Pharmacology, Biochemistry and Behavior 100 (2012) 775–800

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Review

Metabotropic and ionotropic glutamate receptors as neurobiological targets in anxiety and stress-related disorders: Focus on pharmacology and preclinical translational models

Brian H. Harvey [a,*], Mohammed Shahid [b,1]

[a] Division of Pharmacology, Unit for Drug Research and Development, School of Pharmacy, North-West University (Potchefstroom campus), Hofman street, Private Bag X6001, Potchefstroom 2520, South Africa
[b] MSD, Newhouse, Lanarkshire, Scotland, UK

ARTICLE INFO

Available online 25 June 2011

Keywords:
Animal model
Anxiety disorder
Anxiolytic
Posttraumatic stress disorder
Obsessive–compulsive disorder
GABA
Glutamate
Nitric oxide
Ionotropic
Metabotropic
Translational
Drug target

ABSTRACT

Anxiety disorders are amongst the most common and disabling of psychiatric illnesses and have severe health and socio-economic implications. Despite the availability of a number of treatment options there is still a strong medical need for novel and improved pharmacological approaches in treating these disorders. New developments at the forefront of preclinical research have begun to identify the therapeutic potential of molecular entities integral to the biological response to adversity, particularly molecules and processes that may pre-determine vulnerability or resilience, and those that may act to switch off or "unlearn" a response to an aversive event. The glutamate system is an interesting target in this respect, especially given the impact anxiety disorders have on neuroplasticity, cognition and affective function. These areas of research demonstrate expanding and improved evidence-based options for treating disorders where stress in various guises plays an important etiological role. The current review will discuss how these pathways are involved in fear circuitry of the brain and compare the strength of therapeutic rationale as well as progress towards pharmacological validation of the glutamate pathway towards the treatment of anxiety disorders, with a particular focus on metabotropic and ionotropic glutamate receptors. Specific reference to their anxiolytic actions and efficacy in translational disease models of posttraumatic stress disorder, obsessive–compulsive disorder, panic disorder and phobia will be made. In addition, the availability of ligands necessary to assist clinical proof of concept studies will be discussed.

Contents

* Corresponding author. Tel.: +27 18 299 2238; fax: +27 18 299 2225.
E-mail address: Brian.Harvey@nwu.ac.za (B.H. Harvey).
[1] Current address: Orion Corporation ORION PHARMA, Research and Development, Turku, Finland.

0091-3057/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2011.06.014

1. General introduction

Anxiety disorders have a 12 month prevalance of 17% and a lifetime prevalance of 24.9%, and as a group are amongst the most disabling of psychiatric illnesses (Kessler et al., 1994). Despite the availability of psycho- and pharmacotherapies, underdiagnosis and undertreatment of these conditions contribute to their enormous personal and economic costs (Dupont et al., 1996). The major DSM-IV anxiety disorders, including general anxiety disorder (GAD), post-traumatic stress disorder (PTSD), social phobia, panic disorder (PD) with/without agoraphobia, specific phobia, are frequently co-morbid with mood disorders such as major depression and bipolar disorder, but also substance and alcohol abuse disorders, that often compromise effective management of the anxiety disorder (Kessler et al., 2010). There is thus an urgent need to develop broadly acting, more effective anxiolytics with a rapid onset of action, that are better tolerated and with limited abuse potential. Further, these compounds must be rationally designed to target the pathophysiological mechanisms of the illness.

The underlying molecular pathology of the different anxiety disorders remains to be elucidated. Nevertheless, it is clear that multiple risk factors including genetic (Hettema et al., 2001; Smoller et al., 2009), psychosocial and stress/trauma are important contributors towards disease etiology (Harvey et al., 2003a; Gregory et al., 2008; Fig. 1). Excessive and prolonged stress can lead to neuronal damage in vulnerable brain structures such as the hippocampus with potential negative impact on learning and memory function (see McEwen, 2000). Whilst the range of symptoms vary considerably across GAD, social anxiety disorder (SAD), obsessive–compulsive disorder (OCD), PD, PTSD and form the basis for their DSM IV classification, cognitive dysfunction is a common element running across all these anxiety disorders as well as co-morbid indications such as major depression and bipolar disorder (Fig. 1). Indeed disruption of cognition seems to be reflected in the symptom domains for a number of anxiety disorders such as problems in concentration (GAD), uncontrollable re-experiencing of severe trauma related memories (PTSD) and obsessional thoughts (OCD) (APA, 1994). Thus, improving cognitive function in these patients either through psychological and/or pharmacological intervention will continue to form an important element in the therapeutic management of anxiety disorders.

Apart from genetic predisposition, stress-related mental illnesses are dependent on the nature and duration of the stressor, so that environmental adversity may be a means of more effectively separating stress sensitive from stress resilient populations (Connor and Zhang, 2006). However, despite dramatic technological advances in genetics and gene analysis over the past twenty years, progress towards identification of specific disorder-related genes in anxiety but also other psychiatric disorders has been modest and perhaps below expectation (Foster et al., 2010; Lohoff, 2010). Complex disease phenotypes, involvement of multiple genes of small effect as well as small sample size in genetic studies have been suggested as reasons

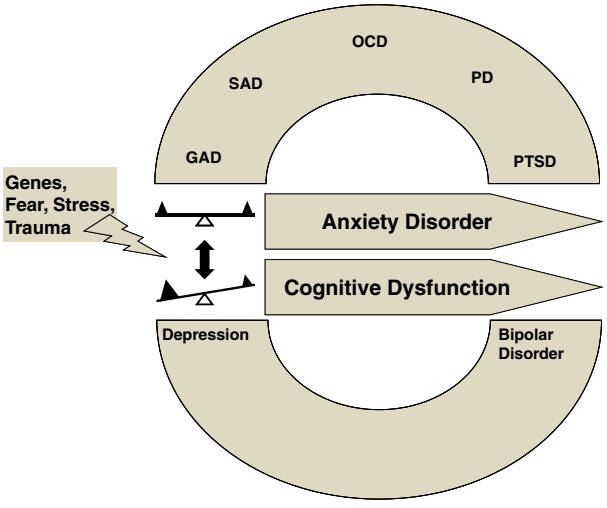

Fig. 1. Risk factors, such as genes, fear, stress and early life trauma, impact neurobiological systems governing cellular resilience, such as neurotrophic function and neuroplasticity. Coping and appropriate adaptation to stress leads to recovery (allostasis), while unresolved adversity will lead to allostatic load and psychopathology in susceptible individuals. Many of these disorders lie on a continuum, with cognitive dysfunction and anxiety closely connected.

for this difficulty (Abdolmaleky et al., 2005). Candidate genes currently considered to be associated with anxiety disorders, as summarized by Smoller et al. (2009) include: 5HT2AR (PD), COMT (PD, OCD), DRD2 and FKBP5 (PTSD). However, with the possible exception of COMT in PD which is supported by a meta-analysis, the reliability of the association with these genes remains questionable.

Fortunately, in recent years significant advances in understanding the psychobiology of anxiety and stress-related disorders and in developing effective interventions has been realized (Stein and Hollander, 2002; Krystal et al., 2010). A hypothetical sequelae of neurobiological events is presented in Fig. 2, where a concerted action by predisposing risk factors (e.g. genetic, stress) and abnormal activation of the hypothalamic-pituitary-adrenal (HPA) HPA-stress axis may compromise neuronal resilience through neurotrophin dysregulation and impaired neuroplasticity (see also Harvey et al., 2003a). Based on preclinical and clinical research these changes have been postulated to act as drivers for neurochemical/neuroendocrine imbalance leading to cognitive and emotional impairment, ultimately contributing towards the development of an anxiety disorder.

As comprehensively reviewed by Bermudo-Soriano and colleagues in this special issue of the journal, there is substantial clinical evidence that supports the involvement of glutamate in anxiety disorders. For instance brain imaging analysis in patients with generalized social phobia demonstrated increased glutamate levels in the anterior cingulate cortex compared to healthy subjects as well as a correlation between the magnitude of the glutamate signal and the severity of the phobic symptoms (Phan et al., 2005). Furthermore, the change in glutamate function could be reversed by anxiolytic treatment (Pollack et al., 2008). In addition, a number of clinical studies have demonstrated the utility of glutamate-active drugs in GAD, including memantine (Feusner et al., 2009), riluzole (Coric et al., 2005; Mathew et al., 2008), metabotropic glutamate receptor (mGlu) 2/3 agonists (Dunayevich et al., 2008) and pregabalin (Baldwin and Ajel, 2007). Similarly, glutamatergic agents have demonstrated usefulness in OCD, including memantine (Stewart et al., 2010), riluzole (Coric et al., 2005) and N-acetyl cysteine (LaFleur et al., 2006). Although PTSD is most closely associated with increased noradrenergic signaling, especially serving as a general alarm system and facilitating the encoding of emotional memories, recent evidence suggests clinical efficacy for glutamatergic agents, for example D-serine and D-cycloserine (Heresco-Levy et al., 2002, 2009). In fact, D-cycloserine shows promising anxiolytic activity in humans under different states of anxiety (Bailey et al., 2007). However, the clinical use of glutamatergic drugs in panic disorder has not been closely examined, although two preliminary studies using mGlu 2/3 agonists failed to demonstrate meaningful efficacy (Bergink and Westenberg, 2005; Kellner et al., 2005).

Whilst the above-mentioned clinical observations need further replication and evaluation in additional anxiety disorders, they concur with extensive preclinical data demonstrating a strong connection between glutamate and the neurobiological response to aversive stimuli. Stress, fear and trauma together with multi-genetic predisposition is recognized to contribute to the risk for development of anxiety pathology (Figs. 1 and 2). Basic research in animals has established a strong connection between stress and brain glutamate function, its association with changes in neuroplasticity (see Spedding et al., 2003) and the subsequent development of an anxiety disorder (see Cortese and Phan, 2005; Krystal et al., 2010). Thus, acute stress can stimulate glutamate release in the rat prefrontal cortex (Bagley and Moghaddam, 1997) whilst repeat exposure to stress can attenuate glutamate release as an adaptive response (Moghaddam, 2002). Glutamate is a potent modulator of events related to synaptic plasticity (Harvey et al., 2003a; Harvey, 2008; Krystal et al., 2010; Peng et al., 2011), while it also regulates hypothalamic function and the neuroendocrine response to stress (van Den Pol et al., 1990; Durand et al., 2008).

To establish the clinical utility and rationale for using glutamatergic active drugs in the various anxiety disorders, this review will consider the role of glutamate in fear and anxiety circuitry in the brain as well as how this relates to the known neuroanatomy and neurobiology of these disorders. We will then present an overview of ionotropic and metobotrobic glutamate receptor ligands and whether these compounds display anxiolytic-like actions in animals. Finally we will present evidence for efficacy using translational disease models of specific anxiety disorders.

2. Glutamate signaling in the central nervous system

Maintenance of a physiological balance between inhibitory and excitatory neurotransmission in the central nervous system (CNS) is critical in determining normal brain function and behavior. This relies on a functional, perhaps yin–yang type, interaction between γ-amino butyric acid (GABA) and glutamate, the major neurotransmitters involved in mediating inhibitory and excitatory synaptic activity, respectively (Harvey, 1996). Glutamate plays an important and diverse role in the CNS. However, overstimulation of the glutamatergic system can provoke

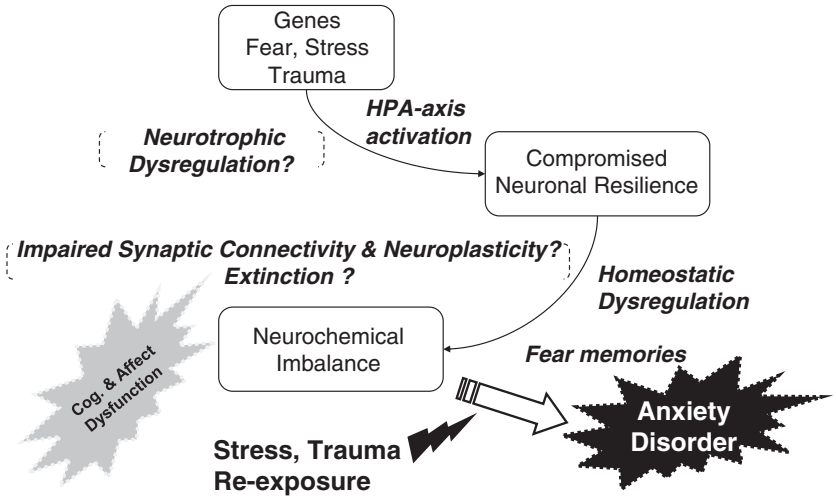

Fig. 2. A hypothetical sequalae of neurobiological events where predisposing risk factors induce abnormal activation of the HPA-stress axis, neurochemical imbalance (e.g. increased glutamate and monoamine release), leading to compromised neuronal resilience. The result is a disabling of critical cortical processes necessary to correctly process extinction of trauma memory, thereby perpetuating a vicious cycle of trauma recollection and re-experiencing. In PTSD, for example, this results in hyperarousal, anxiety and cognitive dysfunction.

hyper-excitability, proconvulsant activity and neuronal damage (Meldrum, 2000). At a cellular level glutamate has a strong influence in controlling neurogenesis and neuroplasticity (Meldrum, 2000; Spedding et al., 2003), whereas in terms of behavior it modulates cognition (e.g. learning and memory) (Lynch, 2006) and affect, as well as response to stress (Moghaddam, 2002), thus making it a promising target for treating depression, anxiety and disorders of cognition. The glutamate pathway analysis presented here will be restricted to the role of ionotropic and metabotropic receptors in anxiety and stress-related disorders.

Receptors mediating the effects of glutamate form a superfamily which has been categorized into two main subfamilies depending on the mode of signal transduction (see Tables 1 and 2). Generally this is either ion mediated (fast; Table 1) or metabotropic (relatively slower; Table 2) which subsequently can modulate a variety of effector systems (e.g. phospholipase C, adenylate cyclase, receptor activated kinases, calcium) leading to intracellular transduction of extracellular stimuli. The properties of glutamate receptors and their distribution in the brain have been covered extensively in the recent literature (see Kew and Kemp, 2005; Nicoletti et al., 2011; Niswender and Conn, 2010; Traynelis et al., 2010) and will only be briefly described here.

Structurally all glutamate receptors share a long N-terminal bi-looped extracellular domain which forms the agonist binding pocket. However, ionotropic and metabotropic receptor subfamilies differ substantially in transmembrane topology with three and seven transmembrane domains, respectively. The ionotropic receptors also have a short cytoplasmic side re-entrant loop which is involved in ion-channel pore formation. Use-dependent receptor desensitization, protein kinase mediated phosphorylation and internalization form the array of cellular mechanisms for augmenting or limiting ionotropic receptor activity (see Traynelis et al., 2010). In the case of the metabotropic glutamate receptors downstream feedback receptor phosphorylation appears to be an important regulatory mechanism for receptor desensitization and endocytosis (see Kim et al., 2008).

A number of useful pharmacological tools have helped to elucidate the function and therapeutic utility of glutamate receptors (Tables 1 and 2). These agents have assisted in driving a better understanding of receptor properties but also novel modes of pharmacological action. For example, the potential for allosteric control allows for modulation of glutamatergic function with reduced target-related side-effect liability. The list of ligands shown in Tables 1 and 2 is not intended to be comprehensive but is designed to show primarily compounds that are also amenable to in vivo analysis. However, as a lot of these compounds have been inadequately characterized, there remains a concern about selectivity versus related and broader off-target receptors, inter-species variation in binding or functional assay conditions, descrepancy between in vitro target engagement and in vivo dose and brain penetration, and the presence of active metabolites and enantiomers.

2.1. Ionotropic glutamate receptors

α-Amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA), N-methyl-D-aspartate (NMDA) and kainate receptors mediate fast (millisecond scale) excitatory neuronal transmission, resulting in Na^+ and/or Ca^{2+} ion conductance. In general AMPA and kainate receptors tend to gate Na^+ more avidly whereas NMDA receptors show preference for stimulating Ca^{2+} entry (Kew and Kemp, 2005; Traynelis et al., 2010; Table 1).

Glutamatergic stimulation of NMDA receptors activates a number of subcellular messengers, such as calmodulin kinase II (CaMKII), mitogen-activated protein kinase/extracellular receptor kinase (MAPK/ERK), mammalian target for rapamycin (mTOR), nitric oxide

Table 1
Summary of the basic and pharmacological properties of ionotropic glutamate receptors.

Receptor subtype	Agonist	Antagonist	Authors (year)
AMPA receptor Glutamate (EC50): ~0.5 mM Main gating ion: Na^+>Ca^{2+} Deactivation kinetics: fast Subunits: GluR1-4 Splice variants: flip, flop for all 4 subunits C-terminal splice variants for GluR2 & GluR4	Orthosteric L-Glutamate, AMPA Cl-HIBO, SYM2081 ACPA Allosteric Aniracetam, CX516, CX614, CX717, Org 24448, Org 26576, IDRA-21, cyclothiazide, PEPA, LY404187, LY392098, LY503430	Competitive NBQX, YM872, NS1209, ZK200775, LY326325, LY215490, Topiramate Non-competitive Argiotoxin 636, IEM-1460, IEM1754 Non-competitive GYKI 52466 LY300164, LY303070 CP-465022, NS3763 CP-526427	Bräuner-Osborne et al., 2000; Alt et al., 2004; Kew and Kemp, 2005; Catarzi et al., 2007; Traynelis et al., 2010; Morrow et al., 2006; O'Neill et al., 2004; Jordan et al., 2005; Woolley et al., 2009; Planells-Cases et al., 2006
Kainate receptor Glutamate (EC50): ~0.5 mM Main gating ion: Na^+>Ca^{2+} Deactivation kinetics: fast Subunits: GluR5-7, KA1-2 c-Terminal splice variants for GluR5, 6, 7	Orthosteric L-Glutamate, kainate (S)-5-iodowillardine SYM2081, ATPA LY339434	Competitive LY382884, UBP296 NS3763, NS1209 Non-competitive None identified	Bräuner-Osborne et al., 2000; Kew and Kemp, 2005; Alt et al., 2004; Planells-Cases et al., 2006; Traynelis et al., 2010
NMDA receptor Glutamate (EC50): ~1 μM Main gating ion: Ca^{2+}>Na^+ Deactivation kinetics: slow Subunits: NR1, NR2A-2D, NR3A 8 NR1	Orthosteric L-Glutamate, NMDA, HA 966, SYM2081 Co-agonist D-serine, D-cycloserine HA966 Allosteric Pregnenolone SO_4	Competitive DAP5, DAP7 CGS 19755, CGP3789 Co-agonist L-701324, ACPC MDL105519, 7 CKA ACEA 1021, ACPC 5,7 DCKA MDL 102 288 Non-competitive Phencylidine, MK801, Ketamine, Memantine, CNS-1102 Ifenprodil, Ro25-6981 (+)CP-101606 Ro-631908 Allosteric Ro631908, Ro256981 CI1041, troxoptodil	Bräuner-Osborne et al., 2000; Kew and Kemp, 2005; Traynelis et al., 2010

Table shows a summmary of some interesting representative ligands including those used as pharmacological tools in in vivo models (Tables 3 and 4). Orthosteric, co-agonist and allosteric : refer to compounds acting through the glutamate, $glycine_B$ receptor or a non-glutamate biding domain, respectively.

Table 2
Summary of the basic and pharmacological properties of metabotropic glutamate receptors.

Receptor class	Agonist	Antagonists	Authors (year)
Group I	Orthosteric	Competitive	Nicoletti et al., 2011, Niswender and
Subtype: mGluR1	L-Glutamate, quisqualate,	LY367385, AIDA, MATIDA	Conn, 2010; Lesage and Steckler, 2010
(a, b, c, d, e, f)	DHPG		
Function: excitatory	Allosteric	Allosteric	Niswender and Conn, 2010
Signaling: G_q/G_{11}; ↑PLC	Ro-677476, Ro-0711401,	CPCCOET, BAY367620,	
	VU71, Ro-674853,	JNJ6259685	
Subtype: mGluR5 (a,b)	Orthosteric	Allosteric	Nicoletti et al., 2011, Niswender and
Function: excitatory	L-Glutamate DHPG, CHPG	MPEP, fenobam, SIB1757,	Conn, 2010; Lesage and Steckler, 2010
Signaling: G_q/G_{11}; ↑PLC		AFQ056, AZD2516, STX107,	
		ADX10059, SIB1893	
Group II	Orthosteric	Competitive	Nicoletti et al., 2011, Niswender and
Subtype: mGluR2	L-Glutamate LY354740,	LY341495, MGS0039	Conn, 2010; Lesage and Steckler, 2010
Function: inhibitory	LY379268, LY404039		
Signaling: G_q/G_{11}, ↑PLC			
	Allosteric	Allosteric	Niswender and Conn, 2010; Hemstapat
	4-MPPTS (LY487379),	Dihydrobenzo[1,4]diazepin-	et al., 2007
	BINA, LY566332	2-one derivatives	
Subtype: mGluR3	Orthosteric site	Competitive	Nicoletti et al., 2011, Niswender and
Function: inhibitory	L-Glutamate, LY354740,	LY341495, MGS0039	Conn, 2010; Lesage and Steckler, 2010
Signaling: G_q/G_{11}, ↑PLC	LY379268 2R,4R-APDC,		
	DCG-IV 1S,3R-ACPD, NAAG		
Group III	Orthosteric	Competitive	Nicoletti et al., 2011, Niswender and
Subtype: mGluR4	L-SOP, L-AP4	MSOP, MAP4, CPPG	Conn, 2010; Lesage and Steckler, 2010
Function: inhibitory	Allosteric		Niswender and Conn, 2010
Signaling: G_i/G_o, ↓AC	PHCCC, VU0155041		
	SIB1893, MPEP		
Subtype: mGluR6 (a, b, c)	Orthosteric	Competitive	Nicoletti et al., 2011, Niswender and
Function: inhibitory	L-SOP, L-AP4	MSOP, MAP4, CPPG	Conn, 2010; Lesage and Steckler, 2010
Signaling: G_i/G_o, ↓AC			
Subtype: mGluR7 (a, b,c, d, e)	Orthosteric	Competitive	Nicoletti et al., 2011, Niswender and
Function: inhibitory	L-SOP, L-AP4, ACPT-1?	MSOP, MAP4, CPPG, LY341495	Conn, 2010; Lesage and Steckler, 2010
Signaling: G_i/G_o, ↓AC	Allosteric	Allosteric	Niswender and Conn, 2010; Mitsukawa
	AMN082	MMPIP	et al., 2005
Subtype: mGluR8 (a, b, c)	Orthosteric	Competitive	Nicoletti et al., 2011, Niswender and
Function: inhibitory	L-SOP, L-AP4,	MSOP, MAP4, CPPG	Conn, 2010; Lesage and Steckler, 2010
Signaling: G_i/G_o, ↓AC	DCPG, PPG		

(NO) synthase (NOS) and nuclear factor-κβ (NF-κβ), all important regulators of synaptic plasticity (Oosthuizen et al., 2005; Kleppisch and Feil, 2009; Li et al., 2010), while the latter is also involved in the inflammatory response (Oosthuizen et al., 2005). Moreover, NMDA-mediated Ca^{2+} influx activates NOS, cyclooxygenases, proteases, lipases and protein kinases (Oosthuizen et al., 2005) that under sustained activation lead to mitochondrial dysfunction and oxidative stress. Neuronal NOS (nNOS) and its interaction with various components of the NMDA receptor cascade, viz. postsynaptic density protein 95, a postsynaptic density scaffold protein required for the coupling of nNOS to the NMDA receptor, protein inhibitor of nNOS (PIN), a cytoskeletal transport protein that inhibits nNOS activity, and carboxy-terminal PDZ (**P**SD95-**D**lgA-**z**o-1) ligand of nNOS (CAPON), a cytoplasmic protein that interferes with NMDA receptor-nNOS coupling, collectively contribute to adaptive plasticity. Interestingly, this cascade of events shows increased response in stress-sensitive individuals, possibly representing a vulnerability factor to developing an anxiety disorder (Wegener et al., 2010).

NMDA-mediated Ca^{2+} entry also activates CaMKII which, via phosphorylation of GluR1, increases AMPA receptor conductance (Fig. 3). Stargazin, a protein associated with AMPA receptors and a CaMKII substrate, promotes AMPA receptor trafficking (Tomita et al., 2005). By stimulating membrane depolarization, AMPA receptor activation can reverse Mg^{2+}-dependent block of the NMDA receptor (Nowak et al., 1984) thus promoting Ca^{2+} entry (Burnashev et al., 1995) with the exit of K^+ via the open NMDA receptor channel. This prolongs current flow through the receptor complex leading to a strengthening of NMDA activity (Tanaka et al., 2000; Tomita et al., 2005). Consequently, synaptic plasticity becomes a function that is dependent on the surface expression of AMPA receptors and under mutual cooperation with NMDA receptors (Selvakumar et al., 2009). Importantly, NO-mediated S-nitrosylation of stargazin increases its binding to AMPA GluR1, resulting in an increase in surface expression of AMPA receptors (Selvakumar et al., 2009), thus suggesting NO to be an inter-cellular messenger mediating NMDA-AMPA receptor cross talk.

