β3-Adrenoceptor as a novel treatment strategy for depressive disorders

Abstract
Depression is a complex psychiatric disorder which affects more than 17% of the population in the United States. There are several generations of anti-depressant drugs. Selective serotonin reuptake inhibitors (SSRIs) are generally considered first line therapy for clinical depression, but this therapeutic modality is limited by a simple kinetic problem: a significant delayed onset of action. Therefore, the search for newer or novel drug targets for depression continues. β3-Adrenoceptors (ARs) together with β1 and β2-ARs, belongs to the G-protein coupled receptor family which has opened new possibilities for exploring the involvement of this receptor in depressive disorders. The present mini review discusses the possibility of β3-ARs application as a novel treatment strategy for the treatment of depression.

Keywords: β3-adrenoceptors, depression, antidepressant

Abbreviations: SSRI, selective serotonin reuptake inhibitors; ARs, adrenoceptors; β3-ARs, β3-adrenoceptors; 5-HT/Serotonin, 5-hydroxytryptamine; TM, transmembrane; NE/NA, norepinephrine/noradrenaline; SNRI, serotonin/noradrenaline reuptake inhibitor; SERT, serotonin transporter; NET, norepinephrine reuptake transport; NARI, noradrenaline reuptake inhibitor; SARI, serotonin antagonist and reuptake inhibitor; TCAs, tricyclic antidepressants; MAOIs, monoamine oxidase inhibitors; SR58611A, (N-[2S]-7-carbethoxyxemthoxy-1,2,3,4-tetrahydronaphth-2-yl)-(2R)-2-hydroxy-2-(3-chlorophenyl) ethanamine hydrochloride; FSL, flinders sensitive line

Introduction
Depression is a chronic, recurring and potentially life threatening illness. According to the report from WHO, it states that approximately 350 million people or about four percent of the world’s population worldwide have depression. Depression affects more than 17% of population in the United State. Major depression is the most common depressive disorder, which is the leading cause of disability in the United States (USA) between the ages of 15 to 44years old. In the USA, literature indicates that, as high as, approximately 60% of all individuals who commit suicide had a depression or another mood disorder. Although depression is the leading cause of disability for both females and males, the burden of depression for females is about two to three times higher than males.

Patients will get depression in different age, but the peak age of depression occurs in 55years old for males and between 35 to 45years old in females. Moreover, genetics might relate to depression. Person with family history of depression is easier to get depression. For example, the first-degree relatives are one and half times easier to get depression than the general population. Depression also greatly affects economy. In the United States, the economic burden of depression in year 2000 was estimated to be $83.1 billion. The largest portion of the economic burden is due to sick days’ cause by depression. WHO predicts that by 2020, depression will rival heart disease as the health disorder with the highest disease burden in the world, therefore more and more patients need to take antidepressants to cure depression.

Given the complexity of the depression and an unclear set of defined etiology, the pathogenesis of depression is also not well understood. Therefore currently the widely prescribed mono-aminergic antidepressants were identified primarily through serendipity instead of rational drug design. For example, the early antidepressants were accidentally found in patients who took antitubercular agent. After taking anti tubercular drug, these patients showed euphoric effects. Although depression was detail described as melancholy back to eighteen centuries ago, but until the middle part of the 19th century that the brain became the focus to understand the pathophysiology of depression. 5-hydroxytryptamine (5-HT, serotonin) is an important monoamine neurotransmitter involved in depression, behavior, appetite and impulse control etc. It is hypothesized to help regulate other neurotransmitter systems too.

In normal people’s brain, the concentration of 5-HT would be in the normal range and would remain in steady state. But decreased 5-HT activity may allow these systems to act in unusual and erratic ways. Other than 5-HT, some studies in humans and animals have shown a relationship between alternations of noradrenergic and depression. β1 and β2 adrenoceptors (ARs) are known to modulate the effects of antidepressant treatment. Little is known about the function of the Gs-protein-coupled β3 sub type. β3-ARs together with β1 and β2-ARs belong to G-protein coupled receptor family characterized by seven transmembrane (TM) domains of 22-28 amino acids, with three extracellular loops and three intracellular loops. The C-terminal region of these receptors is intracellular while the N-terminus is extracellular and glycosylated. The transmembrane domains, TM7 which contains Tyr336 and TM2 which contains Asp83 are central for Gs activation while TM3, TM4, TM5 and TM6 are involved in ligand binding.

