Deleting ghrelin receptor, but not ghrelin, turns up fat-burning thermostat

December 13 2010

Deleting the receptor, not the protein ghrelin itself, turns up the body's fat-burning thermostat, giving aging mice an exothermic boost toward a svelte physique, researchers reported at the American Society of Cell Biology's 50th Annual Meeting in Philadelphia.

The protein's receptor, growth hormone secretagogue receptor (GHS-R), might make a better target than ghrelin for treating obesity, according to Yuxiang Sun, M.D., Ph.D., of the Baylor College of Medicine in Houston, TX.

Sun said that experimentally deleting the receptor from the body cells of laboratory mice prevented obesity by diminishing white adipose tissues and activating brown adipose tissue, thereby increasing heat production.

The new finding that ghrelin may not be as critical to energy expenditure as its receptor, GHS-R, came from research on body temperature regulation at Baylor, Sun explained. GHS-R acts as the "lock" for the "key-like" ligand ghrelin to dock; GHS-R subsequently activates down-stream metabolic signal pathways.

With colleagues from Baylor and other institutions, Sun created two sets of genetically modified mice: one was null for ghrelin, while the other group was null for GHS-R. When challenged by cold and fasting, only the mice without GHS-R maintained a normal body temperature.

Intrigued by this finding, the researchers generated two additional

cohorts of these knockout mice -- a young group 3 to 4 months old and an older group 10 to 12 months old –– to determine whether obesity and physical activity levels were influenced by age.

The scientists compiled a complete energy metabolic profile for each mouse, charting the animal's food intake against energy output. The energy profiles revealed that neither food intake nor activity levels differed in the gene-deleted mice compared to normal mice, regardless of age. But the GHS-R null mice were thinner because they were more exothermic.

Like aging humans, aging mice gain weight by accumulating fat. In contrast, the older GHS-R null mice maintained a lean physiological profile with lower circulating lipids and exhibited the high-energy expenditure levels that characterized the young mice.

These older GHS-R null mice weren't more active. However, without extra effort, they burned as heat more calories and fat. Meanwhile the older ghrelin-deleted mice followed the pattern of obesity in normal again mice: growing older and fatter.

In the ghrelin-deleted and the GHS-R deleted mice, the researchers then compared levels of UCP1, an "uncoupling protein" known as a hallmark regulator of thermogenic functioning in brown fat.

Consistently UCP1 was significantly higher in the brown fat of GHS-R deleted mice than in the ghrelin-deleted mice. The brown fat of the older GHS-R deleted mice included a higher proportion of smaller fat droplets, an indication of enhanced heat production, said Sun.

The 1999 discovery of ghrelin's role in appetite and energy balance ignited hopes that it was the body's long-sought hunger thermostat. Ghrelin remains the only circulating peptide known to stimulate appetite

and promote obesity in both humans and rodents, but it also plays other roles in regulating growth and metabolism.

"All this shows the complexity of ghrelin and its signaling pathway, and suggests the existence of additional unidentified regulators mediating the effect of ghrelin and/or GHS-R," said Sun.

Provided by American Society for Cell Biology