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REVIEW ARTICLE

Research in anxiety disorders: From the bench to the bedside

Matthew Garner [a,*], Hanns Möhler [b], Dan J. Stein [c], Thomas Mueggler [d], David S. Baldwin [a]

[a] *University of Southampton, UK*
[b] *University of Zurich, Switzerland*
[c] *University of Cape Town, South Africa*
[d] *University and ETH of Zurich, Switzerland*

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Abstract

The development of ethologically based behavioural animal models has clarified the anxiolytic properties of a range of neurotransmitter and neuropeptide receptor agonists and antagonists, with several models predicting efficacy in human clinical samples.
Neuro-cognitive models of human anxiety and findings from fMRI suggest dysfunction in amygdala-prefrontal circuitry underlies biases in emotion activation and regulation. Cognitive and neural mechanisms involved in emotion processing can be manipulated pharmacologically, and research continues to identify genetic polymorphisms and interactions with environmental risk factors that co-vary with anxiety-related behaviour and neuro-cognitive endophenotypes.
This paper describes findings from a range of research strategies in anxiety, discussed at the recent ECNP Targeted Expert Meeting on anxiety disorders and anxiolytic drugs. The efficacy of existing pharmacological treatments for anxiety disorders is discussed, with particular reference to drugs modulating serotonergic, noradrenergic and gabaergic mechanisms, and novel targets including glutamate, CCK, NPY, adenosine and AVP. Clinical and neurobiological predictors of active treatment and placebo response are considered.

Anxiety symptoms are common in the community, and anxiety disorders are common in primary and secondary medical care settings (King et al., 2008). The disorders typically persist for many years, and are associated with significant personal distress, reduced quality of life, increased morbidity and mortality, and a substantial economic burden (Wittchen and Jacobi, 2005). Current treatments for anxiety disorders have modest efficacy: many patients do not respond or are unable to tolerate pharmacological approaches (principally antidepressants) and psychological interventions (such as cognitive–behaviour

* Corresponding author. School of Psychology and Division of Clinical Neurosciences, School of Medicine, University of Southampton, SO17 1BJ, UK. Tel.: +44 2380595926; fax: +44 23 8059 4597.
E-mail address: m.j.garner@soton.ac.uk (M. Garner).

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therapy) are often limited in availability. While there have been important advances in our understanding of the basic neuroscience of anxiety and its cognitive and behavioural characteristics, at present it is not possible to reliably predict which patient groups might respond to which treatments and many patients therefore undergo treatment which is sub-optimal.

The Scientific Advisory Panel of the European College of Neuropsychopharmacology hosted a targeted expert meeting on anxiety and anxiolytics immediately prior to the 20th Congress of the ECNP in Vienna, October, 2007. This provided a valuable opportunity for pre-clinical and clinical scientists and clinicians to present and discuss recent findings from a range of research initiatives, with the aim of evaluating the translation of evidence from animal studies and molecular and functional imaging investigations to clinical practice and treatment development. This paper summarizes our discussion of ideas that we hope might ultimately prove fruitful in better understanding the etiology and treatment of anxiety disorders.

1. Diagnosis of anxiety disorders

Anxiety disorders typically follow a chronic or recurring course in which full symptomatic remission is uncommon; they are associated with the temporal accumulation of comorbid disorders and with an increased suicide risk. The five main debilitating anxiety disorders are panic disorder (PD), obsessive–compulsive disorder (OCD), social anxiety disorder (SAD), post-traumatic stress disorder (PTSD) and generalized anxiety disorder (GAD): simple/specific phobias are distinct but less debilitating conditions that are common in community surveys, but not commonly presented in clinical settings.

Current systems for the identification and grouping of anxiety symptoms into distinct anxiety disorders reflects the clinical need to define explicitly mental illness and facilitate reliable diagnosis, (American Psychiatric Association, 1994). Throughout its many versions, the Diagnostic and Statistical Manual (from DSM-I, 1952 to the current DSM-IV, 1994) categorizes and defines sets of explicit diagnostic criteria using a multiaxial and descriptive approach whilst remaining neutral with respect to theories of etiology and maintenance (American Psychiatric Association, 1994). Major advances in our ability to reliably diagnose specific anxiety disorders (i.e. operational criteria established in DSM-III) have undoubtedly facilitated epidemiological investigation into the prevalence, impairment and economic costs of specific disorders, but clinical research has tended to focus on reducing the severity of symptoms associated with disorders, often at the expense of attempting to clarify mechanisms involved in aetiology and maintenance. Given that future classificatory systems are likely to be validated, if not directly influenced, by greater knowledge of pathogenesis, there is a need to better identify and differentiate anxiety spectrums and diagnostic sub-types in terms of genotype, endophenotype and phenotype.