2.1.1. NMDA receptors

The distinct subunit and splice variant related isoforms of the NMDA receptor subfamily has been extensively reviewed (Ciabarra et al., 1995; Sasaki et al., 2002; Traynelis et al., 2010). NMDA receptors require the presence of extracellular glycine which, together with glutamate, binds to two independant sites on NR1 and NR2 subunits to initiate receptor binding. Historically, greater effort was focussed on NMDA receptor blockers with anti-neurodegenerative or anti-pain properties (Table 1), specifically competitive and non-competitive antagonists. Open channel blockers (e.g. dizocilpine or MK801; phencyclidine or PCP; ketamine) share a common risk for psychotomimetic effects (Javitt, 2004), although memantine, by virtue of its lower potency and selective open channel block of the NMDA receptor, has a more tolerable side-effect profile (see Parsons et al., 2007). Although direct orthosteric agonists, with the exception of NMDA, are not broadly evident in the literature, a number of sulfated endogenous neurosteroids (e.g. pregnenolone sulfate) have been reported to enhance or inhibit NMDA receptor activity through an allosteric mechanism (Malayev et al., 2002; Traynelis et al., 2010). Alternatively, modulation of NMDA receptor function through the co-agonist glycine site has attracted attention, e.g. glycine-B site agonists and antagonists (such as D-serine and D-cycloserine, Table 1), while elevation of synaptic glycine levels through inhibition of glycine transporter-1 (GlyT-1) activity also indirectly enhances NMDA receptor

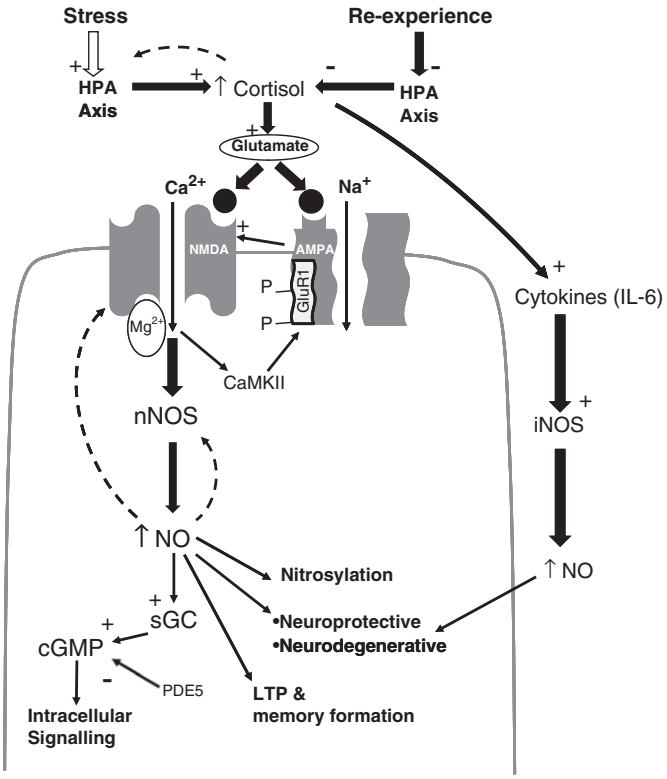

Fig. 3. Effect of acute stress and later re-stress on the HPA-axis, the release of glutamate and the subsequent affects on AMPA and NMDA-NO mediated signaling. Acute stress mediated activation of NMDA-Ca^{2+} ionophore phosphorylates the GluR1 subunit of the AMPA receptor via CaMKII that will bolster AMPA receptor activity, and a further amplification of NMDA directed subcellular events, such as the activation of the NO-cGMP pathway. The latter is an important neuromodulator in various subcellular events critical for regulating mood, anxiety and cognition. In an animal model of PTSD, re-experience induces increased HPA-axis negative feedback that through actions on the immune-cytokine cascade, changes NMDA-NO signaling to one that predominantly involves the inflammatory/immunological NOS (iNOS) pathway with more destructive capabilities (refer to text for detailed description; Tanaka et al., 2000; Oosthuizen et al., 2005; Tomita et al., 2005; Selvakumar et al., 2009). Broken lines indicate a negative feedback system. IL-6, interleukin-6; CaMKII, calmodulin kinase II; NO, nitric oxide; nNOS, neuronal NO synthase; iNOS, inducible/immunologic NO synthase; sGC, soluble guanylyl cyclase; PDE5, phosphodiesterase type 5; LTP, long term potentiation; HPA, hypothalamic-pituitary-adrenal.

activity. The latter rationale has led to the use of GlyT-1 inhibitors as adjunctive treatment in schizophrenia (Javitt, 2008) and, as will be discussed later, positive and negative modulators of the NMDA receptor may have importance in the treatment of anxiety disorders.

2.1.2. AMPA receptors

AMPA receptors regulate basal synaptic activity and, through partial plasma membrane depolarisation, facilitate the activation of other ligand-gated ion channels (LGICs) (e.g. NMDA) or voltage-gated ion channel (VGICs) (e.g. Ca^{2+} channels). As described above, AMPA receptor activation is necessary to relieve Mg^{2+}-dependent inhibition of the NMDA receptor ion channel (Traynelis et al., 2010). Distinct subunits (GluR1-4) and isoforms (flip and flop) have been identified for AMPA receptors (Table 1), and strongly influence agonist affinity, ion gating properties, activation/deactivation kinetics and receptor desensitization of the AMPA receptor (Traynelis et al., 2010). The four AMPA receptor subunits and their isoforms show a more restricted pattern of distribution in brain tissue, raising the possibility of regionally distinct AMPA receptors (Geiger et al., 1995; Isa et al., 1996; Xia and Arai, 2005). This differential distribution in neuronal cell types is consistent with data showing that AMPA receptor activation can enhance not only excitatory postsynaptic potentials (EPSPs) but also inhibitory postsynaptic potentials (IPSPs) (Xia and Arai, 2005). Although post synaptic AMPA receptors are now accepted, there is emerging data suggesting that some of these receptors may also reside on the presynaptic plasma membrane and thus play a role in modulating glutamate release (Dorostkar and Boehm, 2008).

Four different classes of ligands have been identified for the AMPA receptor: agonists, positive allosteric modulators (PAMs), and competitive and non-competitive antagonists (Table 1). L-Quisqualic acid and the more selective AMPA are the prototypical synthetic agonists but are only suitable for in vitro investigation. The demonstration by Ito et al. (1990) that the nootropic agent aniracetam could potentiate AMPA receptor activity through an allosteric mode of action was the impetus for discovering several chemical and distinct pharmacological classes of AMPA receptor PAMs, some of which are provided in Table 1.

While direct AMPA receptor agonists carry the risk for excitotoxicity, an allosteric mechanism may have a lower liability in this respect (Arai and Kessler, 2007). Preventing use-dependent AMPA receptor desensitization is an important approach to prolonging and strengthening of AMPA-mediated signaling (see Lynch, 2002 for review). At least two different classes of AMPA PAMs block AMPA receptor deactivation and/or desensitization (Fig. 4). Aniracetam, as well as CX516, CX717, Org 24448 and Org 26576, partially block AMPA receptor desensitization (Arai and Kessler, 2007; Erdemli et al., 2007). In contrast to these 'partial' potentiators, "full" AMPA PAMs, such as cyclothiazide, CX614 and LY404187, produce a stronger receptor activation due to full block of AMPA receptor deactivation and/or desensitization (Quirk and Nisenbaum, 2002; Arai and Kessler, 2007). Augmentation of AMPA receptor activity is potentially a useful approach for improving cognitive dysfunction in psychiatric disorders (Lynch, 2006). Thus LY451395 has been tested for efficacy in Alzheimers patients (Chappell et al., 2007), while CX516 has been tested as a cognition enhancer in schizophrenia albeit with mixed results (Goff et al., 2008). There is also some evidence to support the potential use of AMPA PAMs in affective disorders (Alt et al., 2006; Machado-Vieira et al., 2009).

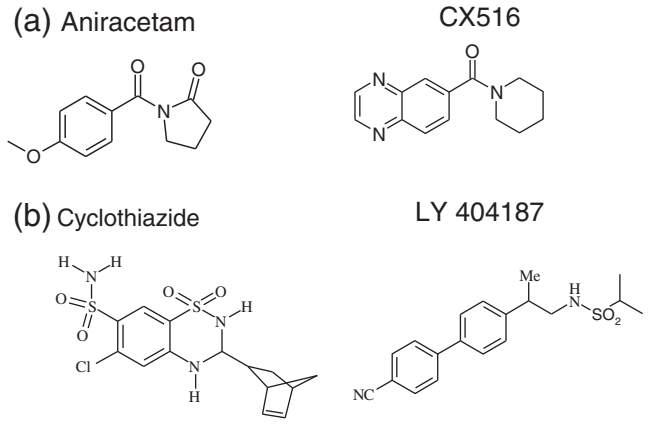

Fig. 4. Examples of some prototypical partial (a) and full (b) blockers of AMPA receptor desensitization.

Competitive and non-competitive AMPA receptor antagonists were considered an interesting mechanism for the treatment of stroke and to prevent neurodegeneration (Lau and Tymianski, 2010; Catarzi et al., 2007). Whether AMPA antagonists are useful in anxiety has only been examined to a limited degree.

2.1.3. Kainate receptors

Kainate receptors and their related subunit families, classified as KA1-2 and GluR5-7, have been reviewed elsewhere (Kew and Kemp, 2005; Traynelis et al., 2010). Although not as extensive as for AMPA and NMDA receptors, the kainate receptor has also undergone medicinal chemistry effort (Bunch and Krogsgaard-Larsen, 2009). Both agonists and antagonists with good affinity and activity have been identified (Table 1), with antagonists presenting with possible utility in epilepsy and neurodegeneration (Jane et al., 2009). However, their use in models of anxiety has not attracted a lot of attention, possibly related to lack of truly selective ligands.

2.2. Metabotropic glutamate receptors (mGluRs)

mGluRs and their 8 distinct gene related protein products (mGluR1-8) (see Niswender and Conn, 2010 for review), can be subdivided according to G-protein coupling and mode of signal transduction into Group I (mGluR1 & 5), Group II (mGluR 2 & 3) and Group III (mGluR 4, 6, 7, & 8) (Table 2). Group I receptors activate G_q/G_{11}-phospholipase C mediated signaling via actions involving inositol phophate hydrolysis and the formation of diacylglycerol, whilst Groups II and III receptors modulate cAMP signaling via the G_i/G_o intracellular pathway (Table 2). Unlike other mammlian G-protein coupled receptor (GPCR) families, the heptahelical transmembrane domains of the mGluR are not directly involved in agonist binding but is similar to the ionotropic glutamate receptors where the native ligand binding domain resides in the extracellular N-terminal portion (Kunishima et al., 2000; Malherbe et al., 2001). With the exception of mGluR6, which seems to be retina specific, the mGluRs, like the ionotropic glutamate subfamily, are widely expressed throughout the mammalian CNS with presence in both neuronal and glial cell types (Swanson et al., 2005). Some differences in cellular localisation exist with Group I mGluRs showing a predominantly postsynaptic/somatodendritic presence, whilst the Group II/III class is mainly presynaptic and involved in modulating glutamate release (Swanson et al., 2005).

Apart from their obligatory activation of phospholipase C-mediated events, group I mGluRs can activate a range of downstream effectors, most notably proteins involved in synaptic plasticity, such as MAPK/ERK and mTOR, while groups II and III also couple to MAPK and other systems that regulate synaptic plasticty (Niswender and Conn, 2010). Signal transduction cross talk also exists between metabotropic and ionotropic glutamate receptors. The most well characterized example of this is the functional interaction between the NMDA and mGluR5 receptor. Activation of the latter receptor on GABAergic interneurones can lead to a downstream enhancement of NMDA receptor evoked activity on pyramidal neurones (Doherty et al., 2000; Mannaioni et al., 2001; Marino and Conn, 2002). This effect can be blocked by the mGluR5 antagonist LY344545 (Doherty et al., 2000). The exact mode of interaction between these two receptors may rely on bi-directional positive feedback, possibly mediated by stimulation of phosphatase calcineurin following mGluR5 receptor activation (Alagarsamy et al., 2005). Importantly, new evidence suggests that mGluR5, AMPA and NMDA receptors together play a role in modulating synaptic plasticity via effects on the NO-cGMP pathway (Boix et al., 2011). These findings emphasize that both mGluRs and ionotropic receptors, together with down-stream messengers such as NO, are important mediators of synaptic plasticity and as such are involved in anxiety disorders.

As summarized in Table 2, a wide array of mGluR ligands including orthosteric binders as well as allosteric modulators have been discovered. However, the level of selectivity, particularly for compounds that target the glutamate binding pocket, still shows scope for improvement. Targetting the allosteric, non-agonist binding site may prove more fruitful in this respect. Indeed, it has been hypothesized that this approach may be useful in limiting the liability for mechanism related side-effects for agonist based approaches.

2.2.1. Group I metabotropic receptors

The group I mGluR selective agonist, (S)-3,5-dihydroxyphenylglycine [(S)-3,5-DHPG], has similar potencies at mGluR1 and mGluR5 and is the most selective group I mGluR agonist (Niswender and Conn, 2010). Indeed, most other group I mGluR agonists also have activity at ionotropic glutamate receptors (i.e., quisqualate) or other mGluR subtypes, e.g. [(1S,3R)-ACPD] (see Table 2). Potent and selective orthosteric antagonists of group I mGluRs include LY367385 and others (see Table 2), and are useful in differentiating mGluR1 relative to mGluR5 effects. PAMs of mGluRs do not activate the receptor directly in most systems but potentiate the response of the receptor to orthosteric agonists, while NAMs antagonize the activity of agonists in a noncompetitive fashion by binding to a site other than the agonist binding site, in this case glutamate (Niswender and Conn, 2010). CPCCOEt is a highly selective mGluR1 NAM (Annoura et al., 1996), and has recently been followed by similar compounds including Bay36-7620, JNJ16259685, FTIDC, YM 298198 (see Table 2; Niswender and Conn, 2010). SIB-1757 and SIB-1893 are highly selective mGluR5 NAMs, as are their structural analogs MPEP and MTEP (see Table 2), which provide increased potency, selectivity, and brain penetration (Lea and Faden, 2006). Despite the pending arrival of structurally distinct and highly selective partial antagonists of mGluR5 (Rodriguez et al., 2005), MTEP and MPEP are commonly used selective mGluR5 antagonists for probing the function of this receptor in the CNS. PAMs of group I mGluRs include Ro 67-7476, Ro 67-4853, and VU71 (see Table 2), while a novel range of multiple mGluR5-selective PAMs have been identified (see Conn et al., 2008).

2.2.2. Group II metabotropic receptors

Prototypical selective group II mGluR agonists are DCG-IV and (2R,4R)-APDC, while systemically active and highly selective group II mGluRs agonists include LY354740 and LY379268 (see Table 2). The latter are commonly used to access group II mGluR function in vivo (Schoepp et al., 1999). Although these compounds are highly selective for group II mGluRs relative to other mGluR subtypes, they cannot differentiate between mGluR2 and mGluR3 (Niswender and Conn, 2010). Multiple selective PAMs of mGluR2 have also been identified (see Table 2), while group II mGluR NAMs that block both mGluR2 and mGluR3 have been reported, such as LY341495 and MGS0039. Recently, additional novel group II mGluR2 and mGluR3 NAMS have

been reported, such as various deriviatives of dihydrobenzo[1,4] diazepin-2-one (Hemstapat et al., 2007) and others (Niswender and Conn, 2010).

2.2.3. Group III metabotropic receptors

L-AP4 is the prototypical orthosteric group III mGluR agonist offering high selectivity over other mGluRs or ionotropic glutamate receptors (Table 2; Schoepp et al., 1999). (S)-3,4-DCPG has recently emerged as a novel agonist with 100-fold selectivity for mGluR8 over mGluR4 (Thomas et al., 2001; Zhai et al., 2002; Table 2). Orthosteric antagonists with high selectivity for group III mGluRs include CPPG and MAP4 (see Table 2). PHCCC is an mGluR4 PAM (Table 2), while SIB-1893 and MPEP are mGluR5 NAMs that possess mGluR4 PAM activity as well (Table 2). AMN082 has been reported as a selective allosteric agonist of mGluR7 suitable for in vivo use (Mitsukawa et al., 2005; Table 2), while MMPIP is a mGluR7-selective NAM (Table 2). Interestingly, AMN082 and MMPIP (Table 2) only have activity on mGluR7 in some cellular contexts. Indeed, while they permit certain mGluR7 directed signals, they may specifically block others, an idea recently coined as permissive antagonism (Kenakin, 2005).

3. Extinction and its role in anxiety disorders

It is increasingly evident that some psychiatric illnesses, and especially those that comprise an element of fear and/or aversive behavior, involve a learned component. Memory or associations with the aversive event/experience trigger a conditioned response that invariably involves a maladaptive response leading to an exagerrated stress response together with fearful and anxious behavior (Myers et al., 2011). Recent work has described the important contribution of glutamate in the extinction of fear memory, particularly via its actions at NMDA, AMPA and mGlu receptors.

Pavlovian conditioning is a form of associative learning where a conditioned stimulus (e.g. light coming on) becomes associated with the occurrence of an unconditioned stimulus (e.g. shock) through a process of extended training, to eventualy illicit a conditioned response (e.g. avoidance behavior) to the presentation of the conditioned stimulus (light) alone (Myers et al., 2011). However, the conditioned response (avoidance behavior) can be extinguished by repeated exposure to the light without co-presentation with the unconditioned stimulus (shock). This process, called extinction, has provided clinicians with a means whereby they can reduce the impact of conditioned responses, for example in patients suffering from PTSD, thereby reducing subsequent maladaptive behavioral responses, e.g. anxiety, hyperarousal, avoidance, flashbacks etc. (Fig. 2; Myers et al., 2011).

The amygdala, medial prefrontal cortex (mPFC) and hippocampus mutually interact to mediate extinction learning and memory and its modulation by context. It is especially the baso-lateral amydala (BLA) and the intercalated cell masses (ICM), the latter responsible for gating impulse traffic from the BLA to the central nucleus of the amygdala, that are critical in this response (Myers et al., 2011). The BLA is central for the essential neuroplastic processes that underly the consolidation and extinction of fear memory, and receives sensory information about discrete conditioned stimuli as well as contexual and spacial cues. After acquisition of fear memory, the BLA triggers a conditioned fear response via projections to the central nucleus of the amygdala, which in turn innervates the hypothalamus and other brain stem regions such as the periaquaductal gray to elicit a behavioral fear response (e.g. freezing, potentiated startle response, aversion). In the current context, it is important to note that repeated omission of the unconditioned response (shock) during extinction relays information pertaining to the conditioned stimulus to the BLA and infra limbic cortex through a process involving NMDA-directed synaptic plasticity. Following NMDA receptor activation, the NO signaling pathway regulates pre- and postsynaptic alterations in the amygdala following fear conditioning (Ota et al., 2010), and is important for both acquisition and consolidation of contextual fear memory (Kelley et al., 2010) as well as being involved in anxiety responses (Guimarães et al., 2005; Kleppisch and Feil, 2009). Suppression of fear conditioned responses takes place via infra limbic mediated inhibition of amygdalar throughput by activating inhibitory GABA neurons in the ICM (Myers et al., 2011). Through the action of GABA interneurons, the mPFC sends projections that terminate in the BLA and on the ICM allowing the mPFC to exert inhibitory control over amygdalar throughput, culminating in extinction (Quirk and Mueller, 2008). Extinction is therefore associated with increased frequency and expression of GABA-related gene expression (Chhatwal et al., 2005; Heldt and Ressler, 2007) and GABA-A receptor membrane insertion in the BLA (Lin et al., 2009), and can be impaired by GABA'ergic interventions (Harris and Westbrook, 1998; Likhtik et al., 2008). The hippocampus also sends projections to the amygdala as well as to the mPFC (Myers et al., 2011). It is therefore not surprising that the hippocampus, traditionally associated with spatial and contexual memory (Kim and Fanselow, 1992), also has a role in context dependence of extinction. The hippocampus encodes contexual information during extinction training and uses that information to promote or oppose expression of extinction memory, probably via its interconnections with the amygdala and mPFC (Myers et al., 2011). Both GABAergic and glutamatergic neurotransmission thus play a central role in disorders involving fear memory consolidation and extinction.

4. Role of glutamate receptors in anxiety and stress-related disorders

The excitatory action of glutamate in the mammalian brain and spinal cord have been known for more than fifty years (e.g. Curtis and Watkins, 1960). Glutamate exerts a diverse array of biological responses that are responsible for its central role in neurodevelopment, synaptic plasticity and memory, as well as neurotoxicity and neurodegeneration (Meldrum, 2000). At both the metabolic and physiological level, the fate of glutamate as well as its functional activity is closely tied to that of GABA, the primary inhibitory transmitter in the brain (Leonard, 2003). GABA originates from glutamate synthesis via glutamate decarboxylase, with excessive glutamate release in turn promoting GABA synthesis (Leonard, 2003). Together with GABA, glutamate plays a major role in regulating the function and bio-behavioral response of other central neurotransmitters whereby glutamate interneurons synapse on other neuronal systems to influence the down-stream signaling of for example noradrenaline, dopamine and serotonin, acetylcholine, histamine as well as neuropeptides (Harvey, 1996).

The blockade of NMDA receptors in the prefrontal cortex increases the release of dopamine and acetylcholine in the nucleus accumbens, thereby implying that hypofunction of prefrontal NMDA receptors is associated with a dysfunction of the corticolimbic circuit (Del Arco and Mora, 2008) that can translate to various neuropsychiatric manifestations. Consequently, partial NMDA receptor agonists may be useful in treating certain of these disorders. If we now consider mGluRs, both group III and group II mGluR agonists suppress the frequency of 5-HT-induced excitatory postsynaptic currents in the prefrontal cortex (Zhang and Marek, 2007) suggesting a close coupling between mGluRs and 5-HT_{2A} receptors that may contibute to the actions of psychotropic drugs. Similarly, 5HT and DA are both strongly regulated by GABA as well as the glutamate-NO pathway (Wheeler et al., 1995; Tao and Auerbach, 2000; Prast and Philippu, 2001), such that dysfunction in GABA/glutamate transmission may be a significant contributor to serotonin and dopamine dysfunction. The opposite also applies, with raised cerebral levels of serotonin inducing a decrease in glutamate transmission and a parallel increase in GABA transmission, particularly in the hippocampus, frontal cortex and cerebellum (Ciranna, 2006). These actions may underlie serotonergic-mediated modulation of cognitive function, analgesia, motor control, anxiety and mood (Ciranna, 2006).

The role of glutamate, GABA (Shiah and Yatham, 1998; Krystal et al., 2002) and glutamate-mediated activation of ionotropic receptor driven acivation of sub-cellular calcium-dependent pathways, e.g. NO, mTOR, is thus increasingly being recognized in the neuropathology and treatment of anxiety and stress-related illnesses (Harvey, 1996; Paul and Skolnick, 2003; Millan, 2006; Li et al., 2010). Indeed, combined action on monoaminergic and nitrergic systems holds promising possibilities (Harvey et al., 2010). This knowledge has opened new avenues of investigation into the treatment of illnesses previously regarded as strictly the domain of monoamine-selective drugs, such as antidepressants, antipsychotics and anxiolytics. Based on the pre-clinical literature, the following sections will consider with what level of success we have been able to harness the glutamatergic system for use in anxiety and stress-related disorders.

4.1. Therapeutic utility of glutamate in anxiety disorders

Preclinical and, to a lesser extent, clinical research has provided a significant scientific rationale for the potential therapeutic utility of glutamate modulators in the treatment of anxiety disorders (Millan, 2003; Bergink et al., 2004; Krystal et al., 2010). Stress, an important risk factor in the genesis of an anxiety disorder, is known to precipitate glutamate release in limbic regions of the rat brain which may in part act to stimulate HPA axis and contribute to glucocorticoid-induced neurotoxicity (Moghaddam, 2002; Harvey et al., 2003a; Figs. 2 and 3). The process of extinction relies heavily on the involvement of the glutamate system (Myers et al., 2011). This had led to the general notion that attenuating glutamatergic neurotransmission in a regionally specific manner would shift the balance away from excitatory towards inibitory GABAergic neurotransmission, leading to anxiolysis. Animal tests of fear responding and anxiety indeed have provided important support for this. These tests include punishment-induced conflict (Geller–Seifter test) or ethological-induced conflict, such as the elevated plus maze (EPM), the social interaction (SI) paradigm, ultrasonic vocalization (USV), the acoustic startle (AS) paradigm, aversive tests (e.g. predator exposure) and conditioned fear models (e.g. fear-potentiated startle). In addition, a number of pathophysiological (translational) models have been validated to closely emulate the bio-behavioral characteristics of a specific human disorder, for example social isolation rearing or maternal separation (anxiety, depression and schizophrenia), single prolonged stress or time dependent sensitisation and predator exposure models (PTSD), lactate-induced panic in rats (panic disorder), predator odor (phobia) etc. Indeed, we will address these translational models in Section 6.

5. Ionotropic glutamate receptors in anxiety: a preclinical perspective

5.1. NMDA receptor modulation

There are various approaches whereby NMDA receptor active drugs may block activation of the NMDA-ionophore complex. These include competitive inhibition of the NMDA site itself e.g. with AP5 (2-amino-5-phosphonopentanoic acid), ifenprodil, dizocilpine (MK-801), non-competitive inhibition by blocking the ion channel e.g. with memantine, modulation of the NMDA/glycine-sensitive site e.g. with D-cycloserine or spermine, blockade of the polyamine binding site (see Bermudo-Soriano and colleagues in this special issue), and modulation of NMDA subunit expression (Myers et al., 2011). Table 3 depicts pre-clinical studies that have explored these therapeutic options in various animal tests of anxiety.

