Neurochemical–neuroendocrine systems in the brain controlling macronutrient intake and metabolism

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Appetite, energy balance and body weight gain are modulated by diverse neurochemical and neuroendocrine signals from different organs in the body and diverse regions in the brain. The hypothalamus plays an important integrative function in this process, acting through a variety of systems that involve a close interaction between nutrients, amines, neuropeptides and hormones. These systems underlie normal nutrient intake and metabolism and are thought to be responsible for shifts in feeding behavior across the circadian cycle and fluctuations relating to gender and age in both rats and humans. Moreover, alterations in these normal neurochemical–neuroendocrine systems may be associated with abnormal eating patterns, such as anorexia nervosa, bulimia and obesity. Understanding the systems that control eating behavior might provide a foundation for the treatment and possible prevention of such disorders.

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Obesity, affecting 30% of our population, is in epidemic proportions and a serious health hazard. Eating disorders, such as anorexia nervosa and bulimia, occur in up to 3% of the adolescent and young adult population. Dieting and food obsessions plague all age groups, greatly interfering with normal daily function and productivity. In affective and seasonal disorders, disturbed eating patterns are a primary symptom. Moreover, loss of appetite and cachexia, during illness as well as in the elderly, preclude proper medical treatment for restoring good health or preserving life. Can an increased understanding of the multiple systems in the body and brain related to energy and nutrient balance help us to treat and ultimately prevent these common eating and body weight disorders?

Integration of diverse signals that determine energy and nutrient balance

In recent years, researchers in neurobiology have used an integrative, interdisciplinary approach to obtain information about the multiple neurochemical and neuroendocrine determinants of energy balance, nutrient stores and body weight[1–4]. These include such diverse signals as: simple nutrients in the blood, including glucose, fatty acids or amino acids; classical neurotransmitter molecules for rapid, short-term communication; larger neuropeptides for slower, more long-term action; and hormones for both neuromodulatory and metabolic processes. These signals, which help to coordinate physiology and behavior, derive from different peripheral organs, e.g. the adrenals, liver, pancreas and gastrointestinal tract, and also from different areas of the CNS, from the hindbrain to the forebrain (Fig. 1). Moreover, they are dynamic in nature, shifting temporally across the daily cycle, as well as from day to day or from one season to the next. These signals are also modulated by gonadal steroids, which produce gender differences in eating patterns and body composition and contribute to changes that occur at different stages of development.

Neurochemical–neuroendocrine systems in the body

In the periphery, a variety of substances have been identified that are now believed to be involved in the complex process of balancing the physiological and behavioral components of energy and nutrient homeostasis. For example, extensive work has been performed on the peptide cholecystokinin, which, along with other peptides, is released from the gastrointestinal tract after a meal and is involved in coordinating several aspects of digestion, absorption and metabolism[4–7]. This peptide also transmits information to the brain, via the vagus nerve, to modulate behavioral processes related to meal termination and satiety. Cholecystokinin administration reduces meal size in humans and animals, and while this peptide may at higher doses induce nausea, recent studies[7] with antagonists that block the action