2. Animal models of anxiety

Animal models make it possible to investigate brain-behavior relations in order to gain insights into normal and abnormal human behavior and its underlying neuropsychobiological processes (van der Staay, 2006). The development of predictive animal models and the availability of genetically modified mice have significantly helped clarify the role of a range of pharmacological molecules in brain circuits relevant to anxiety, with many promising targets derived from preclinical animal models subsequently validated in the clinic. The translation of anxiety phenotypes into testable measures and models in animal experiments has also permitted investigation of interactions between genetic and environmental risk factors, and the resultant changes in brain neurobiology that underlie and confer risk for anxious behaviour.

Many animal models of anxiety examine the natural behavioural patterns of mice and rats to develop ethologically based behavioural tasks (Rodgers et al., 1997). These include 'approach–avoidance' tasks (Cryan and Holmes, 2005) in which animals are exposed to an aversive/threatening environment e.g. open, elevated arms of the elevated plus-maze, light arena (light/dark exploration/emergence tests); and open field tests, with anxiety-like behaviour (phenotype) in each case, inferred from increased avoidance. Other models include social interaction tests (review by File and Seth, 2003), punishment-based conflict procedures (e.g. punished drinking — Vogel et al., 1971), defensive burying tests (Jacobson et al., 2007), predator stress (Blanchard and Blanchard, 1971), and the examination of ultrasonic vocalizations induced by stress such as maternal separation (see Sanchez, 2003), while novel techniques include the use of radiotelemetry to asses a variety of physiological parameters in real time (e.g. core body temperature, Adriaan Bouwknecht et al., 2007). Such models examine behaviour that is functionally rather than superficially related to human anxiety (i.e. they show good face validity) and probe mechanisms derived from theory (possess good construct validity).

Preclinical models have been used to reveal the anxiolytic properties of a range of neurotransmitter and neuropeptide receptor agonists (5-HT, alpha-2-adrenergic receptors, $GABA_A$, oxytocin, galanin, somatostatin, NPY1, cannaboid CB1) and receptor antagonists (CRF1, CCK2, glutamate, substance P NK1, vasopressin, NPY2) and in many cases have predicted efficacy in human clinical samples (i.e. show good predictive validity). Studies in genetically modified mice have investigated the consequences of manipulating specific genes, and a number of mouse strains in which mutations in specific neurotransmission genes have been induced (including knock-out, knock-in and transgenic mice) show altered anxiety-related behaviour (review by Holmes, 2001; Finn et al., 2003; cf Gross and Hen, 2004). Genetic factors can exert their influence during brain development (e.g. neurotrophic factors) or in adulthood by modulating neurotransmission. Investigations of the genes involved in the anxiety phenotype have predominantly focused on animal models that target receptor genes (e.g. serotonin receptors) or receptor subunits (e.g. $GABA_A$) of specific neurotransmitters, with fewer studies examining transporters (e.g. serotonin transporter), neuropeptides (nociceptine) or binding proteins (CRF binding protein), and there have been very few studies of genes involved in the synthesis of specific neurotransmitters (see review by Belzung et al., 2008). While research on targeted genes has yet to directly improve pharmacological treatments for anxiety disorders (most likely because mutations relevant to anxiety are primarily expressed/

involved in brain development and cannot be counteracted retrospectively in adults), it has allowed researchers to clarify epigenetic factors (e.g. maternal care) that can modify gene expression through varied mechanisms (e.g. methylation of DNA that encodes a gene) and confer an increased risk for development of anxiety.

It remains a challenge for the research community to develop animal paradigms that more accurately model specific human anxiety disorders so that the pathogenesis of anxiety subtypes can be better understood and new treatments developed. While this is likely to prove difficult for disorders where cognitive components (e.g. worrying) are a key element such as GAD, there is likely to be more promise for disorders which result from the experience of trauma (PTSD) or which involve discrete fear responses (PD and SP); both which seem to occur in rats and primates (Nutt et al., 2008).