Both competitive and non-competitive NMDA antagonists are effective anxiolytics over a wide range of anxiety tests in animals, although non-competitive antagonists are much less reliable in this regard (Table 3), while they also present with a greater risk of adverse effects (Wiley, 1997). Indeed, ketamine seems to be more anxiogenic in action (Table 3). Similarly, glycine-site antagonists show noteworthy anxiolytic effects, although there are a number of studies that have failed to replicate these findings (Table 3). Interestingly, the partial glycine site agonist, D-cycloserine, has also demonstrated anxiolytic actions but at the same time has shown a penchant to enhance anxiety and fear-related behaviors as well (Table 3). Variation in endogenous glutamatergic tone may affect the action evoked by a partial agonist. Thus under conditions of low and high activity at the glycine site, D-cycloserine may act as an agonist or antagonist, respectively, which may lead to different behavioral outcomes.

Mouse pups separated from their dam/siblings emit distress-like ultrasonic vocalizations (USV), which may be reflective of an anxiety-like state. Repeated maternal separation of rats selectively alters glutamate receptor expression in the hippocampus but not in the prefrontal cortex (Pickering et al., 2006). Indeed, separation-induced USV are suppressed by various classes of NMDA antagonist, including those acting at the glutamate recognition site (D,L-amino-phosphono-valeric acid (AP5) and MDL 100,453) or at the ion channel (MK-801), or by blocking the strychnine-insensitive glycine site (5,7-dichlorokynurenic acid, 5,7-DCKA; Kehne et al., 1991). High affinity NMDA receptor antagonists such as MK 801 dose-dependently reduce USV, whereas low-affinity antagonists, such as memantine and neramexane, seem to enhance these distress calls (Takahashi et al., 2009).

The NMDA receptor is heavily implicated in learning, memory and experience-dependent forms of synaptic plasticity, such as long-term potentiation (LTP; Nicoll and Malenka, 1999), and was the first of the glutamate receptors shown to be implicated in extinction in fear conditioning experiments (Table 4). A vast array of studies have repeatedly demonstrated that NMDA receptor antagonists impair extinction within training, impair retention of extension after training, as well as impair reappearance of a previously extinguished conditioned response (Myers et al., 2011). Furthermore, by recruiting voltage-gated NMDA receptor ion channels, AMPA receptors will also contribute to fear extinction and retention (Fig. 3). The general concensus now is that NMDA receptor-dependent synaptic plasticity within the BLA is involved in encoding fear extinction memory, while consolidation of extinction memory involves NMDA receptor-dependent synaptic plasticity within the infralimbic medial prefrontal cortex (Myers et al., 2011). Interestingly, NMDA receptor activation is required when extinction events are relatively novel but not when they are relatively familiar (Chan and McNally, 2009). Thus, its involvement shifts when a cue is extinguished a second time, i.e. fear acquisition plus extinction followed by re-acquisition and re-extinction.

Contextual fear acquisition and expression in rats is dependant on NMDA receptor mediated neuroplasticity in the BLA. Consistent with this a number of studies have shown that competitive and noncompetitive NMDA receptor blockade disrupts fear extinction (Table 4; Myers et al., 2011) whilst augmentation of receptor activity through the glycine-B co-agonist site with the partial agonist D-cycloserine promotes extinction (Table 4; Myers et al., 2011). Furthermore, genetically engineered mice with overexpression of the NR2B subunit in the forebrain exhibit more rapid fear extinction (Tang et al., 1999). Stressful conditions, especially situational stressors, decreases fear extinction and decreases NMDA receptor subunit expression in the hippocampus, which can be normalized by partial stimulation of the NMDA receptor complex, e.g. using D-cycloserine (Yamamoto et al., 2008). Indeed, stress and re-experience, a putative animal model of PTSD, reduces NMDA receptor binding in rat hippocampus (Harvey et al., 2004a). Similarly, D-cycloserine reverses disruption of fear extinction following early life stress (Matsumoto et al., 2008). Overall these preclinical data suggest that agents capable of upregulating NMDA receptor function may prove useful as adjuncts to cognitive behavioral therapy in the management of anxiety disorder. Indeed this is supported by preliminary clinical evidence showing that D-cycloserine can augment exposure therapy in patients with social

Table 3
Glutamate ionotropic receptor agonists and antagonists in animal models of anxiety.

Substance	Effect on anxiety?	Author(s) (Year)
Non competitive NMDA antagonists		
Ketamine	↑ Anxiety (EPM, SI)	Silvestre et al., 1997
MK801	↓/No effect (CT, SI, EPM)	Xie and Commissaris, 1992; Corbett and Dunn, 1993; Koek and Colpaert, 1991; Jessa et al., 1996; Dunn et al., 1989; Fraser et al., 1996; Criswel et al., 1994; Xie et al., 1995
PCP	↓/No effect (USV CT, EPM)	Vry De et al., 1993; Kehne et al., 1991; Porter et al., 1989; Sanger and Jackson, 1989; Wiley et al., 1995
Memantine, amantadine	↓/No effect (USV, CT, EPM)	Vry De et al., 1993; Karcz-Kubicha et al., 1997
Ifenprodil	↓ Anxiety (EPM)	Fraser et al., 1996
Competitive NMDA antagonists		
NPC 17742	↓ Anxiety (EPM, CT)	Wiley et al., 1995
CPP and CGS19755	↓ Anxiety (CT)	Bennet and Amrick, 1986; Koek and Colpaert, 1991; Corbett and Dunn, 1991
AP5	↓ Anxiety (EPM, SI, USV, FPS)	Dunn et al., 1989; Kehne et al., 1991; Fendt et al., 1996; Campeau et al., 1992
AP7	↓ Anxiety (ASP, CT, EPM, SI)	Anthony and Nevins, 1993; Bennet and Amrick, 1986; Dunn et al., 1989; Plaznik et al., 1994
CGP 37849	↓ Anxiety (OF, CT)	Jessa et al., 1996; Plaznik et al., 1994; Przegaliński et al., 1996
Glycine site ligands		
ACEA 1021 (antagonist)	↓/No effect (EPM)	Wiley et al., 1995
HA 966 (partial agonist)	↓ Anxiety (EPM, SI, CT, USV, ASP)	Trullas et al., 1989; Dunn et al., 1992; Anthony and Nevins, 1993; Karcz-Kubicha et al., 1997
5,7 DCKA (antagonist)	↓ Anxiety (OF, CT, USV)	Plaznik et al., 1994; Kehne et al., 1995; Corbett, 1993
7 CKA (antagonist)	↓/No effect (ASP, CT)	Koek and Colpaert, 1991; Anthony and Nevins, 1993
MDL 102,288/MDL 100,458 (antagonist)	↓ Anxiety (USV)	Kehne et al., 1995; Baron et al., 1997
L-701, 324 (antagonist)	↓/No effect (CT, EPM)	Kotlinska and Liljequist, 1998b; Karcz-Kubicha et al., 1997
ACPC (antagonist)	↓ Anxiety (CT, EPM, ASP)	Anthony and Nevins, 1993; Przegaliński et al., 1996; Karcz-Kubicha et al., 1997
D-cycloserine (partial agonist)	↑ FPS (extinction) and ↑ anxiety (EPM)	Walker et al., 2002b; Ho et al., 2005
	↓ Anxiety (FPS, ASP, EPM)	Anthony and Nevins, 1993; Karcz-Kubicha et al., 1997; Fendt, 2000
	↓ Reinstatement and ↑ extinction in cue-conditioned freezing	Ledgerwood et al., 2003, 2004; Parnas et al., 2005
	↑ Punished drinking	Klodzinska and Chojnacka-Wojcik, 2000
AMPA/kainate receptors		
Kainic acid (agonist)	↓ FPS	Fendt, 2000
NBQX (antagonist)	↑ Anxiety (FPS, EPM)	Fendt, 2000; Karcz-Kubicha and Liljequist, 1995
LY326325 (antagonist)	↑/↓ Anxiety (CT, EPM)	Karcz-Kubicha et al., 1997; Kotlinska and Liljequist, 1998a
Topiramate (antagonist)	↓ Anxiety (APS)	Khan and Liberzon, 2004
LY215490 (antagonist)	↓ Anxiety (CT)	Benvenga et al., 1993
Polyamine site		
Eliprodil (antagonist)	No effect (CT)	Wiley et al., 1998

Substances: MK 801, dizolcipine; PCP, phencyclidine; CPP, 3-(−2-carboxy piperazine-4yl)-propyl-1-phosphonic-acid; CGS 19975, *cis*-4-phosphonomethyl-2-piperidine-carboxylkynurenate; AP5, 2 amino-5-phosphonoheptanoate; AP7, 2 amino-7-phosphonoheptanoate; HA 966, 3-amino-1-hydroxy-2-pyrrolidinone; 5,7 DCKA, 5,7-dichlorokynurenic acid; 7 CKA, 7-chlorokynurenic acid; MDL'102,288, 5,7-dichloro-1,4-dihydro-(((4-((methoxycarbonyl)amino)-6-chloro-1H-indole-2-carboxylic acid; MDL" 100,458, (3(benzoylmethylamino)-6-chloro1H-indole-2-carboxylic acid; MDL 105,519, *(E)*-3-(2-phenyl-2-carboxyethenyl)-4,6-dichloro-1H-indole-2-carboxylic acid; L-701,324, 7-chloro-4-hydroxy-3-(3-phenoxy) phenyl-2(1H)-quinolone; ACPC, 1-aminocyclopropanecarboxylic acid; Memantine, amantadine; LY326325; LY215490, 3*SR*, 4*aRS*, 6*RS*, 8*aRS)*-6-(2(1H-tetrazol-5-yl)ethyl)decahydro-isoquinoline-3-carboxylic acid;LY354740, 1*S*, 2*S*,5*R*,6*S*-2-aminobicyclo(3.1.0)hexane-2-6-dicarboxylate monohydrate; NBQX, dihydroxy-6-nitro-7-sulfamoyl-benzo(*F*)quinoxaline; MPEP, 2-methyl-6-(phenylethynyl)pyridine.
Anxiety tests: CT, conflict test; EPM, elevated plus maze; USV, ultrasonic vocalization; SI, social interaction; ASP, acoustic startle paradigm; FPS, fear-potentiated startle; OF, open field.

anxiety disorder (Hofmann et al., 2006; Guastella et al., 2008), PD (Otto et al., 2010) and OCD (Kushner et al., 2007; Wilhelm et al., 2008). Glycine transport inhibitors which, by raising synaptic glycine levels, can also facilitate the activation of NMDA receptors and should thus in principle mimick the effects of D-cycloserine.

5.2. AMPA receptor modulation

Studies carried out with non-NMDA (AMPA and kainate) receptor ligands are outlined in Table 3. The AMPA receptor appears to have a bidirectional effect on anxiety, with evidence of both anxiolytic and anxiogenic activity for AMPA receptor agonists (Table 3). Generally, agonists are anxiolytic (Fendt, 2000), while anxiogenic activity is more associated with blockade of AMPA receptors (Kotlinska and Liljequist, 1998a; Fendt, 2000), e.g. at least two studies have found the AMPA antagonist NBQX to be anxiogenic (Table 3). However, the AMPA/kainate receptor antagonist LY326325 induces significant anxiolytic activity in the EPM (Kotlinska and Liljequist, 1998a), while topiramate similarly prevents anxiety-like behavior in an animal model of PTSD (Khan and Liberzon, 2004). Direct activation of kainate receptors with kainic acid is also anxiolytic (Fendt, 2000). Variations in anxiolytic/anxiogenic response can be related to variation in endogenous glutamatergic tone under different laboratory settings. Block of a high glutamate tone would yield anxiolysis whereas block of a low tone may precipitate the opposite effect. Loss of AMPA receptors from the plasma membrane can potentially attenuate the capacity for neuroplasticity

Table 4
Ionotropic and metabotropic receptor agonists and antagonists in extinction based studies.

Class and drug	Time of admin	Effect on extinction and extinction retention	Reference
NMDA			
Comp. antagonist			
AP5	Pre-ext	↓ ER; No effect/↓ expression of CR. Time-dependent effects noted.	Lin et al., 2003; Falls et al., 1992; Lee and Kim, 1998; Szapiro et al., 2003; Cammarota et al., 2005; Bevilaqua et al., 2006.
AP5	Pre-ext or pre-re-ext	↓ ER and expression of CR.	Laurent and Westbrook, 2008
CPP	Pre- and 24 h post ext.	↓ ER. Time dependent effects noted.	Santini et al., 2001
CPP	Pre-ext Immed. post-ext	No effect on within-session extinction; ↓ ER. ↓ ER.	Burgos-Robles et al., 2007
Noncomp.antagonist			
MK-801	Pre-ext	↓ ER and fear acquisition. No effect/ ↓ CR expression. Drug pre- or 4 h post-extinction but not 12 h post-extinction ↓ ER	Langton et al., 2007; Cox and Westbrook, 1994; Kehoe et al., 1996; Lee et al., 2006; Baker and Azorlosa, 1996; Liu et al., 2009.
MK-801	Post-ext; prior to unsignalled US	Blocked reinstatement.	Johnson et al., 2000
MK-801	Pre-or post-US habituation	↓ ER if given pre- but not 4 h post-US habituation	Storsve et al., 2010
MK-801	Pre-ext	MK-801 ↓ extinction for novel but not familiar CSs.	Chan and McNally, 2009
Ifenprodil	Pre-ext	↓ Within-session extinction and ER; No effect on expression of CR.	Sotres-Bayon et al., 2007
Ifenprodil	Immed. post-ext Pre-ext Immed. post-ext	↓ ER. No effect ↓ ER.	Sotres-Bayon et al., 2009
Ifenprodil	Pre-ext Immed. post-ext Pre-ext Post-ext	↓ Within-session extinction and ER. No effect ↓ ER for 1st and 2nd extinction; No effect on within-session extinction.	Laurent and Westbrook, 2008
Ro 25-6981	Pre-ext	↓ Within-session extinction but not ER.	Dalton et al., 2008
Partial agonists			
D-cycloserine	Pre-ext	↑ ER, blocked by antagonist	Walker et al., 2002b; Myers and Carlezon, 2010
D-cycloserine	Pre-or post-ext to 2 h	Facilitated ER. Facilitated extinction retention; Impaired reinstatement.	Ledgerwood et al., 2003; 2004; 2005
D-cycloserine	Immed. post-ext	↑ Extinction, but tolerance after multiple dosing that dissipated over time. ↑ ER.	Parnas et al., 2005; Lee et al., 2006; Woods and Bouton, 2006; Weber et al., 2007; Bouton et al., 2008
D-cycloserine	Pre-ext	↑ ER; blocked by MAPK or PI3K antagonist, transcriptional inhibitor, or protein synthesis inhibitor	Yang and Lu, 2005
D-cycloserine	Pre-ext	↑ Extinction only in less anxious mice	Tomilenko and Dubrovina, 2007
D-cycloserine	Pre-ext	↑ 1st but not 2nd extinction unless 2nd extinction involved a different cue	Langton and Richardson, 2008
D-cycloserine	Pre-ext	↑ ER and extinction-induced increase in BLA AMPA/NMDA receptor ratio.	Lin et al., 2010
Spermidine	Post-ext	Drug given immediately but not 6 h post-extinction ↑ ER, blocked by NR2B antagonist.	Gomes et al., 2010
AMPA			
AMPA antagonist			
CNQX	Pre-ext	No effect	Falls et al., 1992
AMPA potentiator			
PEPA	Pre-ext	↑ Within-session extinction and ER, and blocked reinstatement.	Zushida et al., 2007; Yamada et al., 2009
mGluR			
mGluR7 KO N/A	Constitutive	↓ Extinction.	Callaerts-Vegh et al., 2006; Goddyn et al., 2008
mGluR5 KO N/A	Constitutive	↓ Extinction.	Xu et al., 2009
mGluR1 antagonists			
CPCCOEt	Pre-ext	↓ Within-session extinction occurring 48 h but not 2 h after acquisition; ↓ ER after 48 h extinction.	Kim et al., 2007a
mGluR7ag.			
AMN082	Pre-ext	↑ ER.	Fendt et al., 2008
mGluR5 PAM			
CDPPB	Pre-ext	↑ ER.	Gass and Olive, 2009

and may therefore be considered as a type of synaptic depotentiation or loss of LTP (Huang and Hsu, 2001) which in the BLA is believed to act as the substrate for fear memory storage (Sigurdsson et al., 2007). Limited work has investigated the polyamine site in anxiety, eg. spermidine (Table 4), with no clear evidence for anxiolytic activity (Table 3). However, see Bermudo-Soriano and colleagues in this special issue of the journal for further detail on the role of the polyamine site in anxiety and anxiolytic action.

Although AMPA receptors are involved in basal synaptic neurotransmission (Traynelis et al., 2010), they are also involved in experience-dependent forms of synaptic plasticity (Hu et al., 2007; Selvakumar et al., 2009) and there is great interest in investigating AMPA modulating drugs in models of fear extinction (Table 4). As mentioned earlier, through intimate cross-talk interactions between AMPA and NMDA receptors, and the well established role for NMDA receptors in LTP and in the consolidation and extinction of fear memory, AMPA modulators have important considerations in treating disorders of anxiety and cognition, especially since utilizing this interaction would limit the risk of excitotoxicity. BLA administration of an AMPA receptor antagonist, CNQX (6-cyano-7-nitroquinoxaline-2,3-dione), has been found to have little to no effect on subsequent retention of fear extinction (Falls et al., 1992; Lin et al., 2003), while AMPA receptor agonists facilitate contexual fear extinction (Zushida et al., 2007; Yamada et al., 2009), possibly by promoting AMPA receptor internalization. However, this appears paradoxical since high potency agonism would promote internalization of the AMPA receptor thus attenuating glutamate stimulation of both AMPA and NMDA receptors. Clearly these mechanisms need to be more fully characterized. Partial AMPA agonists act in a similar manner as partial NMDA receptor agonists, resulting in an increase in extinction and extinction retention (Table 4). Thus harnessing an action on both AMPA and NMDA receptors would promote extinction of fear memory and can be achieved either by direct partial stimulation of the NMDA receptor, by indirectly bolstering NMDA receptors via a primary action on the AMPA receptor, or by increasing NO-directed NMDA-AMPA receptor cross talk (Selvakumar et al., 2009; Boix et al., 2011). As described earlier, the NO pathway plays a prominent role in the acquisition of conditioned fear memory (Kelley et al., 2010; Ota et al., 2010). Given the importance of glutamate signaling in the BLA for fear extinction, this is an intriguing observation. Indeed conditioned fear is associated with increased cell-surface expression of GluR1 and GluR2 subunits in the BLA (Rumpel et al., 2005), with decreased expression in extinguished animals (Kim et al., 2007a).

However, evidence would suggest that AMPA receptor binding is sufficient but not necessary for AMPA receptor internalization. In fact, simultaneous glutamate binding to NMDA receptors may be required for AMPA receptor endocytosis (Beattie et al., 2000; Mangiavacchi and Wolf, 2004), possibly explaining why pre-extinction training administration of AMPA antagonists into the BLA has no apparent effect on extinction. This would suggest that AMPA receptor internalization in the BLA is mediated primarily by glutamate binding to NMDA receptors. Indeed, NMDA receptor activation has been found to cause AMPA receptor internalization in cultured hippocampal and isolated amygdala preparation (Beattie et al., 2000). Conversely, blockade of NMDA receptors may indirectly increase glutamate activity at the AMPA receptor. Some evidence for this comes from an investigtion examining the molecular mechanism underlying the antidepressant activity of ketamine, indicating that it could be blocked by pretreatment with an AMPA receptor antagonist (Maeng et al., 2008). Consequently, NMDA receptor antagonist-induced disruption of fear extinction may, at least in part, be mediated by enhanced AMPA receptor stimulation. Counter intuitively the AMPA receptor potentiator PEPA facilitates contextual fear extinction (Zushida et al., 2007; Yamada et al., 2009). One possible explanation of this apparent contradictory finding is that PEPA may provoke removal of AMPA receptors from the plasma membrane by agonist induced receptor internalization.

6. Metabotropic glutamate receptors in anxiety: a preclinical perspective

Based on the hypothesis that stress or fear induced glutamate release in cortical and limbic structures may be of relevance to the pathology of anxiety disorders, the presynaptic mGluR2/3 autoreceptors have received the most attention from a drug discovery perspective (Table 5). Indeed considerable progress has been made in the identification of PAMs and agonists of these receptors, some of which have been tested clinically in proof of concept studies. LY354740 is the most advanced molecule which has a remarkable preclinical profile strongly predictive of anxiolytic activity (Swanson et al., 2005). Other metabotropic glutamate receptors also offer promising approaches of relevance to anxiety disorders (see Palucha and Pilc, 2007; Wierońska and Pilc, 2009).

The mGluR5 receptor increases neuronal excitability and NMDA receptor currents in brain regions thought to be involved in anxiety, such as the amygdala (Krystal et al., 2010), leading to the hypothesis that mGluR5 antagonists might dampen the hyperactivity of glutamatergic transmission believed to underlie anxiety disorders. Consistent with this, MPEP and related mGluR5 NAMs have robust efficacy in several animal models of anxiolytic activity (Table 5). Group I antagonists and modulators of Group III mGluRs also show promise with regards to utility in anxiety disorders based primarily on emerging preclinical data (Table 5). Thus mGluR5 knockout mice demonstrate reduced stress-induced hyperthermia (Brodkin et al., 2002a), while mGluR5 antagonists show efficacy in various animal models of anxiety (Table 5). Considering the group III mGluRs, mGluR7 receptor modulators have been found to affect multiple sites involved in mood and anxiety neuronal circuitry (Table 5). Furthermore, mGluR7 knockout mice display upregulated corticosteroid receptor-dependent feedback suppression of the HPA axis, increased serotonin $5HT_{1A}$ receptor transcripts as well as increased expression of hippocampal BDNF (Mitsukawa et al., 2006).

By virtue of their ability to reduce glutamate release in cortical and limbic structures that are activated during stress and/or fear, ligands of the group II mGluR family, but most notably allosteric potentiators and agonists of the mGluR2/3 receptor, display rapid anxiolytic activity with minimal abuse or tolerance potential (Swanson et al., 2005). LY354740, an mGluR2/3 agonist, reduces activation of the basolateral and central nucleus of the amygdala, the prefrontal cortex and lateral and medial perforant paths of the hippocampus, brain regions responsive to stress or fear stimuli (Schoepp et al., 2003), where it blunts disinhibition of synaptic excitatory activity (Linden et al., 2004). The compound also demonstrates significant anxiolytic activity in several rodent stress and anxiety models including fear-potentiated startle, latate induced panic, stress-induced hyperthermia and aversion in the EPM (Table 5; Linden et al., 2004; Nordquist et al., 2007), while in non-human primates it reduces yohimbine-induced anxiety and stress-related elevations in cortisol (Coplan et al., 2001). Moreover, the anxiolytic effects of LY354740 in the EPM are prevented by an mGluR antagonist, while this response is also not evident in mGluR2 or mGluR3 knockout mice (Linden et al., 2005). Interestingly, the anxiolytic ativity of LY354740 requires the expression of one or both mGluR2/3 receptors (Linden et al., 2005).

When considering the contribution of mGluRs to fear extinction, the fact that some subtypes, such as mGluR5, have been implicated in learning and memory and experience-dependent forms of synaptic plasticity (Simonyi et al., 2005) provide a robust rationale for the involvement of mGluRs in the neural mechanisms governing extinction learning (Table 4). Local BLA infusion of the mGluR1 antagonist, CPCCOEt, before extinction training dose-dependently impairs extinction training and subsequent extinction retention, although only when extinction training occurs 48 h after acquisition and not 1 h afterwards (Kim et al., 2007b; Table 4). The latter implies that the mechanisms of short- and long-interval extinction may be different. CPCCOEt also

Table 5
Metabotropic glutamate receptor (mGluR) agonists and antagonists in animal models of anxiety.

