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The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission

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Preface

Mounting evidence suggests that acute and chronic stress, especially the stress-induced release of glucocorticoids, induces changes in glutamate neurotransmission in the prefrontal cortex and the hippocampus, thereby influencing some aspects of cognitive processing. In addition, dysfunction of glutamatergic neurotransmission is increasingly considered to be a core feature of stress-related mental illnesses. Recent studies have shed light on the mechanisms by which stress and glucocorticoids affect glutamate transmission, including effects on glutamate release, glutamate receptors and glutamate clearance and metabolism. This new understanding provides insights into normal brain functioning as well as the pathophysiology and potential new treatments of stress-related neuropsychiatric disorders.

Introduction

Selye originally described stress as a non-specific response of the body to any demand placed upon it¹. Now it is customary to speak of a stressor as an event or experience that threatens the ability of an individual to adapt and cope². As a result, the stressor evokes a stress response, which involves the release of hormones and other cellular mediators that can promote adaptation when the response is efficiently turned on and shut off, but which can also promote pathophysiological processes when the response is overused or dysregulated³.

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Further information

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The brain is central in the adaptation to stress, perceiving and determining what is threatening, and orchestrating the behavioural and physiological responses to the stressor⁴. The brain is also a target of stress, with animal models showing stress-induced remodelling of brain architecture, such as dendritic atrophy and loss of dendritic spines in neuronal populations⁵⁻⁷. The effects of stress on the brain have long been associated with the onset and exacerbation of several neuropsychiatric disorders.

Depending on the age of the animal at the time of exposure, and the duration and type of stressor experienced, stress also has marked and often divergent effects on learning and memory^{8,9}. In relation to these effects, stress is known to influence several distinct cognitive processes, including spatial and declarative memory (which involves the hippocampus), the memory of emotionally arousing experiences and fear (which involves the amygdala), and executive functions and fear extinction (which involves the prefrontal cortex). This Review focuses primarily on the prefrontal cortex (PFC), as it may play an important role in mediating the effects of stress on both cognition and psychopathology. The PFC is an essential component of a neural circuit for working memory^{10,11} — the ability to keep in mind something that has just occurred or bring to mind events in the absence of direct stimulation. PFC neurons show spatially tuned, persistent activity during the delay period of working memory tasks, a phenomenon that is thought to arise from recurrent excitatory connections involving AMPA and NMDA receptor synapses onto PFC pyramidal neurons^{11,12}. The PFC is also essential for behavioural adaptation, inhibiting inappropriate actions and allowing for a flexible regulation of behaviour that enables a proper response to changes in the environment. Multiple lines of evidence from rodent and human studies also implicate the ventromedial PFC as the major site controlling extinction of conditioned fear^{13,14}. Moreover, impaired PFC function and plasticity is thought to be a core pathological feature of several neuropsychiatric disorders¹⁵⁻¹⁷. As stress seems to induce some effects in the PFC that are unique to this region and others that are common to the hippocampus and other regions, regional comparisons will be made where possible (see supplementary online information S1 (table)).

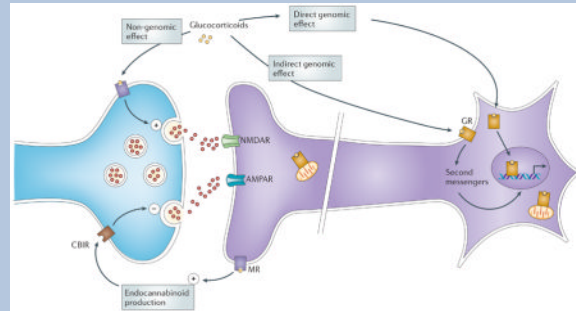
For the purposes of clarity and focus, and to highlight the importance of several recent findings, this Review will mainly address the effects of stress and glucocorticoids on the glutamatergic neurotransmitter system within the PFC (Box 1). However, it must be acknowledged that a host of neurotransmitter and neuromodulatory systems in various brain regions have been shown to be crucial in mediating the effects of stress (see^{10,18,19} for recent reviews), with some having very clear effects on glutamatergic neurotransmission²⁰.

Box 1

Adrenal steroids and neurotransmission

Glucocorticoids are released from the adrenal glands. Basal release varies in a diurnal pattern, and release increases several fold after exposure to a stressor. Glucocorticoids can bind, with different affinities, to glucocorticoid (GR) and mineralocorticoid (MR) receptors, which are expressed throughout the brain and seem to exist in both membrane-bound form and nuclear form. Adrenal steroids can have both rapid and delayed effects. The effects can result from non-genomic mechanisms (mediated by membrane receptors, see the figure), indirect genomic mechanisms (mediated by membrane receptors and second messengers, see the figure) and genomic mechanisms (mediated by cytoplasmic receptors that move to the nucleus and act as transcription factors, see the figure)^{193,194}, as seems now to be the case for all steroid hormones^{195,196}. Although mineralocorticoid and glucocorticoid receptors seem to mediate many of these effects^{197,198}, other membrane-associated receptors, including G-protein coupled receptors, may also be involved in some of these actions^{49,199-201}. In addition, activated glucocorticoid

receptors can translocate to mitochondria and enhance their calcium buffering capacity^{202,203}. Glucocorticoids rapidly induce glutamate release in the hippocampus via a mechanism that is absent when the mineralocorticoid receptor is deleted and which may involve a membrane-associated form of the mineralocorticoid receptor^{42,204}. An indirect way by which glucocorticoids can influence neurotransmission (glutamatergic, as well as GABAergic, cholinergic, noradrenergic and serotonergic) is through cross-talk with the endocannabinoid (eCB) system²⁰⁵. They rapidly stimulate endocannabinoid production in the brain, whereupon eCBs bind to the CB1 and TRPV1 receptors and inhibit neurotransmitter release^{206,207} (see the figure). Although a G-protein coupled receptor is implicated in endocannabinoid production²⁰⁸, there is also evidence for a mechanism blocked by Ru486 — a selective antagonist of the classical cytoplasmic glucocorticoid receptor — in the rapid actions of glucocorticoids in prefrontal cortex²⁰⁹.



Glutamatergic neurotransmission occurs predominantly within the confines of a tripartite synapse (Figure 1). Several points of regulatory control within the synapse, including basal and stimulated presynaptic glutamate release; postsynaptic receptor trafficking and function; and transporter-mediated uptake and recycling of glutamate through the glutamate–glutamine cycle are sensitive to regulation by stress and glucocorticoids. Here we review studies exploring the effects of stress and glucocorticoids on each of these components of the synapse, and attempt to synthesize the findings to understand how stress may either have beneficial effects on cognitive function or noxious effects, which in turn might lead to the development of neuropsychiatric disorders.

The glutamate tripartite synapse

In addition to its role as the major excitatory neurotransmitter in the brain, glutamate is a key intermediary metabolite in the detoxification of ammonia and a building block used in the synthesis of peptides and proteins. Consistent with its multiple intracellular functions, glutamate is present at extremely high concentrations within the cells of the CNS. The high concentrations of intracellular glutamate require that extremely tight regulatory processes be in place to limit extracellular levels and modulate glutamate receptor activity in order to ensure optimal neurotransmission and prevent against potential excitotoxicity (Figure 1).

Neuronal glutamate can be synthesized *de novo* from glucose via the Krebs cycle and the transamination of α -oxoglutarate, and it can be recycled through the glutamate–glutamine cycle²¹. Exocytotic vesicular release of glutamate, which underlies the vast majority of excitatory neurotransmission in brain, is a strictly regulated process in which the synaptic vesicles that store glutamate merge and then fuse with the presynaptic membrane in response to stimulation. In glutamatergic synapses, presynaptic terminals are normally associated with specialized postsynaptic structures (dendritic spines), unlike synapses at which monoaminergic neurotransmitters (dopamine, noradrenaline, adrenaline, serotonin, histamine) are released.

The core of the presynaptic machinery for vesicular neurotransmitter release, including glutamate release, is the so-called soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptor (SNARE) complex. The SNARE complex is formed by the interaction of two synaptic membrane proteins (syntaxin-1 or syntaxin-2 and SNAP-25) and a vesicular protein (synaptobrevin-1 or synaptobrevin -2), and is thought to mediate the fusion of synaptic vesicles with the presynaptic membrane^{22–24}.

Glutamate regulates synaptic transmission and plasticity by activating ionotropic (AMPA and NMDA) and metabotropic glutamate receptors (mGluR1-8). The number and stability of these receptors at the synaptic membrane is an important factor in determining excitatory synaptic efficacy. Several mechanisms have been proposed to control the surface expression of NMDA receptors (NMDARs) and AMPA receptors (AMPA receptors), including PDZ domain-mediated interactions between channel subunits and synaptic scaffolding proteins^{25–27}, clathrin-dependent endocytosis regulated by phosphorylation^{28–30}, and motor protein-based transport along microtubule or actin cytoskeletons^{31–33}. The Rab family small GTPases, which function as key regulators for all stages of membrane traffic³⁴, is involved in the internalization, recycling and spine delivery of NMDARs and AMPARs^{35,36}. The synthesis and degradation of postsynaptic glutamate receptors are dynamically regulated^{37,38}.

