National Institutes of Health
National Institute of Diabetes and Digestive and Kidney Diseases

Neural Plasticity in Energy Homeostasis and Obesity

Virtual Workshop
April 13–14, 2023

EXECUTIVE SUMMARY

Background and Overview

Obesity and associated metabolic syndromes are major public health concerns. Dynamic neural circuits and pathways have increasingly been shown to play critical roles in appetite regulation and energy metabolism. More effective strategies to prevent and treat these metabolic conditions require a greater understanding of how obesogenic environmental and physiological conditions alter the neural networks that control appetite, eating, and energy homeostasis.

The Neural Plasticity in Energy Homeostasis and Obesity workshop was sponsored by the Office of Obesity Research in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The purpose of the workshop was to bring together experts in the neural plasticity of central and peripheral circuits that control food intake, energy homeostasis, and metabolism in healthy and unhealthy states (such as obesity) to review the science. The objectives of the workshop included the following:

- Identify knowledge gaps regarding the functional plasticity within these circuits.
- Determine high-priority areas of research that may lead to therapeutic advances for obesity and other disorders related to metabolic dysregulation and food intake.

Approximately 450 participants from across the United States and other countries registered and attended the workshop.

The major themes of the scientific sessions included the following:

1. Plasticity in Chemosensory Signaling
2. Plasticity in Visceral Sensory and Humoral Feedback Pathways
3. Plasticity in Autonomic and Hormonal Pathways
4. Energy Sensing and Homeostasis: Central Nervous System (CNS) Circuits
5. Neural Plasticity in Feeding-Related Learning and Memory
6. Cellular Regulators of Neural Plasticity

Breakout groups for the themes of Plasticity in Chemosensory and Visceral Sensory Signaling (Sessions 1 and 2), Plasticity of Autonomic Pathways, Endocrine Signals, and Non-Neural Cells (Sessions 3 and 6), and Plasticity Associated with CNS Circuits and Learning and Memory (Sessions 4 and 5) met on the second day of the workshop and supported discussion of key considerations for the field.

The plenary presentation opened the meeting with an outline of the current state of the science of neurobiological regulation of food intake and energy balance. More than 30 brain regions have been linked to the regulation of food intake, adiposity, and thermogenesis. However, it is not yet clear why so many regions are able to influence energy homeostasis and eating behaviors and how these centers are connected. Novel approaches are needed to address broad questions related to the organization and regulation of neural circuits related to energy metabolism. For example, connectomes—or systematic accounts of neuroanatomical connections—make use of comprehensive matrixes of relevant data to

expose known and unknown connections at multiple scales via complex network analysis. Connectomics and other innovative modes of analysis will be critical to further understanding the role of neural plasticity in energy homeostasis and related pathologies.

Scientific Sessions

Meeting speakers presented on topics under each main theme listed above. Following the scientific sessions, moderated discussions were used to identify knowledge gaps and research opportunities relevant to these topics. A summary of emerging studies and roadblocks, gaps, and opportunities for each main scientific theme is outlined below:

Plasticity in Chemosensory Signaling

Emerging Studies

- Taste receptor cells undergo constant renewal and can be modulated by diet, hormones, and inflammation. In general, taste receptor cells are less responsive (particularly to sweet and fat) in obese animals. Obesity is associated with reduced expression of genes associated with cell renewal, immunity, and taste-signaling pathways in taste buds. Sweet taste signals are reduced in obese mice, and fewer taste cells in these mice are responsive to artificial sweeteners.
- Diet-induced taste plasticity can be modeled in *Drosophila melanogaster* and rodents, where high-sucrose diets have been shown to dull sweetness sensation in the peripheral nervous system. Excess dietary sugar resulted in taste and food-learning deficits, overeating, and obesity via cell-autonomous activity in sweet-sensing dopaminergic neurons. Correcting taste deficits by manipulating sweet gustatory neuron excitability protected animals from diet-induced obesity.
- Epithelial sodium channel–mediated (ENaC-mediated) sodium taste activity is necessary for developing and maintaining dendritic fields in the gustatory nucleus tractus solitarii (NTS). The mechanism whereby ENaC-mediated sodium taste activity influences taste response appears to involve the function of glia (resident macrophages of the CNS), which can be pharmacologically manipulated to resemble those of mice with genetic or dietary sodium restriction. Glia are diminished in mice that are fed a low-sodium diet from embryonic days 3 through 12.
- The olfactory system encodes odor information and coordinates with regions of the brain that regulate energy homeostasis. Mice lacking the Kv1.3 voltage-gated potassium channel, which dampens the excitability of olfactory nerves, have increased sensitivity to smell and are resistant to diet-induced obesity. Isocaloric feeding experiments in mice demonstrated that feeding with a high-fat diet (HFD)—rather than the resulting obesity—produced a loss of projections to the olfactory bulb. Mice reared on a HFD have irreversible olfactory learning deficits.

