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Glutamatergic Systems and Anxiety

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1. ANXIETY DISORDERS

Anxiety is a normal emotion experienced by humans and other mammalian species. However, anxiety also exists in pathological forms, and anxiety disorders are the most prevalent of psychiatric disorders. Prevalence rates vary with the diagnostic tools used to estimate them, and with study design, but the most extensive studies suggest that within the United States, 15.7 million people are affected yearly and 30 million at some point in their lives *(1)*. In a US study, 6% of men and 13% of women had suffered from an anxiety disorder in the previous 6 mo *(2)*.

According to current classification in the *Diagnostic and Statistical Manual* (DSM–IV) *(3)* major anxiety disorders include phobias, obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), and generalized anxiety. Although the specific symptomatology and etiology of these disorders varies, as does the recommended psychotherapeutic and pharmacological treatment, all of these disorders are characterized by at least three core clusters of symptoms: autonomic arousal, avoidance, and cognitive disturbance. Arousal of the autonomic nervous system involves sympathetic activation with associated tachycardia, sweating, shortness of breath, dry mouth, and other concomitants of preparation for a "fight-or-flight" response to a real or perceived threat. Avoidance involves physical or psychological distancing from threatening environments or events. Anxiety-related cognitive disturbance focuses on thoughts and feelings about the perceived threat and includes such symptoms as intrusive thoughts (as in OCD and PTSD), difficulty concentrating, vigilance, and excessive worry. Although there are similarities in core symptomatology across anxiety disorders, and with normal anxiety, there are also differences in the symptoms of each individual disorder. Accompanying the core symptoms of arousal, avoidance, and cognitive disturbance present in generalized anxiety and fear are alterations in the neurochemical environment within the brain, and many workers in the field would argue that what distinguishes "normal" anxiety from the anxiety disorders is that the latter reflect a neurobiological disorder of the central nervous system (CNS).

2. NEUROBIOLOGY OF ANXIETY

Emotional behaviors have long been ascribed to the "limbic system," the large relative size of the human limbic areas prompting Donald Hebb, a figure better known in a quite

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different context in the glutamate field, to point out that the evolution of intelligence had not led to a reduction in the importance of emotions, and to speculate that humans are the most emotionally developed animals (cited in ref. *4*). The term "limbic system" is difficult to sustain in the subsequent development of functional neuroanatomy, and these early ideas have been superseded by more specific hypotheses regarding neuronal structures involved in anxiety. Central among such hypotheses are those identifying the amygdala and its connections as the core of a system subserving fear conditioning (e.g., refs. *5–8*), the septo-hippocampal hypothesis of Gray *(9,10),* which posits that neural systems in the hippocampus and related areas, underlying behavioral inhibition, lie at the heart of anxiety mechanisms, whereas systems identified as mediating flight from immediate threat, and including the periaqueductal gray matter of the midbrain and its related hypothalamic circuits, represent the fundamental systems serving fear and panic reactions *(11)*. Each of these complementary hypotheses requires consideration of the role of glutamatergic transmission that might have implications for potential treatments.

2.1. Amygdala and Conditioned Fear

The amygdala has long been implicated in the expression of fear and anxiety. Early work on the Kluver–Bucy syndrome described how amygdala lesions in monkeys resulted in animals that showed little fear of objects and people that were treated as threatening by normal animals. More recently, activation of amygdala during panic attacks *(12,13)* or anticipatory anxiety *(14)* has been cited as evidence for involvement of the amygdala in clinical anxiety. Congruent findings that PTSD (but not panic disorder or OCD) patients show increases in blood flow in the right amygdala when exposed to anxiety-provoking stimuli have also been reported *(15–17)*, whereas in a functional magnetic resonance imaging (fMRI) study *(18)*, social phobic patients (but not controls) showed heightened activation of the amygdala bilaterally in response to presentation of emotionally neutral faces previously associated with an aversive odor.

Animal experimental work has also identified amygdala circuitry as being of central importance in processing of information during fear conditioning, and in the fear-potentiated startle paradigm (e.g., refs. *5, 6,* and *19*). Much of the work evaluating the role of the amygdala in mediating emotions has been the subject of recent excellent reviews (e.g., *19* and *20*). In particular, the amygdala appears to be of central importance in the formation of associations between discrete environmental events and aversive stimuli, and the expression of fear reactions through its projections to brainstem structures governing behavioral, autonomic, and endocrine responses to threat. Formation of associations between environmental contexts (i.e., the entire complex of cues provided by any environment) and aversive stimuli additionally requires the involvement of hippocampal systems projecting to amygdala nuclei. It is of note that both the thalamo-amygdala pathways and afferents from temporal cortex synapse on to lateral amygdala neurons bearing both *N*-methyl-D-aspartate (NMDA) and non-NMDA receptors *(21)*.

There is currently some discussion regarding the roles of amygdala nuclei in processing fear-related information. Although both Ledoux and Davis emphasize the lateral and basolateral part of the amygdala as the area that receives input regarding both aversive events and associated cues, and hold that these areas then provide inputs to the central nucleus, recent studies suggest that the central nucleus may also function independently of the lateral nuclei, receiving highly processed sensory input from entorhinal cortex and related areas (*see* ref. *20* for a review).

2.1.1. Intra-Amygdalar Pathways

Within the amygdala, information regarding at least simple acoustic cues reaches the central nucleus either directly *(7)* or from the lateral amygdala, which itself is thought to receive information from sensory, including auditory, pathways *(5)*. The lateral amygdala projects to the central nucleus both directly, and via relays in the basal and accessory basal amygdala. The lateral amygdala also receives information regarding nociceptive events, whereas the accessory basal nucleus receives input from the spinothalamic tract via the posterior thalamus *(22)* and the central nucleus, both indirectly via the parabrachial area *(23)* and directly from spinal cord *(24)*. The amygdala is therefore well-fitted to integrate information regarding aversive events and environmental stimuli that predict them. Certain lateral amygdala neurons fire in response to both nociceptive stimulation and auditory input *(25)*, offering the possibility of integration of auditory with nociceptive information by associative long-term potentiation (LTP) in the auditory input pathway.

