Overview

Pharmacogenetics of Antidepressants: Is There a Magic Bullet for Treating Depression?

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Depression is one of the most common mental disorders nowadays. Many researchers in psychiatry have investigated the cause of depression. Unfortunately, the problem of individual differences in response to antidepressant treatment still lingers in the clinical field. For setting up the stage for the main topics in the later part of this overview, I start introducing the topics of monoamine hypothesis, the rôle of serotonin in causing clinical depression, as well as advents of antidepressants (briefly describing tricyclic antidepressants, the arrival of selective serotonin-reuptake inhibitor, and novel antidepressants). Then, I introduce the concept of pharmacogenetics, the candidate genes. Afterwards, I consider that genetic factors are recognized to have an independent effect on drug responses. To demonstrate, I highlight five gene studies – serotonin transporter (5-HTT/SLC6A4), serotonin receptor 2A (HTR2A), G-protein β3 subunit (GNB3), brain-derived neurotrophic factor (BDNF), and tryptophan hydroxylase (TPH). But some of candidate gene studies have been conducted, but results were not consistent. Since 2009, Genome-wide Association Studies (GWAS) has provided further grounds for understanding the pharmacogenetic mechanisms of antidepressants and depression treatment. Further research and technological development are still needed.

Key words: antidepressants, monoamines, pharmacogenetics, Genome-wide Association Studies (GWAS)


Introduction

Depression is one of the most common mental disorders nowadays. In the US, 9% of men and 18% of women experience depression once in their lifetime, and more than 10% of the total population experiences another episode of depression more than twice [1]. The World Health Organization predicts that depression is going to take the first place in the burden of mental disorders. The significant danger of depression is that it lowers the quality of life considerably. Depression can affect one’s life in various aspects. It impairs the ability to eat, sleep, work, and socialize [2-5]. A depressive patient loses interest and motivation in life, which can damage one’s self-esteem. Since worsened depression can develop physical prob-
lems or lead to suicide, researchers and clinicians in psychiatry have put much effort in investigating the cause and developing the treatment of depression.

**Monoamine Hypothesis**

Before 1950, the psychiatrists did not explain the cause of depression clearly except genetic factor. The person who tends to be depressive among family members is considered to be highly possible to have depression. But in the early 1950s, many psychiatrists asserted that depression is not just because of congenital or innate tendency and environmental stress. Instead, the psychiatrists considered depression as neurophysiological abnormality of the brain. The reason why this theory is brought up is that many patients who have hypertension and tuberculosis showed prominent symptoms. Several cases from many medical institutions have been reported that the patients who have hypertension and take anti-hypertensive drugs over long periods of time generate severe depression [6, 7], or that the patients who have tuberculosis treated with isoniazid show improved depressive symptoms [8]. From those results, the argument that the main components in anti-hypertensive drugs or tuberculosis medicines might affect brain and cause or improve depressive symptoms is emboldened. At this time, uprising causative agent of depression is monoamine because several research showed that the fact which anti-hypertensive drugs decrease monoamine in the brain [9, 10] and tuberculosis medicines inhibit breakdown of monoamine [11, 12] is true. Therefore, the theory that depression occurs due to decreased monoamine transmission in the brain was raised. Since then, the psychiatry group called this theory as “monoamine hypothesis” and the theory has been well-established to explain about the neurobiological mechanism of developing depression.

Amines are chemical compounds that have similar amino group to ammonia, and there are many different types of amines. Among them, a chemical compound, being also a neurotransmitter in the brain, which has only one amino group is called monoamine. Because there are many different types of monoamines, many researchers tried to find out which monoamine plays a critical rôle to develop depression by experimenting on animals [13-15]. With all those efforts, it turned out that serotonin and noradrenalin (norepinephrine) are the substances. Through a narrow gap of synapse which is closely connected by neurons, nerve cells in the brain, the substances transmit information from brain by being sent from one place and being accepted to other place. If depression is developed because the amount of substances released is scarce or the released substances become scarce due to absorption by the original neurons, in a simple logic, depression would be treated if these substances could be fully supplied.

