Cell Metabolism
Previews

Adiponectin: Starving for Attention

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DOI 10.1016/j.cmet.2007.06.008

Maintaining energy balance involves the dynamic control of appetite and energy expenditure. A new study from the Kadowaki laboratory (Kubota et al., 2007) shows that the adipocyte-derived hormone adiponectin increases appetite and reduces energy expenditure by stimulating AMPK in the hypothalamus.

The hypothalamus integrates signals from the gut and white adipose tissue that regulate appetite and control energy expenditure and metabolism through sympathetic outflows to muscle, fat, and liver (Xue and Kahn, 2006). These signals stem from hormones secreted from adipose tissue (leptin, adiponectin, IL-6), the gut (ghrelin, cholecystokinin, peptide YY), and pancreas (insulin) as well as nutrient signals such as free fatty acids, glucose, and branched-chain amino acids (Xue and Kahn, 2006). For example, leptin acts centrally at the hypothalamus to suppress appetite and increase energy expenditure in skeletal muscle (Minokoshi et al., 2004). Indeed, rodents and humans lacking leptin or its receptor become obese as a result of the failure of these mechanisms. Treating rodents with adiponectin also increases glucose and fat metabolism in muscle (Fruebis et al., 2001), reduces glucose production by the liver, and leads to improvements in insulin sensitivity (Combs et al., 2001). In this issue of *Cell Metabolism*, Kubota and colleagues (2007) show an exciting new role for adiponectin in stimulating appetite and opposing the actions of leptin in the hypothalamus.

Adiponectin is an abundant circulating hormone present in at least three multimeric forms: trimers, hexamers, and high-molecular-weight (HMW) complexes, the latter of which appear to be most biologically active and are reduced with obesity. Both adiponectin and leptin act via their cell-surface receptors (AdipoR1/2 and Ob-R, respectively) to control a common enzyme called AMPK, which has been shown to play a critical role in regulating appetite (Andersson et al., 2004; Minokoshi et al., 2004). Hypothalamic AMPK activity is increased by fasting and reduced by feeding. These effects are mediated by changes in circulating hormones such that leptin, insulin, and glucose reduce AMPK activity while the gut-derived hormone ghrelin increases AMPK activity. The inhibition of AMPK results in the suppression of the appetite-stimulating hormones, neuropeptide Y (NPY), and agouti-related protein, whereas activation of AMPK increases their expression and induces feeding. Thus, the balance between satiety and feeding hinges on whether AMPK is inhibited or activated in the brain.

Compared to their central effects, some hormones such as leptin (Minokoshi et al., 2004) and ciliary neurotrophic factor (Watt et al., 2006) act differently in peripheral tissues and stimulate AMPK activity. The differential signaling mechanisms operating between the brain and peripheral tissues is poorly understood, but it is known that AMPK activity is regulated by changes in nucleotides and is covalently regulated by protein phosphatase 2C and at least three upstream kinases, LKB1, CAMKK2, and TAK1 (Hardie, 2007), with CAMKK2 most likely dominant in the brain (Hurley et al., 2005). In skeletal muscle, the activation of AMPK by adiponectin, like leptin, stimulates fatty acid oxidation through the AMPK-dependent phosphorylation of ACC, which in turn reduces malonyl-CoA and increases mitochondrial β-oxidation, while in the liver it leads to the suppression of hepatic gluconeogenesis through phosphorylation of TORC2.