2.1.2. Output Pathways

The central nucleus of the amygdala projects to other areas (*see also* Chapter 3)controlling the expression of fear responses, and lesions of the central nucleus disrupt the expression of the behavioral, autonomic, and endocrine responses of conditioned fear. Lesions in these projection areas are able to disrupt selectively parts of the fear response, so that damage to the lateral hypothalamus prevents blood pressure, but not freezing responses, whereas lesions of the midbrain central gray disrupt freezing, but not blood pressure responses *(26)*. Similarly, selective disruption of the conditioned release of pituitary-adrenal stress hormones is achieved by stria terminalis lesions *(27)*.

2.1.3. Learning Mechanisms in the Amygdala

LTP has been proposed as a mechanism whereby synaptic transmission is facilitated as a result of use. In the hippocampus CA1 region, the mechanism whereby repeated activation of synapse results in facilitated transmission has been demonstrated to depend on glutamate acting at α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptors to depolarize the postsynaptic membrane, a consequence of the membrane depolarization is the expulsion of Mg^{2+} ions from the lumen of NMDA receptor-gated channels, allowing glutamate acting at these receptors to trigger Ca^{2+} flux through the channel. Ca^{2+} influx triggers a number of intracellular events that lead to enhancement of the fast AMPA receptor-mediated component of synaptic transmission *(28,29)* arising from increased concentration of AMPA receptors within the synapse, and, consequently, increased excitatory postsynaptic potential (EPSP) magnitude in the postsynaptic element following presynaptic activity. This basic mechanism may form the basis for the formation of associations; if a postsynaptic element (say, a spine) has synapses with two presynaptic inputs, then activity in one of them may provide the necessary depolarization to remove the Mg^{2+} block in neighboring synapses, thus allowing NMDA receptor-mediated transmission through the second synapse, and increased probability of presynaptic activity in the second synapse resulting subsequently in activation of the postsynaptic element. If synapse 1 carries information regarding an aversive event (the unconditioned stimulus [US]), and synapse 2 information regarding an environmental event (conditioned stimulus [CS]) occurring contemporaneously with the US, then, following synaptic strengthening, activation of the synapse carrying information about the CS may have similar postsynaptic consequences as activationg the synapse carrying information

regarding the aversive US did before strengthening occurred. Thus, a form of "associative LTP" may in principle underlie simple conditioning. Whether it indeed does so requires further evidence, but it is of considerable interest that prior fear conditioning increases the magnitude of EPSPs in amygdala slices *(30)*. Furthermore, LTP is found in the pathway from medial geniculate body to the lateral nucleus of the amygdala, which is thought to mediate conditioning of fear responses to acoustic stimuli, and tetanic stimulation of the medial geniculate body also results in a long-lasting potentiation of a field potential in the lateral amygdala elicited by a naturally transduced acoustic stimulus *(31,32)*. The stimulation coincidence parameters that are necessary for induction of LTP in the lateral amygdala closely resemble those required for the formation of associations between CS and US in fear-conditioning experiments *(33)*. Taken together, these experiments suggest that that LTP-like mechanisms underlie amygdala-mediated fear conditioning.

2.1.4. Glutamatergic Transmission in Amygdala Circuits

The neural bases of LTP have been most extensively studied in the well-characterized pathways of the hippocampus, and it is not clear whether the same mechanisms underlie LTP in amygdala pathways. Although NMDA receptor-dependent LTP has been demonstrated in pathways from cortex to amygdala *(34,35)*, and some pathways within the amygdala *(36,37)*, NMDA-independent LTP has also been suggested *(38)*. In the thalamo-amygdala pathway, NMDA-independent LTP may be mediated by Ca^{2+} influx through L-type voltage gated Ca^{2+} channels *(39)*. A further possible difference between hippocampal LTP and amygdala LTP (at least in the lateral amygdala) is in the presumed locus of plasticity. Although it is widely accepted that postsynaptic changes are responsible for the increased synaptic efficiency seen in hippocampal CA1 LTP, some forms of amygdala LTP may depend upon presynaptic changes *(40)*. Furthermore, synaptic facilitation resulting from low-frequency activation of the pathway from external capsule to lateral amygdala is independent of both NMDA receptors, and L-type calcium channels, and depends upon Ca^{2+} flux through kainate receptor-operated channels *(41)*. This form of LTP may not require alterations in AMPA receptor location or density within the synapse, and may implicate presynaptic mechanisms, including facilitated glutamate release *(41)*. The facilitation of transmission is also not limited to the synapse carrying the signal leading to the LTP (homosynaptic LTP) but spreads to neighboring synapses (heterosynaptic LTP). Inasmuch as these neighboring synapses may be involved in the processing of different environmental events, this latter property may result in generalization of conditioned fear to other stimuli that have not been specifically associated with a fearful event. This might be a mechanism underlying pathological conditions in which anxiety or fear are triggered inappropriately by innocuous stimuli *(41)*.

2.1.5. Glutamatergic Pharmacology of Amygdala-Mediated Fear Conditioning

The work outlined above suggests that fear conditioning may be amenable to manipulation by several drugs acting at glutamate ionotropic receptors. In keeping with the proposed role of NMDA receptors in the formation of LTP, NMDA antagonists given during acquisition of the conditioned fear response should prevent conditioned fear, and indeed, infusion of 2-amino-7-phosphonopentanoic acid (APV) into the basolateral amygdala (BLA) during acquisition blocked fear conditioning, whereas APV infusions prior to testing (when NMDA receptors may not be required for expression of the plasticity) had no effects *(42,43)*. Though others *(44,45)* have found NMDA blockade in the

right BLA to interfere with both acquisition, and expression of conditioned fear responses, the blockade of expression may be explained by the involvement of NMDA receptors in normal synaptic transmission within amygdala accessory pathways (e.g., ref. *45*). This explanation would also account for the effectiveness of intra-BLA infusions of NMDA antagonists in nonassociative measures of anxiety, such as the plus-maze *(46)* and social interaction tests *(47)*.

