Rapid Rewiring of Arcuate Nucleus Feeding Circuits by Leptin
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sent projections of these neurons. As observed in the axon-labeling studies, the density of AgRP immunoreactive fibers was severely reduced in the PVH of Lepob/ob Lepob mice on P80 compared with that of wild-type littermates (Fig. 2B), and reductions in the density of α-MSH fibers were also observed in Lepob/ob Lepob mice (Fig. 2B). In sharp contrast to the results seen in neonatal mice, treatment of adult Lepob/ob Lepob mice with leptin for 20 days did not restore the density of AgRP and α-MSH immunoreactive fibers in the PVH to wild-type levels (Fig. 2B). The inability of leptin to alter AgRP and α-MSH–immunoreactive fiber density in the PVH of adult Lepob/ob Lepob mice suggests that the developmental action of leptin is restricted largely to the perinatal period.

These data provide direct evidence that leptin functions as an essential factor for brain development, promoting formation of hypothalamic pathways that later convey leptin signals to brain regions regulating food intake and energy consumption. This developmental action appears to be specific for ARH projections and is restricted to a neonatal window of maximum sensitivity that corresponds to a period of elevated leptin secretion. This neonatal “critical period” is also when ARH axons are guided to their targets. Although it is unknown whether leptin alters expression of local guidance cues in the periventricular zone of the hypothalamus, our in vitro findings suggest that leptin induces neurite outgrowth by acting on ARH neurons directly. Because of its direct access to these key components of homeostatic circuits, the neonatal leptin surge represents a likely peripheral signal capable of directing the development of hormone-sensitive central circuits during postnatal life. In this respect, the neonatal surge in leptin may be analogous to the surge in sex steroid secretion that occurs during neonatal life and is known to specify sexually dimorphic patterns of development in the mammalian forebrain (4, 5, 17). Our findings show that leptin has a similar programming action on the architecture of homeostatic neural circuitry, which raises the possibility that this developmental activity may contribute to the onset of leptin-dependent childhood obesity through a direct action on the brain.

**References and Notes**

23. Materials and methods are available as supporting material on Science Online.
24. We thank M. S. Smith and R. O. Ojeda for comments on the manuscript. Supported by NIH grants NS57952, DK55819, DK65900, and R00163.

**Supporting Online Material**

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**Materials and Methods**

Figs. S1 to S3

**References**

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**Rapid Rewiring of Arcuate Nucleus Feeding Circuits by Leptin**

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The fat-derived hormone leptin regulates energy balance in part by modulating the activity of neuropeptide Y and proopiomelanocortin neurons in the hypothalamic arcuate nucleus. To study the intrinsic activity of these neurons and their responses to leptin, we generated mice that express distinct green fluorescent proteins in these two neuronal types. Leptin-deficient (ob/ob) mice differed from wild-type mice in the numbers of excitatory and inhibitory synapses and postsynaptic currents onto neuropeptide Y and proopiomelanocortin neurons. When leptin was delivered systemically to ob/ob mice, the synaptic density rapidly normalized, an effect detectable within 6 hours, several hours before leptin’s effect on food intake. These data suggest that leptin-mediated plasticity in the ob/ob hypothalamus may underlie some of the hormone’s behavioral effects.

Administration of exogenous leptin to leptin-deficient mice and humans decreases food intake and body mass (1–5). These effects are mediated in part by leptin’s ability to modulate hypothalamic function. In the arcuate nucleus (Arc) of the hypothalamus, the signaling form of the leptin receptor is co-expressed with neuropeptide Y (NPY) and agouti-related peptide (AgRP) in a group of orexigenic neurons and with proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript ( CART) in a group of anorexigenic neurons (6–11). Increased NPY activity and reduced POMC activity appear to increase feeding and fat deposition, whereas reduced NPY activity and increased POMC activity decrease feeding and body mass (12–16). Leptin increases the firing rate of POMC neurons in acute slice preparations from the Arc (17). In the ob/ob hypothalamus, the amounts of NPY RNAs are increased, whereas the RNAs for POMC are decreased and leptin treatment of these animals normalizes the amounts of these RNAs (8, 18).