Substance	Effect on anxiety?	Author(s) (Year)
Group 1		
mGluR 1 antagonists		
3-Ethyl-2-methyl-quinolin-6-yl-(4-methoxycyclohexyl)-methanone methanesulfonate (EMQMCM)	↓ Anxiety (EPM, CT) ↓ FPS and freezing (CFC)	Pietraszek et al., 2005
JNJ16259685	No anxiolytic effect (EPM) but ↓ anxiety (CT)	Steckler et al., 2005
LY456236	↓ Stress-induced hyperthermia ↓ anxiety (CLS) ↓ anxiety (CT)	Rorick-Kehn et al., 2005; Varty et al., 2005
4-[1-(2-Fluoropyridine-3-yl)-5-methyl-1H-1,2,3-triazol-4-yl]-N-isopropyl-N-methyl-3,6-dihydropyridine-1(2H)-carboxamide (FTIDC)	No anxiolytic effect (EPM) ↓ stress-induced hyperthermia ↓ anxiety (USV)	Satow et al., 2008
1-Aminoindan-1,5-dicarboxylic acid (AIDA)	↓ Anxiety (EPM,CT) ↓anxiety (FP)	Kłodzińska et al., 2004a; Lima et al., 2008
mGluR5 antagonists		
2-Methyl-6-phenylethynylpyridine (MPEP)	↓Fear-potentiated startle ↑Punished responding ↓Anxiety (EPM, CT,SI, USV, ASP) ↓ stress –induced hyperthermia ↓/no effect (EPM ↓ anxiety (CT, CLP, FP) Inhibition of fear-potentiated startle Increased social contact on social exploration test	Satow et al., 2008; Brodkin et al., 2002b; Iijima and Chaki, 2005; Rorick-Kehn et al., 2005; Nordquist et al., 2007; Spooren et al., 2000;2002; Pietraszek et al., 2005; Tatarczyńska et al., 2001a; Wierońska et al., 2004; Pérez de la Mora et al., 2006; Ballard et al., 2005; Steckler et al., 2005; Varty et al., 2005; Lima et al., 2008; Schulz et al., 2001
3-((2-Methyl-4-thiazolyl)ethynyl)pyridine(MTEP)	↓/No effect on anxiety EPM ↓ FPS and ↓ freezing (CFT) ↓ anxiety (CT, CLS, FP)	Pietraszek et al., 2005; Klodzinska et al., 2004b; Molina-Hernández et al., 2006; Busse et al., 2004; Varty et al., 2005
Fenobam	Attenuation of stress-induced hyperthermia ↓ anxiety (CT, conditioned emotional response task)	Porter et al., 2005
Group II		
mGluR2/3 agonists		
LY354740	↓ Stress-induced hyperthermia ↓Fear-potentiated startle ↓ anxiety (EPM, CT, FP) ↓Lactate-induced panic	Rorick-Kehn et al., 2005;2006; Spooren et al., 2002; Helton et al., 1998; Walker et al., 2002a; Tizzano et al., 2002; Linden et al., 2004,2005; Monn et al., 1997; Tatarczyńska et al., 2001b; Kłodzińska et al., 1999; Benvenga et al., 1999; Porter et al., 2005; Shekhar and Keim, 2000; Helton et al., 1998
Aminopyrrolidine-2.4-dicarboxylatc (APDC)	↓FPS	Walker et al., 2002a
LY487379	↓FPS	Johnson et al., 2003;2005
LY544344	↓ Stress-induced hyperthermia ↓ FPS	Rorick-Kehn et al., 2006; Bueno et al., 2005
LY379268	No anxiolytic activity (EPM) ↓ stress-induced hyperthermia ↓ anxiety (USV)	Satow et al., 2008
LY314582	↓ Stress-induced hyperthermia Small anxiolytic effect (CT)	Spooren et al., 2002; Benvenga et al., 1999
(2S,2'R,3'-dicarboxycyclopropyl)glycine (DCG-IV)	↓FPS	Lin et al., 2005
mGluR2 potentiators		
3-pyridyl-methyl-sufonamides	↓FPS ↓Stress-induced hyperthermia No anxiolytic activity (EPM) ↓ anxiety (CT)	Johnson et al., 2005; Steckler et al., 2005
LY566332	↓ Stress-induced hyperthermia	Rorick-Kehn et al., 2005
N-[4'-cyano-biphenyl-3-yl]-N-(3-pyridinylmethyl)-ethanesulfonamide (CBiPES)	↓ Stress-induced hyperthermia	Johnson et al., 2005
N-[4-(4-carboxyamidophenoxy)phenyl]-N-(3-pyridinylmethyl)-ethanesulfonamide (4-APPES)	↓FPS	Johnson et al., 2005
mGluR2 antagonists		
LY341495	↓ Stress-induced hyperthermia No anxiolytic activity (EPM) No effect on stress-induced hyperthermia Reversal of anxiolytic activity of LY354750 (EPM) No effect on FPS	Iijima et al., 2007; Bespalov et al., 2008; Linden et al., 2005; Tizzano et al., 2002
MGS0039	↓ Stress-induced hyperthermia ↓ freezing (Cond Fear) ↓ burying behavior No anxiolytic activity (EPM)	Bespalov et al., 2008; Yoshimizu et al., 2006; Shimazaki et al., 2004; Chaki et al., 2004
Group III		
mGluR4PAM		
N-phenyl-7-(hydroxylimino)cyclopropa[b]=chromen-1a-carboxamide (PHCCC)	↓ Anxiety (CT)	Stachowicz et al., 2004; 2006
mGluR7 agonists		
L-serine-O-phosphate (L-SOP)	↓ Anxiety (CT)	Tatarczyńska et al., 2001b
(1S,3R,4S)-1-aminocyclopentane-1,2,4-tricarboxylic acid (ACPT-1)	↓ Anxiety (CT)	Tatarczyńska et al., 2002; Pałucha et al., 2004
mGluR7 antagonists		
(RS)-α-cyclopropyl-4-phosphonophenylglycine (CPPG)	Blocks anxiolytic effect of ACPT-I (CT) ↓/no effect on anxiety (CT)	Pałucha et al., 2004; Stachowicz et al., 2006, 2007

(continued on next page)

Table 5 (*continued*)

Substance	Effect on anxiety?	Author(s) (Year)
mGluR8 agonists		
(S)-3,4-dicarboxyphenylglycine (DCPG)	↓ Stress-induced hyperthermia No anxiolytic activity (CT)	Rorick-Kehn et al., 2005; Stachowicz et al., 2005
(RS)-4-phosphonophenylglycine(PPG)	No anxiolytic activity (CT)	Pałucha et al., 2004

Anxiety tests: CT, conflict test; EPM, elevated plus maze; USV, ultrasonic vocalization; SI, social interaction; ASP, acoustic startle paradigm; FPS, fear-potentiated startle; OF, open field; FP, four plate test; CLS, conditioned lick suppression test.

blocks ex vivo induction of synaptic depotentiation in BLA slices from fear-conditioned animals (Kim et al., 2007a). Contrary to this, the group 1 mGluR agonist, DHPG, induces depotentiation in these slices (Kim et al., 2007a). The mGluR5 antagonist, 2-methyl-6-(phenylthynyl)-pyridine, blocks fear potentiated startle, thus preventing the acquisition and expression of fear (Tizzano et al., 2002), while a similar response is obtained using the Group II mGluR2/3 agonist, LY354740 (Helton et al., 1998; Grillon et al., 2003).

Similarly, mGluR2 potentiators are anxiolytic in the fear potentiated startle paradigm and other related models of anxiety (Helton et al., 1998; Table 4). Both mGluR5 (Xu et al., 2009) and mGluR7 (Callaerts-Vegh et al., 2006; Goddyn et al., 2008) knockout mice present with deficits in fear extinction. Contrary to this, the mGluR7 agonist AMN082 facilitates the extinction of amygdala driven aversive memories (Fendt et al., 2008), although it has no effect when administered in the absence of extinction training. This provides a therapeutic rationale for the use of mGluR1 and mGluR7 agonists to treat conditioned fear-based disorders. Indeed, AMN082 has been found to promote extinction of aversive memories (Fendt et al., 2008). Agonists for group II (mGluR2/3)) receptors and antagonists for group I mGluR5 receptors have also shown activity in animal and/or human conditions of fear, anxiety or stress (Swanson et al., 2005). Indeed, intra-amygdala infusions of the mGluR Group II agonists, LY354740 and (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate, significantly disrupt fear-potentiated startle, and is prevented by the Group II receptor antagonist LY341495. Pretraining administration of LY354740 however blocks fear learning (Walker et al., 2002a).

7. Animal models of anxiety and stress-related disorders

Although the different anxiety and stress related disorders present with anxiety as a common overall symptom, each illness nevertheless presents with its own unique range of biological and behavioral manifestations that underlie its differential diagnosis. Differences in underlying neurobiology may imply a differential response to glutamate modulating agents. Moreover, these illnesses all differ with respect to the type and duration of stress that can be associated with an earlier precipitating event. These considerations are important when modeling the human illness in animals. Pathophysiological animal models provide us with a useful tool to investigate the neurobiology and treatment of a neuropsychiatric illness. They offer the possibility of simulating a condition under controlled circumstances that will enable us to study symptoms as they develop and to test prospective treatments (Yehuda and Antelman, 1993). The animal model should in essence induce behavioral alterations that resemble the symptoms of the human disorder, termed face validity, and should mimic the pathophysiological abnormalities characteristic of the disease, termed construct validity. Finally, a good animal model should demonstrate differential response to drugs used to treat the human condition while also show a lack of response to ineffective treatment modalities, termed predictive validity (Oosthuizen et al., 2005; Korff and Harvey, 2006). It is therefore important that any efficacy of glutamate-active compounds, as assessed in standard anxiety tests, be confirmed in suitably validated translational (pathophysiological) animal models.

7.1. Stress and its relevance in pathophysiological models of anxiety disorders

Hans Selye (Selye, 1936) first explained the importance of the stress response in health and disease that would later lead to the concepts of stress vulnerability and resilience. The stress response is geared to promote the development of coping mechanisms in order to resist a stressor and to improve later response to the same stressor. This process of allostasis (McEwen, 1998) requires behavioral, psychological and physiological adaptation that is vital for survival. However, allostasis is constantly challenged by repeated physical/psychosocial stressors that seek to overwhelm these coping mechanisms leading to maladaptive behavioral and neuro-endocrine responses, structural brain changes and the subsequent development of a mental illness, referred to as allostatic load (McEwen, 1998). Stress-related mental illnesses are therefore dependent on genetic predisposition, while stress itself underpins the basic phenomenology of a numbr of psychiatric illnesses. However, the stressors involved in each are markedly different, and is an important consideration in the development of pre-clinical animal models of anxiety/stressed based disorders (Uys et al., 2003).

Distinction can be made between limbic-sensitive and limbic-insenstive (physiologic) stressors (Herman and Cullinan, 1997). Limbic-sensitive stressors are most sensitive to stressors involving high-order sensory processing of the event before the stress response is initiated and thus require “processive” regulation by the prefrontal cortex, hippocampus or amygdala (Herman and Cullinan, 1997). Consequently, limbic-sensitive stressors such as restraint, forced swimming, fear conditioning or exposure to a novel environment constitute stimuli that become stressful only after comparison with prior experience. On the other hand, limbic insensitive or physiological threats that directly compromise survival, such as underwater stress, predator exposure and ether exposure, do not undergo prior interpretation by higher-order brain centers, but gain direct access to the paraventricular nucleus in the hypothalamus to rapidly initiate the stress response in an attempt to regain cardiovascular and respiratory homeostasis (Herman and Cullinan, 1997). Thus, how stressors are presented to the subject will evoke a unique bio-behavioral response that will ultimately determine the gradual progression from health to a mental/psychological disorder. Furthermore, the type of stressor will also dictate the type of biological markers being studied, for example the importance of studying appropriate brain regions following a stress response that requires top-down frontal cortical mediated control of subcortical limbic structures.

Early adverse experiences and especially vulnerability to these events may “shape” a pre-existing genetic vulnerability to stress and disease (Heim and Nemeroff, 2001; Niwa et al., 2010). Thus, young animals raised under adversive rearing conditions, such as social isolation or maternal separation, present with long-lasting behavioral and physiological changes in adulthood that resemble depression and/or schizophrenia, including increased anxiety, compromised cognitive function, poor social interaction as well as various depressive-like behaviors (Möller et al., 2011; Niwa et al., 2010). Depression is strongly correlated to genetic disposition as well as chronic life stress (Kendler et al., 2001), and is reflected in genetic models of depression such as the Flinders Sensitive Line (FSL) rat. FSL rats demonstrate a heightened sensitivity to stress, increased depressive-like behavior as

well as altered serotonergic, cholinergic and glutamatergic function (Overstreet et al., 2005; Wegener et al., 2010).

In PTSD, only 20–30% of trauma victims will go on to develop the illness (Breslau et al., 1991), while a similar response is expectant of an animal model of PTSD (Cohen et al., 2004). Similarly, compulsive behaviors vary significantly within patients with OCD so that spontaneous (naturalistic) compulsive-like or stereotypic behaviors that varies within a given population may be a useful animal model of OCD, e.g. the deer mouse model of stereotypy (Korff and Harvey, 2006). Thus, combined genetic and environmental adversity can effectively separate sensitive from resilient populations (Connor and Zhang, 2006) and will assist not only in understanding the neurobiology of a given anxiety disorder but will aid in predicting recovery and later resilience to developing a given disorder.

7.2. Posttraumatic stress disorder (PTSD)

Although first conceptualized as a normal reaction to an abnormal event, PTSD is directly associated with exposure to an immediate life-threatening event (APA, 1994), and is characterized by a unique psychobiological basis (Yehuda and McFarlane, 1995). In PTSD a disabling of critical cortical processes necessary to correctly process extinction of trauma memory occurs in susceptible individuals, thereby perpetuating a vicious cycle of trauma recollection and re-experiencing. Thus, while it is normal to experience a range of symptoms post-trauma, these gradually diminish over time and are not deemed to be disabling. Such symptoms, however, persist indefinitely in PTSD leading to significant comorbidity and disability (Kessler, 2002). There is also evidence for the importance of multiple re-exposures to trauma in predicting incidence and severity of the disorder (Maes et al., 2001). Increased hypothalamic-pituitary-adrenal (HPA) axis negative feedback in PTSD (Liberzon et al., 1999) and the resulting cortisol 'super-suppression' (Stein et al., 1997) precludes adequate shut-off of the stress response (Yehuda, 1997; Parker et al., 2003), resulting in heightened noradrenergic activity. This represents an important neurobiological construct that drives many of the symptoms of PTSD, including hyperarousal, avoidance and anxiety (Yehuda et al., 1992; Newport and Nemeroff, 2000; Ravindran and Stein, 2009). However, animal studies have emphasized that both the HPA axis response as well as the monoaminergic response to severe trauma differs immediately post trauma as opposed to post re-experiencing (Harvey et al., 2006), which will have important implications in pharmacological treatment.

Cortisol plays a critical role in the interaction between the hippocampus and amygdala during the encoding of emotional memory (Wolf, 2008), particularly through its activation of the glutamatergic system (Takahashi et al., 2002). Although the frontal cortical-amygdala noradrenergic system facilitates the encoding of emotional memories responsible for propagating posttraumatic symptoms, with noradrenergic -α_1 and -α_2 receptors important in expressing the intensity of the adverse experience, glutamate NMDA and AMPA receptor mediated signaling is central to the neurobiology of memory via the initiation of LTP (Myers et al., 2011). Moreover, the neurobiology of stress also involves the effects of glutamate on kindling and the permissive role of GABA, both of which occupy a central role in fear memory circuitry (Myers et al., 2011).

In order to incorporate the above-mentioned attributes, animal models of PTSD have utilized acute intense stressors, e.g. electric shock, underwater trauma, and exposure of animals to a predator, aversive challenges and situational reminders of a life-threatening event (stress–restress) to more closely model the long-term effects on behavioral, autonomic and hormonal responses seen in humans with PTSD (Uys et al., 2003; Cohen et al., 2004; Oosthuizen et al., 2005; Yamamoto et al., 2009). Here we will discuss data from the single prolonged stress (SPS) and time-dependent sensitisation (TDS) models of PTSD (Table 6). SPS has proven to be a well-validated animal model, presenting with increased HPA-axis negative feedback and hypocortisolemia (Liberzon et al., 1997, 1999), increased fear responding and anxiety as well as cognitive impairment (Kohda et al., 2007; Yamamoto et al., 2009). The TDS model, which emphasizes re-experience in its design, has demonstrated impressive face, construct and validity for PTSD, including increased HPA-axis negative feedback and hypocortisolemia (Harvey et al., 2003b; 2006), altered cortical-hippocampal $5HT_{1A}$ and $5HT_{2A}$ receptor binding and impaired spatial memory performance (Harvey et al., 2003b), while stress–restress related biobehavioral changes can be reversed by serotonin-active drugs (Harvey et al., 2004b; Uys et al., 2006). Importantly, stress and subsequent restress demonstrate differential changes in HPA-axis response, as well as changes in cortical and hippocampal monoamines and the subsequent genesis of maladaptive aversive behavior (Harvey et al., 2006).

7.2.1. Ionotropic glutamate receptors in animal models of PTSD

A number of studies have demonstrated the contributory role of ionotropic glutamatergic signaling using SPS alone or followed by re-experience (TDS; Table 6). We have demonstrated that TDS reduces NMDA receptor binding as well as GABA levels in the rat hippocampus (Harvey et al., 2004a). SPS increases accoustic startle in rats (Khan and Liberzon, 2004; Kohda et al., 2007) which can be prevented by topiramate (Khan and Liberzon, 2004), an AMPA/kainate receptor antagonist (Gibbs et al., 2000). Subsequently we have also demonstrated activation of events down-stream of the NMDA receptor, viz. NO synthase (NOS; Fig. 3), in animals exposed to TDS (Harvey et al., 2004a, 2005a). Indeed, new evidence suggests that the glutamate-NMDA-NOS cascade may be an important vulnerability factor in stress-sensitive animals (Wegener et al., 2010). Moreover, stress is a prerequisite prior event necessary to evoke these changes (Wegener et al., 2010; Figs. 2 and 3).

The GlyT-1 plays an important role in modulating extracellular glycine concentrations. Inhibition of GlyT-1 increases extracellular glycine in the CNS and enhances NMDA mediated neurotransmission (Sur and Kinney, 2007). SPS increases contextual freezing together with an increase in hippocampal levels of GlyT-1 (Takahashi et al., 2006; Iwamoto et al., 2007), possibly mediating the development of impaired extinction of fearful memory. PTSD is characterized by a loss of explicit memory function in favor of increased consolidation of fear-memory. Both SPS and TDS impair spatial memory performance in rats (Harvey et al., 2003b; Kohda et al., 2007). In line with these changes in hippocampal-based memory function, SPS induces deficits in hippocampal LTP and LTD (Kohda et al., 2007). Concerning fear memory, SPS increases contextual fear memory while TDS increases conditioned taste aversion memory (Brand et al., 2008), the latter explaining the increased avoidance and anxiety evoked by sensory-mediated recall of the trauma, i.e. visual, olfactory, touch, auditory, and taste. Contextual fear memory is also associated with blunted LTP in the amygdala following SPS (Kohda et al., 2007). Similarly, impaired extinction is a major symptom in PTSD (Bremner et al., 2000; Milad et al., 2006), while SPS has been found to impair fear extinction (Yamamoto et al., 2008), the latter being prevented by D-cycloserine, a partial agonist of the glycine site in the NMDA ion channel (Yamamoto et al., 2008). Considering the important role of altered HPA-axis functioning in PTSD, both SPS and TDS are associated with increased HPA-axis negative feedback and hypocortisolemia (Liberzon et al., 1997; 1999; Harvey et al., 2003b; 2006). Altered HPA-axis actvity in fact may be driving many of the subsequent biobehavioral changes induced by SPS/TDS (Harvey et al., 2004a; 2004b; Uys et al., 2006). Finally, glutamate, glutamine, and creatine levels are decreased in the mPFC of SPS rats compared to controls, suggesting decreased excitatory tone in this brain region (Knox et al., 2010).

AMPA receptors mediate fast EPSPs in most of the brain synapses (Malenka and Nicoll, 1999) and play a critical role in the development and expression of memory-related LTP. Further, as has been noted earlier, AMPA receptors assist in the recruitment of voltage-gated NMDA receptor ion channels (Tanaka et al., 2000; Fig. 3) thus benefitting LTP (Granger et al., 1993; Staubli et al., 1994). Targeting

Table 6
Role of glutamate in pathophysiological animal models of anxiety and stress-related disorders.

Anxiety disorder	Animal model	Result	Reference
PTSD	TDS	↑Anxiety (EPM)	Harvey et al., 2006
		↑Conditioned taste aversion learning.	Brand et al., 2008
		↓NMDA receptor binding and ↓GABA levels in rat hippocampus.	Harvey et al., 2004a
		↑Hippocampal NOS activity, prevented by nNOS inhibitor (early post acute stress)	Harvey et al., 2004a; 2005a
		↑Hippocampal NOS activity reversed by iNOS inhibitor, as well as by ketokonazole (steroid synthesis inhibitor) (late post stress).	Harvey et al., 2004a
	SPS	↑Anxiety (ASR), inhibited by topiramate, an AMPA/kainate receptor antagonist.	Khan and Liberzon, 2004; Kohda et al., 2007
		↑Contextual freezing in rats with ↑hippocampal GlyT-1.	Iwamoto et al., 2007
		↑Contextual fear; prevented by chronic paroxetine (SSRI).	Takahashi et al., 2006
		↓Fear extinction, prevented by D-cycloserine (partial glycine site agonist).	Yamamoto et al., 2008
		↓Glutamate, glutamine, and creatine in mPFC of rats, suggesting ↓ excitatory tone.	Knox et al., 2010
		↓Hippocampal LTP and LTD and blunted LTP in the amygdala.	Kohda et al., 2007
OCD	MBT	MK-801, memantine and amantadine (non-competitive NMDA antagonists) ↓ burying behavior in mice NBQX (AMPA R antagonist) and riluzole (glutamate release inhibitor) had no effect.	Egashira et al., 2008
		Inhibition of NOS prevents excessive burying behavior in mice.	Krass et al., 2010
		↑Burying behavior in mice is related to ↑ levels of NO in brain. Burying and ↑ NO prevented by paroxetine (SSRI).	Umathe et al., 2010
		CX546, (AMPA receptor potentiator) and Ro25-6981 (NR2B subunit-containing NMDA receptor antagonist) ↓ burying behavior in mice.	Iijima et al., 2010
		mGluR5 antagonist (MPEP) ↓ burying behavior.	Spooren et al., 2000; Pérez de la Mora et al., 2006
		mGluR2 antagonists, LY341495 and MGS0039, ↓ burying behavior	Shimazaki et al., 2004
	SAM	D-Cycloserine (partial glycine site agonist) ↓ compulsive lever pressing in rats. MK 801 (non-competitive NMDA antagonist) had no effect.	Albelda et al., 2010
	DMM	Increased striatal glutamatergic activity associated with spontaneous stereotypic behavior in deer mice.	Presti et al., 2004
	DMM	↑Oxidative stress evident in frontal cortex, but not striatum, of high stereotypic deer mice.	Güldenpfennig et al., 2011
Panic disorder	SLIP	↑Panic-like behavior and ↑firing of glutamatergic neurons prevented by LY354740 (group II mGluR agonist). Antipanic effect of LY354740 equal to alprazolam.	Molosh et al., 2010; Shekhar and Keim, 2000
Phobia	ELS	↑Phobic-like fear in BALB/cAnN mice later in life, associated with ↓LTD and ↑AMPA receptor GluR1 subunit expression in BLA.	Thoeringer et al., 2010
		↑Frontal cortical NMDA receptor binding in SIR rats together with ↓social interactive and ↑ self-directed behaviors, and ↑frontal cortical striatal oxidative stress.	Toua et al., 2010; Möller et al., 2011
	TMT	↑Unconditioned freezing and ↑glutamate and GABA in trimethylthiazoline model of phobia	Venton et al., 2006

Abbreviations: TDS, time-dependent sensitization; SPS, single prolonged stress; MBT, marble burying test; SAM, signal attenuation model; DMM, deer mouse model; SLIP, sodium lactate induced panic; ELS, early life stress; SIR, social isolation reared; SOD, superoxide dismutase; LTD, long-term depression; TMT, trimethylthiazoline model.

AMPA receptors therefore represents an alternative approach to bolster/maintain normal NMDA function without the risk of evoking excessive glutamatergic activity. Although AMPA potentiators have procognitive effects in animals (Staubli et al., 1994; Hamlyn et al., 2009; Damgaard et al., 2010), their therapeutic potential in PTSD, or in animal models of PTSD, are less well defined. Nevertheless, studies have found that emotion enhances learning via noradrenaline mediated phosphorylation of GluR1-containing AMPA-receptors leading to an improvement in AMPA trafficking (Hu et al., 2007). Moreover, topiramate an AMPA/kainate receptor antagonist prevents increased startle response in animals subjected to SPS (Khan and Liberzon, 2004), further supportive of a role for AMPA receptors in PTSD.

NO has been suggested to mediate NMDA-AMPA receptor interactions critical for neuroplasticity (Boix et al., 2011). NO is an

important sub-cellular messenger following stress or fear induced glutamate release via the activation of NOS, while NMDA receptor-mediated release of NO plays an important role in neuroinflammation (Harvey, 2008). Altered immune-inflammatory processes are evident in patients with PTSD (Maes et al., 1999; Bauer et al., 2010), while studies using TDS have found an increase in hippocampal NOS activity 7 days after stress–restress that is inhibited by a neuronal NOS inhibitor (Harvey et al., 2005a). Interestingly, this increased activity cannot be reversed by memantine, a noncompetitive open-channel NMDA receptor antagonist, yet is sensitive to inhibition by an NF-κβ antagonist, suggestive of a possible dual role for constitutive and inducible NOS isoforms following trauma (Harvey et al., 2005a). We have noted that the elevation in NOS activity remains sustained for 3 weeks post-trauma but now becomes insensitive to inhibition by a nNOS blocker yet retains sensitivity to a selective iNOS blocker (Harvey et al., 2004a). Importantly, late post-stress increase in NOS activity is also inhibited by ketoconazole, an inhibitor of glucocorticoid synthesis (Harvey et al., 2004a), highlighting the important role for the hypothalamic-adrenal axis in this response. Thus, inflammatory processes and the activation of the inducible isoform of NOS appears to play a more prominent role during chronic stress conditions such as PTSD, possibly mediating the damaging effects of severe chronic stress on neuronal structure and function e.g. hippocampal shrinkage (Harvey et al., 2004a; Oosthuizen et al., 2005; Fig. 3).

7.2.2. Metabotropic glutamate receptors in animal models of PTSD

mGluR modulators are increasingly been identified as promising new avenues to treat anxiety or its co-presenting symptoms, especially due to the ability of these receptors to modulate NMDA receptor function (Krystal et al., 2010). Indeed, mGluR1/5 receptor agonists might promote fear extinction by bolstering neuroplasticity related to long-term depression (Camodeca et al., 1999; Sung et al., 2001; Popkirov and Manahan-Vaughan, 2011). Consequently, ligands for groups I and II mGluRs may have value in the treatment of the cognitive deficits experienced in PTSD (Gravius et al., 2010). However, no work to date has been undertaken with respect to mGluRs in animal models of PTSD. Nevertheless, studies using mGluR8-deficient animals suggest that these receptors may be a potential target for disorders involving altered glutamate and GABA transmission. Thus, anxiety disorders where exaggerated contextual fear or where disturbed declarative memory are evident may be particularly relevant (Fendt et al., 2010).