Glutamate is cleared from the extracellular space via high-affinity excitatory amino acid transporters (EAATs), which are located on neighbouring glial cells (EAAT1-2) and, to some extent, on neurons (EAAT 3–5)³⁹. In glial cells, glutamate is converted into glutamine by glutamine synthetase. Glutamine is then transported back into the glutamatergic neuron, where it is hydrolyzed into glutamate by glutaminase²¹. Owing to the lack of degradative enzymes in the synapse, uptake by EAATs is the primary mechanism through which the action of extracellular glutamate is terminated. The following sections will discuss evidence that stress and glucocorticoids can influence glutamate neurotransmission through actions at several sites within the system, namely at the levels of glutamate release, ionotropic glutamate receptor activity and glutamate clearance and metabolism.

Stress effects on glutamate release

Acute stress and glucocorticoids increase extracellular glutamate levels

Glucocorticoids secreted during the diurnal rhythm and during stress (Box 1) affect the basal release of glutamate in several limbic and cortical areas, including the hippocampus, amygdala and PFC^{40,41}. Converging lines of evidence from animal studies suggest that acute exposure to stress or administration of glucocorticoids rapidly increases glutamate release in these brain areas^{40,42–45}. For example, *in vivo* microdialysis studies have shown that exposure of rats to tail-pinch, restraint- or forced-swim stress induces a marked, transient increase of extracellular glutamate levels in the PFC^{44,45}. However, it has been objected that a large portion of amino acid neurotransmitters sampled by microdialysis is of non-neuronal origin, resulting from reverse transporter activity and/or derived from glial cells^{46,47}. Nevertheless, recent evidence from rapid microelectrode measurements suggest that tail-pinch stress-induced glutamate release is largely of neuronal origin⁴⁸.

In different studies using patch-clamp recordings, application of 100 nM corticosterone, the major glucocorticoid in rodents, to hippocampal slices rapidly enhanced the frequency of miniature excitatory postsynaptic potentials in CA1 pyramidal neurons and reduced paired-pulse facilitation (PPF) — a form of synaptic facilitation that reflects presynaptic release — suggesting that corticosterone increases glutamate release probability in this area⁴⁹. This rapid action of corticosterone was found to be non-genomic and mediated by a mineralocorticoid receptor located in or near the plasma membrane (Box 1)^{49,50}.

Stress also has an effect on depolarization-evoked release of glutamate in the prefrontal and frontal cortex, as shown in studies using isolated synaptic terminals (synaptosomes) in superfusion. This method allows precise and selective measurement of endogenous or labeled neurotransmitter release (see Box 2). Rats subjected to acute footshock-stress in a paradigm that induces learned helplessness⁵¹ showed a marked, rapid change in the depolarization-evoked release of glutamate⁵². The increased release of glutamate in prefrontal and frontal cortex was dependent on glucocorticoid receptor activation. The short latency of the effect suggested that the receptor acted non-genomically, although the results of patch-clamp recordings (see below) are also compatible with the timing of genomic actions. Thus, both genomic and non-genomic pathways may be involved in the effect of stress on glutamate release. A similar rapid effect of corticosterone, mediated by glucocorticoid receptors, has been shown in synaptosomes isolated from rat hippocampus⁵³. As shown by recent findings⁵⁴, recruitment of endocannabinoid signalling could be involved in the enhancement of glutamate release induced by corticosterone.

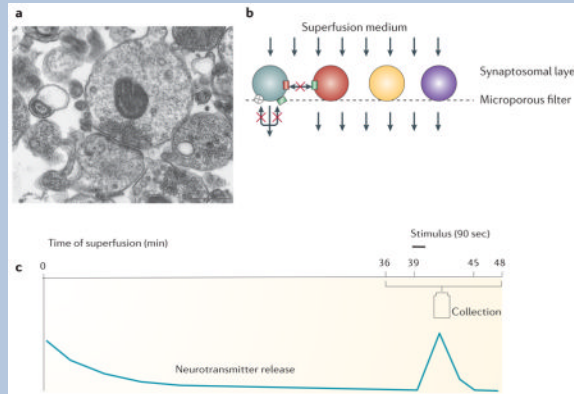
Box 2

Measuring release of endogenous neurotransmitters from purified synaptosomes

The technique for measurement of neurotransmitter release from isolated synaptic terminals (synaptosomes) in superfusion was originally developed by Maurizio Raiteri and co-workers at the University of Genova^{210,211}. The problem they faced was that when neurotransmitter release is evoked from a population of synaptosomes or cells in bulk (i.e. in a test tube), any released molecule will hit receptors and transporters on the same terminal and on neighbouring terminals. This elicits a chain of reactions that in turn modify the release of the same as well as of other neurotransmitters. The problem was solved by applying a thin layer of semi-purified or purified synaptosomes (see the figure, part A.) on a microporous filter and applying a constant up-down superfusion to the sample (see the figure, part B.). Through this method, any released endogenous transmitters and modulators are immediately removed by the superfusion medium before they can be taken up by transporters and activate autoreceptors or heteroreceptors on synaptic terminals. Reuptake can therefore not occur and indirect effects are minimized or prevented. During superfusion all the presynaptic targets (transporters, receptors, channels, enzymes, etc.) can be considered virtually free of endogenous ligands; each of these targets can therefore be studied separately by adding the appropriate ligand at the desired concentration to the thin layer of synaptosomes. Any observed effects on the release of one neurotransmitter can reasonably be attributed to direct actions at the terminals storing that neurotransmitter. Today, superfused synaptosomes represent the method of choice for the functional characterization of the properties of a particular family of nerve endings.

In a typical experiment for measuring the release of endogenous amino acids such as glutamate or GABA, synaptosomes are layered in a thermostated superfusion chamber, the sample is continuously superfused for 36 min with isotonic buffered solution to reach stabilization of basal release; then collection of samples begins, with first 3 min representing basal release of neurotransmitter. At 39 min a stimulus, such as depolarizing concentrations of KCl (15–25 mM), a calcium ionophore (ionomycin), or a receptor agonist is applied for 90 sec. Collection of samples is protracted up to 48 min, with the evoked release-containing sample followed by one more 3-min basal release sample (see the figure, part C). Concentrations of released amino acids in the perfusate samples are successively measured by HPLC.

Over the years this method has been used by many authors to distinguish exocytotic release from release that is due to inversion of neurotransmitter transporters, and to measure changes in release induced by presynaptic receptors. Recently, this method revealed that antidepressant drugs reduce the release of glutamate in the hippocampus (in rats kept under basal conditions), and prevent the increase induced by acute stress in prefrontal/frontal cortex^{51,212}.



The method of synaptosomes in superfusion involves using synaptic terminals detached from whole tissue. Measuring release of endogenous glutamate can also be performed in slices of whole PFC tissue, in which the neural circuitry is preserved. Patch-clamp recordings from PFC slices from rats subjected to footshock-stress showed that exposure to stress increased the amplitude of spontaneous excitatory postsynaptic potentials in pyramidal neurons, an effect abolished by pretreating the rats with the antidepressant desipramine⁵². Moreover, PPF and its calcium-dependence were decreased in PFC slices from stressed rats. Combined, these results are consistent with increased glutamate release, as well as with increased activation of postsynaptic ionotropic glutamate receptors, in the PFC of stressed rats.

In principle, the acute-stress-induced enhancement of stimulus-evoked release of glutamate may be achieved by increasing the number of synaptic vesicles that are already docked to the membrane and ready for release — the readily releasable pool of vesicles (RRP) — or by increasing the probability of release of synaptic vesicles, or both^{55–58}. At the level of presynaptic machinery, footshock-stress induced an increase in the number of SNARE complexes bound to the presynaptic membrane from PFC neurons⁵² (Figure 2), suggesting that at least the first mechanism is involved. Indeed, inducing glutamate release with hyperosmotic sucrose from synaptosomes in superfusion from the prefrontal and frontal cortex of rats exposed to footshock-stress revealed that the RRP was about 2-fold that of control rats⁵⁹. Preliminary data obtained using Total Internal Reflection Fluorescence Microscopy to measure the recruitment of FM1-43-labeled synaptic vesicles to the membrane also suggest a greater RRP after *in vitro* application of corticosterone to prefrontal and frontal cortex synaptosomes⁵⁹.