Insights into emotional cognition has been inferred from fear conditioning paradigms that examine the acquisition and resistance to extinction of defensive behaviours (e.g. freezing, startle) in response to previously innocuous stimuli that have been systematically paired with an innate threat stimulus (Davis, 1990). Such paradigms have proven useful in modeling impaired extinction observed in patients with PTSD, specific and social phobias (Barad, 2005); clarifying the NMDA receptor pharmacology of extinction (see Myers and Davis, 2007) and identifying pharmacological compounds (D-cycloserine) that facilitate extinction in small animals (Ledgerwood et al., 2005) and which can enhance the effects of exposure-based psychological interventions in human anxiety (Ressler et al., 2004). Indeed the experimental analysis of fear extinction and its neural circuitry, and the validity of extinction as a model system for therapeutic intervention for anxiety-related disorders, demonstrates the potential for preclinical animal research to translate rapidly from "bench to bedside" (see Myers and Davis, 2007).

In summary, a broad range of animal models are now available for behavioural neuroscientists examining the anxiety phenotypes. While researchers continue to better standardize rearing, housing and testing conditions, and to evaluate the reliability, validity (primarily predictive and construct validity), and biological or clinical relevance of putative animal models of human anxiety, it remains a challenge for the research community to develop animal paradigms that model specific human anxiety disorders more accurately (van der Staay, 2006).

Despite successful translation of preclinical research of fear conditioning and extinction, we still do not have valid animal models of complex component cognitive processes that occur in anxious humans — perhaps in part because human prefrontal cortex is more developed, having a unique morphology and gene expression, than that of other mammals (Berkowitz et al., 2007).

Using functional Magnetic Resonance Imaging (fMRI) in combination with a drug it is possible to investigate how neurotransmitter systems are involved in neuronal systems engaged by other processes, such as cognitive challenge (modulation phMRI) or to examine the acute effects of the drug itself in the brain (challenge phMRI) (reviewed by Jenkins et al., 2006). What is needed in preclinical fMRI studies is an extension of the current concept of analysing univariate maps derived from time-series data towards an intrasubject correlation analysis (Friston et al., 1997) yielding information on functional connectivity in response to cognitive or pharmacological challenges as recently demonstrated in the rat (Schwarz et al., 2007). Furthermore it would seem productive to integrate preclinical behavioural models with human models of specific anxiety disorders that permit the assessment of behavioural and cognitive components of human anxiety (e.g. the 7.5% CO_2 model of generalized anxiety disorder, Bailey et al., 2007).

3. Neuro-cognitive models of anxiety

Neurocognitive models of anxiety propose a common amygdala-prefrontal circuitry that underlies dysfunctional biases in emotion processing e.g. selective attention to threat, interpretation of ambiguous emotional stimuli and acquisition and extinction of conditioned fear (Bishop, 2007). There is compelling evidence that clinically anxious adults and children, and individuals with sub-clinical levels of anxiety, demonstrate a range of biases in emotion processing; most notably a readiness to selectively attend to threat cues (review by Bar-Haim et al., 2007; Waters et al., 2008) and to interpret emotionally ambiguous stimuli in a negative manner (review by Mathews and MacLeod, 2005).

Findings from fMRI show amygdala hyperactivity to threat in high state anxious and clinically anxious individuals (e.g. Bishop et al., 2004b; Tillfors et al., 2001), with evidence that this specialized sub-cortical network can prioritize the processing of threat information that is presented outside of attention (Bishop et al., 2004b) and awareness (i.e. subconsciously; Etkin et al., 2004). Potentiation of fear-related defense (e.g. startle) behaviors coordinated by the amygdaloid complex and associated structures (bed nucleus of the stria terminalis) has also been demonstrated, with evidence of elevated startle responding in individuals with anxiety disorders including PTSD (Grillon et al., 1998a), OCD (Kumari et al., 2001), panic disorder (Grillon et al., 1994); individuals with sub-clinical levels of social anxiety (Cornwell et al., 2006), anxious children (Waters et al., 2005) and children at greater risk of developing anxiety due to parental anxiety (Grillon et al., 1998b).

