

the crosspoint architecture will yield the most economical solid-state memory. However, this naïve analysis overlooks the difficulty of making electrical contact at the ends of the densely packed row and column electrodes, as well as the complexity of the additional circuitry (drivers and multiplexers) required to write and read each bit. Roughly half the area of a DRAM chip—and therefore half of the cost—is devoted to such supporting circuitry.

Of course, one may lower the cost by giving up performance—for example, by addressing larger arrays with fewer drivers: A smaller proportion of data is accessed in parallel, and the overall data rate is reduced. However, this approach immediately reveals a new limitation: Crosspoint arrays cannot be made arbitrarily large because of the multitude of indirect electrical paths to each element. Here one may learn a lesson from flat-panel display design, where it is well known that “writing” an image on a passive-matrix screen requires that each pixel exhibit threshold behavior

in current versus voltage. The simplest way to obtain a suitable threshold is with a diode that provides a high degree of rectification between forward and reverse voltages. The rectification ratio provides a means of estimating the maximum number of rows and columns that can be reliably addressed. For example, if the ratio were 1000, then the array could have 1000×1000 cells, or 1 million bits (slightly more than 100 kilobytes) capacity. If a proposed new memory device is not inherently nonlinear, it will be necessary to add a diode at each crosspoint, increasing complexity and cost.

From the perspective of cost and performance, the phenomena described in the cited papers are generally not well enough characterized to deserve the label of “a promising new memory technology.” The mere demonstration of bistability is not sufficient. Few of the devices described exhibit rectification. Many are inherently far too slow or consume too much energy to switch. Cycling stability and data retention

times are rarely reported. Truly useful memory elements must satisfy the most demanding of these criteria. Only by being more self-critical and aware of the highly competitive technological and economic environment will the research community advance the quest for the elusive immortal memory.

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NEUROSCIENCE

The Fat-Brain Axis Enters a New Dimension

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The dawn of 2004 marks the end of the first decade of leptin (1). The discovery of the hormone leptin, which is produced by fat cells (adipocytes) and suppresses appetite, dramatically accelerated the pace of research on obesity, the neurobiology of feeding, and diabetes. The ensuing research produced a preliminary roadmap of the central nervous system (CNS) circuitry through which key metabolic signals like leptin exert their effects (2–4). Remarkably, new actions for this hormone continue to be identified. Two papers in this issue, by Pinto *et al.* on page 110 (5) and Bouret *et al.* on page 108 (6), extend substantially the breadth of leptin’s neurobiological actions within the CNS. The two reports suggest that leptin is a crucial regulator of both synaptic plasticity and axon guidance within the hypothalamus. Although much remains to be learned, these studies reveal fresh links between nutrition and neurodevelopment mediated by this adipocyte-derived hormone, with potentially important

implications for the physiology of energy balance and body weight homeostasis.

Pinto and colleagues (5) assessed the acute effects of leptin on synaptic plasticity in the arcuate nucleus of the hypothalamus. The arcuate nucleus is one of the key targets of circulating hormones such as leptin. At least two distinct populations of neurons with opposing actions on food intake reside in the arcuate nucleus (see the figure). The first population produces the “orexigenic” (appetite-stimulating) neuropeptides NPY and AgRP (neuropeptide Y and agouti-related protein). The second population produces the “anorexigenic” (appetite-suppressing) neuropeptides POMC and CART (proopiomelanocortin and cocaine- and amphetamine-regulated transcript). Both populations of neurons express leptin receptors, and are regulated by leptin in opposite ways. Leptin activates the POMC/CART neurons directly but blocks the activity of the NPY/AgRP neurons (2–4). To add to the complexity, NPY/AgRP neurons produce the inhibitory neurotransmitter GABA and send collateral inputs to the POMC/CART neurons that may chronically inhibit these neurons (7).