To date, there is no direct evidence showing that leptin has differential effects on the activity of NPY and POMC neurons. One possibility is that there are differences in the synaptic input to these neurons in ob/ob mice, a possibility consistent with Cajal’s neuronal doctrine. Previous studies of the inputs to NPY and POMC neurons have been difficult mainly because NPY and, to a lesser extent, POMC-derived peptides could only be identified by histochemistry after colchicine treatment in protocols that alter neuronal function. To overcome this obstacle and examine the electro-
physiological properties and the axosomatic inputs to NPY and POMC neurons of normal and ob/ob mice, we generated two lines of bacterial artificial chromosome (BAC) transgenic mice that express either tau-sapphire green fluorescent protein (GFP) under the transcriptional control of the NPY genomic sequence or tau-topaz GFP under the transcriptional control of the POMC genomic sequence (19, 20). Immunohistochemistry for NPY in colchicine-treated animals demonstrated >95% colocalization of NPY with the GFP-expressing neurons in the Arc (Fig. 1A). Similarly, immunohistochemistry against POMC demonstrated >99% co-expression with GFP-expressing neurons in the Arc (Fig. 1B). Analysis of animals carrying both transgenes demonstrated that NPY-GFP and POMC-GFP are expressed in distinct neuronal populations in the Arc (Fig. 1C). We next used these transgenic mice to examine the afferent inputs onto POMC and NPY neurons in the Arc.

We first examined the afferent inputs to POMC and NPY neurons in the Arc in wild-type mice with the use of patch-clamp recordings in acute Arc slice preparations. NPY-GFP or POMC-GFP cells were held at −60 mV in the whole-cell voltage-clamp configuration, and the number of excitatory or inhibitory postsynaptic currents (EPSCs or IPSCs) was determined. NPY neurons had similar numbers of EPSCs and IPSCs (Fig. 2, A and B), whereas there were nearly twice as many IPSCs as EPSCs onto POMC neurons (Fig. 2, C and D). We then determined the relative contribution of mini-postsynaptic currents (mPSCs) arising from spontaneous vesicle fusion to the total number of spontaneously occurring postsynaptic currents (sPSCs) by using tetrodotoxin (TTX) to block all action potential–driven PSCs. TTX had no discernible effect on the average number of EPSC and IPSCs onto wild-type NPY and POMC neurons (compare sPSCs with mPSCs in Fig. 2, A to D). Thus, in acute slice preparations, the vast majority of PSCs onto POMC and NPY neurons appear to arise from spontaneous vesicle fusion at the presynaptic terminal, rather than being driven by action potentials in the presynaptic neurons. A small subset of cells did show a notable amount of TTX-sensitive PSCs (21), suggesting that alterations in the activity of some presynaptic neurons in the slice may affect POMC and NPY activity.

The synaptic currents onto NPY and POMC neurons from ob/ob mice differed from those of wild-type mice. There was a significantly greater number of sEPSCs onto NPY neurons from ob/ob mice (0.70 ± 0.10 Hz for wild type compared with 1.05 ± 0.16 Hz for ob/ob, P < 0.05) (Fig. 2A), which was accompanied by reduction in the frequency of IPSCs (0.73 ± 0.15 Hz for wild type and 0.42 ± 0.07 Hz for ob/ob) (Fig. 2B). The trend toward lower IPSCs onto NPY neurons did not reach statistical significance. These differences were evident before and after treatment with TTX. Taken together, these data demonstrate that ob/ob mice have higher excitatory tone onto NPY neurons.

The frequency of IPSCs onto the POMC neurons was significantly higher in ob/ob mice (1.95 ± 0.46 Hz for wild-type sIPSCs compared with 4.11 ± 1.11 Hz for ob/ob; P < 0.05) with no observable change in the frequency of sEPSCs (1.02 ± 0.23 Hz for wild type and 0.96 ± 0.16 Hz for ob/ob) (Fig. 2C). Similar results were observed before and after treatment with TTX. Thus in hypothalamic slices from ob/ob mice, there were reciprocal alterations in the inputs to NPY and POMC neurons, with a marked net increase in inhibitory tone onto the POMC neurons and a marked net increase in excitatory tone onto the NPY neurons. These observations are consistent with the known effects of these peptides on food intake.