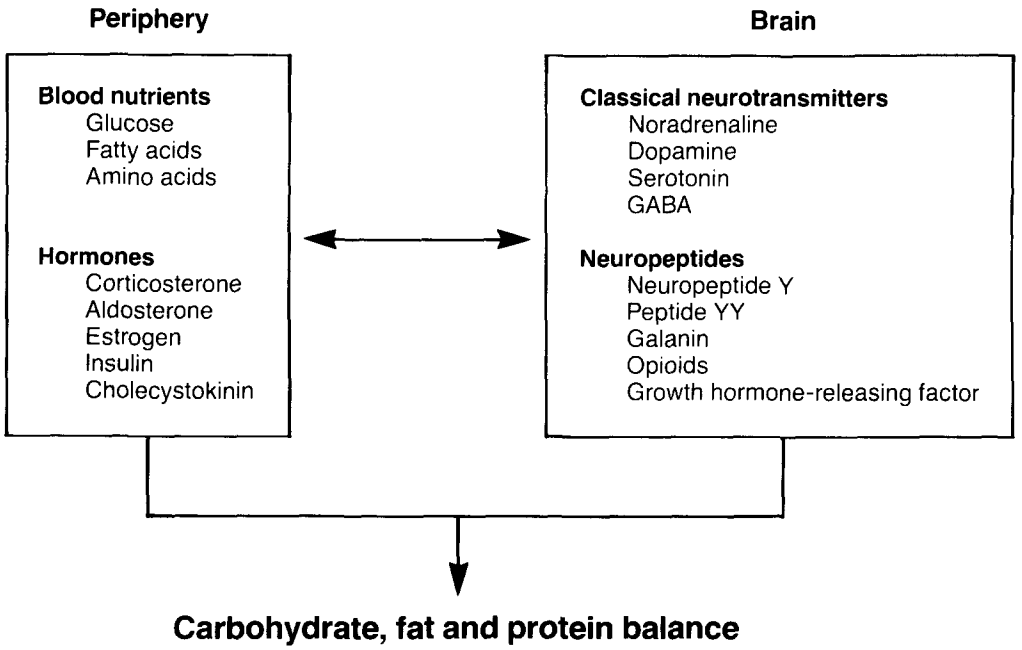

Fig. 1. *Neurochemicals, hormones and nutrients involved in controlling the ingestion and metabolism of macronutrients. A close interaction between nutrient and endocrine signals from the periphery and neurochemical activity in the brain is believed to serve an essential function in determining the availability of carbohydrate, fat and protein, through behavioral as well as metabolic processes.*

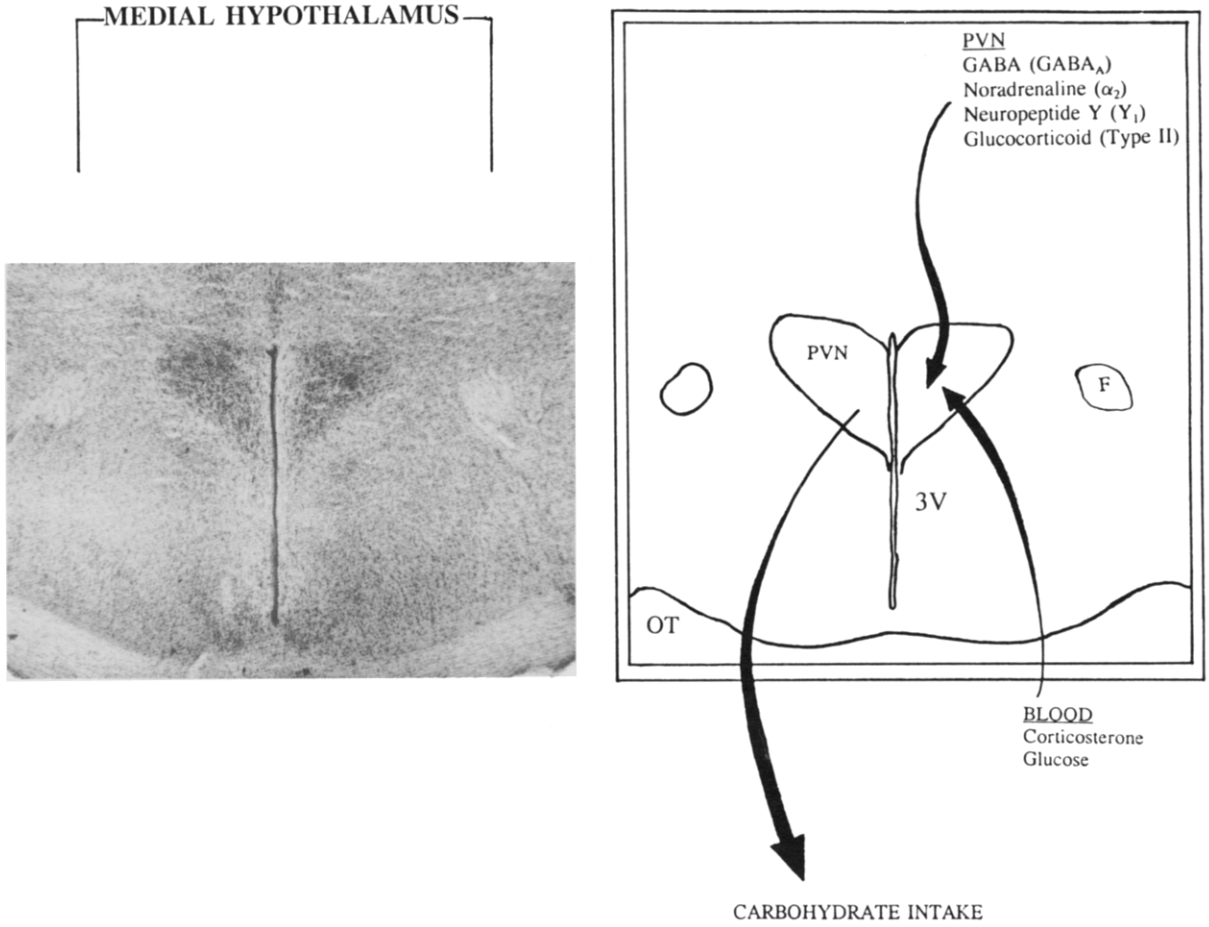

Fig. 2. *Histological photomicrograph and diagram of the hypothalamic paraventricular nucleus (PVN) of the rat showing the neurochemicals and neurohormones believed to act within this nucleus to produce positive carbohydrate balance. The adrenal steroid hormone corticosterone and glucose in the blood have a direct impact on these PVN systems. Abbreviations: F, fornix; 3V, third ventricle; OT, optic tract.*

