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REVIEW

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Obesity- and diet-induced plasticity in systems that control eating and energy balance

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Abstract

In April 2023, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), in partnership with the National Institute of Child Health and Human Development, the National Institute on Aging, and the Office of Behavioral and Social Sciences Research, hosted a 2-day online workshop to discuss neural plasticity in energy homeostasis and obesity. The goal was to provide a broad view of current knowledge while identifying research questions and challenges regarding neural systems that control food intake and energy balance. This review includes highlights from the meeting and is intended both to introduce unfamiliar audiences with concepts central to energy homeostasis, feeding, and obesity and to highlight up-and-coming research in these areas that may be of special interest to those with a

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background in these fields. The overarching theme of this review addresses plasticity within the central and peripheral nervous systems that regulates and influences eating, emphasizing distinctions between healthy and disease states. This is by no means a comprehensive review because this is a broad and rapidly developing area. However, we have pointed out relevant reviews and primary articles throughout, as well as gaps in current understanding and opportunities for developments in the field.

INTRODUCTION

Systems that control ingestive behavior (i.e., eating and drinking), energy absorption, storage, and utilization undergo continual adaptation in response to environmental and internal changes. Such adaptations span many organ systems and involve both peripheral and central integration of humoral and neural signals. Unsurprisingly, biological processes that modulate feeding during health and disease states are complex and multifaceted. The nervous system is the primary interface through which information from the external environment is integrated with internal states to respond to and anticipate energy needs, optimize energy utilization, and make long-term predictions about future energy needs.

Energy homeostasis is the biological process that stabilizes body weight by matching energy expenditure to energy intake over time. The brain receives a variety of neural, nutrient, and hormonal signals that reflect energy availability and integrates these signals with visual, olfactory, and cognitive cues. Specifically, whereas experience-based learning supports predictions regarding nutrient availability, the gastrointestinal (GI) tract is the initial site of nutrient absorption. The routes from gut nutrient detection to the brain are not fully understood but certainly involve vagal and spinal sensory neurons, as well as gut hormones that influence neural activity in central regions beyond the brainstem and hypothalamus. In addition, the chemical senses of taste (gustation) and smell (olfaction) contribute not only to food detection and selection but also to the initiation of anticipatory and post-ingestive processes. A further layer of complexity is provided by emotional and cognitive processes within cortical, amygdalar, striatal, mesolimbic, and hippocampal circuits that can influence ingestive behavior by suppressing the motivation to eat in the face of an acute threat, potentiating motivation to eat during periods of energy deprivation, access to highly palatable foods during physiologically demanding states such as pregnancy and lactation, or by modulating motivation to eat in response to stressors that increase allostatic load.

The robustness of the system controlling energy homeostasis is evidenced by the adaptive, dynamic plasticity that occurs in response to weight loss in healthy-weight humans and animals. For example, although caloric restriction promotes body weight loss, it also increases the drive to eat and reduces energy expenditure. These adaptations limit further weight loss and promote recovery of lost weight. Consequently, when body weight is lost through diet and exercise, most individuals who either have obesity or a healthy body weight regain their lost weight within 5 years [1]. Conversely, when weight gain is induced by overfeeding in healthy-weight individuals, the drive to eat is reduced while energy expenditure increases, helping to restore body weight to baseline [2, 3].

Study Importance

What is already known?

- Functional and structural plasticity in the neural systems that control energy homeostasis has been widely reported. Neural plasticity includes adaptive responses to normal energetic demands and potentially maladaptive responses to energetic surplus. Understanding neural plasticity in the context of healthy and unhealthy changes in body weight was the goal of this workshop.

What does this meeting report add?

- This report summarizes and synthesizes the work of active behavioral neuroscientists focused on the neural circuits that control appetite, eating, satiety, energy homeostasis, and peripheral metabolism.

Given the presence of multiple finely tuned systems that regulate body weight and energy balance, why do some develop obesity? The existence of biological mechanisms that protect against the gain or loss of body weight supports the view that obesity involves the "defense" of an elevated body weight and not the absence of body weight regulation per se. Rather than explaining obesity as a passive accumulation of excess weight, a growing body of evidence has suggested that obesity is a disorder of energy homeostasis. As discussed later in this article, chronic consumption of energy-dense "obesogenic" foods appears sufficient to alter the nervous system and digestion-related viscera in such a way as to increase caloric intake and slow metabolism, which together promote increased body weight and adiposity. Such diet-related adjustments in behavior and physiology likely combined to give humans an evolutionary advantage. However, the ready availability of energy-dense foods in many modern societies, including the United States, is widely viewed as a key factor underlying the increased incidence of obesity and associated chronic diseases.

The ability of diet and other factors to induce plasticity within neural, hormonal, and visceral systems that accommodate physiological or pathological adaptations of food intake and energy expenditure was the subject of a 2-day virtual workshop organized by the National Institutes of Health (NIH) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), "Neural Plasticity in Energy

Homeostasis and Obesity." This report provides a general overview of workshop presentations focused on diet- and obesity-induced plasticity across integrated systems spanning peripheral tissues, chemosensation, and central and peripheral neural circuits; for a recent comprehensive review of neural systems that control eating, see Watts et al. [4]. The shared goal of the workshop and this report is to summarize current understanding and to highlight important open questions regarding how diet and other environmental pressures induce structural and functional plasticity within physiological systems that regulate food intake and body energy balance (Figure 1).

CENTRAL INTEGRATION OF SIGNALS THAT IMPACT EATING AND ENERGY BALANCE

The concept of energy balance provides a useful, although incomplete, framework for examining processes that control food intake and metabolism. In this framework, homeostatic control systems monitor and balance energy intake with energy expenditure to help ensure survival. To achieve this coordination, the brain and spinal cord receive and process exteroceptive signals arising from environmental stimuli and interoceptive signals including those arising from the gut and other organs (e.g., pancreas, liver). Here, we focus on cues that are more directly related to food and ingestion, although it is important to consider how other types of cues (e.g., interoceptive cues associated with anxious states or exteroceptive cues such as predator odors) can also influence feeding.