7.3. Obsessive–compulsive disorder (OCD)

OCD is characterized by intrusive thoughts or images (obsessions) that increase anxiety, and ritualistic actions (compulsions) that decrease anxiety. The disorder also involves a dysfunctional (dopamine-directed) reward system (Harvey et al., 2005b). However, whereas most anxiety disorders are mediated by the amygdala and related circuitry and respond to a range of antidepressants and benzodiazepines, obsessive–compulsive disorders are mediated by fronto-striatal circuitry and respond selectively to serotonin reuptake inhibitors (SSRIs) (Hudson and Pope, 1990; Blum et al., 1995). There is thus a move to include OCD and related conditions as a separate diagnostic category of the up-coming DSM-V. The regulation of fronto-striatal circuitry and of motor function involves a complex interaction between serotonin, dopamine, and glutamate (Fekete et al., 1981; Hollander and Wang, 1995; Cummings, 1996; McDougle et al., 1999). Not surprisingly, up to half of OCD patients fail to respond to treatment with an SSRI (Goodman et al., 1990; 1991). In these cases, other classes of drugs, such as antipsychotics, offer distinct benefit in treatment resistance cases (Stein, 2000).

The prefrontal cortico-striatal-thalamic-cortico (CSTC) circuit is critical to our understanding of the pathophysiology and treatment of OCD (Insel, 1992). The orbitofrontal cortex and the anterior cingulate cortex are overactive in OCD (Alptekin et al., 2001; Lacerda et al., 2003), leading to uncontrolled thoughts and behaviors and inappropriate 'error detection' signals (Rolls, 1999; Alptekin et al., 2001). The anterior cingulate cortex may be more involved in linking the cognitive and motor behavioral manifestations of OCD (Korff and Harvey, 2006). The excessive, uncontrolled and repetitive motor behaviors seen in OCD patients are thus propagated by regional cortical hyperexcitability and a failure of inhibitory mechanisms to control sensory inputs (Cummings, 1996; Alptekin et al., 2001). The expression of emotion, particularly through the recognition of cues of threat/danger, and motivation that engenders the non-specific anxiety symptoms in OCD, is likely to involve fear circuitry, in particular the amygdala (Korff and Harvey, 2006).

An imbalance between dopamine, GABA and glutamate input into the CSTC is critical in determining thalamo-cortical output which becomes overactive in OCD. With regard to glutamate, CSF levels of glutamate and glycine are significantly elevated in OCD patients, with evidence that autoantibodies against the basal ganglia and thalamus may cause OCD by modulating excitatory neurotransmission (Bhattacharyya et al., 2009). Glutamate strongly regulates the release of dopamine and serotonin within the CSTC circuit (Karreman and Moghaddam, 1996; Amargós-Bosch et al., 2007), so that as with the well-known therapeutic benefits of serotonin (e.g. SSRIs) and dopamine (e.g. antipsychotics) active drugs in treating OCD, glutamate active drugs may harbor a wealth of new and untapped potential. Due to the neurobiological complexity of OCD, a definite animal model of OCD remains a significant stumbling block in preclinical drug development. Nevertheless, a number of animal models are used (see Joel, 2006a and Korff and Harvey, 2006 for review), although none of these models on their own fully address the complete behavioral and biological characteristics of OCD.

For the purpose of this review, we will present data from the marble burying test (MBT), the signal attenuation model (SAM) and the deer mouse model (DMM), translational models where data pertaining to the involvement of glutamate are evident (Table 6). The MBT demonstrates some face and predictive validity for OCD. In this test, burying begins as an appropriate investigative activity, but following frustrated investigation of the non-reactive stimulus-object, the behavior begins to persist as a compulsive stereotypy (Korff and Harvey, 2006). Marble burying can also be used to model hoarding, a subtype frequently encountered in OCD patients. Importantly, SSRIs suppress the compulsive behavior in this model (Korff and Harvey, 2006). The SAM, which focuses on the phenomenological similarity between "compulsive" lever pressing behavior in the model and compulsions in OCD patients, has provided evidence for face, construct and predictive validity for OCD (see Joel, 2006b for review). The DMM is unique in that it represents a naturalistic animal model whereby compulsive-like or stereotypic behaviors develop spontaneously, and which varies within a given population, thus akin to the stereotypic behaviors observed in patients with OCD. Moreover, the model has demonstrated noteworthy face, predictive and contruct validity for OCD (Korff et al., 2008; 2009; Wang et al., 2009; Güldenpfennig et al., 2011).

7.3.1. Ionotropic glutamate receptors in animal models of OCD

Magnetic resonance spectroscopy studies provide evidence of elevated glutamate levels in several brain regions in patients suffering from OCD, suggesting that agents that reduce glutamate hyperactivity or its consequences in the CNS might be efficacious as novel therapeutic interventions (Pittenger et al., 2006). Using the MBT in mice, Egashira et al. (2008) observed that the noncompetitive NMDA antagonists memantine, amantadine and MK801 inhibit marble-burying behavior, although MK801 also markedly increased locomotor activity. However the AMPA receptor antagonist NBQX, and the glutamate release inhibitor riluzole showed no effect in this regard. In

the SAM of OCD, systemic administration of the partial NMDA receptor agonist, D-cycloserine, selectively decreased compulsive lever pressing in rats (Albelda et al., 2010). MK 801, however, failed in this regard although increased resistance to extinction. These data are supportive of preliminary clinical evidence describing the effectiveness of memantine as an augmenting agent in severe OCD (Stewart et al., 2010). Again using the MBT, inhibition of NO, an important down-stream messenger following NMDA receptor activation and a powerful pro-oxidant, prevents excessive marble burying behavior in mice (Krass et al., 2010). In a related study, Umathe et al. (2010) found that obsessive–compulsive behaviors in mice appears related to increased levels of NO in brain, while the anti-compulsive effects of paroxetine is related to its ability to decrease brain levels of NO. In line with this evidence, clinical studies have demonstrated significantly elevated plasma nitrate levels, a stable marker of NO, in OCD patients that were also significantly and positively correlated with Yale–Brown Obsession Compulsion Scale scores (Atmaca et al., 2005). These data would concur that OCD may be causally related to increased oxidative stress, which indeed has been described in both humans with OCD (Chakraborty et al., 2009; Ozdemir et al., 2009) as well as in the DMM (Güldenpfennig et al., 2011).

With regard to the AMPA receptor, the AMPA receptor potentiator, CX546, significantly inhibits marble-burying behavior in the MBT, while the NR2B subunit-containing NMDA receptor antagonist, Ro25-6981, also reduces marble-burying behavior. These data suggest that AMPA receptor potentiators and NR2B receptor antagonist may be useful in treating OCD (Iijima et al., 2010).

7.3.2. Metabotropic glutamate receptors in animal models of OCD

Stimulating group I mGluRs, including mGluR1 and mGluR5, are associated with activation of phospholipase C (PLC) leading to the hydrolysis of cell membrane based phosphoinositide phospholipids and the subsequent formation of inositol 1,4,5-trisphosphate (IP3) and diacyl glycerol (Table 2). Interestingly, the glucose isomer and second messenger precursor in PLC-mediated signaling, myo-inositol, has demonstrated efficacy in OCD (see Harvey et al., 2002 for review). Consequently, it can be expected that group 1 mGluRs that function via this signaling system may have benefit in the treatment of OCD. Recent evidence suggest this happens via an alternate neuronal circuitry to the SSRIs (Carey et al., 2004). Indeed, the mGluR5 antagonist, MPEP, has been found to decrease burying behavior in the MBT (Spooren et al., 2000; Pérez de la Mora et al., 2006). Interestingly, the mGluR2 antagonists, LY341495 and MGS0039, which function via inhibition of adenylate cyclase, have also demonstrated this response in the MBT (Shimazaki et al., 2004).

7.4. Panic disorder

Several brain structures that organize defensive reactions and represent the neural substrate of fear and anxiety have been implicated in the functional neuroanatomy of PD, including prefrontal regions, amygdala, hippocampus, and parahippocampal area, hypothalamus, thalamus, and the periaqueductal gray matter (PAG) (Graeff and Del-Ben, 2008). Panic disorder is a severe anxiety disorder characterized by susceptibility to induction of panic attacks by subthreshold interoceptive stimuli such as 0.5 M sodium lactate infusion. Chronic inhibition of GABA synthesis in the dorsomedial hypothalamus/perifornical region of rats induces a vulnerability to panic-like responses after sodium lactate infusion (Johnson et al., 2008), and has been useful in providing an animal model of panic disorder (Table 6). Sodium lactate induced panic (SLIP) increases 'anxiety' (decreased social interaction) behaviors, heart rate, and blood pressure responses in rats. Moreover, SLIP increases the firing rates of glutamatergic neurons, as evinced by retrograde tracing and in situ hybridization for vesicular glutamate transporter 2 (Molosh et al., 2010). LY354740, a potent group II metabotropic glutamate receptor agonist prevents the SLIP response in panic-prone rats (Shekhar and Keim, 2000), probably by inhibiting glutamate release. The response to LY354740 treatment was equally efficacious as alprazolam.

7.5. Phobias

Brain imaging techniques in 'social anxiety' and 'social phobic' individuals reflects increased activity in limbic and paralimbic regions, with the predominance of the amygdala in these studies emphasizing its central role in the pathophysiology of social anxiety disorder (Freitas-Ferrari et al., 2010). Specific phobias, including animal phobias, are the most common anxiety disorders, and have a strong innate and genetic component. Phobia-related animal models have assessed the neurobiology of innate fear of predators in rodents, such as exposure to trimethylthiazoline or TMT (an odorant isolated from fox feces). TMT dose-dependently induces unconditioned freezing and other defensive responses in rodents (Table 6; Rosen et al., 2008), while one such study has demonstrated that high responding animals show a large, biphasic increase in glutamate and GABA in the nucleus accumbens (Venton et al., 2006). Since adverse environmental factors during early life may provoke genetically determined susceptibility to psychopathology (Heim and Nemeroff, 2001), it is of particular interest that adverse early life environment predicts the later development of phobic-like fear responses in BALB/cAnN mice (Thoeringer et al., 2010; Table 6). Emotion enhances learning via noradrenaline mediated phosphorylation of GluR1-containing AMPA-receptors leading to an improvement in AMPA trafficking (Hu et al., 2007). Thoeringer et al. (2010) show that greater susceptibility to developing exaggerated fear responses is accompanied by increased

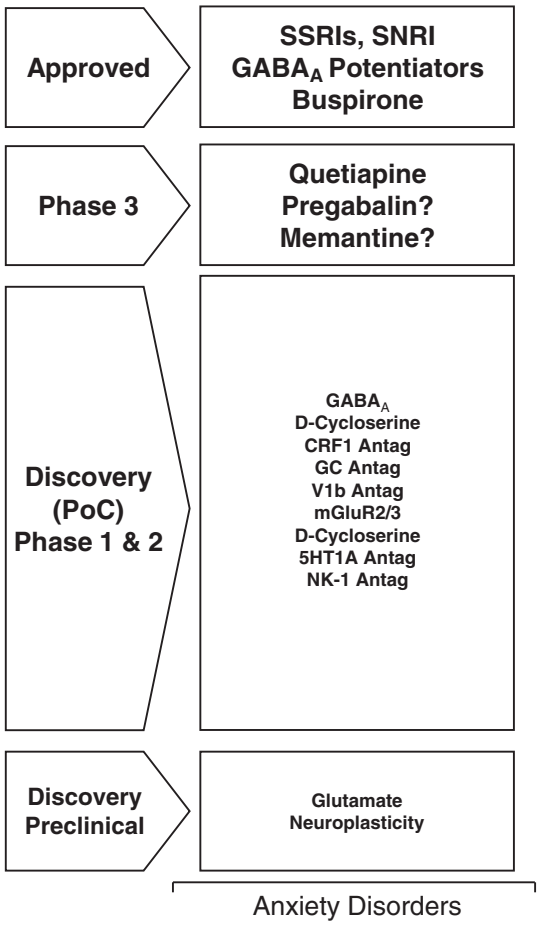

Fig. 5. Current therapies and approaches as well as new molecular entities in drug discovery and development aimed at the treatment of anxiety disorders.

surface trafficking of the AMPA receptor GluR1 subunit in the BSA complex (Thoeringer et al., 2010).

Deficits in interaction with peer groups as well as other core social behaviors (akin to social phobia) are induced by early life stress models, such as rats exposed to social isolation rearing (SIR) or maternal separation (Niwa et al., 2010). SIR in rats induces marked changes in cortical glutamate NMDA receptor binding (Toua et al., 2010), together with significantly reduced social interactive behaviors and increased self-directed behaviors (Möller et al., 2011; Table 6). Similarly, maternal separation involves a dysfunctional glutamatergic system (Takahashi et al., 2009). Since altered glutamate activity is associated with increased oxidative stress, it is of interest that SIR animals have significantly elevated frontal cortex and striatal superoxide dismutase activity, decreased oxidized:reduced glutathione ratio and increased lipid peroxidation (Möller et al., 2011).

8. Future perspective and summary

Current frontline pharmacological treatments and key approaches in drug discovery and development in anxiety disorders is summarized in Fig. 5. Monoamine reuptake inhibitors (e.g. SSRIs, SNRIs), GABA-A receptor potentiators (benzodiazepines) and a $5HT_{1A}$ partial agonist, buspirone, form the main therapeutic options for patients suffering from an anxiety disorder. These generally work with varying success across different anxiety disorders except OCD which responds selectively to SSRIs. However, while these drugs are effective agents, they have a delayed onset of action e.g. SSRIs, and fail to provide an adequate response in a significant proportion of patients (Ballenger, 1999, 2004; van Ameringen et al., 2004). In addition they have significant side effect and safety limitations, including abuse liability (benzodiazepines), sexual dysfunction (SSRI), cardiovascular risk (SNRI) and nausea ($5HT_{1A}$ agonist), which raise tolerability issues and lowers patient adherence. From a clinical perspective it is clear that there is still a strong unmet need for more effective and tolerable therapeutic options.

In order to make gains in efficacy, such as speed of onset and effectiveness in non-responders, alternative novel mechanism-based approaches need to be considered (Fig. 5). HPA-axis and glutamate system related molecular targets appear to represent the main areas of interest, e.g. targeting the mTOR pathway via the NMDA receptor to improve treatment response in depression (Li et al., 2010). Although other innovative approaches (e.g. neurokinin receptors) cannot be excluded, the current analysis has provided a summary of the most promising approaches. Whilst there is a strong scientific rationale for the utility of HPA-axis related approaches such as glucocorticoid, CRF1 or vasopressin 1b receptor antagonists, the level of clinical validation has remained limited despite a considerable period of drug discovery and development effort. In contrast, glutamate system-based drug discovery initiatives, such as mGluR2/3 agonism, have yielded positive clinical data, although require further validation. It is important to be cautious before drawing conclusions from these findings, however, especially given the rather high level of attrition in CNS drug discovery of drugs that explore novel mechanisms (Kola, 2008). The reasons for failure are multivariate and have been discussed extensively in the recent literature (Wong et al., 2008) but include factors such as inadequate target validation, lack of translational biomarkers (for efficacy and target engagement), lack of predictive reliability of animal models and issues in clinical development such as strong placebo response and poor reproducibility. Industry and academia need to collaborate more effectively to resolve challenges facing psychiatric drug discovery. Some critical areas of attention include greater focus on developing better insight on molecular pathology through more effective genetic analysis, identification of translational biomarkers (efficacy and target engagement), stratification and characterisation of patient subgroups to reduce heterogeneity, as well as developing disease relevant models with high face, construct and predictive validity (Wong et al., 2010). Considering the latter point, while many of the glutamate receptor-active ligands covered in this review have demonstrated noteworthy anxiolytic activity in various anxiety tests, few have been evaluated in comprehensively validated translational animal models, such as the select group of pathophysiological models described in Table 6.

With respect to glutamate it is clear that modulation of both metabotropic or ionotropic receptors offer promising opportunities. Given the known role of glutamate and down-stream NO on neuroplasticity, neuroprotection and degeneration (Meldrum, 2000; McLeod et al., 2001; Spedding et al., 2003), as well as their ability to rapidly modify monoaminergic responses, particularly via NO (Prast and Philippu, 2001), glutamate-based pharmacotherapy can have important therapeutic advantages that will benefit a number of troublesome areas of treatment response, including slow onset of action, lack of effective management of cognitive impairment, and lack of adequate clinical response in poor responders (Harvey, 2008). Potential limitations of NMDA receptor activators include mechanism-based excitotoxicity. In this regard, PAMS may offer a better approach if glutamatergic stimulation is required. Alternatively, exploiting novel molecular cross-talk mechanisms to harness a more physiological approach to stimulating glutamate receptors is an attractive alternative, e.g. using AMPA PAMs to bolster NMDA receptor function (see Fig. 3).

For antagonists there are concerns about NMDA receptor block to evoke psychotic manifestations, as well as to negatively impact affect and cognition. Here too PAMs and NAMs of both ionotropic (e.g. AMPA receptor potentiators) and metabotropic glutamate receptors would preferentially affect dysregulated glutamatergic synapses with a lower potential for mechanism related side-effects, e.g. the AMPA PAM CX516 (Goff et al., 2008). Another important issue that is likely to arise for glutamate based approaches is whether these agents will have sufficient efficacy to be suitable for use as monotherapy or will they need to be given in combination with existing drugs. Currently there is inadequate attention given to this issue in the preclinical profiling of emerging glutamatergic agents. It is important to bench mark, in a detailed manner across a range of disease models, the profile of new glutamatergic agents against frontline anxiolytic drugs to more clearly understand the potential benefits and risks. Furthermore, combination studies should be conducted in predictive animal models which would also help towards risk/benefit analysis as well as target validation. It is not only important to check the quality of pharmacological tools used, but also to prudently access alternative non-pharmacological approaches to build confidence in target validation. Transgenic animals or interference RNA technologies may help in this regard. For instance it is conceivable that differential effects may be observed in anxiety indications where cognitive behavioral therapy plays a positive role. Finally, considering the robust role for monoaminergic systems in anxiety, it makes sense to consider targeting combined monoaminergic-glutamatergic pathways in treating anxiety disorders, such as dual serotonergic-nitrergic actions (Harvey et al., 2010).

9. Concluding remarks

Encouraging evidence has emerged from both preclinical and clinical research to support the glutamate system as a promising pathway for discovering improved mechanistically novel therapies for the treatment of anxiety disorders, especially given the central role of glutamate as a regulator of neuroplasticity. Scientific rationale exists for modulators of both ionotropic and metabotropic receptors, although based on currently available evidence, the latter approach seems to be more attractive. In particular agonism at the mGluR2/3 seems to be associated with clinical efficacy, albeit in preliminary clinical studies. Whether ionotropic and metabotropic glutamate modulators would display differential or similar effects across

different subtypes of anxiety disorder remains an interesting area for future investigation. The availability of high quality pharmacological tools needs to be coupled with access to disease relevant animal models with strong predictive validity as well as translational measures of molecular target engagement and efficacy. In order to limit the potential for mechanism related side-effects, it is likely that positive or negative allosteric modulation may yield a better benefit/risk profile. Profiling of interaction with and differentiation from current anxiolytic drugs needs to be investigated in a thorough fashion to assist drug discovery. Finally, industry and the basic research needs to collaborate to resolve barriers limiting progress in psychiatric drug discovery, and particularly towards developing new anti-anxiety agents.

Conflict of interest

Dr Mohammed Shahid was an employee of MSD, a part of Merck, at the time of writing this manuscript.

Dr Brian Harvey has participated as an invited speaker, has received sponsorship, pharmaceutical compound or honoraria, or is a member of an advisory board, for Bristol-Myers Squibb, Organon, Pfizer and Servier, and has received research funding from Lundbeck. Apart from receiving Org 26576 from Organon for research purposes, there are no conflicts of interest to declare of relevance for this work.

Acknowledgements

The authors would like to thank Rachel van Schalkwyk for assistance during the preparation of the manuscript. Dr Harvey is funded by the National Research Foundation and the South African Medical Research Council. None of the funding sources have a vested interest in the author's work cited in this review.

References

Abdolmaleky HM, Thiagalingam S, Wilcox M. Genetics and epigenetics in major psychiatric disorders: dilemmas, achievements, applications, and future scope. Am J Pharmacogenomics 2005;5:149–60.

Alagarsamy S, Saugstad J, Warren L, Mansuy IM, Gereau IV RW, Conn PJ. NMDA-induced potentiation of mGluR5 is mediated by activation of protein phosphatase 2B/calcineurin. Neuropharmacol 2005;49(Suppl 1):135–45.

Albelda N, Bar-On N, Joel D. The role of NMDA receptors in the signal attenuation rat model of obsessive–compulsive disorder. Psychopharmacol (Berl) 2010;210: 13–24.

Alptekin K, Degirmenci B, Kivircik B, Durak H, Yemenez B, Derebek E, et al. tc-99 m HMPAO brain perfusion SPECT in drug-free obsessive–compulsive patients without depression. Psychiatry Res 2001;107:51–6.

Alt A, Weiss B, Ogden AM, Knauss JL, Oler J, Ho K, et al. Pharmacological characterization of glutamatergic agonists and antagonists at recombinant human homomeric and heteromeric kainate receptors in vitro. Neuropharmacology 2004;46:793–806.

Alt A, Nisenbaum ES, Bleakman D, Witkin JM. A role for AMPA receptors in mood disorders. Biochem Pharmacol 2006;71:1273–88.

Amargós-Bosch M, Adell A, Artigas F. Antipsychotic drugs reverse the AMPA receptor-stimulated release of 5-HT in the medial prefrontal cortex. J Neurochem 2007;102: 550–61.

Annoura H, Fukunaga A, Uesugi M, Tatsuoka T, Horikawa Y. A novel class of antagonists for metabotropic glutamate receptors, 7-(hydroxyimino)cyclopropa[b]chromen1a-carboxylates. Bioorg Med Chem Lett 1996;6:763–6.

Anthony EW, Nevins ME. Anxiolytic-like effects of N-methyl-D-aspartate-associated glycine receptor ligands in the rat potentiated startle test. Eur J Pharmacol 1993;250:317–24.

APA, The American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington: American Psychiatric Press; 1994.

Arai AC, Kessler M. Pharmacology of ampakine modulators: from AMPA receptors to synapses and behavior. Curr Drug Targets 2007;8:583–602.

Atmaca M, Tezcan E, Kuloglu M, Ustundag B. Plasma nitrate values in patients with obsessive–compulsive disorder. Psychiatry Clin Neurosci 2005;59:621–3.

Bagley J, Moghaddam B. Temporal dynamics of glutamate efflux in the prefrontal cortex and in the hippocampus following repeated stress: effects of pretreatment with saline or diazepam. Neurosci 1997;77:65–73.

Bailey JE, Papadopoulos A, Lingford-Hughes A, Nutt DJ. D-Cycloserine and performance under different states of anxiety in healthy volunteers. Psychopharmacol (Berl) 2007;193:579–85.

Baker JD, Azorlosa JL. The NMDA antagonist MK-801 blocks the extinction of Pavlovian fear conditioning. Behav Neurosci 1996;110:618–20.

Baldwin DS, Ajel K. Role of pregabalin in the treatment of generalized anxiety disorder. Neuropsychiatr Dis Treat 2007;3:185–91.

Ballard TM, Woolley ML, Prinssen E, Huwyler J, Porter R, Spooren W. The effect of the MGlu5 receptor antagonist MPEP in rodent test of anxiety and cognition: a comparison. Psychopharmacol (Berl) 2005;179:218–29.

Ballenger JC. Current treatments of the anxiety disorders in adults. Biol Psychiatry 1999;46:1579–94.

Ballenger JC. Remission rates in patients with anxiety disorders treated with paroxetine. J Clin Psychiatry 2004;65:1696–707.

Baron BM, Harrison BL, Kehne JH, Schmidt CJ, van Giersbergen PL, White HS, et al. Pharmacologic characterization of MDL 105,519, an NMDA receptor glycine site antagonist. Eur J Pharmacol 1997;323:181–92.

Bauer ME, Wieck A, Lopes RP, Teixeira AL, Grassi-Oliveira R. Interplay between neuroimmunoendocrine systems during post-traumatic stress disorder: a minireview. Neuroimmunomodulation 2010;17:192–5.

Beattie EC, Carroll RC, Yu X, Morishita W, Yasuda H, von Zastrow M, et al. Regulation of AMPA receptor endocytosis by a signaling mechanism shared with LTD. Nat Neurosci 2000;3:1291–300.

Bennet DA, Amrick CL. 2 Amino-7-phosphonoheptanoatic acid (AP7) produces discriminative stimuli and anticonflict effects similar to diazepam. Life Sci 1986;39:2455–61.

Benvenga MJ, Leander JD, Ornstein PL. Anxiolytic effect of the competitive AMPA antagonist 215490 in a pigeon punished responding model. Soc Neurosci 1993;19: 293.

Benvenga MJ, Overshiner CD, Monn JA, Leander JD. Disinhibitory effects of LY354740, a new mGluR2 agonist, on behaviors suppressed by electric shock in rats and pigeons. Drug Devel Res 1999;47:37–44.

