Pharmaco- and therapygenetic aspects in the treatment of anxiety disorders beyond the serotonergic system: a brief review

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Anxiety disorders (ADs) are among the most frequent psychiatric disorders. In addition, key features of ADs include that they are among the earliest mental disorders to manifest and that their first specific treatment frequently occurs several years after the onset of symptoms. Although the heritability of anxiety disorders is well known, the genetic determination of response to different modalities (psycho- or pharmacotherapy) used in treatment of patients with ADs is lesser investigated. Several studies focused on the role of serotonergic genes in the etiopathology and pharmacotherapy of anxiety disorders, however, less attention was paid to variants of other genes. In this review we focus on the cytochrome P 450, BDNF, COMT, MAOA, EAA-3 transporter, dopamine transporter and dopamine receptor gene polymorphisms and their effects with respect to the pharmacogenetics of anxiety disorders. We discuss the current knowledge on pharmacogenetic/therapygenetic aspects of anxiety disorders beyond the serotonergic system.

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Epidemiological data suggest that the group of anxiety disorders (ADs) is the most prevalent class of psychiatric disorders (Kessler et al. 2010), with about one in five adults suffering from an anxiety disorder in the U.S. population (Merikangas and Kalaydjian 2009). The range of lifetime-prevalence data of different ADS are as follows: specific phobia 1.5-12%; social phobia 0.2-9.4%; OCD 0.1-3%; GAD 0.1-6.9%; panic disorder 0.2-5%; PTSD from 1 to over 10% (the wide range of prevalence data mirrors that these are derived from populations of different countries) (Merikangas and Kalaydjian 2009; Kessler et al. 2010).

In general, the onset of different ADs mainly occurs in childhood or adolescence (for example, the National Comorbidity Survey-Replication found that the median age at onset of ADS was 12 years) (Merikangas and Kalaydjian 2009; Kessler et al. 2010), indicating that ADs have an earlier onset compared to other "major" psychiatric diseases such as mood or substance use disorders and nonaffective psychoses (Merikangas and Kalaydjian 2009; Kessler et al. 2010). The genetic contribution to the pathogenesis of ADs is widely known. The heritability of different types of ADs varies from 30% (PTSD) to 67% (agoraphobia) (Domschke and Deckert in press). Linkage and association studies identified several loci of interest and susceptibility genes associated with ADs (for a recent review see Domschke and Deckert (in press). The role of several neurotransmitter systems in the mediation of different anxious symptoms has been raised in the literature. Accordingly, besides the main inhibitory and excitatory amino acid transmitters of the central nervous system (GABA and glutamate, respectively) monoaminergic neurotransmitters (such as serotonin, dopamine and (nor)adrenalin), several neuropeptides (e.g. neuropeptide Y, neuropeptide S, cholecystokinin) and some other transmitters (e.g. endocannabinoids) are also involved in the neurochemistry of anxiety (Durant et al. 2010; Lazary et al. 2011; Wu et al. 2011; Klauke et al. in press).

Pharmacotherapy and different types of psychotherapy are the two widely used and effective treatment modalities for ADs (Ravindran and Stein 2010). The pharmacologic armamentarium for the treatment of ADs includes agents from several different classes of drugs. Accordingly, many classes of antidepressants (e.g. selective serotonin reuptake inhibitors (SSRI), serotonin noradrenaline reuptake inhibitors (SNRI), tricyclic antidepressants (TCA) and monoamine oxidase inhibitors (MAOI)), as well as benzodiazepines (BZD), azapirones (e.g. buspirone), the anticonvulsant agent pregabalin and the antihistamine hydroxyzine are in use for the treatment of ADs (for a review see (Bandelow et al. 2008; Ravindran and Stein 2010) indicating a diverse molecular background of antidepressants.