of endogenously released cholecystokinin indicate that this peptide and its receptors are necessary for the expression of normal satiety. The pancreatic peptide hormone insulin has also been linked to satiety, in addition to regulation of the metabolism and utilization of food[6]. While disturbances in insulin receptors and cholecystokinin release have been detected in genetically obese animals, further research is needed to determine whether these defects are, in fact, critical to the development of this disorder[8].

The steroid hormones of the adrenal gland also play a paramount role in the integration of physiological and behavioral processes geared towards energy homeostasis[9–13]. There are two classes of adrenal steroids, namely, the mineralocorticoids and glucocorticoids. Whereas the mineralocorticoids and their receptors have long been associated with water and salt balance[14,15], recent evidence suggests that they may also play a role in modulating the ingestion and metabolism of fat. This is in distinct contrast to the glucocorticoids and their receptors, which predominantly influence carbohydrate intake and its metabolism[9–13,16,17]. While both actions may be produced by the endogenous hormones corticosterone in the rat or cortisol in humans, there is evidence that the glucoregulatory action of these hormones occurs primarily at the beginning of the natural feeding cycle, when blood levels of the hormone in animals and humans peak, glycogen stores are low, and energy stores must be rapidly augmented, mobilized and converted to glucose[11,18,19]. In addition, an increase in the level of, or the sensitivity to, corticosterone, in conjunction with decreased sensitivity to insulin, is believed to contribute to the development and progression of overeating diets rich in carbohydrates and fats, and also of obesity[1,20,21].

Neurochemical–neuroendocrine systems of the hypothalamus

The integration of metabolic information from the periphery with signals within the CNS requires the involvement and specialized functions of multiple brain areas[3,4,22,23]. These include the lower brainstem, in particular the dorsal vagal complex, which relays and integrates neural information between peripheral autonomic endocrine organs and forebrain structures. Areas of the pons-midbrain and thalamus then interpret this information in relation to signals generated by the sensory properties of foods, which are detected at different levels of the gastrointestinal system. Forebrain structures, such as the nucleus accumbens, amygdala and frontal cortex, then perform a higher-order function that involves the integration of this incoming information with various cognitive factors pertaining to the rewarding and aversive aspects of food[24].

A major function in this sequence of events is performed by the hypothalamus[1,22,24–26]. This struc-

ture, with its extensive vascularity and the neural projections from the lower brainstem, remains closely linked to circulating nutrients and hormones and neural signals from the periphery. This information has a profound impact on the activity of the neurochemical–neuroendocrine systems in the hypothalamus that, in turn, transmit signals to affect behavioral and physiological processes.

A number of neurochemical–neuroendocrine systems have been identified in the hypothalamus that are involved in the process of controlling appetite for specific macronutrients, in addition to affecting energy homeostasis and body weight. The task of establishing under what conditions these systems are physiologically active is a difficult one, requiring a convergence of evidence from an array of interdisciplinary approaches. Even more daunting is the work needed to determine whether these systems actually contribute to the development or maintenance of clinical disorders of eating and body weight.

Carbohydrate balance: noradrenaline, neuropeptide Y, GABA and glucocorticoids

As indicated above, these hypothalamic systems involve the coordinated effort of several brain neurochemicals and hormones, including amino acids, amines, peptides and steroids (Fig. 1). One such system, involved in potentiating carbohydrate intake in response to a decrease in carbohydrate utilization[1–4,11,27,28], appears to function through the amino acid γ-aminobutyric acid (GABA), the amine noradrenaline (NA), and the peptide neuropeptide Y (NPY), in close association with corticosterone as well as glucose circulating in the blood. A primary site of action for these substances in the brain is the medial region of the hypothalamus, in particular, the paraventricular nucleus, where the neurotransmitters and steroid receptors are found to be co-localized (Fig. 2).