Bergink V, Westenberg HG. Metabotropic glutamate II receptor agonists in panic disorder: a double blind clinical trial with LY354740. Int Clin Psychopharmacol 2005;20:291–3.

Bergink V, van Megen HJ, Westenberg HG. Glutamate and anxiety. Eur Neuropsychopharmacol 2004;14:175–83.

Bespalov AY, van Gaalen MM, Sukhotina IA, Wicke K, Mezler M, Schoemaker H, et al. Behavioral characteraization of the mGlu group II/III receptor antagonist, LY-341495, in animal models of anxiety and depression. Eur J Pharmacol 2008;592: 96–102.

Bevilaqua LR, Bonini JS, Rossato JI, Izquierdo LA, Cammarota M, Izquierdo I. The entorhinal cortex plays a role in extinction. Neurobiol Learn Mem 2006;85:192–7.

Bhattacharyya S, Khanna S, Chakrabarty K, Mahadevan A, Christopher R, Shankar SK. Anti-brain autoantibodies and altered excitatory neurotransmitters in obsessive–compulsive disorder. Neuropsychopharmacol 2009;34:2489–96.

Blum K, Sheridan PJ, Wood RC, Braverman ER, Chen TJ, Comings DE. Dopamine D2 receptor gene variants: association and linkage studies in impulsive–addictive–compulsive behavior. Pharmacogenet 1995;5:121–41.

Boix J, Llansola M, Cabrera-Pastor A, Felipo V. Metabotropic glutamate receptor 5 modulates the nitric oxide-cGMP pathway in cerebellum in vivo through activation of AMPA receptors. Neurochem Int 2011;58:599–604.

Bouton ME, Vurbic D, Woods AM. D-cycloserine facilitates context-specific fear extinction learning. Neurobiol Learn Mem 2008;90:504–10.

Brand L, Groenewald I, Stein DJ, Wegener G, Harvey BH. Stress and re-stress increases conditioned taste aversion learning in rats: possible frontal cortical and hippocampal muscarinic receptor involvement. Eur J Pharmacol 2008;586:205–11.

Bräuner-Osborne H, Egebjerg J, Nielsen EO, Madsen U, Krogsgaard-Larsen P. Ligands for glutamate receptors: design and therapeutic prospects. J Med Chem 2000;43: 2609–45.

Bremner JD, Vermetten E, Schmahl C, Vaccarino V, Vythilingam M, Afzal N, et al. Positron emission tomographic imaging of neural correlates of a fear acquisition and extinction paradigm in women with childhood sexual-abuse-related post-traumatic stress disorder. Psychol Med 2000;35:791–806.

Breslau N, Davis GC, Andreski P, Peterson E. Traumatic events and posttraumatic stress disorder in an urban population of young adults. Arch Gen Psychiatry 1991;48: 216–22.

Brodkin J, Bradbury M, Busse C, Warren N, Bristow LJ, Varney MA. Reduced stressinduced hyperthermia in mGluR5 knockout mice. Eur J Neurosci 2002a;16: 2241–4.

Brodkin J, Busse C, Sukoff SJ, Varney MA. Anxiolytic-like activity of the mGluR5 antagonist MPEP a comparison with diazepam and buspirone. Pharmacol Biochem Behav 2002b;73:359–66.

Bueno AB, Collado I, de Dios A, Domínguez C, Martín JA, Martín LM, et al. Dipeptides as effective prodrugs of the unnatural amino acid (+)-2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740), a selective group II metabotropic glutamate receptor agonist. J Med Chem 2005;48:5305–20.

Bunch L, Krogsgaard-Larsen P. Subtype selective kainic acid receptor agonists: discovery and approaches to rational design. Med Res Rev 2009;29:3–28.

Burgos-Robles A, Vidal-Gonzalez I, Santini E, Quirk GJ. Consolidation of fear extinction requires NMDA receptor-dependent bursting in the ventromedial prefrontal cortex. Neuron 2007;53:871–80.

Burnashev N, Zhou Z, Neher E, Sakmann B. Fractional calcium currents through recombinant GluR channels of the NMDA, AMPA and kainate receptor subtypes. J Physiol 1995;485:403–18.

Busse CS, Brodkin J, Tattersall D, Anderson JJ, Warren N, Tehrani L, et al. The behavioral profile of the potent and selective mGlu5 receptor antagonist 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) in rodent models of anxiety. Neuropsychopharmacol 2004;29:1971–9.

Callaerts-Vegh Z, Beckers T, Ball SM, Baeyens F, Callaerts PF, Cryan JF, et al. Concomitant deficits in working memory and fear extinction are functionally dissociated from

reduced anxiety in metabotropic glutamate receptor 7-deficient mice. J Neurosci 2006;26:6573–82.
Cammarota M, Bevilaqua LR, Rossato JI, Ramirez M, Medina JH, Izquierdo I. Relationship between short- and long-term memory and short- and longterm extinction. Neurobiol Learn Mem 2005;84:25–32.
Camodeca N, Breakwell NA, Rowan MJ, Anwyl R. Induction of LTD by activation of group I mGluR in the dentate gyrusin vitro. Neuropharmacol 1999;38:1597–606.
Campeau S, Miserendino Mj, Davis M. Intra-amygdala infusion of the N-methyl-D-aspartate receptor antagonist AP5 blocks acquisition but not expression of fear-potentiated startle to an auditory conditioned stimulus. Behav Neurosci 1992;106:569–74.
Carey PD, Warwick J, Harvey BH, Stein DJ, Seedat S. Single photon emission computed tomography (SPECT) in obsessive–compulsive disorder before and after treatment with inositol. Metab Brain Dis 2004;19:125–34.
Catarzi D, Colotta V, Varano F. Competitive AMPA receptor antagonists. Med Res Rev 2007;27:239–78.
Chaki S, Yoshikawa R, Hirota S, Shimazaki T, Maeda M, Kawashima N, et al. MGS0039: a potent and selective group II metabotropic glutamate receptor antagonist with antidepressant-like activity. Neuropharmacol 2004;46:457–67.
Chakraborty S, Singh OP, Dasgupta A, Mandal N, Das HN. Correlation between lipid peroxidation-induced TBARS level and disease severity in obsessive–compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry 2009;33:363–6.
Chan WY, McNally GP. Conditioned stimulus familiarity determines effects of MK-801 on fear extinction. Behav Neurosci 2009;123:303–14.
Chappell AS, Gonzales C, Williams J, Witte MM, Mohs RC, Sperling R. AMPA potentiator treatment of cognitive deficits in Alzheimer disease. Neurology 2007;68:1008–12.
Chhatwal JP, Myers KM, Ressler KJ, Davis M. Regulation of gephyrin and GABAA receptor binding within the amygdala after fear acquisition and extinction. J Neurosci 2005;25:502–6.
Ciabarra AM, Sullivan JM, Gahn LG, Pecht G, Heinemann S, Sevarino KA. Cloning and characterization of chi-1: a developmentally regulated member of a novel class of the ionotropic glutamate receptor family. J Neurosci 1995;15:6498–508.
Ciranna L. Serotonin as a modulator of glutamate- and GABA-mediated neurotransmission: implications in physiological function in pathology. Curr Neuropharmacol 2006;4:101–14.
Cohen H, Zohar J, Matar MA, Zeev K, Loewenthal U, Richter-Levin G. Setting apart the affected: the use of behavioral criteria in animal models of post traumatic stress disorder. Neuropsychopharmacol 2004;29:1962–70.
Conn PJ, Lindsley CW, Jones CK. Activation of metabotropic glutamate receptors as a novel approach for the treatment of schizophrenia. Trends Pharmacol Sci 2008;30:25–31.
Connor KM, Zhang W. Recent advances in the understanding and treatment of anxiety disorders. Resilience: determinants, measurement, and treatment responsiveness. CNS Spectr 2006;11:5–12.
Coplan JD, Mathew SJ, Smith EL, Trost RC, Scharf BA, Martinez J, et al. Effects of LY354740, a novel glutamatergic metabotropic agonist, on nonhuman primate hypothalamic-pituitary-adrenal axis and noradrenergic function. CNS Spectr 2001;6:607–12,617.
Corbett R. Effects of 5,7 dichlorokynurenic acid on conflict, social interaction and plus maze behaviour. Neuropharmacol 1993;32:461–6.
Corbett R, Dunn RW. Effects of HA-966 on conflict, social interaction and plus maze behaviour. Drug Dev Res 1991;24:201.
Corbett R, Dunn RW. Effects of 5,7 dichlorokynurenic acid on conflict, social interaction and plus maze behaviors. Neuropharmacol 1993;32:461–6.
Coric V, Taskiran S, Pittenger C, Wasylink S, Mathalon DH, Valentine G, et al. Riluzole augmentation in treatment-resistant obsessive–compulsive disorder: an open-label trial. Biol Psychiatry 2005;1:424–8.
Cortese BM, Phan KL. The role of glutamate in anxiety and related disorders. CNS Spectr 2005;10:820–30.
Cox J, Westbrook RF. The NMDA receptor antagonist MK-801 blocks acquisition and extinction of conditioned hypoalgesic responses in the rat. Q J Exp Psychol B 1994;47:187–210.
Criswel HE, Knapp DJ, Overstreet DH, Breese GR. Effects of ethanol, chordiazepoxide and MK-801 on performance in the elevated plus maze and on locomotor activity. Alcohol Clin Exp Res 1994;18:596.
Cummings JL. Obsessive–compulsive disorder in basal ganglia disorders. J Clin Psychiatry 1996;57:1180.
Curtis DR, Watkins JC. The excitation and depression of spinal neurones by structurally related amino acids. J Neurochem 1960;6:117–41.
Dalton GL, Wang YT, Floresco SB, Phillips AG. Disruption of AMPA receptor endocytosis impairs the extinction, but not acquisition of learned fear. Neuropsychopharmacol 2008;33:2416–26.
Damgaard T, Larsen DB, Hansen SL, Grayson B, Neill JC, Plath N. Positive modulation of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors reverses sub-chronic PCP-induced deficits in the novel object recognition task in rats. Behav Brain Res 2010;207:144–50.
Del Arco A, Mora F. Prefrontal cortex-nucleus accumbens interaction: in vivo modulation by dopamine and glutamate in the prefrontal cortex. Pharmacol Biochem Behav 2008;90:226–35.
Doherty AJ, Palmer MJ, Bortolotto ZA, Hargreaves A, Kingston AE, Ornstein PL, et al. A novel, competitive mGlu(5) receptor antagonist (LY344545) blocks DHPG-induced potentiation of NMDA responses but not the induction of LTP in rat hippocampal slices. Br J Pharmacol 2000;131:239–44.
Dorostkar MM, Boehm S. Presynaptic lonotropic receptors. Handb Exp Pharmacol 2008;184:479–527.
Dunayevich E, Erickson J, Levine L, Landbloom R, Schoepp DD, Tollefson GD. Efficacy and tolerability of an mGlu2/3 agonist in the treatment of generalized anxiety disorder. Neuropsychopharmacol 2008;33:1603–10.
Dunn RW, Corbett R, Fielding S. Effects of 5-HT1A receptor agonists and NMDA receptor antagonists in the social interaction test and the elevated plus maze. Eur J Pharmacol 1989;169:1–10.
Dunn RW, Flanagan DM, Martin LL, Kerman LL, Woods AT, Camacho F, et al. Stereoselective R-(+) enantiomer of HA-966 displays anxiolytic effects in rodents. Eur J Pharmacol 1992;214:207.
DuPont RL, Rice DP, Miller LS, Shiraki SS, Rowland CR, Harwood HJ. Economic costs of anxiety disorders. Anxiety 1996;2:167–72.
Durand D, Pampillo M, Caruso C, Lasaga M. Role of metabotropic glutamate receptors in the control of neuroendocrine function. Neuropharmacol 2008;55:577–83.
Egashira N, Okuno R, Harada S, Matsushita M, Mishima K, Iwasaki K, et al. Effects of glutamate-related drugs on marble-burying behavior in mice: implications for obsessive–compulsive disorder. Eur J Pharmacol 2008;586:164–70.
Erdemli G, Smith LH, Sammons M, Jeggo R, Shahid M. Org 26576, a novel positive allosteric modulator, potentiates AMPA receptor responses in hippocampal neurones. J Psychopharmacol 2007;21:A51.
Falls WA, Miserendino MJ, Davis M. Extinction of fear-potentiated startle: blockade by infusion of an NMDA antagonist into the amygdala. J Neurosci 1992;12:854–63.
Fekete M, Szabo A, Balazs M, Penke B, Telegdy G. Effects of intraventricular administration of cholecystokinin octapeptide sulfate ester and unsulfated cholecystokinin octapeptide on active avoidance and conditioned feeding behavior of rats. Acta Physiol Acad Sci Hung 1981;58:39–45.
Fendt M. Expression and conditioned inhibition of fear-potentiated startle after stimulation and blockade of AMPA/Kainate and GABA(A) receptors in the dorsal periaqueductal gray. Brain Res 2000;880:1–10.
Fendt M, Koch M, Schnitzler HU. NMDA receptors in the pontine brainstem are necessary for fear potentiation of the startle response. Eur J Pharmacol 1996;318:1–6.
Fendt M, Schmid S, Thakker DR, Jacobson LH, Yamamoto R, Mitsukawa K, et al. mGluR7 facilitates extinction of aversive memories and controls amygdala plasticity. Mol Psychiatry 2008;13:970–9.
Fendt M, Bürki H, Imobersteg S, van der Putten H, McAllister K, Leslie JC, et al. The effect of mGlu8 deficiency in animal models of psychiatric diseases. Genes Brain Behav 2010;9:33–44.
Feusner JD, Kerwin L, Saxena S, Bystritsky A. Differential efficacy of memantine for obsessive–compulsive disorder vs. generalized anxiety disorder: an open-label trial. Psychopharmacol Bull 2009;42:81–93.
Foster A, Miller del D, Buckley P. Pharmacogenetics and schizophrenia. Clin Lab Med 2010;30:975–93.
Fraser CM, Cooke MJ, Fisher A, Thompson ID, Stone TW. Interactions between ifenprodil and dizocilpine on mouse behaviour in models of anxiety and working memory. Eur Neuropsychopharmacol 1996;6:311–6.
Freitas-Ferrari MC, Hallak JE, Trzesniak C, Filho AS, Machado-de-Sousa JP, Chagas MH, et al. Neuroimaging in social anxiety disorder: a systematic review of the literature. Prog Neuropsychopharmacol Biol Psychiatry 2010;34:565–80.
Gass JT, Olive MF. Positive allosteric modulation of mGluR5 receptors facilitates extinction of a cocaine contextual memory. Biol Psychiatry 2009;65:717–20.
Geiger JR, Melcher T, Koh DS, Sakmann B, Seeburg PH, Jonas P, et al. Relative abundance of subunit mRNAs determines gating and Ca2+ permeability of AMPA receptors in principal neurons and interneurons in rat CNS. Neuron 1995;15:193–204.
Gibbs III JW, Sombati S, DeLorenzo RJ, Coulter DA. Cellular actions of topiramate: blockade of kainate-evoked inward currents in cultured hippocampal neurons. Epilepsia 2000;41(Suppl 1):S10–6.
Goddyn H, Callaerts-Vegh Z, Stroobants S, Dirikx T, Vansteenwegen D, Hermans D, et al. Deficits in acquisition and extinction of conditioned responses in mGluR7 knockout mice. Neurobiol Learn Mem 2008;90:103–11.
Goff DC, Lamberti JS, Leon AC, Green MF, Miller AL, Patel J, et al. A placebo-controlled add-on trial of the ampakine, CX516, for cognitive deficits in schizophrenia. Neuropsychopharmacol 2008;33:465–72.
Gomes GM, Mello CF, da Rosa MM, Bochi GV, Ferreira J, Barron S, et al. Polyaminergic agents modulate contextual fear extinction in rats. Neurobiol Learn Mem 2010;93:589–95.
Goodman WK, McDougle CL, Lawrence LP. Beyond the serotonin hypothesis: a role for dopamine in some forms of obsessive–compulsive disorder. J Clin Psychiatry 1990;51:36–43.
Goodman WK, Price LH, Woods SW. Pharmacologic challenges in obsessive–compulsive disorder. In: Zohar J, Insel T, Rasmussen SA, editors. The psychobiology of obsessive–compulsive disorder. New York: Springer; 1991. p. 162–86.
Graeff FG, Del-Ben CM. Neurobiology of panic disorder: from animal models to brain neuroimaging. Neurosci Biobehav Rev 2008;32:1326–35.
Granger R, Staubli U, Davis M, Perez Y, Nilsson L, Rogers GA, et al. A drug that facilitates glutamatergic transmission reduces exploratory activity and improves performance in a learning-dependant task. Synapse 1993;15:326–9.
Gravius A, Pietraszek M, Dekundy A, Danysz W. Metabotropic glutamate receptors as therapeutic targets for cognitive disorders. Curr Top Med Chem 2010;10:187–206.
Gregory AM, Lau JY, Eley TC. Finding gene-environment interactions for generalised anxiety disorder. Eur Arch Psychiatry Clin Neurosci 2008;258:69–75.
Grillon C, Cordova J, Levine LR, Morgan III CA. Anxiolytic effects of a novel group II metabotropic glutamate receptor agonist (LY354740) in the fear-potentiated startle paradigm in humans. Psychopharmacol (Berl) 2003;168:446–54.
Guastella AJ, Richardson R, Lovibond PF, Rapee RM, Gaston JE, Mitchell P, et al. A randomized controlled trial of D-cycloserine enhancement of exposure therapy for social anxiety disorder. Biol Psychiatry 2008;63:544–9.
Guimarães FS, Beijamini V, Moreira FA, Aguiar DC, de Lucca AC. Role of nitric oxide in brain regions related to defensive reactions. Neurosci Biobehav Rev 2005;29:1313–22.

Güldenpfennig M, Wolmarans D, du Preez JL, Stein DJ, Harvey BH. Cortico-striatal oxidative status, dopamine turnover and relation with stereotypy in the deer mouse. Physiol Behav 2011;103:404–11.
Hamlyn E, Brand L, Shahid M, Harvey BH. The ampakine, Org 26576, bolsters early spatial reference learning and retrieval in the Morris water maze: a subchronic, dose-ranging study in rats. Behav Pharmacol 2009;20:662–7.
Harris JA, Westbrook RF. Evidence that GABA transmission mediates context-specific extinction of learned fear. Psychopharmacol (Berl.) 1998;140:105–15.
Harvey BH. Affective disorders and nitric oxide: a role in pathways to relapse and refractoriness. Hum Psychopharmacol 1996;11:309–19.
Harvey BH. Is major depressive disorder a metabolic encephalopathy? Hum Psychopharmacol 2008;23:371–84.
Harvey BH, Brink CB, Seedat S, Stein DJ. Defining the neuromolecular action of myo-inositol: application to obsessive–compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry 2002;26:21–32.
Harvey BH, McEwen BS, Stein DJ. Neurobiology of antidepressant withdrawal: implications for the longitudinal outcome of depression. Biol Psychiatry 2003a;54:1105–17.
Harvey BH, Naciti C, Brand L, Stein DJ. Endocrine, cognitive and hippocampal/cortical 5HT 1A/2A receptor changes evoked by a time-dependent sensitisation (TDS) stress model in rats. Brain Res 2003b;983:97–107.
Harvey BH, Oosthuizen F, Brand L, Wegener G, Stein DJ. Stress–restress evokes sustained iNOS activity and altered GABA levels and NMDA receptors in rat hippocampus. Psychopharmacol (Berl) 2004a;175:494–502.
Harvey BH, Naciti C, Brand L, Stein DJ. Serotonin and stress: protective or malevolent actions in the biobehavioral response to repeated trauma? Ann N Y Acad Sci 2004b;1032:267–72.
Harvey BH, Bothma T, Nel A, Wegener G, Stein DJ. Involvement of the NMDA receptor, NO-cyclic GMP and nuclear factor K-beta in an animal model of repeated trauma. Hum Psychopharmacol 2005a;20:367–73.
Harvey BH, Brink CB, Stein DJ. Relevance of myo-inositol to the neurobiology and treatment of obsessive compulsive disorder. In: Ling BE, editor. Obsessive compulsive disorer research. New York: Nova Science Publishers; 2005b. p. 67–91.
Harvey BH, Brand L, Jeeva Z, Stein DJ. Cortical/hippocampal monoamines, HPA-axis changes and aversive behavior following stress and restress in an animal model of post-traumatic stress disorder. Physiol Behav 2006;87:881–90.
Harvey BH, Duvenhage I, Viljoen F, Scheepers N, Malan SF, Wegener G, et al. Role of monoamine oxidase, nitric oxide synthase and regional brain monoamines in the antidepressant-like effects of methylene blue and selected structural analogues. Biochem Pharmacol 2010;80:1580–91.
Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. Biol Psychiatry 2001;49: 1023–39.
Heldt SA, Ressler KJ. Training-induced changes in the expression of $GABA_A$-associated genes in the amygdala after the acquisition and extinction of Pavlovian fear. Eur J Neurosci 2007;26:3631–44.
Helton DR, Tizzano JP, Monn JA, Schoepp DD, Kallman MJ. Anxiolytic and side-effect profile of LY354740: a potent, highly selective, orally active agonist for group II metabotropic glutamate receptors. J Pharmacol Exp Ther 1998;284:651–60.
Hemstapat K, Da Costa H, Nong Y, Brady AE, Luo Q, Niswender CM, et al. A novel family of potent negative allosteric modulators of group II metabotropic glutamate receptors. J Pharmacol Exp Ther 2007;322:254–64.
Heresco-Levy U, Kremer I, Javitt DC, Goichman R, Reshef A, Blanaru M, et al. Pilot-controlled trial of D-cycloserine for the treatment of post-traumatic stress disorder. Int J Neuropsychopharmacol 2002;5:301–7.
Heresco-Levy U, Vass A, Bloch B, Wolosker H, Dumin E, Balan L, et al. Pilot controlled trial of D-serine for the treatment of post-traumatic stress disorder. Int J Neuropsychopharmacol 2009;12:1275–82.
Herman JP, Cullinan WE. Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. Trends Neurosci 1997;20:78–84.
Hettema JM, Neale MC, Kendler KS. A review and meta-analysis of the genetic epidemiology of anxiety disorders. Am J Psychiatry 2001;158:1568–78.
Ho YJ, Hsu LS, Wang CF, Hsu WY, Lai TJ, Hsu CC, et al. Behavioral effects of D-cycloserine in rats: the role of anxiety level. Brain Res 2005;1043:179–85.
Hofmann SG, Meuret AE, Smits JA, Simon NM, Pollack MH, Eisenmenger K, et al. Augmentation of exposure therapy with D-cycloserine for social anxiety disorder. Arch Gen Psychiatry 2006;63:298–304.
Hollander E, Wang CM. Obsessive–compulsive spectrum disorders. J Clin Psychiatry 1995;56:53–5.
Hu H, Real E, Takamiya K, Kang MG, Ledoux J, Huganir RL, et al. Emotion enhances learning via norepinephrine regulation of AMPA-receptor trafficking. Cell 2007;131:160–73.
Huang CC, Hsu KS. Progress in understanding the factors regulating reversibility of long-term potentiation. Rev Neurosci 2001;12:51–68.
Hudson JI, Pope Jr HG. Affective spectrum disorder: does antidepressant response identify a family of disorders with a common pathophysiology? Am J Psychiatry 1990;147:552–64.
Iijima M, Chaki S. Separation-induced ultrasonic vocalization in rat pups: further pharmacological characterization. Pharmacol Biochem Behav 2005;82:652–7.
Iijima M, Shimazaki T, Ito A, Chaki S. Effects of metabotropic glutamate 2/3 receptor antagonist in the stress-induced hyperthermia test in singly housed mice. Psychopharmacol (Berl) 2007;190:233–9.
Iijima M, Kurosu S, Chaki S. Effects of agents targeting glutamatergic systems on marble-burying behavior. Neurosci Lett 2010;471:63–5.
Insel TR. Towards a neuroanatomy of obsessive–compulsive disorder. Arch Gen Psychiatry 1992;49:739–44.
Isa T, Itazawa S, Iino M, Tsuzuki K, Ozawa S. Distribution of neurones expressing inwardly rectifying and Ca(2+)-permeable AMPA receptors in rat hippocampal slices. J Physiol 1996;491(Pt 3):719–33.
Ito I, Tanabe S, Kohda A, Sugiyama H. Allosteric potentiation of quisqualate receptors by a nootropic drug aniracetam. J Physiol 1990;424:533–43.
Iwamoto Y, Morinobu S, Takahashi T, Yamawaki S. Single prolonged stress increases contextual freezing and the expression of glycine transporter 1 and vesicle-associated membrane protein 2 mRNA in the hippocampus of rats. Prog Neuropsychopharmacol Biol Psychiatry 2007;31:642–51.
Jane DE, Lodge D, Collingridge GL. Kainate receptors: pharmacology, function and therapeutic potential. Neuropharmacology 2009;56:90–113.
Javitt DC. Glutamate as a therapeutic target in psychiatric disorders. Mol Psychiatry 2004;9:984–97. 979.
Javitt DC. Glycine transport inhibitors and the treatment of schizophrenia. Biol Psychiatry 2008;63:6–8.
Jessa M, Nazar M, Bidzinsky A, Plaznik A. The effect of repeated administration of diazepam, MK-801 and CGP 37849 on rat behaviour in two models of anxiety. Eur Neuropsychopharmacol 1996;6:55–61.
Joel D. Current animal models of obsessive compulsive disorder: a critical review. Prog Neuropsychopharmacol Biol Psychiatry 2006a;30:374–88.
Joel D. The signal attenuation rat model of obsessive–compulsive disorder: a review. Psychopharmacol (Berl.) 2006b;186:487–503.
Johnson DM, Baker JD, Azorlosa JL. Acquisition, extinction, and reinstatement of Pavlovian fear conditioning: the roles of the NMDA receptor and nitric oxide. Brain Res 2000;857:66–70.
Johnson MP, Baez M, Jagdmann Jr GE, Britton TC, Large TH, Callagaro DO, et al. Discovery of allosteric potentiators for the metabotropic glutamate 2 receptor: synthesis and subtype selectivity of N-(−4-2-methoxyphenoxy)phenyl)-N-(2,2,2-trifluoroethylsulfonyl)pyrid-3-ylmethylamine. J Med Chem 2003;46:3189–92.
Johnson MP, Barda D, Britton TC, Emkey R, Hornback WJ, Jagdmann GE, et al. Metabotropic glutamate 2 receptor potentiators: receptor modulation, frequency-dependent synaptic activity, and efficacy in preclinical anxiety and psychosis model(s). Psychopharmacol (Berl) 2005;179:271–83.
Johnson PL, Truitt WA, Fitz SD, Lowry CA, Shekhar A. Neural pathways underlying lactate-induced panic. Neuropsychopharmacol 2008;33:2093–107.
Jordan GR, McCulloch J, Shahid M, Hill DR, Henry B, Horsburgh K. Regionally selective and dose-dependent effects of the ampakines org 26576 and org 24448 on local cerebral glucose utilisation in the mouse as assessed by 14C-2-deoxyglucose autoradiography. Neuropharmacol 2005;49:254–64.
Karcz-Kubicha M, Liljequist S. Evidence for an anxiogenic action of AMPA receptor antagonists in the plus-maze test. Eur J Pharmacol 1995;279:171–7.
Karcz-Kubicha M, Jessa M, Nazar M, Plaznik A, Hartmann S, Parsons CG, et al. Anxiolytic activity of glycine-B antagonists and partial agonists—no relation to intrinsic activity in the patch clamp. Neuropharmacol 1997;36:1355–67.
Karreman M, Moghaddam B. The prefrontal cortex regulates the basal release of dopamine in the limbic striatum: an effect mediated by ventral tegmental area. J Neurochem 1996;66:589–98.
Kehne JH, McCloskey TC, Baron BM, Chi EM, Harrison BL, Whitten JP, et al. NMDA receptor complex antagonists have potential anxiolytic effects as measured with separation-induced ultrasonic vocalisation. Eur J Pharmacol 1991;193:283–92.
Kehne JH, Baron BM, Harrison BL, McCloskey TC, Palfreyman MG, Poirot M, et al. MDL 100, 458 and MDL 102,288: two potent and selective glycine receptor antagonists with different functional profiles. Eur J Pharmacol 1995;284:109–18.
Kehoe EJ, Macrae M, Hutchinson CL. MK-801 protects conditioned responses from extinction in the rabbit nictitating membrane preparation. Psychobiology 1996;24: 127–35.
Kelley JB, Anderson KL, Itzhak Y. Pharmacological modulators of nitric oxide signaling and contextual fear conditioning in mice. Psychopharmacology (Berl) 2010;210:65–74.
Kellner M, Muhtz C, Stark K, Yassouridis A, Arlt J, Wiedemann K. Effects of a metabotropic glutamate(2/3) receptor agonist (LY544344/LY354740) on panic anxiety induced by cholecystokinin tetrapeptide in healthy humans: preliminary results. Psychopharmacol (Berl) 2005;179:310–5.
Kenakin T. New concepts in drug discovery: collateral efficacy and permissive antagonism. Nat Rev Drug Discov 2005;4:919–27.
Kendler KS, Thornton LM, Prescott CA. Gender differences in the rates of exposure to stressful life events and sensitivity to their depressogenic effects. Am J Psychiatry 2001;158:587–93.
Kessler RC. Posttraumatic stress disorder: the burden to the individual and to society. J Clin Psychiatry 2002;61(Suppl 5):4–12.
Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8–19.
Kessler RC, Ruscio AM, Shear K, Wittchen HU. Epidemiology of anxiety disorders. Curr Top Behav Neurosci 2010;2:21–35.
Kew JN, Kemp JA. Ionotropic and metabotropic glutamate receptor structure and pharmacology. Psychopharmacol (Berl) 2005;179:4–29.
Khan S, Liberzon I. Topiramate attenuates exaggerated acoustic startle in an animal model of PTSD. Psychopharmacol (Berl) 2004;172:225–9.
Kim JJ, Fanselow MS. Modality-specific retrograde amnesia of fear. Science 1992;256: 675–7.
Kim J, Lee S, Park K, Hong I, Song B, Son G, et al. Amygdala depotentiation and fear extinction. Proc Natl Acad Sci U S A 2007a;104:20955–60.
Kim J, Lee S, Park H, Song B, Hong I, Geum D, et al. Blockade of amygdala metabotropic glutamate receptor subtype 1 impairs fear extinction. Biochem Biophys Res Commun 2007b;355:188–93.

