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Review

Pharmacogenetics in affective disorders

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Abstract

Pharmacogenetics will be of substantial help in the field of affective disorders pharmacotherapy. The possible definition of a genetic liability profile for drug side-effects and efficacy will be of great help in treatments that need weeks to months to be effective. During the last few years, a number of groups have reported possible liability genes. The efficacy and time of onset of selective serotonin reuptake inhibitors have been associated with a polymorphism in the promoter region of the transporter (SERTPR) in many independent studies, while variants at the tryptophan hydroxylase gene, 5-HT2a receptor and G-protein β3 have been associated with them in pilot studies. Lithium long-term prophylactic efficacy has been associated with SERTPR, TPH and inositol polyphosphate 1-phosphatase variants, though in unreplicated samples. A number of further candidate genes were not associated with these treatments. In conclusion, both acute and long-term treatments appear to be, at least to some extent, under genetic influence and preliminary data have identified possible liability genes.

Keywords: Bipolar disorder; Depressive disorder; Pharmacogenetics; Genetics

1. Introduction

Pharmacogenetics is the use of genetic information to guide pharmacotherapy and improve outcome by providing individualized and science-based treatment decisions. This field has gained increasing attention and holds great promise for clinical medicine (Dettling et al., 2001; Pickar and Rubinow, 2001; Roses, 2000; Segman et al., 1999).

Pharmacogenetic studies generally focus on functional gene variants in a drug-metabolizing enzyme that can be linked to adverse drug reactions (such as in the thiopurine methyltransferase case) (Krynetski and Evans, 1999), on gene variants in a drug target that can be associated with variations in drug response (for example 5-lipoxygenase) (Drazen et al., 1999), and on gene variants in a disease susceptibility gene such as apolipoprotein E that has been correlated with the response to cholinesterase inhibitors in Alzheimer's patients (Poirier et al., 1995).

The emerging field of pharmacogenetics holds great potential, particularly in psychiatry, for refining and optimizing psychopharmacology, given the lack of biologically based treatment guidelines (American Psychiatric Association, 1994b, 1997, 2000; Catalano, 1999).

The pharmacotherapy of affective disorders has reduced morbidity and improved outcomes for millions of individuals worldwide. In fact, since 1950, specific antidepressant drug treatments, able to improve symptomatology and increase the chance of a good long-term outcome, have been used. Unfortunately, not all subjects benefit from treatment, and efficient clinical predictors have not been yet identified, but there is some evidence suggesting that genetic factors play a substantial role (Berrettini, 1998; Orsini, 1987; Pare and Mack, 1971; Sederer, 1986). In 1994, it was reported that, in a family with eight relatives suffering from major depression, individuals tended to respond to the monoamine oxidase inhibitor, tranylcypromine (O'Reilly et al., 1994). Our group analyzed data from 45 pairs of relatives treated with fluvoxamine (Franchini et al., 1998); the sample included individuals with unipolar and individuals with bipolar depression. Among their first-degree relatives, 30 (67%) also responded to fluvoxamine and the families they belonged to showed the higher genetic loading for affective disorders. Subsequently, in a related study, we applied complex segregation analysis to 171 families of bipolar and unipolar probands responsive to fluvoxamine: the results favored a single major locus transmission of mood disorders

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in a subset of 68 families of bipolar probands (Serretti et al., 1998a).

Notwithstanding the above-mentioned evidence, the search for genetic factors predisposing to drug response or side-effects in affective disorders has only started in the last few years.

2. Antidepressants

2.1. SSRI

Selective serotonin reuptake inhibitors are widely used for the treatment of depression because of their efficacy and relatively favorable side-effect profile compared to those of tricyclic antidepressants (Masand and Gupta, 1999; Schloss and Williams, 1998). Pharmacogenomic studies on selective serotonin reuptake inhibitors should focus on genes that are involved in their mechanism of action.