To assess whether the number and type of synaptic inputs to the NPY and POMC neurons correspond to the electrophysiological findings, we used electron microscopic stereology to analyze the synaptic density on NPY and POMC perikarya from ob/ob and wild-type animals. In these experiments, which were performed in a blinded fashion (19), we identified inhibitory synapses by their symmetrical morphology and excitatory synapses by their asymmetric morphology (22). In the hypothalamus, this morphology correlated with the content of glutamate in asymmetric synapses and γ-aminobutyric acid (GABA) in symmetric synapses as confirmed with the use of immuno-electron microscopy (EM) (23, 24) (Fig. 3A).

The ob/ob mice had significantly more synapses onto the perikarya of Arc NPY neurons (30.44 ± 2.46) compared to wild-type littermates (17.34 ± 1.32, P < 0.005). In wild-type mice, inhibitory synapses onto the NPY neurons were more numerous than excitatory ones (14.77 ± 0.97 inhibitory compared with 3.67 ± 0.19 excitatory, P < 0.001), whereas in ob/ob mice the excitatory synapses were more numerous than inhibitory ones (17.96 ± 0.85 excitatory compared
There was also a significant increase in the number of excitatory synapses onto the ob/ob NPY neurons (3.67 ± 0.19 for wild type compared with 17.96 ± 0.85 for ob/ob, P < 0.001) and a significantly lower number of inhibitory synapses (14.77 ± 0.97 for wild type compared with 10.48 ± 0.75 for ob/ob, P < 0.01). This altered synaptic profile of NPY cells in the ob/ob animals is consistent with the increased excitatory tone onto the NPY neurons from ob/ob mice (Fig. 2).

The total number of synapses onto the POMC neurons was lower in ob/ob mice (50.57 ± 2.33 for wild type compared with 23.71 ± 0.93 for ob/ob, P < 0.001). On the POMC cells of wild-type mice, excitatory synapses were more numerous than inhibitory ones (23.71 ± 1.07 excitatory compared with 18.85 ± 0.75 inhibitory, P < 0.05), whereas the POMC cells of ob/ob mice showed a significantly greater number of inhibitory inputs (7.45 ± 0.82 excitatory compared with 15.5 ± 0.66 inhibitory, P < 0.01) (Fig. 3D). There was also a significantly reduced number of excitatory synapses onto the ob/ob POMC neurons (23.71 ± 1.07 for wild type compared with 7.45 ± 0.82 for ob/ob, P < 0.001). Thus, two distinct lines of evidence, electrophysiology and EM analyses, show that there is a net increase in excitatory tone onto the NPY neurons and a net increase in inhibitory tone onto the POMC neurons in ob/ob mice (Fig. 2). For the NPY neurons, there are equivalent differences with the use of both methods. However, in the case of the POMC neurons, the electrophysiological analysis demonstrated increases in inhibitory currents, whereas the EM analysis showed decreases in excitatory synapse number. This suggests that leptin can modulate both synapse number and synaptic activity of these cells. The basis for this subtle difference of leptin deficiency on the POMC cells is unclear.

The above electrophysiological and ultrastructural observations are consistent with the

![Fig. 2. EPSCs and IPSCs on NPY and POMC neurons from wild-type (WT) and ob/ob mice. NPY and POMC neurons were voltage clamped at –60 mV and PSCs were recorded. (A) EPSCs onto NPY neurons (n = 16 cells for both WT and ob/ob). Asterisk indicates P < 0.05. (B) IPSCs onto NPY neurons (18 WT and 14 ob/ob cells). (C) EPSCs onto POMC neurons (19 WT and 14 ob/ob cells). (D) IPSCs onto POMC neurons (19 WT and 16 ob/ob cells; asterisks, P < 0.05). Within each panel, the following are presented: sample traces (30 s) of PSCs from WT and ob/ob mice, mean frequency of PSCs over time, mean frequency of PSCs before and after TTX, and scatter plots depicting the mean frequencies for each cell. The decreases in PSCs after picrotoxin (PTX) or d-AP5/CNQX addition indicate the relative ratio of EPSCs/IPSCs. NPY neurons have similar levels of EPSCs and IPSCs, whereas POMC neurons have many more IPSCs. Also, there is little change in PSC frequency after TTX (compare sPSCs with mPSCs), indicating that the majority of PSCs onto NPY and POMC neurons are independent of presynaptic action potentials. Data are presented as mean ± SEM.](image_url)
known effects of leptin deficiency on food intake. Consistent with the proposed interaction between the NPY (co-expressing AgRP) neurons and POMC neurons in the Arc (17), a large number of AgRP-containing inputs were observed on POMC perikarya, suggesting that many of the inputs to POMC neurons are of local origin (fig. S1). Our data also suggest that there are important excitatory, glutamergic inputs to the Arc neurons that regulate food intake (24, 25).