Kim CH, Lee J, Lee JY, Roche KW. Metabotropic glutamate receptors: phosphorylation and receptor signaling. J Neurosci Res 2008;86:1–10.
Kleppisch T, Feil R. cGMP signalling in the mammalian brain: role in synaptic plasticity and behaviour. Handb Exp Pharmacol 2009;191:549–79.
Klodzinska A, Chojnacka-Wojcik E. Anticonflict effect of the glycine B receptor partial agonist, D-cycloserine, in rats Pharmacological analysis. Psychopharmacol (Berl) 2000;152:224–8.
Kłodzińska A, Tatarczyńska E, Stachowicz K, Chojnacka-Wójcik E. The anxiolytic-like activity of AIDA (1-aminoindan-1,5-dicarboxylic acid), an mGlu 1 receptor antagonist. J Physiol Pharmacol 2004a;55(1Pt 1):113–26.
Klodzinska A, Tatarczyńska E, Chojnacka-Wójcik E, Nowak G, Cosford ND, Pilc A. Anxiolytic-like effects of MTEP, a potent and selective mGlu5 receptor agonist does not involve GABA(A) signaling. Neuropharmacol 2004b;47:342–50.
Kłodzińska A, Chojnacka-Wójcik E, Pałucha A, Brański P, Popik P, Pilc A. Potential anti-anxiety, anti-addictive effects of LY354740, a selective group II glutamate metabotropic receptors agonist in animal models. Neuropharmacol 1999;38: 1831–9.
Knox D, Perrine SA, George SA, Galloway MP, Liberzon I. Single prolonged stress decreases glutamate, glutamine, and creatine concentrations in the rat medial prefrontal cortex. Neurosci Lett 2010;480:16–20.
Koek W, Colpaert FC. Use of a conflict procedure in pigeons to characterize anxiolytic drug activity: evaluation of NMDA antagonists. Life Sci 1991;49:37–42.
Kohda K, Harada K, Kato K, Hoshino A, Motohashi J, Yamaji T, et al. Glucocorticoid receptor activation is involved in producing abnormal phenotypes of single-prolonged stress rats: a putative post-traumatic stress disorder model. Neuroscience 2007;148:22–33.
Kola I. The state of innovation in drug development. Clin Pharmacol Ther 2008;83:227–30.
Korff S, Harvey BH. Animal models of obsessive–compulsive disorder: rationale to understanding psychobiology and pharmacology. Psychiatr Clin North Am 2006;2: 371–90.
Korff S, Stein DJ, Harvey BH. Stereotypic behaviour in the deer mouse: pharmacological validation and relevance for obsessive compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:348–55.
Korff S, Stein DJ, Harvey BH. Cortico-striatal cyclic AMP-phosphodiesterase-4 signalling and stereotypy in the deer mouse: attenuation after chronic fluoxetine treatment. Pharmacol Biochem Behav 2009;92:514–20.
Kotlinska J, Liljequist S. The putative AMPA receptor antagonist, LY326325, produces anxiolytic effects without altering locomotor activity in rats. Pharmacol Biochem Behav 1998a;60:119–24.
Kotlinska J, Liljequist S. A characterization of anxiolytic like action induced by the novel NMDA/glycine site antagonist L-701,324. Psychopharmacol (Berl) 1998b;135:175–81.
Krass M, Rünkorg K, Wegener G, Volke V. Nitric oxide is involved in the regulation of marble-burying behavior. Neurosci Lett 2010;480:55–8.
Krystal JH, Sanacora G, Blumberg H, Anand A, Charney DS, Marek G, et al. Glutamate and GABA systems as targets for novel antidepressant and mood-stabilizing treatments. Mol Psychiatry 2002;7(Suppl 1):S71–80.
Krystal JH, Mathew SJ, D'Souza DC, Garakani A, Gunduz-Bruce H, Charney DS. Potential psychiatric applications of metabotropic glutamate receptor agonists and antagonists. CNS Drugs 2010;24:669–93.
Kunishima N, Shimada Y, Tsuji Y, Sato T, Yamamoto M, Kumasaka T, et al. Structural basis of glutamate recognition by a dimeric metabotropic glutamate receptor. Nature 2000;407:971–7.
Kushner MG, Kim SW, Donahue C, Thuras P, Adson D, Kotlyar M, et al. D-cycloserine augmented exposure therapy for obsessive-compulsive disorder. Biol Psychiatry 2007;62:835–8.
Lacerda AL, Dalgalarrondo P, Caetano D, Camargo EE, Etchebehere EC, Soares JC. Elevated thalamic and prefrontal regional cerebral blood flow in obsessive–compulsive disorder: a SPECT study. Psychiatric Res 2003;123:125–34.
Lafleur DL, Pittenger C, Kelmendi B, Gardner T, Wasylink S, Malison RT, et al. N-acetylcysteine augmentation in serotonin reuptake inhibitor refractory obsessive–compulsive disorder. Psychopharmacol (Berl) 2006;184:254–6.
Langton JM, Richardson R. D-cycloserine facilitates extinction the first time but not the second time: an examination of the role of NMDA across the course of repeated extinction sessions. Neuropsychopharmacol 2008;33:3096–102.
Langton JM, Kim JH, Nicholas J, Richardson R. The effect of the NMDA receptor antagonist MK-801 on the acquisition and extinction of learned fear in the developing rat. Learn Mem 2007;14:665–8.
Lau A, Tymianski M. Glutamate receptors, neurotoxicity and neurodegeneration. Pflugers Arch 2010;460:525–42.
Laurent V, Westbrook RF. Distinct contributions of the basolateral amygdala and the medial prefrontal cortex to learning and relearning extinction of context conditioned fear. Learn Mem 2008;15:657–66.
Lea IV PM, Faden AI. Metabotropic glutamate receptor subtype 5 antagonists MPEP and MTEP. CNS Drug Rev 2006;12:149–66.
Ledgerwood L, Richardson R, Cranney J. Effects of D-cycloserine on extinction of conditioned freezing. Behav Neurosci 2003;117:341–9.
Ledgerwood L, Richardson R, Cranney J. D-cycloserine and the facilitation of extinction of conditioned fear; consequences for reinstatement. Behav Neurosci 2004;118: 505–13.
Ledgerwood L, Richardson R, Cranney J. D-cycloserine facilitates extinction of learned fear: effects on reacquisition and generalized extinction. Biol Psychiatry 2005;57: 841–7.
Lee H, Kim JJ. Amygdalar NMDA receptors are critical for new fear learning in previously fear-conditioned rats. J Neurosci 1998;18:8444–54.
Lee JL, Milton AL, Everitt BJ. Reconsolidation and extinction of conditioned fear: inhibition and potentiation. J Neurosci 2006;26:10051–6.
Leonard BE. Fundamentals of psychopharmacology. 2nd Ed. Chichester: John Wiley and Sons; 2003.
Lesage A, Steckler T. Metabotropic glutamate mGlu1 receptor stimulation and blockade: therapeutic opportunities in psychiatric illness. Eur J Pharmacol 2010;639:2–16.
Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science 2010;329:959–64.
Liberzon I, Krstov M, Young EA. Stress–restress: effects on ACTH and fast feedback. Psychoneuroendocrinology 1997;22:443–53.
Liberzon I, López JF, Flagel SB, Vázquez DM, Young EA. Differential regulation of hippocampal glucocorticoid receptor mRNA and fast feedback: relevance to post-traumatic stress disorder. J Neuroendocrinol 1999;11:11–7.
Likhtik E, Popa D, Apergis-Schoute J, Fidacaro GA, Pare D. Amygdala intercalated neurons are required for expression of fear extinction. Nature 2008;454:642–5.
Lima VC, Molchanov ML, Aguiar DC, Campos AC, Guimarães FS. Modulation of defensive responses and anxiety-like behaviors by group I metabotropic glutamate receptors located in the dorsolateral periaqueductal gray. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:178–85.
Lin CH, Yeh SH, Lu HY, Gean PW. The similarities and diversities of signal pathways leading to consolidation of conditioning and consolidation of extinction of fear memory. J Neurosci 2003;23:8310–7.
Lin CH, Lee CC, Huang YC, Wang SJ, Gean PW. Activation of group II metabotropic glutamate receptors induces depotentiation in amygdale slices and reduces fear-potentiated startle in rats. Learn Mem 2005;12:130–7.
Lin HC, Mao SC, Gean PW. Block of gamma-aminobutyric acid-A receptor insertion in the amygdala impairs extinction of conditioned fear. Biol Psychiatry 2009;66:665–73.
Lin CH, Mao SC, Su CL, Gean PW. Alterations of excitatory transmission in the lateral amygdala during expression and extinction of fear memory. Int J Neuropsychopharmacol 2010;13:335–45.
Linden AM, Greene SJ, Bergeron M, Schoepp DD. Anxiolytic activity of the MGLU2/3 receptor agonist LY354740 on the elevated plus maze is associated with the suppression of stress-induced c-Fos in the hippocampus and increases in c-Fos induction in several other stress-sensitive brain regions. Neuropsychopharmacol 2004;29:502–13.
Linden AM, Shannon H, Baez M, et al. Anxiolytic-like activity of the mGLU2/3 receptor agonist LY354740 in the elevated plus maze test is disrupted in metabotropic glutamate receptor 2 and 3 knock-out mice. Psychopharmacol (Berl) 2005;179:284–91.
Liu JL, Li M, Dang XR, Wang ZH, Rao ZR, Wu SX, et al. A NMDA receptor antagonist, MK-801 impairs consolidating extinction of auditory conditioned fear responses in a Pavlovian model. PLoS One 2009;4:e7548.
Lohoff FW. Overview of the genetics of major depressive disorder. Curr Psychiatry Rep 2010;12:539–46.
Lynch G. Memory enhancement: the search for mechanism based drugs. Nat Neurosci 2002;5:1035–8.
Lynch G. Glutamate-based therapeutic approaches: ampakines. Curr Opin Pharmacol 2006;6:82–8.
Machado-Vieira R, Manji HK, Zarate CA. The role of the tripartite glutamatergic synapse in the pathophysiology and therapeutics of mood disorders. Neuroscientist 2009;15:525–39.
Maeng S, Zarate Jr CA, Du J, Schloesser RJ, McCammon J, Chen G, et al. Cellular mechanisms underlying the antidepressant effects of ketamine: role of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. Biol Psychiatry 2008;63:349–52.
Maes M, Lin AH, Delmeire L, Van Gastel A, Kenis G, De Jongh R, et al. Elevated serum interleukin-6 and interleukin-6 receptor concentrations in posttraumatic stress disorder following accidental man-made traumatic events. Biol Psychiatry 1999;45:833–9.
Maes M, Mylle J, Delmeire L, Janca A. Pre- and post-disaster negative life events in relation to the incidence and severity of post-traumatic stress disorder. Psychiatry Res 2001;105:1–12.
Malayev A, Gibbs TT, Farb DH. Inhibition of the NMDA response by pregnenolone sulphate reveals subtype selective modulation of NMDA receptors by sulphated steroids. Br J Pharmacol 2002;135:901–9.
Malenka RC, Nicoll RA. Long-term potentiation — a decade of progress? Science 1999;285:1870–4.
Malherbe P, Knoflach F, Broger C, Ohresser S, Kratzeisen C, Adam G, et al. Identification of essential residues involved in the glutamate binding pocket of the group II metabotropic glutamate receptor. Mol Pharmacol 2001;60:944–54.
Mangiavacchi S, Wolf ME. Stimulation of N-methyl-D-aspartate receptors, AMPA receptors or metabotropic glutamate receptors leads to rapid internalization of AMPA receptors in cultured nucleus accumbens neurons. Eur J Neurosci 2004;20:649–57.
Mannaioni G, Marino MJ, Valenti O, Traynelis SF, Conn PJ. Metabotropic glutamate receptors 1 and 5 differentially regulate CA1 pyramidal cell function. J Neurosci 2001;21:5925–34.
Marino MJ, Conn PJ. Direct and indirect modulation of the N-methyl D-aspartate receptor. Curr Drug Targets CNS Neurol Disord 2002;1:1–16.
Mathew SJ, Price RB, Mao X, Smith EL, Coplan JD, Charney DS, et al. Hippocampal N-acetylaspartate concentration and response to riluzole in generalized anxiety disorder. Biol Psychiatry 2008;63:891–8.
Matsumoto M, Togashi H, Konno K, Koseki H, Hirata R, Izumi T, et al. Early postnatal stress alters the extinction of context-dependent conditioned fear in adult rats. Pharmacol Biochem Behav 2008;89:247–52.
McDougle CL, Barr LC, Goodman WK, Price LH. Possible role of neuropeptides in obsessive compulsive disorder. Psychoneuroendocrinology 1999;24:1–24.
McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med 1998;338:171–9.

McEwen BS. The neurobiology of stress: from serendipity to clinical relevance. Brain Res 2000;886:172–89.
McLeod TM, Lopez-Figueroa AL, Lopez-Figueroa MO. Nitric oxide, stress, and depression. Psychopharmacol Bull 2001;35:24–41.
Meldrum BS. Glutamate as a neurotransmitter in the brain: review of physiology and pathology. J Nutr 2000;130(Suppl):1007S–15S.
Milad MR, Rauch SL, Pitman RK, Quirk GJ. Fear extinction in rats: implications for human brain imaging and anxiety disorders. Biol Psychology 2006;73:61–71.
Millan MJ. The neurobiology of anxious states. Prog Neurobiol 2003;70:83–244.
Millan MJ. Multi-target strategies for the improved treatment of depressive states: conceptual foundations and neuronal substrates, drug discovery and therapeutic application. Pharmacol Ther 2006;110:135–370.
Mitsukawa K, Yamamoto R, Ofner S, Nozulak J, Pescott O, Lukic S, et al. A selective metabotropic glutamate receptor 7 agonist: activation of receptor signaling via an allosteric site modulates stress parameters in vivo. Proc Natl Acad Sci U S A 2005;102:18712–7.
Mitsukawa K, Mombereau C, Lötscher E, Uzunov DP, van der Putten H, Flor PJ, et al. Metabotropic glutamate receptor subtype 7 ablation causes dysregulation of the HPA axis and increases hippocampal BDNF protein levels: implications for stress-related psychiatric disorders. Neuropsychopharmacol 2006;31:1112–22.
Moghaddam B. Stress activation of glutamate neurotransmission in the prefrontal cortex: implications for dopamine-associated psychiatric disorders. Biol Psychiatry 2002;51:775–87.
Molina-Hernández M, Tellez-Alcántara NP, Pérez-García J, Olivera-Lopez JI, Jaramillo MT. Estrus variation in anticonflict-like effects of the mGlu5 receptor antagonist MTEP, microinjected into lateral septal nuclei of female Wistar rats. Pharmacol Biochem Behav 2006;84:385–91.
Möller M, Du Preez JL, Emsley R, Harvey BH. Isolation rearing-induced deficits in sensorimotor gating and social interaction in rats are related to cortico-striatal oxidative stress, and reversed by sub-chronic clozapine administration. Eur Neuropsychopharmacol 2011;21:471–83.
Molosh AI, Johnson PL, Fitz SD, Dimicco JA, Herman JP, Shekhar A. Changes in central sodium and not osmolarity or lactate induce panic-like responses in a model of panic disorder. Neuropsychopharmacol 2010;35:1333–47.
Monn JA, Valli MJ, Massey SM, Wright RA, Salhoff CR, Johnson BG, et al. Design, synthesis, and pharmacological characterization of (+)-2-aminobicyclo[3.1.0] hexane-2,6-dicarboxylic acid (LY354740): a potent, selective, and orally active group 2 metabotropic glutamate receptor agonist possessing anticonvulsant and anxiolytic properties. J Med Chem 1997;40:528–37.
Morrow JA, Maclean JK, Jamieson C. Recent advances in positive allosteric modulators of the AMPA receptor. Curr Opin Drug Discov Devel 2006;9:571–9.
Myers KM, Carlezon Jr WA. D-cycloserine facilitates extinction of naloxoneinduced conditioned place aversion in morphine-dependent rats. Biol Psychiatry 2010;67:85–7.
Myers KM, Carlezon Jr WA, Davis M. Glutamate receptors in extinction and extinction-based therapies for psychiatric illness. Neuropsychopharmacol 2011;36:274–93.
Newport DJ, Nemeroff CB. Neurobiology of posttraumatic stress disorder. Curr Opin Neurobiol 2000;10:211–8.
Nicoletti F, Bockaert J, Collingridge GL, Conn JP, Ferragutti F, Schepp DD, et al. Metabotropic glutamate receptors: from the workbench to the bedside. Neuropharmacol 2011;60:1017–41.
Nicoll RA, Malenka RC. Expression mechanisms underlying NMDA receptor-dependent long-term potentiation. Ann N Y Acad Sci 1999;868:515–25.
Niswender CM, Conn PJ. Metabotropic glutamate receptors: physiology, pharmacology, and disease. Annu Rev Pharmacol Toxicol 2010;50:295–322.
Niwa M, Matsumoto Y, Mouri A, Ozaki N, Nabeshima T. Vulnerability in early life to changes in the rearing environment plays a crucial role in the aetiopathology of psychiatric disorders. Int J Neuropsychopharmacol 2010;18:1–19.
Nordquist RE, Durkin S, Jaeschke G, Spooren W. Stress-induced hyperthermia: effects of acute and repeated dosing of MPEP. Eur J Pharmacol 2007;568:199–202.
Nowak L, Bregestovski P, Ascher P, Herbet A, Prochiantz A. Magnesium gates glutamate-activated channels in mouse central neurones. Nature 1984;307:462–5.
O'Neill MJ, Bleakman D, Zimmerman DM, Nisenbaum ES. AMPA receptor potentiators for the treatment of CNS disorders. Curr Drug Targets CNS Neurol Disord 2004;3:181–94.
Oosthuizen F, Wegener G, Harvey BH. Nitric oxide as inflammatory mediator in post-traumatic stress disorder (PTSD): evidence from an animal model. Neuropsychiatry Dis Treat 2005;1:109–23.
Ota KT, Monsey MS, Wu MS, Schafe GE. Synaptic plasticity and NO-cGMP-PKG signaling regulate pre- and postsynaptic alterations at rat lateral amygdala synapses following fear conditioning. PLoS One 2010;5(6):e11236.
Otto MW, Tolin DF, Simon NM, Pearlson GD, Basden S, Meunier SA, et al. Efficacy of D-cycloserine for enhancing response to cognitive-behavior therapy for panic disorder. Biol Psychiatry 2010;67:365–70.
Overstreet DH, Friedman E, Mathé AA, Yadid G. The Flinders Sensitive Line rat: a selectively bred putative animal model of depression. Neurosci Biobehav Rev 2005;29:739–59.
Ozdemir E, Cetinkaya S, Ersan S, Kucukosman S, Ersan EE. Serum selenium and plasma malondialdehyde levels and antioxidant enzyme activities in patients with obsessive–compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry 2009;33:62–5.
Palucha A, Pilc A. Metabotropic glutamate receptor ligands as possible anxiolytic and antidepressant drugs. Pharmacol Ther 2007;115:116–47.
Pałucha A, Tatarczyńska E, Brański P, Szewczyk B, Wierońska JM, Kłak K, et al. Group III mGlu receptor agonists produce anxiolytic- and antidepressant-like effects after central administration in rats. Neuropharmacol 2004;46:151–9.
Parker KJ, Schatzberg AF, Lyons DM. Neuroendocrine aspects of hypercortisolism in major depression. Horm Behav 2003;43:60–6.
Parnas AS, Weber M, Richarson R. Effects of multiple exposures to D-cycloserine on extinction of conditioned fear in rats. Neurobiol Learn Mem 2005;83:224–31.
Parsons CG, Stöffler A, Danysz W. Memantine: a NMDA receptor antagonist that improves memory by restoration of homeostasis in the glutamatergic system—too little activation is bad, too much is even worse. Neuropharmacol 2007;53:699–723.
Paul IA, Skolnick P. Glutamate and depression: clinical and preclinical studies. Ann N Y Acad Sci 2003;1003:250–72.
Peng S, Zhang Y, Zhang J, Wang H, Ren B. Glutamate receptors and signal transduction in learning and memory. Mol Biol Rep 2011;38:453–60.
Pérez de la Mora M, Lara-García D, Jacobsen KX, Vázquez-García M, Crespo-Ramírez M, Flores-Gracia C, et al. Anxiolytic-like effects of the selective metabotropic glutamate receptor 5 antagonist MPEP after its intra-amygdaloid microinjection in three different non-conditioned rat models of anxiety. Eur J Neurosci 2006;23:2749–59.
Phan KL, Fitzgerald DA, Cortese BM, Seraji-Bozorgzad N, Tancer ME, Moore GJ. Anterior cingulate neurochemistry in social anxiety disorder: 1H-MRS at 4 Tesla. Neuroreport 2005;16:183–6.
Pickering C, Gustafsson L, Cebere A, Nylander I, Liljequist S. Repeated maternal separation of male Wistar rats alters glutamate receptor expression in the hippocampus but not the prefrontal cortex. Brain Res 2006;1099:101–8.
Pietraszek M, Sukhanov I, Maciejak P, Szyndler J, Gravius A, Wisłowska A, et al. Anxiolytic-like effects of mGlu 1 and mGlu5 receptor antagonists in rats. Eur J Pharmacol 2005;514:25–34.
Pittenger C, Krystal JH, Coric V. Glutamate-modulating drugs as novel pharmacotherapeutic agents in the treatment of obsessive–compulsive disorder. NeuroRx 2006;3:69–81.
Planells-Cases R, Lerma J, Ferrer-Montiel A. Pharmacological intervention at ionotropic glutamate receptor complexes. Curr Pharm Des 2006;12:3583–96.
Plaznik A, Palejko W, Nazar M, Jessa M. Effects of antagonists at the NMDA receptor complex in two models of anxiety. Eur Neuropsychopharmacol 1994;4:503–12.
Pollack MH, Jensen JE, Simon NM, Kaufman RE, Renshaw PF. High-field MRS study of GABA, glutamate and glutamine in social anxiety disorder: response to treatment with levetiracetam. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:739–43.
Popkirov SG, Manahan-Vaughan D. Involvement of the metabotropic glutamate receptor mGluR5 in NMDA receptor-dependent, learning-facilitated long-term depression in CA1 synapses. Cereb Cortex 2011;21:501–9.
Porter JH, Wiley JL, Balster RL. Effects of phencyclidine-like drugs on punished behaviour in rats. J Pharmacol Exp Ther 1989;248:997–1002.
Porter RH, Jaeschke G, Spooren W, Ballard TM, Büttelmann B, Kolczewski S, et al. Fenobam: a clinically validated nonbenzodiazepine anxiolytic is a potent, selective, and noncompetitive mGlu5 receptor antagonist with inverse agonist activity. J Pharmacol Exp Ther 2005;315:711–21.
Prast H, Philippu A. Nitric oxide as modulator of neuronal function. Prog Neurobiol 2001;64:51–68.
Presti MF, Watson CJ, Kennedy RT, Yang M, Lewis MH. Behavior-related alterations of striatal neurochemistry in a mouse model of stereotyped movement disorder. Pharmacol Biochem Behav 2004;77:501–7.
Przegaliński E, Tatarczyńska E, Dereń-Wesołek A, Chojnacka-Wójcik E. Anticonflict effects of a competitive NMDA receptor antagonist and a partial agonist at strychnine-insensitive glycine receptors. Pharmacol Biochem Behav 1996;54:73–7.
Quirk GJ, Mueller D. Neural mechanisms of extinction learning and retrieval. Neuropsychopharmacol 2008;33:56–72.
Quirk JC, Nisenbaum ES. LY404187: a novel positive allosteric modulator of AMPA receptors. CNS Drug Rev 2002;8:255–82.
Ravindran LN, Stein MB. Pharmacotherapy of PTSD: premises, principles, and priorities. Brain Res 2009;1293:24–39.
Rodriguez AL, Nong Y, Sekaran NK, Alagille D, Tamagnan GD, Conn PJ. A close structural analog of 2-methyl-6-(phenylethynyl)-pyridine acts as a neutral allosteric site ligand on metabotropic glutamate receptor subtype 5 and blocks the effects of multiple allosteric modulators. Mol Pharmacol 2005;68:1793–802.
Rolls ET. The neural basis of emotion. In: Rolls ET, editor. The brain and emotion. New York: Oxford university press; 1999. p. 112–38.
Rorick-Kehn LM, Hart JC, McKinzie DL. Pharmacological characterization of stress-induced hyperthermia in DBA/2 mice using metabotropic and ionotropic glutamate receptor ligands. Psychopharmacol (Berl) 2005;183:226–40.
Rorick-Kehn LM, Perkins EJ, Knitowski KM, Hart JC, Johnson BG, Schoepp DD, et al. Improved bioavailability of the mGlu2/3 receptor agonist LY354740 using a prodrug strategy: in vivo pharmacology of LY544344. J Pharmacol Exp Ther 2006;316:905–13.
Rosen JB, Pagani JH, Rolla KL, Davis C. Analysis of behavioral constraints and the neuroanatomy of fear to the predator odor trimethylthiazoline: a model for animal phobias. Neurosci Biobehav Rev 2008;32:1267–76.
Rumpel S, LeDoux J, Zador A, Malinow R. Postsynaptic receptor trafficking underlying a form of associative learning. Science 2005;308:83–8.
Sanger DJ, Jackson A. Effects of phencyclidine and other N-methyl-D-aspartate antagonists on the schedule controlled behaviour. J Pharmacol Exp Ther 1989;248:1215–21.
Santini E, Muller RU, Quirk GJ. Consolidation of extinction learning involves transfer from NMDA-independent to NMDA-dependent memory. J Neurosci 2001;21:9009–17.
Sasaki YF, Rothe T, Premkumar LS, Das S, Cui J, Talantova MV, et al. Characterization and comparison of the NR3A subunit of the NMDA receptor in recombinant systems and primary cortical neurons. J Neurophysiol 2002;87:2052–63.
Satow A, Maehara S, Ise S, Hikichi H, Fukushima M, Suzuki G, et al. Pharmacological effects of the metabotropic glutamate receptor 1 antagonist compared with those of the metabotropic glutamate receptor 5 antagonist and metabotropic glutamate receptor 2/3 agonist in rodents: detailed investigations with a selective allosteric metabotropic glutamate receptor 1 antagonist,FTIDC [4-[1-(2-fluoropyridine-3-

