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The lateral hypothalamus as integrator of metabolic and environmental needs: From electrical self-stimulation to opto-genetics

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ABSTRACT

As one of the evolutionary oldest parts of the brain, the diencephalon evolved to harmonize changing environmental conditions with the internal state for survival of the individual and the species. The pioneering work of physiologists and psychologists around the middle of the last century clearly demonstrated that the hypothalamus is crucial for the display of motivated behaviors, culminating in the discovery of electrical self-stimulation behavior and providing the first neurological hint accounting for the concepts of reinforcement and reward. Here we review recent progress in understanding the role of the lateral hypothalamic area in the control of ingestive behavior and the regulation of energy balance. With its vast array of interoceptive and exteroceptive afferent inputs and its equally rich efferent connectivity, the lateral hypothalamic area is in an ideal position to integrate large amounts of information and orchestrate adaptive responses. Most important for energy homeostasis, it receives metabolic state information through both neural and humoral routes and can affect energy assimilation and energy expenditure through direct access to behavioral, autonomic, and endocrine effector pathways. The complex interplays of classical and peptide neurotransmitters such as orexin carrying out these integrative functions are just beginning to be understood. Exciting new techniques allowing selective stimulation or inhibition of specific neuronal phenotypes will greatly facilitate the functional mapping of both input and output pathways.

1. Introduction and historical perspective

The diencephalon first gained attention in the mid 19th century, after the group around the Swiss neurologist, Walter Hess showed that electrical stimulation of different hypothalamic areas in cats elicited a variety of behaviors, including fight, flight, copulation, and voracious eating [1,2]. The influential discoveries of two hypothalamic areas with opposing effects on food intake and body weight in rats soon followed: a lateral area resulting in eating when electrically stimulated and in aphagia and weight loss when lesioned [3] was dubbed "feeding center" and a ventromedial area resulting in hyperphagia and obesity when destroyed [4] was called "satiety center". In parallel to these studies focusing on food intake, Olds and Milner interested in reinforcement learning discovered the phenomenon of self-stimulation in the brain [5,6]. Soon thereafter, the first paper published by the young Bartley G. Hoebel under the mentorship of Phillip Teitelbaum put the two phenomena together in the journal Science entitled: *"Hypothalamic control of feeding and self-stimulation"*[7] (Fig. 1).

This started a decade of intense investigation of the physiological determinants of these phenomena, culminating in an impressive number of highly visible publications. However, hypothalamic stimulation and lesion studies eventually tapered off, because little was known, at the time, about neural connectivity and neurochemistry both within and outside the hypothalamus. A first bout of anatomical studies was then fueled by the newly discovered neural tract tracing methods with tritiated amino acids in the seventies (see discussion by Swanson [8]). A second bout followed the discovery of leptin in the mid nineties and capitalized on the identification of the "feeding" neuropeptides. Most recently, revolutionary new ways have been developed to selectively stimulate specific types of neurons in restricted brain areas, which definitely relegated the non-selective electrical stimulation to the past. The new opto-genetic approach takes advantage of genetic methodology for insertion of light-sensitive excitatory or inhibitory ion channels into specific neurons and subsequent stimulation by light [9]. Thus, it is now possible to selectively activate or suppress orexin or any other neuron type in the lateral hypothalamus with maximal temporal control [10]. Similarly, "designer receptors" exclusively activated by "designer drugs" (DREADD) can be genetically inserted into specific populations of neurons and then selectively activated or suppressed by administration of the corresponding designer drug [11,12].

This review is a tribute to the seminal work of Bartley G. Hoebel, whose work was dedicated to a neurological understanding of

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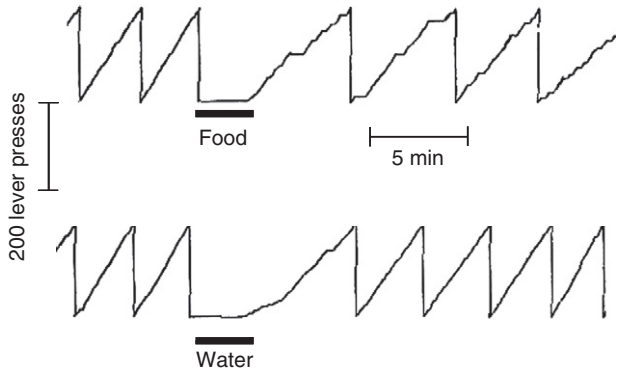

Fig. 1. Sustained inhibition of self-stimulation by intragastric food but not water load in rats as demonstrated by Hoebel and Teitelbaum [7] in 1962. The authors concluded that: "Self-stimulation rate was slowed to about half the normal rate by a stomach load of 18 ml of liquid milk diet. The same amount of water had only a transient effect, suggesting that some consequence of food intake other than taste or stomach distension was responsible for prolonged inhibition" [7].

ingestive behavior, specifically of food and drug reward mechanisms. We will argue that the lateral hypothalamic area by virtue of its connectivity and neurochemistry plays a key role in these behaviors. We believe that the newly developed tracing and stimulating techniques will be essential for a detailed understanding of how these complex pathways and circuits lead to the expression of adaptive behaviors and ultimately to the regulation of energy balance which is so important in health and disease. Given the large body of literature, we will not be able to cite all relevant studies, but several excellent reviews, mainly focusing on the role of orexin/hypocretin neurons, have recently been published [10,13–18].

2. Background of anatomy and chemistry of the lateral hypothalamus

The lateral hypothalamic area or zone is a large and heterogeneous area with several distinct nuclear groups and is one of the most extensively interconnected areas of the hypothalamus, allowing it to receive a vast array of interoceptive and exteroceptive information and to modulate cognitive, skeletal motor, autonomic, and endocrine functions (Fig. 2). The lateral hypothalamic area merges rostrally into the preoptic area and caudally into the ventral tegmental area. It borders medially to the dorsomedial, ventromedial, and arcuate nuclei and the anterior hypothalamic and medial preoptic areas, and laterally to the internal capsule, the optic tract, and more caudal to the subthalamic nucleus. There is no doubt that the LHA consists of numerous distinct nuclei [19,20], but the function and connectivity of most of these subnuclei has not been systematically studied. Generally, the lateral hypothalamic area can be divided into anterior, tuberal (roughly at the level of the ventromedial hypothalamus) and posterior portions based on its efferent connectivity as first described by Saper [20] (for a more detailed review see [21]). Another useful anatomic guide is the distribution pattern of two well studied neuronal populations that express either orexin/hypocretin or melanin-concentrating hormone (MCH) [19].