**Serotonin and Depression**

After serotonin (5-hydroxy-tryptophan) is released from neurons in the brain, it is absorbed by the receptor of neighboring neuronal cells though a gap of synapse. By this process, the information is transmitted from one neuronal cell to another. But all serotonin released are not absorbed by neighboring neuronal cells. Large amount of serotonin is re-absorbed by receptors of the original presynaptic neuronal cells. At this moment, if the amount of serotonin are abnormally re-absorbed too much, serotonin in the postsynaptic neurons is lacking and this seriously influences on various functions of body and mind. Serotonin is pro-
duced when tryptophan, one of the essential amino acids which is not synthesized in the body, is metabolized in the brain [16].

In the body, about 10 mg of serotonin exists, and only 1% of them exists in the brain as a neurotransmitter [17, 18]. The rest is staying in stomach and intestines to help digestion. Serotonin exercises a far-reaching influence on our body and mind because it has various functions that modulate body in so many different ways. Because it has functions to regulate autonomic nervous system, when the amount of serotonin in the brain is increased or decreased, it affects not only regulation of body temperature, cardiovascular activity, muscular contraction, vasoconstriction, and activities of endocrine glands, but also appetite, sleep, memory, mood, and behavior.

For this reason, serotonin has much to do with depression. Also, it regulates dopamine and norepinephrine [19-21], which are also important neurotransmitters that control human’s behavior and emotion. Because serotonin controls aforementioned various parts and works on raphé nuclei, limbic system, and prefrontal area which is the most important region, it is considered to be a conductor of the orchestra toward the complex components of brain.

Advent of Antidepressant Therapy

Tricyclic antidepressants (TCAs)

In the late 1950s, “tricyclic antidepressants” were synthesized and became commoditized as the first antidepressant. “Tricyclic” means that three cyclic structures (annular or ring-shaped) are in the molecular structure. Actually, the fact that these antidepressants improve the effects of serotonin in the brain is verified, and they are used as treatment for depression. The functional principle of tricyclic antidepressant is to inhibit re-absorption of serotonin by blocking the receptor that helps re-absorption. Most of the released serotonin move to the opposite side of receptors of postsynaptic neuronal cell, and the information is more easily transmitted without stagnation. Among tricyclic antidepressants, amitriptyline, imipramine, etc., are developed and widely used.

Some drawbacks existed for those antidepressants. Although they are daily administered for a patient, it takes about two to three weeks to show their effects. Also, they can cause many different side effects by interrupting re-absorption of neurotransmitters besides serotonin. If a patient takes massive dose of tricyclic antidepressants it causes acute intoxication and increases mortality rate by affecting cardiovascular side effects. Because of this reason, this antidepressant could be lethal to the depressive patients who take massive dose to attempt suicide. Tetracyclic antidepressant (such as maprotiline) was once thought to have least potential in causing cardiotoxic side effects. Even up to today, TCA shortcomings of tricyclic antidepressants are not completely resolved.

Selective serotonin reuptake inhibitors: the arrival of fluoxetine

A new type of antidepressant that specifically inhibits serotonin reuptake was developed in the late 1980s to address the problems of then existing tricyclic antidepressants. This novel class of antidepressants was named selective serotonin reuptake inhibitors (SSRIs). The most widely known SSRI is Prozac®, which was launched by Eli Lilly in the United States in 1987. Prozac is by far the most popular antidepressant with over fifty million users worldwide (data from 2005, according to Eli Lilly). The active ingredient in Prozac® is fluoxetine hydrochloride (HCl) which has a dif-
ferent chemical structure from the previously used tricyclic and tetracyclic antidepressants, and it has been found to strongly inhibit the reuptake of serotonin [22] and only partially that of noradrenaline (or norepinephrine). This property of fluoxetine is thought to allow it not only to alleviate depression symptoms, but also to control the symptoms of other diseases induced by serotonin or noradrenaline, such as obsessive-compulsive disorder [23] or panic disorder [24]. Furthermore, fluoxetine rarely acts on neurotransmitters other than serotonin, resulting in few side effects. But Prozac® still has been associated with some minor and severe side effects. This has sparked fierce debate on its use due to unexpected side effects, such as inducing manic switch or suicidal impulses.

