Brown Fat in the Spotlight Again as UC Irvine Study Identifies Promising Obesity Drug Candidate

Arvind Suresh

The Obesity Pandemic

Look around you. Obesity is everywhere. Not even the US army, the bastion of fitness, can protect itself against it. Which is why identifying drug targets for obesity represents an important market for big and small pharmaceutical companies alike. However, despite several years of research into anti-obesity drugs, the current options in the market have not been quite as effective as expected. In the search to identify the ideal drug, researchers at UC Irvine have discovered that ShK-186, an existing drug candidate for treating autoimmune diseases may represent a novel approach to combating obesity. Importantly, ShK-186 targets a completely different class of molecules from the existing drugs, providing a new path for treating obesity and its partner in crime, type 2 diabetes.

ShK-186, a promising drug target

ShK-186 is a peptide toxin derived from the Caribbean sun anemone, *Stichodactyla helianthus*. It has been used in research as an extremely specific blocker of the voltage gated potassium channel Kv1.3. Cells are like tiny batteries that store energy by maintaining the number of charged ions within its membrane. Voltage gated potassium channels as the name suggests are ion channels regulating the flow of potassium ions into the cell to maintain membrane potential. Among the many cellular processes that Kv1.3 regulates, it can activate certain immune cells known as memory T cells which play a key role in meditating autoimmune diseases. Professor George Chandy at UC Irvine along with his colleagues previously discovered that by blocking Kv1.3, ShK-186 was extremely effective in treating autoimmune diseases in mice. It showed such potential in initial animal studies that Airmid, a company co-founded by Prof Chandy licensed the peptide to Kineta, a Seattle based biotech startup. ShK-186 has completed phase 1 first-in-human studies in the clinical trials pipeline and is undergoing further testing.

The current study, led by Dr Sanjeev Kumar Upadhyay, a postdoctoral scholar in Prof Chandy's lab reported the remarkable finding that diet induced obesity in mice can be prevented and treated with ShK-186. The research was published in published in the journal *Proceedings of the National Academy of Sciences*. The authors took clues from previous studies showing that genetically modified mice lacking the Kv1.3 gene (or Kv1.3 knockout mice) did not gain as much weight when fed a high fat diet as normal mice did.

Dr Upadhyay and team treated mice fed a high fat diet that was comparable in the proportion of nutrients to the American fast food diet most commonly consumed and found that ShK-186 treated obesity after the high fat diet period was completed. It was also able to prevent weight gain when given midway through the high fat diet period. Interestingly, they found that ShK-186 was not effective in mice fed a normal diet, suggesting that obesity modified the response to the drug. The animals when treated also had reduced blood glucose, reduced cholesterol and a decrease in adiposity showing that the drug caused improvements in critical markers associated with obesity and insulin resistance.

How ShK-186 works

In trying to decipher how ShK-186 worked, the team was able to zone in on a kind of fat called brown adipose tissue (BAT) or brown fat. There are two kinds of fat in our body, brown fat and white fat, more commonly known as good fat and bad fat respectively. Brown fat is important in keeping the body warm by metabolizing fat to release energy and generate heat. White fat (found in that muffin top you've been trying to get rid of for the last few years) on the other hand acts largely as a store of energy. Since BAT burns lipids faster, it is called 'good fat'. (On a side note, not all white fat is 'bad', it is in fact essential for our body and causes problems only in excessive amounts). Why is brown fat interesting?

ShK-186, the team found was extremely effective at 'activating' BAT. The drug stimulated biochemical pathways that increased glucose uptake (thus reducing blood glucose levels), break down fats and overall created the conditions necessary for burning the excess fat and sugar in the diet. Further supporting the 'burning brown fat' hypothesis, the mice consumed significantly more oxygen as well. The net effect of ShK-186 was an increase in energy expenditure (mostly as heat) without an increase in food intake or locomotor activity (i.e. the mice weren't just running around more to spend the energy). They found similarly marked uptick in the activity of metabolic pathways in the liver that breakdown fat and metabolize glucose. Interestingly more Kv1.3 channels were present in liver cells of mice which were fed the high fat diet prompting the authors to suggest it as a likely reason why the drug is not effective in mice fed a regular diet.

Moving forward, is brown fat the new darling of obesity drugs?

Dr Chandy's paper is a recent addition to the spate of studies that focus on brown fat and energy metabolism in the body. Since brown fat mainly maintains body temperature, it was previously thought that only small mammals that needed to regulate their body temperature had them. In fact, in humans, it was believed to be present only in newborns. However in 2009, two teams, one from Joslin Diabetes Center and one from Maastricht University Medical Centre in The Netherlands discovered that there were small quantities of brown fat in lean adults deep in the neck and collarbone regions. These cells were identified by the expression of a specific protein called uncoupling protein 1 (UCP1). Since then reports have suggested that it may be possible to transform white fat into brown in the body under certain conditions and that there may actually be two kinds of brown fat cells. As can be expected, research teams around the world are now working to break down the underlying biology of brown fat. In the pharmaceutical industry too companies are rushing to cash in on this opportunity. In 2010 a new company called Energesis pharmaceuticals was founded in Cambridge, Mass to focus exclusively on developing drugs to treat obesity and diabetes by targeting brown fat. Another Cambridge based company, Acceleron pharma has recently added a drug to its development pipeline that they suggest increases levels of brown fat and decreases levels of white fat in animals. Based on the ShK-186 report discussed above, Kineta will probably jump into the fray in the near future as well. With a market that is predicted to increase over six-fold in the next decade, you can be assured that they will not be the last. The obesity drug market is burning up!

Note on conflict of interest: Several of the authors in this study are co-inventors on a patent on ShK-186 filed by the University of California. The Chief Scientific Officer of Kineta, Inc was an author on the study and Dr George Chandy is one of the co-founders of Airmid and owns stock in Kineta, Inc.