or mitotically arrested neuronal progenitors. The clinical findings in MCPH support the hypothesis that neuronal progenitors are more vulnerable than other cell types to mutations in genes encoding centrosome proteins.

What has MCPH got to do with the evolution of human intelligence?

It has been suggested that small, cumulative changes in MCPH-associated genes have collectively led to the increase in human brain size. There is a clear relationship between measurable intelligence and brain size within humans and between other mammals. Broadly speaking, herbivores have smaller brains than predators and scavengers. Also, nearly all conditions in which the brain is substantially reduced in size lead to intellectual disability (despite physical abilities often being normal). Humans are regarded (by humans!) as having the greatest cognitive abilities amongst animals, and have proven themselves remarkably adaptable to different conditions on Earth and hence have spread far beyond their ancestral geographical origins. But none of this proves that a larger brain is a cleverer brain, although inherently this might make sense!

For most MCPH-associated genes there is evidence for evolutionary selection and change during the monkey/ape/human lineage, as seen for genes involved in fertility and immunity. Taken together it has been speculated that multiple alterations in MCPH genes (and presumably in other genes with which they interact) have led to the threefold increase in brain size between chimpanzees (our closest relatives) and us. The other evolutionary change that is thought to be related to human brain size is the loss of the masseter muscle gene MYH16 following the evolutionary fixation of a premature nonsense mutation, allowing the young human skull to be able to grow more easily, but this relationship still remains to be proven. There is no such clear major change in an MCPH-associated gene that would make it 'the' candidate to explain a stepwise increase in human versus ape brain size. It is worth noting, however, that there are only 4 amino acid differences between man and mouse in the 714-amino-acid FOXP2 protein and these are thought to have led to the acquisition of human speech. Whilst there is no doubt that each MCPH gene can affect brain size significantly, they are maybe better viewed as modulators of brain size. And it is for this reason that the study of these genes may eventually lead us to discover the chance change(s) that have led to the emergence of the massive parallel processor that is the human brain.

Where can I find out more?

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Primer

The hypothalamus

Clifford B. Saper[1,3,*] and Bradford B. Lowell[2,3]

The hypothalamus is one of the oldest and smallest parts of the brain, constituting just 4 gm of the 1400 gm of adult human brain weight. And yet this tiny area contains highly conserved neural circuitry that controls basic life functions: these include energy metabolism, from feeding through digestion, metabolic control, and energy expenditure; fluid and electrolyte balance, from drinking through fluid absorption and excretion; thermoregulation, from choice of environment through heat production and conservation, and fever responses; wake-sleep cycles and emergency responses to stressors in the environment; and reproduction, from reproductive hormone control through mating, pregnancy, birth, and suckling. In this Primer, we will give an overview of the structure of the hypothalamus, and outline what we know about how that relates to its functional circuitry.

Overview of the hypothalamus

The hypothalamus develops from the most anterior end of the developing neural tube. Most of it is derived from the ventral part of the diencephalon, but its most rostral component, the preoptic area, develops from the telencephalon. In the adult brain, however, it is impossible to distinguish these components.

The hypothalamus is most easily defined from its ventral surface. It is bounded anteriorly by the optic chiasm, laterally by the optic tracts, and posteriorly by the mammillary body. It is surrounded by the blood vessels of the circle of Willis. The hypothalamus is symmetrically duplicated on each side of the brain, with the third ventricle in the midline forming a boundary between the two sides. For most functions, only the activity of one side of the hypothalamus is required.

