Food for Thought: Linking Caloric Intake to Behavior via Sirtuin Activity

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Sirtuins are thought to form crucial links between energy levels and cellular metabolism. Libert et al. now provide evidence that SIRT1 activity in the brain modifies mammalian emotional behavior via monoamine signaling and that changes in this pathway might contribute to human affective disorders

Charles Darwin intended to include a chapter on emotions, their function, and their evolution in his book *The Descent of Man*, but in the end he found the subject so rich and so important that *The Expression of the Emotions in Man and Animals* became an entire book. Ever since, science has been trying to unravel the adaptive significance of behavioral states and emotions, what neural substrates underlie them, and how they go awry in human psychiatric conditions.

In this issue of *Cell*, Libert et al. (2011) tackle all three of these questions in proposing that the metabolically regulated enzyme sirtuin 1 (SIRT1) modulates monoamine oxidase A (MAO-A) levels to link mood and behavior to energy consumption. Moreover, they provide evidence that variability in the *SIRT1* gene contributes to human susceptibility to anxiety disorders.

MAO-A is the brain's primary means of degrading serotonin and noradrenaline and has been a focus of mood disorder research ever since the serendipitous 1952 discovery that inhibiting it has antidepressant effects. MAO inhibitors were the first widely used and effective pharmacotherapy for depression and some anxiety disorders.

Currently there is much excitement about drugs that modulate sirtuins. Research on these enzymes has grown explosively, and often controversially, over the last decade since they were found to mediate, at least in part, the longevity-enhancing effects of caloric restriction in budding yeast. As sirtuin homologs are conserved from bacteria to mammals, and caloric restriction extends life span in higher animals, there is considerable interest in the possibility that sirtuin activation might thwart numerous diseases and prolong human life.

The overarching hypothesis of sirtuin function is that their activity matches cellular physiology to energy availability (Guarente, 2000; Cantó and Auwerx, 2009). Sirtuins are primarily NAD^+-dependent deacetylases, although among the seven mammalian isoforms, some have ADP-ribosyl transferase activity. Much work in yeast focuses on histone deacetylation, but a diverse range of sirtuin substrates has now been identified (Michan and Sinclair, 2007). Sirtuin activity is typically inversely related to caloric intake, and it is thought that this is due to metabolically induced variation in NAD^+:NADH ratios, although caloric restriction often also increases sirtuin expression levels. Given that in animals, behavior is central to adapting to environmental resource levels, the idea that sirtuins might impact neural function is attractive.

Libert et al. tested two strains of mice in assays that measure aspects of affective behavior. Mice lacking SIRT1 expression in the brain spent more time exploring an open space, indicative of lower anxiety levels; struggled more in the forced swim test, suggesting greater stress resilience; and appeared protected against the anhedonic effects of social defeat. Conversely, mice globally overexpressing SIRT1 had higher anxiety scores than controls. In these mice, chronic treatment with an MAO inhibitor, which reduces anxiety, normalized behavioral scores across genotypes.

When the authors tested whole brain monoamine levels, they found that anxiety scores were negatively correlated with changes in serotonin and noradrenaline levels. How SIRT1 affects these neuromodulators was revealed through elegant and systematic in vivo and in vitro experimentation, which showed that SIRT1 deacetylates the transcription factor NHLH2 to control MAO-A expression.

The study concludes with tests of the psychiatric relevance of this pathway and a model for its evolution. *SIRT1* polymorphism frequencies were measured across control and psychiatric patient populations, and both rare and common alleles were associated with anxiety-related disorders, consistent with a previous linkage with depression (see Libert et al., 2011, references therein). In vitro assays of two variant alleles showed them to have increased SIRT1 activity.

The evolutionary considerations are more speculative; a dynamic model of a three-tier food chain predicts that the middle species will experience greatest predation when food is scarcest. Finding that calorie-restricted mice show a moderate decrease in exploratory behavior, the authors suggest that SIRT1 signaling adaptively controls behavior so that hungry, heavily preyed-on animals would be best served by being anxious, vigilant,

and careful, whereas well-fed mice should carelessly radiate and procreate.

At the end of this paper, you feel the need for a deep breath, so wide-ranging and provocative are its contents. Its predictions are so specific and testable and the questions it raises so interesting and numerous that it will be a touchstone for the certain expansion of neurobiological studies of sirtuin function (Figure 1). These enzymes have already been implicated in synaptic plasticity and cognition (Gao et al., 2010), hypothalamic control of energy intake (Satoh et al., 2010), and responses to cocaine (Renthal et al., 2009).