While a large number of pharmacogenetic studies were conducted in patients with mood disorders it is surprising that – despite the significant magnitude of social and personal burdens of ADs – only a relatively few studies have specifically investigated the genetic aspects of response to treatment among individuals with ADs to date (Schosser and Kasper 2009; Domschke and Deckert in press). A PubMed search performed in October 2012 with the terms "pharmacogenetics" and "anxiety" or "anxiolytics" has provided only 84 and 102 results, respectively; while a search with the terms "pharmacogenetics" and "depression" or "antidepressants" provided 322 and 480 results, respectively.

In case of the etiopathology of anxiety disorders, genes of the serotonergic system are the most extensively studied candidates. There are several recent reviews that address this question (Lesch et al. 2003; Maron and Shlik 2006; Lowry et al. 2008; Akimova et al. 2009; Lazary et al. 2011; Fernandez and Gaspar 2012; Domschke and Deckert in press) and there are also various papers, although with inconsistent results, which focus on the role of serotonergic genes in the response to pharmacotherapy in various anxiety disorders (Perna et al. 2005; Kim et al. 2006; Schosser and Kasper 2009; Maron et al. 2010; Yevtushenko et al. 2010; Yevtushenko and Reynolds 2010; Ishiguro et al. 2011; Mekli et al. 2011; Andrisano et al. 2012; Brandl et al. 2012; Corregiari et al. 2012; Narasimhan and Lohoff 2012; Lohoff et al. in press a; Lohoff et al. in press b). Therefore in our present review we focus on other pharmacogenetic aspects beyond those related to the serotonergic system, reviewing the CYP 450 system that has a crucial role in pharmacokinetic processes, and BDNF, COMT, dopamine receptor, dopamine transporter (DAT) and EAAT3 genes, which are important in the pharmacodynamic aspects of the treatment of anxiety disorders.

CANDIDATE GENES IN THE PHARMACOGENETIC STUDIES IN ANXIETY DISORDERS

The cytochrome P450 enzyme system

The cytochrome P450s (CYPs) are members of a superfamily of oxidative enzymes, and act as the major system for *phase I* oxidative metabolism of approximately 80% of the commonly used therapeutic substances (Weizman et al. 2012). Drug metabolising enzymes of the *phase II* reactions (e.g. glucuronyl transferases, acetyltransferases and glutathione S-transferases) also show genetic variability with functional consequences, but since the majority of psychotropics are extensively metabolized by enzymes of *phase I*, most of the clinically relevant metabolism-related pharmacogenetic effects are attributable to *phase I* reactions, with some noteworthy exceptions like the case of lamotrigine (Stingl et al. in press).

The clinically most important isoenzymes of hepatic CYPs, regarding benzodiazepine and antidepressant metabolism, are CYP1A2, CYP2C9/19, CYP2D6 and CYP3A4 (Tiwari et al. 2009; Weizman et al. 2012). Interindividual and interethnic differences within CYP450 genes may contribute to altered activity of different CYP isoenzymes. This genetic variability in enzyme activity may lead to differences in efficacy (i.e. treatment response), side-effects and intoxication frequency between individuals during pharmacological treatment. It is notable that not only genetic effects but also environmental effects (e.g. smoking, caffeine intake, grapefruit juice consumption) and intake of other medications may influence the activity of some isoenzymes of the CYP450 family (Paine et al. 2004; Tiwari et al. 2009; Dome et al. 2010; Brandl et al. 2012; Muller et al. 2012; Weizman et al. 2012; Stingl et al. in press). The degree of genetic variability differs between distinct members of CYP450 enzymes. Accordingly, degrees of polymorphism in genes for CYP2D6 and CYP2C19 are high, for CYP1A2 and CYP2C9 are medium and for CYP3A4 is low (Stingl et al. in press).

In accordance with the paramounting importance of CYP enzymes in the metabolism of psychotropic medications it is not surprising that a large number of investigations concerning the association between different CYP enzyme variants and response and/or side effect profile to antidepressive agents were carried out in patients with major depression (Weizman et

al. 2012). However, although we know that different genetic variations of some CYP enzymes are associated with altered plasma levels of benzodiazepines and antidepressants used in the treatment of ADs, and also that plasma concentrations of these medications may be associated with treatment response in anxiety disorder patients, the number of investigations which deal with the effect of CYP polymorphisms on treatment response in patients with ADs is surprisingly low (Lesser et al. 1992; Fukasawa et al. 2007; Tiwari et al. 2009; Brandl et al. 2012).