Two prominent fiber bundles traverse the lateral hypothalamic area, the medial forebrain bundle extending from the brainstem to the olfactory bulb and integrating neuronal processes from several brain areas including lateral hypothalamic neurons [22], and the fornix, connecting the hippocampal complex with the mammillary nuclei in the posterior ventral hypothalamus. This makes interpretation of electrical stimulation and lesion studies difficult, as involvement of nonspecific fibers of passage must be taken into consideration [22–24].

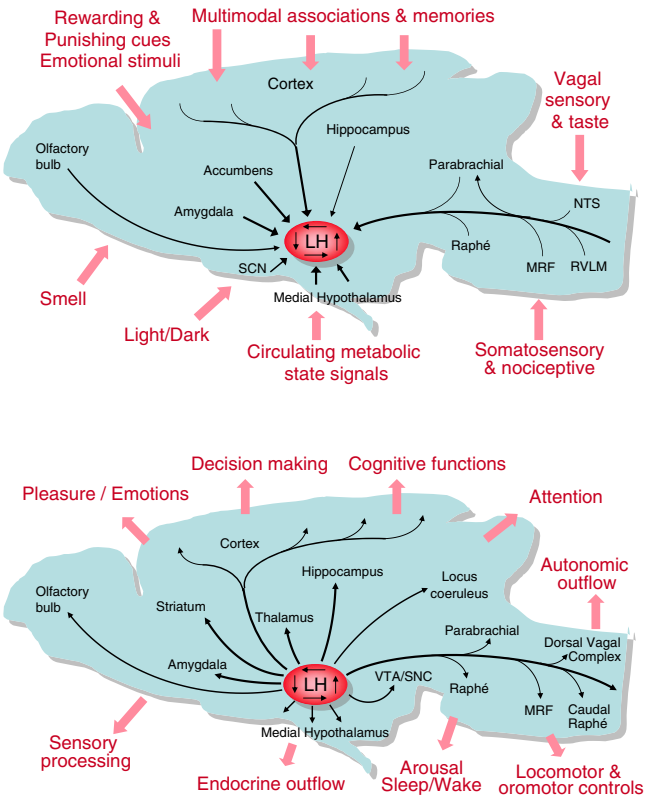

Fig. 2. Schematic diagrams showing major inputs (top) and outputs (bottom) of the lateral hypothalamic area on an outline of the rat brain.

2.1. Connectivity of the lateral hypothalamic area

Afferents to the lateral hypothalamic area have been classically studied with retrograde tracing techniques, but because such tracers can be taken up not only by axon terminals but also by fibers of passage, some caution is necessary, and prospective afferent sites need to be verified with anterograde tracers. Based on such verification, afferents to the lateral hypothalamic area have been demonstrated to originate from various cortico-limbic structures such as the prefrontal/orbitofrontal, insular, and olfactory cortex, amygdala, hippocampal formation, the shell of the nucleus accumbens, and from brainstem structures including most aminergic cell groups such as the nucleus of the solitary tract [21,25]. Afferents from medial portions of the hypothalamus, although generally sparse, are functionally highly significant, as for example, projections from the arcuate nucleus POMC/CART and NPY/AgRP neurons [26–28] (Fig. 3). The perifornical area within the lateral hypothalamus receives substantial NPY-ergic input from the arcuate nucleus, and the strongest feeding response to NPY can be elicited by local injection into the perifornical area [29]. Furthermore, given its size and structural complexity, there is considerable connectivity within the lateral hypothalamic area itself, particularly projections from anterior to more posterior portions [26,30].

More recently, Sakurai and colleagues used a transgenic method to map upstream neuronal populations that have synaptic connections to orexin neurons and confirmed most of the older findings with classical tracing techniques [31] (Fig. 2). In another recent study retrogradely transported neurotrophic viruses where used to map circuits including the lateral hypothalamic area [32]. They revealed projections from the arcuate nucleus, particularly the lateral POMC neuron containing portion, to insular and anterior cingulate cortex via synaptic relays in the lateral hypothalamic area (including orexin and MCH neurons) and midline thalamic nuclei. Similar multisynaptic

