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Perspective

The metabotropic glutamate receptors: Potential drug targets for the treatment of anxiety disorders?

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ABSTRACT

Anxiety-related disorders are a common public health issue. Several lines of evidence suggest that altered glutamatergic neurotransmission underlies anxiety. Thus, novel molecules targeting glutamatergic neurotransmission, such as ligands of the metabotropic glutamate receptors (mGlurs) might be promising candidates for the treatment of anxiety disorders. To date, several ligands selective for each mGlu receptor (mGlur) have been synthesized, and pharmacological significances of these compounds have been demonstrated mainly in animal models. Here we critically review advances in research of these emerging molecular targets for the treatment of anxiety, discuss their advantages over currently used anxiolytics as well as remaining challenges.

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1. Anxiety

Anxiety may be interpreted as an emotional anticipation of an aversive situation and is reflected by species-specific behavioral fear responses to stressful and threatening stimuli characteristic for individual trait anxiety. Anxiety disorders including generalized anxiety disorder (GAD), specific and social phobias, post-traumatic stress disorder (PTSD) obsessive-compulsive disorder (OCD) and panic disorder are a major public health issue worldwide.

To date, anxiety disorders have been treated with medications that target γ-aminobutyric acid (GABA) and serotonergic neurotransmission, like benzodiazepines, partial agonists of the serotonergic 5-HT_{1A} receptor and selective serotonin (5-HT) reuptake inhibitors (SSRIs). Some forms of anxiety, however, are relatively resistant to treatment with these agents (Hammer et al., 2004; Van Ameringen et al., 2004). In addition, either benzodiazepines or SSRIs can be associated with severe side effects, such as sedation, memory deficits, dependence and withdrawal, sexual dysfunction and weight gain. Further, the 5-HT_{1A} receptor partial agonist buspirone has a somewhat limited use, although it is generally well tolerated with few side effects, its efficacy, is less and onset of action is slower than previous drugs such as the benzodiazepines (Cryan and Sweeney, 2011). Thus there is an urgent need to develop alternative treatment strategies (Gorman, 2003).

2. Glutamate and anxiety

Glutamate is the primary excitatory neurotransmitter in the mammalian central nervous system (CNS). It is involved in a wide range of physiological processes that are associated with emotion, cognition and motor functions and acts on both ionotropic (NMDA, AMPA and kainate receptors) and metabotropic glutamate receptors (mGlurs). Consistent experimental evidence indicates that abnormalities of glutamatergic transmission are involved in the pathophysiology of anxiety. In particular, it has been suggested that the anxiety disorders are the result of disrupted inhibitory/excitatory balance within the brain, due to increased activity of the excitatory glutamatergic system (Linden and Schoepp, 2006; Wieronska and Pilc, 2009). Preclinical and to lesser extent, clinical research has provided a rationale for the potential utility of glutamate modulators in the treatment of anxiety disorders (Millan, 2003).

3. Metabotropic glutamate receptors

The mGlurs family consists of eight receptor subtypes divided into three groups based on sequence homology, pharmacological profile and signal transduction pathways. Specifically, group I includes $mGlu_1$ and $mGlu_5$ receptors, localized predominately on postsynaptic neurons, which are coupled to the activation of phospholipase C. Group II mGlurs include the $mGlu_2$ and $mGlu_3$ receptors expressed on pre and postsynaptic neurons (Conn and Pin, 1997). Finally, group III comprises the $mGlu_4$, $mGlu_6$, $mGlu_7$ and $mGlu_8$ receptors which are primarily found on presynaptic terminals of GABAergic and glutamatergic neurons (Pinheiro and

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Mulle, 2008). The mGlurs subtypes of groups II and III are negatively coupled to adenylyl cyclase (Conn and Pin, 1997).

4. Metabotropic glutamate receptors and anxiety

4.1. Group I mGlurs

$mGlu_1$ and $mGlu_5$ receptors are expressed on postsynaptic excitatory terminals in amygdala, limbic cortex, olfactory tubercle, hippocampus and basal ganglia which are brain regions that are implicated in motivational and emotional processes (Shigemoto and Mizuno, 2000).

Regarding $mGlu_1$ receptor modulators, their inhibitory effect on NMDA receptor activity (Heidinger et al., 2002) and their stimulating action on GABAergic transmission (Battaglia et al., 2001) implicated these receptors as a potential target for anti-anxiety treatment. The outcome of preclinical research indicated an anti-anxiety-like effect of different $mGlu_1$ receptor antagonists (AIDA, EMQMCM, JNJ16259685, LY456236). With respect to benzodiazepines, however, the anxiolytic effect displayed by $mGlu_1$ negative modulators was weaker (Varty et al., 2005). Further, in a series of preclinical studies an amnestic effect of these compounds has also been evidenced raising serious doubts on their utility in anxiety (for review please see, Spooren et al., 2010). At the moment, there is no information regarding clinical studies carried out using mGlu1 receptor modulators.

Experimental evidence indicates that the $mGlu_5$ receptor increases neuronal excitability and NMDA receptor currents in brain regions are thought to be associated with anxiety, such as the amygdala (Krystal et al., 2010), leading to the hypothesis that $mGlu_5$ receptor antagonists might attenuate the hyperactivity of glutamatergic transmission believed to underlie anxiety disorders.

Negative allosteric modulators of $mGlu_5$ receptors, MPEP and its derivative, MTEP have shown consistent anxiolytic-like effects in animal models of anxiety (for review, please see Harvey and Shahid, 2012). Based on their pharmacological profile MTEP might be considered as a better candidate for clinical use (Busse et al., 2004).