In keeping with the notion that expression of conditioned responses may depend on upregulation of non-NMDA mediated transmission, local infusion of the AMPA/kainate antagonists CNQX and NBQX into either central or basolateral amygdala blocks expression of fear-potentiated startle *(48,49)*.

2.1.6. A Wider Role of the Amygdala in Affective Behavior

In addition to its well-known role in mediating anxiety and fear, the amygdala also plays a central role in learning about appetitive events. The BLA appears to play an essential role in the attribution of affective value to environmental events that predict either aversive or appetitive events. Although animals may be able to learn about the predictive nature of such cues following lesioning of the lateral amygdala, the cues acquire no affective value of their own. In other words, stimuli associated with fear-producing situations may inform the animal of an imminent aversive event, but the stimulus will not evoke an emotional response. In the case of appetitive conditioning, rats with BLA lesions fail to learn new instrumental responses to obtain a cue previously associated with food or a drug reward. Current theories thus hold that the BLA functions to allow animals to utilize cues associated with primary reinforcers, whether positive or negative, to assess their affective properties, and to use that representation to alter their behavioral response *(50,51)*. Although largely developed to account for data acquired from appetitive conditioning, essentially similar functions are likely to apply to aversive conditioning. According to the model of Everitt and colleagues *(50)*, the affective value of the CS is processed by the BLA, but the consequences for behavioral output depend on the information being conveyed to the accumbens *(52–54)*. This approach predicts that disruption of BLA function might then reduce the organism's ability to assess the affective significance of cues conditioned to motivationally significant events—both positive and negative.

2.1.7. AMPAergic Transmission in Basolateral Amygdala

In the BLA, AMPA receptors mediate fast excitatory postsynaptic potentials in response to activation of glutamatergic inputs from both cortical and subcortical regions *(55,56)*. The BLA contains two major classes of neuron: (1) spiny pyramidal projection neurons and (2) sparsely spined, nonpyramidal local circuit neurons, most of which are γ-aminobutyric acid-(GABA)ergic *(57)*. It is the synaptic contacts of these GABAergic neurons that are likely to be the means by that benzodiazepine anxiolytics infused into the BLA achieve anxiolytic-like effects in rodent models of anxiety such as the Vogel punished licking test *(58)*. The GABAergic local circuit neurons differ from the pyramidal cells in their AMPAergic inputs. Whereas the GABAergic interneurons possess marked immunoreactivity to GluR1 subunits, the pyramidal cells exhibit only light GluR1 immunoreactivity *(59)*. Conversely, although GluR2/3 immunoreactivity has been reported in some interneurons, it is largely limited to pyramidal neurons *(59–61)*, and He and colleagues *(61)*, using a selective GluR2 antibody, conjecture that many

AMPA receptors on interneurons may not contain GluR2. This interpretation is consistent with electrophysiological evidence indicating that, whereas the AMPA component of the synaptic current at inputs to pyramidal cells is independent of calcium (the underlying receptors thus contain GluR2 subunits), in contrast, AMPA receptors on inhibitory interneurons show high permeability to calcium, indicating a low representation of GluR2 *(62)*. This complex arrangement makes it difficult to predict whether drugs acting at AMPA receptors are likely to give rise to anxiolytic or anxiogenic effects, because they will interact with both inhibitory and excitatory inputs to BLA pyramidal cells. However, animals with targeted deletions of GluR1 subunits should differ from mice with deletions of GluR2 or GluR3 subunits. Because GluR1 subunits represent by far the major component of AMPAergic receptors in the GABAergic interneurons, it is likely that targeted deletion of GluR1would result in a profound reduction in their excitability, with a consequent disruption of firing patterns of BLA pyramidal output neurons to which they normally provide an inhibitory control. Inasmuch as BLA neurons are involved in anxiety, one might then expect that GluR1 knockout mice would show increased anxiety as a consequence of reduced activation of GABAergic interneurons, whose outputs are presumably the site of anxiolytic action of benzodiazepines administered into the BLA. We have observed an increased tendency to thigmotaxis in an open field, and reduced open-arm exploration in the plus maze in GluR1 knockouts, as well as increased fear conditioning in a conditioned emotional response measure (Ripley, Mead, and Stephens, unpublished observations).

In the absence of GluR2 subunits in most receptors, the high calcium permeability of AMPA receptors in synaptic contacts onto BLA interneurons may make such synapses especially sensitive to plastic modification. Tetanic stimulation of inputs to BLA inhibitory neurons results in increased synaptic efficacy, which is independent of NMDA receptor activation, and is reflected in an increase in GABAergic inhibitory currents in pyramidal neurons *(62)*. Deletion of the gene-encoding GluR1 subunits can thus be expected not only to reduce the extent to which the inhibitory interneurons modulate pyramidal cell activity, but also to remove the substrate whereby plastic changes in the inhibitory control of pyramidal cell excitatory outputs (including those to accumbens; refs. *63–65*) occur during learning. In principle, this action may account for the loss of the ability of mice in which GluR1 subunits have been deleted to attribute affective properties to environmental cues associated with positive reinforcement *(66,67)*.

An alternative account of these findings might thus be that deletion of GluR1 leads to an impairment of the glutamatergic input from BLA to the ventral striatum *(64,65)* or orbitofronal cortex *(68,69)*, because the medium spiny neuron targets of this amygdala-accumbens pathway also express GluR1 subunit-containing AMPA receptors *(70)*.

The foregoing paragraphs illustrate the complexity of transmission within the amygdala glutamatergic circuits and much remains to be discovered before potential therapeutic agents based on interactions with glutamate systems can be rationally designed.