Pinto *et al.* add to the complexity of this system by reporting that in a leptin-deficient

state, the excitatory and inhibitory synaptic inputs to the POMC and NPY neurons are markedly altered. Using leptin-deficient (ob/ob) mice expressing variants of green fluorescent protein in POMC and NPY neurons, they assessed the electrophysiological properties of both cell groups. They found that a leptin deficiency in the ob/ob mice caused an increase in the excitatory inputs (EPSCs) to the orexigenic NPY/AgRP neurons and a parallel increase in the inhibitory inputs to the anorexigenic POMC/CART neurons. These changes in electrophysiological activity were accompanied by altered numbers of excitatory and inhibitory synapses observed at the ultrastructural level. Thus, lack of leptin increased excitatory inputs (presumably glutamatergic synapses) on NPY/AgRP neurons and decreased excitatory synaptic inputs to POMC neurons. Importantly, leptin repletion in ob/ob mice reversed these effects, both at the electrophysiological and ultrastructural levels. This reversal was very rapid, occurring within hours of leptin administration. Thus, these studies suggest that, in addition to regulating neuronal activity and neuropeptide release and expression, leptin also affects neuronal plasticity in the hypothalamic neurons that are critical to the regulation of body weight homeostasis. The results suggest that the mechanisms underlying leptin’s neurobiological role in the CNS are similar to those that link learning and memory to the phenomenon of long-term potentiation in the hippocampus (8). This type of synaptic plasticity might underlie, at least in part, “hypothalamic memory” and the concept of a

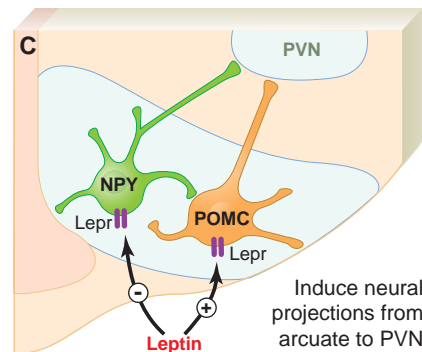
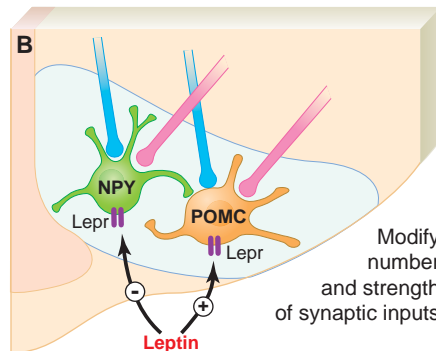
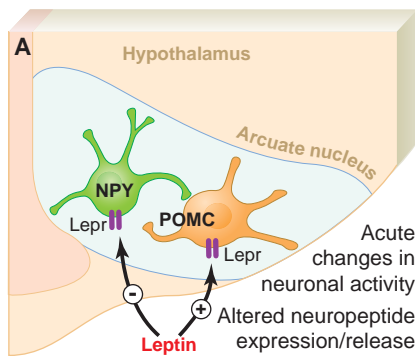
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body weight “set point,” until now a nebulous concept in search of a mechanism. Future studies will need to determine the source of the synaptic inputs to these arcuate neurons, the mechanisms by which leptin signaling brings these changes about, and whether synaptic plasticity in the arcuate nucleus underlies a particular, unique dimension of the physiology of energy balance.

