced energy availability and increased oxidative stress[51, 63]. This phenomenon, which is called excitotoxicity (Fig. 2), can be dramatically demonstrated by exposing cultured neurons to high concentrations of glutamate and by exposing animals to excitotoxins such as kainic acid and domoic acid which, in contrast to glutamate, induced non-desensitizing ion currents and are not actively removed from the extracellular space[64]. There are at least two distinct mechanisms of excitotoxicity. Excitotoxic necrosis involves uncontrolled influx of Na^+ resulting in rapid cell swelling and lysis. Excitotoxic apoptosis is mediated by excessive Ca^{2+} influx which causes alterations in the endoplasmic reticulum and mitochondria resulting in the activation of caspases and nuclear chromatin condensation and fragmentation. Glutamate-induced calcium influx may trigger apoptotic cascades in dendrites, but may also simultaneously elicit changes that prevent necrosis. Calcium influx activates the actin-severing protein gelsolin resulting in actin depolymerisation and reduction in calcium influx through NMDA receptor channels[65]. Glutamate induces caspase activation in dendrites and the caspases can cleave AMPA receptor subunits, thereby reducing Na+ influx and preventing excitotoxic necrosis[66–69].

Mechanisms by which neurons are protected against excitotoxicity include the activities of ATP-dependent Na+ and Ca^{2+} pumps and the expression of Ca^{2+}-binding proteins[51]. When cellular energy levels are low, as occurs during cerebral ischemia, the ion-motive ATPases may be compromised, thereby rendering neurons vulnerable to excitotoxicity. Similarly, oxidative stress as occurs during normal aging or in neurodegenerative disorders, impairs the function of glucose and glutamate transporters, as well as ion-motive ATPases.

Several different neurotrophic factors can protect neurons against excitotoxicity. Basic FGF protects cultured hippocampal and cortical neurons against glutamate toxicity by mechanisms involving changes in the expression of NMDA receptors[15] and antioxidant enzymes[40] (Fig. 2). BDNF and TNF protect neurons against excitotoxicity through a signaling pathway that activates the transcription factor NF-κB which induces the expression of antioxidant enzymes such as Mn-SOD and anti-apoptotic proteins such as Bcl-2 and inhibitor of apoptosis proteins (IAPs)[70–73]. Insulin-like growth factors, signaling via the PI3 kinase – Akt pathway can protect neurons against excitotoxicity in cell culture[74] and in vivo[75]. NGF[76] and

neurotrophin-3[73] have also been reported to exert excitoprotective effects on cultured cortical and hippocampal neurons.

Levels of several different neurotrophic factors are increased in response to epileptic seizures in animal models of epilepsy including NGF, BDNF, bFGF, CNTF, transforming growth factor-β (TGFβ) and TNFα[77]. The most commonly used epileptic seizure model in which kainic acid is admistered to rats or mice has been employed to demonstrate the involvement of endogenous growth factors in modifying neuronal vulnerability to seizures. By employing genetically modified mice, or by pharmacological inhibition of growth factors, it has been shown that BDNF[78,79], TGF-β[80] and TNF[81] play important roles in protecting neurons against seizure-induced damage and death. The potential of treatments with growth factors to reduce seizure-induced brain damage has been evaluated in several preclinical studies in rodents. Chronic infusion of bFGF reduced seizure-induced hippocampal damage[82], grafting of a BDNF-producing cell line protected striatal neurons against kainic acid-induced death[83], and adenoviral vector-mediated expression of GDNF protected hippocampal neurons against seizure-induced death[84].