fMRI studies have confirmed the role of prefrontal cortical regions in regulating the sub-cortical fear system (e.g. Hariri et al., 2000); while dysfunction in prefrontal regulatory structures has been observed in high state anxious individuals when processing threat distracters (Bishop et al., 2004a), individuals with PTSD during task performance and at rest (Shin et al., 2001), in OCD (Chamberlain et al., 2005), and in children with GAD (Monk et al., 2008). These findings are consistent with predictions from cognitive models that emphasize increased activation of threat-related representations, and a failure to use controlled processing to regulate attention and promote alternate non-threat-related representations, as vulnerability factors for anxiety (cf. Bishop, 2007; see Mathews and Mackintosh, 1998; Eysenck et al., 2007). However, future human imaging studies need to clarify the extent to which prefrontal dysfunction varies across interactions between anxiety subtypes, stressor and context. Indeed, recent reviews suggest those disorders involving intense fear and panic — panic disorder, post-traumatic stress disorder, and phobias —

are characterized by prefrontal disinhibition of the amygdala, while disorders such as generalized anxiety disorder and obsessive–compulsive disorder, which involve worry and rumination, are better characterized by overactivity in prefrontal cortical regions (Berkowitz et al., 2007).

Increasing evidence demonstrates that the cognitive and neural mechanisms involved in emotion processing can be manipulated pharmacologically, and genetic polymorphisms associated with greater risk of developing anxiety have also been found to account for variance in emotion processing. Regarding the former, research to date has examined the effects of acute and short term increases and decreases in brain serotonin and noradrenaline in healthy individuals (review by Merens et al., 2007). Short-term (7-day) administration of the selective serotonin reuptake inhibitor (SSRI) citalopram decreases amygdala responses to threat faces presented outside of awareness, the ability to explicitly identify threatening expressions (Harmer et al., 2006), the magnitude of the emotion potentiated startle (Harmer et al., 2004), and the allocation of attention to threat (Murphy et al., 2006). Similarly, short-term administration of the noradrenaline reuptake inhibitor (NRI) reboxetine reduces amygdala activation to threat and potentiates responses to positive social cues in cortical face regions (fusiform gyrus) and reduces the explicit identification of threat (Harmer et al., 2004). More recently, a single dose (60 mg) of the serotonin–noradrenaline reuptake inhibitor (SNRI) venlafaxine has been shown to increase memory for positive personality attributes during free-recall (Harmer et al., 2008). Importantly, pharmacological modulation of emotion processing biases can occur in the absence of changes in mood, thus highlighting a mechanism of action by which drug treatments normalize negative bias in anxiety.

Serotonin transporter gene variation has been shown to affect anxiety-related behaviours (You et al., 2005), cognitive bias (Osinsky et al., 2008), and neural mechanisms involved in threat processing (review by Munafo et al., 2008). Increased startle responding has been associated with the short allele functional polymorphism in the transcriptional control region of the serotonin transporter gene (5-hydroxytryptamine transporter gene-linked region: 5-HTTLPR which is associated with decreased cellular transporter activity), when compared to l/l homozygotes (Brocke et al., 2006). Patients with social phobia who carry one or two copies of the short allele of the serotonin transporter gene show significantly increased levels of symptom severity (anxiety-related traits, state anxiety), and enhanced amygdala responding to anxiety provocation (public speaking), when compared with subjects homozygous for the long allele (Furmark et al., 2004). Research continues to examine whether serotonin genotype and allele distributions differ across anxiety disorders and are associated with symptom severity (e.g. panic disorder, Yoon et al., 2008).

The functional Val158Met polymorphism in the catechol-O-methyltransferase (COMT) gene covaries with panic disorder and limbic and prefrontal brain activation in response to unpleasant stimuli, with individuals who carry at least one 158 val allele showing increased activation in the right amygdala and the orbitofrontal cortex and less deactivation in the ventromedial prefrontal cortex (Domschke et al., 2008). These findings are consistent with evidence that Val load correlates positively with activity in control- and task-related regions during performance under emotional distraction (Bishop et al., 2006).