2.1.8. Dopamine–Glutamate Interactions in Amygdala

The schema outlined above suggests that the amygdala may influence behaviors related to anxiety by two rather separate mechanisms. First, outputs from the central nucleus to assorted brain areas may be responsible for both behavioral responses, such as flight or fight, mediated through hypothalamus and central gray of the midbrain, and

endocrine (via paraventricular nucleus) and vegetative consequences of fear-provoking events. Second, motivational consequences of fear-related stimuli may be organized through outputs to the ventral striatum and orbitofrontal cortex. This latter system offers a substrate for interactions between glutamate and dopamine systems paralleling those involved in appetitive motivation.

A third possible interaction is suggested by the observation that dopamine neurons arising from substantia nigra and ventral tegmental areas of the midbrain provide a rich innervation of the amygdala, and such projections are activated during presentations of conditioned fear stimuli. Blockade of these pathways by administration of either a D1 antagonist (SCH23390) into basal or lateral areas of the amygdala, or a D2 (quinpirole) antagonist into the ventral tegmental area (VTA; both of which treatments result in decreased D1 receptor activation at the amygdala target neurons) decreases freezing to a cue paired with a fear stimulus *(71,72)*. Similarly, either SCH23390 or the D2 antagonist, raclopride, administered into amygdala blocks the acquisition of fear-potentiated startle *(73,74)*, and a D2 antagonist, eticlopride, administered into amygdala attenuates conditioned freezing to a tone presented 24 h later, implicating D2 receptors in acquisition of fear conditioning *(75)*. In these experiments, injections were directed at lateral and basolateral aspects of the amygdala, and although there may have been some spread of the drug to neighboring areas, it seems likely that most of these effects are indeed attributable to these nuclei. A possible explanation of these observations holds that synaptic plasticity in the BLA requires not only coincidence of a sensory-related synaptic input (perhaps the CS) and one that causes a postsynaptic depolarization (perhaps the US), but also dopamine release *(76)*. Dopamine is known to enhance signal-to-noise ratio of strong inputs into postsynaptic elements bearing dopamine receptors, so that it can be hypothesized to enhance neuronal excitability, maximizing the association of the CS and US, while suppressing less significant inputs not related to the task. In particular, DA receptor activation in BLA potentiates the electrophysiological response evoked by electrical stimulation of sensory association cortex, while attenuating spikes elicited by stimulating prefrontal and mediodorsal thalamic inputs to the BLA *(77)*. Dopaminergic systems might thus play a facilitatory role in acquisition of conditioned fear *(78)*.

A further source of interaction between BLA dopamine and glutamate systems derived from the BLA's outputs to prefrontal cortex and nucleus accumbens. Accumbens medium spiny GABA neurons receive glutamatergic inputs from cortico-limbic areas, including prefrontal cortex, hippocampus, and amygdala, and dopamine systems may be important in biasing the selection of particular inputs to influence behavioral output through activation of the medium spiny neurons *(79,80)*. Glutamatergic afferents from the BLA form synapses in close proximity to dopamine terminals, and afferent activity from BLA increases dopamine efflux, which may then act to facilitate processing of further glutamatergic input from BLA *(79)*. The BLA may also affect dopamine release in the accumbens indirectly; BLA glutamatergic projections to medial prefrontal cortex activate feedback mechanisms to the VTA, which regulates firing of dopamine neurons *(81)*.

Dopamine is released in accumbens shell following exposure to both unconditioned and conditioned aversive and stressful events *(82,83)*, though the increased dopamine release may depend on fear conditioning *(83,84),* even in the case of apparently unconditioned experimental situations *(85)*. Consistent with a role of dopamine in fear conditioning, dopamine depletion in the accumbens disrupts aversive conditioning *(86)*.

Dopaminergic–glutamatergic interactions in BLA and accumbens are thus likely to play complex roles in processing of stimuli signaling aversive, as well as rewarding events. Consistent with this account, antipsychotic drugs, including clozapine, haloperidol, and raclopride *(87)* and dopamine D1 antagonists *(87)* given systemically block the acquisition (though not the expression) of conditioned fear in rodents.

Despite such evidence from animal studies, antipsychotic drugs are not recognized by prescribing agencies for the treatment of anxiety disorders, though they have a tradition of use in the control of anxiety associated with psychoses, and in the elderly, and are sometimes used by general practitioners for other forms of anxiety.

2.2. *Output Systems: Fight-and-Flight Systems in the Periaqueductal Gray*

As already outlined, amygdala outputs to the central gray may be important in mediating behavioral responses to cues conditioned to aversive events. The main excitatory input into the central gray is glutamatergic and NMDA receptors are widely distributed within the structure *(88,89)*. Injections of NMDA antagonists into the periaqueductal gray give rise to anxiolytic-like effects in the elevated plus-maze *(90–93)*. Similarly, injection of the glycine antagonist 7-chlorokynurenic into the dorsal periaqueductal gray blocked the anxiogenic effects of penetylenetetrazol in the elevated plus-maze *(94)*. More recently, anxiolytic-like effects of AP7 following injection into the dorsolateral or ventrolateral columns of the central gray in the Vogel punished licking test have been described *(93)*. Although these observations are in a general sense consistent with a role of glutamatergic systems within the periaqueductal gray in anxiety, it is unfortunate that further observations are not available in tests with more face validity as models of flight or of panic.

2.3. *The Septo-Hippocampal Hypothesis of Gray*

Gray and McNaughton *(10)* dispute that anxiety may be equated with conditioned fear, partly on the grounds that conventional anxiolytic drugs are ineffective against fear in animal models in which flight is the predominant response to the threat, whereas they are active in models in which the threat can be avoided passively. Although *panic* attacks may resemble flight behavior (and thus depend on neural circuitry engaged in flight reactions), other anxiety disorders do not engage these systems (located in a hierarchical defence system involving periaqueductal gray, medial hypothalamus, amygdala, and cingulate cortex *[10]*).