Stroke and Traumatic Injury

A stroke occurs as the result of occlusion (clot formation at the site of an atherosclerotic arterial lesion) or rupture of a cerebral blood vessel. As a consequence the brain cells that normally receive their nutrients from the affected vessel suffer from a marked deficiency of glucose and oxygen. Because of their high metabolic requirements neurons affected by the stroke may die; many neurons in the so-called ischemic core undergo excitotoxic necrosis, whereas those in the surrounding penumbra region (in which energy availability is compromised, but not eliminated) may undergo excitotoxic apoptosis[85]. Studies of rodent models of stroke, the most common of which is the middle cerebral artery occlusion – reperfusion model, have demonstrated the ability of glutamate receptor (NMDA and AMPA) antagonists to reduce the death of neurons in the ischemic penumbra and improve functional outcome[86–88]. However, clinical trials of glutamate receptor antagonists in stroke patients have not proved positive, in part because of adverse side-effects of the drugs. Ischemia results in the up-regulation of the expression of several different neurotrophic factors in the penumbral region including bFGF[89], BDNF[90] and TGFβ[91]. The latter and novel neurotrophic factors such as persephin may limit the extent of the brain injury following stroke, and may also have therapeutic potentia[92–95]. Interestingly, exposure of the brain to a mild ischemia prior to a full-blown stroke, results in decreased damage to neurons. This phenomenon, called preconditioning or hormesis[96] is believed to be mediated by activation of glutamate receptors, and up-regulation of neurotrophic factors and heat-shock proteins[97].

As with other types of acute insult to the nervous system, traumatic brain injury (TBI) results in increased oxidative stress, impaired cellular energy metabolism and overactivation of glutamate receptors resulting in cellular Ca^{2+} overload[98, 99]. Accordingly, glutamate receptor antagonists have been reported to be effective in limiting the extent of neuronal damage in animal models of TBI[100, 101]. There is considerable evidence that activation of neurotrophic factor signalling pathways can reduce neuronal damage and improve functional outcome in animal models of traumatic brain and spinal cord injury[102–104].

Alzheimer's Disease

Alzheimer's disease (AD) is an age-related disorder characterized by the dysfunction and death of neurons in brain regions, such as the hippocampus and frontal cortex, involved in learning and memory processes. The neurodegenerative process in AD is believed to involve mitochondrial alterations, membrane-associated oxidative stress, altered proteolytic processing of the β-amyloid precursor protein (APP) and accumulation of neurotoxic forms of

the amyloid β-peptide (Aβ)[105]. Studies of experimental models relevant to AD have provided evidence that Aβ and oxidative stress disrupt neuronal Ca^{2+}, thereby rendering neurons vulnerable to excitotoxicity and the development of cytoskeletal alterations (neurofibrillary tangles) characteristic of dying neurons in AD[106, 107]. Clinical evidence supporting a role for excitotoxicity in AD comes from the demonstration of beneficial effects of the NMDA receptor antagonist memantine in some AD patients[108].

Reduced levels of BDNF have been documented in studies of post-mortem brain tissue from AD patients, suggesting a potential role for compromised neurotrophic support in neuronal susceptibility to AD[109]. Several studies have provided evidence that neurotrophic factors can protect neurons against Aβ toxicity and the pathogenic actions of mutations in presenilin-1 that cause some cases of early-onset inherited AD. For example: bFGF can protect cultured hippocampal neurons from being killed by Aβ[110]; NGF and bFGF can protect cortical synapses against Aβ-induced damage[18]; and a secreted form of APP can protect neurons against excitotoxicity and Aβ toxicity[111]; and bFGF and activity-dependent neurotrophic factor can counteract the pro-excitotoxic actions of a presenilin-1 mutation[112, 113]. Also of interest in regards to the roles of glutamate and neurotrophic factors in AD are data showing that exercise, cognitive stimulation and dietary energy restriction reduce the risk of AD[114], and these same environmental factors increase BDNF production and enhance learning and memory, synaptic plasticity and neurogenesis[115].

Parkinson's Disease

Dopaminergic neurons in the substantia nigra, which control body movements, are among the most prominent populations of neurons to degenerate in Parkinson's disease (PD). Oxidative stress due to aging and dopamine oxidation, and mitochondrial dysfunction due to complex I impairment, may render neurons dopaminergic neurons vulnerable to excitotoxicity in PD[116, 117]. Indeed, activation of glutamate receptors is required for the neurotoxic actions of mitochondrial complex I inhibitors towards dopaminergic neurons[118]. Several different genes have been identified in which mutations cause rare inherited forms of PD and, in several cases, data suggest that the mutant proteins may render neurons vulnerable to excitotoxicity. Wild-type α-synuclein, parkin and DJ-1 have been suggested to serve neuroprotective functions that may be compromised by disease-causing mutations[119–121]. Three neurotrophic factors that have been suggested to protect dopaminergic neurons against PD are GDNF, BDNF and bFGF. Levels of BDNF and bFGF are decreased in the substantia nigra in PD[122–124]. Intrastriatal administration of GDNF and BDNF have proven effective in increasing dopamine levels and improving functional outcome in animal models of PD[125, 126] and clinical trials of GDNF infusion into the striatum of PD patients have been performed, but with limited success thus far[127, 128]. From a disease prevention perspective, it was reported that caloric restriction can preserve striatal GDNF and BDNF levels, reduce dopamine depletion and improve function outcome in a monkey model of PD[59].