Roadblocks, Gaps, and Opportunities

- Taste, food intake, and obesity have dynamic and intricate relationships influenced by multiple factors that are difficult to tease apart (e.g., effects of diet versus obesity or calories versus macronutrients).
- Changes that occur during the onset of obesity are not necessarily important during the maintenance of obesity.
- The molecular mechanisms whereby obesity alters sensory receptor cells are unclear, as are the changes that are the key drivers affecting food intake and whether these changes are reversible.
- Methods are needed for targeted delivery of molecules to sensory tissues in the CNS to modulate metabolism.

- Careful studies are needed to define how obesity affects chemosensory cell function.
- Changing the excitability of olfactory neurons is a potential therapeutic for obesity or olfactory dysfunction.

Plasticity in Visceral Sensory and Humoral Feedback Pathways

Emerging Studies

- Activity in agouti-related protein (AgRP) neurons in the arcuate nucleus (ARC) of the hypothalamus drives, and is a robust predictor of, feeding behavior. Single-trial plasticity has been observed in AgRP neurons—whose activity decreases upon the sight or smell of food—in response to the changing caloric value of food. Long-term plasticity also has been observed. Lateral deep cerebellar nuclei mediate satiation, an effect that is lost during diet-induced obesity.
- Sensory neurons of the vagal afferent pathway signal from the upper, digestive portion of the gut to dopaminergic neurons in the substantia nigra, resulting in the release of dopamine in the dorsal striatum, which is an area known to be involved with habit formation. Sensory neurons of the spinal dorsal root ganglia signal primarily from the lower gut in a separate pathway associated with the ventral striatum (VS). The vagus system is hypothesized to provide the brain with information on digestion, and the function of the spinal system appears to be related to the ability of the brain to consciously perceive sensations in the body.
- Enteroendocrine cells synapse directly with vagal afferents to transduce food stimuli within milliseconds. Especially in the distal portion of the gut, these enteroendocrine cells (also called neuropods) are enriched in microbial-recognition receptors (e.g., toll-like receptor 5 [TLR5]). Deletion of TLR5 in mouse neuropods leads to increased meal size, feeding duration, and body weight, and this effect can be recapitulated when flagellin (a TLR5 activator) is applied to the gut. Flagellin can activate *in vitro* neuropod signaling and *in vivo* vagal firing in a TLR5-dependent manner.
- HFD-induced microbiome changes alter the structure and function of the vagal afferent pathway that regulates meal size and induce concomitant deficits in reward signaling. Gut colonization with HFD-type microbiota reduces vagal innervation to the NTS and dopamine release in the nucleus accumbens (NA) of the VS in response to dietary fat. HFD gut colonization also inhibits the response to a satiety peptide. These effects can be reversed by targeted disruption of gut-derived vagal signaling. Colonization with HFD-type microbiota enhances recruitment of glia to locations along the gut–brain axis (i.e., NTS, nodose ganglia), and pharmacological deletion of these glia prevents the hyperphagic response to HFD feeding, likely through reduction of the HFD-driven loss of vagal innervation in the NTS.

Roadblocks, Gaps, and Opportunities

- Vagal nerve signaling functions are not well understood.
- The mechanisms whereby diet modifies the gut microbiome to alter metabolic function and chemosensory ability still must be elucidated.
- Permanent effects of the perinatal microbiota composition on the gut–brain axis have been observed but not investigated in depth.
- The purpose of the rapid detection of gut bacteria by enteroendocrine cells and the extent of altered feeding behavior in response to these signals remain unknown.

- Previous tools used to eliminate neuronal signaling pathways lacked specificity. Novel methods, such as the use of peptide-conjugated neurotoxins, can be used to eliminate particular types of neurons.

Plasticity in Autonomic and Hormonal Pathways

Emerging Studies

- Effective treatments for obesity (i.e., bariatric surgery, treatment with glucagon-like peptide 1 [GLP-1] analogs) target signaling associated with the gut–brain axis. Neuronal activation in the area postrema (AP) and NTS has been observed in response to bariatric surgery and GLP-1 analogs, but the two interventions likely operate via separate mechanisms.
- Maternal/perinatal HFD alters neurodevelopment in mice, including functional changes in the dorsal vagal complex (DVC)—which encompasses the NTS, AP, and dorsal motor nucleus of the vagus nerve—such as arrested development of critical gamma-aminobutyric acid (GABA) neurons. DVC neurocircuits in mice exposed to a maternal/perinatal HFD appear stressed and exhibit dysregulated gastric responses.
- Blood glucose levels are coordinated by circulating insulin and glucagon, which are regulated in part by autonomic neural circuits (parasympathetic and sympathetic) associated with the pancreas. Neuronal density, innervation, gene expression, activity, and function in pancreatic circuits are remodeled in diabetic mice and humans.
- Metabolic disease correlates with the loss of adipose tissue innervation, which facilitates the exchange of sensory and sympathetic signaling between adipose and the CNS. Loss of adipose innervation is sufficient to cause alterations in the structure and function of fat depots and metabolic dysregulation in mice. The neuro–adipose nexus shares structural similarities with neuromuscular junctions, but details remain unclear regarding its identity as a component of sensory and/or sympathetic circuits and its plasticity in response stimuli.

