PHARMACOGENETICS OF ANTIDEPRESSANTS

FARMAKOGENETIKA ANTIDEPRESIVOV

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Abstract

Background *Antidepressant drug therapy is characterised by a high rate of therapeutic failure, which can not be predicted in advance.*
Pharmacogenetic studies in mood disorders aim to the identification of gene polymorphisms associated with therapeutic efficacy and side effects of antidepressants. During the recent years the possible influence of a set of candidate genes in the pharmacodynamic pathway as possible genetic predictors of antidepressant response efficacy were investigated and will be reviewed here. The functional polymorphism in the upstream regulatory region of the serotonin transporter gene (5-HTTLPR), the A218C gene variant on the tryptophan hydroxylase gene (TPH), the 102TC variant in the 5HT2A receptor, the G-protein beta3-subunit (Gbeta3) C825T gene variant, the glucocorticoid receptor-regulating cochaperone (FKBP5) and the Circadian Locomotor Output Cycles Kaput (CLOCK) genes variants were independently associated with short term SSRIs antidepressant efficacy. Cytochromes P450 appear so be the most important determinant of the pharmacokinetics of antidepressants, especially polymorphic CYP2D6 that metabolizes most of the selective serotonin reuptake inhibitors (SSRI). Also polymorphic MDR1 gene coding for P-glycoprotein (ABCB1), a brain-to-blood efflux drug transporter, seems to be an important detemininant of antidepressant efficacy.

Conclusions *Although in its preliminary phase, the results obtained in the pharmacogenetics of antidepressants are promising for an individualized therapy. Pharmacogenetic testing could help to identify the most effective treatment, improve the quality of life of affected persons and reduce the health-care costs.*

Key words *pharmacogenetics; antidepressants; genetic polymorphism*

Izvleček

Izhodišča *Pri zdravljenju z antidepresivi velik problem predstavlja neodzivnost na zdravljenje, ki je ni mogoče vnaprej napovedati, pojavi pa se kar pri tretjini bolnikov. S farmakogenetskim pristopom so v zadnjih letih odkrili številne genetske polimofizme, ki so povezani z učinkovitostjo zdravljenja z antidepresivi in/ali z neželenimi učinki the zdravil. Prispevek prinaša pregled genetskih dejavnikov, ki lahko vplivajo na farmakodinamiko in farmakokinetiko antidepresivov. Med najpomembnejši polimorfizmi, ki vplivajo na farmakodinamiko in na kratkoročno učinkovitost zdravljenja z antidepresivi, so: polimorfizem (insercija/delecija 44bp) v promoterju gena za serotoninski transporter SERTPR), ki vpliva na hitrost prepisovanja; polimorfizem A218C gena za triptofan hidroksilazo (TPH), polimorfizem T102C gena za serotoninski receptor 2A (5HT2A, polimorfizem C825T gena za beta3-podenoto G proteina (Gbeta3), ko-šaperon, ki uravnava glukokortikoidni receptor (FKBP5) in polimorfizmi gena, ki uravnava cirkadiano aktivnost (Circadian Locomotor Output Cycles Kaput – CLOCK).*

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Na famakokinetiko antidepresivov pa najpomembneje vplivajo citokromi P450, zlasti CYP2D6 preko katerega se presnavlja večina selektivnih zaviralcevi prevzema serotonina (SSRI). Na učinkovitost zdravljenja z antidepresivi pa vpliva tudi polimorfizem gena za p-glikoprotein (MDR1 oz. ABCB1), ki transportira antidepresive preko hematoencefalne bariere.

Zaključki *Čeprav so farmakogenetske raziskave zdravljenja z antidepresivi še v začetni fazi, so rezultati obetavni in kažejo, da farmakogenetsko testiranje lahko pripomore k individualiziranemu in bolj racionalnemu zdravljenju z antidepresivi in k boljši kvaliteti življenja bolnikov.*