The existence of this system was first suggested by central injection studies that demonstrated that GABA, NA and NPY, when administered into the paraventricular nucleus of brain-cannulated animals, stimulate feeding behavior in various species[3,4,27,28]. These neurochemicals appear to act through distinct endogenous receptors, characterized as $GABA_A$ for the amino acid, α_2-noradrenergic for NA, and Y_1 for NPY. Their latencies and durations of action differ, increasing with the molecular weight of the neurochemical, from amino acid to peptide.

These substances share a common main effect[3,4,27,28]. In animals permitted to select their diet from separate sources of pure macronutrients, these neurochemicals specifically potentiate the ingestion of carbohydrate, having little or no impact on the consumption of protein or fat. Moreover, they act specifically to enhance the size and duration of carbohydrate-rich meals, rather than the number of meals, presumably by attenuating the satiety signals generated by ingestion of this nutrient[27,29]. These anabolic neurochemicals may also maintain energy balance through alterations in metabolism[27,28,30,31], which include a decrease in sympathetic activity and energy expenditure as well as an increase in carbohydrate utilization and fat storage.

These neurochemicals and their receptors are not uniformly active across the circadian cycle[26]. Their activities peak sharply at the beginning of the natural

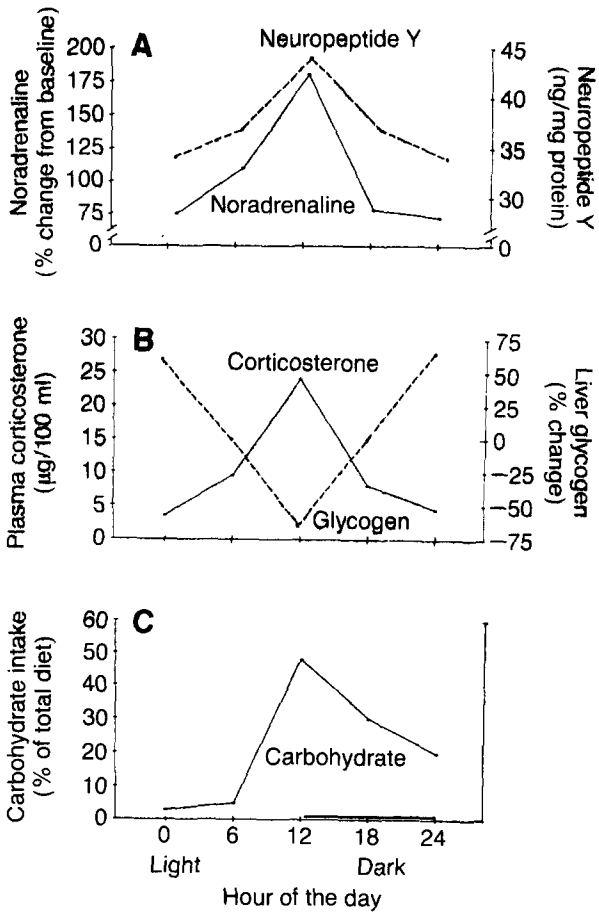

Fig. 3. *Circadian rhythms of brain neurochemicals* **(A)**, *peripheral hormones and glycogen stores* **(B)**, *and natural carbohydrate intake* **(C)**. *At the beginning of the active feeding cycle (dark period for the rat, indicated by the horizontal bar), glycogen stores in the body are very low. In association with this carbohydrate deficit, there occurs a sharp rise in the ingestion of carbohydrate, in association with increased levels of neuropeptide Y and noradrenaline in the paraventricular nucleus and corticosterone in the blood.*

feeding period (Fig. 3), when the body's glycogen stores and blood glucose levels are low. Consistent with this pattern are temporal shifts in the ingestion of carbohydrate (Fig. 3). In both rats and humans, this macronutrient is most strongly preferred during the early hours of the feeding cycle, perhaps since it is most efficient in rapidly replenishing glucose stores in a hungry animal[32–34]. Thus, in association with the carbohydrate-rich meals that naturally occur at this time, there is a peak in the levels or release of the hypothalamic neurochemicals and in the density or responsiveness of their receptors[26–28,35]. Their activity varies in relation to circulating glucose levels and glucose utilization, with GABA very likely providing, through local interneurons, an important translational link between these metabolic signals and the neural signals modulating appetite for carbohydrate.