Central to Gray's account of the neural mechanisms serving *anxiety* is the concept of a "behavioral inhibition system." This system analyzes environmental events that are innately fearful or novel (and thus potentially dangerous), or that have been learned to predict punishment or nonreward. In response to such events, the system induces increases in arousal and attention, and inhibits ongoing behavior, the cardinal features of anxiety states. The key anatomical element of the behavioral inhibition system is the septo-hippocampal system. Anxiolytic drugs affect the function of the septo-hippocampal system by reducing activity in noradrenergic and serotonergic inputs to the system. Since the monoamine neurons are activated by inputs from largely glutamatergic afferents *(95)*, these synapses are potential targets for glutamatergic antagonists to reduce activity in these systems. Additionally, however, signaling within the hippocampal system is also dependent upon glutamate, and antagonists acting at intrahippocampal circuits can also be expected to degrade hippocampal information processing.

In keeping with these ideas, intrahippocampal injection of the competitive antagonist AP7 increased open-arm exploration in the plus-maze in rats previously exposed to restraint stress *(96)*. It should be noted, however, that similar anxiolytic effects were not seen in unstressed animals.

Despite the clear implications of these notions for a potential anxiolytic effect of glutamate receptor antagonists infused locally into the relevant brain areas, no work appears to have been carried out attempting to induce anxiolytic effects through modulation of activity in raphe or coeruleus neurons by administering glutamate receptor antagonists into these areas.

3. BEHAVIORAL PHARMACOLOGY OF GLUTAMATE

3.1. NMDA Receptor Modulation as Potential Treatment of Anxiety

A potential effectiveness of NMDA antagonists as anxiolytic agents was suggested independently by Stephens *(97)*, and by Bennett *(98)* from their effects in animal models. Since these early findings, evidence has accumulated that agents acting at several sites on the NMDA receptor complex are effective in animal models of anxiety. Thus, competitive NMDA antagonists, high-affinity open-channel blockers, glycine site antagonists, and polyamine site antagonists have all been reported to exhibit anxiolytic activity in both punishment and nonpunishment models of anxiety in rodents. The most consistent effects have been observed with competitive NMDA antagonists, though until recently, glycine and polyamine site antagonists had received little research attention. Although the majority of these studies were performed in rodents, a few experiments have examined the anxiolytic effects of NMDA modulation in primates (e.g., *see* ref. *99*). This earlier work has been extensively reviewed and will not be dealt with here. It is important to note, however, that whereas at least competitive antagonists appear to exert consistent effects in standard animal tests predictive of anxiolytic activity, all the antagonists are also active in tests predictive of side effects such as sedation, muscle relaxation, and cognitive dysfunction leading to memory impairments. For this reason, emphasis in the majority of recent studies has been on tests of glycine site antagonists, which have been suggested to have fewer problematic side effects than high-affinity open-channel blockers or competitive antagonists.

Nevertheless, results with glycine site ligands have been mixed, regarding both this anxiolytic activity and lack of side effects. For example, 1-aminocarboxycyclopropane (ACPC), a partial agonist at strychnine-insensitive glycine sites, was inactive in the elevated plus-maze model in rats *(100)*, though it did exhibit anxiolytic activity in the Vogel conflict model in rats *(101)*. In contrast, positive findings were obtained for the racemate and for the active isomer of HA-966 [(±)HA-966 and (+)HA-966, respectively], each of which produced modest anxiolytic effects in the elevated plus-maze *(100,102)*. When tested at sufficiently high doses, D-cycloserine also gave rise to anxiolytic-like effects in elevated plus-maze and conflict models in rats *(100,103)*. The anticonflict effect of D-cycloserine was blocked by coadministration of NMDA, but not glycine, suggesting that the effect may not have been mediated through glycine receptor sites *(103)*. At lower doses, D-cycloserine was not active in the elevated plus-maze, but it did block the anxiolytic activity of ethanol in this procedure *(102)*. In contrast to the positive findings with D-cycloserine, negative findings were reported for several glycine site antagonists, including ACEA 1011, ACEA 1021, MRZ 2/570, MRZ 2/571, and MRZ 2/576, and the glycine prodrug milacemide when tested in conflict models in rats *(100,104)*. The MRZ-type glycine-B full antagonists were also not active in the elevated plus-maze in rats *(100)*.

Another compound, MDL 105,519, has been reported to produce decreases in separation-induced vocalizations in rat pups *(105)*, suggesting anxiolytic potential. These effects, however, were accompanied by muscle relaxant activity, suggesting that the compound was not anxioselective. Another compound, L-701,324, produced dose-dependent anxiolytic effects in the elevated plus-maze in rats and mice without changes in overall activity *(100,106,107)*, but the magnitude of the effect was slightly less than that of diazepam *(108)*. In mice, the anxiolytic effect of L-701,324 in the elevated plus-maze was reversed by administration of glycine *(107)*, consistent with its proposed glycine site of action. In rats tested in the Vogel conflict model, the effects of L-701,324 were less positive: in one study, it produced a modest anticonflict effect *(108)*; in another study, it did not produce an anxiolytic effect *(100)*.

Further, there is no relationship between intrinsic activity at strychnine-insensitive glycine receptors (as measured by a patch-clamp technique) and efficacy in an anxiolytic procedure *(100)*. Although such attempts at correlation of potencies ignore the contribution that pharmacokinetic factors may make to the in vivo efficacy of drugs, they may suggest that the anxiolytic effects of these drugs may not be mediated through interaction with the population of glycine-B receptors measured in this study.

As with other subclasses of NMDA antagonists, the inconsistent nature of the anxiolytic effects of glycine site-selective modulators across procedures and labs contrasts sharply with the robust and reliable effects of benzodiazepines. At least two explanations of this contrast are possible: (1) these models were developed to detect benzodiazepine effects and may not be as sensitive for detection of anxiolytic effects of nonbenzodiazepines or (2) the anxiolytic effects of NMDA antagonists may not be as robust as those of the benzodiazepines.

