Need of beta 3 agonist in today's world as oral hypoglycaemic and antiobesity

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Lowering blood glucose levels in case of patients suffering from type 1 diabetes plays an important role in decreasing the risk of long-term complications. In clinical scenario, fully fledged insulin therapy is often limited by the increased risk hypoglycemia which is severe in nature. [1]

Thus, nowadays newer and safer regimens of oral hypoglycemic drugs are introduced out of which beta 3 adrenergic receptor agonists are showing a promising future in combating the menace of hyperglycemia or diabetes mellitus paired with obesity. These drugs showed significant selectivity for stimulating lipolysis at adipocytes and hence enhances oxygen utilisation and energy consumption. A significant difference in case of β3 adrenergic receptor isoforms have been observed in different species. Recent cloning of human β3 adrenergic receptor has enabled pharmaceutical companies to develop compounds selective for β3 adrenergic receptor. In fat cells, the beta3 adrenergic receptor (b3AR), which belongs to the superfamily of G-protein coupled receptors (GPCRs), functions in a manner contrary to the general adrenergic system in that activation of b3AR actually induces the wasting of metabolic energy. Agonists of this receptor activate the uncoupling protein (UCP) which causes the expenditure of metabolic calories as heat. Indicating that b3AR could be used to dissipate metabolic energy as heat in diabetic and morbidly obese patients instead of storage of this energy as fat. [2] It has also been observed that, along with brown adipocytes, UCP1-expressing adipocytes, showing thermogenic capacity also appear in the white adipose tissue due to factors like cold exposure, endogenous circulating factors formed in muscle, liver and heart such as irisin, fibroblast growth factor, natriuretic peptides, or in response to stimulation by β3-adrenergic agonists. Beta 3 adrenergic receptor agonists have been regarded as antiobesity drugs of high potential devoid of cardiovascular adverse effects seen in case of administration of conventional adrenergic agonists. [3]

Considerable proof for the existence of beta 3 receptors was given by Arch JR et al, in 1984. It was observed that new beta adrenergic ligands, not acting as specific ligands on conventional beta-receptors, had favourable anti-obesity actions on mice suffering from severe obesity and diabetes. Beta 3 adrenergic receptors belong to the family of serpentine receptors and have seven transmembrane segments, each of 22-28 amino acids, with three loops situated intracellularly and three loops situated extracellularly. The beta 3 adrenergic receptor contains 396 amino acids. The N-terminal ending is situated extracellularly and is glycosylated in nature. The C-terminal ending is intracellular, which can be phosphorylated by a protein kinase A or beta receptors kinase. The disulfide bond between the second and the third extracellular loop is essential for the receptor action and for ligand interaction. Also, the beta 3 receptor differs from the beta 1 and beta 2 receptors in terms of structure as well as by pharmacological profile. [4]

Several studies have revealed that this receptor shows a polymorphic action, having Trp64Arg as its variant. Trp64Arg variant was associated with Body Mass Index. This variant has difficult impact on weight loss whereas, another variant of this receptor: Arg64 showed easier impact. Synergistic effect has also been found at b3 adrenergic receptor Trp64Arg type and Insulin receptor substrate 1 gene polymorphism on weight loss. Thus, there is a probability that beta 3 receptor agonists may play a favourable role in case of diabetic patients suffering with obesity. [5]

Nowadays, the threat of diabetes along with obesity has led to a need to develop newer and preferably non-invasive methods of its treatment. However, certain limitations have been witnessed regarding the use of these drugs in human subjects which comprise of:

- Differences in the mechanisms of thermogenesis regulation and differences
in the role of energy expenditure in human bodies and rodent bodies.
- Variations of genetic basis consisting of polymorphisms and mutations leading to retarded target receptor actions.
- Diminished expression of beta 3 adrenergic receptors in adipose tissues of diabetic individuals that can reduce the effectiveness of the therapy at a significant level.\(^6\)

In today's scenario, diabetes along with obesity has been constant threat to the health of people worldwide. A disease which was once unknown to our forefathers have now, become a burden for the medical care fraternity. Thus, the need of the hour is to develop interventions that would not only be effective but also a safe in nature in order to attract the positive compliance of patient populations. The popularity of beta 3 adrenergic receptor agonists may be limited today, but the quality of effect it shows and its contributions in producing energy out of fat catabolism which can be compared to that of, "production of useful results from worthless wastes", it is predicted that the future of oral hypoglycemic therapy will belong to them.

References

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