Nature Reviews Endocrinology: Protein kinases could be the next target in the treatment of diseases associated with obesity

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Scientists at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) review the roles of a groups of proteins called stress kinases in metabolism in an article published in Nature Reviews Endocrinology

Stress kinases are proteins in the body that are associated with obesity and metabolic alterations such as insulin resistance and diabetes. Understanding their mechanisms and routes of action could be crucial for the design of therapeutic strategies to combat the global epidemic of obesity, which affects millions of people worldwide.

One of the key features of obesity is the activation of stress activated protein kinases (SAPKs). In mammals, this class of proteins is composed of the p38 family (p38 mitogen-activated protein kinases) and the JNK family (c-Jun N-terminal kinases). In the review article published in *Nature Reviews Endocrinology*, scientists from the *Centro Nacional de Investigaciones Cardiovasculares* (CNIC) explain that these kinases are essential for the correct adjustment of metabolism to changing conditions. Obesity is characterized by the uncontrolled activation of SAPKs in several organs and tissues, including fat, liver, muscle, immune cells, and the central nervous system. This unregulated

activity makes a major contribution to the development of obesity-related complications and diseases.

“This makes SAPK signaling pathways potential targets for the development of new treatment strategies to combat obesity”, explained Dr Guadalupe Sabio, a group leader at the CNIC and coordinator of the review.

Obesity is the second leading preventable cause of death, after smoking. Obesity also predisposes to diseases like type 2 diabetes, cirrhosis, cancer, and cardiovascular disease, all of which are leading causes of death. Current projections for Spain predict that by 2030 overweight or obesity will affect 27 million adults, accounting for 80% of all men and 55% of all women.

The main goals of this research field are to understand the function of each member of the p38 and JNK protein families and to identify specific inhibitors

Unfortunately, current treatments for obesity are of limited effectiveness and can have several unwanted consequences.

Dr Sabio therefore stresses the “p**ressing need to define the molecular mechanisms that underlie the metabolic disorders associated with obesity so that we can prevent and treat them.**”

Intense research by Sabio’s group and others over many years has provided important insights into the molecular mechanisms through which these kinases regulate metabolism in normal-weight and obese individuals. This work has established the contribution of SAPKs to the development of obesity and insulin resistance.

In the new article, Drs Guadalupe Sabio, Ivana Nikolic, and Magdalena Leiva provide an up-to-date perspective on the role of SAPKs in metabolic regulation in different organs and outline the major discoveries in the field in the past ten years.

For example, JNK and p38 SAPKs are known to act through diverse signaling pathways and mechanisms that affect metabolic processes such as insulin sensitivity, thermogenesis, and lipolysis. In addition, SAPK activity in immune cells triggers inflammation in several tissues and alters systemic metabolism in obesity. The accumulated evidence also shows that SAPKs have tissue and substrate specific functions and that their activation is involved in disorders related to obesity, steatohepatitis, liver cancer, heart failure, and diabetes mellitus.

As Dr Sabio says, “**although the importance of SAPKs is ever more clear, there is still much research to be done; for example, before any clinical intervention to modulate SAPKs it will first be essential to identify the specific functions of each p38 and JNK protein**.”

The authors consider that before embarking on preclinical and clinical trials with SAPK inhibitors, it is important to design specific molecules to treat the different obesity-associated diseases. But they also caution that “this will first require a more profound understanding of the mechanisms involved.”

Obesity is an especially important health problem because it predisposes to serious diseases like type 2 diabetes, cirrhosis, cancer, and cardiovascular disease

The scientists conclude that the main goal in this field is to identify specific inhibitors for each of the individual p38 and JNK members. These molecules can then be tested for their ability to prevent and treat obesity and associated diseases. “The specific organization of SAPK pathways in different tissues provides potential therapeutic openings for the prevention and treatment of metabolic syndrome and associated disorders.”

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- Nikolic, I., Leiva, M., & Sabio, G. (2020). The role of stress kinases in metabolic disease. Nature Reviews Endocrinology. doi:10.1038/s41574-020-00418-5

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