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Review

New perspectives in glutamate and anxiety

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ABSTRACT

Anxiety and stress-related disorders, namely posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), obsessive–compulsive disorder (ODC), social and specific phobias, and panic disorder, are a major public health issue.

A growing body of evidence suggests that glutamatergic neurotransmission may be involved in the biological mechanisms underlying stress response and anxiety-related disorders. The glutamatergic system mediates the acquisition and extinction of fear-conditioning. Thus, new drugs targeting glutamatergic neurotransmission may be promising candidates for new pharmacological treatments. In particular, N-methyl-D-aspartate receptors (NMDAR) antagonists (AP5, AP7, CGP37849, CGP39551, LY235959, NPC17742, and MK-801), NMDAR partial agonists (DCS, ACPC), α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptors (AMPARs) antagonists (topiramate), and several allosteric modulators targeting metabotropic glutamate receptors (mGluRs) mGluR1, mGluR2/3, and mGluR5, have shown anxiolytic-like effects in several animal and human studies.

Several studies have suggested that polyamines (agmatine, putrescine, spermidine, and spermine) may be involved in the neurobiological mechanisms underlying stress-response and anxiety-related disorders. This could mainly be attributed to their ability to modulate ionotropic glutamate receptors, especially NR2B subunits. The aim of this review is to establish that glutamate neurotransmission and polyaminergic system play a fundamental role in the onset of anxiety-related disorders. This may open the way for new drugs that may help to treat these conditions.

Contents

Abbreviations: ACPC, 1-aminocyclopropanecarboxylic acid; AMPARs, AMPA receptors; AP5, DL-2-amino-5-phosphonopentanoic acid; AP7, DL-2-amino-7-phosphonoheptanoic acid; BA, basal amygdala; BLA, basolateral amygdala nucleus; CA, central amygdala; CCF, cue-conditioned freezing; CCK-4, cholecystokinin tetrapeptide; CER, conditioned emotional response; CFC, contextual fear conditioning; CLS, conditioned lick suppression test; CNS, central nervous system; CPPG, alpha-cyclopropyl-4-phosphonophenylglycine CPP, 3-(2-Carboxypiperazin-4-yl)propyl-1-phosphonic acid; dlPAG, dorsal portion of periaqueductal gray matter; EPM, elevated plus maze; FPS, fear-potentiated startle; GAD, generalized anxiety disorder; GABA, γ-aminobutyric acid; GPCRs, G-protein coupled receptors; ICMs, intercalated cell masses; iGluR, ionotropic glutamate receptors; GST, Geller–Seifter conflict test; LA, lateral amygdala; LD, light–dark test; LTP, long-term potentiation; L-SOP, L-serine-O-phosphate; MBT, marble burying test; MCPG, methylcarboxyphenylglycine; mGluR, metabotropic glutamate receptor; MPEP, 2-methyl-6-(phenylethynyl)pyridine; MTEP, 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine; NMDARs, N-methyl-D-aspartate receptors; nNOS, nitric oxide synthase; OCB, open channel blocker; OCD, obsessive–compulsive disorder; PAG, periaqueductal gray; PAGO, partial agonist; PHCCC, (−)-N-phenyl-7-(hydroxyimino) cyclopropa[b]chromen-1a-carboxamide; PTSD, posttraumatic stress disorder; SIH, stress-induced hyperthermia; SIT, social interaction test; (S)-3,4-DCPG, (S)-3,4-dicarboxyphenylglycine ((S)-3,4-DCPG); SSRI, serotonin reuptake inhibitor; Trans-ACPD, 1-aminocyclopentane-trans-1,3-R-dicarboxylic acid; 4PT, 4-plate test; USV, ultrasonic vocalization; VCT, Vogel Conflict Test.

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1. Introduction

Fear and anxiety are crucial and adaptive components of the overall behavioral and autonomic response to potentially threatening situations, namely stress response. However, fear responses may become maladaptive and undergo a process of generalization by which any contextual stimulus can become linked to persistent fear and anxiety symptoms (Garakani et al., 2006a).

Anxiety and stress-related disorders, including posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), obsessive–compulsive disorder (ODC), social and specific phobias, and panic disorder, are a major public health issue. In the United States, anxiety disorders are the most prevalent of psychiatric disorders affecting 15.7 million people each year, and 30 million people at some point in their lives (Lepine, 2002). The European Study of the Epidemiology of Mental Disorders (ESEMeD) estimated that only 20.6% of people suffering from an anxiety disorder sought help from health care services; of these, 20.7% received no treatment (Alonso and Lepine, 2007).

To date, anxiety disorders have been treated with widely prescribed drugs that target γ-aminobutyric acid (GABA) and serotonergic neurotransmission, like benzodiazepines and selective serotonin uptake inhibitors (SSRIs) respectively (American Psychiatric Association, 2006; Garakani et al., 2006a). Although the efficacy of these treatments has proven to be very high in many sufferers, there are several drawbacks which should be considered. Adverse effects include cognitive dysfunction, weight gain, sexual dysfunction, sedation, dependence and withdrawal (Cortese and Phan, 2005). Additionally, many patients are non-responders to these treatments (Hammer et al., 2004). As a result, many sufferers relapse and noncompliance places a strain on scarce resources. By examining in greater detail the mechanisms involved in fear and anxiety we will be able to develop more effective treatments to a wider range of patients.

In the last two decades, the role of glutamate in fear conditioning and anxiety-related disorders is becoming more recognized. There are, however, several drugs that target glutamate receptors that are going through clinical trials (Bergink et al., 2004; Cortese and Phan, 2005; Krystal et al., 2010; Palucha and Pilc, 2007; Wieronska and Pilc, 2009). Research is also ongoing in several molecules that naturally modulate glutamatergic neurotransmission, such as polyamines (Fiori and Turecki, 2008; Gomes et al., 2010; Vaquero-Lorenzo et al., 2008). Polyamines may have a significant influence on the molecular mechanisms related to associative fear memory (Gomes et al., 2010).

The aim of this review is to establish that glutamatergic neurotransmission and the polyaminergic system play a fundamental role in the onset of anxiety-related disorders. First, we will describe the animal models used to study fear and anxiety response so that it may be extrapolated into a human context. We will then go on to consider in greater detail the role of glutamatergic neurotransmission, and its consequent regulation through polyamine metabolism, in associative fear memory formation.

2. Fear conditioning and fear extinction: animal models of anxiety

There are no biological markers of anxiety disorders available for use in clinical practice. Therefore, diagnosis relies on clinical interviews. Surrogate markers of anxiety, such as hyperthermia, tachycardia, increase in blood pressure, and raised cortisol secretion could be useful when evaluating anxiety. However, such peripheral autonomic parameters may not accurately reflect the cerebral mechanisms underlying anxiety and stress response. Therefore, in order to explore potential mechanisms of anxiety, two different types of tests have been developed: natural behavior tests and tests based on classical fear conditioning (see: Table 1).

Natural behavior tests examine the animal's natural response to stressful stimuli. As an example of typical natural behavior tests, the elevated plus maze noncompliance measures the conflict between an animal's natural tendency to explore and the innate fear of heights and open spaces (Blair et al., 2001; Pellow and File, 1986).

On the other hand, conditioned stress tests are based on a common process of associative learning. For example, fear conditioning measures how a neutral stimulus (conditioned stimulus, CS) that does not naturally cause a behavioral response, is paired with a strong aversive stimulus (unconditioned stimulus, US). As a result of this pairing, the conditioned stimulus (CS) acquires the ability to generate endocrine, autonomic, and behavioral responses that are typically expressed in the presence of danger (conditioned response, CR) (Blair et al., 2001). For example, in the Vogel Conflict Test (VCT), previously water-deprived rodents are exposed to punishment with a mild intermittent aversive electrical stimulus whenever they drink (Millan and Brocco, 2003). This is the context in which fear-response is studied.

Fear conditioning is present across animal species, where the same primitive neural circuits may be involved. Hence, fear conditioning has gained much attention as a useful animal model for the investigation of the neurobiological components of learning and stress-related memory (Blair et al., 2001; Rogan et al., 2001), because drugs affecting fear conditioning may have potential utility for the treatment of anxiety-related disorders (Millan and Brocco, 2003).

Once fear conditioning has been learned, it can be very difficult to reverse. Nevertheless, fear conditioning and its associated fear responses can be inhibited by an active process known as fear extinction (Stahl, 2008). Fear extinction occurs when an animal is repeatedly exposed to the CS in the absence of the US. That leads to a decline in the magnitude of the fear-associated response. Like other forms of learning and memory, fear extinction involves encoding, consolidation, retrieval and expression stages, which are mediated by different neural mechanisms (Myers et al., 2011).

Unlike fear conditioning, fear extinction is a labile process that tends to reverse over time. For instance, exposure to the CS alone, after the extinction process has been established, leads to the reappearance of the CR, a phenomenon called reinstatement (Myers et al., 2011). Also, fear conditioning can return if the old fear stimuli are presented in a

Table 1
A summary of the main experimental models of anxiety used in animals — modified from Millan (2003).

Long term anxious states (Trait)
1. Rodent strains displaying high or low anxiety
2. Inter-individual differences within a defined strain
3. Chronic exposure to fear-provoking stimuli
4. Genetic models: transgenic and knock-out models

Acute anxious states (State)
A. Unconditioned
1. Exploration (avoidance, conflict)
Elevated plus-maze (open arms vs closed arms)
Light–dark box (light chambers vs dark chambers)
Open field (central squares vs peripheral squares)
Neophobia/emergence test (novel object)
2. Interaction based
Separation-induced ultrasonic vocalizations
Resident intruder
Active social interaction (unfamiliar rat pairs)
3. Acute response to aversive stimuli (environment or brain stimulation)
Freezing
Ultrasonic vocalization
Startle
Autonomic response (heart rate, arterial pressure, endocrine secretion)
4. Defensive behavior to threatening stimuli
Fear/defense battery
B. Conditioned
1. Non-conflict procedures
Fear-induced freezing
Fear-induced startle
Fear-induced ultrasonic vocalizations
Fear-induced ultrasonic vocalizations
Shock-burying probe (burying of aversive object)
1. Conflict procedures
Vogel Conflict Test
Geller–Seifter (operant, lever-pressing for reward)
Conditioned suppression (no punishment during test session)
Safety-signal withdrawal (no punishment during test session)
Conditioned place aversion
3. Drug discrimination
Anxiogenic drugs

different context from the one in which extinction was learned, a process termed renewal (Myers et al., 2011).

Currently there are many drugs targeting glutamate neurotransmission that affect fear conditioning and extinction, such as AP5, AP7, and D-cycloserine (DCS). The question is whether these drugs may also be used to treat anxiety-related disorders.

3. Neurobiological basis of stress response and anxiety

The anatomic core of fear and anxiety is represented by several interrelated limbic structures: certain nuclei of the amygdaloid complex, the septo-hippocampal system, the periaqueductal gray matter and some areas in the hypothalamus (Charney and Deutch, 1996). These brain structures evaluate the extent to which environmental situations are threatening to the individual and help elaborate the appropriate patterns of defense (Millan, 2003).

The amygdaloid complex and its efferent neuronal projections are involved in the acquisition, consolidation and expression of conditioned fear (Pape and Pare, 2010; Pare et al., 2004; Walker and Davis, 2002) and may have a role in the pathogenesis of anxiety-related disorders (Davidson, 2002). Animal models have showed that electrical activation of the amygdala leads to a pattern of behavioral responses that resemble fear responses caused by stressful stimuli. On the other hand, experimental lesions of the lateral amygdala (LA) or central amygdala (CA) can abolish the acquisition of long-term contextual fear memory (Amorapanth et al., 2000; Blair et al., 2005; Goosens and Maren, 2001; Maren, 1996; Nader et al., 2001; Wallace and Rosen, 2001). Similarly, inhibition of LA and adjacent areas with the GABA receptor agonist muscimol during fear conditioning may impair the acquisition of auditory CS-elicited fear responses (Wilensky et al., 2006). Lesions of the basal amygdala (BA) may also produce a similar effect on fear response (Ledoux, 2003; Ledoux, 2007; Morrison and Salzman, 2010; Onishi and Xavier, 2010).

Neurons from the LA receive inputs from both sensory cortex and thalamus (Blair et al., 2005). During fear conditioning, when a weak input reaching those neurons is paired with the activation caused by a stronger second signal, repetition strengthens that synaptic transmission (Collins and Pare, 2000; Repa et al., 2001; Rogan et al., 1997). In a cellular perspective, this can be explained as the result of a process of active synaptic enhancement (Blair et al., 2005). As an example, experimental interference with macromolecular synthesis in the LA and surrounding areas prevents the consolidation of long-term memory in the associative auditory fear conditioning paradigm (Nader et al., 2000a; Schafe and Ledoux, 2000b). Thus, in the fear conditioning paradigm, the US leads to a change in the way the brain processes the CS (Millan and Brocco, 2003).

Though fear-extinction can suppress the fear-associated response, it does not seem to remove the synaptic changes acquired during fear-conditioning. Thus, fear extinction involves new learning and new synaptic changes in the amygdala (Myers et al., 2011), including downstream changes in second messenger's phosphorylation status and in gene expression patterns within basolateral amygdala nucleus (BLA) (Herry et al., 2008; Myers et al. 2011).

Fear-extinction learning and memory process, as well as its modulation by context, involves three main components: the amygdala, medial prefrontal cortex (mPFC), and hippocampus (Myers et al., 2011; Quirk and Mueller, 2008). Fear-extinction takes place when inputs from hippocampus and mPFC activate glutamatergic neurons in the BLA that synapse on an inhibitory GABAergic interneurons located within the intercalated cell masses (ICMs) of the amygdala, that gate the impulse from the BLA to the CA. In this context, fear-extinction predominates over fear-conditioning when synaptic strengthening in this new circuit is able to produce an inhibitory GABAergic drive strong enough to overcome the excitatory glutamatergic drive associated with a pre-existing fear conditioning circuitry (Stahl, 2008).

4. Glutamate in anxiety and stress-response

Several lines of evidence suggest that limbic glutamatergic neurotransmission plays a pivotal role in the pathogenesis of anxiety disorders (Bergink et al., 2004; Garakani et al., 2006b; Millan, 2003; Vaquero-Lorenzo et al., 2008). Firstly, amygdalar and hippocampal NMDA and metabotropic glutamate receptors are involved in the mechanisms related to fear-conditioning and inhibitory-avoidance memory formation (Bauer et al., 2002; Fanselow et al., 1994; Fendt, 2001; Lee and Kim, 1998; Rogan et al., 1997; Rubin et al., 2004a; Walker and Davis, 2002). Secondly, acute stress enhances glutamate release in the amygdala (Reznikov et al., 2007). Thirdly, NMDARs control neurons secreting corticotrophin releasing factor (CRF) in central amygdala nucleus (Cratty and Birkle, 1999; Shepard et al., 2000) and exert a significant influence upon the activity of monoaminergic pathways (Millan, 2002).