Huntington's Disease

Huntington's disease (HD) is a particularly interesting neurodegenerative disorder in regards to the involvement of glutamate and neurotrophic factors. HD is characterized by the degeneration of striatal, cortical and brainstem neurons resulting in characteristic continuous involuntary motor movements and cognitive and autonomic dysfunction. HD is an inherited disorder caused by polyglutamine expansions in the huntingtin protein. The population of medium spiny striatal neurons that degenerate in HD patients are particularly vulnerable to NMDA receptor-mediated excitotoxicity[129]. Toxin-induced impairment of the function of mitochondrial succinate dehydrogenase results in selective excitotoxic degeneration of striatal medium spiny neurons in animal models[130]. Studies of huntingtin mutant mice have provided

support for an excitotoxic mechanism of neuronal death in HD. Huntingtin mutations perturb mitochondrial function and cellular calcium homeostasis and sensitize neurons to NMDA toxicity[131, 132]. Mutant huntingtin may also promote excitotoxicity by impairing glutamate transport[133]. Studies of huntingtin mutant mice suggest a potential for NMDA receptor antagonists for the treatment of HD[134].

BDNF has taken centre stage in HD. BDNF expression is reduced in affected brain regions of HD patients and huntingtin mutant mice[135–137]. When HD mice were crossed with BDNF+/− mice, the onset of neurodegeneration and motor dysfunction was hastened[138]. Delivery of BDNF to the brain protects striatal neurons[139] and restores synaptic plasticity[140] in mouse models of HD. Interestingly, gene expression profiling data suggest that the molecular changes that occur in the striatum of BDNF-deficient mice are more similar to those that occur in humans HD patients, compared to the molecular alterations in huntingtin mutant mice and mitochondrial toxin-treated rats[141]. Finally, manipulations that increase BDNF production in the striatum and cortex, including environmental enrichment[142], dietary energy restriction[137] and antidepressant treatment[143], forestall the neurodegenerative process in huntingtin mutant mice.

Amyotrophic Lateral Sclerosis

The only treatment that has thus far proven effective in slowing the progression of lower motor neuron degeneration and paralysis in amyotrophic lateral sclerosis (ALS) is drug called riluzole that protects neurons against excitotoxicity[144]. The available evidence suggests that glutamate transport is impaired in ALS and may contribute to excitotoxic death of motor neurons[145]. Mutations in Cu/Zn superoxide dismutase (SOD) cause some cases of inherited ALS, and transgenic mice expressing mutant human Cu/Zn-SOD exhibit progressive degeneration of motor neurons, paralysis and death[146]. The Cu/Zn-SOD mutations have been shown to increase the vulnerability of motor neurons to excitotoxicity by a mechanism involving increased oxidative stress and dysregulation of cellular calcium homeostasis[147]. The excitotoxic death of motor neurons is believed to be mediated primarily by AMPA receptors[148]. Several different neurotrophic factors have been shown to promote the survival of motor neurons in experimental models relevant to ALS pathogenesis including IGF-1, CNTF, BDNF and GDNF[149–152]. There have been several relatively small clinical trials of neurotrophic factor treatment in ALS patients. IGF-1, CNTF and BDNF did not demonstrate a clear clinical benefit in these trials[153–155].