Ključne besede *farmakogenetika; antidepresivi; genetski polimorfizem*

Since the serendipitous discovery of imipramine, in 1957, different classes of antidepressant drugs have been used to treat depressive syndromes. Although their efficacy is well established, still 30–40 % of patients do not show a significant response (> 50 % reduction in baseline score on the Hamilton Rating Scale for Depression – HAMD) to therapeutic doses of antidepressant medications administered for 6–8 weeks of treatment, while 60–70 % fail to achieve full remission (17-item HAMD < 7).[1] Partial remission has been associated with a higher recurrence, a greater functional impairment and a worse quality of live.[2, 3] All antidepressants have a lag phase and it takes at least 3–4 weeks to observe the real effect of treatment administration.[4] Such a delayed response may increase the patients' suffering and the risk of suicidal behaviour and early discontinuation of treatment. Patients have to stay in hospital for longer periods and this results in higher costs. Therefore early identification of responders to a specific antidepressant treatment would be of great usefulness both from a clinical and economical point of view. Unfortunately, in spite of some evidence concerning the predictive power of demographic characteristics, illness features and social factors,[5–7] none of such variables could unequivocally be linked to treatment outcome and antidepressant choice is still based on a trial and error procedure.

Inherited differences in drug response have been described for a variety of compounds supporting the influence of genetic factors on treatment outcome.[8, 9] This has been investigated in antidepressant short term treatment.[10–13]

Further, one important determinant in treatment decision making is the occurrence of side effects, which can negatively impact compliance. This was reported to be of 40 % to 90 % in different studies of antidepressant drugs with an average of 65 %.[14] The prevalence and severity of side effects follow interindividual variations, therefore it is reasonable to hypothesize a genetic basis for drug tolerability.[15] The present paper will review the literature concerning genetic influence on the efficacy and tolerability of antidepressant. Traditional approaches based on the analysis of candidate genes which act throughout pharmacodynamic and pharmacokinetic mechanisms are now integrated by complementary genome-wide approaches.[16]

Pharmacodynamic aspects

The monoamine hypothesis, which identifies the biological basis for depression in a deficiency of brain monoamine neurotransmitters,[17] is still considered a valid model to account for the mechanism of action of antidepressant drugs.[18] Increasing evidence demonstrates that monoaminergic systems and other biological systems implicated in the pathophysiology of depression such as the substance P and stress-hormone systems have reciprocal interactions, and ultimately stimulate neurogenesis.[19, 20] These pathways showed to be affected by several antidepressant treatments, thus they represent the main focus of pharmacogenetic research. Other lines of investigation have included inflammatory cytokines[21] and the endogenous clock system.[22]

Brain monoamine systems

Tryptophan Hydroxylase

Tryptophan hydroxylase (TPH) catalyzes the rate-limiting step in 5-HT biosynthesis. Its prominent role in the pathophysiology of depression is underscored by the fact that tryptophan depletion can induce a transient depressive state in individuals with a known history of depressive disorder.[23] The gene encoding TPH has been cloned and mapped on 11p15.3-p14.[24] It includes two bi-allelic polymorphisms in position 218 (A218C) and 779 (A779C) of intron 7, which are in strong disequilibrium.[25] The A218C polymorphism is located in a potential GATA transcription factor-binding site, therefore it may influence gene expression, and consequently antidepressant (AD) response. The rarer TPH*A-allele of A218C polymorphism showed in fact to be associated with a decreased 5-HT synthesis,[26] even if this finding has not been replicated.

The presence of this allele may predispose to suicidal behaviour as emerged from two recent meta-analyses.[27, 28] The A-allele was also associated with a slower and less marked HAMD improvement in two double-blind trials with fluvoxamine and paroxetine we carried out in our center in Milan.[29, 30] Subsequent studies performed in Japan[31] and Korea[32] failed to demonstrate a correlation between the TPH A218C polymorphism and response to Selective Serotonin Reuptake Inhibitors (SSRIs). Recently a new TPH isoform was discovered and called TPH-2.[33] while the original

isoform is now TPH-1. The gene encoding TPH-2 (chromosome 12) is 150-fold more expressed in mouse brain than the TPH-1 gene,[34] therefore it might represent a promising candidate for pharmacogenetic investigation. Peters and colleagues tested both TPH isoforms in 96 unipolar depressives treated with fluoxetine for 12 weeks.[35] While the TPH-1 gene was associated with general response, TPH-2 variants were implicated in specific response to fluoxetine. These findings are in line with the latest published studies demonstrating that all TPH isoforms are expressed in the human brain, with different levels of each isoform between the brain areas.[36] Two studies examined the relationship between TPH-2 polymorphisms and resistant depression:[37,38] a marginal association emerged with the TPH-2 G1463A single-nucleotide polymorphism.[38]