The hypothalamus is usually divided from rostral to caudal into thirds (Figure 1). The rostral part, the

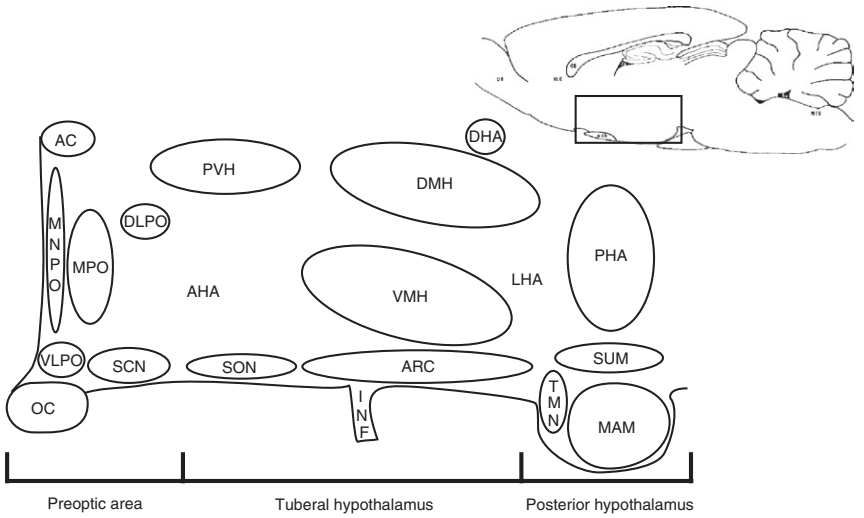

Figure 1. An overview of the hypothalamus.
This figure and the ones that follow are enlargements of the area shown by the box in the inset at the upper right, projected against a midsagittal section of a rat brain. The relative locations of the hypothalamus and its nuclei shown here are very similar in other mammals, including humans. The most rostral part of the hypothalamus, overlaying the optic chiasm, is the preoptic area (left). The tuberal portion (center) overlays the pituitary stalk (infundibulum, INF). The posterior hypothalamus (right) overlays the mammillary bodies. AC, anterior commissure; AHA, anterior hypothalamic area; ARC, arcuate nucleus; DHA, dorsal hypothalamic area; DLPO, dorsolateral preoptic area; DMH, dorsomedial nucleus; LHA, lateral hypothalamic area; MAM, mammillary nuclei; MNPO, median preoptic nucleus; MPO, medial preoptic area; OC, optic chiasm; PHA, posterior hypothalamic area; PVH, paraventricular hypothalamic nucleus; SCN, suprachiasmatic nucleus; SON, supraoptic nucleus; SUM, supramammillary nucleus; TMN, tuberomammillary nucleus; VLPO, ventrolateral preoptic nucleus; VMH, ventromedial nucleus.

preoptic area, lies above the optic chiasm and includes the median and ventrolateral preoptic nuclei, the medial and lateral preoptic areas, and the suprachiasmatic nucleus. It contains key integrative circuitry for thermoregulation, fever, electrolyte balance, wake-sleep, circadian rhythms, and sexual behavior. The middle part is the tuberal hypothalamus, and the pituitary stalk (infundibulum) emerges from the ventral surface of this central region. The tuberal hypothalamus includes the anterior and lateral hypothalamic areas and the dorsomedial, ventromedial, paraventricular, supraoptic, and arcuate nuclei. The tuberal hypothalamus contains integrative circuitry for feeding, but output circuitry for sexual behavior, aggressiveness, and many autonomic and endocrine responses. The posterior part of the hypothalamus includes the mammillary bodies and the areas above them, such as the tuberomammillary, supramammillary, and posterior hypothalamic nuclei. This region provides intense outputs to the arousal system and hippocampus, which are believed to play a role in regulating wakefulness as well as stress responses.

The role of the hypothalamus is essentially integrative, meaning that it brings together a range of sensory inputs necessary to make important decisions about basic life functions. It then compares those inputs to basic setpoints, that is, ideal levels for parameters such as body temperature, blood sodium and glucose levels, and various hormone levels. The hypothalamus then activates autonomic, endocrine, and behavioral responses that try to maintain the body at the key setpoints (homeostasis) or overcome a stressor (allostasis).