We next analyzed the effects of leptin on the synaptic profiles of the NPY and POMC neurons of ob/ob mice. Groups of ob/ob (NPY-GFP or POMC-GFP) mice were treated with either leptin or saline and were evaluated at different time points after treatment. For the 6-hour treatment, a single intraperitoneal injection of 25 µg/g of either leptin or saline was given to the mice in the morning. For the 2-day and 12-day treatments, miniature osmotic pumps were filled with either saline or leptin and implanted subcutaneously into ob/ob mice.

As previously reported, there was no detectable effect of leptin on food intake or body weight at 6 hours (fig. S2). A significant decrease of food intake was evident at 2 days and of both food intake and weight after 12 days (fig. S2). Leptin treatment resulted in marked changes in the number and type of synaptic inputs onto NPY and POMC perikarya as early as 6 hours after hormone replacement, a time when both food intake and body weight change were unchanged. Six hours after a single dose of leptin injection there was a significant decrease in the total number of synapses on NPY perikarya (Fig. 4A and table S1A). This was accompanied by decreased excitatory inputs and increased inhibitory input to the NPY cells. Six hours after leptin treatment there was also an increase in the total number of synapses onto the POMC neurons of ob/ob mice with a significant increase in the number of excitatory inputs (Fig. 4A and table S1B).

After 2 days of leptin treatment, there was a significant decrease in the total number of synapses onto the NPY neurons, with an 85% (sixfold) reduction in the number of excitatory synapses and an almost 70% (twofold) increase in the number of inhibitory synapses. At this time, there was also a doubling of the number of synapses onto the POMC neurons, with an almost 300% increase in the number of excitatory synapses. Similar effects on the synaptology of NPY and POMC neurons of ob/ob mice were also seen after 12 days of leptin treatment (Fig. 4A and table S1). Overall, leptin replacement restored the number of excitatory and inhibitory synapses of the NPY and POMC neurons of ob/ob mice to wild-type numbers (Table 1 and movie S1).

In order to assess whether these changes were associated with functional effects, we next tested whether leptin could also reverse the alterations in synaptic currents observed in ob/ob mice. Saline-treated ob/ob mice showed similar levels of IPSCs onto POMC neurons as untreated ob/ob mice (Fig. 4B). Leptin treatment for 2 days significantly decreased the frequency of sIPSCs onto POMC neurons (P < 0.04) (Fig. 4B). Although there was a trend for leptin to also decrease the number of EPSCs onto NPY neurons (1.50 ± 0.31 ESPCs for saline treatment compared with 1.19 ± 0.28 for leptin), this did not reach statistical significance (P = 0.2). In aggregate, these data show that leptin treatment of ob/ob mice resulted in rapid and marked changes in the synaptic inputs to NPY and POMC neurons in the hypothalamus with a time course that preceded the behavioral response.

Our results raise the question of whether the synaptic rearrangements are also seen in response to other neuromodulators that regulate feeding. To address this, we assessed the effect of peripheral ghrelin injections on the synaptology of the Arc NPY and POMC neurons of wild-type mice. Ghrelin is a pep-

Table 1. The number of excitatory (asymmetric), inhibitory (symmetric), and total synapses of the ob/ob mice after leptin replacement, presented as % of the number of synapses of wild-type mice.