Serotonin transporter

Extracellular monoamines are cleared from the synaptic cleft and carried into the synaptic terminal by plasma membrane proteins that are termed transporters. As these proteins are high-affinity targets for psychostimulants (cocaine, amphetamine) and different classes of ADs, they are suitable candidates for pharmacogenetic research. To date a large amount of studies have involved the serotonin transporter (SERT) gene. The brain SERT is the principal site of action of many antidepressant drugs (SSRI, TCA) and mediates the behavioral and toxic effects of cocaine and amphetamines. SERT knockout mice show robust phenotypic abnormalities when compared to normal mice, with increased anxiety and inhibited exploratory locomotion.[39] The deletion of the SERT gene produces also a reduction in aggressive behavior and home cage activity of knockout mice; this effect is further enhanced by desensitization of 5-HT1A and 5-HT1B receptors.[40]

Ramamoorthy et al. identified and cloned a single gene encoding the human SERT (SLC6A4), localized to chromosome 17q11.1-q12.[41] The gene spans 31 kb and consists of 14 exons.[42] Heils et al. reported a polymorphism in the transcriptional control region upstream of the SERT coding sequence.[43] The polymorphism is located approximately 1000 bp upstream of the transcription initiation site within a region composed of 16 repeat units (5-HTTLPR). It consists of a 44-bp insertion/deletion involving units 6 to 8. It is known that the long (l) 5-HTTLPR allele has twice the SERT expression in the basal state than the short (s) form. As the 5-HTTLPR polymorphism can affect SERT expression and SERT is the main target of SSRIs, it is reasonable to hypothesize the influence of 5-HTTLPR variants on SSRI response. This has been tested in several studies (see Table 1): a better outcome in l-allele carriers[44–51] has been a consistent findings among Caucasian patients. Instead Asian studies produced conflicting results, with some samples showing the same genotype-response association pattern as Caucasians[52–54] and others revealing a better response in 5-HTTLPR s-allele carriers[55,56] or no effect of the 5-HTTLPR.[57] Most likely the small sample sizes, different ethnicity and different definition of responders do not allow drawing a definite conclusion on the role of the 5-HTTLPR polymorphism. This appears to influence treatment outcome independently from other predictors including antidepressant dose and SERT affinity.[48] Recent studies suggest that the 5-HTTLPR polymorphism may also affect antidepressant tolerability. Thus in a double-blind trial of elderly outpatients s-allele carriers treated with paroxetine were characterized by more severe adverse effects and higher discontinuation rates compared to l/l homozygotes while in a subgroup on mirtazapine the s-allele was associated with a better tolerability and fewer discontinuations.[51] Still the s-allele was shown to identify patients at risk for developing insomnia and agitation with fluoxetine treatment.[58] However other studies reported no association between 5-HTTLPR variants and side effects occurring with SSRIs.[59] Two studies demonstrate an increased risk for antidepressant-induced mania with carriage of the s-allele[60,61] but negative findings were also reported.[62,63]

Over the last few years new polymorphisms within the SERT gene have attracted attention as predictors of antidepressant response, their interaction with the 5-HTTLPR waiting to be elucidated Ogilvie et al. identified a different variable number tandem repeat (VNTR) polymorphism in the second intron of the SERT gene (Stin2) which was related to susceptibility to major depression.[64,65] Ito and colleagues reported no association of Stin2 with fluvoxamine response.[66] A single nucleotide polymorphism (rs25531 SNP), located just upstream of the 5-HTTLPR revealed a significant influence on antidepressant response to fluoxetine and, intriguingly, a moderation effect on 5-HTTLPR alleles. In the presence of the G-allele of this SNP, the l-allele of the 5-HTTLPR is associated with non-response, as the s-allele where it is expressed together with the A-allele of the rs25531 SNP.[67]

Norepinephrine transporter

One study determined whether NET gene variants could affect response to minalcipram.[57] Significant associations were reported with the T-128C (T-allele predicting a better response) and A1287G polymorphisms (slower onset of response in A/A genotype carriers).

