

The brain is getting ready for dinner

Previews

Every evening, as we get ready for dinner, in addition to the routine behaviors of preparing the meal itself, we also prepare our bodies to cope with the upcoming meal. This could take the form of making restaurant reservations, changing into appropriate attire, washing hands, priming ourselves with an aperitif, or even consciously avoiding snacks as the meal approaches. A study by Johnstone and colleagues in this issue of *Cell Metabolism* (Johnstone et al., 2006) provides evidence that in parallel to our learned preparatory behaviors, our central nervous system is going through comparable motions as it gets ready for the anticipated meal.

Intense research efforts over the last decade have resulted in a generally accepted molecular model of food intake regulation. According to this model, CNS networks regulating energy balance and body weight are located in brain regions that constantly receive and respond to afferent information about peripheral metabolic status. Communication is principally based on CNS synaptic organization and neurotransmitter secretion and is potently modulated by a diverse, interconnected network of neuropeptides and their receptors (Horvath and Diano, 2004).

Numerous studies have considered how enhancement or blockade of specific neuronal signaling pathways influences food intake, or how dietary changes and pharmacological tools affect neuronal activation and neuropeptide expression. Johnstone and colleagues (Johnstone et al., 2006) chose a different approach, asking whether specific neuronal populations thought to control food intake are activated in association with natural meals. Using a rat model they determined whether the CNS is “trained” to be ready for caloric ingestion at the time of an expected meal. Rats were put on a schedule where they had to consume all of their food during a specific 2 hr time period each day. The researchers then quantified and characterized distinct neuronal populations that were activated at meal time, using expression of *c-fos*, a so-called “early gene,” as a marker of neuronal activation. Most CNS hypothalamic nuclei thought to be involved in the regulation of hunger or satiety had increased *c-fos* expression at specific time points during the anticipated meal, suggesting raised levels of activity in those specific neurons. In contrast, only minimal activity was observed at time points immediately prior to the start of the meal in the same brain areas. An obvious conclusion was that those neuronal populations become

activated only as a direct reaction to ingested calories, increased levels of circulating macronutrients, and/or associated changes in afferent endocrine and neural signaling from the gastrointestinal tract. The possibly most intriguing finding of Johnstone and colleagues regards control rats that were identically meal trained but did not receive a meal at the expected time on the day of analysis. These rats had elevated *c-fos* expression at the same time as fed rats and in many of the same neuronal populations that were activated in the fed groups, including the hypothalamic arcuate nucleus, the lateral hypothalamus, the parvocellular paraventricular nucleus, and the ventromedial hypothalamus, all areas known to be involved in food intake regulation. More detailed characterization of specific neurons activated by meal training revealed an involvement of circuitry utilizing α -melanocyte-stimulating hormone.

A key finding from the Johnstone et al. report is that specific neuronal populations presumably governing functional systems related to eating become “switched on” in the CNS when a meal is expected. However, any conclusions must be regarded as quite preliminary since the feeding regimen, while certainly allowing the rats to anticipate the arrival of food, also involves a high level of caloric deprivation. Perhaps the observed activation in hypothalamic centers reflects the physiological neuroendocrine adaptation to an empty stomach about to receive a large meal. It is noteworthy that no neuronal activation was observed prior to the anticipated meal since many hypothalamic peptides involved in feeding are known to have altered expression as a result of deprivation and/or meal anticipation. As an example, food-deprived rats have elevated hypothalamic NPY, AgRP, and MCH mRNA as well as decreased hypothalamic POMC mRNA (Hillebrand et al., 2002), and hypothalamic NPY levels and expression be-

come elevated prior to the time of food presentation in meal-fed rats (Yoshihara et al., 1996). Further, cephalic insulin, ghrelin, and many other hormones are increased in the blood of meal-fed animals prior to meal time, and these are presumably driven by neuronal circuits that are active at that time (see reviews in Strubbe and Woods, 2004; Figure 1). These ubiquitous observations are not easily reconciled with the lack of change of *c-fos* observed prior to the scheduled meal in the Johnstone et al. report but are consistent with other reports that *c-fos* changes in several hypothalamic nuclei when meal-fed rats anticipate food (e.g., Angeles-Castellanos et al., 2004).

The observation that *c-fos* activation in distinct hypothalamic nuclei occurs independently from actual food intake might have a number of interesting implications. For example, because many of the same neuronal networks are involved in the control of peripheral glucose homeostasis and substrate choice, it may be that the meal-associated neuronal activity prepares peripheral organs to optimally metabolize and store expected incoming nutrients in a 22 hr fasted animal. Alternatively, the within-meal-time *c-fos* activation observed might reflect some aspect of the control over satiation, either to allow an excessive caloric load to be consumed in a short window of time or else to prevent the intake of too many calories at once (Woods, 1991). Another possibility is that the obligatory and simultaneous recruitment of neuronal pattern generators controlling ingestion with circuits controlling all aspects of gastrointestinal functioning necessitates the widespread activation of *c-fos* that was observed. Perhaps water-restricted animals anticipating a short window of water availability would have an analogous activation of *c-fos* in central regulatory areas. Finally, of course, assessing *c-fos* provides limited insight regarding functional