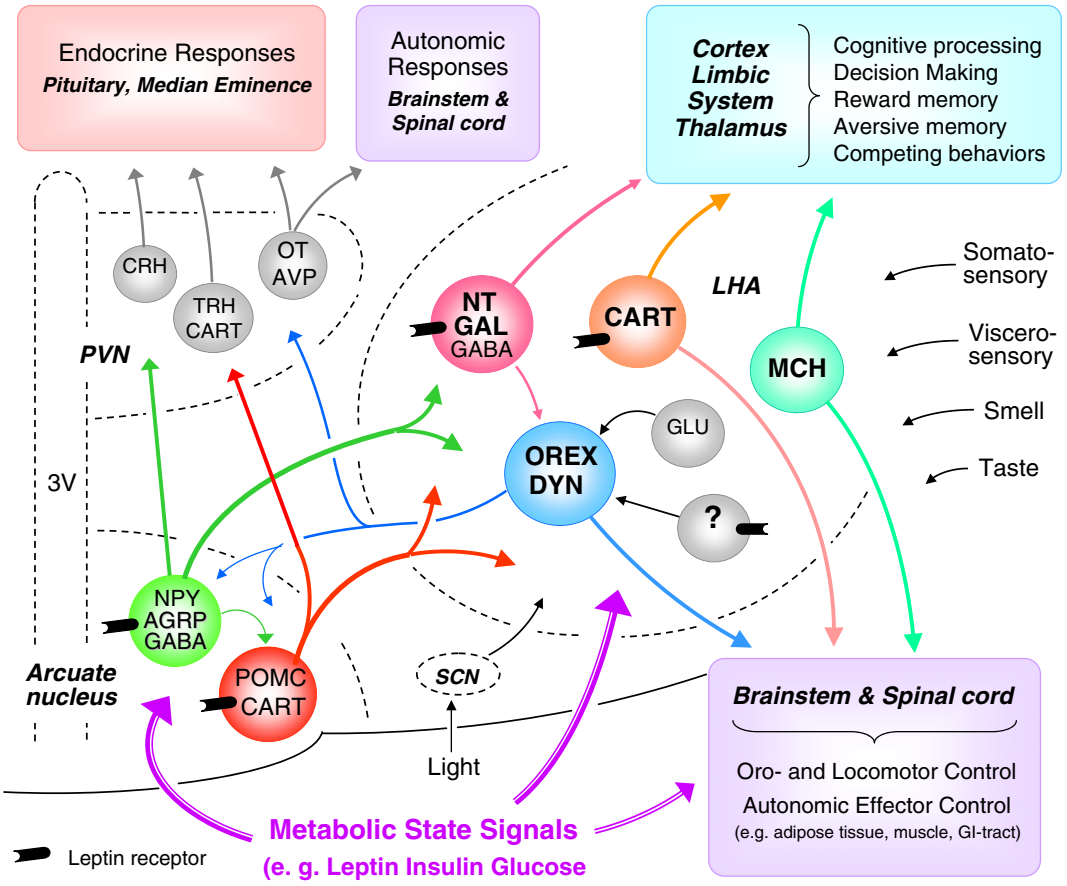

Fig. 3. Interactions of lateral hypothalamic neurons with other hypothalamic areas and major behavioral, autonomic, and endocrine output pathways and functions. This highly simplified diagram does not show the relationship with other important hypothalamic nuclei such as the dorsomedial and ventral hypothalamic nuclei. Also not shown are the massive reciprocal connections from cortex and limbic structures to the lateral hypothalamic area. Arrows entering the three nuclei but not contacting individual neurons signifies potential input to all the different neuron types in that area. Abbreviations: AgRP, agouti-related protein; AVP, arginine-vasopressin; CART, cocaine and amphetamine-regulated transcript; CRH, corticotrophin-releasing hormone; DYN, dynorphin; GABA, gamma-aminobutyric acid; Gal, galanin, Glu, glutamate; MCH, melanin-concentrating hormone; NPY, neuropeptide Y; NT, neurotensin; ORX, orexin/hypocretin; OT, oxytocin; POMC, proopio-melanocortin; TRH, Thyrotropin-releasing hormone; LHA, lateral hypothalamic area; PVN, paraventricular nucleus of the hypothalamus; SCN, suprachiasmatic nucleus; 3V, third ventricle.

projections relaying in the lateral hypothalamus to the nucleus accumbens shell originated in both arcuate POMC and NPY/AgRP neurons [32].

The LHA has vast efferent projections to the entire cortical mantle including the hippocampal formation, extended amygdala, basal ganglia and thalamus, the midbrain and pons, the brainstem and spinal cord, as well as most other nuclei of the hypothalamus [26,33,34] (and see [21] for a review) (Figs. 2 and 3). These projections have been established using mainly retrograde tracer injections into the various projection targets resulting in labeled perikarya in the lateral hypothalamic area, and erroneous co-labeling of fibers of passage is not a problem. More recently, many of these projections have been confirmed on the basis of immunohistochemical studies using antibodies to peptide neurotransmitters, which are almost exclusively produced in lateral hypothalamic neurons such as orexin and MCH (for a review see [35]). Within the hypothalamus the lateral zone has efferent projections to most medial zone nuclei such as the arcuate, paraventricular, dorsomedial, ventromedial, and anterior hypothalamic nuclei [21]. In particular, orexin neurons have been shown to project to the arcuate and paraventricular nuclei [36,37].

With respect to the theme of this review, Mogenson was the first to recognize that the nucleus accumbens, with its efferent projections to the lateral hypothalamus, may provide an interface between motivation and behavioral action [38], and his basic idea has been further developed in more recent review articles [39,40]. Specifically, Zahm has presented an integrative neuroanatomical perspective and proposed a convincing conceptual framework implicating this circuitry in general adaptive responding [39]. Particularly relevant, significant projections from the nucleus accumbens to the hypothalamus have been demonstrated. As shown with various tracing methods, these projections originate mainly from the shell and terminate predominantly in the lateral and perifornical hypothalamus [30,41–44]. In addition to these direct inputs, the nucleus accumbens may influence hypothalamic function via its very strong projections to the ventral pallidum, located ventrally to the nucleus accumbens [40,42], and via the pedunculopontine tegmental area [45]. The ventral pallidum projects directly to the far lateral hypothalamic area [46,47], and this pathway could also be involved in accumbens-induced food intake, as suggested by Stratford and colleagues [48,49].

2.2. Feeding peptides and neurotransmitters in lateral hypothalamic neurons

Several neuronal populations expressing neuropeptides categorized either as orexigenic such as MCH [50], orexin/hypocretin [51], galanin [52,53], or anorexigenic such as neurotensin [54] and CART [55] have been described.

MCH neurons project very broadly throughout the CNS [56,57], and similarly MCH receptors (SLC-1) are distributed equally broad in the brain, with particularly strong *in situ hybridization* signals throughout the cortex, including orbitofrontal, prelimbic, sensorimotor, motor and piriform cortex, as well as in olfactory pathways, nucleus accumbens

shell, striatum, hippocampus, locus coeruleus and NTS[58–60]. Similar to other orexigenic peptides such as NPY and AgRP, MCH expression levels increase with fasting and are restored to fed levels with leptin injections [61]. Furthermore, intracerebroventricular MCH injections increase food intake [62], and MCH overexpression leads to obesity and insulin resistance [63], thus suggesting that MCH acts as a typical orexigenic neuropeptide that may regulate and integrate various aspects of feeding behavior [63].