Key outputs of the hypothalamus

The hypothalamus controls the *autonomic* nervous system via a set of neurons that directly innervates both the parasympathetic and sympathetic preganglionic neurons, as well as various cell groups in the brainstem that control autonomic reflexes. These pre-autonomic neurons are mainly located in the parvicellular part of the paraventricular nucleus and the adjacent lateral hypothalamic area, with smaller numbers in the arcuate nucleus. Individual pre-autonomic neurons project to multiple levels of the spinal cord, where they are thought selectively to innervate neurons of a particular type. Selective physiological stimuli, such as leptin or lipopolysaccharide, stimulate expression of cFos protein in limited subsets of these neurons (arcuate and dorsal paraventricular, respectively), suggesting that these pre-autonomic neurons are organized along functional, rather than strictly anatomical, lines.

There are three sets of *endocrine* outputs from the hypothalamus. The *magnocellular* system consists of large neurons in the supraoptic and paraventricular nuclei that express either oxytocin or vasopressin. These are actually secretory neurons, whose axons traverse the pituitary stalk to end along blood vessels in the posterior pituitary gland, where they provide these hormones systemically for the entire body. The *parvicellular* system comprises smaller neurons in the wall of the third ventricle, including many in the medial part of the paraventricular nucleus and in the arcuate nucleus. These neurons send axons to the floor of the third ventricle at the emergence of the pituitary stalk, or median eminence, where they secrete releasing or release-inhibiting hormones into the hypophysial portal vessels. These are capillary loops in the floor of the median eminence, which then form veins that bring the blood carrying the releasing hormones to the anterior pituitary gland, where they control the secretion of pituitary hormones such as gonadotropins, adrenocorticotropic hormone, thyroid stimulating hormone, growth hormone, and prolactin. The third route for hypothalamic control of the endocrine system is by autonomic innervation of the endocrine glands; for example, autonomic innervation of the pancreas contributes to regulating secretion of insulin and glucagon.

The hypothalamic control of *behavior* is more complex. While it was once thought that the hypothalamus contains ‘centers’ for feeding, aggressive behavior, and so on, which can activate fully formed

behaviors, current thought suggests that it contains circuits that increase the likelihood that the animal will engage in certain behaviors. For example, in a hungry animal there is an increase in wakefulness and locomotor activity that increases the likelihood of the animal encountering food. By facilitating circuitry for licking, chewing, and swallowing, and enhancing pleasurable responses to the sensory stimuli (taste, smell, texture, temperature) of food ingestion, the hypothalamus can drive a relatively complex behavior such as feeding.

For the remainder of this Primer, we will focus on a few responses where important parts of the circuitry have recently been discovered, as examples of how the hypothalamus works.

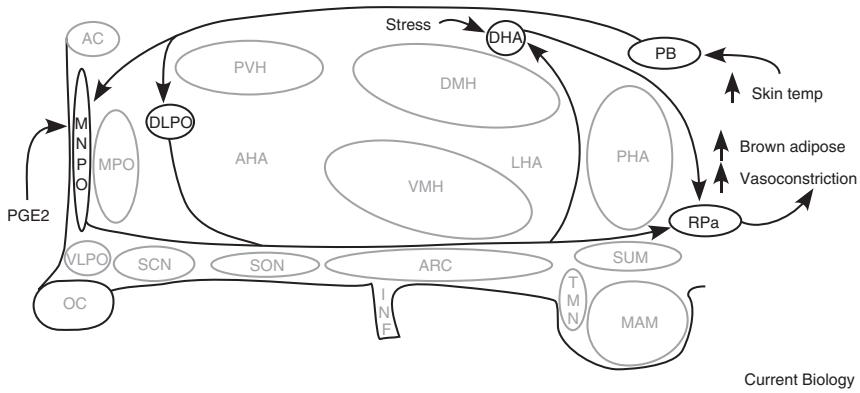

Figure 2. A schematic drawing of the hypothalamic pathways involved in thermoregulation (black).
The remainder of the hypothalamus (gray) is shown as in Figure 1, for orientation. The parabrachial nucleus (PB), which provides thermoreceptor inputs from the skin, and the raphe pallidus nucleus (RPa), which provides output to sympathetic preganglionic neurons that control brown adipose thermogenesis and arterial vasoconstrictor heat dissipation, are located in the brainstem, but for the sake of scale are shown here just to the right of the hypothalamus. PGE2, prostaglandin E2. See text for details.

