Targeting a hunger hormone to treat obesity

October 22 2018, by Catherine Cardinal

Credit: CC0 Public Domain

About 64 per cent of Canadian adults are overweight or obese, according to Health Canada. That's a problem, because obesity promotes the emergence of chronic diseases such as type 2 diabetes, heart disease and some cancers.

To address the issue, researchers are trying to develop a pharmacological solution capable of interfering with the hormones behind weight gain.

Those that regulate appetite are prime targets, including ghrelin.

By blocking the binding of ghrelin to its receptor with a drug, one could theoretically reduce a person's feeling of hunger.

But ghrelin and its receptor also stimulate gastrointestinal motility and secretion of growth hormone, as well as having an impact on mood and behavior – both undesirable side effects.

There is hope however:

With colleagues at the University of Copenhagen, Université de Montréal professor Michel Bouvier and his team at the Institute for Research in Immunology and Cancer have discovered a strategy to specifically tackle hunger.

Find a (path)way

In their study, published in the *Proceedings of the National Academy of Sciences*, the researchers identified that a particular signaling pathway downstream of the receptor, the one involving the Gαq/11 protein, was responsible for hunger.

By specifically blocking this signaling pathway without interfering with the others, a drug could therefore effectively fight obesity while limiting the side effects. Trouble is, this is only partially true.

The molecule YIL781, for instance, prevents some functions of the receptor, but not all of them. Instead of blocking the signaling pathway involving the Gαq/11 protein, it activates it instead, thereby stimulating hunger.

Researchers clearly demonstrated that it is this particular signaling

pathway that allows the ghrelin receptor to stimulate hunger, using mice unable to produce the Gαq/11 protein in the cells of their hypothalamus.

The appetite of these mice remained unchanged when administered YIL781. On the other hand, normal mice ate three times more, on average.

Since it stimulates hunger, the drug YIL781 is unsuitable for treating obesity. However, this molecule has demonstrated that the ghrelin receptor can be partially turned on, providing hope for future research.

More information: Franziska Mende et al. Translating biased signaling in the ghrelin receptor system into differential in vivo functions, *Proceedings of the National Academy of Sciences* (2018). DOI: 10.1073/pnas.1804003115

Provided by University of Montreal