Orexin neurons are distinct from MCH neurons and co-express orexin-A and dynorphin [64]. Their projection pattern is equally widespread throughout the brain, including dense projections to areas in the brainstem and spinal cord, such as the locus coeruleus and dorsal vagal complex [36,64–68]. Orexin-A acts via two receptor isoforms (OxR-1 and OxR-2) that are also broadly expressed throughout the brain. Orexin-A injections into the lateral ventricle increase food intake [69] and systemic injection of an orexin receptor antagonist decreases food intake [70]. Orexin knockout mice exhibit hypophagia and narcolepsy [71]. However, in contrast to other orexigenic neuropeptides such as MCH, orexin gene expression does not increase by fasting but is strongly increased by leptin administration [61,72,73]. Thus orexin is not a typical orexigenic neuropeptide and based on its striking effect on sleep–wakefulness regulation it was suggested that the feeding related properties of orexin might be secondary to its regulation of arousal (a sleeping animal does not eat) [74,75] and regulation of arousal may well interact with other orexin modulated behaviors such as reward and anxiety.

Neurotensin expressing neurons are not restricted to, but are found abundantly in the lateral hypothalamic area [76], and centrally administered neurotensin may suppress food intake by modulation of the mesolimbic dopamine system [77,78]. Consistent with this interpretation are observations that anorexigenic leptin action induces neurotensin expression [79] and are suggested to involve leptin receptor expressing lateral hypothalamic neurotensin neurons ([80] and personal communication with Dr. Martin G Myers).

Galanin expressing neurons are found throughout most of the brain, including the lateral hypothalamic area. When injected into the paraventricular nucleus, galanin stimulates consumption of food, particularly high-fat diets, and alcohol: Conversely, high-fat consumption stimulates galanin gene expression in a positive feedback manner [81,82]. Galanin expression is not changed by fasting or leptin administration [83], but galanin deficient mice show enhanced leptin sensitivity [84]. Several studies demonstrated that central galanin also modulates the mesolimbic DA system [85–88], likely via galanin actions in the ventral tegmental area [87], possibly involving galanin projections from the paraventricular nucleus of the hypothalamus or the locus coeruleus. However, given the intense co-localization of galanin and neurotensin specifically in the perifornical area of the lateral hypothalamus (Fig. 4, unpublished observations), galanin expressing neurons in the lateral hypothalamic area may very well contribute to the modulation of the mesolimbic DA system. More recently, the role of galanin in stress related behavior as well as drug addiction [89,90] has been intensely studied and is thought to involve dopaminergic transduction (see review by Picciotto [91]).

CART expressing neurons are found scattered throughout the lateral hypothalamic area and other brain areas [92]. Intracerebroventricular CART inhibits food intake [93] and has effects on reward and anxiety (for a recent review see [94]). Leptin induces and fasting inhibits CART mRNA expression in the arcuate nucleus and more moderately in the dorsomedial nucleus and medial parts of the lateral hypothalamic area [93]. Research has been hindered by the absence of an identified CART-receptor and lack of antagonists [94].

Most neurons in the lateral hypothalamic area express more than one peptide and in addition may express either one of the classical neurotransmitters glutamate or GABA. The physiological significance of this co-expression of multiple neuotransmitters is in general not well understood and has not been investigated specifically for inputs

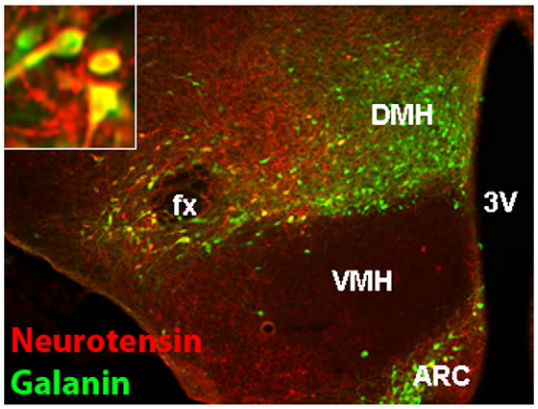

Fig. 4. Co-existence of orexigenic (galanin) and anorexigenic (neurotensin) neuropeptides in the LHA was demonstrated in colchicine-treated reporter mice with green fluorescent protein expression in galanin neurons (green) and co-staining for neurotensin (red).

to and downstream signaling of lateral hypothalamic neurons. Studies in sympathetic neurons expressing the classical neurotransmitters noradrenaline and acetylcholine together with the peptide NPY [95] demonstrate a degree of segregation of transmitters in different synapses [96] and preferential release of noradrenaline at low and NPY at high firing frequencies [97,98]. If such principles apply to lateral hypothalamic neurons it is conceivable that given neurons do not rigidly excite or inhibit downstream neurons, but can preferentially excite and inhibit downstream neurons in an activity-dependent and location-specific manner.

The new opto-genetic and designer drug tools are very promising to answer some of these questions. In a recent study, AgRP and POMC neurons were targeted with channelrhodopsin (ChR2) and light induced stimulation, resulting in increased or decreased food intake respectively, confirming earlier data (as reviewed by Schwartz [99]). However, these studies also showed that the firing frequency in AgRP neurons directly translated into feeding behavior (the higher the firing frequency, the more intense the hyperphagia observed). Furthermore, anorexia evoked by light stimulated POMC neurons required functional MC4R signaling, as expected from earlier findings, but orexigenic effects of optogenetically stimulated AgRP neurons were surprisingly independent of melacocortin receptor function [100]. These data are, however, consistent with other recent findings showing that GABAergic, but melanocortin independent brainstem inputs from AgRP neurons into the parabrachial nucleus are sufficient to explain orexigenic actions from AgRP neurons [101].