Interestingly, the effect of acute stress on depolarization-evoked glutamate release in the PFC could be prevented by treating the rats with various classes of antidepressant drugs, endowed with different primary mechanisms of action, for two weeks prior to the stress exposure⁵². The mechanism whereby antidepressant drugs block the presynaptic effect of stress on depolarization-evoked glutamate release is unknown at present. Stress-induced serum corticosterone levels were similar in antidepressant-treated and untreated rats, suggesting that the drugs do not alter corticosterone release. Instead, they might affect

intracellular signalling downstream of glucocorticoid receptor activation by corticosterone or act directly on the glutamate release machinery. However, the number of SNARE complexes was increased in all stressed rats, regardless of whether they had been previously treated with antidepressants or not. This suggests that the antidepressant drugs acted downstream from the assembly of SNARE complex. For example, they could act at the level of interaction of regulatory and fusogenic proteins with the SNARE complex, modulating the function of the complex itself⁶⁰⁻⁶³. It has been argued⁶⁴ that the effect of antidepressants on glutamate release in the PFC could be involved in the long-term anxiolytic and antidepressant action of these drugs, because they are able to dampen glutamate release in response to acute stress⁵².

Chronic stress and glutamate release

As discussed above, stress acutely enhances glutamate release in the PFC and hippocampus. However, the effects of chronic stress on glutamate release are still mostly unknown. It has been shown that three repeated tail-pinch stressors (at 2.5 hr intervals) in rats produce transient glutamate effluxes in the hippocampus that remain constant in duration and magnitude, whereas in the PFC they decrease upon subsequent applications⁶⁵. These results suggest a selective adaptation of glutamate release to stress in the PFC. A different study tested the response to an acute stressor in rats subjected to 21-day chronic restraint stress. After a subsequent single stress challenge extracellular glutamate levels (measured by microdialysis) in CA3⁶⁶ remained elevated in chronically stressed rats, compared to naïve rats subjected to the same acute stressor, suggesting an altered regulation of the termination of glutamate release after chronic exposure to stressful stimuli.

Effects on ionotropic glutamate receptors

Stress and glucocorticoid effects on glutamatergic transmission

In addition to the rapid and transient increase in presynaptic glutamate release in the PFC after acute stress^{44,45,52}, acute stress also has a delayed and sustained impact on PFC postsynaptic glutamate receptor-mediated responses^{67,68}. Electrophysiological recordings have shown that both NMDAR- and AMPAR-mediated synaptic currents are markedly increased in PFC pyramidal neurons in various models of acute stress⁶⁷. This effect is observed >1 hr post-stress, is sustained for 24 hrs after the cessation of stress and can be mimicked by short-term corticosterone treatment *in vitro*⁶⁷⁻⁶⁹. The acute stress- and corticosterone-induced enhancement of basal glutamatergic transmission is caused by an increased surface expression of NMDA and AMPA receptors at the postsynaptic plasma membrane^{67,68}.

The delayed effect of acute stress or corticosterone treatment on basal PFC glutamatergic transmission is mediated by intracellular glucocorticoid receptors^{67,68}, in contrast to the fast, increase of glutamate release in CA1 hippocampus, which is mediated by membrane-bound mineralocorticoid receptors^{49,70}; this difference could be due to the low expression of mineralocorticoid receptors in the PFC⁷¹. There are other regional differences in the effects of stress on glutamate transmission. For example, acute stress or corticosterone treatment increases AMPAR and NMDAR responses to a similar extent in the PFC^{67,68} but selectively enhances AMPAR-mediated currents in CA1 neurons^{72,68}, midbrain dopamine neurons⁷³ and nucleus accumbens shell neurons^{73,74}. Furthermore, the potentiating effects of acute stress on AMPAR and NMDAR responses in the PFC are independent of each other⁶⁸, which is different from the classic NMDAR-dependent long-term potentiation (LTP) of AMPAR responses in the hippocampus.

The impact of chronic stress on basal PFC glutamatergic transmission is less well understood. A recent study showed that one week of repeated restraint or unpredictable

stress leads to a marked reduction of AMPAR- and NMDAR-mediated synaptic currents in PFC pyramidal neurons from juvenile male rats, which sustains for a few days after stress extinction⁷⁵. No change in basal synaptic currents was observed in striatal neurons, CA1 pyramidal neurons⁷⁵ or dentate gyrus neurons⁷⁶. This suggests that the PFC is more sensitive to chronic stress compared to the striatum or hippocampus, perhaps especially during the adolescent period, when this region is still undergoing significant development⁸.

Stress also affects synaptic plasticity — the ability to potentiate (LTP) or depress (long-term depression (LTD)) the efficacy of glutamatergic transmission — in the hippocampus^{9,71} and PFC. Acute stress inhibits LTP in the amygdala–PFC pathway, in parallel with the suppression of hippocampal LTP⁷⁷. The acute stress-induced impairment of LTP in the hippocampus–PFC pathway is prevented by antidepressant treatment⁷⁸ or GR blockade⁷⁹. Moreover, prior stress exposure prevents the ability of a second episode of stress to suppress LTP in the prefrontal cortex⁸⁰ — a form of emotional metaplasticity that forms the neural basis of stress experience-dependent fear memory⁸¹. Acute stress has divergent effects on LTD: it enhances mGluR-dependent LTD in the hippocampus⁸², but prevents serotonin-facilitated LTD induction in the PFC⁸³. Chronic stress impairs LTP in the thalamus–PFC pathway⁸⁴ and LTP in the hippocampus–PFC connection⁸⁵, and these effects are associated with the disruption of PFC-dependent tasks, such as working memory and behavioural flexibility⁸⁵. Catecholaminergic facilitation of LTP in the infralimbic region of the medial PFC is also impaired by chronic stress and restored by post-stress recovery⁸⁶. These changes in synaptic plasticity could be due to the altered structure of glutamatergic synapses — such as atrophy, dendritic retraction or spine loss — which have been associated with chronic stress^{85,86} (Box 3). Alternatively, they could be due to chronic-stress-induced loss of glutamate receptors and diminished glutamatergic transmission in PFC neurons. In line with this view, the synaptic inhibition in the medial PFC and the fear extinction deficit that have been observed in rats with repeated early stress exposure are ameliorated by the NMDA receptor agonist D-cycloserine⁸⁷.

Box 3

Structural changes induced by stress

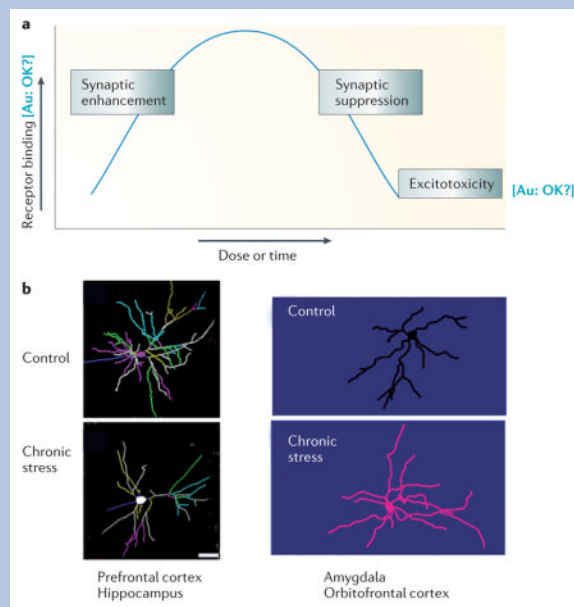
Until recently, much of our information on stress, excitatory amino acids (EAA) and synaptic function has come from studies on the hippocampus, which expresses both mineralocorticoid and glucocorticoid receptors. In the hippocampus, EAAs and glucocorticoids mediate biphasic effects on structure and function (see the figure, part A). Acutely (that is, over hours), low to moderate physiological levels of adrenal steroids and EAA enhance synaptic function and certain types of memory, whereas higher levels of both mediators have the opposite effect²¹³. More chronically (that is, over days to weeks), adrenal steroids and EAAs mediate adaptive plasticity involving spine synapse turnover, dendritic shrinkage and suppression of adult neurogenesis in the dentate gyrus⁷. However, when there is a sudden insult such as a seizure, stroke or other head trauma, EAAs and glucocorticoids induce permanent, irreversible hippocampal damage²¹⁴.

Acute and chronic stress also induce structural changes in other brain areas. Chronic stress causes neurons in the medial prefrontal cortex (medial PFC) to undergo shrinkage and simplification of dendrites and reduction of spine synapse density, whereas the same stress regimen causes neurons in the basolateral amygdala and orbitofrontal cortex (OFC) to grow (see the figure, part B)^{5,6}. With the cessation of stress, these alterations are reversible^{215,216}, except possibly in the basolateral amygdala, where changes persisted for at least 30 d after chronic stress²¹⁷. Moreover, age is a factor in recovery, as the aging

medial prefrontal cortex fails to show recovery in the same time frame as occurs in younger animals²¹⁸.

Structural plasticity can also occur after acute stress. A single traumatic stressor causes basolateral amygdala neurons to grow new spines over the next 10 days, but there is no growth of dendrites²¹⁹. And a single, high dose of injected corticosterone causes delayed dendritic growth over the next 10d²²⁰, mimicking the effects of chronic stress, although we do not know what happens to spines on those dendrites.