Van Nieuwerburgh et al. was not able to find a significant effect of CYP2D6 gene variants on treatment response to paroxetine or venlafaxine among OCD patients in a 12-weeks study (although they found that CYP2D6 variants determined plasma levels of both agents) (Van Nieuwerburgh et al. 2009). On the contrary, in a sample of OCD patients treated with one or more trials of clomipramine or SSRIs Müller et al. found that CYP2D6 status was associated with therapeutic response (Muller et al. 2012).

Brain-derived neurotrophic factor (BDNF)

There are several lines of evidence that suggest that BDNF is involved in both the pathogenesis and treatment of ADs (Chen et al. 2006; Schosser and Kasper 2009; Soliman et al. 2010; Hong et al. 2011; Domschke and Deckert in press).

Rs6265 is a well-known SNP within the BDNF gene resulting in a valine to methionine (Val66Met) substitution, influencing activity-dependent BDNF secretion, brain morphology and memory functions. Furthermore, some results suggest it is also associated with anxiety susceptibility (notwithstanding associations of this SNP with risks of specific types of ADS (PD; OCD; PTSD; etc.) remained unproven), and also has an effect on antidepressant treatment response in depression (Chen et al. 2006; Soliman et al. 2010; Hong et al. 2011; Brandl et al. 2012; Weizman et al. 2012). However, Narasimhan et al. was unable to find an effect of rs6265 on treatment response to venlafaxine in GAD (Narasimhan et al. 2011; Domschke and Deckert in press). Real et al. was also unable to reveal an association between rs6265 and success of treatment with serotonin reuptake inhibitors in patients with OCD, however, in the same study a haplotype of five SNPs – including rs6265 – was found to be associated with treatment response (Real et al. 2009; Brandl et al. 2012; Fullana et al. 2012).

Possible effects of other polymorphisms of BDNF gene on treatment response in ADs were also investigated. In the above mentioned study by Real et al. rs1491850 was found to affect the outcome of antidepressant treatment in OCD (Real et al. 2009; Brandl et al. 2012). Preliminary results also suggest that C270T and rs2049045 SNP may influence treatment response to S(S)RI therapy in OCD (Brandl et al. 2012). Domschke et al. found that the TT variant of another polymorphism in the BDNF gene (rs7124442) was associated with poorer treatment outcome among patients with anxious depression (Schosser and Kasper 2009; Tiwari et al. 2009; Domschke et al. 2010).

Catechol-O-methyltransferase (COMT)

The COMT enzyme is responsible for the inactivation of various catecholamines including dopamin, adrenalin and noradrenalin. It has been hypothesized that there is an interaction between the dopaminergic and serotonergic systems in the development of depression and the response to antidepressive treatment (Weizman et al. 2012). In addition, results of (imaging) genetic studies suggested that COMT is a possible player in the pathogenesis of ADs as well (Kolassa et al. 2010; Maron et al. 2010; Domschke and Deckert in press; Taylor in press).

Recently, Narasimhan et al. (2012) investigated the role of the rs4680 functional variant (also referred to as Val158Met) of the COMT gene in treatment response to venlafaxine in patients with GAD (Narasimhan et al. 2012). After a six-month treatment period, they found that this polymorphism had no effect on treatment outcome if response was defined using the Hamilton Anxiety Scale. At the same time, if response was defined using the Clinical Global Impression of Improvement scale, an influence of this SNP was detectable on treatment outcome (although the association did not withstand the Bonferroni correction) (Narasimhan et al. 2012). The role of some other COMT gene polymorphisms (rs165737; rs165774; rs174696; rs174697 and rs165599) in treatment response – which previously were found to be associated with treatment response in patients with MDD – were also studied in a GAD sample treated with duloxetine or placebo. According to the results, none of the examined COMT SNPs showed significant associations with response to treatment with duloxetine in GAD patients, but two of them were associated with anxiety improvement in the placebo group (Perlis et al. in press).