Consistent with the anxiolytic properties of neuropeptide-Y (NPY), recent evidence shows that lower genetic haplotype NPY mRNA expression predicts higher emotion-induced activation in the amygdala, greater trait anxiety and lower resiliency (endogenous opioid transmission) during a pain/stress induction, (Zhou et al., 2008); findings that parallel the effects of polymorphic variations in genes coding for 5-HTT, COMT and monoamine oxidase A (MAOA) in the regulation of the hypothalamic–pituitary–adrenal axis response to acute psychological and endocrine challenge (Jabbi et al., 2007). Finally, recent studies of the effects of interactions between genetic vulnerability factors on adaptive brain function provide compelling initial evidence of strong interactions between SERT and MAOA polymorphisms in modulating regions implicated in cognitive control (e.g. anterior cingulate cortex; Passamonti et al., 2008).

Thus research to date has suggested a number of genetic risk factors that increase vulnerability for anxiety, and that modulate cognitive and neural mechanisms involved in emotion processing. However, increasing evidence also supports the need to consider anxiety as a product of genetic susceptibility factors modulating the effects of early environmental experiences, and the effect of environmental challenge on gene expression.

Efforts to clarify the underlying structure and commonality of genetic and environmental risk factors across anxiety disorders continue (e.g. Hettema et al., 2005). Meta-analyses have shown that panic disorder, generalized anxiety disorder, phobias, and OCD all have significant familial aggregation largely explained by genetic rather than by shared familial environmental factor; however the role of non-shared environmental experience is significant, "underscoring the importance of identifying putative environmental risk factors that predispose individuals to anxiety" (Hettema et al., 2001). For example, recent data from 8232 respondents across six European countries reveals an association between adverse parenting (e.g. overprotection) and higher risk of anxiety disorder (Heider et al., 2008), while the experience of one or more unexpected, negative, life events increases the risk of generalized anxiety (Blazer et al., 1987). Interestingly, there is evidence that preexisting biological vulnerability factors (e.g. reduced hippocampal volume) can modulate the impact of environmental stress and the likelihood of an anxiety disorder (e.g. PTSD; Gilbertson et al., 2002; Bremner et al., 2003).

The extent to which interactions between genetic and environmental factors confer risk for anxiety remains the subject of much research. In their seminal prospective-longitudinal study Caspi et al. (2003) revealed that individuals with one or two copies of the short allele of the 5-HTT promoter polymorphism exhibited more depressive symptoms, diagnosable depression, and suicidality in relation to stressful life events than did individuals homozygous for the long allele. While research has yet to provide compelling evidence that gene-environment interactions predict diagnosable anxiety symptoms (Kendler et al., 2005) recent efforts that seek associations with anxiety endophenotypes show more promise (presumably, consistent with their greater proximity to genes than to clinical symptoms; Gregory et al., 2008). Children with the combination of the short 5-HTT allele and low social support (according to maternal reports) have increased risk for

behavioral inhibition in middle childhood (Fox et al., 2005); this being consistent with convergent evidence in monkeys that associates the l/s allele with increased levels of the 5-HT metabolite, increased anxiety-related behaviour (Champoux et al., 2002), and greater response at maturity to early environmental stress (Bennett et al., 2002). Taken together, initial findings suggest gene-by-environment interactions can induce persistent structural and functional changes in neural systems that underlie vulnerability to anxiety and anxious behaviour. "Thus the investigation of the molecular factors and associated plastic changes that they induce has the potential to reveal why different individuals experience different levels of anxiety" (Gross and Hen, 2004), and vary in their response to treatment.

4. Current drug treatments and novel pharmacological targets for the treatment of anxiety

Although there are many psychotropic drugs and psychotherapies available for the treatment of patients with anxiety disorders, overall clinical outcomes and the standard of care for most patients are far from optimal.

The efficacy of SSRIs, NRIs, SNRIs, and benzodiazepines in anxiety disorders has focused clinical attention on the role of enhanced sertonergic and noradrenergic neurotransmission, and altered function of the GABA-benzodiazepine chloride ionophore complex in the successful response to pharmacological treatment (see review by Baldwin and Garner, 2008).

Systematic reviews and randomized placebo-controlled trials show rather broad efficacy for SSRIs in the acute and long-term treatment of patients with generalized anxiety disorder (GAD:Baldwin and Polkinghorn, 2005; Bielski et al., 2004); panic disorder (Baldwin et al., 2005; Lecrubier and Judge, 1997), social anxiety (Blanco et al., 2003; Stein et al., 2003), post-traumatic stress disorder (PTSD: Stein et al., 2004; Martenyi et al., 2002) and obsessive-compulsive disorder (OCD: Fineberg and Gale, 2005). The importance of enhanced serotonergic neurotransmission in the treatment response in patients with anxiety disorders is evident in randomized controlled tryptophan depletion studies in patients successfully treated with SSRIs (Bell et al., 2001, 2002; Argyropoulos et al., 2004).