Thermoregulation and fever

The median preoptic nucleus, located in the midline along the anterior wall of the third ventricle (Figure 2), is a key site for integrating thermal inputs from both the skin and from thermosensitive neurons within the brain, such as neurons in the preoptic region that respond to brain temperature. The warm- and cold-sensing neurons in the spinal cord project to adjacent warm- and cold-responsive sites in the lateral parabrachial nucleus in the pons. The parabrachial nucleus is a relay station for transferring many types of ascending visceral sensory information derived from the spinal and cranial nerves to the hypothalamus, and for much descending feedback from the hypothalamus back to the autonomic reflex and motor cell groups.

The median preoptic nucleus sends descending output to two key sites for controlling body temperature (Figure 2). One site consists of a cluster of glutamatergic neurons along the dorsal border of the dorsomedial nucleus (this site is sometimes called the dorsal hypothalamic area, but other authors do not distinguish it from the rest of the dorsomedial nucleus). Activation of these dorsal hypothalamic neurons causes an increase in body temperature. Both the median preoptic nucleus and dorsal hypothalamic area in turn innervate a third key site, the raphe pallidus nucleus. The raphe pallidus neurons in turn innervate sympathetic preganglionic neurons that activate brown adipose tissue (causing thermogenesis) and neurons that cause vasoconstriction of superficial vascular beds (thus reducing heat loss through the skin). These two actions cause an increase in body temperature.

The median preoptic nucleus contains GABAergic neurons that inhibit the raphe pallidus. These neurons express EP3 receptors for prostaglandin E2. During immune stimulation, for example by systemic administration of lipopolysaccharide, prostaglandin E2 is produced by endothelial cells in the preoptic area, and acts on the EP3 receptors in the median preoptic nucleus to cause an elevation of body temperature (fever). Lesions of the median preoptic nucleus or deleting EP3 receptors from just that site prevent such fever responses; however, rats and mice with such lesions still show an elevation of body temperature when they are stressed (for example, by handling or placing them in a new cage). This appears to be due to stress circuitry accessing the dorsal hypothalamic neurons, as lesions in this area or eliminating the vesicular glutamate 2 transporter from these neurons prevents stress fevers.

On the other hand, lesions of the median preoptic nucleus do not affect baseline body temperature. A second population of neurons in the more caudal part of the dorsolateral preoptic area also sends axons to the raphe pallidus. Lesions involving both the median and dorsolateral preoptic populations, but not either one alone, cause an elevation of body temperature by about 2°C. Acute inhibition of either site also causes a rise in body temperature, suggesting that both produce inhibition of the raphe pallidus at baseline, but that either one can compensate for the loss of the other in the case of a chronic lesion.

Feeding and energy metabolism

Attention was first focused on the role of the hypothalamus in feeding and metabolism by the dramatic demonstration in the 1930s and 1940s of massive hyperphagia and obesity after large lesions centered on the ventromedial nucleus, and hypophagia and inanition after large lesions of the adjacent lateral hypothalamus. Such efforts led to the view that there were hypothalamic 'centers' controlling satiety and hunger. However, problems in replicating these findings in studies using smaller, cell-specific lesions made it difficult to identify the cellular substrates of the effects. This situation changed dramatically with the demonstration that the mutation in *ob*/*ob* mice, which have genetic obesity, is in the gene for leptin, a hormone made by white fat cells when there is adequate substrate available. When fat stores are low due either to fasting, adipose