Miguita et al. was not able to find an association between outcome of clomipramine treatment in

patients with OCD and Val158Met polymorphism of the COMT gene (Miguita et al. 2011; Brandl et al. 2012). Results of Zhang et al. also did not support the role of variation of the COMT gene in OCD patients treated with serotonin reuptake inhibitors (Zhang et al. 2004). Notwithstanding, recently Vulink et al. demonstrated the effect of Val158Met SNP on citalopram treatment response among patients with OCD (Vulink et al. 2012). Woo et al. found that the COMT Val158Met polymorphism is associated with treatment response to paroxetine in patients with panic disorder (Woo et al. 2004; Andrisano et al. 2012).

Monoamine oxidase-A (MAO-A)

MAO-A is one of the enzymes that catalyzes the extraneuronal breakdown of catecholamines (Weizman et al. 2012). Genetic variants of MAO-A are associated with susceptibility to some ADs (panic disorder, OCD, GAD and phobias) (Tadic et al. 2003; Samochowiec et al. 2004; Maron et al. 2010; Domschke and Deckert in press; Taylor in press). At the same time, there is scarce data on the pharmacogenetic aspects of MAO-A in ADs: namely, Zhang et al. did not find an association between variants of MAO-A gene and treatment response to SRIs in OCD (Zhang et al. 2004; Brandl et al. 2012).

Dopamine receptors and the dopamine transporter (DAT)

Although their connection – based on sometimes ambiguous results of genetic, neuroimaging, pharmacological, etc. studies – with different kinds of ADs made them attractive targets, from the viewpoint of pharmacogenetics genes for dopamine receptors and DAT have been only scarcely studied in patients with ADs (Rowe et al. 1998; Tiwari et al. 2009; Durant et al. 2010; Maron et al. 2010; Maron et al. 2010; Chang et al. 2012; Warwick et al. 2012; Taylor in press).

The Taq1 polymorphism of the DRD2 gene (a.k.a. rs1800497) was not associated with treatments response to SRIs in OCD (Zhang et al. 2004; Narasimhan and Lohoff 2012). At the same time, Lawford et al. reported that subjects with PTSD carrying the DRD2 A1 allele were more likely to respond to treatment with paroxetine (Lawford et al. 2003). Recently, Perlis et al. found in a sample of patients with GAD that some variants of the DRD3 gene (rs963468; rs167770; rs324023; rs324026) were associated with treatment response to duloxetine (Perlis et al. in press).

In the above-mentioned study by Zhang et al., authors also did not find associations between investigated DRD4 variations and success of SRI therapy (Zhang et al. 2004; Narasimhan and Lohoff 2012).

Miguita et al. investigated the effects of various DAT gene polymorphisms (i.e. the 40-bp VNTR in the 3'UTR; a 30-bpVNTR in intron 8; a VNTR in intron 14) on treatment response to clomipramine in patients with OCD, but they were unable to detect any significant associations (Miguita et al. 2011; Brandl et al. 2012).

Excitatory amino-acid transporter 3 (EAAT3)

Converging results of neuroimaging (MRS) and neurochemical studies (measuring CSF glutamate levels) and also of animal models indicate that glutamatergic transmission is impaired in OCD (Wu et al. 2012; Real et al. in press). Furthermore, genetic studies reported that variants of the SLC1A1 gene encoding the glutamate transporter EAAC1/EAAT3 and also the GRIK2 gene encoding the kainate receptor subunit 2 are probably associated with the risk of OCD (Wu et al. 2012; Real et al. in press; Taylor in press). According to the results of Real et al. who investigated seven SNPs in the *SLC1A1* gene in a sample of 238 OCD subjects, three SNPs (rs301434, rs301435 and rs3087879) were associated with treatment response (but only among those subjects free from stressful life events before onset of OCD) (Real et al. in press).

