Cell Metabolism
Previews

# Life Is Short, if Sweet

Jess Porter Abate[1] and T. Keith Blackwell[1,*]
[1]Section on Developmental and Stem Cell Biology, Joslin Diabetes Center, Department of Pathology, Harvard Medical School, Harvard Stem Cell Institute, Boston, MA 02215, USA
*Correspondence: keith.blackwell@joslin.harvard.edu
DOI 10.1016/j.cmet.2009.10.006

**Insulin is essential for glucose homeostasis, but reducing its activity delays the aging process in model organisms. In this issue of *Cell Metabolism*, Lee et al. (2009) show how these effects of insulin signaling intersect when glucose is fed to *C. elegans*.**

Insulin has essential functions as an anabolic hormone and in maintenance of glucose homeostasis. After consumption of food, particularly sugary foods, bloodstream glucose levels rise. This triggers release of insulin, which stimulates glucose uptake (Figure 1) (Shepherd and Kahn, 1999). Under conditions of insulin insufficiency or resistance, circulating glucose levels are elevated, eventually leading to damage in vascular and renal tissues and other diabetic complications. A major cause of this damage is an increase in intracellular reactive oxygen species (ROS) resulting from metabolic perturbations associated with hyperglycemia (Brownlee, 2005).

While insulin is essential for survival, it also seems to play a role in aging. Studies in model organisms have shown that aging can be delayed by *reductions* in signaling from insulin or related factors (insulin-like signaling) (Russell and Kahn, 2007). Specifically, insulin-like signaling inhibits the transcription factor FOXO (DAF-16 in *C. elegans*), which acts to promote stress resistance and healthy longevity (Figure 1). Analyses of knockout mice and long-lived human cohorts support a link between reduced insulin signaling, FOXO, and longevity (Russell and Kahn, 2007; Lee et al., 2009), suggesting that this longer life might be available not only to simple organisms like nematodes, but also to us. The question remains, however: how can the essential functions of insulin be reconciled with the expected benefits of lowering its activity? In this issue of *Cell Metabolism*, Lee et al. (2009) begin to unravel how these insulin functions influence each other. They show that high glucose levels shorten *C. elegans* life span by increasing insulin-like signaling and that glycerol may be an important mediator of glucose metabolism.

As numerous studies have investigated how insulin-like signaling affects longevity, it is reassuring to see compelling evidence that glucose decreases life span by acting on this pathway in the organism where this story originated (Lee et al., 2009). Glucose feeding reduced life span in wild-type animals and essentially negated the longevity benefits associated with either mutations in the insulin receptor DAF-2 or RNA interference (RNAi) against the insulin-like peptide INS-7. While this reduction of *daf-2* mutant life span might seem to suggest a *daf-2*-independent effect of glucose, it must be remembered that the insulin receptor is only partially impaired in these mutants, so that increased insulin activity deriving from elevated glucose would likely be devastating. Glucose also inhibited the propensity of *daf-2* mutants to develop into dauer larvae, a diapause state that allows the animal to withstand adverse conditions. Importantly, glucose did not further reduce the truncated life spans associated with the absence of either DAF-16 or heat shock factor (HSF-1), which cooperates with DAF-16. Finally, glucose increased expression of several insulin-like genes and led to other gene expression changes that overlapped with effects of inhibiting DAF-16.

One of the genes downregulated by both glucose and DAF-16 is *aqp-1*, which encodes an aquaporin glycerol channel (Lee et al., 2009). Lack of *aqp-1* mimicked many effects of glucose, including reduction of wild-type but not *daf-16(−)* life span, downregulation of DAF-16 and HSF-1 targets, upregulation of *ins-7*, and modulation of DAF-16 activity. Glycerol was elevated by glucose feeding and also reduced life span, suggesting that AQP-1 and glycerol may function downstream of glucose in a pathway that affects life span through insulin-like signaling. These provocative results suggest that glycerol might be involved in glucose metabolism in mammals. In mice, aquaporin channels allow movement of glycerol from adipocytes to the liver (both corresponding to the *C. elegans* intestine), and knockout of an adipocyte aquaporin channel is associated with abnormal glycerol metabolism, insulin resistance, and obesity (Maeda et al., 2008).