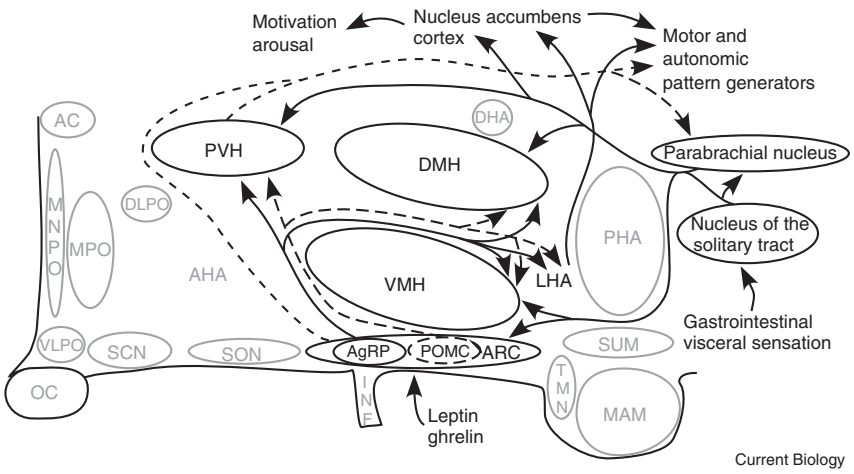

Figure 3. A schematic drawing of the hypothalamic pathways involved in regulation of feeding (solid lines, pathways that promote feeding; dashed lines, POMC pathways that inhibit feeding). The remainder of the hypothalamus (gray) is shown as in Figure 1, for orientation. The nucleus of the solitary tract and the parabrachial nucleus, which provide visceral sensory input to the hypothalamus, and the motor and autonomic pattern generators responsible for licking, chewing, swallowing, etc. are located in the brainstem, but for the sake of scale are shown here just to the right of the hypothalamus. The nucleus accumbens and cortical and limbic areas, responsible for motivation, arousal, and food selection, are located in the forebrain rostral to the hypothalamus, but are shown here above it. See text for details.

tissue lipodystrophy, or uncontrolled insulin-deficient diabetes, leptin levels fall, hunger is increased and energy expenditure is reduced. Leptin acts on specific receptors that are concentrated in the arcuate, dorsomedial, ventromedial and premammillary nuclei — the part of the hypothalamus that was ablated by the ventromedial nucleus lesions. These profoundly influential studies definitively established that appetite and body weight are under intense biological control, as opposed to "willpower" or lack thereof, and that neurons in the hypothalamus are key to this control.

These observations focused attention on specific neuronal circuits that were either activated or suppressed by leptin, and which therefore would play a role in regulation of feeding and energy metabolism. Many of the actions of leptin, as well as other factors that regulate energy metabolism, are brought about by the activation of the melanocortin system (Figure 3). Melanocortin neurons contain pro-opiomelanocortin (POMC), the precursor for α-melanocyte stimulating hormone (α-MSH), β-endorphin, and other neuropeptides. POMC neurons in the hypothalamus are mainly located in the lateral part of the arcuate nucleus and use α-MSH to activate melanocortin-4 receptors (MC4R) located in the paraventricular nucleus and elsewhere. Leptin also acts on a second population of neurons in the medial part of the arcuate nucleus. These neurons, which contain agouti-related protein (AgRP) as well as GABA and neuropeptide Y (NPY), are inhibited by leptin.

AgRP is a natural inverse agonist of the MC4R, and the POMC and AgRP neurons project to many of the same targets. Fasting and/or leptin deficiency coordinately activates AgRP neurons and inhibits POMC neurons; feeding and leptin repletion, on the other hand, do the opposite. As might be expected, POMC and AgRP neurons have opposite effects on their downstream target neurons, as well as behavior and metabolism. These state-dependent changes in AgRP and POMC neuron activities then bring about homeostatically appropriate changes in hunger and energy expenditure. Indeed, optogenetic and chemogenetic studies have shown that experimental activation of AgRP neurons dramatically stimulates hunger and decreases energy expenditure, even in animals that are nutritionally replete. Chemogenetic inhibition of AgRP neurons, on the other hand, attenuates hunger induced by caloric depletion. Manipulation of POMC neurons, in contrast, generally produces opposite effects — but the effects take longer to occur.