Glutamate receptors seem to play an important role in fear-mediated learning, affecting both hippocampal-dependent associative learning and amygdala-dependent emotional processing during and after a stressful event (Nair and Singh, 2008). Amygdalar and hippocampal NMDARs are involved in the acquisition and expression of contextual and fear conditioning (Cortese and Phan, 2005).

4.1. Glutamate pharmacology

Glutamate is the main excitatory neurotransmitter in the human Central Nervous System (CNS). Glutamate has been involved in many

biological processes, such as neurodevelopment, learning and memory formation (possibly through long-term potentiation and depression) (Barkus et al., 2010; Kew and Kemp, 2005). Moreover, glutamate may have a pivotal role in several psychiatric conditions (such as schizophrenia, mood disorders and anxiety) (Vaquero-Lorenzo et al., 2008) and in neurodegenerative disorders (Alzheimer's disease and Huntington's disease).

Glutamate can exert its actions through two different types of receptors: ligand-gated ion channel receptors (ionotropic) and G-protein-coupled metabotropic receptors. Ligand-gated ion channel receptors consist of N-methyl-D-aspartate receptors (NMDARs), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPARs), and kainate receptors (KARs) (Kew and Kemp, 2005) (see: Fig. 1). This group mediates fast excitatory neurotransmission (Hirsch et al., 1997).

On the other hand, three metabotropic glutamate receptor types have been described: group I (mGluR1 and mGluR5), mainly postsynaptic, coupled to the activation of phospholipase-C (Giouzeli et al., 2004); group II (mGluR2 and mGluR3), both pre- and postsynaptic; and group III (mGluR4, mGluR6, mGluR7 and dmGluR8). Both groups II and III are coupled to inhibition of adenylyl cyclase (Wieronska and Pilc, 2009). Metabotropic glutamate receptors mediate slow glutamate neurotransmission (Krystal et al., 2010; Wieronska and Pilc, 2009).

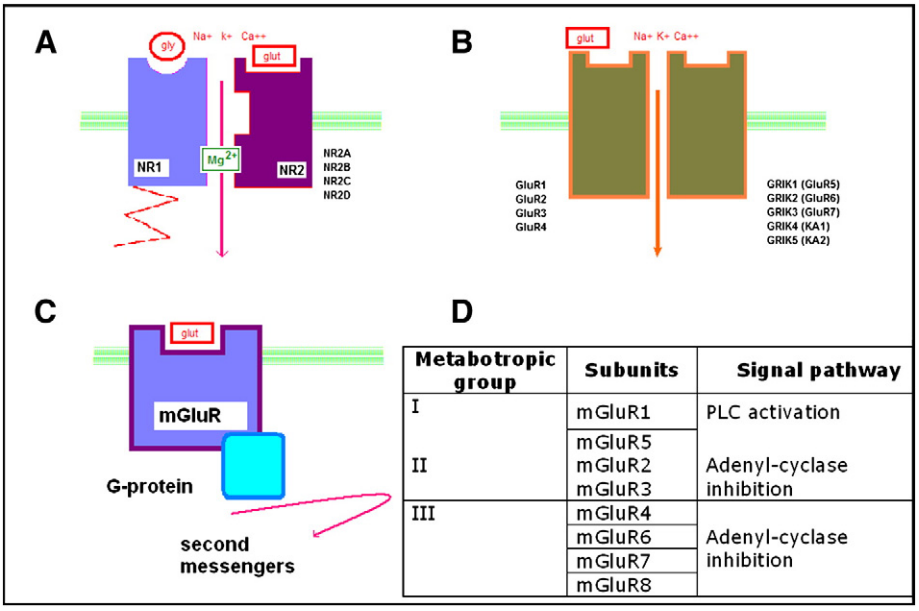
Each NMDAR complex consists of four (occasionally five) subunits: two NR1 subunits (generated by alternative splicing of a single gene, NR1), and two or three NR2 subunits (coded by four related genes, NR2 A–D). Recently, a third type of NMDA receptor subunit (NR3), which dramatically reduces ion permeability, has been described (Konradi and Heckers, 2003; Loftis and Janowsky, 2003; Mueller and Meador-Woodruff, 2003; Mueller and Meador-Woodruff, 2004; Nishi et al., 2001). This situation leads to an enormous heterogeneity in terms of neurochemical modulation profiles (Riaza Bermudo-Soriano et al., 2007).

Non-NMDA ionotropic receptor complexes are tetramers formed by the addition of subunits GluR1-4, for AMPARs, and GluR5-7 (low-affinity for glutamate, GRIK1-3) and KA1-2 (high-affinity for glutamate, GRIK4 and 5) for kainate receptors. AMPARs are primarily postsynaptic, and KARs can be both post- and presynaptic, regulating glutamate release (Frerking and Nicoll, 2000; Konradi and Heckers, 2003; Lerma, 2001; Lerma et al., 2001).

Both ionotropic and metabotropic glutamate receptors are distributed throughout the brain in a similar pattern. Limbic and paralimbic regions (hippocampus, amygdala, orbitofrontal cortex, anterior cingulated cortex, medial prefrontal cortex and insula), which have been extensively linked to stress-response and anxiety-related disorders, are abundantly innervated by glutamatergic pyramidal cells. Glutamate pyramidal cells in the PFC sent afferents to several limbic regions, particularly to hippocampus and amygdala (Myers et al., 2011). Moreover, up to 85–95% of the neurons in BLA are glutamatergic and project to ventral striatum and PFC. Immunochemistry studies have revealed that NR1, NR2A, NR2B, and, possibly, NR2C and NR2D may be primarily located in cortical layers II/III, V, VI and IV. AMPARs are mainly expressed in layers II/III and V–VI. Both NMDA and AMPA receptors are also expressed in astrocytes, a cellular type tightly linked to the control of glutamatergic neurotransmission (Hicks and Conti, 1996) (Fig. 2).

Several factors regulate the activity of ionotropic glutamate receptors. Activation of NMDAR complex needs two molecules of glutamate (acting on the NMDA site of NR2), and two molecules of glycine (acting on the glycineB site of NR1), while AMPA/kainate receptors are glycine-independent (Konradi and Heckers, 2003). The effects of post-translational modifications and the modulatory effects by Mg^{2+}, Zn^{2+}, H^{+}, histamine, araquidonic acid, steroids, citoeschelleton protein actin, phosphorylation status, redox status and polyamines, have been extensively studied (Ekegren, 2005; Williams, 1997a; Williams, 1997b).

At resting membrane potential, NMDARs are normally blocked by Mg^{2+}. This block is removed during membrane depolarization of the postsynaptic cell, leading to the activation of the receptor complex. However, the NMDAR's channel can only be opened when presynaptically-released glutamate is bound to the receptor if Mg^{2+} block has



Metabotropic group	Subunits	Signal pathway
I	mGluR1	PLC activation
II	mGluR5 mGluR2 mGluR3	Adenyl-cyclase inhibition
III	mGluR4 mGluR6 mGluR7 mGluR8	Adenyl-cyclase inhibition

Fig. 1. Glutamate receptors. (A) NMDARs are formed by 2 NR1 and 2 NR2 subunits. NR1 subunits are coded by a single gene generating 8 splice variants. In contrast, each NR2 subunit NR2 (A–D) is coded by a different gene. Under physiological circumstances, Mg^{2+} blocks NMDAR's pore. Glutamate released at the synaptic cleft may be insufficient to repeal Mg^{2+}. In contrast, concurrent membrane depolarization may be able to expel Mg^{2+}, leading to cation entry through the pore (Na^{+}, K^{+}, y Ca^{2+}). Glycine coactivation is necessary for NMDARs to be opened. (B) AMPARs and KARs are made up of 4 subunits (GluR1-4 in AMPARs, and GRIK1-5 in KARs). In this case, glutamate release into the synaptic cleft is enough to open AMPAR and KARs. (C) Metabotropic receptors (mGluR) are not directly coupled to cationic channels. In contrast, mGluR activation may exert its effects through G-coupled protein and through second messenger pathways. (D). Group I mGluRs may activate phospholypase-C (PLC) (Giouzeli et al., 2004), while group II and group III may inhibit adenyl-cyclase (AC) — Modified from (Konradi and Heckers, 2003; Riaza Bermudo-Soriano et al., 2007).

already been removed (postsynaptic depolarization combined with presynaptic stimulation). Since NMDA and AMPA receptors are co-expressed in the same locations, the activation of AMPARs, as a result of glutamate release, can generate excitatory postsynaptic potentials (EPSPs) that may be detected by NMDARs (Hestrin, 1992a; Hestrin, 1992b; Hicks and Conti, 1996). Therefore, NMDARs may act as synchrony detectors (Blair et al., 2001). This process may be particularly relevant during synaptogenesis and neural circuitry plasticity (Konradi and Heckers, 2003).

Glutamate not only exerts its effects through direct activation of glutamate neurotransmission but it also modulates the release of other neurotransmitters involved in stress-response, such as serotonin (Becquet et al., 1993; Cheramy et al., 1986), dopamine (Jedema and Moghddam, 1996), monoamines and GABA (Cortese and Phan, 2005).

4.2. Hypothalamic–pituitary–adrenal (HPA) axis and glutamate

The hypothalamic–pituitary–adrenal (HPA) axis is the core structure regulating human stress response. Cortisol release from adrenal glands is a normal reaction to everyday stress. However, excessive cortisol release, due to long-term chronic activation of the HPA axis, may lead to detrimental effects on hippocampal neurons (Duman et al., 1997; Ernst et al., 2009; McKinnon et al., 2009; Sapolsky, 2003).

Chronic stress and the resultant increase in circulating cortisol may lead to glutamate-mediated neurotoxicity in hippocampus (Sapolsky, 2003a). In particular, animal paradigms that replicate chronic stress exposure, like immobilization and the forced swimming test, lead to a significant increase in cortisol release by adrenals and glutamate release and uptake in hippocampus and prefrontal cortex (PFC) (Moghaddam, 1993). Moreover, chronic stress has demonstrated to increase AMPA gene expression in hippocampus, making this region particularly vulnerable to neurotoxicity (Schwendt and Jezova, 2000).

Stress-induced brain changes may be region-specific (Cortese and Phan, 2005). Chronic stress may lead to hippocampal neuronal atrophy and death, reduced regeneration, reduced dendritic branching, and may be able to impair hippocampal-dependent spatial learning tasks (i.e., Morris water maze, and radial arm maze) (Isgor et al., 2004; Luine et al., 1994). On the other hand, chronic stress has been associated with hypertrophy and increased dendritic neuronal branching in BLA (Vyas et al., 2002) and in the bed nucleus of stria terminalis (Vyas et al., 2003), and, interestingly, may enhance the acquisition of amygdala-dependent aversive learning, such as fear conditioning (Conrad et al., 1999; Cortese and Phan, 2005; Shors et al., 1992; Shors and Mathew, 1998).

Stress may lead to changes in glutamatergic neurotransmission (Nair and Singh, 2008). For example, stress caused by single immobilization in rats leads to an increase in the levels of mRNA coding for the NR1 subunit in the paraventricular nucleus (PVN) of hypothalamus (Ziegler et al., 2005), and raised NMDAR binding in

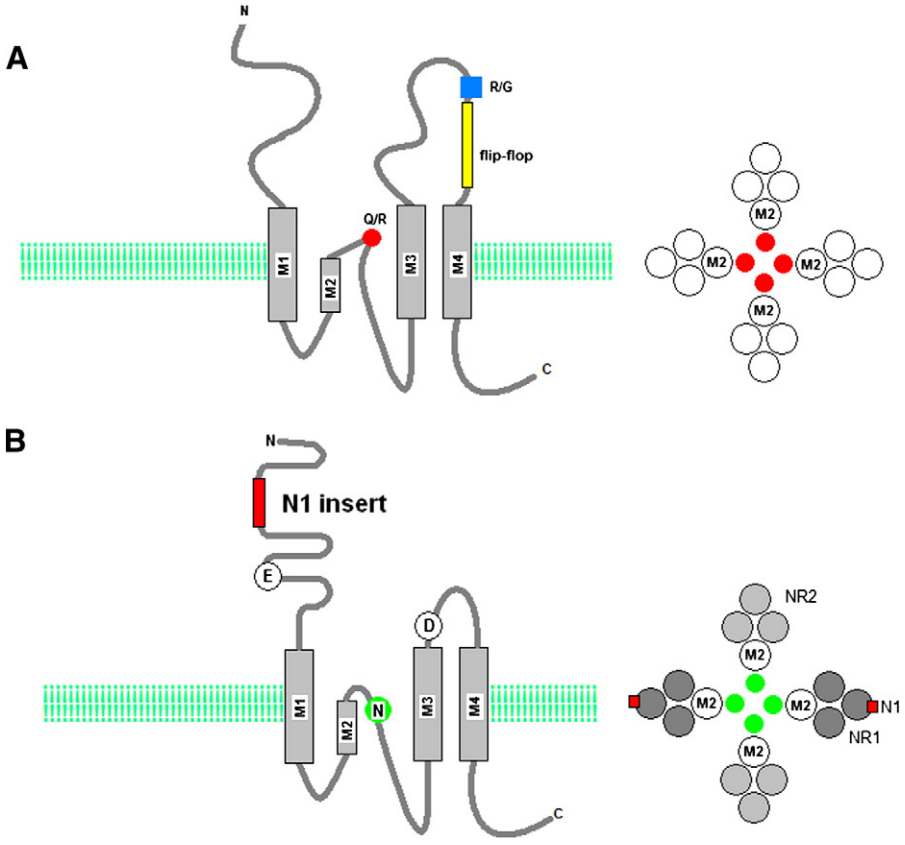


Fig. 2. Ionotropic glutamate receptors. (A) AMPARs are made up of 4 or 5 subunits. Each subunit has 4 transmembrane domains (M1-4), a cytosolic, and an extracelular region. These subunits (GluR1, 2, 3, and 4) may show two splice forms: flip and flop. Flop subunits desensitize quicker than flip subunits. AMPARs containing GluR2 subunits exhibit limited Ca^{2+} and are less likely to be modulated by polyamines than those formed by GluR1, GluR3 and GluR4 (Jayakar and Dikshit 2004a). M2 helix, which is located inside the channel's pore, may undergo the postraslational substitution of glutamine (Q) for arginine (R), which leads to a reduction of channel's conductance. This arginine at Q/R position may repeal spermine. AMPAR-integrating subunits may also suffer another postraslational edition (arginine to glutamine, R/G) near flip–flop domain; glutamine-edited AMPA subunits lead to a quick desensitization. (B) NMDARs are formed by 4 subunits: 2 NR1 and 2 NR2. Some NR1 subunits contain a highly cationic 21-aminoacid sequence (N1 insert). NR1 subunits lacking N1 insert show high sensibility to spermine modulation. Several positions that may affect NMDARs' sensibility to spermine and pH, such as Glu-342 (N-Terminal), and Asp-669 (E), have also been included in the figure. Interestingly, blockade by Mg^{2+} or by spermine may be determined by an asparagine residue in M2 domain (Williams, 1997b; Riaza Bermudo-Soriano and Chinchilla Moreno, 2007).

hypothalamus (Herman et al., 2000). Similar changes may be observed after exogenous corticosterone administration (Brann and Mahesh, 1997c). However, pretreatment with the NMDAR antagonist dizocilpine reduced ACTH secretion caused by immobilization stress, suggesting NMDAR is involved in the neurobiological response to stress (Nair and Singh, 2008).