Exteroceptive signals include ambient temperature; social cues; and the sight, odor, and sound of food-related stimuli. In contrast, interoceptive signals include those that give rise to the conscious perceptions of hunger, thirst, satiety, and nausea, and those that can impact ingestive behavior and metabolism in the absence of conscious perceptions (e.g., infection, low blood pressure). Many interoceptive signals are conveyed to the central nervous system (CNS) by vagal and spinal afferents whose peripheral axons innervate the stomach, intestine, and hepatic portal vein. The cell bodies of vagal afferents are located in the nodose ganglia, and their central axons project to the caudal nucleus of the solitary tract (NTS) in the caudal medulla. The cell bodies of spinal visceral afferents are located in the dorsal root ganglia (DRG), and their central axons terminate within the

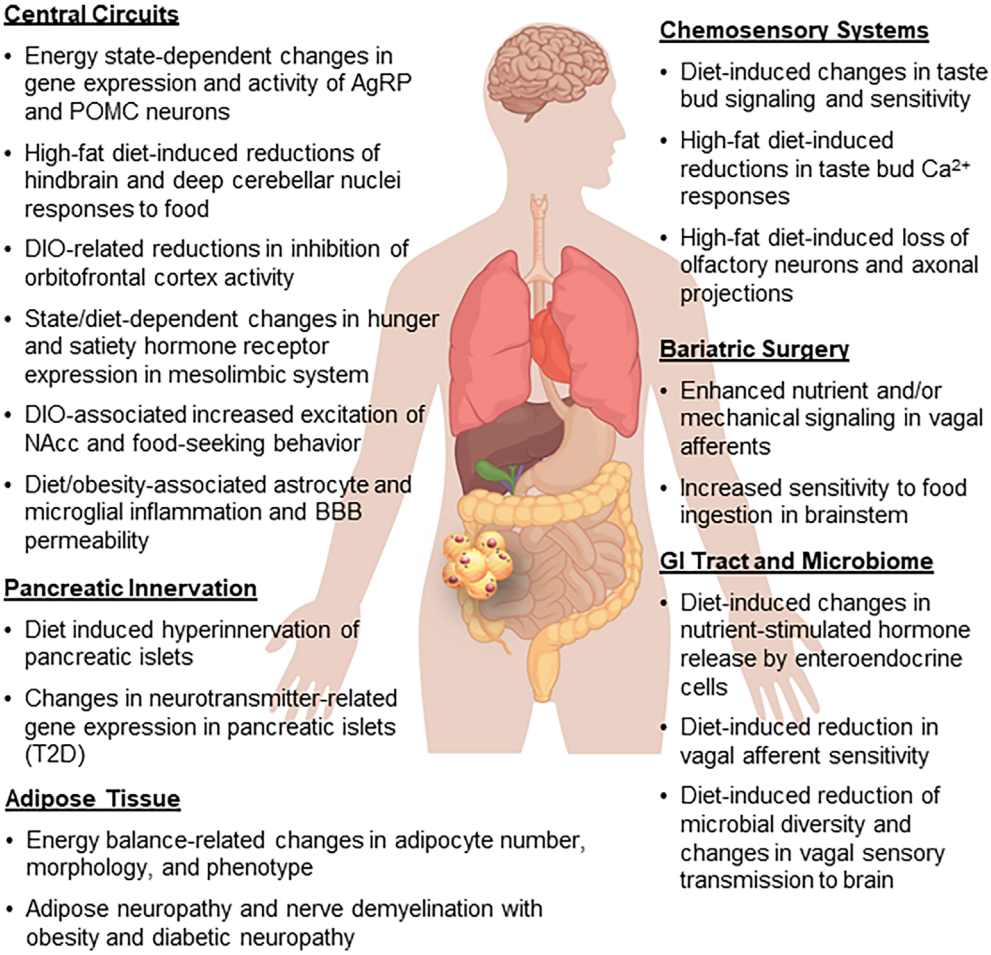

FIGURE 1 Site-specific plasticity involves central circuits and peripheral chemosensory systems across multiple organs. Plasticity is influenced by energy balance and factors that affect energy balance, including diet-induced obesity (DIO), high-fat diet, bariatric surgery, the gut microbiome, and pathophysiology of obesity and type 2 diabetes (T2D).

dorsal horn of the spinal cord that projects to the brain. Additional interoceptive signals include humoral factors secreted by peripheral tissues and organs, including the gut, pancreas, and adipose tissue. Such signals may modulate the activity of vagal and spinal visceral sensory neurons and can have direct actions on neurons within the CNS [5–7].

The integration of interoceptive signals is exemplified by the ability of leptin (produced by adipocytes and other tissues including those in the stomach) to enhance GI satiety signaling to the brain during food intake [8, 9]. Conversely, when leptin signaling is reduced during states of caloric deficit, central responsiveness to GI satiety signals is blunted, leading to larger meals [9, 10]. These findings help explain how interoceptive feedback about body adiposity (i.e., stored energy) can promote adaptive adjustments in energy intake during individual meals. The integration of exteroceptive and interoceptive signals with humoral signals is understudied, but it likely contributes to the accurate central representation of ever changing internal and external states [11, 12]. In human and animal models, chronic exposure to obesogenic diets alters interoceptive signaling pathways that normally limit intake, such that the impact of adipose- and/or nutrient-derived feedback cues are suppressed or "outcompeted" by signals that promote continued food consumption. These types of effects can be transient or long-lasting.

Defining the brain regions that integrate interoceptive feedback through vagal, spinal, chemosensory, and hormonal routes is an area of active research [4]. Neurons within the dorsal horn and NTS project directly and/or polysynaptically to the brainstem, hypothalamic, and corticolimbic regions that are important for controlling food intake and energy balance. Vagal and spinal sensory neurons and neurons within the dorsal horn and NTS express receptors for humoral factors that signify states of caloric deficit or repletion. NTS neural activity is modulated by circulating leptin and gut hormones such as cholecystokinin (CCK) and glucagon-like peptide 1 (GLP-1). In addition, subsets of DRG neurons express receptors for leptin, GLP-1, and other circulating factors [13, 14], suggesting that these humoral factors modulate sensory signaling to the spinal cord. Other key integration nodes include the hypothalamic arcuate nucleus (ARC), the paraventricular hypothalamus (PVH), and the lateral hypothalamic area, all of which contain neurons that express a variety of hormone receptors, and all receive direct and multi-synaptic input from the NTS and spinal cord [4]. Parallel spino-striatal and spino-cortical pathways may represent additional circuits for eating-related reward/reinforcement and conscious perception of gastric fill and other GI sensory signals [4]. However, published studies have not addressed whether obesogenic diet consumption alters neural signaling through spinal DRG neurons and ascending sensory pathways, or how plasticity in these pathways might alter reward and/or conscious perception of gastric fill in a manner that influences food intake.