PHARMACOGENETIC FACTORS IN THE BACKGROUND OF ANXIOGENIC SIDE EFFECTS OF MEDICATIONS

Our knowledge concerning the genetic background of anxiety provides information not only with respect to therapeutic and adverse effects of anxiolytic medications and other medications used in the treatment of anxiety disorders, but can also be utilized to predict anxiogenic and depressogenic side effects of various other medications and therefore help to identify those patients in whom application of these pharmacotherapies is likely to lead to such adverse effects. Rimonabant, an endocannabinoid 1 receptor (CB_1) antagonist used as an appetite suppressant led to the emergence of depression and anxiety in about 20% of the patients taking it prompting the withdrawal of the medication from the market. This adverse effect of rimonabant is probably based on an interaction between CB_1 receptors and the serotonergic system in the amygdala modulating depression and anxiety.

An interaction between the CB_1 receptor gene (CNR1) and the serotonin transporter gene has been earlier reported in mediating anxiety, with a significantly higher trait anxiety in those carrying the ss variant of the 5-HTTLPR and the GG genotype of the CNR1 rs2180619 polymorphism, due to a combined effect of a low expression of inhibitory CB_1 receptors and low expression of the serotonin transporter responsible for removing serotonin after release (Lazary et al. 2009). During stressful events, serotonin release increases in the amygdala activating postsynaptic $5HT2_C$ receptors, leading to increased anxiety (Bagdy et al. 2001) and through Gq activation (Turu et al. 2009) increased synthesis of the endocannabinoid 2-AG which acts as a retrograde neurotransmitter binding to presynaptic inhibitory CB_1 receptors which in turn inhibit further release of serotonin (Lazary et al. 2011; Bagdy 2012). This negative feedback circuit shows higher activity in 5-HTTLPR ss carriers who manifest higher extracellular serotonin concentration due to a lower expression of the serotonin transporter, and is influenced by CB_1 antagonists which may be one mechanism in the background of their anxiogenic effect (Lazary et al. 2009; Lazary et al. 2011; Kirilly et al. 2012; Kirilly et al. in press). Therefore investigating the CNR1 and 5-HTTLPR genotype may prove to be a useful tool in identifying those patients who would be at a risk of psychiatric side effects upon the use of CB_1 antagonists.

RESULTS OF THERAPYGENETIC STUDIES IN ANXIETY DISORDERS

The term therapygenetics was coined by Eley et al. to describe those lines of psychiatric genetic investigations which aim at revealing the effect of specific genetic variants on success of psychotherapy. In the last few years a series of such investigations was conducted (Eley et al. 2012).

Bryant et al. found in a preliminary study that genetic variations affecting expression of SERT (namely the multimarker genotype which is the combination of 5-HTTLPR and rs25531) are associated with response to cognitive behavior therapy (CBT) in patients with PTSD (Bryant et al. 2010). Authors found that PTSD subjects with low-expressing genotypes (s or Lg genotype carriers) had fewer treatment gains from CBT than patients with the high-expressing variant (La/La homozygotes) (Bryant et al. 2010). A recent study conducted by Eley et al. investigated whether treatment response of children receiving CBT for an AD is associated with the 5-HTTLPR genotype. Authors found that children with the ss genotype had better symptomatic response to CBT at follow-up compared to those carrying the sl or ll genotypes (Eley et al. 2012). A subsequent study was unable to confirm the results of Eley et al. on the association between 5-HTTLPR and response to CBT, however, this study was conducted in an adult population and participants suffered from depression and not from ADS (Bockting et al. in press).

A study by Lonsdorf et al. found that the functional catechol-O-methyltransferase (COMT) Val-158Met polymorphism had an effect on response to CBT in patients with panic disorder (response was diminished in met/met homozygotes as compared to patients carrying at least one val allele), while no influence of the SERT multimarker genotype (5-HTTLPR and rs25531) could be identified (Lonsdorf et al. 2010).