Psychiatric Disorders

Perturbed glutamatergic signaling has been implicated in the pathogenesis of several psychiatric disorders including anxiety disorders and depression, bipolar disorder and schizophrenia[156–159]. The bulk of the evidence supports a role for reduced levels of glutamatergic signaling in schizophrenia including the fact that glutamatergic neurons modulate dopaminergic neurotransmission, the ability of certain glutamate receptor antagonists (phencyclidine, for example) to induce psychosis, and the modulatory effects of antipsychotic drugs on glutamatergic signaling[160, 161]. Studies of animal models and therapeutic intervention trials have suggested a potential benefit of glutamate receptor-modulating agents for the treatment of anxiety and depression; with drugs that act on metabotropic and NMDA glutamate receptors being particularly promising[162–165]. Reduced levels of serotonergic and noradrenergic signaling occur in depression and, accordingly, drugs that increase synaptic levels of serotonin and norepinephrine (serotonin and norepinephrine reuptake inhibitors) are effective therapies for this disorder[166]. There is considerable evidence implicating reduced levels of BDNF signaling in the pathogenesis of depression including: reduced levels of BDNF in the hippocampus in animal models of depression and in the plasma of depressed human

subjects[167, 168]; antidepressants increase BDNF levels, increase glutamate sensitivity and promote neurogenesis in the hippocampus[169, 170]; and exercise increases BDNF levels and has antidepressant-like actions[115]. Reduced BDNF signaling is also implicated in the pathogenesis of bipolar disorder[171] and schizophrenia[172, 173].

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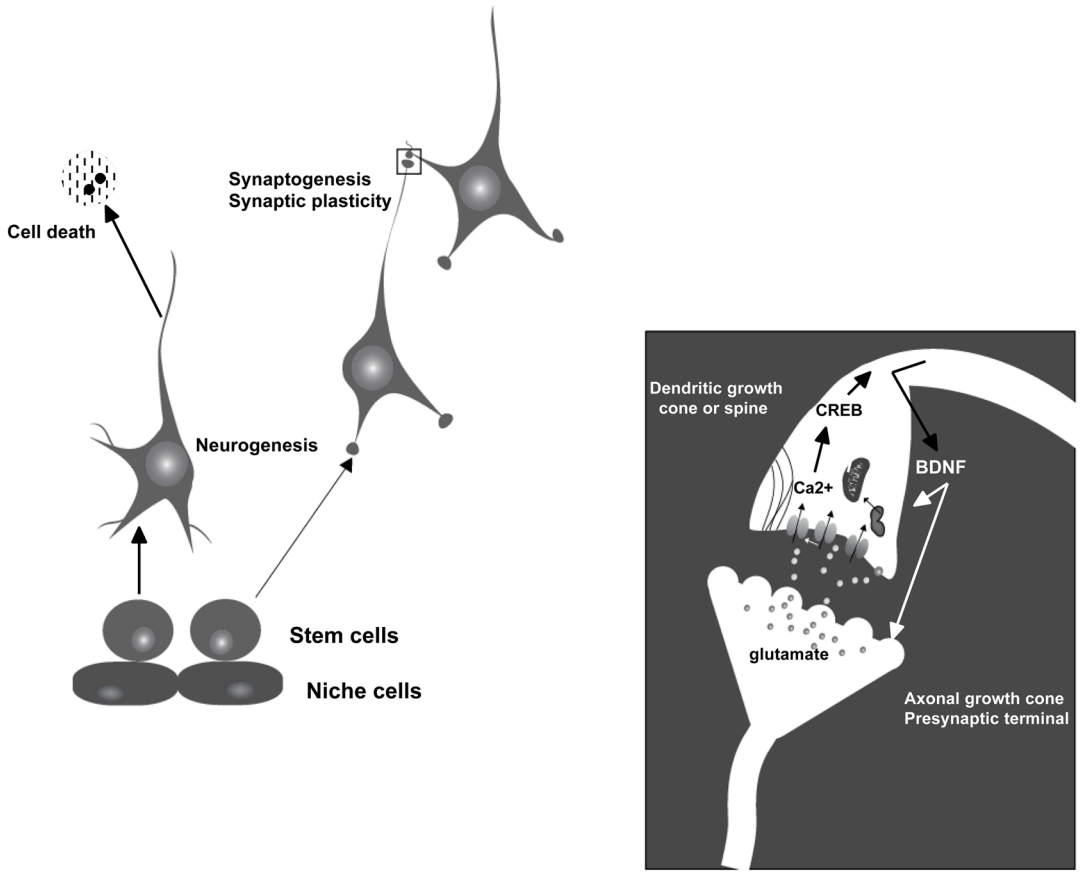

Figure 1.
Interactions of glutamate and BDNF in the regulation of developmental and adult neuroplasticity.