**Development of novel Antidepressants**

In 1993, six years after the advent of Prozac, serotonin and norepinephrine reuptake inhibitors (SNRIs) were developed. SNRIs simultaneously inhibit the reuptake of serotonin and noradrenaline, which is a neurotransmitter also thought to be associated with depression. The first SNRI was manufactured by Wyeth in the United States, with the trade name Effexor. In addition to SNRIs, other novel antidepressants, including norepinephrine-dopamine reuptake inhibitors (NDRIs) and noradrenergic and specific serotonergic antidepressants (NaSSAs), were also developed. Meanwhile antidepressants containing thyroid hormone, melatonin, or ketamine either have been recently developed or are underway [25-27]. These drugs have been developed to improve the efficacy and address the adverse effects of existing drugs.

Unfortunately, however, the problem of individual differences in response to treatment still lingers in the clinical field. Indeed, the dosage required for effective treatment is different for each patient. For example, the standard dose of a particular drug may not be sufficient for one patient while inducing severe side effects in another patient. Whichever the case, a more suitable treatment regimen is required to enhance the personal therapeutic efficacy of the treatment.

**The Concept of Pharmacogenetics**

Although factors that influence responses to drugs are diverse and thought to interact in a complex manner, genetic factors are recognized to have an independent effect on drug responses. In fact, some studies reported that responses to antidepressants show familial concordance in patients with depression [28-30]. The reason for investigating genetic factors is due to the knowledge that there should be reliable biological factors modulating the damage and pain inflicted on patients by the above-mentioned insufficient treatment outcomes, and that genetic biomarkers can fulfill that rôle.

Many researchers and clinicians working on depression have been conducting various studies using candidate genes since the 1990s, with the ultimate goal of allowing patients to select the most personally effective drug. In the early days of pharmacogenetics research, most of these candidate genes are selected among the key genes associated with proteins having been involved in the mechanisms of action of the antidepressants [31].

**Candidate Gene Studies in Treating Depression**

**Serotonin transporter (5-HTT/SLC6A4) and serotonin receptor 2A (HTR2A)**

The genes that have been most vigorously studied as candidate genes, and thus have the most accumulated evidence, are SLC6A4 and HTR2A,
which are associated with serotonergic transmission. SLC6A4 encodes a serotonin transporter (5-HTT or SERT) responsible for the reuptake of serotonin into the presynaptic neuron. Because of this function, it has been the target of many antidepressants, which have in turn sparked research interest in polymorphisms associated with this gene. While some studies found significant results, others did not. The most investigated polymorphism thus far is a 44-bp repeat insertion/deletion polymorphism in the promoter region of the gene (5-HTTLPR); a meta-analysis study suggested that the long (L) allele of 5-HTTLPR is significantly associated with a better treatment response to SSRI compared to the short (S) allele, in a Caucasian group [32, 33]. This is thought to result from the S allele reducing the transcriptional activity of the 5-HTT gene promoter, which in turn decreases 5-HTT expression, leading to reduced serotonin (5-HT) reuptake [34].

Many studies suggest that the 5-HT receptor 2A gene (HTR2A) is associated with treatment response to SSRIs. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial is the most notable study; this large-scale study examined 1,953 patients with major depressive disorder (MDD) and showed the potential of HTR2A as a significant indicator of treatment outcome [35]. There have been other studies suggesting an association of this gene with the response to SSRIs [36, 37]. But some further studies reported that the results were more heterogeneous than those for SLC6A4, and others failed to find a significant association between HTR2A and other antidepressants (other than SSRI), or showed mixed results [38-42].

**G-protein β3 subunit (GNB3)**

The GNB3 gene is involved in the generation of second messengers signaling cascades, such as those evoked by hormones and neurotransmitters. Researchers have long concentrated research efforts on G-proteins, because they are widely known to be associated with multiple pathways responsible for controlling cellular responses. Moreover, some studies have shown an association between the levels of G-protein α subunit expression and depression. Immediately after these studies, several researchers began to shed light on the association between genetic polymorphisms of the G-protein β3 subunit and depression or the response to antidepressant treatment, and have found significant results.