Monoamine oxidase A

MAO-A is a major degrading enzyme in the metabolic pathways of monoamine neurotransmitters (NE, DA, 5-HT). The gene encoding MAO-A – chromosome Xp11.23[68] – is supposed to influence the mechanism of action of SSRIs through an interaction with SERT.[69] A polymorphism located 1.2 kb upstream the MAO-A coding sequences (VNTR) was reported to affect the transcription of the MAO-A promoter.[68] Its influence on AD treatment efficacy was investigated in three studies which yielded negative results.[31,70,71]. More recently in a sample of Chinese inpatients with major depressive disorder the 3-repeat variant of the MAO-A VNTR was positively associated with antidepressant treatment outcome in females.[72]

Table 1. *5-HTTLPR polymorphism and antidepressant treatment response.*

Razpr. 1. *Polimorfizem 5-HTTLPR in odziv na zdravljenje z antidepresivi.*

Authors Avtorji	Study design Zasnova študije	Positive association with response Pozitivna povezava z odzivom	Ethnicity Preisko-vanci
Smeraldi et al., 1998	N = 99 (BP + MDD) Fluvoxamine	L-allele P = 0.017	Caucasian
Zanardi et al., 2001	N = 155 (BP + MDD) Fluvoxamine	L-allele P = 0.029	Caucasian
Zanardi et al, 2000	N = 64 (BP + MDD) Paroxetine	L-allele (s-allele slower) P < 0.001	Caucasian
Pollock et al., 2000	N = 95 (late life MDD) Paroxetine	L-allele (s-allele slower) P = 0.028	Caucasian
Arias et al., 2001	N = 102 (MDD) Citalopram	L-allele (s-allele more no remission) P = 0.006	Caucasian
Minov et al., 2001	N = 104 (MDD) Various ADs and ECT	No association	Caucasian
Joyce et al., 2003	N = 169 (MDD) Fluoxetine or Nortryptiline	L-allele (ss slower response In patients > 25y)	Caucasian
Durham et al., 2004	N = 206 (MDD geriatric) Sertraline or placebo	L-allele (sertraline group)	Mostly Caucasian
Serretti et al., 2004	N = 221 (MDD + BP) Fluvoxamine or Paroxetine	L-allele (ss poor response)	Caucasian
Kraft et al, 2005	N = 96 (MDD) Fluoxetine	L-allele if rs25531 = A S-allele if rs25531 = G	Mostly Caucasian
Murphy et al., 2004	N = 122 (MDD geriatric) Paroxetine	L-allele P < 0.05	Mostly Caucasian
Murphy et al., 2004	N = 124 (MDD geriatric) Mirtazapine	No association	Mostly Caucasian
Kim et al., 2000	N = 120 (MDD/Korean) Fluoxetine or Paroxetine	S-allele P = 0.007	Asian
Yoshida et al., 2002	N = 66 (MDD/Japanese) Fluvoxamine	S-allele	Asian
Yu et al., 2002	N = 121 (MDD/Chinese) Fluoxetine	L-allele P = 0.013	Asian
Ito et al., 2002	N = 66 (MDD/Japanese) Fluvoxamine	No association	Asian
Lee et al., 2004	N = 128 (MDD/Korean) Various ADs	L-allele Ss genotype poor longterm (1-3 yrs) prognosis	Asian
Kato et al., 2005	N = 81 (MDD/Japanese) Paroxetine or Fluvaxamine	L-allele	Asian

Legend: MDD – Major Depressive Disorder, BP – Bipolar disorder, AD – Antidepressant
Legenda: MDD – depresivna motnja, BP – bipolarna motnja, AD – antidepresiv

Catechol-o-methyltransferase

COMT is involved in the catabolic pathways of NE and DA. Moreover this enzyme can indirectly affect brain 5-HT given reciprocal interactions between DA and 5-HT. Lachman and collaborators[73] reported a functional polymorphism consisting on a transition of guanine to adenine at codon 158 leading a substitution of Val to Met in MB-COMT (and in position 108 in S-COMT). It has been shown that the Met allele results in a three to four fold lower enzymatic activity than Val allele.[74, 75] Two recent studies report that patients with Met-Met homozygosity are less likely to respond to mirtazapine[76] and citalopram.[77]

