New therapeutic targets to fight type 2 diabetes

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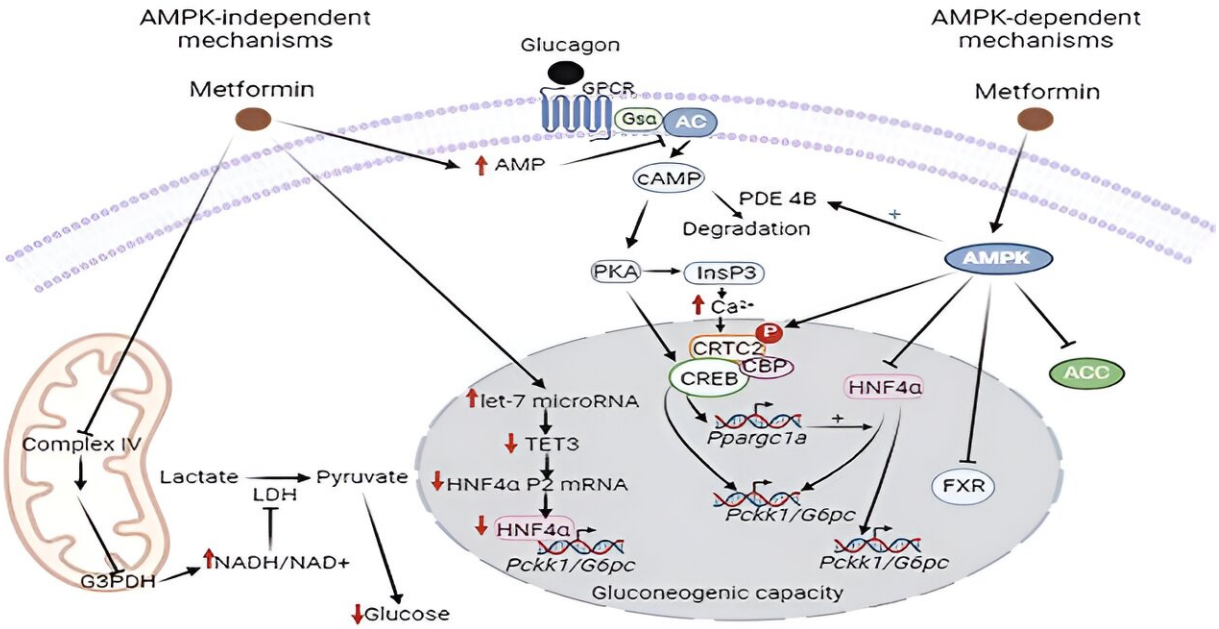

Designing combination therapies based on the different factors involved in the control of glucose synthesis by the liver could be a more effective strategy to address the treatment of the disease. Credit: University of Barcelona

One of the most confusing aspects for patients with type 2 diabetes mellitus is that they have high fasting glucose levels. This is because in these insulin-resistant patients, glucose production by the liver is triggered, a process that is still full of questions for the scientific

community.

Now, a review article published in the journal *Trends in Endocrinology & Metabolism* presents a comprehensive overview of the most important advances in understanding this mechanism. It also helps to identify new drug targets in the fight against type 2 diabetes mellitus, which the World Health Organization (WHO) considers one of the pandemics of the 21st century.

The study is led by Professor Manuel Vázquez-Carrera, from the Faculty of Pharmacy and Food Sciences of the University of Barcelona, the UB Institute of Biomedicine (IBUB), the Sant Joan de Déu Research Institute (IRSJD) and the Center for Biomedical Research Network on Diabetes and Associated Metabolic Diseases (CIBERDEM).

Among the participants in the study are the experts Emma Barroso, Javier Jurado-Aguilar and Xavier Palomer (UB-IBUB-IRJSJD-CIBERDEM) and Professor Walter Wahli, from the University of Lausanne (Switzerland).

Therapeutic targets to fight the disease

Type 2 diabetes mellitus is an increasingly common chronic disease that results in high levels of circulating glucose—the cellular energy fuel—due to a deficient insulin response in the body. It can cause severe organ damage and is estimated to be under-diagnosed in a high percentage of the affected population worldwide.