PLASTICITY DURING EARLY DEVELOPMENT

Changes in neural systems that regulate food intake and energy balance during adulthood may stem from the developmental programming of relevant circuits. As such, research in this area seeks to uncover targets for therapeutic interventions aimed at maladaptive neuroplasticity of eating-related circuits during pre- and postnatal development. For example, vagal sensory inputs to the caudal brainstem arrive during embryonic development in rodents such that the essential brainstem circuits for vagally mediated digestive processes are established before birth. However, significant axonal outgrowth, synaptic refinement, and remodeling of central circuits that control food intake continue for at least 3 weeks postnatally [15, 16]. Therefore, early-life events and exposures, including stress and diet, can profoundly alter neurocircuit development in ways that can be both adaptive and maladaptive, with consequences for energy homeostasis in adulthood, which has been reviewed by Rinaman et al. [17]. One emerging concept is that developmental changes in neural circuits can sensitize or desensitize responses to sensory signals. A classic developmental model of circuit formation points to the postnatal surge of leptin as a critical signal that supports axonal outgrowth from the ARC to specific hypothalamic target sites [18]. Interestingly, leptin or leptin receptor deficiency in mice enhances the development and density of GLP-1 axonal inputs to the hypothalamus, accompanied by increased activation of PVH neurons in response to GI vagal sensory stimulation [19]. It will be important to determine whether these effects are reversible and whether they are sufficient to explain why a maternal high-fat diet promotes susceptibility to body weight gain in offspring [20].

In humans, the developmentally comparable period with the leptin surge in mice is the last trimester in utero [21]. However, whether this period shows comparable sensitivity to the long-term consequences of maternal obesity and long-term effects on the development of energy balance circuits is currently unknown. This is a particularly important area of study, given the increasing incidence of overweight and obesity in pregnant women in many countries across the globe [22]. Estimates have suggested that, worldwide, nearly 39 million pregnancies per year are complicated by maternal obesity, which is a risk factor for obesity and metabolic disease in offspring [20].

In rodents, maternal consumption of an obesogenic diet during gestation and/or lactation promotes inflammation-like cytoarchitectural changes in the brains of offspring that include astroglial activation, microglial infiltration, and cytoskeletal disruption [23], accompanied by alterations in the functional dynamics of gamma-aminobutyric acid (GABA)-A receptors within the dorsal vagal complex (DVC). When the offspring of obesogenic diet-fed dams reach adulthood, tonic activation of slower GABA-A α2/3 subunit-containing receptors may increase the inhibition of vagal motor outflow to the GI tract [24]. Reduced vagally mediated gastric motility and emptying of gastric contents into the intestine delay intestinal exposure to nutrients during a meal [25], thereby prolonging meal duration and increasing food intake. Descending axonal projections from pre-autonomic neurons in the hypothalamic PVH that project to the DVC are altered in offspring of dams maintained on an obesogenic diet [26], which may contribute to the observed dysregulation of vagally mediated GI functions.

Maternal obesogenic diet consumption reportedly reduces hypothalamic neurogenesis in the offspring [27] and may induce plasticity in striatal components of the central reward system [28]. Offspring of obesogenic diet-fed dams display lessevoked release of striatal dopamine, altered spontaneous activity of D1 receptor-expressing neurons, and reduced axonal projections of D2 receptor-expressing neurons [28]. Maternal high-fat–diet maintenance also induces sex-dependent epigenetic modifications to central and peripheral leptin receptors in the offspring [29, 30]. Notably, for many of these forms of plasticity, it remains unclear whether it is the chronic consumption of obesogenic foods or maternal obesity itself that has the greatest impact on the offspring.

PLASTICITY IN GUSTATORY AND OLFACTORY CHEMOSENSORY SYSTEMS

Taste (gustation) and smell (olfaction) are critical for detecting and selecting foods. Sensory transduction of chemical tastants in the oral cavity and odorants in the nasal epithelium engages glossopharyngeal, facial, and vagal primary sensory afferents (for taste) that innervate the rostral NTS, as well as olfactory receptors (for smell) that signal through olfactory nerve inputs to the olfactory bulb. Central processing of these chemosensory signals informs expectations and predictions regarding the properties of food and the outcomes of its ingestion. Thus, plasticity within chemosensory circuits can potentially influence ingestive behavior and the development of obesity.

Plasticity in chemosensory circuits has been studied both during development and in adulthood. Early studies of the rodent taste system focused on the responsivity of primary taste nerves to sodium and how these responses are altered by low- or high-sodium diets administered during critical periods of development, e.g., Hill et al. [31]. Human studies have reported a positive relationship between sodium consumption in adulthood and preference for sodium [32]. Gustatory plasticity and its capacity for reversal may be due to the high rate of turnover of taste cells within the tongue [33, 34], coupled with the continuous establishment of their innervation by primary sensory afferents that carry taste signals to the brainstem. However, the precise mechanisms are poorly understood; see May and Dus [35] for review.

Dietary changes in sugar levels also change behavioral and/or neurophysiological taste responses to sweet stimuli in invertebrates, rodents, and humans, which has been reviewed in May and Dus and Sung et al. [35, 36]. In rodents, an increase in dietary sucrose for 4 weeks blunts the sensory nerve responses to sucrose and reduces the number of chemosensory cells without weight changes. Removal of sugar from the diet restores both effects [36, 37]. Beyond the effects of dietary sugar, a high-fat diet reduces calcium responses of taste receptor cells to several stimuli, including sweet and bitter [38, 39]. These decreases were not due to higher adiposity because some of these deficits were seen following high-fat–diet consumption without weight gain.

Together, these studies highlight the complexity of diet-induced plasticity within the taste system, with interactions between diet composition and responsivity to different taste stimuli. The mechanisms by which these diet-induced alterations in gustatory sensitivity ultimately influence food choice or intake are poorly understood. However, diet-induced chemosensory plasticity in flies has been causally linked to changes in food preferences and intake [40]. In humans, reducing dietary sugar increases the perception of sweetness intensity, but much remains unknown regarding the peripheral sensory effects of increased dietary sucrose [41]. Nonetheless, the shift in taste perception reported in humans is consistent with the findings described earlier in rodents and flies and highlights the potential contribution of chemosensory plasticity to eating.

Although olfaction is less well-studied than gustation in the context of obesity or dietary environment, recent studies have suggested that the olfactory system influences metabolism and energy homeostasis. For example, consumption of excess dietary fat results in a loss of axonal projections from the nasal epithelium to the olfactory bulb in male and female mice before obesity, thereby altering olfactory circuitry [42]. Enhancing the excitability of the primary output neurons of the olfactory bulb either through drug targeting [43] or genome editing of a voltage-dependent potassium channel in these neurons [44] is sufficient to reduce the obesogenic effect of chronic exposure to a high-fat diet [45]. However, contrary to what is seen in the taste system in response to dietary manipulations of sodium, diet-induced loss of olfactory sensory axonal input to the olfactory bulb persists after dietary reversal [46].

Chemosensory systems are dynamically regulated by circulating levels of insulin, glucose, leptin, and gut hormones, including GLP-1 [45, 47, 48]. Indeed, GLP-1 can enhance mitral cell excitability by reducing the conductance of the potassium channel (Kv)1.3 [49] and is involved in a unique microcircuit that shapes its firing frequency [50]. Obesity is associated with altered circulating levels of metabolic hormones assessed before and after food intake in humans and rodents [51, 52], although it is unclear whether and how such alterations influence chemosensory systems.