These hypothalamic neurochemicals also work in close association with the glucocorticoid corticosterone, whose main function is to enhance carbohydrate stores in the body[10,13]. Recent evidence suggests that an important action of this steroid in the brain is to synergize with the NA and NPY systems,

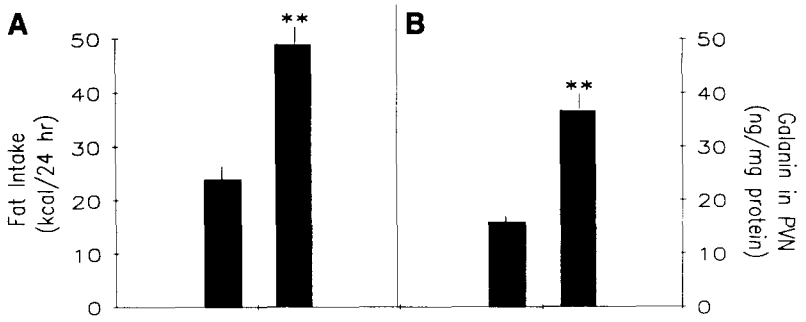

Fig. 4. *Relation between the peptide galanin (GAL) in the paraventricular nucleus (PVN) and fat ingestion in rats.* **(A)** *When injected directly into the PVN, GAL causes animals to consume large amounts of fat (filled bar) relative to what they normally eat after vehicle injection (shaded bar).* **(B)** *Measurements of endogenous GAL levels in the PVN show higher concentrations of this peptide in animals that naturally consume large amounts of fat over the course of the daily cycle (filled bar), compared to low-fat eaters (shaded bar). ** refers to significant difference at p<0.001 between shaded and filled bars.* (Based on unpublished results obtained by Leibowitz, S. F., Akabayashi, A. and Alexander, J. T.)

enhancing neurotransmitter synthesis and receptor activity[12,27,28,35]. A behavioral consequence of this action, mediated by specific type II glucocorticoid receptors in the paraventricular nucleus, is the potentiation of carbohydrate ingestion that then further enhances glucose availability[12,27,28]. Once again, this interaction is expressed primarily during the initial hours of the natural feeding cycle (Fig. 3), when corticosterone levels normally peak[11,16,18].

A variety of evidence suggests that disturbances in the endogenous activity of these neurochemicals and steroids may contribute to the development or maintenance of abnormal patterns of eating and body weight gain[1,4,20,21,26–28,36–39]. For example, when pharmacologically or surgically deprived of their natural neurotransmitter or steroid, animals fail to exhibit normal carbohydrate feeding, both in the initial hours of the active feeding cycle or in response to the physiological challenge of food deprivation. Conversely, with excessive hypothalamic infusions of NA, NPY or corticosterone, animals respond by overeating carbohydrate, which may then lead to increased fat deposition and body weight gain. In fact, in animals that are genetically obese or that spontaneously overeat palatable, energy-rich diets, excessive levels of circulating corticosterone and endogenous hypothalamic levels of NA and NPY or their receptors can be detected, possibly produced in part by disturbances in glucose homeostasis.

There is evidence that the stimulatory action of these neurochemicals on carbohydrate ingestion may be inhibited by a different system in the medial hypothalamus, which involves the action of the monoamine serotonin (5-HT), its amino acid precursor tryptophan, and also possibly cholecystokinin[1,3–5,7,24,40,41]. In addition to reducing carbohydrate ingestion, these neurochemicals stimulate metabolic rate and sympathetic activity and, when chronically administered, reduce body weight gain. Moreover, pharmacological and biochemical evidence indicates that 5-HT, like NA and NPY, is most active at the start of the natural feeding cycle, when it acts to terminate the carbohydrate-rich meals of that period and gradually switches the animal's preference towards protein[40,41]. This action of 5-HT, mediated by 5-HT_{1B} receptors, is mimicked by drugs that release endogenous 5-HT and may also be potentiated by rising blood levels of the 5-HT precursor, tryptophan, which occur in response to a carbohydrate-rich meal. The importance of endogenous 5-HT receptors in this process is reflected in the finding that serotonergic receptor antagonists stimulate natural feeding of carbohydrate and block the action of exogenous 5-HT on mechanisms of satiety[4,40,42].

Fat balance: galanin, opioid peptides and mineralocorticosteroids

A different set of substances in the hypothalamus appear to specifically control the ingestion and production of fat. These substances include the peptide galanin (GAL), the opioid peptides, and the mineralocorticoid aldosterone[9,11,17,43,44]. Each of these substances is believed to act within the medial hypothalamus to potentiate fat intake. Their potency is reflected in the fact that a single injection of GAL into the paraventricular nucleus is effective in increasing the total fat consumed in meals over the next 24-hour period (Fig. 4).