Mice lacking adiponectin (*adipo*$^{-/-}$) or its receptor AdipoR1 have impaired insulin action, but in marked contrast to leptin-deficient animals, they are not obese (Kubota et al., 2007). Kubota et al. show that both receptors AdipoR1 and AdipoR2 colocalize with the leptin receptor in the hypothalamus and that cerebrospinal fluid (CSF) contains low levels of adiponectin that comes from the blood. They find that intravenous injection of adiponectin raises CSF levels in *adipo*$^{-/-}$ mice. The forms of adiponectin found in the CSF are restricted to the trimeric and hexameric forms, and not the HMW form present in blood, and this may be an important point of difference between an earlier study in which HMW recombinant adiponectin was infused into the brain and induced weight loss and increased energy expenditure (Qi et al., 2004). In agreement with previous studies (Andersson et al., 2004; Minokoshi et al., 2004) Kubota et al. observed that fasting increased AMPK activity in the arcuate hypothalamus (ARH), which was reversed by refeeding (Figure 1). As fasting induces changes in a number of nutrients and hormones, multiple approaches were used in this study to link the increased fasting AMPK activity with elevations in CSF adiponectin. First, when adiponectin hexamers were injected directly into the brain, AMPK activity was increased, resulting in feeding and a reduction in energy expenditure. These effects were eliminated following the ablation of AdipoR1 (AdipoR1 siRNA) or AMPK signaling (AMPK dominant-negative). What, then, happens in the *adipo*$^{-/-}$ mice that lack adiponectin?

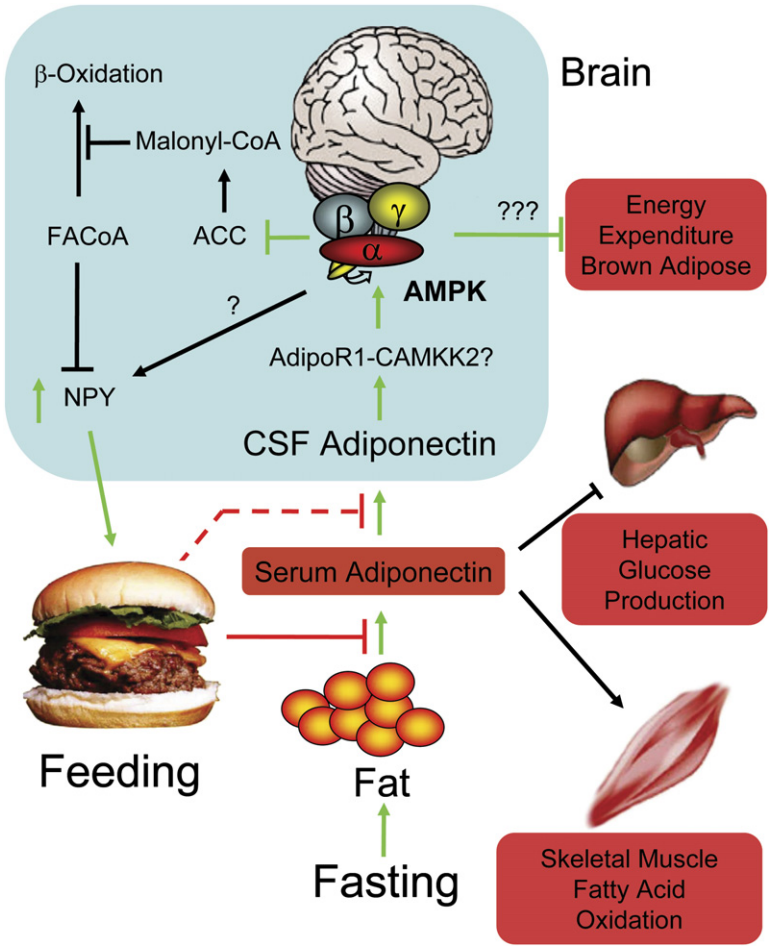

Figure 1. Appetite Control by Adiponectin
Fasting triggers increased adiponectin in the cerebrospinal fluid (CSF) and activation of AMPK in the brain, which increases NPY and induces feeding (green arrows). Feeding reduces adiponectin and lowers appetite (red arrows). In obesity, the capacity to lower adiponectin in response to feeding is suppressed, preventing the switching off of appetite (dashed red arrow). CAMKK2, Ca^{2+}/calmodulin-dependent protein kinase kinase 2β; ACC, acetyl-CoA carboxylase; FACoA, long-chain fatty acyl-CoA; NPY, neuropeptide Y; ?, unknown pathway.