The actions of AgRP and POMC neurons are brought about by projections to other brain sites, one notable structure being the paraventricular nucleus (Figure 3). MC4R-expressing neurons, a subset of the neurons in this complex neural hub, play a major role in mediating the effects of the melanocortin system on hunger. The MC4R-expressing neurons responsible for regulating energy expenditure, on the other hand, appear to be located elsewhere, possibly in the spinal cord or the hindbrain. Because AgRP neurons also release GABA and NPY, which, like AgRP, are inhibitory, not all of these actions of AgRP neurons are necessarily brought about by action on MC4Rs.

Cues other than leptin also provide inputs that regulate feeding and metabolism. These include visceroceptive inputs (food taste, presence of food in the gastrointestinal tract, signaled by cranial nerves VII, IX, and X), olfactory cues, hormones (such as ghrelin, a peptide made by the stomach that signals lack of food, or cholecystokinin, made by the pancreas and the gut wall that signals the presence of food), and central neurons that are sensitive to the levels of certain metabolites, such as glucose. In addition, there are likely to be important inputs from forebrain circuits that deal with reward, motivation, and decision-making.

How MC4R-expressing neurons engaged by AgRP and POMC neurons ultimately provide feedback to circuits that control hunger is presently unknown. Of particular interest is how the circuits engaged by these MC4R-expressing neurons regulate the reward value of food and related cues, modulate motivation, and ultimately affect decision making. The substrates of this dialog present some of the biggest questions for the field. Previously, complexities within the brain made such topics essentially unapproachable. Fortunately, this has changed with the recent development of Cre-recombinase-enabled tools which make possible, in conjunction with neuron-specific

Cre-expressing mice, cell-specific manipulation of neural activity and precise cell-to-cell mapping of connectivity. These approaches are allowing investigators to follow the 'labeled lines' of information as they course through and beyond the hypothalamus, and are starting to reveal discrete, highly specific wiring diagrams that underlie hypothalamic regulation of feeding and metabolism.

Sleep and wakefulness

A hypothalamic circuit for sleep and wakefulness was first proposed by Walle Nauta in 1946, when he showed that lesions of the preoptic area caused insomnia in rats, while lesions of the posterior hypothalamus at the mammillary level caused excessive sleepiness. He proposed that neurons in the posterior hypothalamus promote wakefulness, and that they might be inhibited by preoptic neurons that promote sleep.

Several groups of neurons in the posterior half of the hypothalamus that promote wakefulness have been discovered over the last thirty years, including histaminergic neurons in the tuberomammillary nucleus, orexin (or hypocretin) neurons in the lateral hypothalamic area, and glutamatergic neurons in the supramammillary region (Figure 4). Each of these cell groups has extensive and diffuse direct projections to the cerebral cortex which are believed to be excitatory. In addition, arousal-promoting neurons in the brainstem, including noradrenergic (locus coeruleus), serotonergic (dorsal and median raphe), dopaminergic (ventral periaqueductal gray matter), cholinergic (pedunculopontine and lateral dorsal tegmental nuclei), and glutamatergic (parabrachial nucleus) components, all pass through the lateral hypothalamus and project directly to the cerebral cortex, contributing to the waking state.

Sleep-promoting neurons have been identified in the ventrolateral preoptic and median preoptic nuclei (Figure 4). Lesions of the ventrolateral preoptic nucleus, in particular, cause rodents to lose as much as 50% of total sleep. Ventrolateral preoptic neurons contain the inhibitory neurotransmitters GABA and galanin, are most active during sleep, and innervate most of the components of the arousal system