There are distinct differences between the substances that stimulate fat consumption and those that potentiate the ingestion of carbohydrate. As described above, the latter are particularly active during the early hours of the feeding cycle and are dependent upon corticosterone and its glucocorticoid receptors, which normally peak at this time. This is in contrast to the peptides that stimulate fat intake, which are most potent during the later hours of the cycle and can function independently of corticosterone, which is at low blood levels when these peptides are active[43,44]. In animals and humans, appetite for fat progressively rises over the course of the natural feeding cycle[11,32,33], and this appetite shift may, in part, be attributed to the increased action of these neuropeptides. GAL has been shown to be co-localized with endogenous opiates in the paraventricular nucleus[45], and a possible synergistic interaction between GAL and the opiates is suggested by other studies indicating that these compounds function together to modulate pain sensitivity[46]. It is suggested that they may also function together in the hypothalamus to influence nutrient intake.

While these peptides act independently of the glucocorticoid receptors, there is evidence that a different steroid receptor, the mineralocorticoid type I receptor, may be involved in the process of maintaining fat balance. GAL potentiates the release of the mineralocorticoid aldosterone, and stimulation of the type I steroid receptor enhances both fat intake and fat deposition, most effectively towards the end of the feeding cycle[9,11,17]. The importance of the peptide and steroid receptors under physiological conditions is demonstrated by the finding that antagonists of the opioid, GAL and mineralocorticoid receptors inhibit spontaneous fat ingestion[47–49]. Moreover, endogenous GAL gene expression and peptide synthesis, specifically in the paraventricular nucleus (Fig. 4), are found to be positively correlated with an animal's natural appetite for fat, which in turn is positively correlated with body weight.

In the same manner that 5-HT inhibits the action of NA and NPY on carbohydrate intake, the monoamine

dopamine (DA), acting through DA D_2 receptors in the area of the fornix just lateral to the paraventricular nucleus (Fig. 2), may serve to attenuate the effect of GAL and the opiates on fat intake[3,4,24,26,50]. Injection of DA into the hypothalamus inhibits the ingestion of fat, as well as protein, and reduces body weight. A similar response occurs after systemic injection of amphetamine, which releases hypothalamic DA. It is also seen after administration of the structurally similar sympathomimetic amine phenylpropanolamine, a commercially available diet product, and in response to intravenous infusions of nutrients that enhance extracellular levels of hypothalamic DA. Conversely, neuroleptic drugs that antagonize DA receptor activity enhance fat intake and body weight gain, a commonly observed side-effect of these agents in patients chronically treated with anti-psychotics[24].

Protein balance: growth hormone-releasing factor and opioid peptides

In rats and humans, appetite for protein, similar to that for fat, increases gradually over the course of the active cycle, perhaps to enhance nutrient stores and prepare for a long inactive period of little eating[32–34]. The finding that the opioid peptides potentiate protein intake in addition to fat ingestion suggests that these neurochemicals may assist in balancing the intake and perhaps storage of these two nutrients[44]. Another peptide, growth hormone-releasing factor (GRF), may also be active in this process[51]. Hypothalamic administration of GRF stimulates feeding, in particular protein intake, and the action of this peptide is antagonized by opioid receptor antagonists. Since GRF stimulates the release of growth hormone, which in turn promotes protein synthesis and growth, it is possible that GRF in the medial hypothalamus helps to coordinate central behavioral and peripheral physiological functions relating to protein balance[51].

Developmental patterns and gender differences in appetite for macronutrients

Gender differences in eating patterns and body weight may also be attributed to differences in the activity of these neurochemicals and steroids[24,26,28,52]. For example, female rats exhibit a stronger preference for carbohydrate relative to male rats, which normally prefer protein. This preference pattern, similarly seen in humans[53], is evident very early in life, perhaps before weaning. Some recent evidence suggests that it may be attributed, in part, to a natural surge in hypothalamic NPY synthesis, detected in females shortly before and around puberty[54] when appetite for carbohydrate also peaks[52]. It may also be due to the hyperactive adrenal activity seen in females[55]. Shifts in carbohydrate preference may additionally occur in relation to shifts in circulating levels of the gonadal steroid hormone estrogen in animals and humans[56].

In contrast to appetite for carbohydrate, which rises before puberty, preference for fat is very low before puberty but then dramatically increases shortly after puberty, in rats and humans[52,53]. This growing preference for fat-rich diets, associated with a rise in fat deposition and body weight gain and a propensity towards obesity, develops simultaneously with a sharp increase in hypothalamic levels of GAL-like immunoreactivity, which may occur with a rise in gonadal steroids[57,58]. High estrogen levels in obese women[59] may be expected to result in enhanced GAL synthesis, leading to a further increase in fat intake and body weight gain. In normal weight (Fig. 4) as well as genetically obese rats[60], a close relationship exists between GAL levels or gene expression and both spontaneous fat intake and body weight.