A study investigating the effect of the Val66Met (rs6265) SNP in the BDNF gene on response to CBT in patients with OCD found that met allele carriers had a lower response compared to patients not carrying the met allele (Fullana et al. 2012). At the same time, there was no effect of the rs6265 polymorphism of the BDNF gene on response to CBT in children with ADs; however, the same study demonstrated that presence of the T allele of the nerve growth factor (NGF) gene rs6330 polymorphism was associated with better treatment response (Lester et al. 2012).

At the same time, Hedman et al. found that none of the genetic variations including 5-HTTLPR, COMT Val158Met and BDNF Val66Met influenced the effectiveness of CBT in SAD (Hedman et al. 2012).

DISCUSSION

As compared to the voluminous literature on pharmacogenetic results in affective disorders, to date there are only a relatively few papers on pharmacogenetics findings in ADs (Schosser and Kasper 2009; Domschke and Deckert in press). Moreover, existing results so far are frequently controversial and unconfirmed. At the same time, since a large proportion of patients with different kinds of ADs do not sufficiently benefit from initial pharmacological and/or psychological treatment (i.e. their response- and full remission rates are considerably low), pharmacogenetic studies are needed to provide better prediction of treatment response at the level of individuals (Van Ameringen et al. 2009; Diemer et al. 2010; Reinhold et al. 2011; Ipser and Stein 2012; Marazziti et al. 2012; Domschke and Deckert in press).

Considering the three facts that 1) pharmacological treatment regimens for major depression and for ADS are quite similar; 2) these two groups of disorders are highly comorbid; and 3) there are a number of promising genetic candidates which have emerged from pharmacogenetic studies in major depression, we may suppose that in the near future those genetic variants which would be associated with treatment response in affective disorders will also be investigated in AD patients.

Results of these future studies may open up new avenues toward improved, more successful – and at the same time, personally tailored – treatment of anxiety disorders.

Abbreviations:
AD – anxiety disorder
BDNF – brain derived neurotrophic factor
CBT – cognitive behavior therapy
COMT – catechol-o-methyltransferase
CYP – cytochrome P450
DAT – dopamine transporter
EAAT – excitatory amino acid transporter
GAD – generalized anxiety disorder
MAO-A – monoamine oxidase A
MDD – major depressive disorder
OCD – obsessive-compulsive disorder
PD – panic disorder
PTSD – post traumatic stress disorder
SNP – single nucleotide polymorphism
VNTR – variable number tandem repeats

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A szorongásos betegségek kezelésének farmakogenetikai aspektusai a szerotonerg rendszeren túl: rövid összefoglalás

A szorongásos betegségek a leggyakoribb mentális problémák közé tartoznak. Ezen kórképeket a korai betegségkezdet és gyakran a tünetek megjelenése és az adekvát kezelés kezdete között eltelt hosszú időszak jellemzi. A szorongásos betegségek genetikai meghatározottsága jól ismert, ugyanakkor a genetikai tényezők szerepe ezen zavarok gyógyszeres és pszichoterápiára adott válaszában kevéssé kutatott tudományterület. Bár számos vizsgálat foglalkozott a szerotonerg rendszer génjeinek szerepével, kevesebb tanulmány látott napvilágot olyan farmakokinetikai génvariánsokkal kapcsolatban, mint a citokróm P450 enzimrendszer, illetve a farmakodinámiás összefüggések szintjén a BDNF, COMT, MAO-A, a dopamine transzporter illetve a dopaminreceptorok, vagy az excitátoros aminosavtranszporter gén variánsai. Összefoglaló tanulmányunkban a szorongásos zavarok kezelésére adott terápiás válasz genetikai meghatározottságának szakirodalmát tekintjük át a szerotonerg rendszer génjein túlmenően, kitérve a pszichoterápiára adott válasz lehetséges genetikai meghatározóira is.

Kulcsszavak: szorongásos betegségek, farmakogenetika, terápiás válasz, szorongásoldók, benzodiazepinek, szelektív szerotonin visszavétel gátlók, pánikbetegség, PTSD