β3 mainly distributed in white and brown fat tissue which is used as modulator of lipolysis and thermo genesis. β3 is also widely distributed in CNS, gut, urinary system, cardiovascular system, liver and portal circulation. In these systems, β3 mediate different physiological responses of the human body. β3-ARs are involved in thought process and possibly related to the negative thoughts associated with depression. That is why more researchers made efforts to design potent and selective β3-ARs for drug discovery.
Discussion

Currently, monoamine hypothesis is a popular hypothesis to explain the mechanism of depression. It supports the role of Norepinephrine (NE) and serotonin (5-HT) in depression. It states deficiency of brain monoaminergic activity caused the mental depression. And the treatment is focused on increasing this activity. A link between brain monoamines and depression was first found in the 1950s when it was known that the drug reserpine which treated hypertension turned out to cause depression. Finding that reserpine lowered brain 5-HT and caused sedative effects, the monoamine hypothesis suggested that the reduced level of monoamines noradrenaline (NA) and serotonin may be the cause of depression. Various mechanism may increase the availability of brain monoamines include inhibiting the intraneuronal metabolism of the monoamine, blocking the presynaptic inhibitory receptors or blocking the reuptake of the monoamine from the synapse.4

However there are still many things monoamine hypothesis cannot explain. For example, the drugs that increase serotonin or noradrenergic transmission are not necessarily effective in treating depression. But this hypothesis is very important to understand depression and help to develop a safe and effective pharmacologic agent for depression treatment.9 There are also links between pharmacological treatments and circadian rhythms in depression, which might represent another option for the development of a new antidepressant.10

There is lot of antidepressant drugs aimed to increase 5-HT concentration. Currently, the most common class of antidepressants used is the SSRIs, accounting for 80% of all antidepressants on the market.11 First-generation antidepressants launched in the late 1960s and 1970s are represented by the tricyclic antidepressants (TCAs) and monoamine Oxidase inhibitors (MAOIs). TCAs increase both 5-HT and NA concentrations in the CNS. They have fallen out as first-line therapy due to their side effects and are dangerous in overdose due to potent actions at cardiac ion channels. The serious side effects of MAOIs antidepressant called “cheese effect”. The hypertensive crisis was seen when the concomitant intake of tyramine-containing foods with MAOIs. The reason is MAOIs would inhibit the catabolism of dietary amines.5

Currently only when there is intolerance or lacking efficacy to the newer drugs, MAOIs can be prescribed to patients.12 Second-generation drugs introduced in the 1980s and 1990s, such as the selective serotonin reuptake inhibitor (SSRI), serotonin/noradrenaline reuptake inhibitor (SNRI) are indubitably safer. SSRIs block the reuptake of serotonin by the serotonin transporter (SERT) located on the presynaptic membrane, thereby increasing synaptic concentrations of serotonin. SERT is the important site for many antidepressants and represents an essential target of interest in antidepressant pharmacogenetics. By inhibiting SERT, more serotonin is available for neurotransmission. SNRIs selectively block both the SERT and NE reuptake transport (NET), thereby increasing both synaptic concentrations of NE and 5-HT. SNRIs are the most recent antidepressants and venlafaxine is one of them. They act like the first TCAs but with less undesirable side effects.13

Currently available NA reuptake inhibitor (NARI) is reboxetine and it works by blocking NET to increase NE in the synaptic cleft. The only antidepressant that target on the noradrenergic and dopaminergic system instead of serotonin system is bupropion which is NE and DA reuptake inhibitor.14 Other than these reuptake inhibitors, there are some antidepressants directly modulate on the receptors such as serotonin antagonist and reuptake inhibitor (SARI) and norepinephrine/serotonin specific antagonist (NASSA). SARIs act by antagonizing serotonin receptors such as 5-HT1 and serotonin reuptake inhibition. Also most act as α1-adrenergic receptor antagonists. Trazodone is the first antidepressant with both inhibiting SERT and 5-HT,1α,2C. It is used as monotherapy or in combination with other antidepressants for the depression treatment.15