The antidepressant action of selective serotonin reuptake inhibitors is usually explained with a serotonin hypothesis. In fact, the main neurobiological target of selective serotonin reuptake inhibitors is the serotonergic neurotransmitter system, which includes synthesis, release and reuptake, receptors, G proteins, second-messenger cascade, and gene expression regulation. Levels of serotonergic neurotransmission in the forebrain are a key to mood: high activity results in euphoria, low activity results in dysphoria; according to this hypothesis, depression is thought to be caused by chronically low levels of serotonergic transmission. Conversely, an increase of serotonin transmission is supposedly involved in manic states (Jacobs and Fornal, 1995; Maes and Meltzer, 1995). Selective serotonin reuptake inhibitors interfere with the activity of the serotonin transporter (SERT), a reuptake molecule that removes serotonin from the synaptic cleft; thus, the putative low levels of synaptic serotonin in depressed patients are elevated, and depression is relieved (Schafer, 1999). The most current versions of the serotonin model hypothesize that selective serotonin reuptake inhibitors are effective against depression not because of their acute effects on serotonergic transmission, but because of long-term adaptive changes in monoamine neurotransmission that arise from the chronic inhibition of serotonin reuptake (Leonard, 1996). In particular, while the acute effects could be ascribed to the inhibition of serotonin reuptake in dorsal raphe nucleus, activation of somatodendritic autoreceptor 5-HT1a, decrease of serotonin release, the long-term effects could be linked to the desensitization of the somatodendritic autoreceptor 5-HT1a, increase of serotonin release, increase of serotonin concentration in terminal areas (Artigas et al., 1996; Bel and Artigas, 1993). Moreover, molecular and pharmacological studies showed that selective serotonin reuptake inhibitors contribute to modification of cellular mechanisms that follow receptor activation by neurotransmitters. In particular, changes in protein kinase C, protein kinase A, and other postsynaptic substrates have been observed (Bel and Artigas, 1993; Perez et al., 1995, 1991).

The cDNA for the human SERT, the initial site of action for selective serotonin reuptake inhibitors, was isolated in 1993 (Lesch et al., 1993), and subsequently a polymorphism in the promoter region of the transporter (SERTPR) (Heils et al., 1997; Lesch et al., 1996) and a variable number of tandem repeats polymorphism in the second intron (Lesch et al., 1994; Ogilvie et al., 1996) were described. Other SERT polymorphisms were also found (Battersby et al., 1999; Flattem and Blakely, 2000; Michaelovsky et al., 1999; Nakamura et al., 2000), but the most interesting studies to date have examined the effects of the SERTPR polymorphism (Lesch and Mossner, 1998). SERTPR polymorphism consists in the presence or absence of a 44 base-pair segment producing either a long (L) or short (S) allele. It was found that this polymorphism can influence transcriptional activity of the SERT gene: in vitro, the basal activity of the long variant was more than twice that of the short form (Heils et al., 1996).

The gene coding for SERT has been proposed as a possible candidate for involvement in the pathogenesis of major psychoses. It has been associated with both major depressive and bipolar disorders (Collier et al., 1996a,b; Coyle et al., 2000; Rees et al., 1997), although subsequent studies have not replicated these results (Bellivier et al., 1997; Esterling et al., 1998; Ewald et al., 1998; Furlong et al., 1998; Gutierrez et al., 1998; Hoehe et al., 1998; Kelsoe et al., 1996; Lenzinger et al., 1999; Mendes de Oliveira et al., 1998; Mundo et al., 2000; Oruc et al., 1997; Ospina-Duque et al., 2000; Saleem et al., 2000). The gene also proved to be associated, based on conflicting evidence, with a number of other conditions.