As to the mechanism underlying these effects, we know most about the hippocampus. Here, EAAs and glucocorticoids synergize to produce the effects summarized in Figure A²²¹. EAA transporters in astrocytes and neurons play an important part in this^{160,222}. In addition, chronic stress effects on shrinkage of dendrites in the CA3 region of the hippocampus are mediated in part by brain-derived neurotrophic factor (BDNF)²²³, whereas loss of spines in the CA1 region of the hippocampus are mediated in part by tissue plasminogen activator secretion by EAA-releasing neurons²²⁴ and by BDNF²²³. Effects of chronic stress on dendrite shrinkage in CA3 are blocked by NMDA blockers²²¹ and NMDA blockade also prevents chronic stress induced shrinkage of medial prefrontal cortex neurons²²⁵.



Stress and glucocorticoid effects on glutamate receptor trafficking and mobility

Emerging evidence shows that AMPARs and NMDARs undergo dynamic exocytosis–endocytosis and lateral diffusion — processes that play a key role in controlling excitatory synaptic efficacy^{88,89}. This suggests that stress and glucocorticoids may affect glutamatergic transmission through altering glutamate receptor trafficking and mobility. A glucocorticoid receptor-mediated, slowly-developing increase in the surface mobility of GluR2-containing AMPARs has been found in cultured hippocampal neurons after corticosterone treatment, which may underlie the facilitating effect of glucocorticoids on the recruitment or endocytosis of AMPA receptors during bi-directional synaptic plasticity^{90,91}. Consistent with this possibility, mice trained in the spatial water maze task under stressful conditions show enhanced synaptic expression of AMPAR GluR2 subunits in the hippocampus than those trained under non-stressed conditions. This enhanced expression may underlie the

facilitation of spatial learning and memory by stress in these mice⁹². In the rat PFC, the surface expression of NMDAR and AMPAR subunits, as well as the density of synaptic NMDAR and AMPAR clusters, is substantially elevated by acute stress or a short corticosterone treatment^{67,68}. This suggests that the acute stress-induced synaptic potentiation in the PFC may be attributed to the increased delivery of glutamate receptors from intracellular or extrasynaptic surface pools to the synaptic membrane.

The impact of chronic stress on postsynaptic glutamate receptors in the PFC (and other brain areas) is less well understood (see supplementary online information S1 (table)). A history of chronic corticosterone exposure has been found to impair fear extinction in rats, with an associated reduction of NR2B and GluR2 and/or 3 subunit expression selectively in the ventromedial PFC⁹³. Recently, it was shown that repeated restraint or unpredictable stress in rats causes a loss of surface AMPAR and NMDAR subunits in PFC neurons⁷⁵, which contrasts with the facilitating effect of acute stress on glutamate receptor surface expression^{67,68}. The level of total GluR1 and NR1 subunits in the PFC is also markedly reduced by exposure to repeated stress.⁷⁵ Thus, disrupted membrane trafficking and/or altered degradation or synthesis of glutamate receptors may contribute to the loss of PFC glutamatergic transmission in chronically stressed animals.

Intracellular signalling underlying stress and glucocorticoid effects on glutamate receptors

The classical glucocorticoid receptor is a ligand-inducible nuclear transcription factor⁹⁴. The delayed potentiating effect of short-term corticosterone treatment on excitatory postsynaptic responses in the PFC is abolished by glucocorticoid receptor antagonists and inhibitors of gene transcription or protein translation⁶⁸, suggesting that it is a glucocorticoid receptor-mediated genomic effect. Serum- and glucocorticoid-inducible kinases (SGKs), a family of immediate early genes activated by glucocorticoid receptors, have been found to control the enhancing effect of acute stress on glutamate receptor trafficking and function in the PFC⁶⁸ (Figure 3). The transcription, subcellular localization and enzymatic activity of SGKs are under the stringent regulation of various stimuli, such as oxidative stress or hormones⁹⁵. SGKs participate in a wide variety of physiological functions, including activation of ion channels and carriers, regulation of transport, gene transcription, neuroexcitability, cell proliferation, and apoptosis⁹⁶. Interestingly, SGK1 exhibits a fourfold higher expression in the hippocampus of fast-learning than slow-learning rats in the water maze learning task, and enhanced SGK expression in CA1 facilitates memory consolidation of spatial learning in rats⁹⁷. Thus, SGK potentially plays a crucial role in glucocorticoid-induced memory facilitation by increasing the abundance of glutamate receptors in the synaptic membrane of neurons in limbic regions controlling cognition^{67,68,92}.

The key molecule linking glucocorticoid receptors and SGK activation to the increased surface expression of NMDARs and AMPARs following acute stress is Rab4^{68,69}, a member of the Rab family that mediates receptor recycling between early endosomes and the plasma membrane⁹⁸. Rab proteins coordinate all the intracellular transport steps in the exocytic and endocytic pathways⁹⁹. Many Rab proteins are regulated by the GDP dissociation inhibitor (GDI)¹⁰⁰, which functions as a cytosolic chaperone of Rab¹⁰¹. SGK phosphorylates GDI and thereby promotes the formation of GDI–Rab4 complex, thus facilitating the functional cycle of Rab4 and Rab4-mediated recycling of AMPARs to the synaptic membrane⁶⁹ (Fig 3).

Whether other signalling pathways are also involved in effects of stress and glucocorticoids on glutamate receptors awaits investigation. In the hippocampus, a single corticosterone injection fails to upregulate *Sgk1* mRNA¹⁰². However, acute stress has been found to trigger the activation of MAPK–EGR1 pathway via a glucocorticoid receptor-mediated genomic

mechanism¹⁰³, and inhibition of the hippocampal MAPK pathway abolishes the glucocorticoid-induced increase in contextual fear conditioning¹⁰³. Moreover, in the PFC, but not the hippocampus, of mice, acute restraint stress causes an increase in the expression of *Arc* (activity-regulated cytoskeletal-associated protein)¹⁰⁴, an immediate early gene that plays a key role in activity-dependent synaptic modification^{105,106}. In addition, changes in adhesion molecules could potentially be involved in the effect of short-term glucocorticoids on excitatory synapses⁹².

The intracellular signalling pathway that mediates the effect of chronic stress on glutamate receptors remains largely unknown. One key mechanism for remodelling synaptic networks and altering synaptic transmission is post-translational modification of glutamate receptors and their interacting proteins through the ubiquitin pathway at the postsynaptic membrane¹⁰⁷. Recently it was found that the loss of glutamate receptors in rat PFC neurons after repeated stress is attributable to increased ubiquitin–proteasome-dependent degradation of GluR1 and NR1 subunits⁷⁵.

Implications for cognitive function

Given the role of glutamate receptor trafficking in learning, memory and other behaviours^{108,109}, it is plausible that glucocorticoids regulate PFC-mediated cognitive processes by influencing postsynaptic glutamate receptor channels. Indeed, the GR–SGK-induced enhancement of PFC glutamatergic transmission may underlie the facilitated working memory induced by acute stress: exposing rodents to an acute stressor improves their performance in a working memory task, and this effect is abolished by blocking glucocorticoid receptor or SGK function in the PFC^{67,68}. This finding fits well with acute stress- or glucocorticoid-induced facilitation of working memory (which involves the PFC) or declarative memory (which involves the hippocampus) observed in humans^{110–112}. By contrast, chronic stress or glucocorticoid treatment impairs PFC-dependent cognitive functions in rats^{5,113} and humans^{114,115}, similar to the stress-induced deficits in hippocampus-dependent cognitive processes¹¹⁶. It awaits investigation whether the suppression of PFC glutamatergic transmission by repeated stress underlies the working memory impairment and other cognitive symptoms often observed in stress-related mental disorders.

Effects on clearance and metabolism

Most studies examining the effects of stress on brain structure and physiology focus on neurons. However, emerging data suggest that stress may also affect glial cell function, including glutamate clearance and metabolism in these cells. These data are discussed below.

Glutamate transporters on glial and, to a lesser extent, neuronal, membranes rapidly bind synaptic glutamate, thereby influencing synaptic transmission and plasticity¹¹⁷. The locations of the transporters within the tripartite synapse are optimized for preventing glutamate spillover and activation of extrasynaptic glutamate receptors. Consistent with this function, in the hippocampus, glial glutamate transporter activity influences the level of stimulation of peri- and extrasynaptic NMDA receptors and mGluRs, but has little direct effect on synaptic AMPA-mediated excitatory postsynaptic potentials¹¹⁸. The effects of astrocytic remodelling on glutamatergic neurotransmission in the hypothalamus of lactating rats provides a clear example of how reduced astrocytic coverage of synapses can have dramatic effects on extrasynaptic glutamatergic neurotransmission¹¹⁹. Modulation of EAAT2 (the major glutamate transporter, expressed predominantly in glia) expression and function can affect neuronal vulnerability to excitotoxic events³⁹, which is thought to be mediated by the relative activation of extrasynaptic to synaptic NMDA receptors^{120–125}.