Beta1 adrenoreceptor

These receptors serve as important regulators of central nervous system mediated behavior and of several neural functions, including mood, memory, neuroendocrine control, stimulation of autonomic function and are involved in the mediation of AD effects.[78] This may also explain why beta-blocker medications are associated with side effects such as depression and lethargy.[79]
Beta1 adrenergic receptor gene ADRB1 was mapped on 10q24-q26.[80] A polymorphism in the intracellular cytoplasm tail, consisting of a G/C transversion at position 1165 of the ADRB1 gene, was shown to alter the receptor-Gs protein interaction, with functional consequences on signal transduction.[81] This polymorphism was also found to affect response to »noradrenergic« antidepressant agents, even if the finding was only marginally significant.[82]

Dopamine receptors

DA containing neurons are located primarily in the midbrain and a number of experimental observations suggested that a decreased dopaminergic neurotransmission might be associated with depression. Moreover, an interaction between the serotonergic and dopaminergic systems in the nucleus accumbens has been established, since motivation and hedonia have been associated with DA release in the nucleus accumbens.[83] In spite of these data suggesting a pathogenic role for the dopamine system in depressive disorders, no significant association of DRD2 and DRD4 variants with SSRI efficacy was observed in a large sample (N = 364) of depressed inpatients collected in our center in Milan.[84]

5-HT1A receptor

These receptors are located on cortical and limbic neurons, both at postsynaptic and presynaptic level where they act as autoreceptors, preventing the further release of 5HT with a negative feedback. Pindolol is thought to accelerate the onset of AD action by blocking 5-HT1A autoreceptors.[85] A SNP in the promoter region of the 5-HT1A gene (G to C substitution at position – 1019[86]) was associated with the diagnosis of major depression in a case-control study[87] and, more recently, with antidepressant treatment outcome. Since 2004 five independent studies reported

either a better response to SSRI drugs in 5-HT1A – 1019C/C homozygotes[88] or a worse response in G-allele carriers.[89–91] A different Gly272Asp polymorphism was explored in Japanese MDD outpatients treated with fluvoxamine. Asp allele carriers showed a more marked reduction in depressive symptomatology compared to Gly/Gly homozygotes.[92] This finding was not confirmed by subsequent studies.[93]

5-HT2A receptors

The activation of 5-HT2A receptors in medial prefrontal cortex and anterior cingulate cortex is thought to mediate the hallucinogenic properties of LSD, whereas in amygdala the 5-HT2A receptor activation is a component of antidepressant response. The 5-HT2A receptors may mediate some of the AD effects seen in experimental animal models of depression.[94] An antidepressant drug such as nefazodone was found to (partially) exert its therapeutic effect via a 5-HT2A receptor antagonism.[95] The gene coding for 5-HT2A receptor was mapped to chromosome 13q14-q21.[96] A T to C substitution at position 102 was implicated in AD response,[97] even if the finding could not be replicated in two independent samples.[71, 88] In addition more side effects were reported in patients with the 5-HT2A-102C/C genotype who were treated with either paroxetine or mirtazapine for 8 weeks.[98] Another polymorphism in the promoter region of the 5-HT2A gene (-1438 G/A SNP) was independently explored by three research groups:[57, 99, 100] one study showed a greater improvement of »core« depressive symptomatology and somatic anxiety in 5-HT2A–1438G allele carriers.[100] Finally the T/T variant of the 5-HT2A -C1420T SNP revealed a marginal association with a worse response to SSRI treatment.[71]

5-HT6 receptor

is a G-protein coupled receptor which stimulates adenylyl cyclase. In the rat it shows high affinity for ADs such as mianserin and clomipramine.[101] 5HT6 receptor antagonists seem to improve retention performance in experimental animals which has implicated a role for 5HT6 in cognition enhancement.[102, 103] Kohen et al. reported a silent polymorphism consisting of a thymidine to cytosine substitution at position 267 (TC 267) within the first exon of the 5-HT6 receptor gene.[104] This SNP was investigated for association with AD response in two studies, the first one, thirty-four MDD patients receiving various ADs, yielded negative results.[105] More recently, in a study involving a larger MDD sample (N = 71), 5-HT6 receptor CT heterozygotes were found to have a better response to AD treatment than homozygotes (CC + TT genotypes).[106]