Glutamate and the HPA axis are interconnected. Actually, microinjections of glutamate into the rat PVN resulted in an increase of ACTH and corticosterone levels, an increase in CRF release, but also increased the amount of c-Fos positive CRF neurons, and elevated the cortex arousal (measured with electrocorticogram) (Brann and Mahesh, 1997b; Kita et al., 2006). Furthermore, increase in glutamate-induced release of CRF and levels of corticosterone are NMDAR-mediated (Brann and Mahesh, 1997a; Mathew et al., 2001), since they may be abolished when NMDAR antagonist is applied (Joanny et al., 1997).

4.3. Glutamate neurotransmission is involved in the synaptic mechanisms underlying associative fear learning

This section assesses the role of glutamate neurotransmission in the neurobiological mechanisms underlying fear-related memory.

Neural changes associated with fear conditioning in the LA may result from a process of associative long-term potentiation (LTP) (Chapman et al., 1990). When drugs interfering with LTP are injected into the LA both acquisition and expression of fear conditioning are disrupted, what suggests that the CS–US association may be possibly due to an active process of fear memory storage (Blair et al., 2001).

The short-term fear memory process taking place in LA seems to depend on calcium (Ca^{2+}) (Malenka, 1991). In the fear-conditioning model, the CS is able to induce excitatory postsynaptic potentials (EPSPs) at sensory input synapses located on the LA pyramidal neurons. Depolarization induced by US in the same LA neurons leads to raised Ca^{2+} influx through NMDARs and may finally cause the LA neuron to fire action potentials. Those action potentials may also propagate backwards into dendrites, converging with the EPSPs triggered by other inputs, what facilitates Ca^{2+} entry through voltage-gated calcium channels (VGCCs). Experimental blockade of NMDA receptors by the antagonist AP5 blocks fear acquisition and expression (Jasnow et al., 2004; Zhao et al., 2005). Ca^{2+} entry through NMDARs (Malenka and Nicoll, 1999) may be enough to produce synaptic changes associated with short-term fear memory, however, Ca^{2+} flux through both NMDARs and VGCCs may be mandatory to activate the molecular mechanisms that lead to long-term memory (Bauer et al., 2002; Blair et al., 2001; Blair et al., 2005; Rodrigues et al., 2004). Although LA may not be the only site where such changes occur (Poremba and Gabriel, 2001), it is very likely the site where changes relevant to behavioral fear learning come about (Blair et al., 2001; Blair et al., 2005).

Hebbian LTP has been extensively studied as a model of associative memory formation (Huang et al., 2000a; Martin and Shapiro, 2000; Rogan et al., 2001) and several molecular mechanisms for the so-called “coincidence detection” have been described (Tsien, 2000). High-frequency (tetanic) stimulation of afferents to the hippocampus leads to LTP (Bliss and Lomo, 1973). LTP may only occur in active presynaptic afferents (Lynch et al., 1977) and is considered to be associative (the coactivation of strong and weak inputs onto the same neuron can lead to strengthening of the weak inputs) (Lev and Steward, 1979). Tetanic stimulation of the presynaptic afferents may be so strong that it will be able to simultaneously induce a robust depolarization of the postsynaptic neuron (Blair et al., 2001). Alternatively, LTP can also be obtained by paired simultaneous activation of the presynaptic and the postsynaptic neurons (Magee and Johnston, 1997b). Although much of our understanding of the neurobiological mechanisms of Hebbian LTP has been obtained from studies developed in neocortex and hippocampal pyramidal cells (Bliss and Collingridge, 1993; Malenka and Nicoll, 1999), they may also be applied to fear conditioning taking place in the amygdala (Blair et al., 2001; Blair et al., 2005).

Synaptic enhancement underlying associative LTP depends on Ca^{2+} influx into the postsynaptic cell (Malenka, 1991). This Ca^{2+} influx leads to the activation of intracellular signals that will finally increase glutamate-evoked currents, via Ca^{2+}-calmodulin-kinases pathway, NMDA receptor's phosphorylation, and through raised AMPAR expression (Isaac et al., 1995; Konradi and Heckers, 2003; Liao et al., 1995). Two different receptors are believed to explain the fact that Ca^{2+} influx only occurs when the pre-and postsynaptic cells are concurrently activated, and not when either neuron is activate alone (Blair et al., 2001): NMDARs (Malenka and Nicoll, 1999) and VGCCs (Sabatini and Svoboda, 2000a).

Both NMDARs and VGCCs might be able to function as Hebbian coincidence detectors (Blair et al., 2001). VGCCs are generally located in spines and dendrites adjacent to glutamatergic synapses (Sabatini and Svoboda, 2000b). NMDA receptor's induced Ca^{2+} influx may be enhanced by the activation of VGCCs (Johnston et al., 1999). L-type VGCCs show a high activation threshold, so they are opened only during a robust postsynaptic depolarization. Such condition may only be reached when back-propagating action potentials (BPAPs) get access to dendrites of the postsynaptic neurons (Johnston et al., 1999). Those BPAPs may then be amplified when they hit the EPSPs (Stuart and Hausser, 2001), giving place to a higher and confined increase in Ca^{2+} influx and LTP in active synapses (Blair et al., 2001; Magee and Johnston, 1997a; Stuart and Hausser, 2001).

Both in vitro and in vivo experimental models have suggested that Hebbian LTP, mediated by the activity of NMDAR and VGCCs in LA, may account for fear conditioning (Blair et al., 2001). Pyramidal neurons located in LA receive excitatory afferents from cortex and auditory thalamus. Those cells express both NMDARs and AMPARs on their dendrites and spines (Ledoux, 2007; Ledoux and Farb, 1991), which may be contributing to EPSPs elicited after presynaptic stimulation of auditory thalamic afferents to LA (Weisskopf and Ledoux, 1999). In that context, fear conditioning depends upon a LTP-dependent strengthening of those synapses (McKernan and Shinnick-Gallagher, 1997; Rogan and Ledoux, 1995).

LTP can be blocked by both NMDAR and VGCC antagonists (Bauer et al., 2000). Blocking of NMDAR with antagonist APV (Bauer et al., 2000; Huang et al., 2000b) or by Ca^{2+}-chelator BAPTA (Huang and Kandel, 1998), during tetanic stimulation, is able to abolish LTP. A similar but less intense phenomenon can be observed in the paired stimulation model of LTP in LA (Huang and Kandel, 1998). In paired-induced LTP model, neither NMDAR antagonist MK-801 nor APV disrupted LTP, suggesting that other mechanisms different from NMDARs activation may be involved (Weisskopf and Ledoux, 1999). In contrast, LTP was abolished when either BAPTA, L-type VGCC antagonist nifedipine, or VGCC antagonist verapamil was added (Bauer et al., 2000; Weisskopf and Ledoux, 1999).

Fear conditioning depends on NMDAR and VGCC (Blair et al., 2001). NMDAR antagonist APV into LA and adjacent basal nucleus impairs the acquisition of new fear responses, including auditory fear conditioning (Lee and Kim, 1998), contextual fear conditioning (Fanselow et al., 1994; Maren, 1996a), and fear-potentiated startle (Miserendino et al., 1990; Walker and Davis, 2000). Besides, APV also prevents the expression of previously learned fear (Lee and Kim, 1998; Maren et al., 1996; Fendt, 2001; Lee et al., 2001), although some inconsistent results have also been reported (Walker and Davis, 2000a). Nifedipine has demonstrated to be able to disrupt fear conditioning (Weisskopf and Ledoux, 1999), while L-type VGCC antagonist verapamil may interfere with the acquisition, but not the expression, of previously learned conditioned fear (Bauer et al., 2000; Blair et al., 2001).

Memory storage and underlying synaptic plasticity processes necessary for fear conditioning may depend on the function of NR2B subunits (Day et al., 2010). NDMARs incorporating NR2B subunits

produce longer EPSPs than those incorporating only NR2A subunits (Monyer et al., 1994). Experimental overexpression of the NR2B subunit in hippocampus enables LTP and enhances learning of hippocampal-dependent tasks (Tang et al., 1999). Hippocampal LTP leads to increased tyrosine phosphorylation at the NR2B subunits (Rosenblum et al., 1996; Rostas et al., 1996). NR2B subunits in the insular cortex have been associated with memory for novel tastes (Rosenblum et al., 1997). Interestingly, a single minute glutamate release can activate NR2B-containing NMDARs for up to 300 ms (Flint et al., 1997; Monyer et al., 1994). Thus, even a low frequency of glutamate release could be enough to maintain glutamate persistently bound to NMDARs (especially NR2B-containing NMDARs) throughout the CS when LA cells are being depolarized by the US (Blair et al., 2001).

NR2B subunit in the BLA is necessary for the acquisition of conditioned fear (Day et al., 2010). While nonselective NMDAR antagonists block NMDARs in general, independently of their heteromeric composition, ifenprodil can selectively block NR2B (Rodrigues et al., 2001). Unlike the effects of APV, infusion of ifenprodil into LA prior to testing blocks the acquisition, but not the expression, of tone-conditioned fear, suggesting that NR2B subunits may have a central role in synaptic plasticity (Blair et al., 2001).

Accordingly to what has been explained before, when recently CS-evoked EPSP and BPAP collide in LA pyramidal cells, Ca^{2+} influx (through NMDARs and VGCCs) activates second messenger pathways, including the mitogen-activated protein kinase (MAPK) pathway and protein kinase A (PKA) pathway (Bourtchouladze et al., 1998; Schafe et al., 1999b, 2000), that lead to raised AMPARs permeability and synapse strengthening. Such coincidence allows CS to exert a significant action over effector circuits controlling stress response (Blair et al., 2001). Although short-term fear memories are immediately stored by synaptic changes taking place in LA when US and CS overlap, long-term memories involve protein synthesis to consolidate those immediate short-term synaptic enhancements into permanent synaptic modifications (Blair et al., 2001; Nader et al., 2000b; Schafe et al., 1999, 2000; Schafe and Ledoux, 2000a).

4.4. Animal models show a link between glutamate neurotransmission and anxiety

Animal models have paved the way for a better understanding of the mechanisms underlying stress-response and anxiety (Cortese and Phan, 2005).

A growing body of evidence suggests that drugs increasing the excitability of output neurons in BLA enhance aversive conditioning, whereas those treatments that are able to decrease the excitability of these neurons may exert anxiolytic effects (Ledoux, 1994; Maren, 1996; Sajdyk and Shekhar, 1997b). This later phenomenon may be achieved by either rising GABA neurotransmission or by decreasing the excitatory glutamatergic tone in the BLA. Moreover, both GABAergic (inhibitory) and glutamatergic (excitatory) neurotransmission may be modulated by presynaptic excitatory amino acid receptors, apparently through activation of mGluRs autoreceptors (Bergink et al., 2004; Palucha and Pilc, 2007; Salt and Eaton, 1995; Wieronska and Pilc, 2009). In consequence, pharmacological agents that block glutamate output in BLA may be of therapeutic use for treating anxiety-related disorders (Bergink et al., 2004).

Sleep deprivation, which has been demonstrated to induce panic attacks in humans with panic disorder and to worsen generalized anxiety disorder, may affect glutamate metabolism in animal's brain cortex. A study that used the sleep deprivation model in rats measured glutamate and aspartate in the medial prefrontal cortex, measured by magic-angle spinning proton magnetic resonance spectroscopy (^{1}H-MRS) (Uhde et al., 2004). This study found a significant increase in the levels of glutamate and aspartate in the medial prefrontal cortex of those rats exposed to 6 h of sleep deprivation, compared with rats with normal sleep/wake cycles (Cortese and Phan, 2005). From a behavioral perspective, total sleep-deprived (SD) rats spent a more time in the open arms of the elevated plus maze (EPM) (reduced fear-like and increased risk-taking behaviors). This may be associated with a significant increase in thalamic and hippocampal glutamate levels. An inverse relationship between glutamate in the medial prefrontal cortex and risk taking in the EPM was observed (Cortese et al., 2010).

Stress may also affect glutamate metabolism in non-human primates. Magnetic resonance spectroscopic imaging studies have revealed that glutamate–glutamine-γ-aminobutyric acid (Glx) may be altered in response to stress (Mathew et al., 2003). Mother–infant macaque dyads reared on difficulty of food procurement, a method known to produce lasting stress-related behavioral and hormonal effects, showed increased Glx/creatinine compared with matched normal control subjects, at the age of 10. Although measures of Glx may be somewhat controversial, several studies suggest that variations in Glx may mainly reflect changes in glutamate levels (Bartha et al., 2000; Cortese and Phan, 2005; Kaiser et al., 2005; Ke et al., 2000). The meaning of these biological changes may seem somewhat dim.

Genetically-modified animals lacking glutamate receptors may be useful for the evaluation of anxiety-like behavior. Mice lacking the NR1 subunit of the NMDAR, specifically in the granule cells of the dentate gyrus, exhibit normal LTP in the CA1 region but dramatically reduced LTP in both the medial and lateral perforant path inputs to the dentate gyrus (Niewoehner et al., 2007). In addition, these dentate gyrus NR1 knockout mice exhibit a very selective impairment in short-term spatial working memory, and may also show less anxiety-like behavior (Niewoehner et al., 2007a). Recently, another mice line lacking the NR2B subunit of the NMDAR specifically from hippocampal granule and pyramidal cells in the dentate gyrus and CA1 subfields respectively, may be less prone to anxiety (Barkus et al., 2010; von et al., 2008).