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Fig. 3. Synapse type and density in WT and ob/ob mice. (A) Representative electron micrographs showing symmetrical, putative inhibitory synapses expressing GABA and asymmetrical, putative excitatory synapses expressing glutamate (scale bar, 1 µm) from the arcuate nuclei of mice that are of the same background strain (C57BL/6) as the GFP transgenic mice. GABA and glutamate are labeled with 10-nm immunogold particles. (B) Electron micrographs showing perikaryal membranes of NPY and POMC GFP neurons. The ob/ob and WT mice display marked differences in the ratio of symmetrical (inhibitory) to asymmetrical (stimulatory) synaptic inputs onto these neurons (Scale bar, 1 µm). (C) Arcuate NPY neurons possessed a higher total number of axosomatic synapses in ob/ob mice compared with WT littermate controls, where the stimulatory inputs dominated over the inhibitory inputs in the ob/ob Arc. The y axis represents the number of synapses per 100 µm of perikaryal membrane. Error bars indicate SEM, with 30 to 36 cells, taken from five to six animals, analyzed per data point. Asterisks indicate P < 0.005 (total), P < 0.001 (excitatory), and P < 0.01 (inhibitory). (D) POMC neurons possessed lower total numbers of axosomatic synapses in ob/ob mice compared with WT littermate controls, where the inhibitory inputs dominated over the stimulatory inputs in the ob/ob Arc. The y axis represents the number of synapses per 100 µm of perikaryal membrane. Error bars indicate SEM, with 35 to 40 cells, taken from five to six animals, analyzed per data point. Asterisks, P < 0.001.
Changes in synaptic density and properties in the hypothalamus of ob/ob mice peripherally have been shown to stimulate food intake and lead to a modest increase in body weight (26). After 4 days of twice-daily injections of 10 μg of ghrelin per mouse, we observed an increase in food intake but not body weight (fig. S3). This result was associated with significant changes in the synaptic inputs to the POMC neurons, with a significant decrease in the numbers of excitatory inputs (19.69 ± 2.67 inputs for saline treatment compared with 7.48 ± 1.83 for ghrelin, P < 0.05) and a significant increase in the number of inhibitory inputs (7.58 ± 1.41 for saline compared with 17.74 ± 1.51 for ghrelin, P < 0.01, 21 to 28 cells per group, taken from three to four animals) on POMC neurons relative to the saline-treated mice. We did not observe any significant differences in the number of either excitatory or inhibitory inputs onto the NPY neurons. This shift in the synaptic profile of POMC neurons by ghrelin is the opposite of that induced by leptin and is consistent with ghrelin’s orexigenic action. This observation, together with our findings on leptin’s action, gives impetus to the suggestion that plasticity in specific cells of the Arc, and perhaps elsewhere, in adults may underlie changes in feeding behavior.

Leptin is a key component of a long-term system that maintains stability of body weight, and its effects are mediated in part by modulation of a short-term system that controls hunger and satiety in response to other hormonal and nutritional signals. The observation that leptin has potent and rapid effects on the wiring of key neurons in the hypothalamus before any change in feeding behavior and body weight suggests that rapid, leptin-induced rewiring of the synaptic inputs to the NPY and POMC cells in ob/ob mice may account for some portion of its behavioral effects. The rapid effect of leptin in normalizing the synaptic inputs to the NPY and POMC neurons also suggests that the structural alterations in the ob/ob hypothalamus do not result from leptin deficiency during development. These results further suggest that, by changing the afferent inputs to key neurons, leptin may change the threshold for response of key hypothalamic neurons to other stimuli (such as one or more short-term signals), a possibility that fits well with its role as a long-term signal regulating body weight.

Although synaptic plasticity has never been shown to be associated with changes in energy homeostasis and feeding behavior, synaptic reorganization in adult hypothalamus has been described previously (27–29). The observation that ghrelin can also alter synaptic density further suggests that the modulation of synaptic inputs in the adult hypothalamus may be a general phenomenon in feeding behavior, consistent with many reports showing dynamic structural changes in other regions of the brain associated with various behavioral paradigms (30).

