UNIVERSITÉ DE GENÈVE

PRESS RELEASE

Geneva | May 17th, 2019

WARNING: embargoed until May 21th, 2019, 3pm GMT

The insulin under the influence of light

By understanding how day-night alternation affects the effect of insulin in tissues, researchers at UNIGE are highlighting the role of circadian rhythms in diabetes.

The disruption of our internal clocks seems to play a significant role in the explosion of metabolic diseases observed in recent decades, and particularly of diabetes. Indeed, if the importance of day-night alternation on the effect of insulin and on the body's glycaemic management is beginning to be known, what about the mechanisms involved? How does the organism synchronize its clocks? By understanding how the brain links the effects of insulin to light, researchers at the University of Geneva (UNIGE) are deciphering how insulin sensitivity fluctuates according to circadian cycles, but also according to the organs involved. At the heart of their discovery are neurons of the ventromedial hypothalamic nucleus, a part of the brain that masters this delicate balance. These results, to be discovered in the journal *Cell Reports*, should also encourage diabetic patients and their doctors to consider the best time to take insulin to properly control its effect and limit the risk of hypoglycaemia.

Roberto Coppari, Professor at the Diabetes Centre of UNIGE Faculty of Medicine.

High resolution pictures

The balance between the secretion and action of hormones is essential for the body to function properly. Thus, the secretion of several hormones, including insulin, varies over a 24-hour period and any change in this rhythm seems to predispose to metabolic diseases. To synchronize itself, the body takes into account two essential elements: the alternation of light and darkness as well as that of feeding and fasting. Indeed, the light perceived by retinal neurons is transmitted to the brain, which in turn regulates the peripheral clocks located in the different parts of the body.

"Our hypothesis was that insulin sensitivity varied according to the daily 24-hour cycle but also according to the tissues. Since we already knew that some neurons in the ventromedial hypothalamic nucleus (VMH) – a region of the hypothalamus – controlled the sympathetic nervous system output to skeletal muscle in mice, we looked at these neurons – called VMH SF1 neurons – in regulating insulin action in this tissue", explains Roberto Coppari, Professor at the Diabetes Centre of UNIGE Faculty of Medicine, who led this work.

From the brain to the organs: different mechanisms depending on the tissue

First, the scientists performed a complete evaluation of insulin action in different tissues in mice (gastrocnemius and soleus muscles, both located in the leg, adipose tissue, and liver) and observed significant variation in all tissues involved. By keeping mice in a cycle of 12 hours of light and 12 hours of darkness, insulin sensitivity was logically the lowest during the rest period. They then repeated the same measurements on animals in which the SIRT1 gene (a gene linked to the regulation of core clock molecular components) was deleted only in the few thousands of VMH SF1 neurons. “Indeed, we already knew that mice with an alteration of this gene in VMH SF1 neurons had propensity to insulin resistance. But by which mechanism?”, explains Giorgio Ramadori, a researcher at the Diabetes Centre and the first author of this study. By modulating the time of exposure to light, the researchers demonstrated that the SIRT1 gene of the VMH SF1 neurons plays a key role in the action of insulin in the gastrocnemius muscle, “but not in other tissues,” Roberto Coppari analyses. “This teaches us two things: on the one hand, different neurons have the task of conveying light/darkness cycle inputs to diverse organs, but on the other hand the disruption of only one of these regulatory pathways is enough to increase the individual’s risk of developing diabetes.”

To better assess the effect of light on tissue sensitivity to insulin, researchers measured insulin-induced glucose absorption. It turns out that a small disturbance in photic inputs (e.g. an hour of light exposure in the middle of the dark cycle, or light removal for 2 days) is enough to cause a negative effect. Indeed, increased or decreased light exposure can profoundly influence the sensitivity of tissues to insulin and the alteration, however minimal, of this mechanism is sufficient to significantly disrupt metabolic homeostasis. This would explain why people exposed to light at the wrong time – workers in shift patterns, for example – are more likely to develop metabolic diseases (e.g. diabetes).

Taking into account the time of day

Today, more than 450 million people worldwide have diabetes and many of them need daily insulin injections. When endogenous insulin is not produced in sufficient amounts, such as in people with type 1 diabetes insulin, therapy is the only treatment available, but this approach is not without risk – including a potentially severe hypoglycaemia that can lead to coma and even death. “In practice, the amount of insulin administered to patients is calculated on the basis of carbohydrate intake,” says Roberto Coppari. If, as our results indicate, insulin sensitivity varies with time of day and individuals’ circadian rhythm, this parameter should be taken into account for patients to better manage their treatment and limit its risks. “Beyond insulin, the influence of time of day on the effectiveness of drug treatments should be studied much more broadly.”

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DOI: 10.1016/j.celrep.2019.04.093

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