Thus far, the most investigated polymorphism in the GNB3 gene is rs5443 (C825T), and the main finding, including that of a meta-analysis reported in 2014 [43], is that rs5443 T allele carriers show better treatment responses [44-46]. But some studies actually reported significantly better responses in patients with fewer T alleles [47-49], while other studies on Asians, as with other similar genetic studies, reported no significant association between the T allele and the treatment response [50-52].

**Brain-derived neurotrophic factor (BDNF)**

Recently, evidence has been accumulating for the rôle of brain-derived neurotrophic factor (BDNF) in the pathophysiology of depression. As several studies revealed that BDNF plays a pivotal rôle in neurogenesis and neuroplasticity, as well as in the serotonergic system, which is the main target of antidepressants, BDNF has become the focus in studies on depression recovery. Indeed, meta-analysis studies revealed that plasma BDNF levels are significantly lower in MDD patients in remission compared to those in acute depression [53]. Another meta-analysis study showed that serum BDNF level after treatment for MDD is significantly higher in responders than that in non-
responders [54]. Of about 3,000 reported single nucleotide polymorphisms (SNPs), rs6265 (G196A or V66M) is an SNP found in the BDNF gene that has been studied the most as it is known to have a functional rôle. A recent meta-analysis reported that MDD patients with the Met/Met or Met/Val genotype for rs6265 show better responses to antidepressants, especially SSRIs, and that this effect is more prominent among Asians [55]. Similarly, studies conducted in Korea showed that patients with a Met allele showed better responses to citalopram and escitalopram than those with a Val allele [56, 57].

A study on fluoxetine, another type of SSRI, could not confirm that the different genotypes of the BDNF polymorphism have any differences in treatment responses, despite the fact that the subjects were Asian (namely Chinese patients and healthy controls). [58] In addition, a study on mirtazapine, an NaSSA, did not find any association between the afore-mentioned polymorphism and the treatment response [59]. Furthermore, most studies have not shown an association between V66M and the risk of developing MDD [57, 60]. One meta-analysis in particular reported that V66M has not been associated with an increased risk of developing MDD; however, they have not shown an association when the analysis was restricted to male subjects [61].

**Tryptophan hydroxylase (TPH)**

Two isoforms of tryptophan hydroxylase (TPH) are known to be important, and TPH1 is the one that has been most studied in the psychiatric field. TPH is the rate-limiting enzyme in the biosynthesis of 5-HT [62]. The TPH1 gene has been the focus of many studies because one functional SNP in this gene – rs1800532 (A218C) - is located in the potential GATA transcription factor binding site. One study has been found an association between this genetic polymorphism and bipolar disorder [63], which triggered many researchers to begin studying the association between A218C and major depression. Some studies have confirmed the association between TPH1 and antidepressant treatment response, and were found that A allele carriers show poorer treatment responses [64-66]. Moreover, a haplotype analysis has revealed an association between major depression and TPH1 [67].

On the other hand, many other studies, especially those on Asians, have failed to produce significant results [50, 68-71]. The two TPH isoforms are expressed at similar levels in areas of the brain such as the frontal cortex, the hippocampus, and the amygdala. In particular, TPH2 has attracted much research interest, as it is predominantly expressed in the central nervous system (CNS) [72, 73]. Since Zill et al. [73] first reported an association between the TPH2 gene and major depression, several studies have been conducted to replicate the results, with some having succeeded in producing significant results [74, 75], while others have failed [76, 77]. Such contrasting outcomes have thwarted researchers’ efforts to draw a consistent conclusion.

**Genome-wide Association Studies (GWAS)**

Unfortunately, researches have yet to identify a clear link between a specific gene and susceptibility to depression. Rather than the possibility of only a single gene being responsible for the development or treatment of depression, it is more likely that many genes acting together may cause a patient to become susceptible to depression. Several researchers had been struggling with inconsistent results and failed to replicate results on several candidate genes. But the advancement of
DNA analysis technology introduced around 2007, the concept of genome-wide association studies (GWAS), causing a paradigm shift in candidate gene research. Whereas previous studies selected candidate genes based on *a priori* hypotheses, the development of hypothesis-free GWAS has enabled the launch of several studies focusing on depression and antidepressants around 2009. Those studies have in turn provided further grounds for understanding the pharmacogenetic mechanisms of antidepressants and depression treatment. GWAS has opened doors to genotyping and analysis of millions of polymorphisms throughout the whole genome. Theoretically speaking, GWAS is an appropriate strategy for analyzing the association between diseases and genes because individuals share 99.9% of their genomes. Furthermore, GWAS is sufficient to address the problem of small sample sizes in candidate gene studies, especially the problem of a significant reduction of sample size during follow-ups, and the resulting biases.