Intracellular signal transduction pathways

G-protein Beta-3 subunit

G-proteins are key components of intracellular signal transduction in all cells of the body including neurons. Inactive G-proteins are trimers coupled with receptors on the cell-membrane. The active form is a GTP bound alpha monomer resulting from the dissociation of a beta-gamma dimer.[107] Chronic treatment with fluoxetine showed to attenuate GTP binding to gamma subunit in the dorsal raphe nucleus of rats, thus inducing desensitization of 5HT1A receptors.[108] Beta subunit is subdivided into three subtypes. The gene encoding beta3 subunit (GNB3) is located at human chromosome 12p13, in a region which harbors other five genes.[109] Its sequence spans 7.5 kb and includes 11 exons and 10 introns. A polymorphism in GNB3 exon 10 (C825T SNP) has been shown to modulate signal transduction and ion transport activity.[110] GNB3 825T variant is associated with the occurrence of the splice variant Gbeta3s, which, despite a deletion of 41 amino acids, is functionally active in reconstituted systems. To date four independent studies have demonstrated a better antidepressant response in patients with one or two copies of the Gbeta3 T-allele.[50, 111–113] Hong and colleagues reported the only negative study in an Asian sample.[88]

Stress hormone system

Stressful or traumatic events occurring in early life significantly increase the risk for depression in adulthood.[114] To further underscore the relationship between stress response and depressive disorder, genes coding for components of the stress hormone system have so far been associated with AD treatment outcome.

CRH receptor 1

A number of animal studies have displayed the antidepressant properties of CHR receptor I antagonists.[115, 116] A three SNP haplotype within the corticotrophin releasing hormone receptor 1 (CRHR1) could be associated with response to desipramine or fluoxetine in a sample of Mexican-Americans.[117]

Glucorticoid receptor gene

A research group in Munich (Germany) identified a functional polymorphism of the glucorticoid receptor (GR) gene (ER22/23EK) and a series of SNPs within the gene encoding the hsp90 co-chaperone FKBP5 (a part of the mature GR heterocomplex that regulates GR sensitivity) which were shown to modulate the onset of response to various classes of antidepressant drugs.[118] However no replication followed.

ACE – substance P system

Angiotensin converting enzyme

There is increasing evidence pointing to the involvement of the substance P system in the pathophysiology of depression. NK1 receptor antagonists have shown preclinical activity in several paradigms of anxiety and depression.[119, 120] Mutant mice lacking the NK1 receptor gene have an increased firing rate of dorsal raphe serotonergic neurons, an effect that can also be seen after the administration of substance P antagonists.[121] When given chronically, NK1 antagonists promote an enhancement of serotonergic transmis-

sion in the hippocampus that seems to be mediated by interaction with other neurotransmission systems.[122] Clinical efficacy of such drugs has also been demonstrated among patients with major depression, although the results have been inconclusive.[123] In the central nervous system substance P is colocalized with the angiotensin converting enzyme (ACE) which is thought to participate in its degradation. An intronic insertion (I) / deletion (D) polymorphism determines functional variants of the ACE gene with a secondary impact on substance P levels and antidepressant activity. Indeed the D allele, which determines higher ACE plasma levels,[124] was recently associated with higher substance P levels[125] and a faster response to antidepressant treatments,[126] including total sleep deprivation,[127] particularly among females.[128] Interestingly, this polymorphism also influences HPA-axis reactivity in depressed patients, with patients carrying the D/D genotype having the highest cortisol response in the Dex-CRH test administered at admission.[129] More recently another component of the ACE-substance P system, the angiotensin II receptor gene (ATI), was added to outcome predictors in major depression.[130]

Proinflammatory cytokines

Interleukin 1-Beta

Interleukin-1 (IL-1), produced mainly by blood monocytes, mediates the host reactions of acute phase response. In female rats IL-1 may induce a behavioural complex called sickness behaviour, characterized by loco-motor retardation, sleep disorders, soporific effects, anorexia, weight loss, hyperalgesia, decreased social exploration, and inhibition of sexual behaviour.[131] This animal behaviour, which resembles human depression, can be inhibited by chronic antidepressant treatment.[132] Increased production of IL-1 has been reported in patients with major depression and dysthymia.[133, 134] IL-1, like other cytokines, may cause hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and reduction in 5-HT levels which ultimately result in the onset of depression.[132] The association of a biallelic polymorphism (-511C/T SNP) located in the promoter region of the IL-1beta gene to fluoxetine response was studied in 119 depressed patients who underwent a 4-week treatment with fluoxetine. Trial results showed a trend towards T/T homozygotes having milder depressive symptoms and a more favourable fluoxetine response compared to C-allele carriers.[135]