As selective serotonin reuptake inhibitors act directly on the SERT, differences at this locus may result in differences in therapeutic response (Lesch, 2001). Consistent with this, several studies found an association of the short (S) allele in the SERTPR site with a poor response to antidepressant treatment (Table 1). The majority of those studies were performed in the center of Milan (Italy) with homogeneous methods. Briefly, lifetime diagnoses were assigned by trained psychiatrists and supervised by an independent senior psychiatrist on the basis of unstructured clinical interviews and medical records, according to DSM-IV criteria (American Psychiatric Association, 1994a) and following a best estimate procedure (Leckman et al., 1982). The presence of any concomitant Axis I diagnosis, major depressive single episode, together with somatic or neurological illnesses impairing psychiatric evaluation were exclusion criteria. Subjects had not taken nonreversible monoamine oxidase inhibitors or slow-release neuroleptics for at least 1 month before entering the study. All patients were evaluated at baseline and weekly thereafter until the 6th week, using the 21-item Hamilton Rating Scale for Depression (HAM-D-21) (Hamilton, 1967) administered by trained senior psychiatrists blind to genetic data and to treatment. After a 7-day washout period, fluvoxamine was titrated to reach 300 mg

Table 1
SERTPR variants and SSRI treatment in affective disorders

Author	Sample	Drug	Result
Smeraldi et al. (1998)	30 BP, 69 MD	Fluvoxamine	l allele subjects were more likely to respond ($p=0.017$)
Zanardi et al. (2001)	47 BP 108 MD (replication sample)	Fluvoxamine	l allele subjects were more likely to respond (all samples, $p=0.029$; without pindolol, $p=0.002$)
Zanardi et al. (2000)	46 MD 18 BP	Paroxetine	s allele associated with less favorable and slower response ($p<0.001$)
Pollock et al. (2000)	95 late-life depression	Paroxetine	s allele associated with slower response ($p=0.028$)
Kim et al. (2000)	120 Korean MD	Fluoxetine and paroxetine	s/s genotype showed better response ($p=0.007$)
Arias et al. (2001)	102 MD	Citalopram	s/s genotype was significantly more frequent in no remission group ($p=0.006$)

daily from day 8 until the end of the trial, paroxetine was used at 20–40 mg. Pindolol 2.5 mg t.i.d. was added blind to approximately half of the sample randomly selected. Concomitant psychotropic drugs were not allowed, except flurazepam at bedtime (up to 45 mg) or lithium carbonate maintenance. A decrease in HAM-D scores to 8 or less, with Delusion factor equal to 0 (items 2, 15, 20) (Bech et al., 1993; Bellini et al., 1992; Sobin and Sackeim, 1997), was considered the response criterion. The effect of poor response of SERTPR*s/s was observed for both fluvoxamine and paroxetine without differences between the two drugs. Augmentation with pindolol consistently reduced the genetic effect, while sex, diagnosis, the presence of psychotic features, and the severity of depressive symptomatology did not influence the association. At least two centers replicated the short-term finding (Italy and USA), the USA center observed the same influence of SERTPR*s/s using paroxetine but in a sample of elderly people, while a Korean group reported a significant association but in the opposite direction (Kim et al., 2000). However, some differences between this and other studies should be pointed out. First, from a genetic point of view, polymorphism frequencies in Asian populations differ greatly from those in western countries (Kunugi et al., 1997), Subsequently the number of l/l patients in the sample was low (N=5). The low rate of responders in this sample could indirectly confirm a positive role of l/l variants, in fact a less restrictive response criterion (50% HAM-D score decrease versus a final score of 8) was used. Recently, SERTPR short variants have been associated with poor outcome after 12 weeks of treatment, an effect that was not evidenced after 4–6 weeks (Arias et al., 2001). This finding is of potential interest because it could explain discrepant results of studies focusing on short-term observations, in fact it is well known that subjects who are responders in the short-term (4–8 weeks) may not maintain the response in the longer observations (3–6 months) (Linden et al., 1997) and should not be considered full responders (Quitkin et al., 1987, 1984). Longer observation periods are therefore a better choice.

Results from basic studies added information to the SERTPR finding: individuals with the s/s genotype have shown a blunted prolactin response to a fenfluramine challenge (Whale et al., 2000), a test that correlates inversely with antidepressant response to selective serotonin reuptake inhibitors (Cleare et al., 1998; New et al., 1999).