Combining an SSRI with compounds with 5-$HT1_A$ and 5-$HT1_B$ autoreceptor antagonist properties may increase synaptic 5-HT and thereby facilitate the onset of action of SSRIs, and combining 5-HT reuptake inhibition with 5-HT_{2c} antagonism may result in greater efficacy in relieving anxiety symptoms and improving sleep. The melatonin M1 and M2 agonist agomelatine (which also has 5-HT_{2c} antagonist properties) has anxiolytic properties in animal models (Millan et al., 2005), in relieving anxiety in patients with major depression (Loo et al., 2002, 2003), and in GAD (Stein et al., 2008); and the 5-HT_{2c} antagonist SB242084 augments citalopram response in animal models (Cremers et al., 2004). However, the initial promise for 5-HT_{2C} antagonists (e.g. deramciclane in GAD: Naukkarinen et al., 2005) and 5-HT_3 antagonists (Costall and Naylor, 1993) has yet to be confirmed consistently within large randomised placebo-controlled studies (Lecrubier et al., 1993).

The NRI reboxetine is efficacious in acute treatment of panic disorder but efficacy in other anxiety disorders has not been demonstrated in RCTs. Indeed different anxiety disorders may be characterized by different perturbations of the noradrenergic system: administration of presynaptic ά2 receptor antagonists (e.g. yohimbine) is anxiogenic and the centrally acting partial ά2 receptor agonist clonidine is anxiolytic in panic disorder patients (Charney et al., 1984; Coplan et al., 1992) but not in patients with OCD (Rasmussen et al., 1987; Hewlett et al., 1992) or GAD (Charney et al., 1989).

Benzodiazepines are potent anxiolytics but can be associated with problematic sedation, memory problems, tolerance and discontinuation symptoms. Novel compounds seek to target synaptic and extrasynaptic GABA receptor subtypes (Farrant and Nusser, 2005) in order to selectively control neuronal excitability in networks involved in anxiolysis. Indeed, circuits operating with $GABA_A$ receptors containing the alpha2 subunit were found to mediate anxiolysis (Löw et al., 2000), while those containing the alpha 1 subunit mediate sedation (Rudolph et al., 1999). This extends broader research linking particular neuronal networks defined by $GABA_A$ receptor subtypes with the regulation of clearly defined behavioural patterns in animal and human models (review by Mohler, 2006).

Many neurotransmitters exert direct or indirect effects on the $GABA_A$ receptor, including neurosteroids, corticotrophin-releasing factor (CRF), arginine–vasopressin (AVP), NPY, cholecystokinin (CCK), substance P, neurotensin, glutamate, somatostatin, norepinephrine, dopamine, acetylcholine, serotonin, and N-methyl-D-aspartate. Non-BZ approaches to enhancing the effects of GABA include increasing its synthesis (topiramate, valproate); inhibiting its breakdown (vigabatrin); inhibiting its reuptake (tiagabine, see Pollack et al., 2005) and the use of GABA analogues (e.g. pregabalin, gabapentin) to modify calcium ion channels of 'over-excited' pre-synaptic neurons and regulate post synaptic activity by reducing the release of excitatory neurotransmitters, such as aspartate, substance P and glutamate (Stahl, 2004).

While predictive animal models and the availability of genetically modified mice have helped clarify the role of glutamate in brain circuits relevant to anxiety, clinical validation of promising targets derived from preclinical animal models (particularly GluR2 agonists, and mGluR5 antagonists), is needed (see Cryan and Dev, 2008 for review). Three groups of metabotropic G-protein coupled glutamate receptors ($mGlu_{1-8}$) regulate glutamate release and modify post-synaptic excitability. In Group I, an $mGlu_1$ receptor agonist (*trans*-ACPD) enhances the startle response in rodents (Grauer and Marquis, 1999); and an $mGlu_5$ receptor antagonist (MPEP) has been found to exert anxiolytic-like effects (Ballard et al., 2005). In Group II, LY354740, an agonist at $mGlu_2$ receptors, limits glutamate release through a presynaptic mechanism and has an anxiolytic profile in animal models, where its effects are reversed by flumazenil; it prevents CO_2-induced anxiety in panic patients, and reduced anxiety symptoms in patients with GAD (Swanson et al., 2005). There are few ligands for Group III mGlu receptors, although the $mGlu_6$ receptor agonist MSOP has shown anxiolytic-like effects. Other novel glutamatergic agents include NMDA antagonists e.g. memantine, riluzole and the partial agonist D-cylcoserine.

