Too many calories send the brain off kilter

October 2 2008

An overload of calories throws critical portions of the brain out of whack, reveals a study in the October 3rd issue of the journal *Cell,* a Cell Press publication. That response in the brain's hypothalamus—the "headquarters" for maintaining energy balance -- can happen even in the absence of any weight gain, according to the new studies in mice.

The brain response involves a molecular player, called IKKß/NF-kappaB, which is known to drive metabolic inflammation in other body tissues. The discovery suggests that treatments designed to block this pathway in the brain might fight the ever-increasing spread of obesity and related diseases, including diabetes and heart disease.

"This pathway is usually present but inactive in the brain," said Dongsheng Cai of the University of Wisconsin-Madison. Cai said he isn't sure exactly why IKKß/NF-kappaB is there and ready to spring into action in the brain. He speculates it may have been an important element for innate immunity, the body's first line of defense against pathogenic invaders, at some time in the distant past.

" In today's society, this pathway is mobilized by a different environmental challenge—overnutrition," he said. Once activated, "the pathway leads to a number of dysfunctions, including resistance to insulin and leptin," both important metabolic hormones.

Earlier studies showed that overnutrition can spark inflammatory responses in the peripheral metabolic tissues, including the muscles and liver, and therefore cause various metabolic defects in those tissues that

underlie type 2 diabetes. As a result, scientists identified IKKß as a target for an anti-inflammatory therapy that was effective against obesity-associated diabetes.

Yet whether metabolic inflammation and its mediators played a role in the central nervous system remained uncertain. Now, the researchers show that a chronic high-fat diet doubles the activity of this inflammatory pathway in the brains of mice. Its activity is also much higher in the brains of mice who are genetically predisposed to obesity, they found.

The researchers report that that increased activity of the IKKß/NF-kappaB pathway can be divorced from obesity itself -- infusions of either glucose or fat into the brains of mice alone led to this inflammatory brain reaction.

Further studies revealed that this activity in the brain leads to insulin and leptin resistance. Insulin lowers blood sugar by causing cells of the body to take it up from the bloodstream. Leptin is a fat hormone important for appetite control.

Moreover, the researchers found that treatments preventing the activity of IKKß/NF-kappaB in the animals' brains protected them from obesity.

While chronic inflammation is generally considered a consequence of obesity, the new results suggest the inflammatory reaction might also be a cause of the imbalance that leads to obesity and associated diseases, including diabetes. As Cai says, it appears that inflammation and obesity are "quite intertwined." An abundance of calories itself promotes inflammation, while obesity also feeds back to the neurons to further promote inflammation in a kind of vicious cycle.

The findings could lead to treatments that might stop this cycle before it

gets started.

"Our work marks an initial attempt to study whether inhibiting an innate immune pathway in the hypothalamus could help to calibrate the set point of nutritional balance and therefore aid in counteracting energy imbalance and diseases induced by overnutrition," the researchers said. "We recognize that the significance of this strategy has yet to be realized in clinical practice; currently, most anti-inflammatory therapies have limited direct effects on IKKß/NF-kappaB and limited capacity to be concentrated in the central nervous system. Nonetheless, our discoveries offer potential for treating these serious diseases."

If realized, such a strategy would likely offer a safe approach given that the critical pathway appears to be unnecessary in the hypothalamus under normal circumstances, they noted.

Source: Cell Press