The molecular and neural mechanisms of chemosensory plasticity in vertebrates are poorly understood, but studies from invertebrate systems may shed some light. Studies in fruit flies have shown that shifts in metabolic pathways alter transcription and chromatin to change the responses of the sensory cells [53]. Although it is unknown whether similar mechanisms are at play in vertebrates, there is evidence that consumption of high dietary sugar blunts signal transduction downstream of taste cells in flies, rodents, and humans [35, 39], although reversibility has not been examined. Recent studies in rodents have suggested that microglial activity influences the density of taste nerve terminal fields within the brainstem, and that dietary manipulations (including low sodium) may affect microglial migration before and during early stages of taste nerve development [54]. These are but a few of the many outstanding questions regarding how dietary environment and obesity affect the structure and function of peripheral taste and olfactory systems.

PLASTICITY IN CENTRAL NUTRIENT-DETECTING SYSTEMS

Nutrient-induced signaling from gut to brain occurs within seconds to minutes after food is swallowed to influence ongoing food intake by increasing or limiting meal size. Similar to brainstem NTS neurons that respond to circulating factors and sensory input from the GI tract, agouti-related peptide (AgRP)-expressing neurons in the ARC of the hypothalamus respond to multiple short- and long-term feedback signals regarding the body's current metabolic and physiological status [55, 56], relaying these signals to other hypothalamic nuclei and additional downstream targets. Although AgRP neural activity increases during states of negative energy balance, AgRP neural activation is sufficient but not necessary for the initiation of eating [57, 58], and the role played by AgRP neurons may be redundant with the roles played by other populations of GABA-A ARC neurons [59–61].

However, an apparently unique role for AgRP neurons in eating-related behavioral responses to environmental cues is evidenced by their rapid suppression in action potential firing when established food cues are encountered and the animal switches from food-seeking to consummatory behavior. AgRP neural activity remains suppressed when consumed or infused nutrients are detected in the GI tract, with the magnitude of suppression proportional to caloric intake [57]. Thus, increased activity of AgRP neurons appears to drive food-seeking during caloric deficit, whereas reduced activity of these neurons corresponds to caloric repletion. Indeed, if a novel consumed food contains no calories, the initial suppression of AgRP neural activity in response to consumption of this food rapidly reverses as the animal returns to foraging [62, 63]. Furthermore, calorie-free foods and their associated cues fail to suppress AgRP neural activity or terminate food-seeking, thereby exemplifying a hypothalamic nutrient-detecting system that ensures adequate caloric intake while also protecting against overconsumption.

The activity of feeding-related neurons and neural circuit activity can be modulated not only by post-ingestive signals but also by alterations in energy demand and availability, such as what occurs during pregnancy, in response to significant changes in diet or ambient temperature, or during illness or disease. These situations can trigger plasticity in homeostatic control systems at the genetic, cellular, and circuit levels. For example, transient states of energy deficit (e.g., after fasting) or surplus (e.g., after caloric repletion) differentially alter gene expression and neural activity of AgRP and proopiomelanocortin (POMC) neurons within the hypothalamic ARC. In these conditions, AgRP neurons are activated and inhibited, respectively, whereas the opposite occurs in POMC neurons. These alterations can be accompanied by shifts in the balance of inhibitory and excitatory inputs to these neurons that can ultimately cause robust changes in body weight [64–66]. Indeed, preventing synaptic plasticity by conditional deletion of N-methyl-D-aspartate (NMDA) receptors in AgRP neurons prevents fasting-induced AgRP activation and markedly reduces body weight and food intake [67], highlighting the importance of plasticity within these systems.

Similar to energy deprivation, cold exposure also rapidly activates AgRP neurons, and this is required for cold-induced food intake [68]. However, the normal coupling of energy homeostasis to thermoregulation is impaired by high-fat–diet feeding. Mice maintained on a high-fat diet do not increase their energy intake during cold exposure, an effect associated with reduced AgRP neuron activity [69]. In contrast, exercise promotes the inhibition of AgRP neurons, at least in part by increasing the ratio of inhibitory to excitatory synaptic inputs [70]. This synaptic plasticity in ARC neurons in response to different metabolic challenges is initiated through different sensory channels and central neural circuitries. A primary source of information is provided by post-ingestive feedback from the GI tract, which engages ARC-projecting PVH neurons to ultimately induce synaptic plasticity, as well as fasting-induced activation of AgRP neurons [66].

Despite general knowledge regarding various hormonal and multi-synaptic neural pathways mediating GI sensory feedback to the PVH, the precise routes of the feedback signals that drive hypothalamic neural plasticity are undefined. Potential candidates include the caudal NTS and the deep cerebellar nuclei [71], where obesogenic diets cause a blunted response to GI signals [71, 72], suggesting that neurons in these brainstem regions are integral to centrally mediated synaptic plasticity observed in AgRP (and possibly other) hypothalamic neurons. Indeed, recent studies have demonstrated that, unlike lean mice, obese mice eating an obesogenic diet fail to suppress AgRP neural activity in response to intragastric infusion of fat [55]. Another source of peripheral feedback to the PVH may be an ascending noradrenergic hindbrain-hypothalamic circuit [73], but its function has not been studied, to our knowledge, in obese mice. Further research should provide a more complete circuit-based understanding of how diet-induced plasticity alters long-term energy homeostasis. It also will be important to determine how functional plasticity in these pathways interacts with higher brain regions (e.g., orbitofrontal cortex [OFC]; see the following section) to potentially impact motivational state and decision-making [74].

Plasticity in eating-related learning, memory, and motivation systems

In both human and animal models, a growing literature has indicated that consumption of obesogenic diets and increased adiposity induces plasticity in brain systems that underlie decision-making, motivation, reward, and learning processes, including prefrontal cortical, mesocorticolimbic, and hippocampal circuits [75–78]. Meta-analyses of results from human studies have found that increased adiposity (as indicated by body mass index [BMI]) is associated with reduced performance on several neurocognitive tasks that measure impulse control, decision-making, and reward valuation, e.g., Vainik et al. [79]. These complex processes rely on the integration of internal states with learned expectations, external cues, and other factors to ultimately determine whether eating is initiated.

The OFC is particularly important for decision-making, reward valuation, and impulse control; see Wikenheiser and Schoenbaum [80]

for review. Recent studies using electrophysiology in ex vivo slices from adult rodents revealed that diet-induced obesity reduces inhibitory transmission onto OFC pyramidal neurons [81] and impairs the ability of endocannabinoids to regulate this local inhibition [82]. This reduction in inhibition ultimately enhances OFC activity and thereby reduces the flexibility of decision-making related to eating in obese male mice [83].