Other potential targets for anxiolytic drugs include receptors for CCK, NPY, adenosine and AVP. Although CCK-4 antagonists block the anxiogenic effects of CCK infusion, the efficacy of CCK-4 antagonists has not been demonstrated in placebo-controlled studies in patients with anxiety disorders. Neuropeptide Y may down-regulate norepinephrine neurotransmission and can exert anxiolytic-like effects that are reversed by the alpha-2 antagonist idazoxan. Ligands at differing receptors exert differing effects: anxiolysis appears to be mediated by NPY_1 and NPY_5 receptors, whereas sedation may be mediated through the NPY_5 receptor only: anxiolytic effects are seen with NPY_1 agonists and NPY_2 antagonists. AVP is produced in the hypothalamus and is involved in regulation of corticotrophin secretion: antagonism of vasopressin V_{1b} receptors (by SSR149415) is effective in rodent models of anxiety and depression, these effects probably occurring through receptors in limbic structures (Griebel, 2002).

Other opportunities for drug development include HPA axis modulators (e.g. cortico-trophin releasing hormone receptor 1 antagonists (Zobel et al., 2000), and the steroid synthesis inhibitor ketaconazole), neurotrophic medications (CREB, BDNF — Levatiracetam) and neurokinin, melatonin antagonists (substance P antagonists).

Selective non-peptide antagonists for tachykinin receptors have been available for many years, but drug development has largely focused on the substance-P-preferring receptor known as neurokinin-1 (NK1). NK1 receptor antagonists have shown antidepressant and anxiolytic effects in animal models (Stout et al., 2001), and an early randomised controlled trial with the substance P antagonist MK 869 demonstrated greater relief of anxiety symptoms than was seen with the SSRI paroxetine, in patients with major depression (Kramer et al., 1998). Although subsequent studies with this compound have not confirmed its efficacy, clinical investigations with other related compounds still offer some promise (Kramer et al., 2004) with compounds that combine substance P antagonist and 5-HT re-uptake blocking properties in development.

5. Predictors of treatment response

The identification of clinical markers that are predictive of treatment response and that might help inform the selection of appropriate pharmacological interventions remains an important goal for anxiety research. Despite initial evidence of clinical and biological candidate predictors, many individuals still respond poorly.

Clinical predictors of response to venlafaxine or the SSRI fluoxetine include duration of anxiety symptoms (Perugi et al., 2002; Simon et al., 2008), the presence of co-morbid dysthymia (to venlafaxine; Perugi et al., 2002), history of depression or panic disorder (to venlafaxine; (Pollack et al., 2003), and the severity of psychosocial impairment (Rodriguez et al., 2006). A lower likelihood of response to escitalopram treatment is seen with lower baseline symptom severity (Stein et al., 2006a), and a history of benzodiazepine use is associated with lower response to treatment with venlafaxine (Pollack et al., 2003).

Novel genetic predictors of response in depression include the dopamine transporter VNTR polymorphism, with homozygous carries of the DAT1 10-repeat allele (10/10) and heterozygous allele (9/10) showing more rapid response to all classes of medications (e.g. SSRIs, tricyclics, mirtazapine, venlafaxine) and greater reductions in symptom severity (measured using the Hamilton Depression Rating Scale) than is seen with homozygous (9/9) carriers (Kirchheiner et al., 2007). While there is some evidence that I/I and I/s carriers of the serotonin promoter genotype also show greater response to SSRIs and mirtazapine (Kirchheiner et al., 2007) further studies are required to confirm this clinical association in depression and extend promising findings in social anxiety (Stein et al., 2006b) to identify similar genetic predictors of response in other anxiety disorders.