Moreover, modulation of EAAT2 expression affects hippocampal LTD¹²⁶. As the transporters are generally highly efficient in clearing glutamate from the extracellular space^{39,127}, any effects of altered EAAT function are likely to be most pronounced under conditions of elevated glutamate release, such as under stress. Considering that individual astrocytes serve large numbers of synapses, with minimal overlap in the synapses served by neighbouring astrocytes^{128,129}, the failure of a single astrocyte could impair glutamate removal at thousands of synapses¹¹⁸.

Effects of stress and glucocorticoids on glial cell number

Studies published over a decade ago revealed the potential contributions of glial cell pathology to stress-related psychiatric disorders such as major depressive disorder and bipolar disorder. For example, PFC regions of post-mortem brain samples from individuals suffering from mood disorders showed markedly reduced glial cell numbers and density^{130–132}. Depressed subjects also show reduced immuno-staining of glial fibrillary acidic protein (GFAP) — the main intermediate filament protein in mature astrocyte — in the PFC and other brain regions including the amygdala and cerebellum^{133–137}. Classically, GFAP has been used as a marker for mature astrocytes, but more recent studies that highlight the complex relationship between GFAP expression and a variety of astrocytic functions suggest that the expression may be heavily physiologically regulated¹³⁸. It is therefore unclear if the findings in postmortem brain tissue from patients reflect a loss of GFAP expressing cells or a reduction in the amount of GFAP expressed by the cells. Considering the central role of astrocytes in amino acid neurotransmitter metabolism, these findings, which are suggestive of glial cell pathology, were rapidly associated with emerging reports of abnormal GABA and glutamate content in the brains of patients with mood disorders^{139,140} that appeared around the same time.

Rodent models assessing the impact of stress on glial cells have largely focused on the effects of chronic stress. Chronic unpredictable stress was associated with reduced proliferation of glial progenitor cells¹⁴¹, decreased numbers of GFAP-positive cells and reduced expression of GFAP in the prelimbic cortex^{141,142} (Figure 4). Rats exposed to early life stress had a reduced density of GFAP-immunoreactive astrocytes in the frontal cortex in adulthood, demonstrating the potential long-term effects of stress on glial cells¹⁴³. Chronic stress-induced reductions in GFAP-immunoreactive astrocyte levels were also found in the hippocampus in rats and tree shrews^{144,145}. Another recent study employing a shorter-term repeated stress exposure accompanied by a blast-induced traumatic brain injury found inflammation and increased GFAP immunoreactivity in the PFC and hippocampus from the animals that had experienced both the chronic stress and the trauma but not in animals that had been exposed to the stress alone¹⁴⁶. This finding suggests that physical injury or inflammation may stimulate a region of reactive gliosis that can be associated with an increased GFAP expression¹³⁸. This reactive gliosis-associated increase in GFAP expression could provide an explanation for the increased GFAP expression observed under certain stress conditions, such as those involving repeated restraint stress¹⁴⁷.

Glucocorticoids can alter the level and expression of GFAP in the PFC and other regions in rat brain, with both short and long term corticosterone treatments resulting in > 20% reduction in GFAP levels^{148,149}. These changes were paralleled by changes in *GFAP* mRNA expression, indicating a genomic effect. This effect of glucocorticoids was not generalized to other astrocytic proteins or major structural neuronal proteins¹⁴⁸. However, later studies that reported increased levels of GFAP expression in the hippocampus after chronic glucocorticoid treatment^{150,151} suggest that the effects are diverse and complex, with glucocorticoids potentially having regional and dose-related effects on GFAP expression.

Effects of stress and glucocorticoids on glial cell glutamate uptake

Changes in GFAP expression in the brains of stressed animals of course do not provide direct evidence of altered glutamate clearance (and, by extension, glutamate neurotransmission). However, there is evidence to suggest GFAP can modulate glutamate uptake activity through effects on transporter trafficking and surface expression¹⁵². A few studies have provided more direct measures of the effect of stress on glutamate uptake. An early study employing synaptosomal preparations from acutely restrained rats suggested that acute stress increases glutamate uptake in the frontal cortex and hippocampus¹⁵³. Later studies have yielded mixed results in the hippocampus following acute stress exposure, showing either a glucocorticoid-mediated suppression of glutamate uptake¹⁵⁴ or no effect on uptake¹⁵⁵.

In relation to chronic stress, one study showed a decrease in cortical glutamate uptake following 21 days of restraint stress exposure¹⁵⁶. A recent study also found a reduction in hippocampal glutamate clearance in hippocampal slice preparations from chronically stressed rats as well as evidence of increased glutamate release from hippocampal synaptosomes¹⁵⁷. Another recent study using slice preparations from hippocampal, striatal and PFC regions reported no change in glutamate clearance immediately or 24 hours following various types of footshock exposure. However, increased glutamate uptake from hippocampal slices of helpless animals was observed immediately after exposure, and reduced rates of glutamate uptake in all three regions of the helpless animals 21 days later was reported¹⁵⁸. This suggests a potential biphasic time course of the regulation of glutamate uptake following stress exposure. Yet another study, demonstrating a negative correlation between EAAT2-expression levels in the hippocampus, occipital and retrosplenial granular cortex of rats and the level of helplessness 5 weeks after exposure to foot shock stress¹⁵⁹, provides evidence that the stress-related effects on EAAT2 function are long-lasting and associated with behavioural changes. Together with the findings discussed above, these data suggest that chronic stress impairs both the mechanisms that regulate glutamate release and the mechanisms that regulate glutamate clearance. These longer-term effects on the balance of glutamate release and uptake following chronic stress could contribute to the finding of sustained elevations of extracellular glutamate concentrations in the hippocampus of rats subjected to chronic stress, discussed above⁶⁶.

Emerging evidence suggests that glucocorticoids may have a role in mediating the effects of stress on EAAT2 regulation. Rats chronically exposed to high levels of glucocorticoids exhibited increases in GLT-1b (an isoform of GLT-1 (EAAT2)) expression in the hippocampus¹⁶⁰. In addition, activation of glucocorticoid receptors increased EAAT2 expression and enhanced glutamate uptake in primary astrocytes derived from cortical tissue¹⁶¹. However, the complex and seemingly biphasic regulation of EAAT2 by glucocorticoids is highlighted by the fact that EAAT2 mRNA expression was increased by adrenalectomy and inhibited by subsequent glucocorticoid replacement, whereas chronically elevated levels of glucocorticoids increased EAAT2 protein expression throughout the hippocampus¹⁶⁰.

Other processes could also mediate the stress-induced effects on glutamate uptake. Highly conserved promoter sequences, including those for epithelial growth factor (EGF), transforming growth factor α (TGF α), and tumor necrosis factor α (TNF α), have been identified in the regulatory region of *EAAT2* in rodents and humans¹⁶². Circulating TNF α levels in particular, increase with chronic stress¹⁶³ and have been shown to downregulate astrocyte-mediated glutamate transport through the direct downregulation of GLT-1^{164,165}. *In vitro* studies also show that neuronal activity is linked to genomic and non-genomic regulation of astrocyte-specific synaptic functions such as trafficking and membrane stabilization or clustering of EAAT2 protein^{166,167}. Thus, extracellular levels of glutamate

itself can act to rapidly increase the function of glutamate transporters, to limit excitotoxicity following excessive glutamate release. Interestingly, post-mortem studies showed lower mRNA expression levels of *SCLIA2* and *SCLIA3* (the genes encoding the glial glutamate transporters) in the PFC¹⁶⁸ and locus coeruleus¹⁶⁹ of patients with major depressive disorder and lower EAAT2 immunoreactivity in the orbitofrontal cortex of depressed individuals compared with controls¹³⁶.

Effects of stress on glutamate metabolism

Postmortem studies of the PFC of depressed individuals have shown reduced levels of the glutamate-ammonia ligase gene (*GLUL*) that encodes glutamine synthetase (which converts glutamate into glutamine) in glia^{168,170}, and a trend for reduced glutamine synthetase-immunoreactivity in the orbitofrontal cortex of patients with major depressive disorder compared to controls¹³⁶. However, few studies have examined the effects of stress on glutamine synthetase regulation. Rats exposed to chronic unpredictable stress showed reductions in glutamate–glutamine cycling in the PFC¹⁷¹. However, there was no evidence of reduced glutamine synthetase expression, suggesting that other, non-transcriptional regulatory factors may mediate the stress-induced changes. It is also possible that other steps in the metabolic cycle, such as the decreased uptake of glutamate into the glial cell, as discussed above, may contribute to the stress effect on glutamate metabolism.