3.1.1. Where in the Brain Do NMDA Antagonists Exert Their "Anxiolytic" Effects?

A number of recent studies have used central, site-directed injection of NMDA antagonists in an effort to determine the brain area(s) in which the anxiolytic effects of these drugs are mediated. Brain areas that have received attention in recent research are the hippocampus, the amygdala, periaqueductal gray, and the ventral tegmental area. The anxiolytic effects of the glycine site partial agonist ACPC produced anticonflict effects when injected ip and intrahippocampally whereas the competitive NMDA antagonist CGP 37,849 was active in the conflict test only when injected ip *(101)*. Curiously, the anxiolytic effects of both of these compounds was blocked by pretreatment with the benzodiazepine antagonist, flumazenil. Why blockade of the benzodiazepine-binding site of $GABA_A$ receptors should influence the action of NMDA antagonists is unclear, but there may be an interaction of glutamate and GABA systems in mediation of the anxiolytic effects of these NMDA antagonists *(109)*. Similarly, intrahippocampal injection of the competitive antagonist AP7 showed no anxiolytic effect in the elevated plus-maze in nonstressed rats; however, in stressed rats, intrahippocampal injection of AP7 was anxiolytic *(110)*. These results suggest that site selectivity within the NMDA receptor complex, as well as stress, affect neural mediation of the anxiolytic effects of NMDA antagonists in the hippocampus. The periaqueductal gray also appears to be important in mediation of the anxiolytic effects of some NMDA antagonists. In previous studies, Guimarães and colleagues *(90,91)* showed that injections of NMDA antagonists into the periaqueductal gray produced anxiolytic effects in the elevated plus-maze. In their more recent study,

they report that injection of a nonselective glutamate antagonist, glutamic acid diethylester, that blocks both NMDA and AMPA/kainate receptors, also has anxiolytic effects in this model *(91)*. Similarly, injection of the glycine antagonist 7-chlorokynurenic into the dorsal periaqueductal gray blocked the anxiogenic effects of penetylenetetrazol in the elevated plus-maze *(94)*. Another glycine-site antagonist/partial agonist, R(+)HA-966, blocked the acquisition and expression of conditioned fear-induced immobility when injected into the ventral tegmental area, but not when injected into the mesoprefrontal area *(111)*. In addition, the extinction of conditioned fear was blocked by an intra-amygdala injection of the competitive NMDA antagonist, AP5 *(112)* whereas intra-amygdala injection of MK-801 did not block acquisition of an anxiogenic effect caused by exposure to a stressor *(46)*. In summary, then, the anxiolytic effects of NMDA antagonists may be mediated in different brain areas depending on the site within the receptor complex at which the specific compound acts. Further, the results of brain site injection studies suggest the possibility of differential distribution of heterogeneous NMDA receptor subunits comprising the binding sites.

As suggested above, stress may modulate the anxiolytic effects of NMDA antagonists. A related and developing area of interest is the evaluation of anxiolytic effects of NMDA antagonists in compromised animals. In a study examining the anticonvulsant effects of NMDA antagonists, Löscher and his colleagues have shown that the effects of competitive and phencyclidine (PCP)-like antagonists on motor behavior are similar in amygdala-kindled rats whereas the effects of these compounds differ in uncompromised rats *(113)*. These results suggest that there may be some fundamental differences in the brains of epileptic rats that change their response to NMDA antagonists. Since anxiety disorders may also involve temporary or permanent changes in brain function *(114)*, it is possible that the effects of NMDA-based anxiolytic agents may also differ in anxious vs nonanxious rats. Several recent studies have investigated this possibility by examining the anxiolytic effects of NMDA antagonists in animals that had been exposed to a stressor or that were undergoing ethanol withdrawal. Adamec and colleagues have developed a preclinical model that they suggest to have features of PTSD, in which long-lasting anxiogenic-like effects in an elevated plus-maze are engendered in rodents following a single exposure to a cat *(115)*. More recently, they have shown that MK-801 and the competitive NMDA antagonists, AP7 and CPP, block the acquisition of this anxiety-like response to a stressor, but have no effect on expression of the response if administered soon after predator exposure *(116)*. When administered a short time before testing in the elevated plus-maze, however, MK-801 (but not the competitive NMDA antagonists) still maintained an anxiolytic effect in these stressed rats. Similarly, intrahippocampal injection of AP7 produced anxiolytic effects in the elevated plus-maze in rats exposed to restraint stress, but not in nonstressed rats *(96)*. Anxiolytic effects in the elevated plus-maze were also observed following systemic injection of AP7 or CGP 37,849 (another competitive NMDA antagonist) in rats stressed by withdrawal from ethanol following induction of dependence *(117)*. Interestingly, MK-801 was only marginally effective and HA-966 was ineffective in attenuation of the anxiogenic effects of ethanol withdrawal, suggesting that the source or cause of "anxiety" is important in determination of anxiolytic efficacy of site-selective NMDA antagonists. Further, the results of the few studies in this area suggest that NMDA antagonists may be differentially effective in the treatment of different types of anxiety disorders or conditions (e.g., generalized anxiety vs PTSD vs ethanol withdrawal).

A final study that should be mentioned used a traditional method of evaluating anxiolysis (i.e., elevated plus-maze), but effected NMDA receptor modulation via a novel method *(118)*. In this study, phosphodiester antisense oligodeoxynucleotide administration was used to reduce synthesis of the NMDA-NR1 subunit. Mice treated with antisense spent more time in the open arms of an elevated plus-maze whereas mice treated with vehicle or with the corresponding sense nucleotide did not show this anxiolytic effect. These results suggest that the NMDA-R1 subunit may be important in mediation of the anxiolytic effects of NMDA antagonists, though changes in trafficking of other subunits following disruption of NR1 should also be considered.

