EXPLORING BETA 3 ADRENOCEPTORS FOR POTENTIAL CLINICAL APPLICATIONS.

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ABSTRACT
Sympathetic adrenoceptors are among the most explored receptors for modifying various physiological functions in search of different therapeutic options. One of the latest additions to the family of adrenergic receptors is the beta 3 adrenergic receptor, which though has caught the fancy of the researchers, is yet to get the status of a clinically significant receptor. Information on this receptor is sparse and spread out in to different domains of either experimental Pharmacology or Therapeutic research. This article presents the various aspects of the beta 3 receptor, including its location, structure, agonists, antagonists and clinical implications in a comprehensive review. We find that, beta 3 adrenergic agonists have important role to play in the treatment of various human disorders such as depression, irritable bowel syndrome, overactive bladder, diabetes mellitus and heart failure. Currently several molecules are at various stages of development and further clinical studies are required to establish the beta 3 receptor agonists as valuable therapeutic options for various pathological conditions.

Keywords: β3-adrenoceptor, subtypes of β3-adrenoceptor, β3-adrenoceptor agonists, β3-adrenoceptor antagonists, clinical implications for β3-adrenoceptor agonists.

INTRODUCTION
The last entry to the family of beta adrenergic group of receptors has been beta 3 receptors (β3-AR), which was first successfully cloned in rat tissue in the year 1991. Since 1991, β3-ARs have been extensively studied by scientists in the hope of newer directions in drug discovery. Though in many cases, the exact nature of function or the interspecies difference of this receptor has remained elusive, still much work has been done in finding a wide gamut of potential clinical application of β3-AR agonist.

Location of Beta 3 Receptors:
Initially the beta 3 receptors were found to be expressed in the white and brown adipose tissue. But subsequently, apart from adipose tissue, the β3-ARs were found to be expressed in human beings in the following locations also:
- Brain
- Small and large intestines
- Liver and portal circulation
- Urinary bladder
- Myometrium
- Heart
- Gall bladder
- Prostate
- Bronchi
- Vascular endothelium

STRUCTURE OF BETA 3 RECEPTORS:
Genes that encode the beta 3 receptor (ADRB3, hCG21141) are located on chromosome 8. The beta 3 receptor has 51% identity with beta 1 adrenoceptor and 46% identity with beta 2 adrenoceptor. All beta receptors are linked to G proteins. The G proteins are connected to adenylyl cyclase. Agonist binding thus causes a rise in the intracellular concentration of the second messenger cAMP. Antagonists have an opposite effect. Beta 3 receptors are serpentine receptors and have seven transmembrane segments (TM), each consisting of 22–28 amino acids, with three intracellular and three extracellular loops. The total number of amino acids in beta 3 receptor is 396. The extracellular component is the N-terminal ending which is glycosylated. The intracellular component is the C-terminal ending which does not possess a site which can be phosphorylated by a protein kinase A (PKA) or beta receptors kinase (betaARK), unlike the site present at the beta 1 and beta 2 type receptors. The disulfide bond between the second and the third extracellular loop between Cys 110 and Cys 361 is required for the receptor activity and ligands interaction. Transmembrane domains TM3, TM4, TM5 and TM6 are also required for interaction with the ligand. Transmembrane domains TM2 and TM7 cause G-protein activation and thus initiation of its effect. In humans three different forms of the beta 3 adrenergic receptor are described: form A with 396 amino acids, forms B and C that have beside the C-terminal 12 and 6 amino acids, respectively.
AGONISTS AND ANTAGONISTS OF BETA 3 RECEPTORS:

A variety of agonists have been recognized for beta 3 receptors till date. The agonists for these receptors include Amibegron (SR-58611A)18, 19 Solabegron (GW-427,353)20, L-796,56821 and CL-316, 24322. The antagonists for beta 3 receptor include SR 59230A23, L-748,328 and L-748,33724.

CLINICAL IMPLICATIONS FOR BETA 3 RECEPTOR AGONISTS:

Potential Indications in which beta 3 receptor agonists has been explored:

1. Anxiety and Depressive Disorders:

Stimulation of beta 3 adrenoceptors in brain has shown to be effective as a treatment for depression and stress disorders in animal models25. Activation of beta (3) adrenoceptors increases brain tryptophan content suggesting an elevation of brain serotonin (5HT) synthesis18. The characterization of the first selective orally active and brain-penetrant beta3-adrenoceptor agonist, SR58611A (amibegron), opened new possibilities for exploring the involvement of this receptor in stress-related disorders26. It was under development by Sanofi Aventis till 2008 July, after which the development was stopped26.