Glutamate agonists and antagonists have been tested in different animal models of anxiety (Table 1). Two main paradigms may be distinguished, conditioned behavior models (that use conflict tests) and unconditioned behavior models (social interaction test, SIT, the elevated plus maze, EPM, the ultrasonic vocalization paradigm, USV and the acoustic startle paradigm, ASP) (Bergink et al., 2004; Millan, 2003).

A growing number of NMDAR antagonists, acting at different sites on the NMDAR, have been assessed using unconditioned tests of anxiety in rodents (for detailed information see: Table 2). For example, 3-(2-Carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP) increased social interaction and increased the time spent in the open arms of the elevated plus maze (EPM) in rats, what could be interpreted as a reduction in anxiety (Corbett and Dunn, 1993; Dunn et al., 1989a). The NMDAR competitive antagonist, AP5, has shown anxiolytic-like effects in several rodent studies of unconditioned anxiety (EPM and social interaction test, SIT), in amygdala (Sajdyk and Shekhar, 1997a), in medial septum (Elvander-Tottie et al., 2006), and in ventral hippocampus (Nascimento Hackl and Carobrez, 2007). However, in other studies AP5 injections have also shown no significant effects (Lehmann et al., 2000; Menard and Treit, 2000), or could even induce anxiety-like behaviors (Barros et al., 2000). Whereas AP5 injection in ventral hippocampus may be associated with an increase in the amount of time spent on the open arms of EPM (Nascimento Hackl and Carobrez, 2007), AP5 injections in dorsal hippocampus might have no significant effect (Barros et al., 2000; Nascimento Hackl and Carobrez, 2007; Padovan et al., 2000), suggesting functional dissociation between ventral and dorsal hippocampus (Barkus et al., 2010). AP5 injections have also shown anxiolytic-like effects in rat conditioned anxiety paradigms (Campeau et al., 1992; Fendt et al., 1996; Lehmann et al., 2000; Menard and Treit, 2000; Plaznik et al., 1994). Studies measuring the effect of AP7

Table 2
A summary of NMDA receptor pharmacology in animal models of anxiety.

Drug	Action	Animal model	Species (strain)	Route	Dose range	Effect	Reference
Competitive antagonists							
AP-5	*NMDAR antagonist*	EPM	Rat	i.c (amygdala)	2.5 μg	No significant effect	Lehmann et al. (2000)
		EPM	Rat	i.c (ventral hippocampus)	6 and 24 mmol	Anxiolytic	Nascimento Hackl and Carobrez (2007)
		EPM	Rat	i.c (dorsal hippocampus)	6 and 24 mmol	No significant effect	Nascimento Hackl and Carobrez (2007)
		EPM	Rat	i.c (dorsal hippocampus, CA1)	2.0–5.0 μg	No significant effect	Barros et al. (2000)
		EPM	Rat	i.c (BLA)	2.0–5.0 μg	No significant effect	Barros et al. (2000)
		EPM	Rat	i.c (medial septum)	5 μg	Anxiolytic	Elvander-Tottie et al. (2006)
		EPM	Rat	i.c (dorsolateral septum)	5 μg	No significant effect	Menard and Treit (2000)
		EPM	Rat	i.c (dorsal hippocampus)	10.0 nM	Anxiolytic	Padovan et al. (2000)
		SPA	Rat	i.c (central amygdala)	2.5 μg	Anxiolytic	Lehmann et al. (2000)
		FPS	Rat	i.c (caudal pontine reticular nucleus)	0.125–0.5 nmol	Anxiolytic	Fendt et al. (1996)
		FPS	Rat	i.c (amygdala)	2.5 μg	Anxiolytic	Campeau et al. (1992)
		SIT	Rat	i.c (BLA)	100 pM	Anxiolytic	Sajdyk and Shekhar (1997b)
		SBP	Rat	i.c (dorsolateral septum)	5 μg	Anxiolytic	Menard and Treit (2000)
		SPA	Rat	i.c (dorsolateral septum)	5 μg	Anxiolytic	Menard and Treit (2000)
AP-7	*NMDAR antagonist*	EPM	Rat	i.c (PAG)	0.2, 2.0 and 20.0 nM	Anxiolytic	Guimaraes et al. (1991)
		EPM	Rat	i.c (ventromedial PAG)	2.0 nM	Anxiolytic	Molchanov and Guimaraes (2002)
		VCT	Rat	i.c.v	0.5 μg	Anxiolytic	Plaznik et al. (1994)
		VCT	Rat	i.c (PAG)	0.4 μg	Anxiolytic	Molchanov and Guimaraes (2002)
		VCT	Rat	i.c (hippocampus)	0.5 μg	Anxiolytic	Jessa et al. (1995)
		VCT	Rat	i.c (dorsomedial nucleus of hypothalamus)	0.2 and 2.0 nM	No significant effect	Jardim and Guimaraes (2001)
		VCT	Rat	i.c (dorsomedial part of ventromedial hypothalamus)	0.2 and 2.0 nM	Anxiogenic	Jardim et al. (2005)
		VCT	Rat	I.c.v	0.5 μg	Anxiolytic	Plaznik et al. (1994)
CGP37849	*NMDAR antagonist*	VCT	Rat	i.p	1.25–5.0 mg/kg	Anxiolytic	Przegalinski et al. (1996)
		VCT	Rat	i.c (hippocampus)	0.01–1.0 μg	No significant effect	Przegalinski et al. (1996)
		VCT	Rat	i.p	1.0–2.5 mg/kg	Anxiolytic	Plaznik et al. (1994)
		VCT	Rat	i.p	2.5 mg/kg	Anxiolytic	Jessa et al. (1996)
CGP39551	*NMDAR antagonist*	VCT	Rat	i.p	5 mg/kg and 20 mg/kg	Anxiolytic	Plaznik et al. (1994)
LY235959	*NMDAR antagonist*	VCT	Rat	i.c (dlPAG)	4 nmol	Anxiolytic	Tonetto et al. (2009)
NPC 17742	*NMDAR antagonist*	G–S (modified)	Rat	i.p	4.0 mg/kg	Anxiolytic	Willetts et al. (1993)
Non-competitive antagonist							
MK-801 (Dizolcilpine)	*NMDAR antagonist*	SIT	Rat	i.p	0.03 mg/kg	Anxiolytic	Corbett and Dunn (1991)
		SIT	Rat	i.p	0.03 mg/kg	Anxiolytic	Corbett and Dunn (1993)
		VCT	Rat	i.p	0.0025 mg/kg	Anxiolytic	Jessa et al. (1996)
		VCT	Rat	i.p	0.005 and 0.01 mg/kg	Anxiolytic	Plaznik et al. (1994)
		VCT	Rat	i.c (hippocampus)	0.1 and 1.0 μg	Anxiolytic	Jessa et al. (1996)
		VCT	Rat	i.p	0.04, 0.01, or 0.2 mg/kg	Anxiolytic	Xie et al. (1995)
Ketamine	*NMDAR antagonist*	EPM	Rat	p.o	7 mg/kg	Anxiogenic	Silvestre et al. (1997)
		VCT	Rat	p.o	7 mg/kg	Anxiogenic	Silvestre et al. (1997)
		SIT	Rat	p.o	7 mg/kg	Anxiogenic	Silvestre et al. (1997)
Glycine site							
Glycine	*Glycine B agonist*	VCT	Rat	i.p	>800 mg/kg	No significant effect	Chojnacka-Wojcik et al. (1996)
L-701324	*Glycine B antagonist*	EPM	Rat	p.o	2.5 and 5.0 mg/kg	Anxiolytic	Kotlinska and Liljequist (1998)
		VCT	Rat	p.o	2.5 and 5.0 mg/kg	Anxiolytic	Kotlinska and Liljequist (1998)

(continued on next page)

Table 2 (*continued*)

Drug	Action	Animal model	Species (strain)	Route	Dose range	Effect	Reference
5,7-Dichlorokynurenate	*Glycine B antagonist*	VCT	Rat	i.c.v	5 μg	Anxiolytic	Plaznik et al. (1994)
7-chlorokynurenate	*Glycine B antagonist*	VCT	Rat	i.c (dorsomedial hypothalamus)	4 nM	Anxiogenic	Jardim and Guimaraes (2004)
MRZ 21576	*Glycine B antagonist*	VCT	Rat	i.p	2.5–10 mg/kg	No significant effect	Karcz-Kubicha et al. (1997)
L701324	*Glycine B antagonist*	EPM	Rat	i.p	0.1–10 mg/kg	No significant effect	Karcz-Kubicha et al. (1997)
		VCT	Rat	i.p	0.1–10 mg/kg	No significant effect	Karcz-Kubicha et al. (1997)
ACPC	*Glycine B (PAGO)*	VCT	Rat	i.p	200 mg/kg	Anxiolytic	Przegalinski et al. (1996)
		VCT	Rat	i.p	200 mg/kg	Anxiolytic	Chojnacka-Wojcik et al. (1996)
		VCT	Rat	i.c (hippocampus)	3–30 μg	Anxiolytic	Przegalinski et al. (1996)
D-cycloserine	*Glycine B (PAGO)*	EPM	Rat	i.p	5, 10, or 30 mg/kg	Anxiogenic (in low-anxiety rats)	Ho et al. (2005)
		FPS	Rat	i.p	3.25, 15, or 30 mg/kg	Anxiolytic	Walker and Davis (2000)
		FPS	Rat	i.c (amygdala)	10 μg	Anxiolytic	Walker and Davis (2000)
		VCT	Rat	i.p	200 and 300 mg/kg	Anxiolytic	Klodzinska and Chojnacka-Wojcik (2000)
		FPS	Rat	i.p	30–300 mg/kg	Anxiolytic	Anthony and Nevins (1993)
		CCF (reinstatement)	Rat	s.c	15.0 mg/kg	Anxiolytic	Ledgerwood et al. (2004)
		CCF (extiction)	Rat	s.c i.c (BLA)	2.5, 5.0, 10.0, and 15.0 mg/kg	Anxiolytic	Ledgerwood et al. (2003)
		CCF (extinction)	Rat	s.c	15 mg/kg	Anxiolytic	Parnas et al. (2005)
		CCF (extinction)	Rat (high and low anxiety rats)	i.p	15 mg/kg	Anxiolytic	Lehner et al. (2010)

CCF, cue-conditioned freezing; FPS, fear-potentiated startle; EPM, elevated plus maze; FPS, fear-potentiated startle; FST, forced swim test; GS, Geller–Seifter test; NMDAR antagonist, NMDA receptor antagonist; PAGO, partial agonist; SBP, Shock burying probe; SIT, social interaction test. Route: p.o, per orum; i.p, intraperitoneal; i.c, intracerebral; i.c.v, intracerebroventricular; and s.c, subcutaneous.

injections have demonstrated axiolytic-like properties in the EPM paradigm (Guimaraes et al., 1991; Molchanov and Guimaraes, 2002; Plaznik et al., 1994), or in Vogel Conflict Test (VCT) (Jessa et al., 1995; Molchanov and Guimaraes, 2002), but not when injected in dorsomedial part of ventromedial hypothalamus (Jardim et al., 2005). Other NMDAR competitive antagonist, like NPC 17742 (Willetts et al., 1993), CGP37849 (Jessa et al., 1996; Plaznik et al., 1994; Przegalinski et al., 1996), and CGP39551 (Karcz-Kubicha et al., 1997), may also have anxiolytic-like effects.

Non-competitive NMDAR antagonists have also been extensively studied. In particular, NMDAR non-competitive channel blocker, MK-801 (dizolcipine), may have anxiolytic effects on the EPM (Bertoglio and Carobrez, 2003; Fraser et al., 1996; Karcz-Kubicha et al., 1997; Wieronska et al., 2003), in the SIT (Corbett and Dunn, 1991; Corbett and Dunn, 1993; Dunn et al., 1989b), and in conflict intake studies (Corbett and Dunn, 1993; Jessa et al., 1996; Plaznik et al., 1994; Soderpalm et al., 1995; Xie et al., 1995). Other non-competitive NMDAR antagonists have also exhibited anxiolytic-like effects in rodent models. For example, PCP (phencyclidine) may reduce anxiety on the EPM (Wiley et al., 1995), and in rat conflict intake studies (Porter et al., 1989). The effects of ketamine in the EPM and SIT may be somewhat contradictory, what could be explained by the fact that this drug might exert some of its effects through other receptor classes (Becker et al., 2003; Hayase et al., 2006; Silvestre et al., 1997). The effects of non-competitive NMDAR antagonists seem to be less specific as compared to the effects of competitive NMDAR antagonist (Bergink et al., 2004; Wiley, 1997).

The administration of NMDAR antagonists before or immediately after extinction trials block extinction learning, suggesting NMDAR are involved in acquisition and consolidation of extinction (Kaplan and Moore, 2011). This effect of NMDAR antagonists on fear extinction may be attributable to the disruption of glutamate transmission of sensory information to the amygdala (Davis et al., 2006).

Given the fact that NMDAR antagonists block fear extinction, some studies have examined the effects of NMDAR agonist, D-cycloserine (DCS), on fear extinction. Binding to NMDAR, DCS acts as a partial agonist at the glycine site and enhances receptor efficacy (Norberg et al., 2008). Rats given high doses of DCS (15 and 30 mg/kg) showed a more robust extinction of fear-potentiated startle when tested 24 after the extinction session (Walker and Davis, 2002), suggesting DCS mediates extinction by acting on memory consolidation after such training (Kaplan and Moore, 2011). Long-term facilitation is only seen in animals showing within-session extinction (Langton and Richardson, 2010). Interestingly, DCS does not interfere with the reacquisition of fear learning, but prevents reinstatement of conditioned freezing in rats (Ledgerwood et al., 2004). Though DCS enhances fear extinction learning it does not eliminate the renewal effect nor it alters the context-specificity of the learning, and therefore may not protect against relapse (Kaplan and Moore, 2011).

DCS is most effective when administered immediately before or after fear extinction/exposure therapy, suggesting that the augmenting effects of DCS take place during the period of memory consolidation that occurs after training (Kaplan and Moore, 2011). In animal studies using NMDAR antagonists at various intervals after extinction training, fear extinction occurs in waves lasting 1–2 days after training, a period when hippocampal–neocortical synaptic connections are strengthened (Santini et al., 2001).