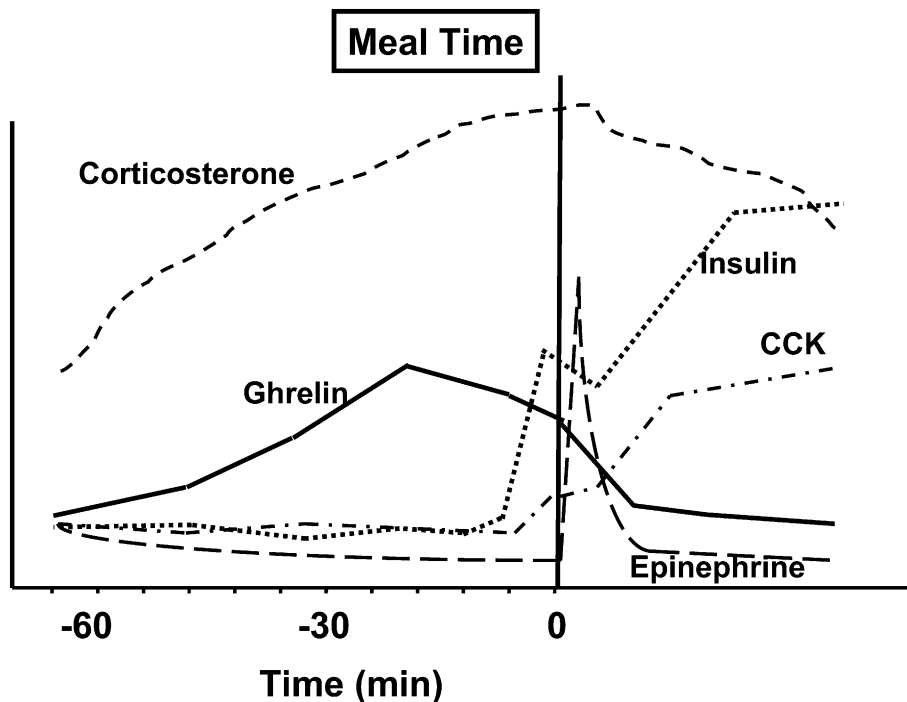


Figure 1. Time courses of several hormones relative to the start of anticipated meals

Several circulating factors have been identified as afferent signals into the CNS network that controls food intake and other aspects of energy regulation (Strader and Woods, 2005; Horvath and Diano, 2004). For example, based on its orexigenic properties and increased secretion before anticipated meals, the stomach hormone ghrelin has been proposed to play a role in meal initiation or meal preparation (Cummings et al., 2001; Drazen et al., 2006). Other gut peptides such as cholecystokinin and glucagon-like peptide 1 are thought to contribute to meal termination and satiety (Strader and Woods, 2005). However, an integrated, temporally resolved picture of how and by which precise signaling pathways the brain controls the timing of meals remains incomplete. Data in the figure are approximated from several sources (e.g., Strubbe and Woods, 2004).

relevance of neuronal “activity,” and the absence of *c-fos* expression does not by any means exclude enhanced neuronal activity.

While open questions regarding the findings of Johnstone et al. remain, studies in humans indicate that some specific brain areas are activated by hunger (Tataranni et al., 1999). Further, the elegant work of Rolls and colleagues using simultaneous electrophysiological recording from several sites within CNS circuits controlling food ingestion indicates that distinct brain areas do in fact respond

to the anticipation and the ingestion of food (Rolls, 1997); and other novel techniques for observing simultaneous intracellular changes in neuronal circuits involving feeding are being explored (e.g., Watts et al., 2006). Nevertheless, the functional neuroanatomy studies by Johnstone et al. represent a potentially important approach to help unravel the frontiers of an important research area, revealing another intriguing link between the psychology of food intake and the molecular regulation of hunger and satiety. The next meal is not far, and we bet-

ter start getting ready. According to Johnstone et al., so will our brain.

**Matthias H. Tschöp,¹
Tamara R. Castañeda,¹
and Stephen C. Woods¹**

¹Department of Psychiatry
Obesity Research Center—Genome
Research Institute
University of Cincinnati
College of Medicine
Cincinnati, Ohio 45237

Selected reading

Angeles-Castellanos, M., Aguilar-Roblero, R., and Escobar, C. (2004). *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 286, R158–R165.

Cummings, D.E., Purnell, J.Q., Frayo, R.S., Schmidova, K., Wisse, B.E., and Weigle, D.S. (2001). *Diabetes* 50, 1714–1719.

Drazen, D.L., Vahl, T.P., D’Alessio, D.A., Seeley, R.J., and Woods, S.C. (2006). *Endocrinology* 147, 23–30.

Horvath, T.L., and Diano, S. (2004). *Nat. Rev. Neurosci.* 5, 662–667.

Johnstone, L.E., Fong, T.M., and Leng, G. (2006). *Cell Metab.* 4, this issue, 313–321.

Rolls, E.T. (1997). *Crit. Rev. Neurobiol.* 11, 263–287.

Strader, A.D., and Woods, S.C. (2005). *Gastroenterology* 128, 175–191.

Strubbe, J.H., and Woods, S.C. (2004). *Psychol. Rev.* 111, 128–141.

Tataranni, P.A., Gautier, J.F., Chen, K., Uecker, A., Bandy, D., Salbe, A.D., Pratley, R.E., Lawson, M., Reiman, E.M., and Ravussin, E. (1999). *Proc. Natl. Acad. Sci. USA* 96, 4569–4574.

Watts, A.G., Khan, A.M., Sanchez-Watts, G., Salter, D., and Neuner, C.M. (2006). *Physiol. Behav.*, in press.

Hillebrand, J.J., de Wied, D., and Adan, R.A. (2002). *Peptides* 23, 2283–2306.

Yoshihara, T., Honma, S., and Honma, K. (1996). *Am. J. Physiol.* 270, E589–E595.

Woods, S.C. (1991). *Psychol. Rev.* 98, 488–505.

DOI 10.1016/j.cmet.2006.09.001