yl)-5-methyl-1H-1,2,3-triazol-4-yl]-N-isopropyl-N-methy 1–3,6-dihydropyridine-1(2H)-carboxamide]. J Pharmacol Exp Ther 2008;326:577–86.
Schoepp DD, Jane DE, Monn JA. Pharmacological agents acting at subtypes of metabotropic glutamate receptors. Neuropharmacology 1999;38:1431–76.
Schoepp DD, Wright RA, Levine LR, Gaydos B, Potter WZ. LY354740, an mGlu2/3 receptor agonist as a novel approach to treat anxiety/stress. Stress 2003;6:189–97.
Schulz B, Fendt M, Gasparini F, Lingenhöhl K, Kuhn R, Koch M. The metabotropic glutamate receptor antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) blocks fear conditioning in rats. Neuropharmacol 2001;41:1–7.
Selvakumar B, Huganir RL, Snyder SH. S-nitrosylation of stargazin regulates surface expression of AMPA-glutamate neurotransmitter receptors. Proc Natl Acad Sci U S A 2009;106:16440–5.
Selye H. A syndrome produced by diverse nocuous agents. Nature 1936;138:32.
Shekhar A, Keim SR. LY354740, a potent group II metabotropic glutamate receptor agonist prevents lactate-induced panic-like response in panic-prone rats. Neuropharmacol 2000;39:1139–46.
Shiah IS, Yatham LN. GABA function in mood disorders: an update and critical review. Life Sci 1998;63:1289–303.
Shimazaki T, Iijima M, Chaki S. Anxiolytic-like activity of MGS0039, a potent group II metabotropic glutamate receptor antagonist, in a marble-burying behavior test. Eur J Pharmacol 2004;501:121–5.
Sigurdsson T, Doyère V, Cain CK, LeDoux JE. Long-term potentiation in the amygdala: a cellular mechanism of fear learning and memory. Neuropharmacology 2007;52: 215–27.
Silvestre JS, Nadal R, Pallares M, Ferre N. Acute effects of ketamine in the holeboard, the elevated plus maze, and the social interaction test in Wistar rats. Depress Anxiety 1997;5:29–33.
Simonyi A, Schachtman TR, Christoffersen GR. The role of metabotropic glutamate receptor 5 in learning and memory processes. Drug News Perspect 2005;18:353–61.
Smoller JW, Block SR, Young MM. Genetics of anxiety disorders: the complex road from DSM to DNA. Depress Anxiety 2009;26:965–75.
Sotres-Bayon F, Bush DE, LeDoux JE. Acquisition of fear extinction requires activation of NR2B-containing NMDA receptors in the lateral amygdala. Neuropsychopharmacol 2007;32:1929–40.
Sotres-Bayon F, Diaz-Mataix L, Bush DE, Ledoux JE. Dissociable roles for the ventromedial prefrontal cortex and amygdala in fear extinction: NR2B contribution. Cereb Cortex 2009;19:474–82.
Spedding M, Neau I, Harsing L. Brain plasticity and pathology in psychiatric disease: sites of action for potential therapy. Curr Opin Pharmacol 2003;3:33–40.
Spooren WP, Vassout A, Neijt HC, Kuhn R, Gasparini F, Roux S, et al. Anxiolytic-like effects of the prototypical metabotropic glutamate receptor 5 antagonist 2- methyl-6-(phenylethynyl)pyridine in rodents. J Pharmacol Exp Ther 2000;295:1267–75.
Spooren WP, Schoeffter P, Gasparini F, Kuhn R, Gentsch C. Pharmacological and endocrinological characterization of stress-induced hyperthermia in singly housed mice using classical and candidate anxiolytics (LY314582, MPEP and NKP608). Eur J Pharmacol 2002;435:161–70.
Stachowicz K, Kłak K, Kłodzińska A, Chojnacka-Wojcik E, Pilc A. Anxiolytic-like effects of PHCCC, an allosteric modulator of mGlu4 receptors, in rats. Eur J Pharmacol 2004;498:153–6.
Stachowicz K, Kłak K, Pilc A, Chojnacka-Wójcik E. Lack of the antianxiety-like effect of (S)-3,4-DCPG, an mGlu8 receptor agonist, after central administration in rats. Pharmacol Rep 2005;57:856–60.
Stachowicz K, Chojnacka-Wójcik E, Kłak K, Pilc A. Anxiolytic-like effects of group III mGlu receptor ligands the hippocampus involve GABAA signaling. Pharmacol Rep 2006;58:820–6.
Stachowicz K, Chojnacka-Wójcik E, Kłak K, Pilc A. Anxiolytic- like effect of group III mGlu receptor antagonist is serotonin-dependent. Neuropharmacol 2007;52: 306–12.
Staubli U, Rogers G, Lynch G. Facilitation of glutamate receptors enhances memory. Proc Natl Acad Sci U S A 1994;91:777–81.
Steckler T, Lavreysen H, Oliveira AM, Aerts N, Van Craenendonck H, Prickaerts J, et al. Effects of mGlu1 receptor blockade on anxiety-related behavior in the rat lick suppression test. Psychopharmacol (Berl) 2005;179:198–206.
Stein DJ. Neurobiology of the obsessive–compulsive spectrum disorders. Biol Psychiatry 2000;47:296–304.
Stein DJ, Hollander E. Textbook of anxiety disorders. Washington, USA: American Psychiatric Press; 2002.
Stein MB, Yehuda R, Koverola C, Hanna C. Enhanced dexamethasone suppression of plasma cortisol in adult women traumatized by childhood sexual abuse. Biol Psychiatry 1997;42:680–6.
Stewart SE, Jenike EA, Hezel DM, Stack DE, Dodman NH, Shuster L, et al. A single-blinded case-control study of memantine in severe obsessive–compulsive disorder. J Clin Psychopharmacol 2010;30:34–9.
Storsve AB, McNally GP, Richardson R. US habituation, like CS extinction, produces a decrement in conditioned fear responding that is NMDA dependent and subject to renewal and reinstatement. Neurobiol Learn Mem 2010;93:463–71.
Sung KW, Choi S, Lovinger DM. Activation of group I mGluRs is necessary for induction of long-term depression at striatal synapses. J Neurophysiol 2001;86:2405–12.
Sur C, Kinney GG. Glycine transporter 1 inhibitors and modulation of NMDA receptor-mediated excitatory neurotransmission. Curr Drug Targ 2007;8:643–9.
Swanson CJ, Bures M, Johnson MP, Linden AM, Monn JA, Schoepp DD. Metabotropic glutamate receptors as novel targets for anxiety and stress disorders. Nat Rev Drug Discov 2005;4:131–44.
Szapiro G, Vianna MR, McGaugh JL, Medina JH, Izquierdo I. The role of NMDA glutamate receptors, PKA, MAPK, and CaMKII in the hippocampus in extinction of conditioned fear. Hippocampus 2003;13:53–8.
Takahashi T, Kimoto T, Tanabe N, Hattori TA, Yasumatsu N, Kawato S. Corticosterone acutely prolonged N-methyl-D-aspartate receptor-mediated Ca^{2+} elevation in cultured rat hippocampal neurons. J Neurochemistry 2002;83:1441–51.
Takahashi T, Morinobu S, Iwamoto Y, Yamawaki S. Effect of paroxetine on enhanced contextual fear induced by single prolonged stress in rats. Psychopharmacol (Berl) 2006;189:165–73.
Takahashi A, Yap JJ, Bohager DZ, Faccidomo S, Clayton T, Cook JM, et al. Glutamatergic and GABAergic modulations of ultrasonic vocalizations during maternal separation distress in mouse pups. Psychopharmacol (Berl) 2009;204:61–71.
Tanaka H, Grooms SY, Bennett MV, Zukin RS. The AMPAR subunit GluR2: still front and center-stage. Brain Res 2000;886:190–207.
Tang YP, Shimizu E, Dube GR, Rampon C, Kerchner GA, Zhuo M, et al. Genetic enhancement of learning and memory in mice. Nature 1999;401:63–9.
Tao R, Auerbach SB. Regulation of serotonin release by GABA and excitatory amino acids. J Psychopharmacol 2000;14:100–13.
Tatarczyńska E, Klodzińska A, Chojnacka-Wójcik E, Palucha A, Gasparini F, Kuhn R, et al. Potential anxiolytic- and antidepressant-like effects of MPEP, a potent, selective and systemically active mGlu5 receptor antagonist. Br J Pharmacol 2001a;132: 1423–30.
Tatarczyńska E, Kłodzińska A, Kroczka B, Chojnacka-Wójcik E, Pilc A. The antianxiety-like effects of antagonists of group I and agonists of group II and III metabotropic glutamate receptors after intrahippocampal administration. Psychopharmacology (Berl) 2001b;158:94–9.
Tatarczyńska E, Pałucha A, Szewczyk B, Chojnacka-Wójcik E, Wierońska J, Pilc A. Anxiolytic- and antidepressant-like effects of group III metabotropic glutamate agonist (1S,3R,4S)-1-aminocyclopentane-1,3,4-tricarboxylic acid (ACPT-I) in rats. Pol J Pharmacol 2002;54:707–10.
Thoeringer CK, Pfeiffer UJ, Rammes G, Pamplona FA, Moosmang S, Wotjak CT. Early life environment determines the development of adult phobic-like fear responses in BALB/cAnN mice. Genes Brain Behav 2010;9:947–57.
Thomas NK, Wright RA, Howson PA, Kingston AE, Schoepp DD, Jane DE. (S)-3,4-DCPG, a potent and selective mGlu8a receptor agonist, activates metabotropic glutamate receptors on primary afferent terminals in the neonatal rat spinal cord. Neuropharmacology 2001;40:311–8.
Tizzano JP, Griffey KI, Schoepp DD. The anxiolytic action of mGlu2/3 receptor agonist, LY354740, in the fear-potentiated startle model in rats is mechanistically distinct from diazepam. Pharmacol Biochem Behav 2002;73:367–74.
Tomilenko RA, Dubrovina NI. Effects of activation and blockade of NMDA receptors on the extinction of a conditioned passive avoidance response in mice with different levels of anxiety. Neurosci Behav Physiol 2007;37:509–15.
Tomita S, Stein V, Stocker TJ, Nicoll RA, Bredt DS. Bidirectional synaptic plasticity regulated by phosphorylation of stargazin-like TARPs. Neuron 2005;45:269–77.
Toua C, Brand L, Möller M, Emsley RA, Harvey BH. The effects of sub-chronic clozapine and haloperidol administration on isolation rearing induced changes in frontal cortical N-methyl-D-aspartate and D1 receptor binding in rats. Neuroscience 2010;165:492–9.
Traynelis SF, Wollmuth LP, McBain CJ, Menniti FS, Vance KM, Ogden KK, et al. Glutamate receptor ion channels: structure, regulation, and function. Pharmacol Rev 2010;62: 405–96.
Trullas R, Jackson B, Skolnick P. Anxiolytic properties of 1-aminocyclopropanecarboxylic acid, a ligand at strychnine-insensitive glycine receptors. Pharmacol Biochem Behav 1989;34:313–6.
Umathe SN, Bhutada PS, Jain NS, Mundhada YR, Borkar SS, Dhumal B. Role of nitric oxide in obsessive–compulsive behavior and its involvement in the anti-compulsive effect of paroxetine in mice. Nitric Oxide 2010;21:140–7.
Uys JD, Stein DJ, Daniels WM, Harvey BH. Animal models of anxiety disorders. Curr Psychiatry Rep 2003;5:274–81.
Uys JD, Muller CJ, Marais L, Harvey BH, Stein DJ, Daniels WM. Early life trauma decreases glucocorticoid receptors in rat dentate gyrus upon adult re-stress: reversal by escitalopram. Neuroscience 2006;137:619–25.
Van Ameringen M, Mancini C, Pipe B, Bennett M. Optimizing treatment in social phobia: a review of treatment resistance. CNS Spectr 2004;9:753–62.
van den Pol AN, Wuarin JP, Dudek FE. Glutamate, the dominant excitatory transmitter in neuroendocrine regulation. Science 1990;250:1276–8.
Varty GB, Grilli M, Forlani A, Fredduzzi S, Grzelak ME, Guthrie DH, et al. The antinociceptive and anxiolytic-like effects of the metabotropic glutamate receptor 5 (mGluR5) antagonists, MPEP, and the mGluR1 antagonist, LY 456236, in rodents: a comparison of efficacy and side-effect profiles. Psychopharmacol (Berl) 2005;179:207–17.
Venton BJ, Robinson TE, Kennedy RT. Transient changes in nucleus accumbens amino acid concentrations correlate with individual responsivity to the predator fox odor 2,5-dihydro-2,4,5-trimethylthiazoline. J Neurochem 2006;96:236–46.
Vry De J, Benz U, Schreiber R, Traber J. Shock-induced ultrasonic vocalisation in young adult rats: a model for testing putative anxiolytic drugs. Eur J Pharmacol 1993;249:331–9.
Walker DL, Rattiner LM, Davis M. Group II metabotropic glutamate receptors within the amygdala regulate fear as assessed with potentiated startle in rats. Behav Neurosci 2002a;116:1075–83.
Walker DL, Ressler KJ, Lu KT, Davis M. Facilitation of conditioned fear extinction by systemic administration or intra-amygdala infusions of D-cycloserine as assessed with fear-potentiated startle in rats. J Neurosci 2002b;22:2343–51.
Wang L, Simpson HB, Dulawa SC. Assessing the validity of current mouse genetic models of obsessive–compulsive disorder. Behav Pharmacol 2009;20:119–33.
Weber M, Hart J, Richardson R. Effects of D-cycloserine on extinction of learned fear to an olfactory cue. Neurobiol Learn Mem 2007;87:476–82.
Wegener G, Harvey BH, Bonefeld B, Müller HK, Volke V, Overstreet DH, et al. Increased stress-evoked nitric oxide signalling in the Flinders sensitive line (FSL) rat: a

genetic animal model of depression. Int J Neuropsychopharmacol 2010;13:461–73.
Wheeler D, Boutelle MG, Fillenz M. The role of N-methyl-D-aspartate receptors in the regulation of physiologically released dopamine. Neuroscience 1995;65:767–74.
Wierońska JM, Pilc A. Metabotropic glutamate receptors in the tripartite synapse as a target for new psychotropic drugs. Neurochem Int 2009;55:85–97.
Wierońska JM, Smiałowska M, Brański P, Gasparini F, Kłodzińska A, Szewczyk B, et al. In the amygdale anxiolytic action of mGlu5 receptors antagonist MPEP involves neurpeptide Y but not GABAA signaling. Neuropsychopharmacol 2004;29:514–21.
Wiley JL. Behavioral pharmacology of N-methyl-D-aspartate antagonists: implications for the study and pharmacotherapy of anxiety and schizophrenia. Exp Clin Psychopharmacol 1997;5:365–74.
Wiley JL, Cristello AF, Balster RL. Effects of site selective NMDA receptor antagonists in an elevated plus model of anxiety in mice. Eur J Pharmacol 1995;294:101–7.
Wiley JL, Compton AD, Holcomb JD, McCallum SE, Varvel SA, Porter JH, et al. Effects of modulation of NMDA neurotransmission on response rate and duration in a conflict procedure in rats. Neuropharmacol 1998;37:1527–34.
Wilhelm S, Buhlmann U, Tolin DF, Meunier SA, Pearlson GD, Reese HE, et al. Augmentation of behavior therapy with D-cycloserine for obsessive–compulsive disorder. Am J Psychiatry 2008;165:335–41.
Wolf OT. The influence of stress hormones on emotional memory: relevance for psychopathology. Acta Psychol 2008;127:513–31.
Wong EH, Nikam SS, Shahid M. Multi- and single-target agents for major psychiatric diseases: therapeutic opportunities and challenges. Curr Opin Investig Drugs 2008;9:28–36.
Wong EH, Tarazi FI, Shahid M. The effectiveness of multi-target agents in schizophrenia and mood disorders: relevance of receptor signature to clinical action. Pharmacol Ther 2010;126:173–85.
Woods AM, Bouton ME. D-Cycloserine facilitates extinction but does not eliminate renewal of the conditioned emotional response. Behav Neurosci 2006;120:1159–62.
Woolley ML, Waters KA, Gartlon JE, Lacroix LP, Jennings C, Shaughnessy F, et al. Evaluation of the pro-cognitive effects of the AMPA receptor positive modulator, 5-(1-piperidinylcarbonyl)-2,1,3-benzoxadiazole (CX691), in the rat. Psychopharmacology (Berl) 2009;202:343–54.
Xia YF, Arai AC. AMPA receptor modulators have different impact on hippocampal pyramidal cells and interneurons. Neuroscience 2005;135:555–67.
Xie Z, Commissaris L. Anxiolytic-like effects of the noncompetitive NMDA antagonist MK801. Pharmacol Biochem Behav 1992;43:471–7.
Xie ZC, Buckner E, Commissaris RL. Anticonflict effect of MK-801 in rats: time course and chronic treatment studies. Pharmacol Biochem Behav 1995;51:635–40.
Xu J, Zhu Y, Contractor A, Heinemann SF. mGluR5 has a critical role in inhibitory learning. J Neurosci 2009;29:3676–84.
Yamada D, Zushida K, Wada K, Sekiguchi M. Pharmacological discrimination of extinction and reconsolidation of contextual fear memory by a potentiator of AMPA receptors. Neuropsychopharmacol 2009;34:2574–84.
Yamamoto S, Morinobu S, Fuchikami M, Kurata A, Kozuru T, Yamawaki S. Effects of single prolonged stress and D-cycloserine on contextual fear extinction and hippocampal NMDA receptor expression in a rat model of PTSD. Neuropsychopharmacology 2008;33:2108–16.
Yamamoto S, Morinobu S, Takei S, Fuchikami M, Matsuki A, Yamawaki S, et al. Single prolonged stress: toward an animal model of posttraumatic stress disorder. Depress Anxiety 2009;26:1110–7.
Yang YL, Lu KT. Facilitation of conditioned fear extinction by D-cycloserine is mediated by mitogen-activated protein kinase and phosphatidylinositol 3-kinase cascades and requires de novo protein synthesis in basolateral nucleus of amygdala. Neuroscience 2005;134:247–60.
Yehuda R. Sensitization of the hypothalamic-pituitary-adrenalaxis in posttraumatic stress disorder. Ann N Y Acad Sci 1997;821:57–75.
Yehuda R, Antelman SM. Criteria for rationally evaluating animal models of posttraumatic stress disorder. Biol Psychiatry 1993;33:479–86.
Yehuda R, McFarlane AC. Conflict between current knowledge about posttraumatic stress disorder and its original conceptual basis. Am J Psychiatry 1995;152:1705–13.
Yehuda R, Southwick S, Giller EL, Ma X, Mason JW. Urinary catecholamine excretion and severity of PTSD symptoms in vietnam combat veterans. J Nerv Ment Dis 1992;180:321–5.
Yoshimizu T, Shimazaki T, Ito A, Chaki S. An mGluR2/3 antagonist, MGS0039, exerts antidepressant and anxiolytic effects in behavioral models in rats. Psychopharmacol (Berl) 2006;186:587–93.
Zhai J, Tian MT, Wang Y, Yu JL, Köster A, Baez M, et al. Modulation of lateral perforant path excitatory responses by metabotropic glutamate 8 (mGlu8) receptors. Neuropharmacology 2002;43:223–30.
Zhang C, Marek GJ. Group III metabotropic glutamate receptor agonists selectively suppress excitatory synaptic currents in the rat prefrontal cortex induced by 5-hydroxytryptamine2A receptor activation. Pharmacol Exp Ther 2007;320:437–47.
Zushida K, Sakurai M, Wada K, Sekiguchi M. Facilitation of extinction learning for contextual fear memory by PEPA: a potentiator of AMPA receptors. J Neurosci 2007;27:158–66.