3.2. *Non-NMDA Receptor Modulation as Potential Treatment of Anxiety*

Evidence for the usefulness of non-NMDA receptor antagonists for the treatment of anxiety disorders is considerably weaker than that for NMDA receptor antagonists. To a great extent this reflects the poor availability of drugs that have selective actions at AMPA and kainate receptors and that show good brain penetration and useful pharmacokinetic properties in rodents. Additionally, AMPA receptors are so universally involved in fast transmission throughout the CNS that only a narrow window is available at which selective anxiolytic effects of antagonists might be observed without concurrent disruption of behavior through their sedative and muscle relaxant actions. Nevertheless, positive effects of AMPA antagonists have been described in animal models predictive of anxiolytic action in the clinic.

NBQX is a quinoxalinedione derivative that has little affinity for NMDA receptor sites, but that acts as a mixed AMPA/kainate receptor antagonist. In the four-plate test in mice, NBQX enhanced punished activity at a dose of 0.033 mmol/kg, but higher doses could not be effectively tested since they depressed locomotor activity *(119)*. An agonist at kainate receptors containing the GluR5 subunit, ATPA, had clear anxiogenic-like effects in this test, decreasing punished locomotor activity at a dose (0.002 mmol/kg) that had no effect on spontaneous locomotor activity in unpunished mice. These observations suggest that kainate receptors may be involved in signaling information regarding punishment, consistent with the role for amygdala kainate receptors in anxiety postulated by Li et al. *(41)*. Alternatively, NBQX may have exerted its effect through AMPA receptors. A similar problem of interpretation of the relative roles of AMPA and kainate receptors in mediating anxiolytic effects is provided by LY326325. This mixed AMPA/kainate antagonist induced a dose-dependent increase in a punished drinking test, without concomitant effects on unpunished drinking *(106)*. These effects occurred over a dose range (2.5–5mg/kg, ip) that did not influence locomotor activity. In the plus-maze assay, however, LY326325 (0.5–5 mg/kg) did not alter the percentage of entries into the open arms, though one dose (1 mg/kg) gave rise to a small, though significant increase in the time spent on the open arm. These observations stand in contrast to a previous report from the same group *(120)* in which LY326325 induced a dose-dependent *decrease* in time spent in the open arms, as well as the percentage entries into the open arms. In this study NBQX also caused a dose-dependent reduction in the time spent in the open arms. The authors conclude that AMPA receptor antagonists may give rise to anxiogenic-like behavior in the plus-maze, but the lack of consistency across test situations and the susceptibility of the plus-maze as a model of anxiety to interference from locomotor effects of drugs *(121)* cast doubt on this interpretation. NBQX has also been reported to possess

only limited ability to antagonize the discriminative stimulus provided by the $GABA_A$ channel blocker, pentylenetetazole *(122)*, which has been argued to be based on the anxiogenic properties of pentylenetetrazole *(123)*.

In an extensive study of three quinoxalinedione competitive antagonists of AMPA/kainate receptors (CNQX, DNQX, and NBQX) and a noncompetitive AMPA receptor antagonist (GYKI 52466) in the Vogel test of punished drinking, none of these drugs, tested up to dose ranges that reduced exploratory activity in the rat, were found to increase punished drinking, allowing the authors to conclude that AMPA/kainate receptors probably are not directly involved in the control of rat emotional behavior *(124)*. However, administration of the agonist, S-AMPA, intracerebroventricularly at a dose of 2 μg/5 μL, significantly enhanced the ability of electric shock to suppress drinking in thirsty rats. Interpretation of this observation in terms of an anxiogenic effect of the agonist is complicated, however, by observations that the same dose decreased activity, and even gave rise to "prodromal" symptoms of epileptic activity in some animals. Lastly, given the theoretical importance of behavioral inhibition in the action of anxiolytic drugs *(10)*, it is of interest that NBQX at a very low dose (10–1000 ng/rat) increased premature responding in a two-lever choice reaction time task, without altering response speed or accuracy *(125)*. Nevertheless, in another model of behavioral inhibition, differential reinforcement of low response rates, Stephens and Cole *(126)* found no effects of NBQX.

The ability of AMPA/kainate antagonists to exert anxiolytic-like effects in animal models is thus unreliable. This is surprising given the inevitable importance of these receptors in mediating neurotransmission in CNS circuits involved in processing emotional information, and the quite specific role for glutamatergic fast transmission envisaged in neuronal circuitry accounts of conditioned fear and anxiety outlined in Subheading 2. It seems likely that failure to find anxiolytic-like actions may be accounted for by the nonselective behavioral effects of these drugs, so that behavioral disruption masks their anxiolytic-like effects in many behavioral assays. A possible way of avoiding such nonspecific effects is to administer the drug centrally into areas of the brain accredited with a specific role in anxiety. Few attempts have been made at this kind of experiment, possibly because of the low solubility of the quinoxalinedione compounds at physiological pH values. However, bilateral infusions of CNQX (0.5 μg) into amygdala-impaired performance of a previously acquired passive-avoidance task, as well as decreasing reactivity to footshock, blocking footshock-induced decreases in locomotor activity, and increasing open-arm activity in the plus-maze, to a similar extent to midazolam *(127)*. These observations are consistent with an anxiolytic action of CNQX, though it should be noted that this drug possesses significant affinity for the glycine-B site of NMDA receptors, at which it acts as an antagonist *(128)*. Because specific glycine-B receptor antagonists also possess anxiolytic-like properties *(106)*; *see* previous discussion), and other behavioral effects of CNQX are attributable to an action at this site *(129)*, it is possible that the anxiolytic effects *(127)* are also mediated by CNQX's action at NMDA receptors.