NASSAs enhance both serotoninergic and noradrenergic transmission and simultaneously blocking 5HT1 and 5HT2 receptors. Mirtazapine is the only NASSA currently available which is evolved from the earlier antidepressant, Mianserin. Mirtazapine has a unique pharmacological profile, including potent block α1-adrenergic auto receptors, heteroreceptors and antagonism of both 5-HT1 and 5-HT2 receptors.16 There are many debates about whether the existing antidepressants are harmful to cause suicide or more beneficial to prevent suicide, but there is no clear evidence of a positive correlation between suicide and antidepressants prescription especially in adults of 18 years or older. When prescribing antidepressants, physicians should inform the patients of the possible risk and monitor them closely in the early stage of treatment and especially SSRIs have time delay issue. Therefore faster acting and higher efficacy antidepressants are in a high demand. β3-ARs agonist has been shown as a possible therapeutic target for the treatment of type 2 diabetes, overactive bladder disorder as well as depression.15 SR58611A (N-[2S)-(7-carbethoxy methoxy-1,3,4-tetrahydronaphth-2-yl]-(2R)-2-hydroxy-2-(3-chlorophenyl) ethanamine hydrochloride) is a β3 selective agonist, which is a useful agent to test the antidepressant-like effects of β3 receptors. The structure is listed as Figure 1.

Figure 1 2D structure of SR58611A.

It can strongly activate β3 receptors without activating other receptors such as β1 and β2. It is reported that SR58611A displays high efficacy and potency at the rat and human β3 receptor. The selectivity for rat β3 are 280- and 140-fold compared with β1 and β2 receptors, and is inactive at a number of other central targets involved in the regulation of stress-related disorders.16 Several studies reported that SR58611A has antidepressant effects in the animal model of depression.17 Currently, no depression like syndrome that fully recapitulates the human syndrome has been developed in rodents since animals lack self-reflection, self-consciousness and consideration. Moreover, depressed mood, suicidality or low self-esteem is rarely accessible in animals. Also human genetic vulnerability cannot be reproduced in laboratory rodents due to genes that underlie human vulnerability to depression. Therefore, most research used environmental triggers and neurobehavioral end points in laboratory animals to screen for antidepressant drugs.20

However, as other mental disorders, depression contains endophenotypes such as physiological, neuroanatomical and
endocrinological change that can be reproduced and evaluated in animals. McKinney and Bunny propose the minimal requirements for a valid animal model of depression should first, reasonably analogous to the human disorder in its symptomatology; second, cause behavioral changes that can be monitored objectively; third, produce behavioral changes that are reversed by the same treatment modalities that are effective in humans and lastly should be reproducible between different investigators. The finders sensitive line (FSL) rat has been treated as a useful animal model of depression. SR58611A showed antidepressant potential by using FSL rat.

According to Stemmelin J et al., they used two acute animal models (forced-swimming model, tonic immobility test) to investigate the effects of SR58611A and one chronic model (chronic mild stress models) for characterization of antidepressants. The forced-swimming test in rats is the most extensive used rodent model which can reflect a behavioral despair. SR58611A produced comparable in terms of the amplitude of the effects of the other two antidepressant fluoxetine or imipramine. Imipramine is a tricyclic antidepressant which is a reuptake inhibitor to NE and 5-HT. Fluoxetine is a selective serotonin reuptake inhibitor which belongs to SSRI antidepressant drugs. All these drugs were given intraperitoneally (i.P) or per os (p.o). In order to support these behavioral data, SR58611A modified spontaneous sleep parameters in similar manner as fluoxetine. In order to prove SR58611A has anti-depressant properties, some researchers placed cortical electrodes on the sensorimotor cortex of rats for reliable visual discrimination of wakefulness, slow-wave sleep and rapid eye movement or paradoxical sleep. In summary, although there is limited evidence, but there are some evidence that the pharmacological stimulation of β3-Adrenoceptor may represent an innovative approach for the treatment of depressive disorders.

The possible mechanism of β3-ARs has antidepressant effects are because it can increase brain tryptophan (Trp) content, suggesting an increase in brain 5-HT synthesis. Since synthesis of serotonin is relied on the availability of its precursor, the essential amino acid Trp. Therefore, low availability of Trp to the brain, which results in a big decrease in 5-HT synthesis, may result for the serotonergic deficiency evidenced in depression. Moreover, it was reported that β3-ARs can increase the release of NE in hippocampal, hypothalamus, prefrontal cortex and the firing rate of NE neurons in locus coeruleus. It is also can be the possible mechanism for β3-ARs.

**Conclusion**

In terms of efficacy of the effects to other antidepressant drugs, β3-ARs have antidepressant-like properties that are comparable in acute models as well as chronic models. Also β3-ARs can modify spontaneous sleep parameters similar as fluoxetine are supported by electrocorticography results. Therefore, there is some evidence for us to conclude that the pharmacological stimulation of β3-ARs may represent an innovative method of the treatment of depression. Moreover, it can avoid of important disadvantage of classical antidepressant compounds such as motor activity, cognition and so on.

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**Conflict of interest**

Author declares that there is no conflict of interest.

**References**