In a complementary study, Bouret *et al.* (6) describe another unanticipated regulatory role for leptin: that of a neurotrophic growth factor during development of the hypothalamus. Specifically, leptin is required for the normal innervation of targets—particularly the paraventricular nucleus of the hypothalamus—by the arcuate POMC and NPY/AgRP neurons. Using an elegant *in vitro* tracing method, they assessed the timing and density of the innervation of several areas downstream of leptin signaling. The density of innervation of the paraventricular nucleus, dorsomedial hypothalamic nucleus, and the lateral hypothalamic areas was severely reduced in leptin-deficient mice. Each of these areas is crucial for regulating food intake and body weight (2–4). Surprisingly, leptin replacement in adult animals was largely ineffective in reversing these aberrant innervation patterns. In contrast, leptin replacement in the perinatal period, at a time when a surge of leptin in the blood of rodents has been established (9), completely restored the density of innervation to that found in wild-type mice. Leptin also increased the extension of neurites in arcuate nucleus explants (organotypic cultures), suggesting that the effects of leptin are due at least in part to direct actions on these arcuate nucleus neurons. This “neurotrophic” role for leptin is consistent with earlier observations that leptin deficiency reduces brain size and slows CNS development in rodents (10). Moreover, the findings suggest a critical period during which leptin can, with increased potency, regulate the development of these projections. Such a finding is reminiscent of a sex steroid surge that induces sexually dimorphic forebrain development (11).

Like most new and exciting observations, the current studies prompt many questions. Although both studies focused on leptin, the observation that ghrelin (a natural appetite-stimulant) also alters synaptic inputs to POMC and NPY neurons, but in a direction opposite to that of leptin, suggests that such regulation may be inherent to the function of this system. Another unanswered question is whether the effects observed in these studies are unique to the arcuate nucleus. Bouret and



colleagues did assess the effects of leptin on the projections of the dorsomedial nucleus to the paraventricular nucleus and in another hypothalamic circuit. However, previous observations that leptin deficiency affects more global measures of brain development (10) suggest that leptin deficiency has more widespread effects in the CNS, at least in rodents. Finally, it is clear that adult *ob/ob* mice do respond to leptin by decreasing food intake and body weight (12). Moreover, the Pinto *et al.* study demonstrates that at least in the case of the arcuate nucleus, adult *ob/ob* mice do respond to leptin replacement. How do these facts relate to the Bouret *et al.* finding that the observed effects of leptin on arcuate projections are largely limited to the neonatal period?

Whatever the answers to these questions, it is intriguing to speculate about the potential physiological and disease relevance of the new findings in light of recent evidence indicating that perinatal and *in utero* nutrition have long-term effects into adulthood (13). The observations of Bouret *et al.* are consistent with the concept that under- and overnutrition during critical periods of hypothalamic development may induce long-lasting and potentially irreversible effects into adulthood. Like the study of Pinto *et al.*,

Leptin and neurodevelopment. Leptin acts on the neurocircuitry of the hypothalamus in three ways. (A) Leptin acts directly on the neurons of the arcuate nucleus by binding to the leptin receptors (Lepr) that they express. The altered activity of these neurons in response to leptin results in changes in their production and release of the neuropeptide NPY and the POMC product, α -melanocyte stimulating hormone. (B) By acting on an unknown site, leptin produces rapid changes in the strength and number of excitatory and inhibitory synapses that have inputs on NPY and POMC arcuate neurons. (C) Leptin induces neurite outgrowth of arcuate neurons, stimulating projections from the arcuate to the paraventricular nucleus (PVN) of the hypothalamus during a critical postnatal period.

these observations may also help to provide a neuroanatomical and functional framework for a hypothalamic body weight set point. This type of hypothalamic programming (imprinting) may be analogous to that seen in studies of the stress (hypothalamic-pituitary-adrenal) axis in which perinatal stress has long-lasting effects (14). Moreover, both mechanisms may help to regulate other classic homeostatic hypothalamic set points such as the regulation of body temperature, water intake, and sleep. The Pinto *et al.* study also suggests that leptin affects not only the transcription and release of neuropeptides, but also the functional activity of “classic” neurotransmitters like GABA and glutamate, which may ultimately be the most relevant mediators of metabolic signals like leptin (7, 15). Finally, both studies

are exciting in that they represent the merger of the once-separate research fields of obesity and developmental neurobiology. Given the rising incidence of obesity and diabetes in modern societies, it is likely that this line of investigation will continue to grow in importance for many years to come.

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