The hippocampus is important for many forms of memory, including visuospatial navigational memory and episodic memory. These aspects of memory are essential for a range of eating-related behaviors, including successful foraging and associative memory processes that link specific food sources with the consequences of their ingestion. Consistent with these roles, the hippocampus expresses receptors for many metabolic and endocrine signals, including insulin, leptin, GLP-1, and ghrelin; see Kanoski and Grill [84] for review. Activation of these receptors in the hippocampus promotes neural plasticity and memory in healthy-weight rodents. For example, activation of ghrelin receptors increases food intake and promotes learned food-motivated responses [85–87], whereas activation of GLP-1 receptors can reduce these behaviors [88, 89].

A growing body of evidence has suggested that hippocampal-dependent learning and memory processes are modulated by a gut-vagus nerve-hippocampal axis [84]. Neuroanatomical tracing studies have indicated that projections from the medial NTS to the medial septum (which innervates the hippocampus) represent a potential relay through which vagal sensory signals from the gut might reach the hippocampus [90]. However, the presence of functional synaptic connections along this potential gut-to-hippocampal signaling pathway, and the chemical phenotypes of neurons within it remain to be defined. Studies have shown that gastric distension and infusion of nutrients directly into the gut of rodents, or direct vagal nerve stimulation in humans, increases activity within the hippocampus [91, 92]. In this regard, ablation of gut-specific vagal sensory neurons impairs performance in hippocampal-dependent tasks in a manner related to reduced brain-derived neurotrophic factor (BDNF) in the dorsal hippocampus [93]. Additionally, suppressing ghrelin receptor signaling to vagal sensory neurons is sufficient to impair hippocampal-dependent memory [94]. However, the relative importance of hippocampal endocrine signaling versus direct interaction with vagal afferents for long-term energy homeostasis remains unclear.

Despite an extensive literature on the role of mesolimbic systems in the pursuit of food [76, 95], relatively little is known about how these systems and the behaviors they subserve are altered by obesity or by consumption of obesogenic foods [77, 96]. Recent rodent studies have suggested that eating an obesogenic diet is sufficient to alter striatal function in ways that promote food-seeking, even before the onset of obesity. For example, consumption of an obesogenic diet is sufficient to enhance excitatory transmission in the nucleus accumbens (NAc) core (NAcc) and promote cued food-seeking behaviors [97, 98]. Interestingly, these neural and behavioral alterations persist for weeks after cessation of eating the obesogenic diet and are more pronounced in populations that are susceptible to diet-induced weight gain; see Ferrario [75] for review. The former finding suggests that diet-induced plasticity in NAcc may contribute to initial weight gain by promoting food-seeking in response to environmental stimuli associated with food (i.e., food cues). The precise mechanisms through which consumption of obesogenic foods trigger glutamatergic plasticity in the NAcc are poorly understood, although recent work has shed some light [99].

Similar to the hippocampus and neocortex, the NAc expresses receptors for a range of signaling factors whose levels rise and fall according to states of energy depletion and repletion (e.g., ghrelin, GLP-1, and insulin). For example, insulin receptor activation in the NAc enhances excitatory neurotransmission and local dopamine release and is required for flavor-nutrient preference learning [100]; see Patel et al. and Ferrario and Reagan [101, 102] for review. Furthermore, effects of insulin on the mesolimbic system are blunted in diet-induced obesity [100, 101, 103], although the necessity of increased adiposity for these effects has not been demonstrated. Interestingly, whereas intra-NAc insulin is sufficient to suppress food intake in hungry rats, it does not affect cue-triggered food-seeking [104]. Thus, there appears to be a dissociation between the ability of insulin acting within the NAc to influence food-seeking versus consumption. Studies such as these and others that have examined effects of hunger and satiety hormones on mesolimbic systems [105–107] highlight interactions between mesolimbic motivational systems and endocrine systems.

Nonneuronal regulators of central plasticity

Until recently, the neuron-centric view of CNS function has largely overlooked nonneuronal cells (e.g., astrocytes, microglia, endothelial cells, tanycytes) as major contributors to ingestive behavior and metabolic homeostasis. However, astrocytes and microglia can sense changes in nutrients; energy need state; and circulating levels of glucose, leptin, insulin, neurotrophic factors, and sex hormones [108–112]. Astrocyte-initiated signaling events can influence synapse formation, synaptic strengthening, and glutamate clearance from the synaptic cleft [113]. Astrocytic signaling alters neuronal activity within the caudal NTS [114], and astrocytic (but not neuronal) BDNF/tropomyosin receptor kinase B (TrkB) signaling within the ventromedial hypothalamus promotes robust body weight gain [111]. In addition, fission and fusion processes in astrocytic mitochondria are sufficient to protect against diet-induced obesity [115]. Thus, astrocytes appear capable of sensing environmental events and modulating neuronal communication.

Within days after introducing an obesogenic diet, CNS microglia take on a reactive morphology [116], reflecting the acute inflammatory effects of such diets. Activated microglia have been linked to disruption of the blood–brain barrier (BBB), increasing CNS exposure to circulating metabolites and cytokines associated with obesogenic foods, which has been reviewed by Nampoothiri et al. and Stranahan [117, 118]. However, a role for microglia in the control of body energy balance is a matter of debate. Increased astrocytic and microglial activation in mice reportedly mediates the body weight and metabolic

adaptations of diet-induced obesity [119] and has been referred to as "brain scarring" to indicate a pathological condition [116]. Conversely, other studies have interpreted glial activation and increased BBB permeability as salutary physiological responses that may help maintain energy balance in the face of altered dietary factors [120, 121]. It will be important to determine whether diet- and/or obesity-induced activation of glia and increased BBB permeability are causally linked, as well as the circumstances under which astrocytes and microglia play beneficial versus pathological roles. Consumption of obesogenic diets in rodents also activates microglia along the gut-brain axis [122], adding to the complexity of diet-induced inflammatory processes.

PLASTICITY IN PERIPHERAL NUTRIENT-DETECTING SYSTEMS

Although digestion and nutrient detection begin in the oral cavity, nutrient absorption begins within the small intestine of the upper GI tract, a key region for diet-induced plasticity of the gut-brain axis. The potentially powerful role of endogenous gut hormones in glucose regulation, food intake, and body weight homeostasis is supported by the recent therapeutic success of gut hormone analogues to treat diabetes and obesity [123]. The canonical textbook view indicates that nutrient sensing and absorption across the intestinal villi stimulates resident enteroendocrine (EE) cells to release gut hormones into the local intestinal tissue environment. Hormones escaping this environment are processed through the liver and subsequently enter the systemic circulation. Some circulating gut hormones and metabolites access receptors within the brain on a timescale of minutes. However, the most rapid and direct effects (timescale of seconds) of gut hormones occur via G-protein-coupled receptors in the local intestinal environment, including receptors expressed by vagal sensory, spinal sensory, and enteric neurons whose processes reach into the lamina propria of intestinal villi [124].

