!SPECTIVENEUROENDOCRINOLOGY

Linking smell to metabolism and aging

The olfactory system can have direct effects on energy homeostasis

JENNIFER L. GARRISON AND ZACHARY A. KNIGHT Authors Info & Affiliations

ENCE10 Nov 2017Vol 358, Issue 6364pp. 718-719DOI: 10.1126/science.aao5474

The sense of smell, or olfaction, allows animals to survey the chemical landscape of the outside world and use this information to guide behavior. Olfactory cues are particularly important for the regulation of feeding, but how odor perception influences other aspects of energy homeostasis remains poorly understood. Recent work has begun to uncover some of these connections, revealing an unexpected role for olfaction in the control of metabolism and longevity.

The idea that olfaction and metabolism could be connected goes back at least to the work of Ivan Pavlov, who showed that odors and other sensory cues associated with food could trigger hormonal and autonomic responses in anticipation of a meal (*1*). These "cephalic phase" responses, such as salivation and secretion of gastric acid, are thought to help prepare the body to accommodate the rapid influx of nutrients that occurs during eating. But how chronic changes in odor exposure affect metabolism has been less clear.

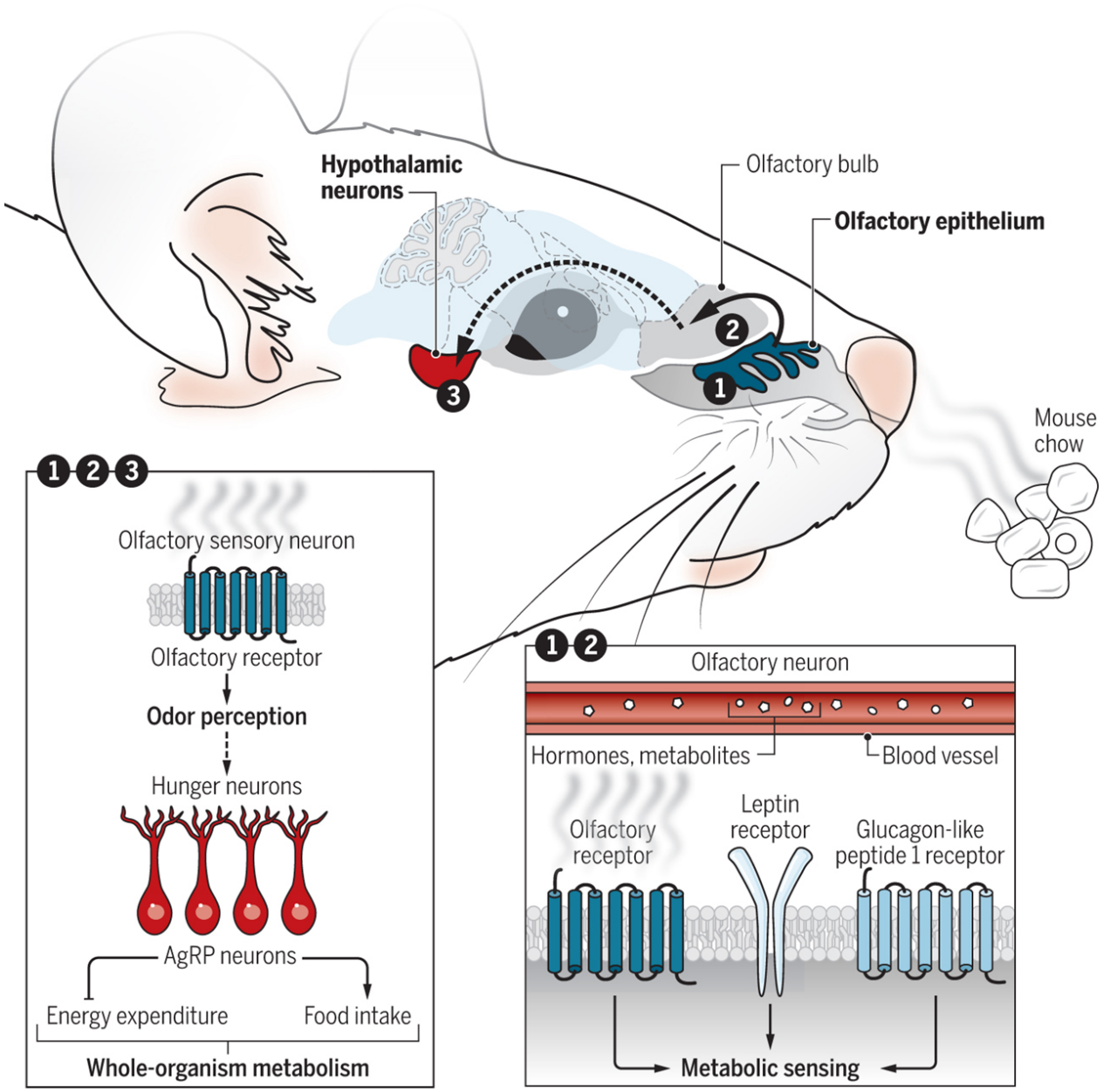
To address this question, a recent study manipulated the olfactory system in the mouse and measured the effect on energy homeostasis (*2*). By ablating olfactory sensory neurons in adult mice, they generated mice that had a reduced ability to smell. These hyposmic mice exhibited normal food intake and body weight on a regular diet, but were resistant to obesity caused by a high-fat diet. This leanness was due to both reduced food intake and, surprisingly, increased energy expenditure. Mechanistic studies revealed that this enhanced energy expenditure was caused by an increase in the

activity of brown adipose tissue, a specialized thermogenic organ that functions to dissipate heat in mammals.