Endogenous clock system

Circadian Locomotor Output Cycles Kaput (CLOCK)

The endogenous control of circadian rhythms is under the control of a central pacemaker localized in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus. Several genes are thought to interact in rhythms control and they are called »clock« for their function of regulation of timing in biological functions.[136] In particular the Circadian Locomotor Output Cycles Kaput (CLOCK) gene was identified in mice[137] and in humans.[138] The mRNA of human CLOCK gene has been found in the SCN, hippocampus, piriform cortex and cerebellum,[138] all areas involved in biological rhythms. One polymorphism, named 3111 T/C located in the 3' flanking region, has been shown to affect mRNA stability and half-life.[139] The C allele has been associated with significantly higher »eveningness« in healthy subjects and with a delay in preferred timing for activity or sleep episodes, with no changes in sleep architecture.[140]. In mood disorders the same C variant was associated with higher recurrence rates in bipolar patients,[141] increased lifetime sleep disturbances[142] and persistence of insomnia during antidepressant treatment.[143]

Pharmacokinetic aspects

Cytochrome P450 enzyme complex

The cytochrome P450 (CYP) superfamily exists in over 50 isoenzymes that catalyze the oxidation of many drugs and chemicals. In humans seven isoforms – CYP1A, CYP2A6, CYP2B6, CYP2C, CYP2D6, CYP2E1 and CYP3A enzymes – account for approximately 70 % of the liver cytochromes. CYP2D6 has been implicated in the metabolism of most antidepressant drugs.[144] So far, up to 75 different alleles have been reported for CYP2D6, more than 15 of these encode an inactive or no enzyme at all, while others consist of gene duplications.[145] Such gene variants have shown a clear influence on drug metabolism – individulas are classified as poor (PM), intermediate (IM), extensive (EM) and ultra-rapid (UM) metabolizers according to their inherited genetic profile[146] –, however their effect on AD response and tolerability is less consistent and still under investigation.

A direct correlation was observed between the number of functional CYP2D6 gene copies and plasma levels of some TCAs such as nortryptiline.[147] From these pharmacokinetic studies it has been extrapolated that starting doses of nortryptiline are probably enough to reach therapeutic plasma levels in subjects with no or only one functional copy of the CYP2D6 gene, among whom higher doses might increase toxicity. On the contrary high-normal doses of the drug may be required for patients with 2–4 copies.[145] Dose adjustments according to CYP2D6 genotype have been proposed for TCAs in view of their small therapeutic »windows«.[148]

Like TCAs, CYP2D6 variants have been shown to modify the plasma concentrations of the SSRI paroxetine[149] and the SNRI venlafaxine.[150] For the latter a relationship between PM status and the increased occurrence of cardiovascular side effects or toxicity has been reported. On the contrary no relationship between CYP2D6 genotype, tolerability and efficacy was observed in a sample of geriatric inpatients on paroxetine.[98] So, even if dose recommendations based on CYP2D6 genotypes have been put forward for SSRIs too, the relevance of such dose-adjustments is questionable given their flat dose-response curve.[151] The impact of CYP2D6 variants might be greater for SSRI + TCA combined treatments. Indeed co-administra-

tion of paroxetine and desipramine in EM who had at least two functional copies of the CYP2D6 gene was found to result in a 5-fold decrease in desipramine clearance.[152]

P-glycoprotein

P-glycoprotein is a member of the highly conserved superfamily of ATP-binding cassette (ABC) transporter proteins. It acts as a pump that, in view of its localization – liver, kidney and small capillars of the blood-brain barrier[153] –, appears to regulate the clearance of xenobiotics and access to the brain for psychotropic drugs.[154] The gene encoding p-glycoprotein – formerly MDR1, now ABCB1 – is localized to chromosome 16. An intronic ABCB1 polymorphism was found to be associated with remission to antidepressant therapy but not with drug plasma levels.[155] It is therefore likely that ABCB1 variants influence antidepressant response by affecting the transport of drugs across the blood-brain barrier, with a mechanism that does not implies modification of drug plasma concentration.