In summary, the lateral hypothalamic area with its rich inputs and outputs is in an ideal anatomical position to integrate both internal and external information and access all major output axes, behavioral, autonomic, and endocrine. However, much future research will be necessary to identify the details of input–output relationships of functionally specific sub-areas of the larger lateral hypothalamic area. These studies show clear evidence that arcuate feeding circuits are segregated into peptiderdic transmission and transmission via classic neurotransmitters and much has to be learned for their relative importance for feeding and other behaviors. Optogenetic tools will allow the study of other hypothalamic neurons in discrete brain sites and their functional (modulation of neuronal activity) and behavioral importance.

3. Role of the lateral hypothalamic area in sensing of the internal milieu

Sensing the internal milieu by the brain, including the availability of nutrients, is fundamental for the orchestration of optimal adaptive

responses under given environmental conditions. Although the basomedial hypothalamus and caudal brainstem have been identified as key areas involved in nutrient sensing (as reviewed in [102,103]), there is accumulating evidence for a similar role of the lateral hypothalamus and other brain areas. There are two ways by which a brain area can sense availability of nutrients, through neural inputs from primary nutrient-sensing areas elsewhere in the brain (or periphery) and by direct action of nutrient availability signals on neurons and glial cells within a given area. In the case of the lateral hypothalamic area, neural inputs from both the arcuate nucleus and the caudal brainstem (as discussed above) are likely to convey information about the availability of nutrients, although the relevant experiments necessary to demonstrate such a function, namely selective elimination of these inputs, have not yet been carried out.

After food is ingested, a cascade of signals is generated along the alimentary canal and the metabolic pathways in various organs after absorption. Together, these hormonal, metabolite, and neural signals provide comprehensive information regarding availability of nutrients acutely and long-term. The gustatory system is at the interface between environment and internal milieu and will be discussed together with the other external sensory modalities below.

3.1. Glucose and insulin as signals for acute fuel availability

Glucose sensing was already a hot topic soon after the hypothalamic centers were discovered. Using *in vivo* extracellular recording in a number of species, the pioneering work of the Japanese researcher Yutaka Oomura identified and characterized glucose sensitive neurons throughout the central and peripheral nervous system, including the lateral hypothalamus [104–106]. These and other earlier studies from the pre-leptin era on food intake-related functional aspects of the lateral hypothalamus are discussed in an extensive review by Bernardis and Bellinger [107].

While many of the earlier *in vitro* studies used glucose concentrations well above the physiological range found in normal brain tissue [108,109], the general observation of glucose-inhibited and glucose-excited neurons in the lateral hypothalamus was confirmed in studies using more physiological glucose concentrations. Specifically, it was demonstrated that while physiologically relevant glucose concentrations decrease excitability and inhibit orexin neurons, they increase excitability of co-mingled MCH neurons [110,111] and that a distinct population of orexin neurons exhibits only a transient inhibitory response to sustained rises in glucose levels, allowing cell firing to maintain sensitivity to small fluctuations while simultaneously encoding a large range of basal glucose concentrations [112].

It was originally thought that neuronal metabolism of glucose via the GLUT2 glucose transporter, glucokinase and the ATP-sensitive potassium channel (K_{ATP}) was necessary for glucose to change neuronal excitability, but several alternative mechanisms of glucose sensing have recently been described. First, the sweet taste receptor T1R2 is expressed in lateral hypothalamus and may activate neurons in a metabolism-independent fashion [113]. Second, orexin neurons may function as lactate sensors, as lactate produced in astrocytes and taken up by neighboring neurons through the monocarboxylate transporter (MCT1/2) may sustain spontaneous activity of orexin neurons and keep them sensitized for excitation by other stimuli, independent of glucose [114].

With the availability of c-Fos immunohistochemistry as a neuronal activity stain, it was also found that hypoglycemia induced by acute insulin administration in rats stimulated neurons throughout the lateral hypothalamic area, many of them co-expressing orexin [115]. A similar activation of lateral hypothalamic orexin and other neurons was found after acute food deprivation in rats [116] and monkeys [117], as well as after food restriction and 2-deoxy-D-glucose administration in rats [118]. However, these studies do not rule out activation of distant glucose sensing mechanisms and mediation by neural inputs to the lateral hypothalamus.

Finally, in a recent study in mice, it was shown that the transcription factor Foxa2, a downstream target of insulin signaling, regulates the expression of orexin and MCH during fasting. Constitutive activation of Foxa2 in the brain resulted in increased neuronal orexin and MCH expression and increased food consumption, metabolism, insulin sensitivity, and increased physical activity in the fed state (reaching the level in fasted mice) [119].

3.2. Leptin as a signal for availability of stored nutrients

Within the hypothalamus, the arcuate nucleus, with its NPY and POMC neurons, had been originally thought to play an exclusive role in integrating metabolic signals such as leptin. But clearly, leptin receptors are located in other hypothalamic areas such as the ventromedial, dorsomedial, and premammillary nuclei, as well as the lateral and perifornical areas, where they likely contribute to leptin's effects on food intake and energy expenditure. Indeed with novel transgenic tracing methods specific to leptin receptor expressing neurons, it was it was shown that LHA leptin receptor neurons modulate the mesolimbic dopamine system in the ventral tegmental area. While some leptin receptor-bearing lateral hypothalamic neurons project directly to the ventral tegmental area [72], they also locally synapse onto orexin (but not MCH neurons), which in turn also project to dopamine neurons in the ventral tegmental area [73]. Furthermore, leptin action in these lateral hypothalamic neurons, some of which also co-express neurotensin (personal communication with Dr. Martin G. Myers), increases orexin gene expression and decreases food intake [73]. Thus, orexin neurons do not themselves express leptin receptors but receive input from neighboring leptin receptor-expressing neurons [73] (Fig. 3). In addition, leptin responsive POMC/CART and NPY/AgRP neurons in the arcuate nucleus project to the lateral hypothalamus [27] and some of them make close anatomical contacts with orexin and MCH neurons [27,120]. It will be interesting to determine whether these two leptin-sensitive inputs to orexin neurons play different roles.