The effects of DCS decrease over repeated sessions (i.e., with chronic use). Indeed, DCS is more effective when given a limited

number of times and when administered close to the extinction training session (Norberg et al., 2008). A single acute dose of DCS leads to the greatest effects (Norberg et al., 2008).

Drugs targeting non-NMDA receptors may alter the expression of anxiety-like behavior in animals. While injections of AMPA/Kainate receptor agonist kainic acid into the dorsal portion of the PAG may enhance fear-potentiated startle (FPS) (Fendt, 2000), AMPAR antagonists may have anxiogenic-like activity in studies of unconditioned and conditioned paradigms (Kapus et al., 2008; Kotlinska and Liljequist, 1998; Matheus and Guimaraes, 1997; Menard and Treit, 2000; Sajdyk and Shekhar, 1997b) (see: Table 3).

Metabotropic glutamate receptors may be involved in anxiety (Palucha and Pilc, 2007). Drugs targeting mGluRs are promising agents for the treatment of anxiety-related disorders (Krystal et al., 2010). Several studies have assessed the potential of mGluR ligands in animal models of anxiety (Wieronska and Pilc, 2009). First mGluR modulators were somewhat unselective and did not easily pass blood–brain barrier, but the newer mGluR modulator may have more suitable profiles (Wieronska and Pilc, 2009).

Several mGluR1 antagonists have shown anxiolytic-like effects in animals. For instance, AIDA (Klodzinska et al., 2004), EMQMCM (Pietraszek et al., 2005), JNJ16259685 (Steckler et al., 2005), and LY456236 (Varty et al., 2005) (see: Table 4). Studies carried out with the mGluR2/3 antagonist, LY354740, have shown that this orally active, competitive, and selective drug may have anxiolytic activity in mice and rats in a variety of tests evaluating anxiety-like behaviors, such as EPM, stress-induced hyperthermia (SIH), Geller–Seifter conflict test (GST), Vogel Conflict Test (VCT), and others (Helton et al., 1998; Monn et al., 1997; Wieronska and Pilc, 2009) (see: Table 5).

Negative allosteric modulators of mGluR5, MPEP (Gasparini and Spooren, 2007) and its derivative, MTEP (Busse et al. 2004), have been studied in depth and have shown anxiolytic-like profiles in animal models of anxiety (Klodzinska et al., 2000; Klodzinska et al., 2004; Palucha and Pilc, 2007; Ritzen et al., 2005; Wieronska and Pilc, 2009) (Table 6). Due to its selectiveness and potency, MTEP could be considered a better candidate for clinical use (Busse et al., 2004; Cosford et al., 2003). MTEP may cause less off-target effects than MPEP (which also causes allosteric modulation of mGluR4 and inhibition of the norepinephrine transporter) (Mathiesen et al., 2003; Ritzen et al., 2005; Wieronska and Pilc, 2009).

Some drugs acting over the third class of mGluRs have also been investigated in great detail (Stachowicz et al., 2004, 2006, 2007, 2009; Tatarczynska et al., 2001, 2002) (Table 7). However, to date, most of them are not selective and barely pass the blood–brain barrier (Wieronska and Pilc, 2009). The non-selective agonist of all group III mGluRs, ACPT-1 shows high affinity to mGluR4 and mGluR8 and weak affinity to mGluR7 (Wieronska et al., 2007). Allosteric positive modulator of mGluR7, AMN082, may have anxiolytic-like activity, particularly in the SIH test (Fendt et al., 2008; Julio-Pieper et al., 2010; O'Connor et al., 2010; Siegl et al., 2008; Stachowicz et al., 2008; Ugolini et al., 2008; Wieronska and Pilc, 2009).

4.5. Human studies linking glutamatergic neurotransmission and anxiety

Several lines of evidence from human physiological, genetic, and behavioral studies, suggest that glutamate neurotransmission may play a significant role in the pathogenesis of anxiety-related disorders (Cortese and Phan, 2005). For instance, a significant link between glutamate polymorphisms in the gene coding for NMDAR subtunid NR2B (GRIN2B) (Arnold et al., 2004) and OCD has been published. In particular, a significant positive association between 5072T/G SNP (Single Nucleotid Polymorphism located in the 3′ untranslated region of GRIN2B), and both ODC diagnosis and symptom severity has been reported. Biochemical studies have also revealed a possible connection between glutamate and anxiety disorders. Thus, psychotropic drug-naïve ODC patients show higher cerebrospinal fluid (CSF) glutamate levels compared to controls (Chakrabarty et al., 2005). Although, no significant correlation between ODC severity and CSF glutamate levels has been detected (Bhattacharyya et al., 2009; Chakrabarty et al., 2005).

Given the fact that ionotropic glutamate receptors could possibly mediate fear-related memory formation and that NMDAR antagonists block fear extinction, many clinical trials have assessed the potential efficacy of drugs targeting glutamate neurotransmission in anxiety-related disorders (Cortese and Phan, 2005; Krystal et al., 2010). These drugs could potentially enhance the extinction or interfere with the reconsolidation of fear-related memories (Krystal et al., 2010).

Unfortunately, NMDAR non-competitive antagonists phencyclidine (PCP) or Ketamine can elicit behavioral disturbances and

Table 3
A summary of AMPA/kainate receptor pharmacology in animal models of anxiety.

Drug	Action	Animal model	Species	Route	Dose range	Effect	Reference
CNQX	*AMPAR antagonist*	EPM	Rat	i.c (BLA)	50 pM	Anxiolytic	Sajdyk and Shekhar (1997b)
		EPM	Rat	i.c (PAG)	1.0 and 3.0 nM	Anxiolytic	Matheus and Guimaraes (1997)
		EPM	Rat	i.c (dorsolateral septum)	5 μg	Anxiolytic	Menard and Treit (2000)
		VCT	Rat	i.p	0.05–5 mg/kg	No significant effect	Czlonkowska et al. (1997)
		SPA	Rat	i.c (dorsolateral septum)	5 μg	Anxiolytic	Menard and Treit (2000)
		SPB	Rat	i.c (dorsolateral septum)	5 μg	No significant effect	Menard and Treit (2000)
NBQX	*AMPAR antagonist*	EPM	Rat	i.c (dorsal hippocampus, CA1)	0.4 or 1.0 μg	No significant effect	Barros et al. (2000)
		EPM	Rat	i.c (BLA)	0.4 or 1.0 μg	No significant effect	Barros et al. (2000)
		VCT	Rat	i.p	0.1–5 mg/kg	No significant effect	Czlonkowska et al. (1997)
		VCT	Rat	i.p	3 mg/kg	Anxiolytic	Kapus et al. (2008)
		FPS	Rat	i.c (dlPAG)	0, 50, and 100 nmol	Anxiogenic	Fendt (2000) Fendt (2000)
LY326325	*AMPAR antagonist*	VCT	Rat	i.p	2.5–5.0 mg/kg	Anxiolytic	Kotlinska and Liljequist (1998)
Piracetam	*AMPAR positive modulator*	VCT	Rat	p.o	500 mg/kg/day (14 days)	Anxiolytic	Bhattacharyya et al. (1993)
Kainic acid	*AMPAR/KAR agonist*	FPS	Rat	i.c (dlPAG)	15 mg/kg	Anxiolytic	Fendt (2000)
Topiramate	*AMPA/KAR agonist*	ASP	Rat	p.o	10 mg/kg or 30 mg/kg	Anxiolytic	Khan and Liberzon (2004)

AMPAR antagonist, AMPA receptor antagonist; ASP, acoustic startle paradigm; FPS, fear-potentiated startle; EPM, elevated plus maze; FPS, fear-potentiated startle; SBP, Shock burying probe; SPA, shock-probe avoidance. Route: p.o, per orum; i.p, intraperitoneal; i.c, intracerebral; i.c.v, intracerebroventricular; and s.c, subcutaneous.

Table 4
Pharmacology of mGluR1 and anxiety.

Drug	Action	Animal model	Species	Route	Dose range	Effect	Reference
AIDA	*mGluR1 antagonist (competitive)*	EPM	Rat	i.p	0.5 and 2.0 mg/kg	Anxiolytic	Klodzinska et al. (2004)
		VCT	Rat	i.p	1.2 mg/kg	Anxiolytic	Klodzinska et al. (2004)
		4PT	Mouse	i.p	0.5, 8.0 mg/kg	No significant effect	Klodzinska et al. (2004)
CPCCOEt	*Non-comptetitive mGluR1α antagonist*	VCT	Rat	i.c (hippocampus)	5 and 15 μg	Anxiolytic	Tatarczynska et al. (2001b)
EMQMCM	*mGluR1 antagonist*	G-S	Rat	i.p	0.6 and 5.0 mg/kg	No significant effect	Pietraszek et al. (2005)
		EPM	Rat	i.p	0.6 and 5.0 mg/kg	No significant effect	Pietraszek et al. (2005)
		FPS	Rat	i.p	5.0 mg/kg	Anxiolytic	Pietraszek et al. (2005)
		CFC	Rat	i.p	0.6 and 5.0 mg/kg	Anxiolytic	Pietraszek et al. (2005)
JNJ16259685	*mGluR1 antagonist*	EPM	Rat	i.p	2.5–10.0 mg/kg	No significant effect	Steckler et al. (2005)
		VCT	Rat	i.p	2.5–10.0 mg/kg	Anxiolytic	Steckler et al. (2005)
LY456236	*mGluR1 antagonist*	VCT	Rat	i.p	10 mg/kg	Anxiolytic	Varty et al. (2005)
		CLS	Rat	i.p	30 mg/kg	Anxiolytic	Varty et al. (2005)
		SIH	Mouse	i.p	10.0 and 30 mg/kg	Anxiolytic	Rorick-Kehn et al. (2005)
MCPG	*mGluR antagonist*	EPM	Rat	i.c (dorsal hippocampus, CA1)	0.5 and 2.5 μg	No significant effect	Barros et al. (2000)
		EPM	Rat	i.c (BLA)	0.5 and 2.5 μg	No significant effect	Barros et al. (2000)
Riluzole	*Glutamate release inhibitor*	CER	Rat	p.o	10 mg/kg	Anxiolytic	Mirza et al. (2005)
S4CPG	*mGluR I comptetitive antagonist (specially mGluR1α)*	VCT	Rat	i.c (hippocampus)	10 and 20 μg	Anxiolytic	Tatarczynska et al. (2001)
Trans-ACPD	*Non-selective mGluR I/II agonist*	FPS	Rat	i.c (central amygdala)	30 nM	Anxiogenic	Koch (1993)
3HPG	*mGluR I agonist*	EPM	Rat	i.c (hippocampus, CA1)	0.022 μg 0.066 μg 0.2 μg	No significant effect	Szapiro et al. (2001)
		1-trial inhibitory avoidance and contextual fear	Rat	i.c (hippocampus, CA1)	0.022 μg 0.066 μg 0.2 μg	Anxiolytic	Szapiro et al. (2001)

CCF, cue-conditioned freezing; CER, conditioned emotional response; CFC, contextual fear conditioning; CLS, conditioned lick suppression test; EPM, elevated plus maze; FPS, fear-potentiated startle; FST, forced swim test; GS, Geller–Seifter test; VCT, Vogel Conflict Test; 4PT, 4-plate test. Route: p.o, per orum; i.p, intraperitoneal; i.c, intracerebral; i.c.v, intracerebroventricular; and s.c, subcutaneous.

perceptual abnormalities (depersonalization, derealization, visual and auditory hallucinations), which partially resemble some of the symptoms seen in patients suffering from PTSD (Chambers et al., 1999; Krystal et al., 1994). Non-competitive NMDAR antagonists can also produce serious adverse effects (convulsions, sedation), which limit the use of these drugs in the clinical context. Ketamine's behavioral effects could be explained by the dense cortical localization of NMDARs (Bergink et al., 2004). Ketamine's primary mechanism of action is blocking NMDAR at the PCP site within the ionotropic channel. Ketamine has a high affinity for the NMDAR, with slow open-channel blocking/unblocking kinetics, and a specific type of channel closure (called "trapping block"). Simultaneously, ketamine induces a robust presynaptic release of glutamate by increasing the firing rate of glutamatergic neurons (Moghaddam et al., 1997).

The risks associated with the use of NMDAR antagonists, like ketamine, hindered clinical research with these drugs. The aim of any pharmacological intervention targeting glutamate neurotransmission in anxiety-related disorders would be that excessive glutamate exposure in specific fear-related areas be blocked, whereas normal glutamatergic neurotransmission should be kept unaffected. Consequently, direct inhibition or activation of the glutamate system may not be a good approach. New ways of fine-tuning the glutamatergic system are now emerging, such as modulation of glycine site, compounds targeting AMPAR, and metabotropic modulators (Bergink et al., 2004).

Accordingly, the glycine-site partial agonist, D-cycloserine (DCS), could potentially have a beneficial role in the extinction of fear in human patients suffering PTSD, phobias, OCD, and panic disorder (Otto et al., 2010; Richardson et al., 2004). Given the fact that some of the available behavioral therapies for anxiety are based on fear extinction (Guastella et al., 2007; Langton and Richardson, 2009; Langton and Richardson, 2010; McCallum et al., 2010), it would be of great interest to assess whether or not DCS may have the ability to increase the speed and efficiency of exposure-based therapies (Norberg et al., 2008).

The glycine site partial agonist, DCS has complex modulatory effects at NMDAR. When local glycine levels are enough to saturate glycine B sites, DCS may reduce NMDAR activity as much as 40%–50% (Emmett et al., 1991; Norberg et al., 2008). Moreover, DCS indirectly increases glutamatergic activity in previously "silent" synapses (Gomperts et al., 1998). DCS may improve the efficacy of exposure-based psychotherapies by enhancing fear extinction, interfering with NMDA-dependent (re)consolidation of fear memories, and by enhancing neuroplasticity (Krystal, 2007; Norberg et al., 2008).

Thus, much attention is now being paid to the potential utility of DCS for the treatment of anxiety-related disorders (Norberg et al., 2008). Treatment with DCS resulted in a significant improvement in anxiety symptoms of patients suffering from chronic PTSD (Heresco-Levy et al., 2002, 2009). In a randomized, double-blind, placebo-controlled study (Ressler et al., 2004), patients suffering from acrophobia were exposed to virtually-generated heights and received

Table 5
Pharmacology of mGluR2/3 and anxiety.

