Surprise finding suggests diabetes drug could release rather than prevent blood sugar

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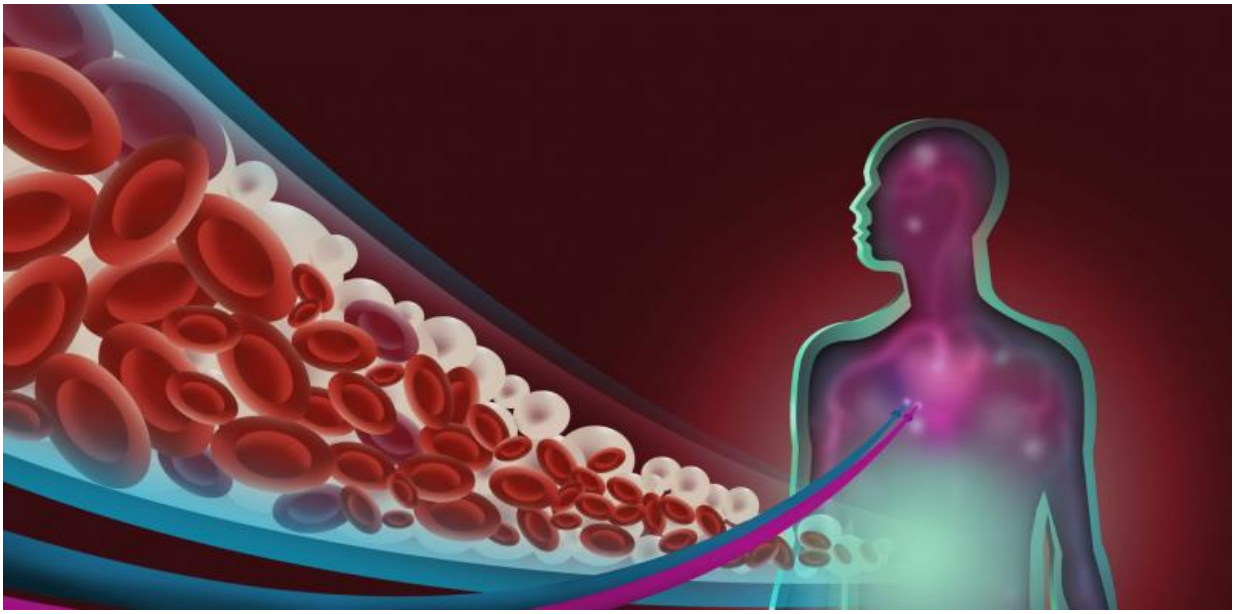

Nearly all medications have some sort of side effects, some more unpleasant and dangerous than others. They may occur because a treatment affects the body in ways that weren't previously anticipated, or simply because not every patient is identical.

This means there is a continual need for us to evaluate and study the medications we use. We discovered previously unidentified effects

associated with a commonly prescribed diabetic medication. We found evidence that, in some cases, the treatment could actually promote the release of sugars into the blood – the opposite of what it's designed to do. While our results, published in the *Journal of Biological Chemistry*, are very preliminary, they do point to a need for further investigations into how these medications work.

Diabetes affects around 347m people worldwide, a number that is growing in part due to rising levels of obesity. Type 2 or "adult-onset" diabetes occurs when cells in the body fail to respond to insulin, the chemical signal that regulates sugar and fat metabolism. This results in high sugar levels in the blood, which if untreated can damage blood vessels and nerves, leading to heart disease, strokes, kidney damage and loss of sight.

Exercise and diet changes can reduce the progression of diabetes if diagnosed early. Over time, however, most people require some form of medication. Treatments available today typically suppress sugar production and encourage the pancreas to release more insulin. This is because in a type 2 diabetes patient, the body often ignores the effects of naturally-produced insulin and, in response, produces more blood sugars, a process activated by the hormone glucagon.

New solution

Until recently, these medications were the only way to treat the disease before it had reached the stage when patients had to inject insulin themselves. In the past few years, however, a new treatment has emerged that both targets the effects of diabetes and promotes weight loss.

These therapies are based on a hormone known as glucagon-like peptide-1 or GLP-1. When you eat something, the intestine releases the hormone in order to promote insulin secretion. At the same time, it

makes the stomach empty itself more slowly and makes us feel full – good news if you want a drug that can tackle obesity and diabetes at the same time.

Unfortunately, GLP-1 breaks down rapidly in the body. So in response, scientists created a number of artificial injectable versions that mimic its effects but last for much longer. While these GLP-1 mimetics have been approved for use and for treating diabetes, they are not without controversy and there is a continuous scientific and moral requirement for clinicians and scientists to evaluate and investigate their effectiveness and mechanism of action.

Our research, led by Cambridge University's pharmacology department and Warwick University's medical school, found that one such GLP-1 mimetic may, under specific conditions, activate the molecules in the body's cells that recognise the signal from the hormone glucagon. Were this to happen in the liver, it could promote the release of sugars into the blood -– precisely the process that it is supposed to prevent.

It's important to stress that these results are only initial findings and that more in-depth analysis is required. Our results, however, are likely to prove quite controversial. A limited number of published studies previously suggested that GLP-1 cannot bind to the glucagon receptor molecule at all, ruling out the possibility of this effect. Our research contradicts this.

The key difference is that we studied how the treatment was affected by another molecule called RAMP2 that is found in varying amounts around the body. We found that without the presence of this molecule, the GLP-1 was able to bind with the glucagon receptor and so promote sugar release.

Ramping up the receptors

The problem is that we know very little about RAMP2. Studies in mice have suggested that its levels vary in different tissues. Levels of RAMP2 appear to be lower in the liver than other areas of the body. This means there's a chance GLP-1 mimetics could activate the glucagon receptors in liver tissue, promoting the release of sugars.

In our study, we found GLP-1 only has a limited ability to interact with glucagon receptors. But because the GLP-1 drugs are designed to reside in the body for much longer than the natural GLP-1 molecule, this may increase the chances of interaction. Another study earlier this year found that prolonged use (for more than 12 weeks) of the same GLP-1 mimetic in type 2 diabetes patients led to an increase in glucagon secretion, correlating with the results of our own study.

Our study in no way suggests that GLP-1 mimetics are at all dangerous for patients currently using them. Indeed, the beneficial effects for many patients currently outweigh the risks. But it does not mean that we should not continue to evaluate and investigate this treatment as new information about its interaction with the body emerges.

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