Pyruvate and Satiety: Can We Fool the Brain?

In the last few years, our understanding of the physiological systems that regulate food intake and body weight has increased enormously. A growing number of factors and signaling molecules involved in food intake and its hormonal regulation indicate that this behavior is coordinated by highly complex processes (1–4). Orexigenic and satiety systems, although finely balanced, seem more effective in protecting against starvation than overfeeding, thus predisposing us to obesity (5). As the obesity epidemic spreads, concerns are growing about its significant health and economic consequences (6), emphasizing the need for a more complete understanding.

The “Fuel Gauge” for Nutrients

Hypothalamic neurons can directly sense circulating nutrients (7, 8), however, the exact molecular mechanisms by which the sensing neurons recognize energy need and translate it into signals for feeding behavior remain largely unknown. The 5'-AMP-activated protein kinase (AMPK) has been proposed to serve as a fuel sensor in the hypothalamus (9–12), an evolutionarily conserved function that is important even in yeast (13). Activation of AMPK is prompted by an increase in the AMP:ATP ratio or by other upstream kinases (14). Whether AMPK activation is the real fuel gauge must still be ascertained, but many have demonstrated that AMPK activation is correlated to glucose levels (9, 10, 15). In this issue, Lee et al. (16) have used neuroblastoma cell lines to study correlations between glucose levels, AMPK activation, and agouti-related protein (AgRP) expression. AgRP is a well-known, potent stimulator of feeding behavior (2, 3). Degrees of AMPK phosphorylation were linearly and inversely correlated with increasing glucose concentrations at physiological levels. Thus, small modifications in glucose levels can be sensed by neurons to generate hunger or satiety signals. Other research is needed to clarify the exact molecular steps linking glucose to AMPK phosphorylation and AMPK phosphorylation to AgRP synthesis and release.

The Need for a Model

Lee et al. used two neuroblastoma cell lines to directly test the effect of glucose on AgRP expression, avoiding the disadvantages of indirect, confusing effects brought by interactions of cells with other neuronal systems and changes in blood hormones or substrates. In this simplified system, glucoprivic conditions elicited low cellular ATP concentration and increased AMPK phosphorylation, which in turn stimulated AgRP expression (Fig. 1A). Lee et al. also observed that inhibition of glycolysis by 2-deoxy-D-glucose, a nonmetabolizable glucose analog that inhibits glucose utilization, increased AgRP expression in the neuronal cell lines (Fig. 1B). Therefore, they propose that glucose metabolites in the glycolysis pathway may be the effector molecules primarily responsible for regulation of AMPK activation and AgRP expression. Because pyruvate effectively suppressed the increase in AgRP expression induced by 2-deoxy-D-glucose in these cells, the authors suggest that downstream metabolites of the glycolysis pathway beyond pyruvate might be responsible for

Abbreviations: AgRP, Agouti-related protein; AMPK, 5'-AMP-activated protein kinase; CoA, coenzyme A.

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regulation of AgRP expression (Fig. 1B). Moreover, over-expression of a dominant-inhibitory mutant of AMPK significantly decreased low-glucose-induced AgRP expression, thus confirming the role of cerebral AMPK in the central effects of glucose.

Not Just Glucose

Neurons rely mainly on glucose for their energy supply but still retain the ability to respond to changing levels of fatty acids. Central administration of oleic acid inhibits food intake and glucose production (7). Precursors in fatty acid biosynthesis, such as the intermediate product of the synthesis of fatty acids, malonyl-coenzyme A (CoA), have also been proposed as possible mediators of the hypothalamic signaling pathway that monitors energy status. Phosphorylated AMPK activates catabolic pathways that generate ATP, while inhibiting anabolic, ATP-consuming pathways such as those implicated in fatty acid synthesis. Although interesting results implicate malonyl-CoA as a mediator linking the synthesis of hypothalamic fatty acid to the inhibition of food intake, they do not define the signaling mechanism beyond malonyl-CoA in the pathways regulating the expression of hypothalamic orexigenic (neuropeptide Y and AgRP) and anorexigenic (pro-opiomelanocortin) neuropeptides mRNAs (17).

Many studies suggest that modulation of intraneuronal ATP levels triggers a cascade of events via AMPK that modulate feeding behavior to restore energy status of cells (12, 16, 18). Therefore, the common pathway for sensing glucose, fatty acids, and other nutrient levels might be represented by the energy status of the cell. These key findings should provide novel intervention opportunities for manipulation of feeding behavior.

The work by Lee et al. (16) presented in this issue is another brick in support of the general hypothesis that energy status of the nutrient-sensing cells of the brain is the major switch for the control of neuropeptide expression and feeding behavior (19). Detailed understanding of the mechanisms of nutrient sensing could lead to new approaches to prevent or reverse obesity.

Vittorio Locatelli and Antonio Torsello
Department of Experimental and Environmental Medicine and Biotechnology
University of Milano-Bicocca
20052 Monza, Italy

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