3.3. Signals from the gut

Ghrelin, a hormone secreted mainly from the gastric mucosa and showing the highest circulating levels in the absence of digestible nutrients, increases c-Fos expression in orexin but not MCH neurons when administered intracerebroventricularly [121,122] and directly depolarizes and increases firing frequency of orexin neurons *in vitro* [123]. Local administration of ghrelin into the lateral hypothalamic area increases food intake and wakefulness [124] and central pretreatment with anti-orexin antibody attenuated peripheral ghrelin-induced increase in food intake [121]. These findings strongly suggest that at least one site of action for endogenous ghrelin to stimulate arousal, foraging, and appetitive behavior is orexin neurons in the lateral hypothalamus [123].

A potential role for the lateral hypothalamic area in the effects on food intake by other gut hormones is much less clear. Although, as expected from a putative satiety hormone, direct lateral hypothalamic injections of GLP-1 suppressed and its receptor antagonist Exendin-9 increased short-term food intake in rats [125], GLP-1 unexpectedly depolarized orexin neurons and increased their spike frequency *in vitro*[126]. It is thus not clear whether the two gut hormones ghrelin and GLP-1, which have clearly opposite effects on food intake, act on different populations of orexin neurons. Except for a report of no effect of intraperitoneal injection of PYY(3–36) on orexin gene expression in mice, there are no data available suggesting a role for the LHA in the satiating effects of the other lower gut hormone PYY.

In addition to a direct action via the circulation and blood barrier transport mechanisms, gut hormones and mechanical signals can

potentially reach the lateral hypothalamic area via neural pathways including vagal afferents and medullary-hypothalamic projections including A2 catecholaminergic and GLP-1 expressing NTS neurons [127,128]. Functional input from vagal afferents to lateral hypothalamic neurons was demonstrated using extracellular recording techniques in intact rats [129]. This latter study further showed a remarkable degree of convergence on single lateral hypothalamic neurons of inputs from various sources. About half of all neurons tested responded to both vagal and cerebellar (somatic) input, and of all neurons doubly responsive, 60% were also glucose sensitive. Also, when the vagal and cerebellar inputs were stimulated simultaneously, a summation of the responses was observed [129].

In summary, glucose, insulin, ghrelin, and leptin have been quite convincingly demonstrated to directly act on various types of lateral hypothalamic neurons and to provide negative (insulin, leptin) and positive (ghrelin) feedback in the control of food intake. However, the specific circuitries and physiological roles of glucose-inhibited and glucose-stimulated neurons within the lateral hypothalamic area remain unclear.

3.4. Role of the lateral hypothalamic area in monitoring environmental stimuli and conditions

3.4.1. Olfactory, gustatory, somatosensory, and visual and information. Using single unit recording in intact animals, it was already shown during the height of the hypothalamic feeding center days that lateral hypothalamic neurons in the far-lateral hypothalamus receive olfactory and gustatory input [130–134]. Gustatory pathways from the parabrachial taste area to the lateral hypothalamus were confirmed with tracing techniques [135]. Extensive studies in Rhesus monkeys further identified both glucose excited and glucose inhibited LH neurons as recipients of olfactory and gustatory inputs [136–139]. The lateral hypothalamus also receives direct, monosynaptic input from nociceptive neurons in the spinal cord [140] and periaqueductal gray [141], and noxious stimuli increased Fos protein expression in orexin neurons [142].

3.5. Threat and stress

Besides input from nociceptive somatosensory afferents, orexin neurons are activated by immobilization and cold stress [143]. Because it was demonstrated that corticotrophin-releasing factor (CRF)-immunoreactive terminals make direct contact with orexin neurons and that CRF increases the firing rate of a subpopulation of orexin neurons in a CRF receptor-1 dependent fashion, it is likely that stress-induced arousal depends on a CRF-orexin pathway [143,144].

4. The LHA and behavioral effector pathways

4.1. Reward seeking

As mentioned in the introduction, one of the hallmarks of the lateral hypothalamus is its support of electrical self-stimulation, but that because of the indiscriminate activation of local neurons and fibers of passage with electrical stimulation, its underlying neurology is far from clear. Recent studies strongly implicate projections of lateral hypothalamic orexin neurons to the midbrain ventral tegmental area in this behavior. Orexin fibers innervate ventral tegmental dopamine neurons [145–147] which express orexin-1 receptors [148–150], and both dopaminergic and non-dopaminergic neurons in the ventral tegmental area are excited by orexins [151,152]. Ventral tegmental area orexin signaling is involved in cocaine and morphine-induced hyperlocomotion and place preference through the mesolimbic dopamine system, partly by potentiating NMDA-mediated excitatory currents in dopaminergic neurons [150,152]. Orexin-deficient mice are less susceptible to develop drug dependence [153], and orexin injection into the ventral tegmental area can reinstate an extinguished preference for drugs of abuse [154].

Our own observations implicate lateral hypothalamic orexin neurons in natural food reward. We used nucleus accumbens mu-opioid-induced intake of palatable food that was pioneered by the group of the late Anne Kelley as a model of reward-driven food intake in metabolically satiated rats [155–159], which is accompanied by activation of orexin neurons in the perifornical lateral hypothalamus [158,160], and can be blocked by inhibiting lateral hypothalamic activity with GABA receptor agonists [158] or glutamate receptor antagonist [48]. This suggests that glutamatergic neurons within the hypothalamus mediate the response, consistent with the finding that accumbens shell projections terminate in the anterior LH, rich in glutamatergic neurons that connect with orexin neurons in the more posterior lateral hypothalamus [30]. Because medium-spiny accumbens output neurons express GABA, the most parsimonious explanation is that stimulation of food intake is mediated by GABA-projections from the accumbens to the lateral hypothalamic area. These projection neurons seem to be normally (tonically) active and inhibit certain lateral hypothalamic neurons (e.g. orexin neurons) probably by presynaptically inhibiting glutamate release from local interneurons (Fig. 3). Inhibition of accumbens-lateral hypothalamus projection neurons leads to an arrest of GABA release from their terminals, disinhibition of these lateral hypothalamic neurons, and increased food intake. This model would fit the observation that activation of NMDA receptors in the lateral hypothalamus by glutamate is necessary for food-deprivation-induced food intake [161] and that injection of the GABA-antagonist bicuculline into the anterior lateral hypothalamic area increases ingestion of sweet milk [162].