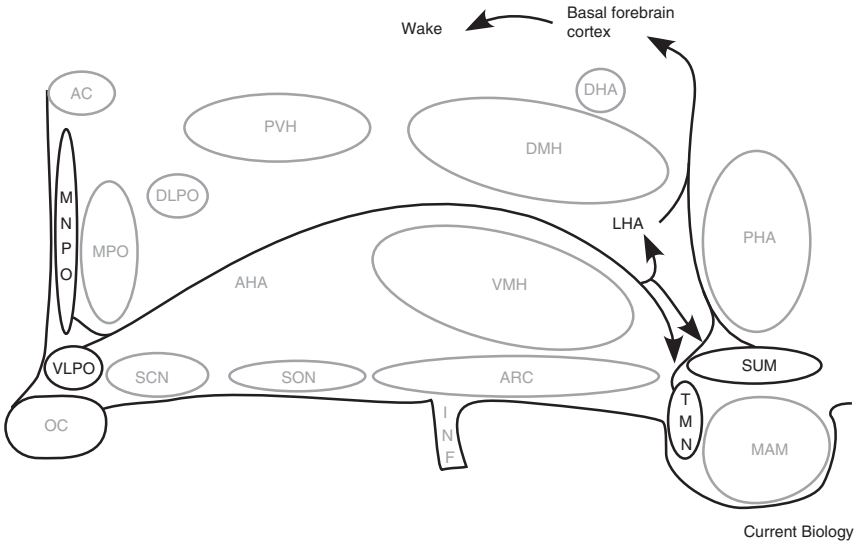

Figure 4. A schematic drawing of the hypothalamic pathways involved in the regulation of sleep and wakefulness (black).
The remainder of the hypothalamus (gray) is shown as in Figure 1, for orientation. The basal forebrain and cerebral cortex, which are rostral to the hypothalamus, are illustrated above the hypothalamus, for the sake of scale in this drawing. See text for details.

whose axons pass through the lateral hypothalamus. Ventrolateral preoptic neurons have been found to be inhibited by many of the arousal system neurotransmitters, such as norepinephrine, serotonin, and acetylcholine. This mutual inhibition between the ventrolateral preoptic nucleus and the arousal systems provides the conditions for a flip-flop switch. This is a type of switch that is built into electrical circuits when the designer wants the switch to be bistable — stable in either the fully on or fully off position — but to avoid intermediate states. This relationship insures rapid transitions from one state to the other, and is thought to explain the relatively rapid transitions most animals make between waking and sleeping states.

The orexin neurons, in the lateral hypothalamus, are thought to play a particularly important role in stabilizing this switch. These neurons have potent descending projections to the other components of the arousal system, which they potentiate. Thus, while the orexin neurons are firing, it is very difficult for the ventrolateral preoptic neurons to overcome the wake system, and a waking state is stabilized. Animals or people who lack the orexin neurons suffer from the disorder known as narcolepsy, in which they have excessive sleepiness, marked by overwhelming sleep attacks that occur during the normal wake period. Narcolepsy is one of the few neurological disorders that is known to occur due to loss of a single neurotransmitter.

Social responses: sex versus aggression

The search for the structural basis of sexual behavior was aided by early studies that demonstrated that the medial preoptic nucleus contains neurons that are responsive to sex steroids, and that it is sexually dimorphic, being larger and having more neurons in males than in female rodents. Subsequent studies showed that individual neurons in the medial preoptic nucleus fire during sexual stimulation and that lesions of this area disrupt both male and female sexual behavior. The outputs of the medial preoptic nucleus include a major projection to the ventrolateral part of the ventromedial nucleus of the hypothalamus (Figure 5). Lesions in this latter site prevent both male (mounting) and female (lordosis) sexual behavior. Both the medial preoptic nucleus and the ventromedial nucleus have strong projections to the lateral periaqueductal gray matter that are thought to mediate the motor and autonomic patterns associated with sexual behavior.