To test this idea further, the authors used complementary manipulations to generate mice with enhanced smelling ability. These mice exhibited increased body weight in the absence of any change in food intake (*2*). Together, these observations reveal that the olfactory system can regulate body weight via direct effects on energy expenditure, rather than solely through changes in food intake as has traditionally been assumed. Other recent studies have also suggested connections between olfaction and metabolism, although the exact relationship remains unclear (*3*, *4*).

What are the implications of these findings? It is well established that metabolism is a critical determinant of not only body weight, but also aging. Thus, we might predict that loss of smell could influence life span, and this has indeed been demonstrated in invertebrates: Disrupting olfactory neuron function, either through mutation or laser ablation, extends life span in both worms and flies (*5*, *6*). In these simpler organisms, the smell of food decreases life span, but only when the animals are calorie restricted (*7*). These data support the idea that olfactory perception may alter how an organism uses energy, and suggest the intriguing possibility that modulating smell could be a viable strategy for anti-aging interventions.

The mechanisms by which the olfactory system influences metabolism are unknown, but one possibility is suggested by the recent discovery that food odors can regulate "hunger neurons" in the hypothalamus (*8*–*10*). These cells, known as agouti-related protein (AgRP) neurons, are activated by food deprivation, and their activity powerfully influences food intake, energy expenditure, and peripheral metabolism. Traditionally, AgRP neurons were thought to be regulated exclusively by nutrients and hormones that circulate in the blood, but it is now appreciated that these cells also respond rapidly to sensory cues associated with food. Indeed, the smell of food alone can inhibit the AgRP neurons of a hungry mouse within seconds (*8*–*10*). How chronic disruption of this olfactory input would affect physiology has not been tested, but it is possible that such manipulations could dysregulate AgRP neurons and cause long-term metabolic changes.



Connecting olfaction to metabolismDetection of food odors by sensory neurons in the olfactory epithelium is rapidly communicated to hypothalamic neurons that control hunger, thereby modulating whole-organism metabolism. Neurons in the olfactory epithelium and bulb can also monitor hormones and nutrients in the blood, which may enable the olfactory system to regulate energy balance independently of odor perception. GRAPHIC: A. KITTERMAN/*SCIENCE*

An alternative hypothesis is that the olfactory system has direct effects on energy metabolism independent of its function in odor detection. It has long been noted that olfactory structures express an unusually high density of receptors for metabolic hormones, such as insulin, leptin, and ghrelin, and further that the olfactory bulb has enhanced access to the circulation resulting from an incomplete blood-brain barrier (*11*). Although these observations are often cited to explain the fact that food deprivation can increase olfactory sensitivity, it is also possible that the presence of these metabolic receptors signals a broader function for olfactory tissues in energy homeostasis.

In this regard, recent studies have identified several olfactory receptors in mice that "moonlight" as metabolic sensors in the periphery. These include OLFR558, which senses isovalerate in the intestine (*12*), and OLFR78, which senses lactate in the carotid body (*13*). It is conceivable that evolution could have co-opted the olfactory system, with its extraordinary ability to detect complex patterns of chemosensory signals in the form of odorants, to monitor internal nutrients in a similar way (see the figure).

These speculations aside, a number of basic questions about the mechanisms underlying the connection between olfaction and metabolism remain to be addressed. For example, it is unclear whether the metabolic responses to manipulations of the olfactory system (*2*, *3*) are due to specific changes in the sensing of food odors, and, if so, which food odors are involved. It is likewise unknown how detection of food odors is communicated from the olfactory bulb to the hypothalamic circuits that regulate energy balance, and what specific information these signals convey (e.g., nutrient content, toxicity, availability). In this regard, odor information received in the olfactory bulb is transmitted along two anatomically distinct pathways: One mediates learned responses to odors (via the piriform cortex) and the other controls innate behaviors (via the cortical amygdala). The relative contribution of these two pathways to the modulation of hypothalamic circuits by the smell of food has not been tested, but a role for the innate pathway would suggest that certain food odors are evolutionarily hardwired to elicit physiologic responses. If so, it would be fascinating to know why these odorants have been selected by evolution to act as metabolic signals.

A final question regards the extent to which these observations in rodents and invertebrates apply to human biology. Compared to mice, humans express fewer functional odorant receptor genes (1100 in mice versus 390 in humans) and have a proportionally smaller olfactory bulb. Humans also lack a functional vomeronasal organ, an accessory olfactory structure used by many animals to detect pheromones (*14*). It has been speculated that these changes were driven in part by the evolution of color vision in primates, which may have enabled the visual system to co-opt functions previously performed by olfaction. In this context, is it plausible that olfactory responses in mice would be conserved in humans? Although it is true that humans rely less on smell than many animals, the commonly held view that human olfaction is feeble or in some sense vestigial is based more on folklore than scientific evidence (*14*). Indeed, smell plays a critical role in the perception of food flavor in humans, and decreased enjoyment of food is a common disturbance in people suffering from olfactory deficits (*15*). Whether such individuals also experience metabolic impairments independent of changes in food intake is unknown, but recent work in rodents suggests this question is worth investigating.

Acknowledgments

Our work is supported by grants from the American Federation for Aging Research to J.L.G.; the New York Stem Cell Foundation, Rita Allen Foundation, and American Diabetes Association to Z.A.K.; and the U.S. National Institutes of Health to J.L.G. (R35GM11982) and Z.A.K. (DP2DK10953, R01NS094781, R01DK106399). We thank J. Carlson for discussions.