The challenges for research in pharmacogenetics come from the identification of further appropriate candidate genes. Among genes recognized as potentially relevant for antidepressant effects, the SERT gene is probably the most important, but other genes have been investigated in association with treatment response in mood disorders.

Another candidate gene, probably implicated in the clinical response to SSRI treatment, is the tryptophan hydroxylase gene that codes for the rate-limiting enzyme of serotonin biosynthesis. This gene has been cloned (Boularand et al., 1990) and mapped on 11p15.3-p14 (Craig et al., 1991). Two biallelic polymorphisms in strong disequilibium have been identified on position 218 (A218) and 779 (A779C) of intron 7 (Nielsen et al., 1997). The polymorphism A218C is located in a potential GATA transcription factor binding site, so that it may influence gene expression (Jonsson et al., 1997), and consequently the antidepressant response. In fact, two studies evidenced an association between tryptophan hydroxylase gene variants and response to both fluvoxamine and paroxetine (Table 2). To date, these data have not been replicated. As was seen with the

Table 2
Candidate gene variants and SSRI treatment in affective disorders

Author	Gene	Drug	Sample	Result
Serretti et al. (2001d)	TPH	Fluvoxamine	73 BP, 144 MD	A/A genotype was associated with slower response (no pindolol $p=0.001$)
Serretti et al. (2001c)	TPH	Paroxetine	34 BP, 87 MD	A/A and A/C genotypes were associated with slower response (no pindolol $p=0.011$)
Serretti et al. (2001b)	DRD2, DRD4	Fluvoxamine and paroxetine	167 BP, 197 MD	No association

SERTPR, pindolol appeared to reduce the effect of tryptophan hydroxylase gene variants, while clinical variables did not significantly influence this effect. The effect of the two polymorphisms appeared to be additive (Serretti et al., 2001d).

Serotonergic and dopaminergic systems are much interconnected in the brain. Although in vitro studies on synaptosomal uptake of monoamines suggest that selective serotonin reuptake inhibitors selectively inhibit 5-HT uptake rather than that of other monoamines, in vivo microdialysis experiments showed that selective serotonin reuptake inhibitors are not entirely selective for 5-HT (Pozzi et al., 1999). There is convincing evidence that the serotonergic projections inhibit dopamine function in the midbrain (Kapur and Remigton, 1996). As a result, 5-HT receptor agonists, serotonin precursors, and selective serotonin reuptake inhibitors enhance the inhibition of the dopamine system. The indirect increase in dopamine release could provide a possible mechanism for the involvement of DA in the therapeutic action of selective serotonin reuptake inhibitors, though not unequivocally (Clark et al., 1996). In detail, selective serotonin reuptake inhibitors could enhance dopamine function in the nucleus accumbens through increased expression of postsynaptic dopamine D2 receptors (Ainsworth et al., 1998). Moreover, in a group of depressive patients, there was a significant linear correlation between treatment response and change in dopamine D2 receptor binding in the basal ganglia. These results suggest an association between changes in the dopaminergic system and treatment response in major depression (Klimer et al., 1999). Polymorphism within the dopamine D2 receptor gene causing a structural change from serine to cysteine at codon 311 of DRD2 (S311C) was reported (Itokawa et al., 1993); this substitution occurs in the third intracellular loop of the receptor and it is putatively functional (Jonsson et al., 1996). Similarly, a polymorphism located in the third exon of the dopamine D4 receptor gene (DRD4) (Van Tol et al., 1991, 1992) was associated with the potency of dopamine to inhibit cAMP formation (Asghari et al., 1995). However, the only study testing these two polymorphisms failed to evidence associations with selective serotonin reuptake inhibitors efficacy (Table 2).