Using this nucleus accumbens-driven intake of high-fat food in satiated rats, we showed that local bilateral injection of orexin receptor-1 antagonist into the ventral tegmental area blocked accumbens-induced palatable food intake [163] (Fig. 5). Findings by Harris and Aston-Jones suggest that largely separate orexin neuron populations in the lateral (lateral to fornix) and medial portions of the lateral hypothalamic area mediate reward- and stress-guided behaviors, respectively [154,164,165]. In contrast, we found significant increases in Fos-activated orexin neurons after accumbens DAMGO only in the perifornical area, but not in the more lateral orexin neuron population [163]. There is considerable literature demonstrating that metabolic stress such as food deprivation and restriction, insulin-induced hypoglycemia, and 2DG-induced glucoprivation, activates orexin neurons [115–118], although such activated orexin neurons can be found in both the medial and lateral fields [118]. Given the importance of the hypothalamic orexin neurons in these diverse functional aspects, it will be important to further examine functional specificity of subpopulations [166].

In addition, orexin neurons feed back specifically to cholinergic striatal interneurons via the paraventricular nucleus of the thalamus [167]. The seminal work by the group of Berridge and colleagues identified a “liking” hotspot in the shell of the nucleus accumbens where mu-opioid activity enhances positive hedonic reactions to palatable foods in rats [168,169]. Together, these findings strongly suggest a role for an accumbens—LH orexin—VTA circuit in the expression of natural food reward.

While most of the above described experiments use pharmacological levels of drug applications, it remains elusive if endogenous orexin levels stimulate dopaminergic VTA neurons and if this would translate into DA release and behavioral changes. A recent study by Tsai et al. [170] used an optogenetic approach to test the behavioral effects of different firing frequencies in dopaminergic DA neurons in the VTA. The study convincingly showed that light evoked high frequency phasic firing, but not low frequency tonic firing, caused a conditioned place preference and transient DA release in the nucleus accumbens [170]. Therefore, phasic dopaminergic activity is sufficient

to evoke behavioral conditioning. Thus, future experiments using neuron specific stimulation/inhibition of LHA (e.g. orexin) neurons should reveal exiting new insights linking neuronal activity with appetitive behavior and reward function.

4.2. Food intake

Although reward seeking is an important component, a number of other neural systems are required for the orchestration of ingestive behavior. These include access to appropriate oro-motor and locomotor functions and its autonomic support, which are generally organized in the hindbrain and spinal cord. One approach we and others have used to address hindbrain participation in orexin-induced food intake is 4th ventricular administration of orexin in rats [68,171]. We demonstrated that sub-populations of about 20% and 10% of lateral hypothalamic orexin and MCH neurons, respectively, project to the nucleus of the solitary tract and dorsal motor nucleus with axon terminals in close contact to neurons expressing tyrosine hydroxylase and GLP-1, both allegedly involved in satiation and suppression of food intake. Similar contacts were frequently observed with neurons of the nucleus of the solitary tract,

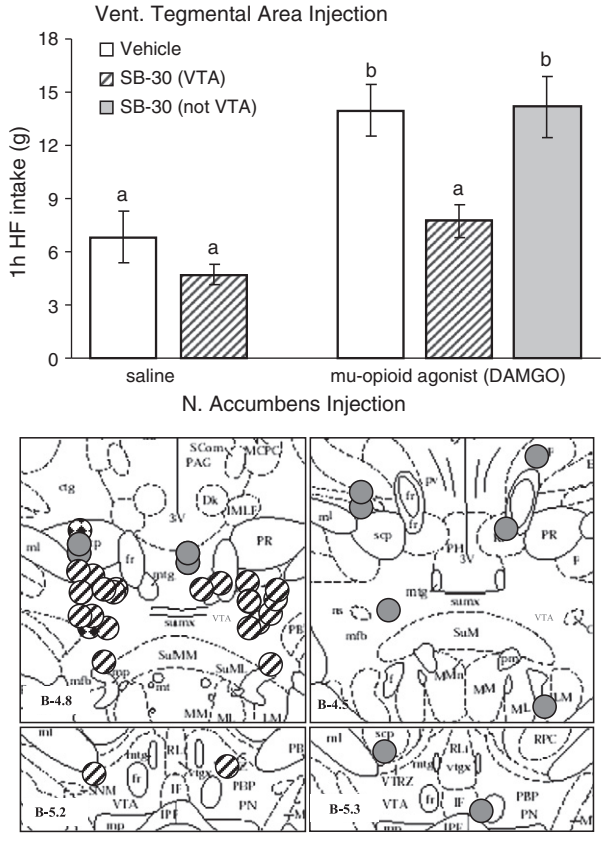

Fig. 5. Orexin-1R antagonist administration into the VTA blocks high-fat intake induced by accumbens administration of DAMGO. a: Vehicle or the orexin receptor antagonist SB334867 (15 nmol/side) was injected into the VTA and saline or DAMGO (250 ng) into the nucleus accumbens after overnight access to high-fat chow for pre-satiation. The robust DAMGO-induced feeding response over saline baseline ($p<0.001$) was almost completely abolished by VTA pretreatment with the orexin receptor antagonist. In animals with either one or both of the bilateral cannula tips not within the VTA, the orexin receptor antagonist was unable to block DAMGO-induced high-fat feeding. Bars that do not share the same letter are significantly different from each other (based on ANOVA, followed by Bonferroni-adjusted multiple comparisons test, $p<0.05$). b: Verification of orexin receptor antagonist injection sites aimed at the VTA. Striped circles depict animals with both sites within the VTA ($n=11$), gray circles depict animals with one or both sites outside the VTA ($n=6$), and diamond-filled circles depict animals with unilateral injections ($n=2$). Injection sites are superimposed on images from the Paxinos and Watson stereotaxic atlas.

activation of which by gastrointestinal food stimuli was demonstrated by the expression of nuclear c-Fos immunoreactivity, and orexin-A administration to the fourth ventricle induced significant Fos-expression in many of the catecholaminergic neurons. Finally, fourth ventricular orexin injections significantly stimulated chow and water intake in nonfood-deprived rats, and direct bilateral injections of orexin into the dorsal vagal complex increased intake of palatable high-fat diet [68].