In patients, the glucose synthesis pathway in the liver (gluconeogenesis) is hyperactivated, a process that can be controlled by drugs such as metformin.

"Recently, new factors involved in the control of hepatic

gluconeogenesis have been identified. For example, a study by our group revealed that growth differentiation factor (GDF15) reduces the levels of proteins involved in hepatic gluconeogenesis," says Professor Manuel Vázquez-Carrera, from the UB's Department of Pharmacology, Toxicology and Therapeutic Chemistry.

To make progress in the fight against this pathology, it will also be necessary to further study pathways such as TGF-β, which is involved in the progression of metabolic dysfunction-associated fatty liver disease (MASLD), a very prevalent pathology that often coexists with type 2 diabetes mellitus.

"TGF-β plays a very relevant role in the progression of liver fibrosis and has become one of the most important factors that may contribute to increased hepatic gluconeogenesis and, therefore, to type 2 diabetes mellitus. Therefore, studying the involvement of the TGF-β pathway in the regulation of hepatic gluconeogenesis could help to achieve better glycemic control," says Vázquez-Carrera.

However, acting on a single factor to improve the regulation of gluconeogenesis does not seem to be a sufficient therapeutic strategy to adequately control the disease.

"It would be important to be able to design combination therapies that could consider the different factors involved to improve the approach to type 2 diabetes mellitus," Vázquez-Carrera says.

"Today there are several molecules—TGF-β, TOX3, TOX4, etc.—that could be considered therapeutic targets for designing future strategies to improve patients' well-being. Their efficacy and safety will determine their therapeutic success. We cannot lose sight of the fact that controlling the overactivation of hepatic gluconeogenesis in type 2 diabetes mellitus has an additional difficulty: it is a key pathway for

making glucose available in fasting situations, it is finely modulated by numerous factors and this makes regulation difficult."

Interestingly, other factors involved in the control of gluconeogenesis have also been identified in patients hospitalized with COVID-19 who showed high glucose levels. "Hyperglycemia was very prevalent in patients hospitalized with COVID-19, which seems to be related to the ability of SARS-CoV-2 to induce the activity of proteins involved in hepatic gluconeogenesis," the expert notes.

Metformin: The unknowns of the most prescribed drug

The mechanisms of action of metformin, the most commonly prescribed drug for the treatment of type 2 diabetes, which reduces hepatic gluconeogenesis, are still not fully understood.

It has now been discovered that the drug decreases gluconeogenesis via inhibition of complex IV of the mitochondrial electron transport chain. This is a mechanism independent of the classical effects known until now through activation of the AMPK protein, a sensor of the cell's energy metabolism.

"Inhibition of mitochondrial complex IV activity by metformin—not complex I as previously thought—reduces the availability of substrates required for hepatic glucose synthesis," says Vázquez-Carrera.

In addition, metformin can also reduce gluconeogenesis through its effects on the gut, leading to changes that ultimately attenuate hepatic glucose production in the liver.

"Thus, metformin increases glucose uptake and utilization in the gut, and

generates metabolites capable of inhibiting gluconeogenesis when they reach the liver via the portal vein. Finally, metformin also stimulates the secretion of GLP-1 in the intestine, a hepatic gluconeogenesis inhibitory peptide that contributes to its anti-diabetic effect," he explains.

For now, the team led by Vázquez-Carrera continues its research work to decipher the mechanisms by which GDF15 could regulate hepatic gluconeogenesis.

"In parallel, we want to design new molecules that increase circulating GDF15 levels. If we have potent inducers of GDF15, we could improve glycaemia in people with type 2 diabetes mellitus by reducing hepatic gluconeogenesis, but also by other actions of this cytokine," concludes the researcher.

More information: Emma Barroso et al, Increased hepatic gluconeogenesis and type 2 diabetes mellitus, *Trends in Endocrinology & Metabolism* (2024). DOI: 10.1016/j.tem.2024.05.006

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