2.2. Other antidepressant treatments

Worldwide, the large majority of depressed subjects are treated with selective serotonin reuptake inhibitors; however, a substantial number of subjects are treated with tricyclic antidepressants, monoamine oxidase inhibitors, and a range of other somatic treatments. A few studies investigated the pharmacogenetics in these treatments by analyzing some candidate genes.

In the gene for monoamine oxidase A, the principal enzyme for the degradation of biogenic amines, a polymorphism located 1.2 kb upstream of the monoamine oxidase A coding sequences has been shown to affect the transcriptional activity of the MAO-A gene promoter (Deckert et al., 1999; Denney et al., 1999; Sabol et al., 1998). Mutations in guanine nucleotide binding proteins (G-proteins), which represent the essential regulatory components in the transmembrane coupling system of many receptors (Birnbaumer et al., 1990; Gilman, 1987), could affect antidepressant efficacy (Ram et al., 1997). The 5-HT2a receptor, a postsynaptic receptor present in many neocortical areas (Burnet et al., 1995), may also influence the efficacy of serotonergic agents (Burnet et al., 1995). Chronic administration of tricyclic or monoamine oxidase inhibitors results in down-regulation of the 5-HT2 receptors and also selective serotonin reuptake inhibitors have been associated with a decreased responsiveness of 5-HT2 (Glennon and Dukat, 1995).

In the studies so far performed using these polymorphisms, monoamine oxidase A variants were not associated with antidepressant response, but G-protein β3 and 5-HT2A variants were associated with response to various treatments (Table 3). None of these studies has yet been replicated.

Sleep deprivation is a rapid and effective antidepressant treatment (Wirz-Justice and Van den Hoofdakker, 1999), but long-lasting benefit is only observed in a small part of the subjects; pharmacogenetic studies could be therefore useful for explaining this observation. Three studies were performed in two different centers (Italy and Germany); SERTPR long variant was associated with a good response (Benedetti et al., 1999b), an effect similar to what has been observed for selective serotonin reuptake inhibitors, while

Table 3
Candidate gene variants and other antidepressant treatments

Author	Gene	Drug	Sample	Result
Muller et al. (2000)	MAOA	Moclobemide	64 MD	No association
Zill et al. (2000)	G-protein β3	SSRI, TCA, ECT, combinations	10 BP, 78 MD	TT homozygosity associated with response ($p=0.01$)
Serretti et al. (1999a)	DRD4	Sleep deprivation	124 BP	No association
Benedetti et al. (1999b)	5HTT	Sleep deprivation	68 BP	l/l patients showed better mood amelioration ($p=0.05$)
Schumann et al. (2001)	DRD3	Sleep deprivation	52 MD	No association
Mundo et al. (2001)	5HTT	SSRI, TCA	56 BP	Patients with manic or hypomanic episodes induced by antidepressant treatment had an excess of s alleles ($p<0001$)
Minov et al. (2001)	5-HT2A (T102C)	SSRI, TCA, ECT, combinations	173 MD	C containing variants associated with response ($p=0.023$)

some of the dopamine receptor genes were not associated with outcome (Table 3).

3. Antipsychotic medication

Patients with an affective disorder may receive antipsychotic medication at some point in the course of their illness. Up to date, no pharmacogenetic study with antipsychotics has been performed in affective disorders. Indirect clues may come from studies of schizophrenia where there is growing evidence of associations with treatment response and side-effects. Most of the research has focused on clozapine. Keeping in mind the potential risks and the need for long-term close monitoring, the identification of molecular genetic predictors of response to clozapine would be particularly useful. A number of candidate genes were proposed, with conflicting results: 5-HT receptors 2A, 2C, 6, and 7, dopamine receptors D2, D3, and D4 (Fang and Gorrod, 1999; Kawanishi et al., 2000; Kerwin and Owen, 1999; Masellis et al., 2000). One particular aspect of antipsychotic treatment deserves special attention in mood disorders, namely the risk of tardive dyskinesia (Cavallaro et al., 1993). This is a serious complication afflicting a significant minority of subjects treated with antipsychotics on a long-term basis. Several studies indicated that the risk of tardive dyskinesia might actually be higher in patients with a mood disorder than in patients suffering from schizophrenia (Jeste and Caligiuri, 1993; Keck et al., 2000; Schulze et al., 2001a). Genetic investigations suggested that the risk of tardive dyskinesia might be associated with variants in the locus for dopamine D3 receptor, 5-HT2A and 5-HT2C, cytochrome *P*450 1A2, SERT, though not all the studies agree on this (Basile et al., 2001, 2000; Chong et al., 2000; Eichhammer et al., 2000; Garcia-Barcelo et al., 2001; Liao et al., 2001; Lovlie et al., 2000; Schulze et al., 2001b; Segman et al., 1999, 2001, 2000; Steen et al., 1997).