Some gut sensory EE cells synapse directly with vagal afferents to enable transduction of nutrient signals to neural activity on a timescale of milliseconds. These morphologically and functionally distinct subsets of EE cells have been called neuropods to highlight their unique synaptic associations with sensory afferents [125, 126]. EE cells in general, and neuropod cells in particular, may provide the key physiological mechanism through which dietary caloric sugars are rapidly distinguished from noncaloric sweeteners after consumption. Some neuropod cells express the sweet taste receptor T1R3, which is activated both by sugar and by noncaloric sweeteners. However, neuropod cells release glutamate in response to sugar and ATP in response to noncaloric sweeteners; importantly, vagal sensory afferents respond differentially to glutamate versus ATP [125]. This T1R3-mediated signaling from neuropods to vagal afferent neurons permits rapid nutrient-based signaling from gut to brain that does not depend on circulating levels of gut hormones. EE cells (including neuropods) also express microbial recognition receptors, making them well-equipped to sense diet-induced changes in the gut microbiome, such as those that occur during exposure to obesogenic diets [125, 127]. For example, EE cells express toll-like receptor 5 (TLR5; a microbial recognition receptor for bacterial flagellin), and TLR5 signaling within the distal intestine promotes EE cell release of satiety hormones that bind to receptors on sensory afferents [126]. There are many unanswered questions regarding the anatomical and functional associations that exist between EE cells/neuropods and the CNS. For example, it is unclear whether all types or only specific subtypes of intestinal EE cells can assume neuropod morphology and form synapses with extrinsic spinal and/or vagal nerves and whether this occurs throughout the length of the intestine or only within certain segments. It also is unclear whether non-synaptic paracrine signaling mechanisms exist in addition to synaptic mechanisms and, if so, whether the two types of signaling play different functional roles.

Plasticity in the GI tract

Intriguingly, genetic deletion of TLR5 from neuropods and other EE cells in mice leads to increased food intake and body weight gain [128], similar to the effect of an obesogenic diet. When rodents are maintained on an obesogenic diet for as little as 2 weeks, vagal afferent neuronal sensitivity to mechanical gastric tension, satiety hormones, and nutrients is suppressed [129]; importantly, these effects precede significant increases in body weight or adiposity. Because the presumed consequence of reduced sensitivity to meal-related satiety signals would be consumption of larger meals, it seems logical that diet-induced reductions in satiety signals would precede obesity. The process of satiation that leads to meal termination (i.e., control of meal size) is largely achieved by vagal sensory input to the caudal NTS [130]. Thus, consumption of obesogenic diets may promote overeating in part by altering vagal sensory signals [131] and/or by inducing central neural plasticity that alters how the brain responds to sensory feedback.

Plasticity in the gut microbiome and effects on signal transmission to the brain

Obesogenic diets can change the composition of the rodent gut microbiome in ways that impact the brain, including altered interactions between EE cells and vagal afferents that communicate nutrient-related signals to the caudal NTS. Obesogenic diet-induced microbial and neuronal changes are both necessary and sufficient to alter food intake and to impact reinforcing effects of food, evidenced in part by reduced striatal dopamine responses. Beyond the expected shift in gut microbial populations due to altered availability of lumenal substrates, intake of obesogenic foods contributes to the alteration of brain signaling systems by reducing microbial diversity and shifting the relative abundance of distinct microbial populations, increasing gut permeability and increasing bacterial proinflammatory products [132]. Transplanting obesogenic-primed gut microbes to lean, chow-fed recipients is sufficient to induce the typical outcomes of an obesogenic diet, including increased food intake, weight gain, blunted

responses to gut satiety hormones, and microglial proliferation along the gut-brain axis [133, 134]. However, the specific type of gut bacteria that contribute to the development of obesity remains unclear, as do the precise neural mechanisms through which the gut microbiome modulates host behavior.

These findings support the view that obesogenic, diet-induced alterations in gut microbiota induce plasticity in vagal sensory transmission to the brainstem and hypothalamus (see the Plasticity in central nutrient-detecting systems section), highlighting the emerging consensus for the sensory vagus as a key upstream mediator of diet-induced plasticity in central control of motivated behavior.

For example, in lean, chow-fed rats, intestinal processing of palatable foods containing high levels of fat and sugar engages vagal and spinal signaling pathways that increase reward-linked striatal dopamine levels; however, interestingly, the same foods evoke less striatal dopamine release in obese rats maintained on an obesogenic diet [135]. These data suggest that striatal dopamine transmission encodes the nutritional and/or caloric value of consumed foods to thereby influence meal size and caloric intake [136], and that this encoding is disrupted in diet-induced obesity. Furthermore, studies comparing germ-free rats with rats that received chow- or obesogenic diet-primed microbiota transplants confirmed that obesogenic diet-type microbiota are associated with reduced striatal dopamine signaling and decreased motivation to work for food, as assessed by operant lever pressing in Kim et al. [137].

Mice will work to receive optogenetic stimulation of gut vagal sensory neurons [138], indicating that gut vagal sensory fiber activation is reinforcing. The neural circuits for this reinforcement include an ascending multi-synaptic pathway from gut vagal afferents to dopamine neurons in the substantia nigra that, in turn, innervate the dorsal striatum [138]. In recent work, rats with obesogenic diet-type microbiome transplants were found to have blunted striatal dopamine responses to nutrients, but striatal dopamine signaling was restored after lesioning their CCK receptor-expressing GI vagal sensory neurons [137]. These findings support the view that vagal signaling pathways contribute to the reinforcing effects of GI signaling and also contribute to suppression of dopamine-mediated reinforcement during obesogenic diet exposure. Vagal gut-brain signaling is also required for the effect of intestinal fat to inhibit hypothalamic AgRP neurons, whereas spinal gut-brain signaling relays the presence of intestinal glucose to the hypothalamus [56]. A potential role of spinal sensory pathways in the reinforcing effects of intestinal nutrients remains to be demonstrated. In addition, it is unclear whether impaired vagal signaling contributes to the onset or the maintenance of obesity.

Plasticity after bariatric surgery

Vertical sleeve gastrectomy (VSG) and Roux-en-Y gastric bypass (RYGB) each produce early and rapid postsurgical reductions in food intake that may initially be due to reduced gastric capacity. Over time, cumulative food intake may begin to recover as humans (and experimental animals) shift their feeding patterns. Following these surgeries, weight loss stabilizes at ~10% to 30% of initial body weight, depending on surgery type [139]. Stable, long-term weight loss maintained after bariatric surgery is thought to result from altered sensory feedback to the CNS [140]. The mechanisms underlying this increased sensitivity are unknown but could reflect increased vagal sensory recruitment by peripheral signals and/or plasticity that increases postsynaptic NTS neuronal responses to vagal inputs. For example, bariatric surgery in mice sensitizes brainstem neurons to respond to ingested meals. All bariatric surgeries result in the consumption of smaller, more frequent meals, consistent with the increased release of gut hormones and increased sensitivity of central neural circuits to satiation signals. Dietary preferences post-surgery also shift toward foods with lower caloric density, presumably contributing to the maintenance of weight loss [141]. This may be partly due to aversive learning signals because consumption of high-fat, high-sugar obesogenic foods after VSG can produce malaise. However, evidence also has been found for enhanced intestinal nutrient and/or mechanical signaling through GI vagal afferent pathways to promote enhanced meal-induced neuronal activation in the brainstem [142].