Clinical studies of eating and body weight disorders

The ultimate goal of these studies in animals is to determine whether the neurochemical–neuroendocrine systems also function in some manner in humans, and whether disturbances in these systems contribute to the development and maintenance of clinical disorders of eating behavior, energy metabolism and body weight gain. While research in this area is only in its early stages, similarities between lower mammals and humans are suggested by the common effects on eating and body weight observed with various pharmacological agents, including antidepressants, antipsychotic agents, stimulants and peptides[2–4,24,44,61]. Moreover, as indicated above, some similarities in rats and humans have been detected in their circadian rhythms and gender differences of nutrient selection, and in both species, distinct subpopulations have been found to exist which exhibit strong nutrient preferences and differential weight gain[1,2,32,52]. Drugs most commonly used today in the management of disorders, such as obesity, anorexia nervosa and bulimia, have their primary effect in modulating the balance between the monoamines 5-HT and NA. Drugs affecting the peptides remain under investigation.

The possibility that disturbances in brain neurochemical systems may contribute to the development of abnormal eating patterns in humans has yet to be demonstrated. However, recent clinical studies, revealing altered levels of amines and neuropeptides in the cerebrospinal fluid (CSF) of patients with anorexia nervosa or bulimia, are consistent with this possibility[62]. For example, similar to food-restricted animals[35], underweight anorexics, who consume predominantly carbohydrate, exhibit a rise in the level of NPY in the CSF correlated with changes in CSF cortisol. Also notable is the finding that normal-weight bulimics, who have abstained from bingeing for a month, show abnormally high levels of an NPY-like peptide, peptide YY, which may mediate the urge for energy-rich foods (Fig. 5). Bulimia is also associated with decreased plasma cholecystokinin, brain serotonergic activity and satiety level after a meal, while anorexics after weight restoration exhibit increased 5-HT activity. Common eating problems, such as food cravings, seasonal appetite disturbances and stress-related eating, have also been attributed to dysfunctions in specific neurochemical systems involving the action of NA, 5-HT, NPY or opioid peptides[1–4,24,41,63].

Shifts and disturbances in appetite and body weight gain in humans may also be linked to changes in hormones[1,2]. This is clearly observed in Cushing's disease and Addison's disease, in which excessive endogenous corticosterone production or cortisone replacement therapy, respectively, is associated with enhanced appetite for carbohydrate and fat. Recent evidence suggests further that the hyperphagia and increased weight gain exhibited by diabetics may be

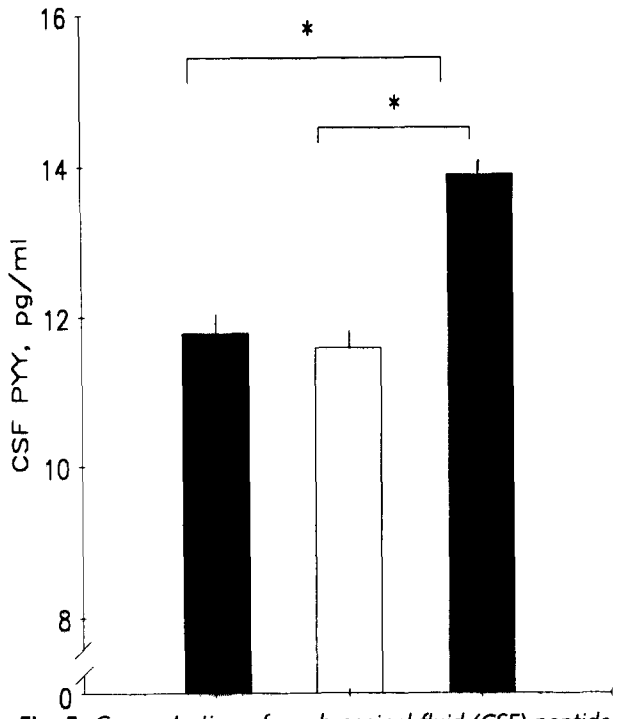

Fig. 5. *Concentration of cerebrospinal fluid (CSF) peptide YY (PYY) in healthy volunteer women (shaded bar) and in patients with normal-weight bulimia nervosa. Bulimic subjects that had abstained from bingeing for 30 days (filled bar) showed a dramatic increase in CSF levels of PYY compared to controls and bulimic subjects after bingeing (empty bar), which may contribute to the increased appetite of these patients for energy-rich foods. * refers to significant difference at* $p<0.05$ *between bars indicated.* (Based on results described in Ref. 62.)

attributed to an enhanced production of hypothalamic NPY, which is normally controlled by insulin[63]. Moreover, gender differences in appetite for food, with females preferring carbohydrate and males preferring protein, may be attributed to differences in both the adrenal and gonadal steroids, which in turn modulate the activity of brain neurotransmitters such as 5-HT, NA and NPY (Refs 24, 50, 51, 54).