4. Lithium

Genetic factors are supposed to play a role in determining lithium efficacy in mood disorders (Abou-Saleh and Coppen, 1986; Alda, 1999; Cavazzoni et al., 1996; Grof et al., 1994; Maj et al., 1984; Mendlewicz, 1979, 1972; Morabito et al., 1982; Nylander et al., 1999; Smeraldi et al., 1984a,b; Turecki et al., 1996). However, pharmacogenetic studies on long-term lithium efficacy present two main difficulties, phenotype definition and choice of the candidate genes.

Phenotype definition is a crucial issue (Pickar and Rubinow, 2001; Veenstra-VanderWeele et al., 2000). The explicit and consistent definition of the drug-response phenotype is extremely important; in particular, the long-term efficacy of lithium treatment is difficult to establish (Goodwin and Jamison, 1990). Complete absence of illness episodes during lithium treatment is observed in a limited number of subjects, while most patients experience a decrease in the number of illness episodes and/or in their severity (Goodwin and Jamison, 1990). The recurrence rates before and during prophylaxis therefore appear to be a more suitable dependent variable (Franchini et al., 1994; Gasperini et al., 1993; Serretti et al., 2001a), though this method may also have limitations (Serretti, 2002).

The choice of candidate genes must rely on the mode of action of lithium salts used in prophylaxis of affective disorders, but this is still unknown. Disturbances of the serotoninergic neurotransmitter system have been repeatedly implicated in the mechanism of action of lithium. In fact, some studies reported on effects of lithium at the different levels of precursor uptake, synthesis, storage, catabolism, release, and receptors (Artigas et al., 1989; Baptista et al., 1990; Carli et al., 1997a; Carli and Reader, 1997; Goodwin, 1989; Hotta et al., 1986; Odagaki et al., 1990; Pei et al., 1995; Price et al., 1989).

The weight of this evidence suggests that the primary actions of lithium on 5-HT may be presynaptic, with many secondary postsynaptic effects (El-Mallakh, 1996).

Studies investigating polymorphisms of the serotonin pathway are listed in Table 4. In particular, SERTPR and tryptophan hydroxylase gene variants were associated with lithium efficacy, while 5-HT2A, 5-HT2C, 5-HT1A were not (Table 4). Other neurotransmitters could be involved as well: lithium efficacy in controlling dopamine stimulants-related behaviours (Barnes et al., 1986; van Kammen et al., 1985) and manic states (Goodwin and Jamison, 1990) suggest that lithium activity may be mediated by dopamine receptors (Acquas and Fibiger, 1996; Benedetti et al., 1999a; Carli et al., 1997b; Dziedzicka-Wasylewska et al., 1996; Gottberg et

