BETA-3 ADRENERGIC RECEPTOR AGONISTS TO TREAT PULMONARY HYPERTENSION

Summary:

Pulmonary hypertension (PH), defined as the increase of mean pulmonary blood pressure above normal values, encompasses a series of disorders characterized by the increase of pulmonary vascular resistance and progressive deterioration of the right ventricle. The incidence of pulmonary hypertension in the population is high and it is associated with high morbidity and mortality. Approximately two thirds of patients with left ventricular dysfunction (systolic or isolated diastolic) develop pulmonary hypertension. Currently, there is a lack of treatments for pulmonary hypertension.

CNIC and CLINIC researchers have described a novel effective treatment for pulmonary hypertension of different etiology, both chronic and acute. They have found that selective stimulation of beta-3 adrenergic receptors has a beneficial effect in pulmonary hypertension.

Innovative aspects:

Present estimates suggest a PH prevalence of about 1% of the global population worldwide, which increases up to 10% in individuals aged 65 or more. The most frequent cause of PH is heart failure (group II PH in the current classification) followed by lung disease (group III PH). Few therapies with high cost and limited beneficial effect are currently available for PAH (group I).

Advances in the development of new pharmacological therapies have focused on idiopathic pulmonary hypertension, the least frequent subgroup (prevalence of 6 cases per million people). In this subgroup the first line treatment is calcium-antagonists, which are only effective over the long term in 1% of the cases. Other treatments using vasodilators, such as prostaglandins, 5-phosphodiestarase inhibitors or endothelin receptor antagonists provide benefits in a higher percentage of patients, although their clinical and hemodynamic effect is small (mean PAP reduction of 2-10%). In addition, these treatments have not proven consistent efficiency in pulmonary hypertension secondary to a left cardiac pathology (the most frequent), nor in any of the remaining pulmonary hypertension groups in general.

Therefore, the problem of treating pulmonary hypertension is still far from being satisfactorily resolved and the need to develop new therapies still exists. There has been little research on β3-adrenergic receptors in the field of cardiovascular diseases. Stimulation of these receptors is associated with the production of nitric oxide and the relaxation of vascular tone.

Researchers from CNIC and CLINIC have satisfactorily found that the selective stimulation of beta-3 adrenergic receptors has a beneficial effect on pulmonary hypertension. Thus, it has been observed that the administration of selective agonists of beta-3 adrenergic receptors in models of chronic PH and acute PH provokes a favorable response to this disease: reduction of pulmonary pressure, increase

of oxygen saturation, reduction of pulmonary vascular resistances, etc. Also, compared to other vasodilators commonly used in this disease, selective beta-3 adrenergic receptor agonists do not produce significant changes in systemic blood pressure or heart rate, thus minimizing possible harmful side effects on systemic circulation.

Competitive advantages:

- Currently, there is no approved or recommended treatment for PH groups II and III.
- β3AR agonists would be the first pharmacological treatment for PH due to left heart disease or pulmonary disease.
- β3AR agonists have demonstrated an additional cardioprotective effect (prevention of left ventricular fibrosis and remodeling) in experimental studies using animal models of heart failure.
- Administration of a selective beta-3 adrenergic receptor agonists in chronic and acute pulmonary hypertension models elicits a positive response against the disease: reduction of pulmonary pressure, increased oxygen saturation levels, reduction of pulmonary vascular resistance, etc.
- Distinctive pharmacodynamic properties of β3AR, such as their upregulation in disease and resistance to desensitization, suggest that they may be attractive targets for therapeutic intervention.
- Mirabegron (Betmiga®), is an oral β3AR agonist used for other condition (overactive bladder syndrome) with a good safety profile.

Key words: Pulmonary hypertension, beta-3 agonist, beta-3 adrenergic receptor, pulmonary vascular resistance.

Technology type: treatment, small molecule

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