Scientists closing in on new obesity drug

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Obesity and diabetes are among the fastest growing health problems in the world, and the hunt is in for a pill that can fight the problem. Now a Danish/British team has come up with a smart tool that will speed up the scientific hunting process, and we may be one step closer to a pill against obesity.

The body has a variety of functions that decide if we get overweight or not. For instance hormones control our appetite and the uptake of food.

In recent years science has taken on the quest of investigating these physiological functions and finding a medical way to fight obesity.

One way that has attracted scientific interest is to work with a special protein, that can stimulate different physiological activities such as the production of appetite controlling hormones and hormones that control the intestinal uptake of food.

The particular protein is found in the cell membranes in intestines, in immune cells and in fat, and it is called FFA4. The protein is activated by long-chain free fatty acids released from the food such as omega-3 fatty acids. When this happens, it releases hormones that inhibit our appetite and increase sugar uptake from the blood.

"In some people this protein is not activated and they have a much higher risk of becoming obese. This can be explained by the involvement of the protein in hormone secretion and regulation of inflammation and insulin sensitivity", explains postdoc Bharat Shimpukade from Department of Physics, Chemistry and Pharmacy at University of Southern Denmark.

Together with Professor Trond Ulven from the same department and colleagues from University of Glasgow he is the co-author of a new paper on the subject in *The Journal of Biological Chemistry*.

"We want to find a way to activate this protein, because that may help us to develop a drug against obesity or diabetes", says Bharat Shimpukade. Molecules can activate proteins, so the job is "just" to find the right molecule. 1"But there is almost an infinite number of possible molecules that we can synthesize, and it is extremely time consuming to test molecules randomly for their possible ability to activate this particular protein", explains Bharat Shimpukade.

The job could therefore take years and years of painstaking experiments in laboratories – but this can now be avoided thanks to the new development by the research-team.

"We have developed a computer model of FFA4 that can help us to select the correct molecules for synthesis by first testing if they bind in the computer model. This way we can test thousands of molecules in a very short time before going into the laboratory. This will speed up the process of finding the right compounds that can be developed to efficient drugs against obesity or diabetes", says Bharat Shimpukade.

The model has been confirmed and refined by detailed experimental studies.

In 2012, the same team discovered the first selective activator of FFA4, a compound that is now important for studying the functions of the protein.

"It works well at activating the protein. But we cannot administer it as a drug to a patient, because it is not stable enough in the body. We need a more water-soluble molecule with higher stability: It must not be broken down in the body before it has done the job. On the other hand, we don't want it to stay in the body forever."

Bharat Shimpukade has now set out to find the winner-molecule that will activate the protein in all the right ways and stay in the body for the time needed. And of course he is using the new model.

"I have been looking for a couple of months now, and I hope to be able to continue till I find the perfect molecule that can lead to a new cure", says Bharat Shimpukade.

More information: *J Biol Chem.* 2014 May 24. pii: jbc.M114.561449.

[Epub ahead of print] The molecular basis of ligand interaction at free fatty acid receptor 4 (FFA4/GPR120). Hudson BD, Shimpukade B, Milligan G, Ulven T. www.ncbi.nlm.nih.gov/pubmed/24860101

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