Table 4
Lithium in pharmacogenetic studies

Author	Gene	Sample	Result
Serretti et al. (1998b)	DRD3	43 BP, 12 MD	No association
Serretti et al. (1999c)	DRD2, DRD4, GABAA- alpha-1	100 BP, 25 MD	No association
Del Zompo et al. (1999)	5HTT	67 BP	l allele associated with nonresponders ($p=0.04$)
Serretti et al. (2001a)	5HTT	167 BP, 34 MD	s/s genotype associated with worse response ($p=0.005$)
Serretti et al. (1999d)	TPH	90 BP, 18 MD	TPH*A/A variant showed a trend toward a worse response ($p=0.046$)
Serretti et al. (2000)	5-HT receptor 2A, 2C, 1A	102 BP, 22 MD	No association
Steen et al. (1998)	INPP1	18 BP	Difference between responders and nonresponders ($p=$n.s.)
Lovlie et al. (2001)	PLC-gamma1	18 BP	No association

al., 1989, 1988; Post and Weiss, 1995; Richelson, 1995). However, dopamine D2, D3, and D4 receptors were not associated with lithium outcome.

The mechanism of action of lithium differs from that of antidepressants particularly as to activity on second messengers, therefore future candidate genes should be investigated in those pathways. Inositol polyphosphatase 1-phosphatase is another suitable candidate (Gerfen et al., 1988; Manji et al., 1995; Rhee et al., 1989). Lithium, at therapeutic concentrations, inhibits inositol polyphosphatase 1-phosphatase, which is involved in recycling inositol polyphosphates to inositol. Thus, it was proposed that lithium action is mediated through depletion of free inositol (Berridge et al., 1989; Godfrey, 1989; Kofman and Belmaker, 1993; Manji et al., 1999a; Moore et al., 1999), which initiates a cascade of secondary changes in the protein kinase C signaling pathway and gene expression in the CNS, effects that could be ultimately responsible for lithium's therapeutic efficacy (Jope and Williams, 1994; Manji and Lenox, 1998; Moore et al., 1999).

In this regard, inositol polyphosphatase 1-phosphatase variants showed a marginal association with lithium efficacy in a small sample. In the same sample, the phospholipase C-gamma1 gene was not associated with lithium efficacy (Table 4). It should be noted that these findings only applied to subjects with good versus poor response, which means that the analysis was more conservative but with a loss of power, as compared to analyses of continuous measures.

However, a number of other mechanisms have been proposed (Klein and Melton, 1996) but have so far not been tested in pharmacogenetic studies (Serretti, 2002). Briefly, lithium, at therapeutically relevant concentrations, is an inhibitor of glycogen synthase kinase 3β (GSK-3β) in vitro (Ikonomov and Manji, 1999; Manji et al., 1999c). It induces the phosphorylation of some protein components of the second-messenger system. In particular, it has been reported to modulate the receptor G-protein coupling or the G proteins (Avissar et al., 1988; Chern et al., 1995; Choi and Toscano, 1988; Manji et al., 1995; Mork et al., 1992; Risby et al., 1991; Yamashita et al., 1988). It influences the neuroprotective protein Bcl-2 (Chen and Chuang, 1999; Moore et al., 2000; Nonaka et al., 1998), the activation protein-1 and activation protein-2 family of transcription factors (Asghari et al., 1998; Damberg et al., 2000; Feinstein, 1998; Jope, 1999; Kumer and Vrana, 1996; Manji et al., 1999b, 1995; Ozaki and Chuang, 1997; Zigova et al., 1999), Fos protein (Asghari et al., 1998; Lee et al., 1999), tyrosine hydroxylase (Chen et al., 1998), gamma-aminobutyric acid (Petty, 1995), myristoylated alanine-rich C kinase substrate (Lenox et al., 1991, 1992) and the cysteine string protein (Cordeiro et al., 2000).

5. Conclusion

The emergence of pharmacogenetics will require advances in the selection of appropriate candidate genes. Such genes are to be sought for among those related to the mechanism of drug action and illness pathophysiology. Some examples of good candidates could be: neurotrophin-3, cAMP response element-mediated protein, cAMP response element-binding protein, dopamine transporter, glucocorticoid receptors, inositol monophosphatase, protein kinase C, 5-HT receptor 1D, proteins implicated in synaptic transmission such as myristoylated alanine-rich C kinase substrate, glycogen synthase kinase 3β, cysteine string protein, AP-1 and AP-2 transcription factors, neuroprotective protein Bcl-2 and c-*fos*.