In sum, the evidence suggests that acute stress and acute glucocorticoid treatments induce adaptive changes that lead to increased glutamate clearance, thereby preventing spillover of the excessive release of presynaptic glutamate into the extrasynaptic space. However, chronic stress, and possibly chronic glucocorticoids treatment, seem to result in sustained glial cell alterations and reduced rates of amino acid neurotransmitter cycling in the PFC, suggesting that chronic stress causes a reduced glutamate clearance capacity relative to the levels of glutamate release. Increased levels of extrasynaptic glutamate could lead to cellular damage through activation of extrasynaptic glutamate receptors, resulting in disruption of cellular functions and neurodegeneration¹²⁰. This process could be involved in the cellular changes^{130,131,133,134,136,172,173} and volume reductions that are commonly observed in the PFC and hippocampus of patients with stress-related disorders, such as mood and anxiety disorders^{174,175}. In a preliminary report, extracellular hippocampal glutamate content, measured by *in vivo* microdialysis, were correlated with reduced hippocampal volume in individuals with seizure disorders¹⁷⁶, lending support to this hypothesis outlined above, although it does not prove that the relationship between extracellular glutamate levels and hippocampal volumes is causal.

Conclusions and future directions

Stress has been shown to induce complex structural changes in various brain regions (Box 3). With regard to the glutamatergic synapse, stress can have either plasticity-enhancing effects that are associated with improved cognition and function or noxious effects that are associated with impaired function, depending on the type, intensity and duration of the event, and this may contribute to the pathophysiology of psychiatric disorders (see supplementary online information S1 (table)). Recent studies are beginning to elucidate how stress-induced changes in various aspects of glutamate neurotransmission are causally linked to each other and to the glucocorticoid responses to stress.

Acute stress seems to have the general effect of increasing glutamatergic neurotransmission in the PFC and other regions associated with memory, learning and affect, by inducing both genomic and non-genomic changes at various sites within the tripartite synapse. The presynaptic release of glutamate is rapidly increased by mineralocorticoid or glucocorticoid receptor-mediated effects on the machinery that regulates glutamate release. At the

postsynaptic site, acute stress seems to increase the surface expression and density of ionotropic glutamate receptors, resulting in synaptic potentiation, with the mechanism and timing of these effects varying between brain regions. Although few studies have adequately examined the effects of acute stress on glutamate clearance and metabolism, there seems to be an increased expression of EAAT2 and possibly other glutamate transporters, matching the increased synaptic release of glutamate following acute stress exposure. Together, these changes could contribute to the adaptive stress response on cognitive functions, demonstrated by findings that moderate acute stress facilitates classical conditioning¹⁷⁷, associative learning^{92,178} and working memory^{67,68}.

Emerging studies now suggest that chronic stress exposure has different effects on the glutamate synapse. Data from early studies suggest that chronic stress causes prolonged periods of stimulated glutamate release following acute stress exposure, at least in the hippocampus. Possibly as a compensatory response to elevated synaptic glutamate activity, there are changes in the surface expression of AMPAR and NMDAR subunits that seem to be associated with a decreased transmission efficiency and potentially impaired synaptic plasticity. Initial rodent studies suggest that the PFC may be specifically sensitive to the stress-induced effects on postsynaptic receptor function. Lastly, there is growing evidence from animal studies that chronic stress has effects on glial cell morphology, metabolism and function in the PFC and possibly also the hippocampus. These long-lasting chronic stress-induced changes in glutamatergic transmission may be linked to the impairments in spatial and contextual memory performance and attentional control^{5,7}, and the impaired synaptic plasticity in the hippocampus–PFC connection that have been observed in rats after chronic stress⁸⁵. The decreased ability to clear extracellular glutamate as a result of impaired glial cell uptake and metabolism, combined with stress-induced changes in glutamate release and glutamate receptor function, could provide a pathophysiological mechanism leading to many of the structural changes (Box 3) observed in brain regions of individuals with stress-associated psychiatric disorders, such as mood and anxiety disorders.

These findings suggest a new line of drug development that should be aimed at minimizing the effects of chronic stress exposure on the function of the glutamatergic neurotransmitter system^{64,179} (Figure 5). Findings from animal studies that chronic administration of antidepressant drugs such as SSRIs, SNRIs, tricyclics and atypical antidepressants reduce the stress-induced up-regulation of glutamate release in superfused synaptosomes from prefrontal/frontal cortex⁵² support the hypothesis that pharmacological modulation of presynaptic release of glutamate may provide a means of preventing the effects of stress. Other studies have demonstrated that drugs such as riluzole^{180–182} and ceftriaxone¹⁸³, which increase glutamate clearance, can prevent or reverse the effects of chronic stress and chronic glucocorticoid exposure on amino acid neurotransmitter cycling; on glial expression within the PFC; and on despair and anhedonia in animal models of depression^{171,184,185}. This points to glutamate clearance mechanisms as potential new targets for novel drug development. Positive and negative allosteric modulators of metabotropic glutamate receptors, which can influence glutamate release and extracellular glutamate levels, have also been shown to have antidepressant-like actions¹⁸⁶ and are now being investigated for use in various psychiatric indications. Further, drugs that directly target ionotropic receptors have become targets for psychiatric drug development¹⁷⁹. Specifically, NMDA receptor antagonists such as ketamine have been shown to produce a rapid and sustained antidepressant response in both preclinical animal models and small controlled clinical trials¹⁸⁷. The results of recent studies suggest that this NMDAR antagonist antidepressant effect may be related to a rapid increase in glutamate release, resulting in activation of AMPA receptors and downstream changes in synaptic protein synthesis and dendritic spine formation^{188–190}. The antidepressant effect of the NMDA receptor antagonist-induced glutamate surge may at first seem contradictory to the model presented above. However, it is

possible that the rapid increase in glutamate release following ketamine treatment can transiently compensate for the decreased transmission efficiency and impaired synaptic plasticity associated with chronic stress and stress-related disorders. A recent study that demonstrated that acute treatment with NMDA channel blockers rapidly ameliorates chronic unpredictable stress-induced decreases in the expression levels of synaptic proteins and spine number and the frequency and amplitude of synaptic currents in the PFC¹⁹¹, further supports this line of reasoning. Additional support for this hypothesis comes from studies showing that positive allosteric modulators of AMPA-type glutamate receptors have antidepressant-like properties in rodent models of depression¹⁹².

In conclusion, recent studies are beginning to show that acute stress and glucocorticoids can facilitate learning and memory in both the PFC and hippocampus and that chronic stress may contribute to the pathophysiology of several psychiatric disorders through effects on the glutamatergic synapse, especially within the PFC. The identification and characterization of the physiological mechanisms that regulate the presynaptic release, post-synaptic receptor expression and trafficking, and clearance and metabolism of glutamate allows the opportunity to use novel pharmacological interventions to improve and retain memory function and to treat and possibly prevent some psychiatric disorders.

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Glossary

FM1-43 FM1-43 is an amphiphilic fluorescent dye, that can intercalate into the phospholipid bilayer of biological membranes, allowing to stain presynaptic vesicles

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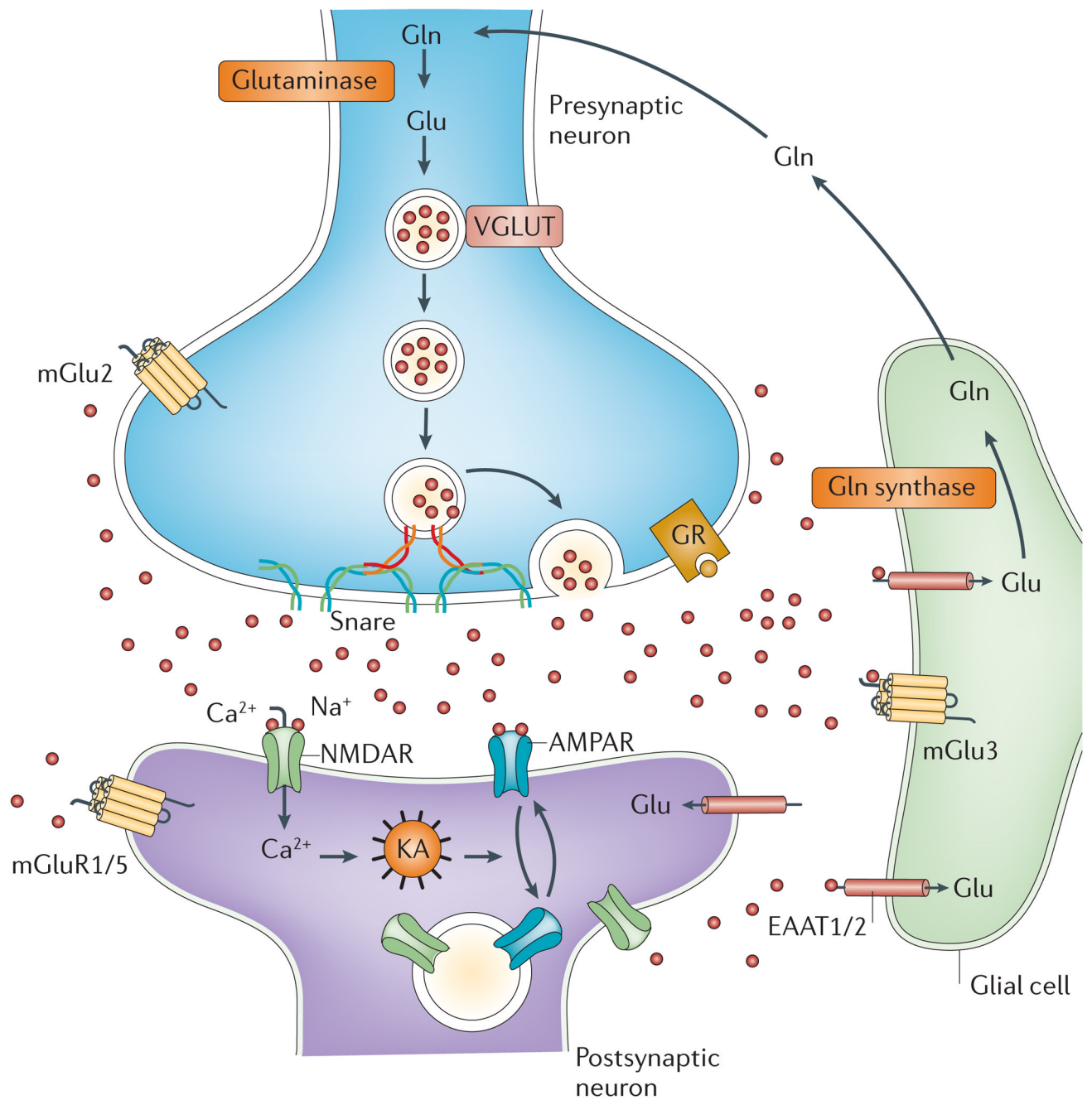