There have been three major large-scale GWA studies: the Genome-based Therapeutic Drugs for Depression (GENDEP; Uher, R., et al. [78]), the Sequenced Treatment Alternatives to Relieve Depression (STAR*D; Garriock, H.A., et al. [79]), and the Munich Antidepressant Response Signature (MARS; Ising, M., et al. [80]). Although GWA studies initially were considerably expensive, scholars’ efforts to identify haplotypes through the HapMap Project markedly have lowered the required costs. But the limitations of GWAS began to surface as more studies were conducted. GWA studies generally identify genetic mutations shared by at least 5% of the population. But common variants alone cannot sufficiently explain the heritability of diseases because of “missing heritability” resulting from the so-called “common disease-common variant hypothesis,” upon which those studies are conducted. Another indication of the need to research rare variants is that common variants are usually shared by different ethnicities and cultures while rare variants are not. Furthermore, GWA studies have limitations in analyzing diseases caused by different types of genetic mutations, such as copy number variant (CNV).

**Conclusion**

In this overview, I have pointed out the development of antidepressants and pharmacogenetics. Table 1 summarizes the current research findings of the candidate gene studies in treating depression with support of being associated with antidepressant efficacy. What’s more, extended from genetics, fields such as epigenetics, proteomics, and metabolomics are being suggested and researched in the biological ground. In addition, the development of personal genomics which uses the next generation sequencing, and the technological development including neuroimaging are widening the newest knowledges of biological psychiatry.

Many other ongoing efforts exist to achieve better responses of antidepressants in depressive patients. Sadly, despite the efforts of numerous researchers and clinicians including myself, the development of the “magic bullet,” which diagnoses and treats depression dramatically, seems so distant. Does “magic bullet” ever exist? Although it might seem like an illusion, such cravings and faith have contributed largely to the current advanced psychiatry, and I expect superior treatments to be developed which enlighten the future of treating depressive patients.
Table 1. Summary of the major positive findings of the candidate gene studies in treating depression with support of being associated with antidepressant efficacy

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variants</th>
<th>Main findings</th>
<th>References</th>
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<tbody>
<tr>
<td>SLC6A4</td>
<td>5-HTTLPR</td>
<td>In a Caucasian group, the L allele is significantly associated with a better treatment response to SSRI compared to the S allele.</td>
<td>Serretti et al. 2007 [32], Porcelli et al. 2012 [33]</td>
</tr>
<tr>
<td>HTR2A</td>
<td>rs7997012</td>
<td>A better response to SSRI of the A allele was reported in the STAR*D studies.</td>
<td>McMahaon et al. 2006 [35], Peters et al. 2009 [36]</td>
</tr>
<tr>
<td>GNB3</td>
<td>rs5443(C825T)</td>
<td>The T allele carriers show better treatment responses to antidepressant medication.</td>
<td>Hu et al. 2015 [43], Zill et al. 2000 [44], Lee et al. 2004 [45], Keers et al. 2007 [46]</td>
</tr>
<tr>
<td>BDNF</td>
<td>rs6265 (G196A; V66M)</td>
<td>The patients with the Met allele show better responses to SSRIs, especially more prominent in Asians.</td>
<td>Yan et al. 2014 [55], Chang et al. 2012 [56], Choi et al. 2006 [57], Serretti et al. 2001 [64], Ham et al. 2007 [65], Arias et al. 2012 [66]</td>
</tr>
<tr>
<td>TPH1</td>
<td>rs1800532 (A218C)</td>
<td>The A allele carriers show poorer treatment responses to antidepressant medication.</td>
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References


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