4. METABOTROPIC GLUTAMATE RECEPTORS

In addition to its effects at ionotropic receptors, glutamate acts at a family of G protein-coupled metabotropic receptors *(130)*, classified into three subgroups (*see also* Part II). To date eight metabotropic receptors and multiple splice variants have been cloned group I receptors (mGluR1 and mGluR5) increase phospholipase C activity and phosphoinositol

hydrolysis, are located postsynaptically, and modulate ion channel activity. In contrast, group II receptors (mGluR2 and mGluR3) and group III receptors (mGluR4, 6, 7 and 8) inhibit adenylyl cyclase activity and, with the exception of GluR6, are located presynaptically where they regulate release of glutamate and other transmitters (refs. *131*, and *132)*; but *see* ref. *133* for discussion of postsynaptic distribution of group II receptors). In principle, such receptors may act to facilitate GABAergic or inhibit glutamatergic mechanisms, and might for that reason be expected to possess anxiolytic properties. There is increasing evidence that compounds acting at metabotropic receptors possess anxiolytic-like properties in animal models.

4.1. Group I Metabotropic Receptors (mGluR1 and mGluR5)

Systemic administration of the mGluR5 antagonist, MPEP, gives rise to anxiolytic-like effects in a number of spontaneous models including social interaction, elevated plus-maze, shock-probe, and marble-burying tests, and conditioned models such as the Geller–Seifert conflict test, Vogel punished drinking procedure, and four-plate test *(134–137)*. However, in a parametric comparison with the standard benzodiazepine anxiolytic, diazepam, MPEP was not as effective in increasing punished responding in a modified Geller–Seifter conflict test *(137)*. These anxiolytic-like effects of MPEP may be mediated by mGluR5 receptors in hippocampus since administration of (S)-4-carboxy-3-hydroxyphenylglycine (S-4C3HPG), a mixed group I antagonist and group II agonist, *(138)*, or of the more selective group I competitive antagonist (S)-4CPG and noncompetitive antagonist, CPCCOEt *(139),* into this region, gives rise to anxiolytic-like effects. group I antagonists blocked memory consolidation of contextual conditioning *(140)*, which is hippocampus-dependent, and fear conditioning leads to a transient upregulation of mGluR5 receptors in hippocampus *(141)*.

However, there is also accumulating evidence that mGluR5 receptors in the amygdala may play a role in fear conditioning *(142)* because MPEP blocked the expression of fear-potentiated startle when a discrete light cue, previously paired with shock, was used as the fear stimulus. Such potentiation by discrete cues is thought to be processed by amygdala mechanisms *(6)*. Bilateral infusion of MPEP into the lateral amygdala prevented the acquisition of conditioned fear assessed as fear-potentiated startle, but had no effect when administered immediately after training (to assess consolidation), or immediately before the test (to assess effects on expression of conditioned fear) *(143)*. These behavioral effects were paralleled in studies of LTP, in which MPEP blocked induction, but had no effects when administered following induction of LTP. Interestingly, it has been known for some time that administration of a mGluR agonist, trans-1-amino-cyclopentane-1,3-dicarboxylate, into amygdala facilitates potentiates auditory startle *(144)*.

Thus, mGluR5 receptors in the lateral amygdala appear to play a role in the early stages of synaptic plasticity underlying fear conditioning, but apparently do not contribute to expression of that conditioned fear. Clearly, these processes cannot be involved in putative anxiolytic effects of mGluR5 antagonists.

Perhaps these effects of group I antagonist reflect their ability to prevent glutamate-induced excitation through group I receptors *(131)*.

4.2. Group II/III Metabotropic Receptors

Administration of LY354740, an agonist of mGlurRII receptors, has been reported to possess anxiolytic-like effects in a range of standard tests using both spontaneous and

conditioned behaviors *(145,146)*. These effects may represent an action of LY354740 at hippocampal receptors, because administration of both this compound and another group II agonist, L-CCG-I, into the CA1 region of dorsal hippocampus of rats, increased punished licking in the Vogel test *(139)*. Nevertheless, Moore and colleagues *(147)* found no ability of LY354740 to increase punished responding in a conflict test, at doses that reduced responding during the nonpunished component; the same doses increased responding during a time-out component, reduced the number of reinforcers obtained on a DRL schedule, and shifted responding on an FI60-sec schedule toward the early part of the interval. These results are more consistent with effects of LY354740 on rates of responding, enhancing low rates while decreasing high rates, than with specific effects on punished behavior.

Group II receptors in the amygdala have also been implicated in fear responses and fear conditioning. LY354740 infused into the BLA disrupted the ability of a tone, previously conditioned to footshock, to potentiate a startle response *(148)*, an effect that could be antagonized with the group II antagonist, LY341495.

The ability of agonists at group II receptors to induce anxiolytic-like effects may reflect their ability to reduce glutamate release in several brain areas via activation of presynaptic receptors *(149)*, though they also act to hyperpolarize basolateral amygdala neurons *(150)*, and play a role in long-term depression of synaptic transmission in amygdala circuits *(151–153)*.

5. CLINICAL EVIDENCE

The slow progress in the clinical development of glutamate antagonists means that there is little evidence available from patients that can be used to test the predictions that antagonists should have clinically effective anxiolytic properties. Nevertheless, there are limited relevant data available from the use of ketamine during anaesthesia for surgery or for epidural catheter placements, where anxiety may be significant. Intravenous administration of 5 mg of ketamine given 5–10 min before epidural catheter placement significantly decreased anxiety as assessed using a visual analogue scale *(154)*, or when given orally to children, at a dose of 12.5 mg/kg prior to oral surgery *(155)*. A recent pilot study with PTSD patients also suggests that the glycine site partial agonist agonist, D-cycloserine, may improve anxiety, avoidance behavior, and numbing *(156)*.

6. CONCLUSIONS

Glutamatergic systems play essential roles in the signaling of emotions and in learning about environmental cues informing about threatening situations. In keeping with this functional role for glutamate, animal experimental evidence suggests a potential utility of both NMDA and non-NMDA receptor antagonists for the treatment of forms of anxiety. Despite the clear evidence from behavioral neuroscience of a potential utility of such compounds, little evidence of relevance is available from the clinic. It is less clear whether such treatments will have advantages over current therapies.

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