Drug response is just as complex as disease genetics, resulting not only from underlying genotypic variation at several mostly unknown loci, but also from variation in gene expression, post-translational modification of proteins, drug dose, drug interactions, diet, and other nongenetic factors. Therefore, we expect to see relatively slight effects of individual genes regarding drug response as well. In fact, pharmacogenomic markers reported on to date confer only about a twofold increased likelihood of response (Drazen et al., 1999; Poirier et al., 1995). Pharmacogenomic approaches (Sibille and Hen, 2001), using animal and in vitro models, the use of the DNA microarray technology (a technique that gives information on thousands of genes simultaneously) (Service, 1998; Shoemaker et al., 2001) are very promising strategies that could partially overcome the limitations of candidate gene approach.

The definition of response is a further complicating issue (Pickar and Rubinow, 2001; Veenstra-VanderWeele et al., 2000). While short-term analyses in the range of 4–8 weeks may be relatively free from biases, long-term follow-ups are often exposed to biases deriving from concomitant medications, environmental influences and a number of other factors. On the other hand, careful avoidance of biases is highly costly, at times unethical and useless because it would lead to the exclusion of a large part of subjects treated in clinical settings, yielding results that could hardly be extended to everyday practice (Barbui and Hotopf, 2001; Kraemer et al., 2001). Pharmacogenetic studies involve comparison between groups of patients, without the inclusion of healthy controls, or trios (including both parents of the subjects) because the aim is to identify gene variants that are correlated with response. This may lead to stratification biases, therefore, careful attention to patient ethnicity is important. The use of unlinked genetic markers may help to reduce this bias (Pritchard and Rosenberg, 1999).

Another point to be considered is the statistical aspect of these investigations. The attributable fraction should be calculated and reported in every study in order to allow the potential practical impact of the lability gene (Cohen, 1988). In a recent paper by Drazen et al. (1999), one genotype had a 100% positive predictive value for nonresponse to the drug. However, because the susceptibility genotype is uncommon (6–9% of patients), less than 10% of the nonresponse can be attributed to this genotype. Therefore, if patients with susceptibility genotype avoided taking the drug, its efficacy

would only improve from 46% to 51% in the remaining patients. The test may not, therefore, identify the majority of nonresponders. In order to be of practical use, additional SNPs need to be identified, each explaining a small portion of drug response variance (McCarthy and Hilfiker, 2000). In our studies, we observed that candidate genes variants explained variances ranging from 2% to 7%, those are in the range expected in case of multifactorial disorders (Risch, 1990), but they are not yet in the range for practical applications, where high specificity and sensitivity are required.

The analysis of molecular mechanisms linked to drug response may be useful for the understanding of neurobiology of affective disorders. A first step in this direction comes from SERTPR. A worse response to antidepressants has been reported for the SERTPR*s/s subjects (see previous paragraphs): a significant association was reported between the SERTPR polymorphism and anxiety features in normals (Lesch et al., 1996) and among affective subjects (Serretti et al., 1999b). It is well known that anxiety features are a negative prognostic factor for antidepressant treatments. We may therefore hypothesize that a given genetic predisposition (SERTPR*s) may confer susceptibility to anxiety features and a worse antidepressant response in subjects affected by mood disorders. Abnormalities in the SERT function may in fact confer only a small susceptibility to illnesses, because adaptative mechanisms may partially compensate. In the case of dramatic alterations of serotonin turnover observed during antidepressant treatment, the partial transporter abnormalities would lead to a worse antidepressant response. This is a first example of a model that includes genetic, clinical, and treatment factors.

Finally, the pharmaceutical industry has the potential to apply pharmacogenomics strategies; premarketing studies could include genetic analyses in order to identify both whether a compound is clinically effective and for whom it is likely to be most effective (Pickar and Rubinow, 2001).

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