Functional neuroimaging techniques also show promise in the prediction of treatment response in patients with anxiety disorders. Pre-treatment orbitofrontal activity predicts outcome with drug treatment (Rauch et al., 2002; Saxena et al., 1998) or psychological treatment (cognitive behaviour therapy, CBT) (Brody et al., 1998) in patients with OCD (review by Karleyton et al., 2006). In anxious children and adolescents, significant negative associations are seen between left amygdala activation and measures of improvement with either CBT or SSRI treatment (McClure et al., 2007). In social phobia, higher anterior, lateral temporal cortical perfusion at baseline predicts response to SSRI treatment (Van der Linden et al., 2000) and the degree of amygdala-limbic attenuation following pharmacological treatment and CBT predicts overall improvement at one year (Furmark et al., 2002). In patients with GAD, response to open-label treatment with venlafaxine is predicted by greater pretreatment reactivity to threat cues (fear faces) in rostral ACC and lesser reactivity in the amygdala (Whalen et al., 2008). These findings emphasize the role of limbic regions (amygdala and hippocampus) in anxiety, and identify mechanisms that might underlie the response to treatment in anxiety disorders.

Interestingly, recent research has identified activity in similar regions in responders to placebo. For example, PET imaging of the placebo response in unipolar depression reveals regional metabolic increases in frontal structures that include both prefrontal and anterior cingulate cortex; and metabolic decreases in parahippocampus and thalamus — consistent with patterns of change observed in responders to active antidepressants (e.g. fluoxetine — Mayberg et al., 2002). Convergent evidence in other medical disorders (chronic pain, irritable bowel syndrome, Parkinsons disease) and in healthy volunteers further supports the role of i) "top-down" processes dependent on frontal cortical areas, that generate and maintain cognitive expectancies and involve neural systems mediating reward-expectancy (i.e. the mesolimbic dopaminergic pathway — de la Fuente-Fernández et al., 2006); and ii) disorder-specific neuronal responses in brain structures and neurochemical processes involved in the response to pharmacological treatment (see review by Faria et al., 2008); however the functional neuroanatomy/pharmacology of the placebo response in anxiety has not yet been examined.

6. Conclusions

The research reviewed encourages the continued integration of psychopharmacological observations, with insights from

behavioural genetics, cognitive neuroscience and functional neurophysiology to provide comprehensive models of anxiety that identify commonalities across and dissimilarities between specific anxiety disorders and their subtypes.

The boundaries between anxiety disorders remain unresolved though subtyping has helped reduce the hetrogeneity observed in broader definitions. An endophenotypic approach that seeks quantitative traits hypothesized to more closely represent the genetic risk for complex anxiety disorders than can observable symptoms and behaviors should help identify commonality between disorders that share high levels of comorbidity and selective response to treatment. To date cognitive, imaging, and molecular data as well as results from demographic, comorbidity, family, and treatment studies have been used to identify promising markers in anxiety disorders, particularly OCD (see Fineberg et al., 2007). However, while recent research in OCD has revealed substantial endophenotypic differences between OCD and anxiety disorders, depression, schizophrenia, and addictions (Fineberg et al., 2007; Chamberlain et al., 2005) the identification of reliable endophenotypes in GAD, social anxiety, PTSD and panic disorder remains a goal for future research. In doing so, improvements in our understanding of anxiety may mirror those observed in the psychiatric disorders for which endophenotypes have been already been proposed (e.g. schizophrenia, Braff and Freedman, 2002; bipolar disorder Lenox et al., 2002; ADHD, Castellanos and Tannock, 2002). This may in turn aid diagnosis, classification, treatment, clinical research and the development of refined preclinical models of anxiety, by reducing the complexity of symptoms and behaviors into units of analysis that are more readily modeled in animals (Gould and Gottesman, 2006).

Role of the funding source

The Scientific Advisory Panel of the European College of Neuropsychopharmacology hosted a targeted expert meeting on Anxiety and Anxiolytics immediately prior to the 20th Congress of the ECNP in Vienna, October, 2007. This 2 day meeting provided a valuable opportunity for pre-clinical and clinical scientists and clinicians to present and discuss recent findings from a range of research initiatives. In the run-up to this meeting, the ECNP requested that one output of the forum should be a summary/review of these discussions for submission to European Psychopharmacology.

Contributors

MG prepared the first draft of this review which was revised following comment from all co-authors. HM, DJS, TM led sessions at the Targeted Expert Meeting which was convened by DSB.

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