Studies of aggressiveness in animals have also focused on the

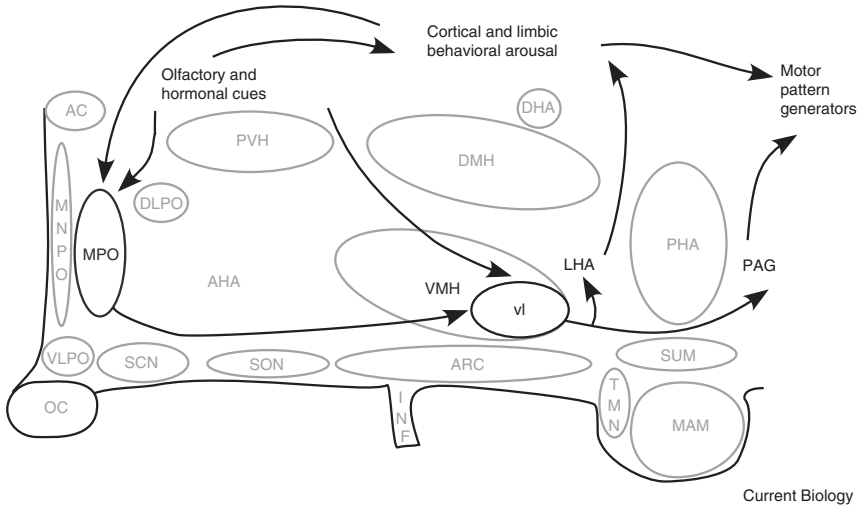

Figure 5. A schematic drawing of the hypothalamic pathways involved in the regulation of aggressive vs. sexual behavior toward a conspecific animal (black).
The remainder of the hypothalamus (gray) is shown as in Figure 1, for orientation. For ease of illustration, olfactory cues which largely come from the medial amygdala and hormonal cues such as sex steroids, which enter the brain directly, are shown above the paraventricular nucleus. Cortical and limbic areas that process visual and other sensory cues and contribute to behavioral arousal during either activity are shown above the hypothalamus. The midbrain periaqueductal gray matter (PAG) activates brainstem and spinal pattern generators responsible for motor and autonomic responses associated with either sexual and aggressive behaviors; all of these are shown just to the right of the hypothalamus. See text for explanation. VMHvl, ventrolateral part of the ventromedial nucleus.

ventromedial nucleus as playing an important role in coordinating aggressive attack behaviors. Recent studies have shown that overlapping populations of neurons in the ventrolateral part of the ventromedial nucleus of male mice show cFos activation during both aggressive encounters (with an intruder male) and during sexual encounters (with a female mouse). Interestingly, at least some of these neurons were activated initially under both scenarios, but later continued to fire only with one or the other type of encounter. Neurons that responded to male intruders continued to fire at high rates during the encounter, but those responding to females tended to decrease firing as the encounter progressed. Optogenetic activation of neurons in the same region caused male mice to attack other mice of both sexes, as well as inanimate objects. But during a sexual encounter, the same stimulation would not provoke attack.

These observations suggest that these ventromedial nucleus neurons, which gate two polar opposite types of social interactions, must share many of the same inputs. However, they must have distinct sets of output pathways, and these remain to be elucidated. In addition, they must have interactions that allow activation of sexual response to profoundly inhibit aggressive response. The resolution of these questions and many others about how these two systems interact would be facilitated by the development of molecular tools that differentiated between the two populations of neurons.

Conclusions

Our experience over the last few years has indicated that the hypothalamus is composed of myriad very specific circuits which are devoted to important life functions. The examples above are just a small sampling of some of the prominent circuits that have come to light in the last few years. This wealth of new data is due in part to the fact that so many of the hypothalamic circuits have distinct peptide neurotransmitters, which allow us to manipulate and map specific populations of neurons using modern tools such as conditional knockouts, cell-specific mapping tools, and chemo- and optogenetics.

The picture that is emerging, however, is that the regulatory circuits that control basic life functions are extraordinarily robust, redundant, and complex, as one might imagine for circuitry on which the life of the animal depends. The differentiation of hypothalamic circuitry into hundreds, perhaps thousands of chemically, connectionally, and functionally distinct cell populations stands in stark contrast to the cerebral cortex, which hosts a range of complex functions using a small number of cell types and neurotransmitters, and a highly stereotyped architecture which is similar from one cortical column and area to the next, despite the extensive variations in function. The differences in computational power between the cerebral cortex of a mouse and a human is largely due to the number of such columnar processing units and distinct cortical areas, and their interconnections. Conversely, the similarity in the basic life functions between a mouse and a human has resulted in the conservation of a large number of very specific hypothalamic neuronal circuits. The availability of genetic tools for manipulating those circuits in mice is likely to give us critical insights into how the same circuits in humans shape our lives.

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