2. Inflammatory bowel disease and functional gut disorders:

Beta 3 ARs are expressed in enteric neurons and GW427353 (Solabegron) is a human selective beta3-AR agonist with visceral analgesic effects. Some of the effects of Solabegron involve release of somatostatin (SST) and actions on enteric neurons. Thus, β3-AR activation may be a promising approach to reduce enteric neuron hyperexcitability. The action of Solabegron could be the neurophysiologic correlate of its beneficial effect in patients with irritable bowel syndrome27.

3. Overactive Bladder (OAB):

It was discovered that the adrenergic receptor in the human bladder responsible for detrusor muscle relaxation was the Beta 3-AR28. Thus, beta 3 receptor agonism was identified as a potential therapeutic option for treating overactive bladder. Two beta 3 agonists, Mirabegron and Solabegron have been studied quite extensively and have shown to reduce the symptoms of OAB in both preclinical and clinical studies. Of these two molecules, Solabegron is in Phase one of development and Mirabegron in Phase three. In June 2010, Astellas Pharma submitted a market authorization application for mirabegron to the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan. Astellas is currently seeking approval for the indication of urgency, urinary frequency, and urge urinary incontinence associated with overactive bladder (OAB) based on the efficacy and safety results of Phase three studies, conducted globally29.

4. Obesity and Diabetes:

A agonist of the beta (3)-AR is known to simultaneously increase lipolysis, fat oxidation, energy expenditure and insulin action and thus is an attractive target for the treatment of diabetes and obesity30. Encouraging data has emerged from clinical studies wherein CL-316,243, a highly selective, albeit rodent specific beta (3)-AR agonist was observed to increase lipolysis, fat oxidation and insulin action in humans. More recently, beta (3)-AR agonists directed at the human receptors are showing promising results in their ability to increase energy expenditure in humans following a single dose. However, they do not appear to sustain their effects when administered chronically.

In animal studies, beta 3 agonist SR 58611A has shown its effectiveness in improving glucose tolerance in lean and obese mice over a dosing period of 14 days31. This improvement was achieved at a dose less than a dose which was required to stimulate adipose tissue lipogenesis and at a dose which did not affect food intake or body weight. It is possible that SR 58611A has implication in the treatment of the glucose intolerance in diabetes mellitus than in obesity31.

THEORETICAL POTENTIAL INDICATIONS OF BETA 3 RECEPTOR AGONISTS:

As an extension of the pharmacological action, beta 3 receptor agonism has shown promise in a number of clinical conditions. Though all of them have not been yet substantiated in human studies, they hold the promise of further research and development of newer therapeutic strategies in future.

1. Beta 3 receptor agonism in vasorelaxation:

Beta 3 receptors present on endothelial cells have been identified to induce vasorelaxation of human coronary microarteries in invitro studies12. Data from animal studies and circumstantial observations from clinical trials suggest that beta 3-AR activation is beneficial in severe heart failure and that beta 3-AR agonists are a promising therapeutic option for the treatment of this disease32.

Figure 1: The beta 3 adrenoceptor structure16

[Diagram of the beta 3 adrenoceptor structure]
2. Beta 3 receptor agonism in myometrial relaxation:

Selective beta 3-AR agonist BRL 37344 has shown to induce relaxation of human myometrial contractions with a similar potency to that of the most commonly used tocolytic agent, ritodrine but with fewer adverse vascular effects\(^3\). Preclinical studies have also demonstrated the effect of beta 3 receptor agonist in relaxation of pregnant myometrium\(^4\).

3. Beta 3 receptor agonism in treatment of portal hypertension:

It has been observed that there is a marked hepatic and mesenteric up-regulation of beta (3)-ARs in human cirrhosis and in two different animal models of cirrhosis. The beta (3)-AR-agonists thus should be further evaluated for therapy of portal hypertension\(^5\).

CONCLUSION AND FUTURE DIRECTIONS

We conclude that beta 3 receptor agonists have proved their potential in treatment of various human disorders like irritable bowel syndrome, OAB, and diabetes mellitus and are in various stages of clinical development for the same. As an extension of their pharmacological action, beta 3 receptor agonists have also shown promise as a therapeutic option in portal hypertension, heart failure and preterm labour. If properly exploited, beta 3 receptors can become as recognized as the other adrenergic receptors for clinical therapeutics.

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