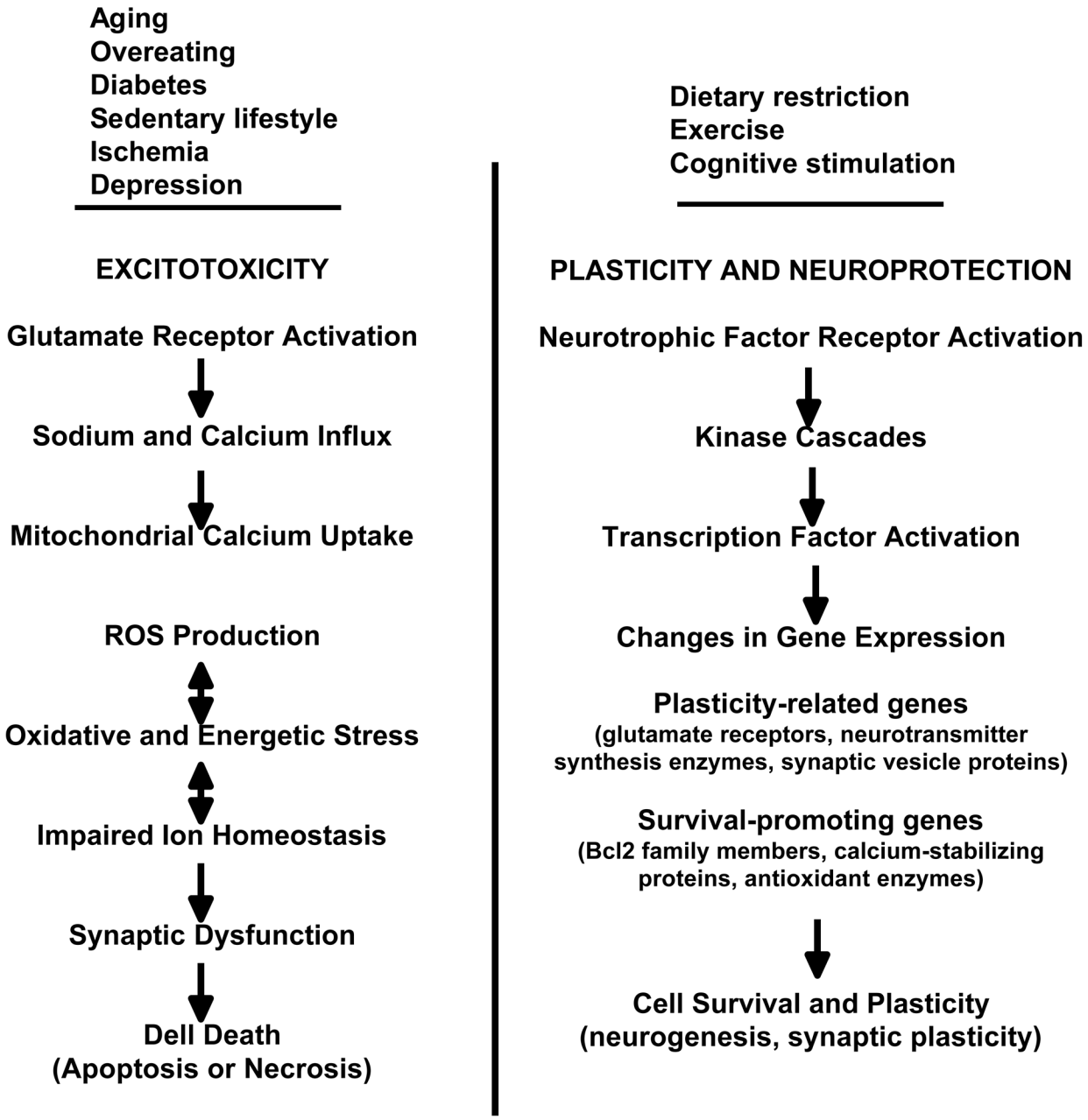

Figure 2.
Mechanisms of excitotoxicity and neuroprotection by neurotrophic factors.