Concluding remarks

In recent years, research in animals as well as in humans has provided very exciting, albeit preliminary, evidence for the possible existence of specific neurochemical–neuroendocrine systems that modulate intake of specific macronutrients, in addition to metabolism and body weight gain. With the additional evidence that these systems may be disturbed in human patients exhibiting eating and body weight disorders, the critical question to address is whether effective treatment of these disorders can include pharmacological, nutritional and behavioral therapy that modulates the activity of these systems. While considerable work will be required to investigate and answer this question, there is clearly a profound need for such research, in light of the rapidly increasing medical and behavioral problems in nutrition that exist in modern society. From exciting new evidence obtained in recent years, there is good reason to expect that a joint effort by neurobiologists, molecular geneticists, psychologists and clinicians will yield effective tools for controlling, as well as eventually preventing, the multiple eating and body weight disorders which plague our society today.

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Acknowledgements
Research in the author's laboratory described in this article was supported by NIMH grant MH43422.

Itching for an explanation

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Itch is a distinct sensation arising from the superficial layers of skin and mucous membranes. It is elicited by histamine and probably other endogenous chemicals that excite subpopulations of unmyelinated primary afferents and spinal neurones projecting through the anterolateral quadrant to the brain. The two popular views, which propose either that itch is signalled by a labelled line system of peripheral and central itch-specific neurones or that itch is the subliminal form of pain, both fail to explain convincingly many known features. Alternative theories emphasize central processes that extract the relevant information from afferents with broad sensitivity spectra for pruritogenic and noxious stimuli. Thus, itch presents an irritating challenge for the specificity theory of somatosensation.

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Itch is a well-appreciated but poorly understood sensation. Yet itch represents a major clinical problem affecting skin, mucous membranes and the upper respiratory tract, and its understanding is important for theories of somatosensation. This review will describe what is known about itch, and discuss the possible underlying neural mechanisms. To date there is no universally accepted single hypothesis that both explains all the observed features of itch and is clearly supported by all experimental evidence.

Itch, prickle, tickle and pain

Itch is an unpleasant sensory experience associated with the desire to scratch. While the sensations of itch and pain share some features, the two can be distinguished on a number of grounds. Prickle and tickle are associated, yet distinct sensations. Prickle is typically caused by the movement of rough fabrics over the skin, and some evidence exists that prickly stimuli cause low levels of firing in peripheral nociceptors[1]. Tickle is almost certainly mediated by low-threshold mechanosensitive afferent neurones. While humans can quite easily recognize the distinct features of these sensations, many mammals respond with a similar stereotypical behaviour[2], and this has impeded the development of appropriate animal models of itch.

Starting from scratch – the historical perspective

Itch was a sensation known in the ancient world. In 450 BC, Herodotus described the great effort of Egyptians to avoid mosquito bites – sleeping on high towers and tightly wrapping themselves in fishing nets. However, in early experimental studies on cutaneous sensations, itch was initially ignored. The theory of specific nerve energies of Johannes Müller[3] did not recognize itch as a separate sensory experience, and the description of 'skin spots' for different sensations did not originally include itch[4]. Later studies did recognize itch 'spots' (highly localized areas occurring about one per square millimetre) from which itch could be elicited by tactile stimuli. Initially these itch spots were thought to coincide with pain spots, and that itch resulted from weak stimuli and pain from stronger ones[5,6]. Bishop[7] reported that electrical stimulation of these sites gave rise to itch, and Shelly and Arthur[8–10] made extensive studies of

Box 1. Stimuli that can elicit or augment itch

Physical
Mechanical. Light touch, pressure, suction.
Thermal. Warming.
Electrical. Focal transcutaneous repetitive stimulation, transcutaneous constant current stimulation, intraneural microstimulation.

Chemical
Non-specific irritants. Acids, alkalis.
Inflammatory mediators. Histamine, kallikrein, bradykinin, prostaglandins.
Histamine-releasing substances. Compound 48/80, protamine, C3a.
Peptidases. Mucunain, papain, trypsin, mast cell chymase.
Neuropeptides. Substance P, vasoactive intestinal polypeptide, neurotensin, secretin.
Opioids. Morphine, β-endorphin, enkephalin analogues.