In this context, the potent and selective $mGlu_5$ receptor antagonist fenobam (McN-3377) which acts at the allosteric modulatory site shared with MPEP and lacks GABAergic activity has shown an important anxiolytic activity either in animals or in humans (Pecknold et al., 1982; Porter et al., 2005). Interestingly, clinical research suggested that fenobam might be devoid of the adverse effects typical of benzodiazepines (muscle relaxation, sedation and potentially dangerous interaction with alcohol) (Goldberg et al., 1983).

Clinical studies with this nonbenzodiazepine compound were interrupted, however, due to psychostimulant side effects observed in some patients (Pecknold et al., 1982), that could be attributable to a potential interaction of fenobam with the dopaminergic system (Palucha and Pilc, 2007).

Further, a preclinical study also revealed that fenobam produces its anxiolytic activity at the doses that impair spatial learning (Jacob et al., 2009).

4.2. Group II mGlurs

Group II receptors, are localized primarily presynaptically in diverse brain areas as the cortex, thalamus, striatum, amygdala and hippocampus (Shigemoto and Mizuno, 2000) which are thought to play a critical role in anxiety (Linden et al., 2004; Nicoletti et al., 2011; Swanson et al., 2005). Hyperactivity of glutamatergic transmission in these structures is hypothesized to be associated with the pathogenesis of anxiety (Linden et al., 2004; Swanson et al., 2005). The activation of $mGlu_{2/3}$ receptors provides a negative feedback mechanism to prevent excessive presynaptic glutamate release in limbic regions implicated in the pathophysiology of affective disorders (Chavez-Noriega et al., 2002; Schoepp and Marek, 2002).

Different $mGlu_{2/3}$ receptor agonists (LY354740, LY544344, LY314582, LY566332, CBiPES) have shown activity in a wide range of preclinical animal models of anxiety. Among these compounds, however, the consistent anxiolytic-like profile of the $mGlu_{2/3}$ receptor agonist LY354740 was well documented (Harvey and Shahid, 2012). In this context, LY379268, a novel selective agonist, which was claimed to possess higher affinity for $mGlu_{2/3}$ receptors compared with LY354740 (Monn et al., 1999) did not replicate the anti-anxiety-like profile of LY354740. Both anxiogenic and anxiolytic effects of this $mGlu_{2/3}$ receptor ligand have been reported (Imre et al., 2006; Satow et al., 2008; Wieronska et al., 2012; Grivas et al., 2013).

Surprisingly, preclinical research also indicated an apparent anxiolytic action of $mGlu_{2/3}$ receptor antagonists compounds (LY341495, MSG0039) (Iijima et al., 2007; Shimazaki et al., 2004). Aiming to elucidate further this issue an additional study was performed using a broad range of animal models of anxiety but its′ results did not confirm the antianxiety-like behavior of LY 341495 observed in the former reports. The authors concluded that the apparent anxiolytic action of LY341495 might be ascribed to its stimulating properties on animals′ motor activity (Bespalov et al., 2008).

The efficacy of $mGlu_{2/3}$ receptor agonists as anxiolytics has been evaluated in a series of clinical trials. Specifically, LY354740 was found anxiolytic in a human fear-potentiated startle paradigm conducted in healthy volunteers (Grillon et al., 2003) and expressed an antipanic profile in a small study that was carried out in panic disorder patients (Levine et al., 2002). In a double-blind placebo-controlled study, however, LY354740 was not efficacious to reduce panic symptoms (Bergink and Westernberger, 2005). Clinical trials conducted to evaluate the effects of LY354740 on GAD have reported a significant anxiolytic effect of this $mGlu_{2/3}$ receptor agonist (Michelson et al., 2005; Dunayevich et al., 2008). In addition, LY544344, a derivative of LY354740 with higher bioavailability compared to LY354740, decreased the cholecystokinin tetrapeptide (CCK-4)-induced subjective anxiety and panic symptoms in healthy volunteers (Kellner et al., 2005) and was found effective in the treatment of GAD in a double-blind placebo-controlled study (Dunayevich et al., 2008). Despite the fact that both LY354740 and LY544344 were well tolerated further development was interrupted due to the occurrence of convulsions observed in preclinical studies after repeated treatment with high doses of these compounds (Dunayevich et al., 2008).

4.3. Group III mGlurs

$mGlu_4$ receptors are found mainly in cerebellum, $mGlu_6$ are localized in retina, $mGlu_7$ are widely expressed in brain stem and forebrain, while $mGlu_8$ receptors are distributed in cerebellum, hippocampus and olfactory bulb (Schoepp, 2001). Group III metabotropic receptors share mainly presynaptic expression and are directly involved in the regulation of glutamate and GABA transmission (Schoepp, 2001), which makes them interesting targets for the development of anxiolytic drugs.

Among the subtypes of group III receptors the $mGlu_6$ receptor might not play a role in anxiety since it is mainly expressed in retina (Shigemoto and Mizuno, 2000). Unraveling the specific functions of individual type III receptor subtype has proven difficult, because of the lack of receptor subtype selective compounds. Therefore, preclinical information regarding the involvement of specific mGlurs of Group III in anxiety is still limited (Spooren et al., 2010). In spite of it, in a series of preclinical studies, compounds that exhibit either agonistic (L-AP4, (S)-3,4-DCPG,

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