# Food for thought -- regulating energy supply to the brain during fasting

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If the current financial climate has taught us anything, it's that a system where over-borrowing goes unchecked eventually ends in disaster. It turns out this rule applies as much to our bodies as it does to economics. Instead of cash, our body deals in energy borrowed from muscle and given to the brain.

Unlike freewheeling financial markets, the lending process in the body is under strict regulation to ensure that more isn't lent than can be afforded. New research by scientists at the Salk Institute for Biological Studies reveals just how this process is implemented.

"We have all seen the sub-prime mortgage crisis," says Marc Montminy, M.D., Ph.D., a professor in the Clayton Foundation Laboratories for Peptide Biology who led the current study. "If you take out a loan, sooner or later you've got to pay your debt, and the same is true in fasting metabolism."

The Salk researchers' findings, which are published ahead of print in the Oct. 5 edition of the journal *Nature*, may pave the way for novel therapies for sufferers of metabolic diseases in whom such regulation can spiral out of control.

Most tissues in our bodies respond to fasting by switching from their usual high-octane energy source—glucose—to burning a low-octane, cheaper alternative-fat. For our brains, however, only the high-performance fuel will do. If no food-derived glucose is available, the

body must manufacture its own supply to maintain the brain in the manner to which it is accustomed. It does so by taking energy from muscle in the form of protein and converting it to glucose in the liver, a process known as gluconeogenesis. The sugar is then shipped via the bloodstream to the brain to keep it running smoothly.

Gluconeogenesis needs to be turned on rapidly in response to fasting, but shutting it off again is just as crucial. "You don't want gluconeogenesis to be prolonged," says postdoctoral researcher and co-first author Yi Liu, Ph.D. "Because it uses muscle as a protein source, it will eventually lead to muscle wastage." Adds Montminy, "The question has always been how is the production of glucose turned on, and how is shut off again?"

Previous work by the Montminy lab and others has shown that two key proteins, CRTC2 and FOXO1, are needed to turn on glucose-making genes during fasting. CRTC2 is activated by glucagon, a hormone whose levels go up when we stop eating. FOXO1, on the other hand, is activated when levels of the food-stimulated hormone insulin drop below a certain threshold. CRTC2's and FOXO1's activity needs to be tightly regulated, since producing too much glucose would result in over-borrowing of energy from muscle tissue.

To uncover the mechanism that ensures that this doesn't happen, the Salk researchers created mice containing the gene for luciferase, a light-emitting enzyme usually found in fireflies, engineered in such a way that it was only turned on when CRTC2 was active. Using imaging equipment, they could then detect CRTC2 activity in the livers of live mice simply by measuring how much they glowed.

When the mice were fasted, CRTC2 was rapidly activated, and the livers lit up, but to the scientists' surprise, after six hours the light went out. Experimentally decreasing the levels of CRTC2 or FOXO1 confirmed there was a two-stage fasting-response. Lowering CRTC2 reduced

gluconeogenesis only early on, while less FOXO1 only affected late glucose production. As in a relay race, during fasting the baton for glucose production appeared to be passed from CRTC2 in stage one to FOXO1 in stage two.

The crucial switch from CRTC2 to FOXO1 comes in the form of SIRT1, a nutrient sensor that accumulates in the late fasting stage. Yi discovered that SIRT1 has opposite effects on CRTC2 and FOXO1: it sends the former to the recycling bin, while it activates the latter, and thus the baton is safely transferred from CRTC2 to the FOXO1.

Why does the body want to change between these two regulators of glucose production? Again, it comes down to body economics. CRTC2 acts as a rapid response unit to quickly produce high levels of glucose when it detects glucagon. Switching to FOXO1 later on slows down this production to more sustainable levels, while at the same time helping to produce ketone bodies, an alternative fuel the brain can use that does not require taking protein from muscle. "It is just like paying your loan back," says Montminy. "Later on you produce blood sugar at a different rate than you did at the beginning."

Knowledge of how this nutrient switch is working may help design new drugs to regulate sugar levels in diabetes patients. In, particular, chemical activators of the SIRT1 switch may be key. "This way we could provide control for patients with insulin resistance," says Montminy, "as typically their blood sugars are elevated after overnight fasting because the switches that regulate the glucose-producing enzymes are too active." Perhaps, then, a pharmacological rescue package for patients whose lending systems have been left unregulated may be on the horizon.

Source: Salk Institute