Despite the remarkable benefits for body weight loss and near-instant diabetes remission afforded by bariatric surgery, postsurgical hypoglycemia is a newly recognized problem [143]. This suggests the presence of additional plasticity in physiological systems that maintain glucose homeostasis. Furthermore, some patients do not respond to bariatric surgery, and patients with type 2 diabetes mellitus typically lose less weight than patients without diabetes [144]. Current strategies to determine whether individual patients will benefit from bariatric surgery are lacking, and this is an important future goal. It also remains unclear why significant weight loss after bariatric surgery does not trigger adaptive increases in the drive to eat and/or reductions in energy expenditure, both of which are well-known physiological adaptations to negative energy balance during weight loss in humans and rodents. Bariatric surgery is an intriguing model to understand how these adaptive responses to body weight loss are counteracted, which could generate new insights and strategies for preventing weight regain in individuals who lose body weight through lifestyle interventions rather than through surgical or pharmacological interventions.

Plasticity in pancreatic neural circuits

Multiple lines of evidence have indicated that obesity and diabetes are associated with structural and functional changes in the pancreas. Both nonobese diabetic mice and mice with diet-induced obesity develop hyper-innervated pancreatic islets, which are also observed in humans with type 2 diabetes [145]. Sympathetic and parasympathetic fibers each contribute to the observed hyperinnervation in diabetic, hyperglycemic mouse models [146], although the cause of increased innervation remains unclear. Sympathetic islet hyperinnervation has been confirmed in pancreatic islets of individuals with type 2 diabetes, but not in those with type 1 diabetes [147], and enlargement of parasympathetic pancreatic ganglia was observed postmortem in pancreatic tissue obtained from an individual with obesity and unknown

glycemic status. Spinal and vagal sensory innervation of the pancreas has not been studied in humans with obesity or diabetes, to our knowledge, but remodeling of pancreatic sensory inputs has been noted during pancreatitis or pancreatic tumors. Altered pancreatic innervation likely affects pancreatic function; e.g., vagal efferent parasympathetic nerves control the release of pancreatic polypeptide, which is dysregulated in obesity [148].

The mechanisms contributing to structural and functional neural plasticity in the pancreas with obesity or diabetes are largely unknown. However, type 2 diabetic rats display large shifts in the expression of genes that regulate synaptic function and structure in sympathetic ganglionic neurons [149]. Pancreatic islets in humans with diabetes are characterized by changes in expression of genes involved in neurotransmitter degradation, adrenergic signaling, and neurotransmitter pathways [147]. Emerging technologies enabling multiplex imaging of cleared human pancreatic tissue obtained via biopsy [150] hold promise for more detailed examination of alterations in pancreatic innervation in humans with obesity and/or diabetes. Approaches such as in vivo calcium imaging of pancreatic innervation could be used to identify alterations in pancreatic nerve function with greater temporal resolution. The application of single-cell RNA sequencing and spatial transcriptomics to ganglia innervating the pancreas should also generate new insights into the mechanisms contributing to obesity-associated changes in pancreatic innervation.

Plasticity in white adipose tissue innervation and function

Excess body fat is initially stored in white adipose tissue (WAT), the key organ whose enlargement during body weight gain defines obesity. Several studies have suggested that the inability of WAT to further expand, followed by ectopic lipid storage in the liver and other body tissues, may trigger metabolic disease [151]. Thus, much research has focused on WAT, revealing it to be a multicellular organ system composed of preadipocytes, fibroblasts, capillary endothelial cells, macrophages and numerous other immune cells, and stem cells. WAT is innervated by sympathetic axons and spinal sensory nerves, both of which modulate body fat deposition. The neuro–adipose nexus shares structural similarities with neuromuscular junctions, and details are now emerging regarding its identity as a component of sensory and/or sympathetic circuits and its plasticity in response to environmental alterations [152].

The physiological roles of WAT include endocrine, metabolic, and immune functions, with neural inputs regulating adipogenesis, lipolysis, and browning. WAT tissue mass increases during states of positive energy balance, including obesity, and falls during states of negative energy balance. WAT is a highly dynamic tissue system, changing not only in mass but also in the number, morphology, and phenotypes of adipose cells, presumably in response to altered innervation and nerve activity. In this regard, WAT provides a unique model for studying plasticity and remodeling of peripheral nerves [153]. Improved understanding of this process may reveal insights regarding how nerves might be induced to regrow in order to regain healthy brain–adipose communication, which is critical for regulating energy balance. However, the densest innervation is around brown/beige adipocytes and relatively sparse among white adipocytes, as confirmed in human WAT [151, 154]. Most of these WAT axons have en passant varicosities that contain synaptic vesicles, indicating that nerve products could dissipate locally in the tissue. Potential changes in adipose innervation patterns could significantly alter adipose metabolic processes. Sympathetic denervation of WAT (including denervation of both brown and white adipocytes and arteries) leads to adipocyte proliferation (hyperplasia), whereas selective sensory denervation of WAT increases adipocyte cellular size, but not number [155, 156]. Interestingly, these experimentally induced alterations in adipocyte number and size are not accompanied by significant alterations in body weight, perhaps due to compensatory changes in the innervation and nerve activity in other fat depots.

Obesity, type 2 diabetes, and aging are each associated with reduced neural input to adipocytes. Adipose neuropathy in mice is sufficient to alter the structure and function of fat depots and promote metabolic disease [153]. In conjunction with obese and diabetic neuropathy, adipose nerves become demyelinated [157], which presumably impacts brain–adipose communication and function in ways that remain to be examined. Similar to the effects of experimental denervation, defective adipose tissue innervation occurs independent of body weight gain in rodents and cannot be restored by normalizing body fat (e.g., through dietary restriction via pair feeding). Leptin replacement in *ob/ob* mice (which lack endogenous leptin) fully restored their otherwise reduced sympathetic innervation of WAT. This occurred via effects on central neural pathways that included hypothalamic neurons [158], but potential demyelination and remyelination of WAT innervation was not investigated. Thus, the known neurotrophic role of leptin to promote axonal growth in the hypothalamus may extend to peripheral nerve growth in adipose tissue. Nevertheless, the extent to which WAT innervation contributes to body weight homeostasis remains unresolved because surgical, chemical, or genetic denervation of inguinal WAT depots is insufficient to change body weight in experimental rodent models. Improved understanding of this process may reveal insights regarding how nerves might be induced to regrow in order to regain healthy brain–adipose communication, which is critical for regulating energy balance. An important future direction is understanding how the neurotransmitters and neuropeptides supplied by adipose innervation contribute to tissue metabolism in vivo, including receptor-mediated mechanisms that impact adipocytes and immune cells in lean and obese states. Independent of body weight, a healthy adipose depot is likely conferred by functioning local innervation.