It is not known whether the effects of leptin on the neural circuit in ob/ob mice are a result of direct actions on the postsynaptic neurons (i.e., the Arc NPY and POMC neurons themselves), the presynaptic neurons that project to them, or via some other mechanism. Although it is possible that direct effects of leptin on NPY and POMC neurons in ob/ob mice lead to the reciprocal modulation of the number and type of synaptic inputs, proof of this awaits further experiments, such as restoring leptin signaling specifically in individual cell types.

The results presented here provide an opportunity to delineate the intracellular events that induce the assembly and disassembly of synaptic membrane proteins that modulate syn...
apse formation and reveal a striking effect of leptin on the synaptic inputs to two key peptideergic neurons that are components of hypothalamic feeding circuits. Further studies of the mechanism underlying leptin-induced plasticity could provide important insights into leptin’s action, the regulation of feeding, the pathogenesis of obesity, and potentially the regulation of other complex behaviors.

References and Notes
19. Materials and methods are available as supporting material on Science Online.
21. S. Pinto et al., unpublished data.

Contextually Evoked Object-Specific Responses in Human Visual Cortex
David Cox, Ethan Meyers, Pawan Sinha*

Human visual recognition processes are remarkably robust and can function effectively even under highly degraded viewing conditions. Contextual information may play a critical role in such circumstances. Here, we provide neurophysiological evidence that contextual cues can elicit object-specific neural responses, which have hitherto been believed to be based on intrinsic cues alone. Specifically, we find that the “fusiform face area” (FFA) maintains its selectivity for faces without regard to whether the faces are defined intrinsically or contextually. This finding further elucidates the role of the FFA and reveals neural correlates of contextual processing in the service of robust object recognition.

In the marathon scene in Fig. 1, it is simple for us to locate the athletes’ faces. However, the ease with which we accomplish this task belies its complexity. Although some of the faces in the image can be classified as such via their local intrinsic information (the pattern of eyes, nose, and mouth), for many others, the intrinsic information is almost entirely missing. The latter rely on contextual cues, such as the accompanying bodies, for their definition as faces. The importance of contextual cues in determining how an object is interpreted has been demonstrated in many behavioral studies (1–3) and in the work of several artists (Fig. 1D). From these demonstrations, it is apparent that perceptually, both intrinsic and contextual cues can be effective for defining object identity. A large body of work has probed the neural correlates of intrinsically defined object perception (4–8). When intrinsic information is present, neural responses can be modulated based on how interpretable it is (9). However, the neural correlates of contextual influences on object perception remain largely unknown. Previous studies have attempted to discover brain regions generically associated with the processing of contextual relations (10); however, we investigated the contribution of context to object representations themselves. In particular, we asked whether object-specific responses, which have been shown to be driven by intrinsic information, can alternatively be elicited by contextual cues alone when the intrinsic information is highly impoverished.

We chose the domain of faces to investigate the influence of context on object-specific neural responses. Convergent evidence suggests that there is an area in the ventral temporal lobe (dubbed the “fusiform face area” or FFA), which is involved in the processing of faces (11–15). We investigated how the activity of this area is modulated by contextual cues using functional magnetic resonance imaging (fMRI) techniques. We hypothesized that if context information is incorporated in facial representations, we would observe fusiform activity to stimuli in which faces are implied by context even in the absence of intrinsic facial information. We therefore created six stimulus categories, designated “a” through “f” for ease of reference. Stimulus a was images of bodies with highly degraded faces. The contextual body cues imply the presence of faces even though the intrinsic facial information is obliterated. Control conditions were as follows: b, images of bodies and degraded faces arranged in an incorrect spatial configuration; c, images of degraded faces alone (without bodies); d, images of bodies alone (with heads removed); e, clear images of faces; and f, images of natural scenes containing no faces or bodies. A sample set of stimuli used in our experiment is shown in Fig. 2.

While being scanned in a 3.0 Tesla (3T) magnetic resonance imaging (MRI) machine, nine adult subjects viewed images and performed a one-back task, signaling a repeated image with a button press. Stimuli were grouped into 20-s blocks of a single stimulus condition, and each imaging run consisted of one block each of all six conditions, interleaved with 12-s fixation blocks (17).