Figure 1. The tripartite glutamate synapse

Neuronal glutamate is both synthesized *de novo* from glucose (not shown) and from glutamine (Gln) supplied by glial cells. Glutamate is then packaged into synaptic vesicles by vesicular glutamate transporters (vGluT). SNARE complex proteins mediate the interaction and fusion of vesicles with the presynaptic membrane. After release into the extracellular space, glutamate binds to ionotropic (NMDA, AMPA) and metabotropic (mGluR 1–8) receptors on the membranes of both post-synaptic and pre-synaptic neurons and glial cells. Upon binding, the receptors initiate various responses, including membrane depolarization, activation of intracellular messenger cascades, modulation of local protein synthesis and, eventually, gene expression (not shown). Surface expression and function of NMDARs and

AMPA receptors are dynamically regulated by protein synthesis and degradation and receptor trafficking between the postsynaptic membrane and endosomes. The insertion and removal of postsynaptic receptors provide a mechanism for long-term modulation of synaptic strength. Glutamate is cleared from the synapse through excitatory amino acid transporters (EAATs) on neighbouring glial cells (EAAT1 and 2) and, to a lesser extent, on neurons (EAAT 3–5). Within the glial cell, glutamate is converted to glutamine by glutamine synthetase and the glutamine is subsequently released via system N transporters and taken up by neurons through System A sodium-coupled amino acid transporters to complete the glutamate–glutamine cycle.

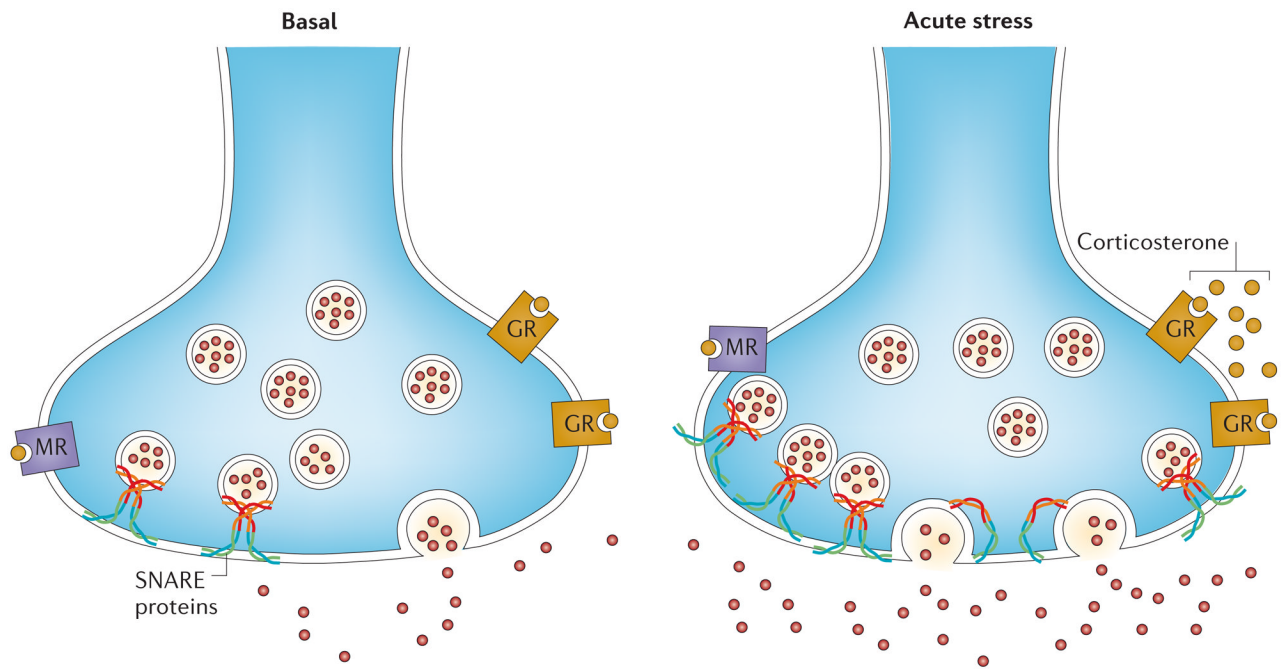


Figure 2. Acute stress rapidly enhances glutamate release in prefrontal/frontal cortex
 Acute footshock stress enhances depolarization-evoked release of glutamate from presynaptic terminals of rat prefrontal/frontal cortex⁵². The acute stress response involves a rapid increase of circulating levels of corticosterone, which binds to membrane-located glucocorticoid receptors (GRs). This induces a rapid GR-mediated increase of presynaptic SNARE protein complexes (which mediate fusion of synaptic vesicles) in the presynaptic membrane⁵². Because the number of SNARE complexes per vesicle is reputed to be constant, this suggests that acute stress induces an increase of the readily releasable pool of glutamate vesicles. The signalling pathways downstream of glucocorticoid receptor activation that induce the increase of the readily releasable pool are unknown.

