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Study links insulin action on brain's reward circuitry to obesity

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Researchers reporting in the June issue of *Cell Metabolism* have what they say is some of the first solid proof that insulin has direct effects on the reward circuitry of the brain. Mice whose reward centers can no longer respond to insulin eat more and become obese, they show.

The findings suggest that insulin resistance might help to explain why those who are obese may find it so difficult to resist the temptation of food and take the weight back off.

"Once you become obese or slide into a positive energy balance, insulin resistance in [the brain's reward center] may drive a vicious cycle," said Jens Brüning of the Max Planck Institute for Neurological Research. "There is no evidence this is the beginning of the road to obesity, but it may be an important contributor to obesity and to the difficulty we have in dealing with it."

Previous studies had focused primarily on insulin's effect on the brain's hypothalamus, a region that controls feeding behavior in what Brüning describes as a basic stop and start "reflex." But, he says, we all know people overeat for reasons that have much more to do with neuropsychology than they do with hunger. We eat based on the company we keep, the smell of the food and our mood. "We may feel full but we keep eating," Brüning said.

His team wanted to better understand the rewarding aspects of food and specifically how insulin influences higher brain functions. They focused

on key neurons of the midbrain that release dopamine, a chemical messenger in the brain involved in motivation, punishment and reward, among other functions. When insulin signaling was inactivated in those neurons, mice grew fatter and heavier as they ate too much.

They found that insulin normally causes those neurons to fire more frequently, a response that was lost in animals lacking insulin receptors. The mice also showed an altered response to cocaine and sugar when food was in short supply, further evidence that the reward centers of the brain depend on insulin to function normally.

If the findings hold in humans, they may have real clinical implications.

"Collectively, our study reveals a critical role for insulin action in catecholaminergic neurons in long-term control of feeding," the researchers wrote." The further elucidation of the exact neuronal subpopulation(s) and cellular mechanisms responsible for this effect may thus define potential targets for the treatment of obesity."

As a next step, Brüning said they plan to conduct functional magnetic resonance imaging (fMRI) studies in people who have had insulin artificially delivered to the brain to see how that may influence activity in the reward center.

Provided by Cell Press