Among the most important questions raised by the current study is whether regulation of MAO-A levels is the sole route by which SIRT1 impacts brain function. The normalization of behavioral scores by MAO inhibitors is supportive but by no means conclusive, and the relationship between monoamine levels and behavior is complex. For example, depleting serotonin levels in healthy humans does not evoke mood changes. Given the multitude of SIRT1 substrates now identified, it will be essential to test whether other signaling pathways are involved and whether altered synaptic plasticity contributes to behavioral changes (Michan and Sinclair, 2007; Gao et al., 2010).

At the systems level, SIRT1 is found at moderate levels throughout the brain, and determining through which structures it acts to modulate which aspects of behavior, and if it always operates via the same pathways, will be fascinating. Conversely, elucidating whether factors other than caloric intake, such as neuronal activity or neuromodulatory signaling cascades, regulate sirtuin activity will be crucial. And does SIRT1 act distinctly at different developmental stages? Interestingly, NHLH2 is most abundant in the embryonic brain.

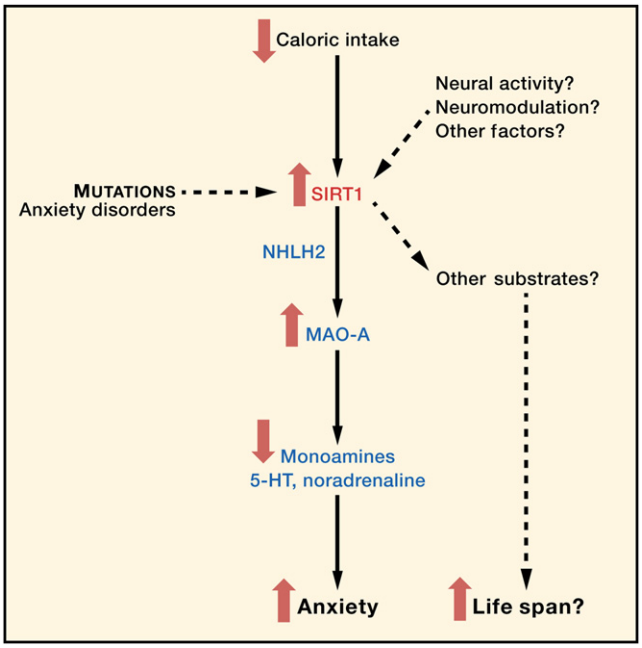

Figure 1. A Pathway for Linking Caloric Intake to Anxiety Levels
Decreased calorie consumption increases SIRT1 levels and activity, which leads to greater NHLH2 deacetylation and increased MAO-A expression. Elevated MAO-A levels decrease serotonin (5-HT) and noradrenaline concentrations in the brain and promote anxious behavior. The other factors that control SIRT1 activity and how the modification of other SIRT1 substrates affect behavior, and possibly life span, remain to be determined.

Tying anxiety levels conclusively to caloric intake will also take more work, and the decreased exploratory drive of calorie-restricted mice needs to be linked directly to sirtuin signaling. In terms of human relevance, one wonders whether the growing number of people adopting calorie-restricted diets might allow further testing of these hypotheses. The evolutionary model is appealing, but the dynamics of behavioral responses to food deprivation are complex (Wang et al., 2006); vigilance and fearfulness must be balanced with action and opportunity taking. Whether a straightforward relationship between food availability and anxiety is optimal remains to be confirmed.

Finally, the authors emphasize that their findings make SIRT1 inhibitors excellent candidate anxiolytic drugs. This idea is certainly testable, and we look forward to seeing the results. However, given that *activating* sirtuins has been suggested for treating or preventing aging, diabetes, cardiovascular disease, some forms of cancer, and Alzheimer's disease, not to mention sirtuins' proposed role in learning, the pharmacology is likely to be challenging (Kaeberlein, 2008). MAO inhibitors fell out of favor not because they lacked clinical efficacy but because of side effects and safety issues.

Sirtuin research in the central nervous system is certain to grow rapidly in the coming years. Given the brain's complexity and the current controversies in the sirtuin field—including whether NAD^+:NADH balance is the principal controller of activity (Cantó and Auwerx, 2009) and whether the life-extending effects of sirtuin homologs previously observed in nematodes and fruit flies were due to genetic background effects (Burnett et al., 2011)—it's sure to be an engrossing time. One can bet that this work will be but one chapter in a very long book.

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