It turns out that they have reduced AMPK activity as well as reduced levels of appetite-controlling NPY following a fast and reduced food intake. In a final series of experiments, Kubota et al. took advantage of the knowledge that leptin decreases AMPK activity and suppresses food intake and found that the suppressive effect of leptin on AMPK activity was reversed by adiponectin injection. Importantly, Kubota et al. demonstrated that *adipo*$^{-/-}$ mice have much higher sensitivity to a chronic low dose of leptin. In summary, these observations support the idea that adiponectin increases in response to fasting and promotes feeding by activating AMPK and inhibiting the actions of the appetite suppressor leptin.

Serum adiponectin levels are reduced in obese humans and *ob*/*ob* mice, which would be expected to reduce appetite, but there is a problem: the normal reduction in CSF adiponectin levels accompanying refeeding is impaired in obese *ob*/*ob* mice. This implies that in obesity, loss of appetite control occurs on two fronts: leptin insensitivity resulting from upregulation of the suppressor of cytokine signaling 3 (SOCS3) and a reduction in the ability to switch off AMPK signaling and feeding (Steinberg et al., 2006), which is now combined with an inability to suppress CSF adiponectin levels and reduce appetite in response to feeding. The discovery of adiponectin's role in stimulating appetite has led Kubota et al. (2007) to propose a "fat-centric" hypothesis in which the opposing central actions of leptin and adiponectin provide a homeostatic mechanism for maintaining fat levels/energy stores, with the brain acting as a wired "server" under the hormonal control of the fat cell. An important unexplored question with ramifications for the present obesity epidemic is whether obese human adiponectin levels in the CSF behave like those of the mouse and whether strategies for restoring the capacity of refeeding to reduce CSF adiponectin levels in obese individuals can be devised to switch off appetite.

REFERENCES

Andersson, U., Filipsson, K., Abbott, C.R., Woods, A., Smith, K., Bloom, S.R., Carling, D., and Small, C.J. (2004). J. Biol. Chem. *279*, 12005–12008.

Combs, T.P., Berg, A.H., Obici, S., Scherer, P.E., and Rossetti, L. (2001). J. Clin. Invest. *108*, 1875–1881.

Fruebis, J., Tsao, T.S., Javorschi, S., Ebbets-Reed, D., Erickson, M.R., Yen, F.T., Bihain, B.E., and Lodish, H.F. (2001). Proc. Natl. Acad. Sci. USA *98*, 2005–2010.

Hardie, D.G. (2007). Nat. Rev. Mol. Cell Biol., in press.

Hurley, R.L., Anderson, K.A., Franzone, J.M., Kemp, B.E., Means, A.R., and Witters, L.A. (2005). J. Biol. Chem. *280*, 29060–29066.

Kubota, N., Yano, W., Kubota, T., Yamauchi, T., Itoh, S., Kumagai, H., Kozono, H., Takamoto, I., Okamoto, S., Shiuchi, T., et al. (2007). Cell Metab. *6*, this issue, 55–68.

Minokoshi, Y., Alquier, T., Furukawa, N., Kim, Y.B., Lee, A., Xue, B., Mu, J., Foufelle, F., Ferre, P., Birnbaum, M.J., et al. (2004). Nature *428*, 569–574.

Qi, Y., Takahashi, N., Hileman, S.M., Patel, H.R., Berg, A.H., Pajvani, U.B., Scherer, P.E., and Ahima, R.S. (2004). Nat. Med. *10*, 524–529.

Steinberg, G.R., Watt, M.J., Fam, B.C., Proietto, J., Andrikopoulos, S., Allen, A.M., Febbraio, M.A., and Kemp, B.E. (2006). Endocrinology *147*, 3906–3914.

Watt, M.J., Dzamko, N., Thomas, W.G., Rose-John, S., Ernst, M., Carling, D., Kemp, B.E., Febbraio, M.A., and Steinberg, G.R. (2006). Nat. Med. *12*, 541–548.

Xue, B., and Kahn, B.B. (2006). J. Physiol. *574*, 73–83.