

P019 Hypothalamic fuel sensing by 5'-AMP-activated protein kinase (AMPK)

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Within the feeding control centres of the basomedial hypothalamus, glucose-excited (GE) neurons increase, and glucose-inhibited (GI) neurons decrease their activity as glucose concentrations rise. At present, the mechanism(s) by which glucose and other stimuli regulate the activity of either neuronal cell type is unclear. Here, we investigate the roles of the metabolic sensor 5'-AMP-activated protein kinase (AMPK) in the nutrient sensing mechanism of GI neurons, which are generally thought to be Neuropeptide Y (NPY) positive. Examined in cultured hypothalamic neurons, changes in intracellular free Ca^{2+} concentration measured with fluo-3 or an NPY promoter-driven adenovirally-expressed ratiometric pericam revealed that the effects of glucose withdrawal on GI neurons were mimicked by the addition of the pharmacological AMPK activator, 5-amino-imidazole-4-carboxamide riboside (AICAR; $n=9/9$ cells from six preparations). Conversely, addition of the AMPK inhibitor Compound C silenced these GI neurons ($n=3/3$ GI neurons from three preparations), mimicking the effects of the adipocyte hormone, leptin ($n=7/9$ GI neurons from five preparations). Changes in cellular voltage responses under perforated patch clamp were consistent with the effects on intracellular Ca^{2+} . By contrast, activation of GE neurons by glucose was unaffected by manipulation of AMPK activity. These data suggest that changes in AMPK activity regulate the activity of GI neurons through effects on presently unidentified targets.