Other recent studies have also shown that glucose feeding shortens *C. elegans* life span, but suggested involvement of additional mechanisms (Schlotterer et al., 2009; Schulz et al., 2007). Schulz et al. (2007) reported that a glucose mimetic that cannot be metabolized increases life span, an effect attributed to stress-pathway stimulation by ROS arising from increased respiration. ROS are also increased by glucose, however (Schlotterer et al., 2009), indicating that further analysis will be required to understand the possible effects of glucose metabolic pathways on longevity. In the latter study, overexpression of glyoxalase-1 protected against the life span-shortening effects of glucose. This enzyme detoxifies methylglyoxal, a glucose metabolite involved in diabetic complications. This observation should also be explored further, because only one transgenic strain was analyzed, but it suggests that *C. elegans* might be amenable to analysis of glucose toxicity mechanisms that lead to diabetic complications.

While caution should be exercised in extrapolating from simple model organisms to people, the results of Lee et al. (2009) could have profound implications for understanding how insulin affects us. While the "good" effects of insulin are undoubtedly essential, including prevention of

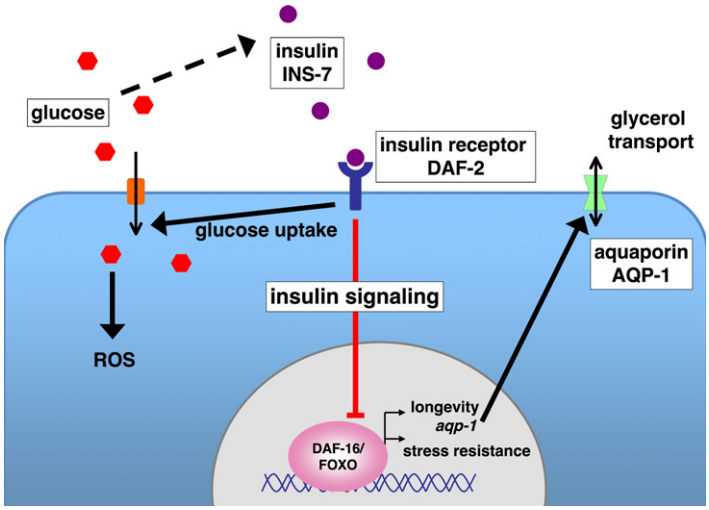


**Figure 1. Effects of Glucose on Insulin-like Signaling and Longevity**
Glucose stimulates release of insulin, which induces glucose uptake. Insulin-like signaling also inhibits FOXO/DAF-16, which positively regulates *aqp-1* and other stress resistance and longevity genes. High glucose levels may increase cellular ROS. In *C. elegans*, these events all appear to occur in the intestine, although insulin-like signaling responses vary among tissues.

hyperglycemia and resultant tissue damage, it seems that one might want to get by with needing as little insulin as possible, in order to minimize its inhibition of the life span-extending effects identified in animal models. The present study may also have implications for understanding effects of calorie restriction, a condition that prolongs life in essentially every organism examined (Bishop and Guarente, 2007). By identifying a specific life span-inhibitory effect of glucose, its results raise the question of whether the effects of limiting calories and glucose might be distinguishable. Evidently, we can't have our cake and eat it too just yet, but hope remains that a better understanding of how low insulin activity increases life span could allow these prolongevity mechanisms to be harnessed without impairing the essential activities of insulin. In the meantime, this work provides additional motivation to skip dessert.

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# A Tale of Two Carboxypeptidases

**Malcolm J. Low**[1,*]
[1]Departments of Molecular & Integrative Physiology and Internal Medicine, Brehm Center for Type 1 Diabetes Research & Analysis, University of Michigan, Ann Arbor, MI 48109-5622, USA
*Correspondence: mjlow@umich.edu
DOI 10.1016/j.cmet.2009.10.005

**Proopiomelanocortin (Pomc) neurons play a central role in energy homeostasis. Despite the complexity of Pomc posttranslational processing, regulation of *Pomc* gene expression often takes center stage. Complementary papers that zero in on distinct carboxypeptidases (Plum et al., 2009; Wallingford et al., 2009) now refocus the spotlight on regulated peptide cleavage.**

Hypothalamic proopiomelanocortin (Pomc) neuronal circuits play a critical role in tightly matching body weight to a fixed set point, primarily by inhibiting appetite and feeding behavior (Cone, 2005). Multiple regulatory steps in Pomc biosynthesis ultimately determine Pomc-derived peptide tone in the CNS in response to hormonal, metabolic, and *trans*-synaptic inputs to Pomc neurons (Figure 1). Indeed, Pomc has served as a paradigm for investigating posttranslational processing of prohormones into multiple bioactive peptides (Pritchard and White, 2007). Among the well-characterized enzymes are the prohormone convertases subtilisin/kexin type PC1 and PC2, carboxypeptidase E (Cpe), and peptidylglycine α-amidating monooxygenase (PAM). Spontaneous loss-of-function mutations in *PCSK1* or *Cpe* cause obesity in humans