Drug	Action	Animal model	Species	Route	Dose range	Effect	Reference
BINA	*mGluR2/3 agonist*	EPM	Rat	i.p	10.0–32.0 mg/kg	Anxiolytic	Galici et al. (2005)
		SIH	Mouse	i.p	32.0 mg/kg	Anxiolytic	Galici et al. (2005)
CBiPES	*mGluR2/3 agonist*	SIH	Mouse	s.c	100.0 mg/kg	Anxiolytic	Johnson et al. (2005)
LCCG-1	*mGluR2/3 agonist*	EPM	Rat	i.c (dorsal hippocampus)	60 nM	No significant effect	Smialowska et al. (2007)
LY354740	*mGluR2/3 agonist*	EPM	Rat	p.o	3.0 mg/kg	Anxiolytic	Helton et al. (1998)
		EPM	Mouse	p.o	1.0–10.0 mg/kg	Anxiolytic	Monn et al. (1997)
		EPM	Mouse	s.c	20 mg/kg	Anxiolytic	Linden et al. (2004)
		G–S	Pigeon	i.m	0.001–1.0 mg/kg	No significant effect	Benvenga et al. (1999)
		FPS	Rat	p.o	1.0–10.0 mg/kg	Anxiolytic	Helton et al. (1998)
		FPS	Rat	p.o	20 and 200 mg/kg	Anxiolytic	Grillon et al. (2003)
		FPS	Human	p.o	20.0–200.0 mg/kg	Anxiolytic	Grillon et al. (2003)
		FPS	Rat	i.c (amygdala)	0.3	Anxiolytic	Walker et al. (2002)
		CO_2-challenge panic	Rat	p.o	3.0 mg/kg	Anxiolytic	Schoepp et al. (2003)
		VCT	Rat	i.p	0.5–1.0 mg/kg	Anxiolytic	Klodzinska et al. (1999)
		4PT	Mouse	i.p	4.0–8.0 mg/kg	Anxiolytic	Klodzinska et al. (1999)
		Lactate-induced panic	Rat	i.p	0.3–0.6 mg/kg	Anxiolytic	Shekhar and Keim (2000)
		Yohimbine-induced anxiety	*Macaca radiate*	p.o	1.0 mg/kg	Anxiolytic	Coplan et al. (2001)
		CO_2-induced panic	Human	p.o	200.0 mg/kg	Anxiolytic	Schoepp et al. (2003)
		Panic disorder	Human	p.o	100.0–200.0 mg/kg	No significant effect	Bergink and Westenberg (2005)
LY314582	*mGluR2/3 agonist*	SIH	Mouse	p.o	1.0–10.0 mg/kg	Anxiolytic	Spooren et al. (2002)
LY544344	*mGluR2/3 agonist*	FPS	Rat	p.o	0.01–0.1 mg/kg	Anxiolytic	Bueno et al. (2005)
		SIH	Mouse	p.o	30.0 mg/kg	Anxiolytic	Rorick-Kehn et al. (2006)
		CCK-4-induced panic	Human	p.o	20.0–80.0 mg/kg	Anxiolytic/anxiogenic	Kellner et al. (2005)
		CCK-4 challenge panic	Rat	p.o	80 mg/kg	Anxiolytic	Kellner et al. (2005)
LY487379	*mGluR2/3 agonist*	FPS	Rat	i.p	3.0 mg/kg	Anxiolytic	Johnson et al. (2005)
		FPS	Rat	s.c	0.1–1.0 mg/kg	Anxiolytic	Johnson et al. (2005)
LY341495	*mGluR2/3 antagonist*	MBT	Mouse	i.p	1.0–10.0 mg/kg	Anxiolytic	Shimazaki et al. (2004)
		SIH	Mouse	i.p	1.0 mg/kg	Anxiolytic	Iijima et al. (2007)
		FPS	Rat	i.p	1.0 mg/kg	No significant effect	Tizzano et al. (2002)
		EPM	Mouse	i.p	3.0–6.0 mg/kg	Anxiogenic	Linden et al. (2005)
		EPM	Mouse	i.p	1.0 mg/kg	No significant effect	Linden et al. (2005)
L-SOP	*mGluR2/3 agonist*	EPM	Rat	i.c (dorsal hippocampus)	520 nM	Anxiolytic	Smialowska et al. (2007)
MGS0039	*mGluR2/3 antagonist*	MBT	Mouse	i.p	3.0–10.0 mg/kg	Anxiolytic	Shimazaki et al. (2004)
		CFS	Rat	i.p	2.0 mg/kg	Anxiolytic	Yoshimizu et al. (2006)
		SIH	Mouse	i.p	1.0–3.0 mg/kg	Anxiolytic	Iijima et al. (2007)
		EPM	Mouse	i.p	1.0 mg/kg	Anxiogenic	Chaki et al. (2004)
4-APPES	*mGluR2/3 agonist*	FPS	Rat	s.c	0.1 mg/kg	Anxiolytic	Johnson et al. (2005)

CFC, contextual fear conditioning; EPM, elevated plus maze; FPS, fear-potentiated startle; GS, Geller–Seifter test; MPT, Marble burying test; SBP, Shock burying probe; SIH, shock-induced hyperthermia; SIT, social interaction test; 4PT, 4-plate test. Route: p.o, per orum; i.p, intraperitoneal; i.c, intracerebral; i.c.v, intracerebroventricular; and s.c, subcutaneous.

either oral DCS or placebo. Patients receiving DCS treatment showed significant reductions in acrophobia symptoms compared to the placebo group; this improvement lasted for at least 3 months (Ressler et al., 2004). The administration of DCS (50 mg, p.o) before extinction therapy has demonstrated to enhance treatment outcomes for social anxiety disorder in a randomized controlled trial (Guastella et al., 2008).

Acute administration of DCS may enhance amygdala-dependent fear extinction both in animals and humans (Banasr et al., 2010; Davis et al., 2006; Hofmann et al., 2006; Norberg et al., 2008; Otto et al., 2010; Ressler et al., 2004). A recent study carried out with functional magnetic resonance imaging (fMRI) scanning assessed the mechanisms by which DCS administration may be useful in exposure therapy in humans suffering from spider phobia; 23 spider-phobic and 23 non-phobic participants were randomized to DCS 100 mg or placebo. During scanning, participants viewed spider, butterfly, and Gaussian-blurred baseline images in a block-design paradigm. In the phobic group, DCS enhanced prefrontal (PFC), dorsal anterior cingulate (ACC), and insula activations, while DCS enhanced ventral ACC and caudate activations in the control group. Interestingly, reported distress during provocation was correlated with amygdala activation in those phobic individuals that were on placebo, but phobics receiving DCS showed significant orbitofrontal cortex activation. These results may suggest that during initial phobic symptom provocation DCS may activate brain regions involved in cognitive control and interoceptive integration, including the ACC, PFC, and insula (Aupperle et al., 2009). Another fMRI study evaluated how DCS may modify amygdala activity during the processing of repeated facial expressions. Fourteen healthy males were randomly assigned to DCS 500 mg or placebo prior to functional magnetic resonance imaging acquisition, and were exposed to 4 separate runs, consisting of a single block of a repeated facial expression (happy or fearful) bracketed by fixation blocks. Anatomic analyses showed that, while individuals on placebo exhibited significant amygdala activation and response habituation, those that had previously received DCS showed blunted amygdala responses to emotional faces across the experiment (Britton et al., 2007).

The non-competitive NMDAR antagonist, memantine, which is being currently used as a memory-enhancing drug in patients suffering moderate to severe Alzheimer's disease (Cortese and Phan, 2005), has also shown anxiolytic effects. As glutamatergic corticostriato–thalamo–cortical over-activity may be involved in OCD, some authors have assessed the potential efficacy of this drug for the treatment of OCD (Zdanys and Tampi, 2008). Two case reports have investigated the use of memantine (5–15 mg/day, p.o) in treatment-resistant OCD (Pasquini and Biondi, 2006; Poyurovsky et al., 2005), with apparently favorable

Table 6
Pharmacology of mGluR5 in anxiety.

Drug	Action	Animal model	Species (strain)	Route	Dose range	Effect	Reference
Fenobam	*Non-competitive mGluR5 antagonist*	G–S	Rat	p.o	10.0–30.0 mg/kg	Anxiolytic	Porter et al. (2005)
		VCT	Rat	p.o	10.0–30.0 mg/kg	Anxiolytic	Porter et al. (2005)
		SIH	Rat	p.o	10.0–30.0 mg/kg	Anxiolytic	Porter et al. (2005)
MPEP	*mGluR5 antagonist*	EPM	Rat	p.o	0.1 and 1.0 mg/kg	Anxiolytic	Spooren et al. (2000)
		EPM	Rat	i.p	3.0 and 10.0 mg/kg	Anxiolytic	Tatarczynska et al. (2001)
		EPM	Rat	i.p	10.0 mg/kg	Anxiolytic	Wieronska et al. (2004)
		EPM	Rat	i.c (amygdala)	8.0 nM	Anxiolytic	Perez de la et al. (2006)
		G–S	Rat	p.o	10.0–30.0 mg/kg	No significant effect	Spooren et al. (2000)
		G–S	Rat	i.p	30.0 mg/kg	Anxiolytic	Brodkin et al. (2002a,b)
		G–s	Rat	i.p	3.0 and 10.0 mg/kg	Anxiolytic	Busse et al. (2004)
		G–S	Rat	p.o	10.0–30.0 mg/kg	Anxiolytic	Ballard et al. (2005)
		G–S	Rat	i.p	1.0 and 3.0 mg/kg	Anxiolytic	Pietraszek et al. (2005)
		G–S	Rat	p.o	10.0–30.0 mg/kg	Anxiolytic	Ballard et al. (2005)
		VCT					
		VCT	Rat	i.p	2.5 mg/kg	Anxiolytic	Steckler et al. (2005)
		VCT	Rat	i.p	1.0 and 10.0 mg/kg	Anxiolytic	Klodzinska et al. (2000)
		VCT	Rat	i.p	1.0 and 10.0 mg/kg	Anxiolytic	Tatarczynska et al. (2001)
		VCT	Rat	i.p	1.0 and 10.0 mg/kg	Anxiolytic	Pilc et al. (2002)
		VCT	Rat	i.p	3.0–10.0 mg/kg	Anxiolytic	Varty et al. (2005)
		VCT	Rat	p.o	10.0 mg/kg	Anxiolytic	Buttelmann et al. (2006)
		FPS	Rat	p.o	30.0 mg/kg	Anxiolytic	Schulz et al. (2001)
		FPS	Rat	p.o	10.0 and 30.0 mg/kg	Anxiolytic	Brodkin et al. (2002a,b)
		FPS	Rat	p.o	5.0 mg/kg	Anxiolytic	Cosford et al. (2003)
		CLS	Rat	i.p	3.0 and 10.0 mg/kg	Anxiolytic	Varty et al. (2005)
		CER	Rat	p.o	10.0–30.0 mg/kg	Anxiolytic	Ballard et al. (2005)
		SE	Rat	p.o	0.3 and 1.0 mg/kg	Anxiolytic	Spooren et al. (2000)
		USV	Rat	i.p	10.0 and 30.0 mg/kg	Anxiolytic	Brodkin et al. (2002a,b)
		USV	Rat	i.p	1.0 and 10.0 mg/kg	Anxiolytic	Iijima and Chaki (2005)
		SIH	Mouse	p.o	15.0 and 30.0 mg/kg	Anxiolytic	Spooren et al. (2000)
		SIH	Mouse	i.p	10.0 and 30.0 mg/kg	Anxiolytic	Rorick-Kehn et al. (2005)
		MBT	Mouse	p.o	7.0 and 30.0 mg/kg	Anxiolytic	Spooren et al. (2000)
		4PT	Mouse	i.p	30.0 mg/kg	Anxiolytic	Tatarczynska et al. (2001)
		LDET	Rat	i.c (amygdala)	2.0 nM	Anxiolytic	Perez de la et al. (2006)
		SPB	Rat	i.c (amygdala)	8.0 nM	Anxiolytic	Perez de la et al. (2006)
MTEP	*mGluR5 antagonist*	EPM	Rat	i.p	0.3, 1.0 and 3.0 mg/kg	Anxiolytic	Klodzinska et al. (2004)
		EPM	Rat	i.p	0.6 and 5.0 mg/kg	No significant effect	Pietraszek et al. (2005)
		EPM	Rat	i.c (lateral septal nuclei)	5.0 and 10.0 μg/μl	Anxiolytic	Molina-Hernandez et al. (2006)
		EPM	Rat	i.p	5.0 and 10.0 μg	Anxiolytic	Molina-Hernandez et al. (2006)
		G–S	Rat	i.p	3.0–10.0 mg/kg	Anxiolytic	Busse et al. (2004)
		G–S	Rat	i.p	3.0–10.0 mg/kg	Anxiolytic	Pietraszek et al. (2005)
		CFS	Rat	i.p	1.25 and 2.5 mg/kg	Anxiolytic	Pietraszek et al. (2005)
		CLS	Rat	i.p	3.0–10.0 mg/kg	Anxiolytic	Varty et al. (2005)
		VCT	Rat	i.p	0.1 and 3.0 mg/kg	Anxiolytic	Klodzinska et al. (2004)
		VCT	Rat	i.p	3.0–10.0 mg/kg	Anxiolytic	Varty et al. (2005)
		FPS	Rat	i.p	2.5 and 5.0 mg/kg	Anxiolytic	Pietraszek et al. (2005)
		FPS	Rat	i.p	0.3 and 3.0 mg/kg	Anxiolytic	Cosford et al. (2003)
		FPS	Rat	i.p	3.0–10.0 mg/kg	Anxiolytic	Busse et al. (2004)
		4PT	Mouse	i.p	0.3–3.0 mg/kg	Anxiolytic	Klodzinska et al. (2004)

CCK-4, cholecystokinin tetrapeptide; CER, conditioned emotional response; CFC, contextual fear conditioning; CLS; conditioned lick suppression test; EPM, elevated plus maze; FPS, fear-potentiated startle; GS, Geller–Seifter test; LDET, light–dark exploration test; MPT, Marble burying test; SBP, Shock burying probe; SIH, shock-induced hyperthermia; SIT, social interaction test; USV, ultrasonic vocalizations; VCT, Vogel Conflict Test; 4PT, 4-plate test. Route: p.o, per orum; i.p, intraperitoneal; i.c, intracerebral; i.c.v, intracerebroventricular; and s.c, subcutaneous.

outcomes. However, no controlled trials of glutamatergic augmenting agents have been reported to date. A recent single-blinded case–control study (Stewart et al., 2010), evaluating the efficacy of memantine augmentation treatment in patients suffering severe OCD, found a significant decrease in the Yale-Brown Obsessive Compulsive Scale score among patients receiving memantine adjunctive therapy. Another study by Aboujaoude group (Aboujaoude et al., 2009) examined the effect of memantine augmentation on severe ODC patients who had failed to respond to treatment with a serotonin reuptake inhibitors (SSRIs). Although, almost half the subjects had a meaningful improvement in symptoms (assessed with Y-BOCS scores), the study was limited by its relatively small sample size, and by significant baseline differences among groups regards severity of illness and previous SSRI treatment responses. Although, these studies provide promising results for the effectiveness of memantine augmentation strategy in severe OCD, randomized double-blind placebo-controlled trials are needed (Stewart et al., 2010). Similar results have also been achieved by another recent study (Feusner et al., 2009), in which memantine showed preferential efficacy in the treatment of OCD over GAD. A pilot trial on memantine in PTSD produced consistent

Table 7
Pharmacology of group III mGlu receptor ligands in anxiety.