To further characterize the role of hindbrain orexin signaling in ingestive behavior, Baird and colleagues used sucrose licking microstructure analysis [171]. Fourth ventricular administration of orexin increased both meal size and meal frequency. Prolonging meals without affecting early ingestion rate or lick burst size suggested that orexin affected inhibitory postingestive feedback rather than taste evaluation [171]. This interpretation was supported by the observation that third ventricular orexin, while still able to increase meal frequency, was no longer able to increase meal size in rats with lesions of the area postrema and adjacent NTS [171]. Together, the findings suggest that areas in the hindbrain mediate the increase in consummatory (meal size) and the hypothalamus and other forebrain sites mediate the appetitive (meal frequency) components of orexin-induced hyperphagia.

The hypothalamic effect on meal frequency (meal initiation) could be mediated by orexin projections to the arcuate nucleus NPY/AgRP and POMC/CART neuron populations [172]. Specifically, POMC neurons are presynaptically inhibited by orexin *in vivo*[173]. This pathway may also play a permissive role in food intake induced by mu-opioid stimulation of the nucleus accumbens [160].

In summary, we have come a long way in better understanding what is happening in the classical "feeding center". A circuitry that includes at least parts of the lateral hypothalamic area, the midbrain dopamine system with its numerous cortico-limbic targets, and the nucleus accumbens, appears to be important for reward seeking and the initiation of appetitive behavior. Equally important circuits including reciprocal connections with the medullary oromotor pattern generators and projections to the brainstem and spinal cord autonomic preganglionic neurons prepare the internal milieu for an ingestive bout and sustain ingestive behavior.

5. The LHA and autonomic effector pathways

5.1. Gut, pancreas, and hepatic functions

Again, electrical stimulation and lesions of the LHA were the first to show changes in gastrointestinal [174], pancreatic [175], hepatic [176,177], and adipose tissue functions [178], as mediated by the sympathetic and parasympathetic nervous system. However, only the discovery of neuropeptides and other technological advances made it possible to identify the specific pathways and confirm some of these earlier claims.

We demonstrated that local administration of minute amounts of orexin-A into the dorsal motor nucleus of the vagus nerve increased gastric motility and intragastric pressure [179]. Together with demonstrating orexin receptor-1 on gastric retrogradely identified vagal motor neurons [179,180] and our anatomical findings discussed above, these observations strongly suggest that lateral hypothalamic orexin neurons can directly influence gastrointestinal functions via vagal excitatory motor neurons in preparation for handling ingested nutrients. Similarly, central orexin administration appears to stimulate pancreatic exocrine secretion in a vagus-dependent but gastric acid secretion-independent fashion [181], and hypoglycemia-induced increases in vagal efferent signaling to the pancreas depends on orexin-signaling in the dorsal motor nucleus of the vagus [182].

Orexin projections to the spinal cord appear to specifically innervate sympathetic preganglionic neurons, which are activated

and synchronized by orexin in an orexin receptor-1 dependent fashion [183].

5.2. Energy expenditure

We also examined in detail orexin-A innervation of the caudal raphé nuclei in the medulla, known to harbor sympathetic preganglionic motor neurons involved in thermal, cardiovascular, and gastrointestinal regulation. All three components of the caudal raphé nuclei, raphé pallidus, raphé obscurus, and parapyramidal nucleus, are innervated by orexin-A-immunoreactive fibers [184]. Using confocal microscopy, we demonstrate close anatomical appositions between varicose orexin-A immunoreactive axon profiles and sympathetic premotor neurons identified with either a transneuronal retrograde pseudorabies virus tracer injected into the interscapular brown fat pads, or with *in situ* hybridization of pro-TRH mRNA [184]. Furthermore, orexin-A injected into the fourth ventricle induced c-Fos expression in the raphé pallidus and parapyramidal nucleus [184]. These findings suggest that orexin neurons in the hypothalamus can modulate brown fat thermogenesis, cardiovascular, and gastrointestinal functions by acting directly on neurons in the caudal raphé nuclei, and support the idea that orexin's simultaneous stimulation of food intake and sympathetic activity might have evolved as a mechanism to stay alert while foraging [184].

Fourth ventricular administration of melanin-concentrating hormone in freely moving rats decreased core body temperature but did not change locomotor activity and food and water intake [58]. We conclude that the rich hypothalamo-medullary melanin-concentrating hormone projections in the rat are mainly inhibitory to nucleus of the solitary tract neurons, but are not involved in the control of food intake. Projections to ventral medullary sites may play a role in the inhibitory effect of melanin-concentrating hormones on energy expenditure [58,185].

6. Conclusions and perspective

An exciting new discovery more than 50 years ago showed that electrical stimulation of the lateral hypothalamic area induces feeding and self-stimulation behavior. However, only the continuous progress in neuroanatomical, neurochemical, and genetically-based techniques has allowed us to have at least a glimpse of understanding the neurology behind these phenomena. As could have been suspected 50 years ago, the lateral hypothalamus “does it not alone”; it is the rich connectivity with key downstream effector circuits and mechanisms and feedback from the metabolic periphery that underlies these phenomena. Despite these new insights, there are still more questions than answers. One issue is the connectivity and functional specificity of lateral hypothalamic sub-areas. Are all orexin or MCH neurons serving the same physiological functions, or are there different orexin or MCH-fields that serve different aspects of a unifying function or different functions altogether? Another unsolved issue is the physiological significance of co-expression of multiple classical and peptide neurotransmitters in a given neuron. We believe the new generation of methodological tools such as the ability to selectively stimulate specific neurons will greatly facilitate exciting future research.

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