SUMMARY AND OVERVIEW

Body energy balance is homeostatically regulated through complex interactions involving peripheral tissues, hormones and cytokines, and neural circuits. The rapidly developing field of brain connectomics

offers powerful tools to understand the large-scale organization of neural networks that orchestrate ingestive behaviors via autonomic and endocrine actions [159, 160]. Powerful new experimental techniques are being developed and applied to manipulate, image, and analyze these interacting systems in conscious animals. However, much remains to be learned regarding signal integration from diverse organs, how this integration regulates eating, metabolism and energy expenditure, and how it alters homeostasis during obesity.

Research presented during this 2-day workshop supports the view that plasticity at any level of the bidirectional peripheral-brain axis can promote metabolic stress and obesity. Despite strong preclinical rodent models of diet-induced obesity, the physiological and behavioral impact of consuming obesogenic foods is difficult to demonstrate outside of the laboratory. It is even more difficult to dissociate diet-induced obesity in humans from the effects of other factors that may contribute to excessive body weight gain, including food insecurity, sedentary lifestyle, chronic stress, pollution, disrupted sleep, drug use, and genetic predisposition. Nonetheless, it seems logical to focus on dietary factors, including the specific properties of food, that promote adaptive plasticity or dysregulation in energy control systems in addition to understanding healthy physiology and its regulation.

There is consensus that obesogenic foods are highly processed, palatable, calorically dense, and nutrient- and fiber-poor. The highly palatable nature of obesogenic foods promotes overconsumption above what is needed to maintain established demands [161], leading to increased adiposity and body weight gain. The combination of these factors and others, e.g., those proposed in the carbohydrate-insulin model (see Ludwig and Ebbeling and Hall et al. for discussion [162, 163]), ultimately establishes a revised homeostatic balance that can progress to metabolic dysregulation in humans and in the animals we feed, including livestock, laboratory research animals, and household pets. As reviewed in this workshop report, obesogenic diets seem to reduce the detection and/or transmission of sensory feedback signals that promote satiation and satiety. Revealing the mechanistic details underlying this plasticity is an active area of research and may lead to improved therapeutic approaches for curbing the deleterious effects of diet on body weight and adiposity.

RESEARCH GAPS AND OPPORTUNITIES

The speakers and organizers of this workshop identified a number of research gaps and opportunities for additional investigation. Some of these were included in the preceding narrative, organized by topic. Several additional research challenges and questions for future investigation were discussed during the workshop, including the following:

- Most brain regions are characterized by heterogeneous rather than homogeneous neural populations and subpopulations that express unique genes and form unique afferent and efferent connections. For example, there are multiple subpopulations of neurons in the hypothalamic ARC that express *AGRP* or *POMC* [147], multiple subpopulations of noradrenergic neurons in the NTS that are differentially responsive to vagal sensory input [164], and multiple subpopulations of vagal afferent neurons in the nodose ganglia that are differentially responsive to gut mechanical and chemical stimuli. The physiological relevance of neural subpopulations that code distinct sensory events is currently unknown. It will be important to fully characterize unique subpopulations of neurons within these and other central and peripheral areas that control food intake and energy balance, and then to investigate plasticity in gene expression, cellular function, and/or connectivity that occurs in response to obesogenic diet or other manipulations that promote obesity.
- Food and Drug Administration-approved treatments for weight loss currently include bariatric surgery and drugs that target nutrient-stimulated hormone receptors, e.g., for GLP-1 and gastric inhibitory peptide. We need to improve our understanding of how these treatments impact eating behavior and whole-body energy balance and how these behavioral and physiological effects may change over time. We also need to understand the basis for common positive and negative side effects of these treatments, such as reduced craving for drugs and alcohol, nausea, vomiting, loss of lean mass, and altered food reward [165, 166].
- How do the central and peripheral systems that control energy balance adapt to changes in factors other than diet, including ambient temperature, increased energetic demands, chronic stress, and other environmental impacts? In what situations are these adaptations beneficial, and when do they transition into promoting unhealthy or disease states? Are these adaptations reversible, and on what timescales? Improved knowledge around these issues may let us take advantage of plasticity to shape and direct responses to environmental demands (e.g., preventing reduced metabolism during dieting for weight loss or preventing increased food intake after exercise, as well as exploiting adaptive chemosensory plasticity for food design and weight loss).
- What are the relative roles of autonomic (vagal and spinal) afferents innervating metabolically important tissues and organs such as the pancreas, digestive tube, adipose tissue, muscle, and liver in these physiological and pathophysiological adaptations? For example, the rich vagal innervation of the gut has received much more attention than innervation by spinal sensory afferents. In this regard, one roadblock to progress is that the anatomical distribution of DRG makes spinal sensory neurons difficult to access, manipulate, and image in experimental models. More research effort should be directed toward understanding the role of spinal sensory transmission and central interaction with vagal inputs that control food intake and energy balance.
- Motivational reward systems and central learning and memory processes interact with homeostatic networks to influence food choice and intake, often driving intake above homeostatic need. Preclinical studies that have examinined the mechanisms through which obesogenic foods or weight gain alter these systems to promote unhealthy eating behavior are in their infancy, and important

questions remain regarding the degree to which diet- or obesity-induced alterations in these broader aspects of behavior and brain function can be reversed.

- There is mounting evidence that obesity alters emotional regulatory systems in ways that promote anxiety, depression, and impulse control disorders. The mechanisms through which these emotional systems interact with homeostatic and broader peripheral nervous systems to promote these states remains unclear, and the variables that enhance or dampen these interactions are not well-characterized (e.g., microbiota, dietary environment, sleep/wake cycles, in addition to degree of adiposity).
- Overweight, obesity, and metabolic dysregulation are distinct physiological states. However, transitions from one to the other regarding neural plasticity are not well-defined. In addition, overeating must necessarily precede common weight gain. Therefore, it is imperative to use models and approaches that enable researchers to distinguish causes from effects of increased adiposity, as well as metabolic and homeostatic dysregulation.O

AUTHOR CONTRIBUTIONS

Carrie R. Ferrario, Heike Münzberg-Gruening, Linda Rinaman, Padma Maruvada, Diana Cummings, and Bradley M. Cooke wrote the initial draft of this manuscript. All other authors made substantial contributions to editing and refining the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

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