Drug	Action	Animal model	Species (strain)	Route	Dose range	Effect	Reference
ACPT-1	*mGluR4/6/7/8 agonist*	EPM	Rat	i.c (amygdala)	10 μg	Anxiolytic	Wieronska et al. (2005)
		VCT	Rat	i.c (hippocampus) i.c.v	1.875, 3.75 and 7.5 nmol	Anxiolytic	Tatarczynska et al. (2002)
		VCT	Rat	i.c (hippocampus)	7.5 and 15 nmol	Anxiolytic	Palucha et al. (2004)
		VCT	Rat	i.c (amygdala)	7.5 nmol	No significant effect	Stachowicz et al. (2007)
CPPG	*mGluR4/7/8 antagonist*	VCT	Rat	i.c (amygdala)	75 nmol	Anxiolytic	Stachowicz et al. (2007)
CPPG+ACPT-I	*mGluR4/7/8 antagonist/agonist*	VCT	Rat	i.c (amygdala)	7.5 nmol	No significant effect	Stachowicz et al. (2007)
CPPG+Metergoline	*mGluR4/7/8 antagonist+5-HTR antagonist*	VCT	Rat	i.p	2 mg/kg	No significant effect	Stachowicz et al. (2007)
CPPG+ritanserin	*mGluR4/7/8 antagonist+5-HT2A/C antagonist*	VCT	Rat	i.p	0.5 mg/kg	No significant effect	Stachowicz et al. (2007)
L-AP4	*mGluR4/7/8 agonist*	VCT	Rat	i.c (hippocampus)	0.22, 0.66 or 2.0 μM	No significant effect	Szapiro et al. (2001)
L-SOP	*mGluR4/7/8 agonist*	VCT	Rat	i.c (hippocampus)	100 μg	Anxiolytic	Tatarczynska et al. (2001)
MSOP	*mGluR4/7/8 antagonist*	VCT	Rat	i.c (hippocampus)		Anxiolytic	Chojnacka-Wojcik et al. (1997)
PHCCC	*mGluR4 antagonist*	VCT	Rat	i.c (hippocampus)	12 nmol	Anxiolytic	Stachowicz et al. (2006)
		VCT	Rat	i.c (BLA)	3.125 and 6.25	Anxiolytic	Stachowicz et al. (2004)
(S)-3,4-DCPG	*mGluR8 agonist*	VCT	Rat	i.c (BLA)	10, 50 and 100 nmol	No significant effect	Stachowicz et al. (2005)
		VCT	Rat	i.c (hippocampus)	10, 50 and 100 nmol	No significant effect	Stachowicz et al. (2005)

ACPT-I: (S,3R,4S)-1-aminocyclo-pentane-1,3,4-tricarboxylic acid; CPPG: alpha-cyclopropyl-4-phosphonophenylglycine; EPM, elevated plus maze; L-SOP: L-serine-O-phosphate; PHCCC: (−)-N-phenyl-7-(hydroxyimino) cyclopropa[b]chromen-1[a]; (S)-3,4-DCPG, (S)-3,4-dicarboxyphenylglycine ((S)-3,4-DCPG); VCT, Vogel Conflict Test. Route: p.o, per orum; i.p, intraperitoneal; i.c, intracerebral; i.c.v, intracerebroventricular; and s.c, subcutaneous.

improvement on a delayed recall measure of memory, variable reduction of depressive symptoms, and variable reduction in hyperarousal symptoms (Battista et al., 2007).

The beneficial effects of DCS in anxiety disorders contrast with findings from the use of DCS as a corrective treatment for neurocognitive deficits in schizophrenia and Alzheimer's disease. In the treatment of schizophrenia and Alzheimer's disease, DCS has been applied in chronic daily doses, unlike the extinction-augmenting applications used in treatments of conditioned fear. Isolated dosing might be more effectively than chronic dosing for specific learning-based purposes, consistent with the demonstration of desensitization of the NMDAR in cell culture with prolonged exposure to DCS and other glycine ligands (Norberg et al., 2008).

DCS is most effective when administered immediately before or after fear extinction/exposure therapy, suggesting that the fear-extinction facilitatory effects of DCS take place during the period of memory consolidation that occurs after training. One potential benefit of administering DCS immediately after exposure therapy sessions is the possibility for the clinician to administer DCS only after those sessions in which within-session extinction has occurred, consistently with animal studies showing that DCS leads to long-term gains only for animals exhibiting within-session extinction (Langton and Richardson, 2010; Norberg et al., 2008). This selective administration may also reduce the chance of tolerance due to chronic administration (Norberg et al., 2008). According to the literature, the effects of DCS augmentation do not disappear upon treatment discontinuation, what could represent potential improvement over existing pharmacological therapy augmentation strategies (Norberg et al., 2008).

Riluzole, a drug that reduces glutamate release and consequently increase the expression of glutamate receptors, may also be effective in the treatment of mood and anxiety disorders. In particular, patients diagnosed for GAD underwent a significant decrease in anxiety sensitivity and ruminative worry after treatment with riluzole (100 mg/day) (Mathew et al., 2005, 2008; Pittenger et al., 2008). Remission (assessed with a Hamilton Anxiety Scale score <7) was achieved in 53% of GAD patients, with rapid onset of action, and tolerability. Riluzole augmentation was well-tolerated and efficacious in treatment-resistant OCD in open-label trials both in adults (Coric et al., 2005) and in children (Grant et al., 2007).

Antiepileptic drugs, with some activity over ionotropic glutamate receptors, such as lamotrigine (Hertzberg et al., 1999), topiramate (Berlant and van Kammen, 2002; Berlant, 2004), and tiagabine (Connor et al., 2006; Davidson et al., 2007), have shown to be effective in double-blind, placebo-controlled trials for PTSD (Berlin, 2007). Other antiepileptic drugs, such as carbamazepine, valproate, gabapentin, vigabatrin, phenytoin, and levetiracetam, have achieved promising results in open-label trials (Berlin, 2007). The anticonvulsivant drug, phenytoin, which may reduce glutamate and increase GABA neurotransmission (Cortese and Phan, 2005), has showed significant efficacy in the treatment of accident-related, early abuse, and combat PTSD in a, by reducing avoidance, intrusions, and arousal symptoms (Bremner et al., 2005; Douglas et al., 2004). Interestingly, such effects may last for at least 3 months. Possibly, stress-activated limbic kindling may be involved in the pathogenesis of PTSD (Berlin, 2007). In addition, topiramate, which also modulates glutamatergic and GABA neurotransmission, has demonstrated efficacy in the treatment of social phobia (Van et al., 2004).

In the last years, detailed knowledge about the involvement of mGluRs in anxiety and stress-related disorders has been gathered (Palucha and Pilc, 2007). A growing amount of studies evaluating the effects of mGluR ligands both in animals (see: Tables 4–7) and humans have been published. Drugs acting at group I and group III mGluRs are in the early phases of clinical trials for the treatment of anxiety disorders (Krystal et al., 2010). Animal models had previously demonstrated that mGluR5 antagonists might reduce anxiety (Ballard et al., 2005; Busse et al., 2004; Jaeschke et al., 2007; Porter et al., 2005). Potent and selective mGluR5 antagonist, fenobam, acts at allosteric modulatory site shared with MPEP. Fenobam is an atypical anxiolytic

agent that has demonstrated to exert a robust anxiolytic activity both in rodents and human (in which a double-blinded trial has been published) (Porter et al., 2005).

Allosteric modulators of mGluR2/3 may have a promising role for the treatment of anxiety disorders (Krystal et al., 2010). Anxiolytic effects of LY354740 have been observed using the human fear-potentiated startle paradigm in healthy volunteers (Grillon et al., 2003). LY354740 administration was associated with a reduction in the self-reported level of anxiety, and a significant decrease in fear-potentiated startle to shock anticipation (Grillon et al., 2003). Moreover, LY354740 has displayed anxiolytic effects preventing CO_2-induced panic attacks in patients that had been previously diagnosed of panic disorder (Bergink and Westenberg, 2005).

The efficacy of LY354740 as an axiolytic has been assessed on a number of clinical trials. A double-blind placebo-controlled randomized study with paroxetine (60 mg) as an active comparator evaluated the efficacy of LY354740 (100 or 200 mg) in outpatients suffering panic disorder (Bergink and Westenberg, 2005). LY354740 was well tolerated (gastrointestinal complaints were the most common side-effects) but failed to show significant differences in efficacy from placebo.

LY544344, a peptidyl modified derivative from LY354740, with a better absorption profile, may also have anxiolytic activity in humans (Krystal et al., 2010). In fact, LY544344 administration led to a significant decrease in cholecystokinin tetrapeptide-induced subjective anxiety rating and panic symptoms in health volunteers (Kellner et al., 2005). Twelve healthy human volunteers were administered LY544344 (80 mg p.o) for 1 week in a randomized placebo-controlled cross-over study before 50 mg cholecystokinin tetrapeptide (CCK-4) was injected intravenously. CCK-induced panic and anxiety symptoms and stress hormone release were measured. A significant reduction in the number of CCK-4-induced panic symptoms and of CCK-4-induced subjective anxiety ratings were detected when subjects with no CCK-4-elicited adrenocorticotropin (ACTH) release were not included in the statistical analysis (Chakrabarty et al., 2005; Kellner et al., 2005).

LY544344 seems a promising drug to treat anxiety disorders (Dunayevich et al., 2008). A double-blind, placebo-controlled, 8-week study was designed to evaluate the efficacy, safety, and tolerability of LY544344 in the treatment of GAD (Dunayevich et al., 2008). Patients were randomized to double-blind treatment with LY544344 16 mg b.i.d. (n = 28), LY544344 8 mg b.i.d. (n = 36), or placebo (n = 44). LY544344 16 mg b.i.d.-treated patients showed significantly greater improvement from baseline in Hamilton Anxiety and Clinical Global Impression-Improvement scores, as well as response and remission rates compared with placebo-treated patients. Despite the fact that LY544344 was well tolerated and there were no significant differences in the incidence of adverse events among the three groups, this trial was discontinued due to the occurrence of convulsions in preclinical studies (Krystal et al., 2010).

The safety profile of new mGluR modulators has been assessed (Palucha and Pilc, 2007). Possible effects of mGluR modulators on motor coordination or locomotor activity, could confound the interpretation of behavioral data. Unlike benzodiazepines, mGluR1 antagonists are not likely to produce motor disturbances. However, learning deficits and disruption of prepulse inhibition (PPI), similar to that seen in schizophrenia, has been observed in mice lacking mGluR1. So it might be speculated that mGluR1 antagonists could lead to psychotomimetic effects, which seems unlikely with EMQMCM. Compared to benzodiazepines, fenobam may be free of such adverse effects as muscle relaxation, sedation, and potentially dangerous interactions with alcohol. However, trials with fenobam were discontinued due to psychostimulant adverse effects in some patients, what could be attributable to "off-target" activity, perhaps on the dopamine transporter (Palucha and Pilc, 2007). Both MTEP and MPEP may have a narrow therapeutic window. Although, mGluR5 antagonists lack the adverse effects seen with benzodiazepines, multiple MTEP and MPEP administration, when applied at higher doses (3 mg/kg) may lead to tolerance to anxiolytic action. Dysphoric effects with MPEP, due to its effects on brain reward function, and possible adverse effects on learning, working memory and spatial learning, have also been described (Palucha and Pilc, 2007). Future studies should assess the safety profiles of these new drugs in more depth.

In conclusion, this findings support the potential efficacy of drugs targeting ionotropic and metabotropic glutamate receptors for the treatment of anxiety disorders. These drugs could potentially enhance the extinction or interfere with the reconsolidation of fear-related memory processes. Additional studies, however, are necessary in order to investigate in depth the efficacy and tolerability of these novel drugs.

5. Polyamines, stress and glutamate

Due to the fact that ionotropic glutamate receptors have been involved in the biological mechanisms related to fear conditioning and anxiety disorders, much attention is now being paid to those molecular factors that could potentially modulate glutamatergic neurotransmission. A growing interest in naturally modulating polyamines has recently emerged. In the last decades, several authors have investigated the role of polyamines in the pathogenesis of some neuropsychiatric disorders, in particular, stress-related conditions (Vaquero-Lorenzo et al., 2008) and suicidal behavior (Chen et al., 2010; Klempan et al., 2009).

The next section will take the reader through the basic aspects of polyamine metabolism, how polyamines modulate NMDAR, AMPAR, and KARs, and finally the links between polyamines and anxiety-related conditions.

5.1. Polyamines and their metabolism

Natural polyamines (putrescine, spermidine, spermine, cadaverine, and agmatine) are low molecular weight water-soluble aliphatic molecules widely distributed throughout procariot and eucariot species (Moinard et al., 2005). Polyamines have been involved in many physiological functions, such as cell growth and proliferation, apoptosis, synthesis of nucleic acids and proteins, immunity, and control of gut function and nutritional status (Riaza Bermudo-Soriano et al., 2009).

At physiological pH, polyamine primary and secondary amino groups are fully protonated, what makes putrescine, spermidine and spermine act as divalent, trivalent or tetravalent cations, respectively (Seiler et al., 1996). Due to their cationic nature, polyamines can establish electrostatic interactions with anionic charges present in many common macromolecules such as phospholipids, nucleic acids, and proteins (including some types of receptors) (Moinard et al., 2005). The fact that cationic charges on polyamines are distributed at fixed distances with methylen moieties between them, makes natural polyamines establish interactions with other molecules more specifically that many inorganic cations (Davis et al., 1992; Igarashi and Kashiwagi, 2000; Kilpeläinen, 2002; Marton and Pegg, 1995; Thomas and Thomas, 2001).