Perspectives in psychopharmacogenetics

In spite of the popular claim that pharmacogenetics holds promises for an individualized approach to psychopharmacology, important shortcomings have so far hampered the use of research data in clinical practice:

1. the literature provides us with an increasing number of candidate genes, however only few of them could be consistently associated with drug efficacy or tolerability
2. even those genes with a proven influence on drug behavior could show opposite effects in different studies
3. only a small amount of variance in individual response to psychotropic drugs could be explained by genetic factors.

Accordingly, improving the consistence of results across studies and expanding the number of candidate genes appear to be priorities in the agenda of today's psychopharmacogenetics.

In the study of clinical response focus is classically decreasing in overall psychopathology. However increasing evidence suggests that single candidate genes can have a selective impact on few clusters of symptoms rather than on the global clinical pictures of mood disorders. For instance the therapeutic effect of 5-HTTLPR variants is principally directed to somatic anxiety.[52, 54] Similarly the C/C genotype of the CLOCK gene was associated with persistence of insomnia during SSRI treatment while it had no effect on overall antidepressant response.[143] This may imply that a major cause of contrasting findings in published studies is the presence of different symptom profiles in their samples. So future pharmacogenetic analyses should target symptom dimensions.

Each candidate gene may also be related to factors that independently affect treatment outcome. For example personality traits and disorders are known to worsen the outcome of treated mood disorders; therefore genes that are associated with these factors should predict a poor drug response. Accordingly recent studies demonstrate an excess of anxiety traits in the presence of the 5-HTTLPR s-allele[156, 157] which was already linked with a negative prognosis of antidepressant treatment (see above). Most findings in the field of pharmacogenetics could be obtained by exploring a relatively small number of candidate genes which encoded proteins that were involved in drug activity. In spite of some appreciable results this hypothesis-driven approach is probably too restrictive and leaves out a large number of candidate polymorphisms. Indeed all observed gene variants do not reach the putative 50 % of variance explained by genetic factors in the complex trait of antidepressant response. *Pharmacogenomics* may then aid in identifying more candidates by discovering those genes that are activated or deactivated in response to treatment.[158] One popular method of experimental genomics is expression array.[16] This involves hybridization of fluorescent or radioactively labeled mRNA species to cDNA arrays. So thousands of mRNA transcripts are analyzed simultaneously, those that change after treatment are related to candidate genes. Alternatively, *proteomics* evaluates gene activity by detecting protein expression instead of mRNA transcripts.[159] Both animal and human tissues have been used for these studies. Most literature has investigated antidepressant treatment related genome-wide mRNA expression changes in rodent brain tissue.[160–163] A few studies have investigated the effects of antidepressant treatment on peripheral blood monocytes.[164] Overall results have been largely inconsistent. In fact whole genome SNP analyses have an expected high number of false positive associations due to the high degree of multiple testing. To bypass this problem the last few years have witnessed the development of new experimental designs that combine the methods of linkage analysis, pharmacogenomics and proteomics. Examples of such sequential approaches were already published with promising results.[165, 166]

Besides individualizing drug treatment pharmacogenetics/pharmacogenomics would offer a good solution to the problem of biological diversity in psychiatric disorders. Thus response to a given drug could be used to identify homogeneous forms within pathophysiologically heterogeneous syndromes, which may facilitate the discovery of new susceptibility genes for psychiatric conditions. This strategy has been proposed and successfully applied to lithium response in bipolar disorder.[167] However the emerging literature has extended the influence of single genes to a wide range of psychological and psychopathological phenomena in addition to drug response. The SERT gene is an emblematic example of such multiple effects. Indeed the 5-HTTLPR polymorphism has been associated with different characteristics of mood disorders – age of onset,[168, 169] illness recurrence,[62, 170] drug response (see above), reactivity to stressful life events,[171] personality traits[172] and several psychiatric diagnoses such as alcoholism,[173] smok-

ing,[174] psychosomatic disorders,[175] eating disorders,[176, 177] suicide,[178] autism[179] and attention deficit hyperactivity disorder.[180] Future studies will clarify whether such phenotypes are all simultaneously present or at different times in the same individuals. Complex phenotypic profiles will then be obtained by pooling together such different features on the basis of their linear association with gene variants.[181] This is a simple methodology to resume solitary data in comprehensive models, and we suggest it as a starting-point for future research on the role of crucial genes in modulating human behaviors.

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