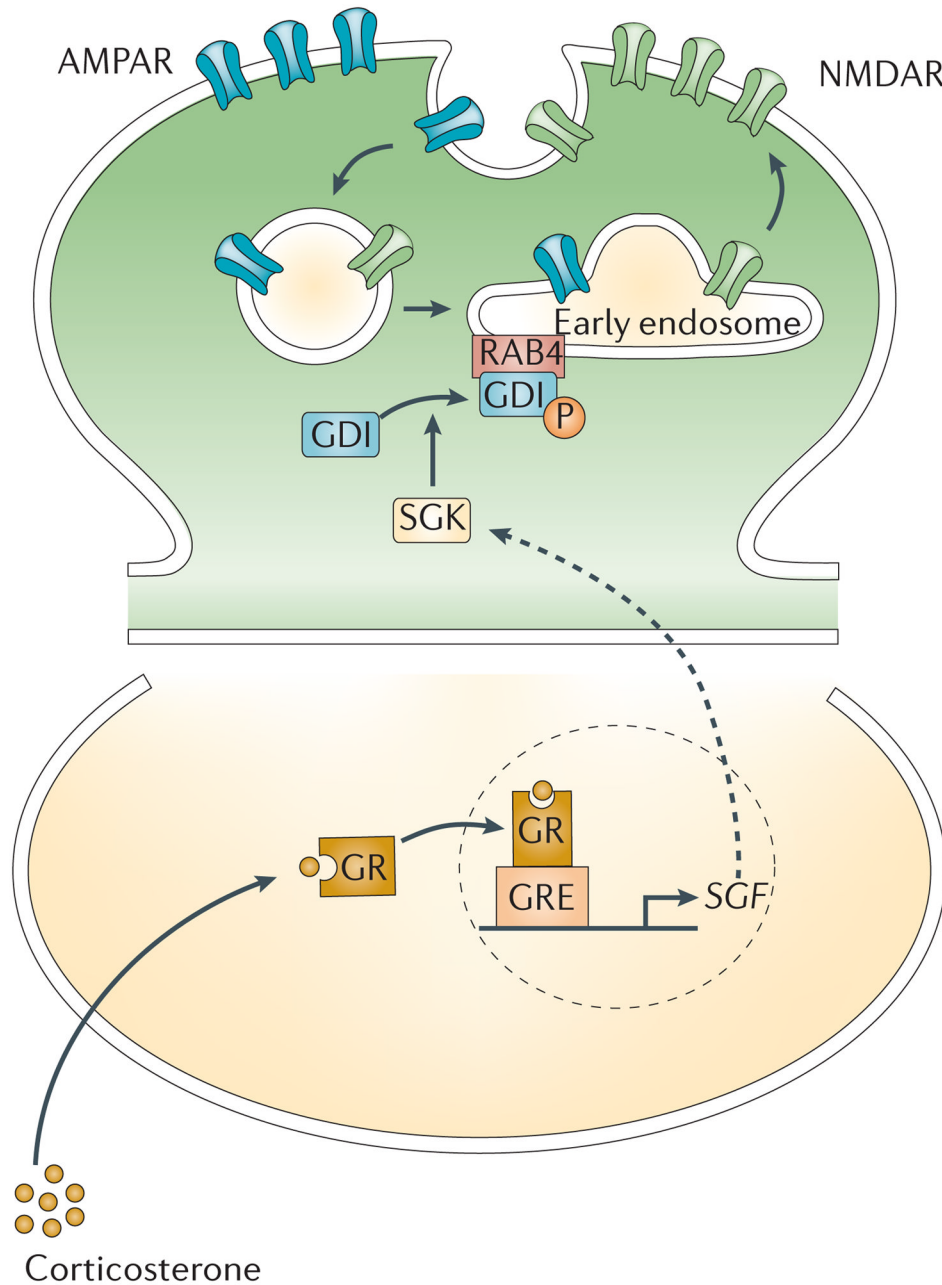


Figure 3. Stress induces changes in glutamate receptor trafficking and function in the prefrontal cortex

In response to acute stress, activation of glucocorticoid receptors (GRs) triggers the upregulation of transcription of the gene encoding serum- and glucocorticoid-inducible kinase (SGK) 1/3⁶⁸. SGK1/3 phosphorylates GDP dissociation inhibitor (GDI) and thereby increases the formation of GDI-Rab4 complexes⁶⁹. Consequently, Rab4-mediated recycling of NMDARs and AMPARs from early endosomes (EE) to the plasma membrane is enhanced, and this results in increased glutamate receptor expression at the synaptic membrane and potentiated glutamatergic transmission^{67,68}.

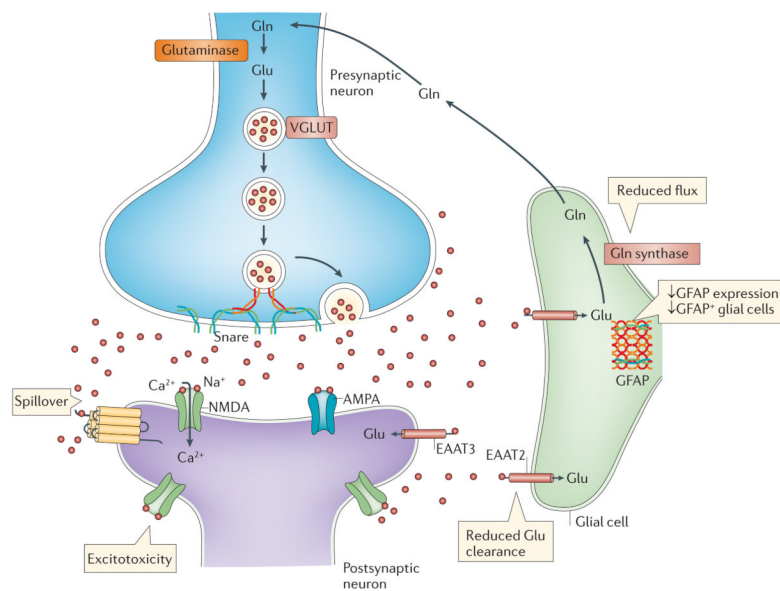


Figure 4. Chronic stress affects glial cells and glutamate metabolism

Accumulating evidence suggests that chronic stress has significant effects on glial cell function. Several studies have demonstrated decreases in the expression of glial fibrillary acid protein (GFAP) and in the number of GFAP-expressing glial cells in the hippocampus and PFC following exposure to chronic stress¹⁴². Chronic stress may also impair the ability to effectively clear synaptic glutamate through glial excitatory amino acid transporters (EAATs). This may lead to glutamate spillover and, ultimately, increased activation of extrasynaptic glutamate receptors resulting in excitotoxicity, a process that has been proposed to occur in several neurodegenerative disorders^{127,226} and possibly after exposure to chronic stress¹⁷¹. Finally, chronic stress may decrease the rates of flux through the glutamate–glutamine cycle, resulting in reduced glutamate metabolism¹⁷¹.

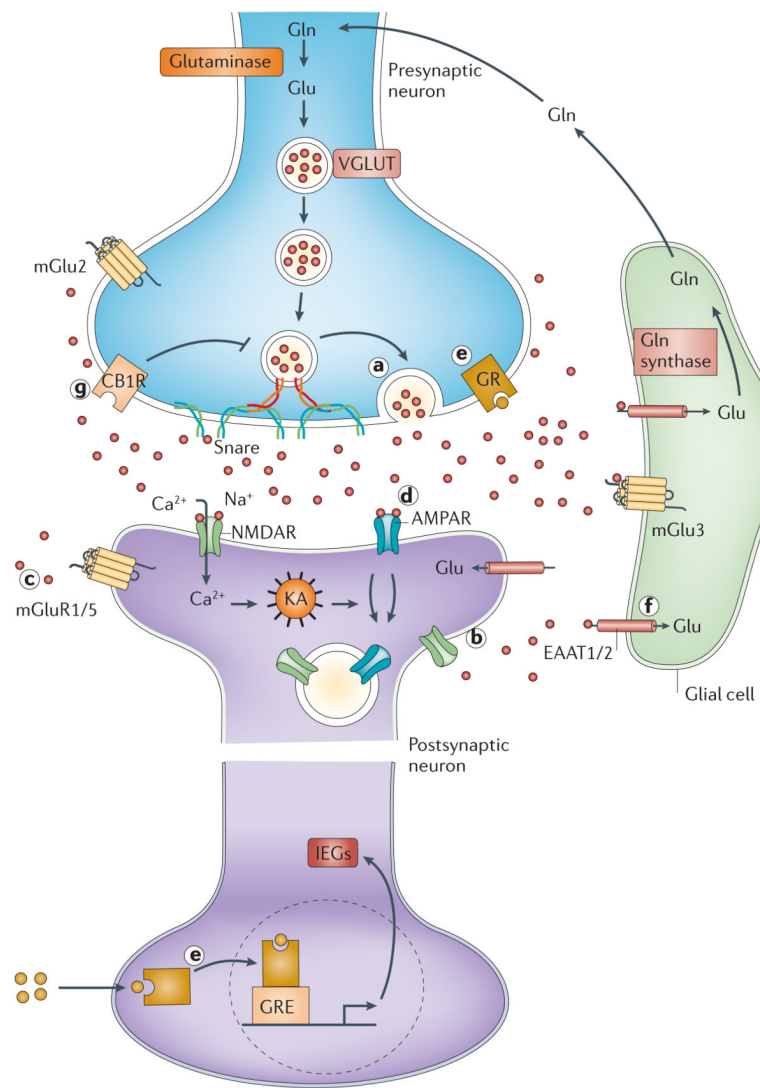


Figure 5. Pharmacological targets

Observations of stress-induced effects on the glutamate synapse have suggested several unique forms of pharmacological interventions for stress related disorders such as mood and anxiety disorders¹⁷⁹. Drugs that modify glutamate release (a), such as lamotrigine and rilzuole, have been shown to have antidepressant-like actions in rodent models and in clinical trials^{171,227,228}. In addition, negative and positive allosteric modulators of group II mGluRs that also modulate presynaptic glutamate release (not shown), have been shown to have antidepressant-like actions in rodent models¹⁸⁶. Drugs targeting NMDA receptors (b), especially NMDA antagonists (ketamine, RO 25-6981, and CP101,606) have demonstrated rapid and robust antidepressant-like effects in both rodent models and clinical trials^{187,188}. Positive and negative allosteric modulators of the mGlu 5 receptor (c) have been shown to possess antidepressant and anxiolytic properties in preclinical studies¹⁸⁶. Drugs targeting AMPA receptors (d), especially agents that potentiate the activation of AMPA receptors, have both nootropic (cognition-enhancing) properties and antidepressant-like effects in rodent models¹⁹². Various agents that regulate glucocorticoid signalling have effects on memory and possess mood and anxiety modifying properties²²⁹ (e). Drugs such as rilzuole and ceftriaxone that indirectly facilitate glutamate transport into glia (f), possess both

neuroprotective and antidepressant-like effects^{171,184,185}. Considering endocannabinoids are reduced in the PFC and hippocampus in animal models of depression, and CB1 receptor stimulation in the PFC and hippocampus is anxiolytic and antidepressant, targeted pharmacological augmentation of endocannabinoid signalling (g) has recently been proposed as a promising therapeutic strategy for the treatment of mood and anxiety disorders²³⁰.