Polyamine's synthesis and catabolism are strictly regulated in order to control its cellular levels (Moinard et al., 2005). Natural polyamines are synthesized from amino acids ornithine and methionine (Davis et al., 1992; Marton and Pegg, 1995; Morgan, 1999). First, ornithine is irreversibly converted to putrescine in a reaction that is catalyzed by the rate-limitant enzyme ornithine-decarboxylase (ODC, EC 4.1.1.17). Subsequently, spermidine and spermine are synthesized by the consecutive addition of amino-propyl moieties (Moinard et al., 2005).

Polyamine catabolism is mainly regulated by the rate-limitant enzyme acetyl-CoA spermidine/spermine-N^1-acetyl-transferase

(SSAT-1, EC 2.3.1.57) (Moinard et al., 2005; Seiler, 2004; Vujcic et al., 2002; Wang et al., 2001; Wang and Casero, 2006).

5.2. Polyamines and neuropsychiatric disorders

A growing body of evidence suggest that polyamine metabolism may be disrupted in several mental disorders (Fiori and Turecki, 2008), like anxiety (Vaquero-Lorenzo et al., 2008), psychosis (Andrews, 1985; Das et al., 1989, 1998; Middleton et al., 2002; Pfeiffer et al., 1970; Ramchand et al., 1994; Richardson-Andrews, 1983; Svinarev, 1986), depression and suicidal behavior (Andrews, 1985; Dahel et al., 2001; Fiori and Turecki, 2008; Guipponi et al., 2008; Sequeira et al., 2006, 2007; Turecki, 2006).

Interestingly, polyamines have been associated with stress response. Physical, chemical or emotional stress elicit a significant increase in polyamine levels in many tissues, particularly in brain regions involved in fear-conditioning, like amygdala and hippocampus (Gilad and Gilad, 2003). The magnitude of this effect seems to positively correlate on the intensity and duration of the stressful stimuli. Animal models of psychological stress show a significant increase in brain putrescine content, while spermidine or spermine show little or no change (Gilad and Gilad, 2003; Rhee et al., 2007). In addition, hypothalamus–pituitary–adrenal (HPA) axis may be connected to polyamine metabolism, as adrenocorticotrophin (ACTH) is the main enhancer of polyamine synthetic enzyme, ornithine-decarboxilase (ODC) activity in the adrenal glands (Bastida et al., 2007; Vaquero-Lorenzo et al., 2008).

5.3. Polyamines modulate ionotropic glutamate receptors

Under physiological circumstances, polyamines modulate the electrochemical activity of NMDARs (Aizenman et al., 2002; McGurk et al., 1990; Pellegrini-Giampietro, 2003; Traynelis et al., 1995) and AMPARs (Pellegrini-Giampietro, 2003), both of which have been extensively linked to fear learning and memory formation (Izquierdo and Medina, 1997; Jasnow et al., 2004). But polyamines may act differently, depending on their particular type and their levels (Williams et al., 1990, 1994). In general terms, putrescine weakly antagonizes NMDARs, both spermidine and spermine show an NMDAR agonistic effect, and spermine blocks most types of AMPARs and KARs (Williams et al., 1990, 1994).

Acting over NMDARs, polyamines may enhance both [^{3}H]TCP and [^{3}H]MK-801 binding at low micromolar range, whereas higher levels may lead to no significant change (Williams, 1997a, 1997b). Similarly, while low polyamine levels may enhance NMDA-induced currents, high levels may ameliorate or even inhibit them, resulting in a biphasic concentration dose–response curve (McGurk et al., 1990; Rock and Macdonald, 1995; Sprosen and Woodruff, 1990; Williams et al., 1991). This effect depends on the different subunits integrating NMDARs (Williams, 1997a, 1997b).

Spermine is responsible for the plateau-like shape of current-potential curves for non-NMDA glutamate receptors. As membrane potential (Vm) rises, spermine (highly cationic at physiological pH) is forced to enter into the channel pore, blocking Ca^{2+} flux through it. However, with Vm higher over +50Mv, spermine molecules are forced out of the pore and Ca^{2+} permeability is restored. This effect can only be observed in mGluR2 subunits lacking cationic arginine at Q/R moiety at the transmembrane M2 domain (Stromgaard and Mellor, 2004).

5.4. There is a link between polyamines and anxiety-related conditions

Polyamines may be involved in the regulation of fear-conditioning response (Camera et al., 2007; Gomes et al., 2010). Thus, systemic or intra-amygdalar administration of NMDA-agonist spermidine improves the acquisition and consolidation of auditory or contextual fear-conditioning, whereas arcaine, which antagonizes polyamine-binding site on NMDA receptors, or NMDA antagonist MK-801, block it (Camera et al., 2007; Mikolajczak et al., 2002; Rubin et al., 2001, 2004b). Systemic administration of spermidine improves the consolidation of fear conditioning. This facilitatory effect of systemically injected spermidine on memory is in agreement with the view that polyamines modulate memory by facilitating NMDAR activity (Berlese et al., 2005; Guerra et al., 2006; Rubin et al., 2004b).

Interestingly, intra-amygdalar injection of polyamines causes a biphasic effect on fear conditioning, in a similar pattern of what can be observed for NMDAR activity. Although low doses of spermidine improve fear memory formation, high doses of spermidine have no effect (Rubin et al., 2004a). In fact, polymines modulate acquisition and/or early consolidation of inhibitory avoidance (Rubin et al., 2000, 2001) and fear conditioning tasks (Rubin et al., 2004a). The immediately post-training intrahippocampal and intra-amygdalar administration of low doses of spermidine improves memory of the inhibitory avoidance (Rubin et al., 2000, 2001) and fear conditioning tasks (Rubin et al., 2004a). The facilitatory effect of low doses of spermidine on the memory of the inhibitory avoidance task is restricted to the acquisition and early consolidation phases, as it does not alter late consolidation and retrieval (Berlese et al., 2005).

Facilitatory effects of spermidine could be antagonized by minute amounts of arcaine, an antagonist of the NMDAR polyamine binding site, suggesting that NMDAR is involved in the memory improvement induced by spermidine (Rubin et al., 2000, 2001; 2004b). The injection of arcaine into the amygdala, at doses higher than those required to block the facilitatory effects of spermidine, may impair memory of inhibitory avoidance and fear conditioning tasks (Rubin et al., 2004b), what suggest an endogenous “polyaminergic tonus” might exist, and could possibly modulate memory processing under physiological circumstances (Camera et al., 2007). Nevertheless, negative results have also been published. In this experimental context, post-training intrahippocampal administration of arcaine (Rubin et al., 2000) or ifenprodil (da Silva et al., 2006) may have no effect on memory of inhibitory avoidance task in rats.

NR2B-specific antagonist, ifenprodil, may selectively block synaptic plasticity in LA, without disrupting normal synaptic transmission (Blair et al., 2001). Although, systemic administration of arcaine (5.0 mg/kg, i.p) before training improves the memory of the social recognition task, systemic administration of ifenprodil has no effect on that social recognition paradigm (Mikolajczak et al., 2002). Hence, the fact drugs targeting NMDAR polyamine site show amnestic activity in aversive, but not in non-aversive, tasks may be explained by its preferential effect on the amygdala. If that is the case, polyamine antagonists might be useful to prevent the formation of aversive memories, and then they might be useful in stress-related conditions, like PTSD (Hageman et al., 2001). Moreover, modulation of fear conditioning by arcaine is time-dependent; administration 0, 60 or 180 min after training impairs fear conditioning, whereas with no significant effect can be observed 360 min after training (Camera et al., 2007). This observation is in agreement with the observations by Berlese (Berlese et al., 2005), who found that the effect of intrahippocampal spermidine on memory of inhibitory avoidance is also time-dependent (Berlese et al., 2005). Systemic or intra-amygdala injection of ifenprodil, before training, disrupts the acquisition of contextual and tone fear-conditioning in rats (Rodrigues et al., 2001), and intraverebroventricular administration of ifenprodil also reverses memory facilitation caused by spermidine and NMDA in the inhibitory avoidance task (olfactory bulbectomized mice) (Tadano et al., 2004). Indeed, systemic administration of NMDAR antagonist at the polyamine binding site, eliprodil, has shown no significant effect on short (Sternberg memory scanning and paired words) or long-term memory (delayed free recall o pictures for long-term memory) in humans (Patat et al., 1994). Due to the fact that polyamines are known to have limited access to the brain (Camera et al., 2007), they have been overlooked as compounds that might cause

Table 8
A summary of the main studies evaluating agmatine antidepressant and anxiolytic-like activities in animals.

Author	Animal model	Route	Outcome
Zomkowski et al. (2002)	FST (ratas) TST (ratas)	I.p ó i.c.v	Agmatine shows antidepressant-like activity
Aricioglu and Altunbas (2003)	FST (ratas)	I.p	Agmatine shows antidepressant-like activity, similar to imipramine
Aricioglu and Altunbas (2003)	EPM (ratas)	I.p	Agmatine (40 mg/kg) show anxiolytic-like effects. Similar potency as benzodiazepines Doses >80–100 mg/kg show lack of efficacy
Lavinsky et al. (2003)	EPM (ratas)	I.p	Agmatine exerts anxiolytic-like effects
Gong et al. (2006)	VDCT (ratas y ratones)	s.c p.o	Agmatine exerts anxiolytic-like effects
	LDTT (ratas y ratones)	s.c	
	SIT (ratas y ratones)	p.o	

EPM: elevated plus-maze; FST: forced swim test; TST: tail suspensión test;; VCT: Vogel Conflict Test; LDTT: Light–dark transition test; SIT: social interaction test; i.p: intraperitoneal; i.c.v: intracerebroventricular; p.o: per orum; and s.c: subcutaneous.

central effects when given systemically. Only minute amounts of polyamines (within picomol range) are necessary to improve memory in the CNS, what may compensate their limited access to the brain (Camera et al., 2007).

Recently, a positive association between SAT-1-1415T/C SNP (rs1960264) and anxiety has been reported (Vaquero-Lorenzo et al., 2008). In particular, the T genotype was significantly more frequent in males suffering from anxiety disorders than in healthy male controls. Remarkably, rats over-expressing the main enzyme regulating polyamine catabolism, SSAT-1, show significantly higher brain putrescine levels, and show spatial learning and memory test performance impairment compared to their non-modified counterparts (Halonen et al., 1993; Kaasinen et al., 2004).

Some studies have recently examined the possible link between agmatine and stress response. Some authors have found increased agmatine levels in patients suffering from depression (Fiori and Turecki, 2008; Halaris et al., 1999). Rats exposed to cold restraint stress during 4 h leads to a significant increase in plasmatic and cortical agmatine levels, an effect not observed under normal temperature or after shorter stress periods (Aricioglu and Altunbas, 2003). Intraperitoneal administration of low doses of agmatine (0.01–50 mg/kg) (Zomkowski et al., 2002), may exert an antidepressant-like effect in some animal models of stress (FST, *forced swim test*, and TST *tail suspensión test*). That antidepressant-like effect may not be linked to significant changes in motor activity. A similar effect was seen with intracerebroventricular administration of agmatine (1–100 nmol/lateral ventricles) in the FST. Accordingly, intraperitoneal administration of agmatine may exert an antidepressant-like activity in the FST paradigm (Aricioglu and Altunbas, 2003), which may be as strong as that caused by (30 mg/kg). Antidepressant-like effect paradigms of agmatine, both in TST and in FST, does not seem to be blocked by NMDAR antagonist MK-801 (Zomkowski et al., 2002), but may be significantly abolished with previous administration of α_2 antagonist and 5-HT_{1A} antagonist, yohimbine (Zomkowski et al., 2002).

Recent data from rodents have determined that agmatine may have anxyolitic-like activity (VCT, SIT) (Gong et al., 2006). Agmatine (40 mg/kg) has also shown to be as good anxyolitic as benzodiazepines in rats (Aricioglu and Altunbas, 2003; Lavinsky et al., 2003). Higher doses of agmatine may not show more efficacy than placebo, what could be due to the fact that agmatine may exert neurotoxic effects at high doses. Accordingly, intravenous agmatine administration to rhesus monkey may lead to maintained weight loss, lethargy and increases in blood urea (Piletz et al., 2003). A summary of the main studies of antidepressant and anxiolytic-like activities of agmatine are shown in Table 8.

6. Conclusions

Anxiety is a major health issue that generates enormous disability, social, laboral, and economic burden. To date, routine treatments available for anxiety disorders include drugs targeting GABA and serotonin neurotransmission (benzodiazepines and SSRIs, respectively). Unfortunately, adverse side effects induced by those drugs may have a negative effect on compliance, increasing the risk of relapse.

A growing body of evidence suggests that glutamatergic neurotransmission may be involved in the biological mechanisms underlying stress response and anxiety-related disorders. The glutamatergic system mediates the acquisition and extinction of fear-conditioning. Thus, new drugs targeting glutamatergic neurotransmission seem to be an appealing promising target for anxiety-related disorders. In particular, NMDAR antagonists (AP5, AP7, CGP37849, CGP39551, LY235959, NPC17742, and MK-801), NMDAR partial agonists (DCS, ACPC), AMPAR antagonists (topiramate), mGluR1 negative allosteric modulators (AIDA, EMQMCM, JNJ16259685, LY456236), mGluR2/3 positive allosteric modulators (LY354740), and mGluR5 negative allosteric modulators (MPEP, MTEP), have shown anxiolytic-like effects in several animal models.

In humans, genetic, behavioral, and pharmacological studies have suggested that glutamatergic neurotransmission may be involved in anxiety-related conditions, such as PTSD, OCD, phobias, and panic disorder. Additionally, clinical trials have demonstrated that drugs acting at glutamate system may have some efficacy in the treatment of anxiety disorders. Promising results have been reported for NMDAR antagonists (memantine, some antiepileptic drugs), and NMDAR partial agonists (DCS), mGluR2/3 allosteric modulators (LY354740 and LY544344).

Several studies have suggested that polyamines may be involved in the mechanisms underlying stress-response and anxiety-related disorders. This could mainly be attributed to their ability to modulate ionotropic glutamate receptors, specifically NR2B subunits. The NR2B antagonist ifenprodil impairs fear conditioning. Agmatine may have anxiolytic effects in some animal models of anxiety (VCT and SIT). Thus, polyamines seem to be a promising new target for the treatment of anxiety-related disorders.

Throughout this paper we have compiled a battery of evidence which should leave the reader in no doubt as to the key role played by glutamatergic neurotransmission in the onset of fear response and anxiety. To this end, our recommendation is that more pharmacological research and development be done into the targeting of these pathways to open up an alternative range of treatment to the ones currently available.

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