Roadblocks, Gaps, and Opportunities

- The critical and sensitive windows and mechanistic basis for brainstem and autonomic neurocircuit development must be defined before possible interventions are developed.
- The effects of other early-life adaptations or adverse events on the neurodevelopment associated with energy homeostasis are understudied.
- The relative contributions of the parasympathetic and sympathetic systems in energy homeostasis are not currently known.
- Innervation of tissues beyond the gut (e.g., pancreas, adipose) and the plasticity of these circuits play unclear roles in metabolic health and disease.
- Targeted denervation approaches (e.g., chemical, surgical, viral, genetic) can be implemented to reveal the importance of tissue regulation by components of the autonomic nervous system.
- Targeted neuromodulation (e.g., vagal nerve stimulation) might be effective in treating obesity and metabolic disease.

Energy Sensing and Homeostasis: CNS Circuits

Emerging Studies

- Activation of AgRP neurons potently stimulates feeding behavior. Rapid activation of a subset of AgRP neurons has been observed in response to cold exposure and is hypothesized to play a role in the adaptive increase in food intake associated with thermogenesis. AgRP neurons are required for hyperphagia (but not increased energy expenditure) in response to cold, and this response is attenuated in mouse models of diet-induced obesity.
- Excitatory input from the ARC to satiety neurons in the paraventricular hypothalamus (PVH) results in the sensation of fullness; inhibitory input from ARC AgRP neurons causes hunger. Fasting induces long-lasting activation of AgRP neurons, and excitatory input from a subset of excitatory neurons in the PVH that are activated by fasting causes this plasticity. In the ARC, excitatory input to satiety neurons from vesicular-glutamate transporter 2 neurons is enhanced by α-melanocyte-stimulating hormone secreted by pro-opiomelanocortin (POMC) neurons.
- A surge of leptin during a critical postnatal period is required for the development of AgRP projections and suppression of pre-proglucagon (i.e., GLP-1–producing) neuron inputs from the NTS to the PVH. Genetic deletion of leptin or exposure to a maternal HFD reduces AgRP projections to the PVH; however, leptin mutants exhibit increased GLP-1 inputs to the PVH, and maternal HFD mice exhibit decreased GLP-1 inputs to the PVH. Both models of dysfunctional energy metabolism exhibit changes to the network structure and ensemble activity of the PVH.
- Exercise in mice reversibly alters orexigenic/anorexigenic circuit plasticity in the ARC, activating POMC neurons and inhibiting neuropeptide Y neurons.

Roadblocks, Gaps, and Opportunities

- Advanced methods can be used to understand the role of thermoregulation in maintaining energy balance and the mechanisms whereby obesity dysregulates the systems regulating thermogenic feeding and metabolism.
- The extent and mechanisms of the coordinated metabolic response to exercise (e.g., modified synaptic connections, roles for various nutrient sensors, sex- or circadian-dependence effects) have not fully been elucidated.
- Synaptic tracing and brain-wide signaling activity information in the Allen Brain Atlas can be used to generate comparative brain heat maps.

Neural Plasticity in Feeding-Related Learning and Memory

Emerging Studies

- VS pathways mediate motivation triggered by food cues and are subject to diet-induced plasticity. Striatal responses to food cues are stronger in mammals with obesity and predict future weight gain and poor weight loss outcomes. Cue-triggered food-seeking behavior is robust in obesity-prone rats and can be inhibited by selectively blocking excitatory glutamatergic transmission in the NA. Short-term feeding (i.e., before obesity) with a "junk" food (i.e., high-sugar/high-fat) diet increases NA excitatory glutamatergic transmission in obesity-prone but not obesity-resistant rats.
- The orbitofrontal cortex (OFC) modulates decision-making and impulse control by integrating sensory information into motor outputs. Endocannabinoid-mediated GABAergic synaptic transmission in the OFC is impaired in obese rats due to excess synaptic glutamate resulting from glutamate transporter-1 (GLT-1) dysfunction in proximal astrocytes; these deficits can be restored

with N-acetylcysteine (NAC), which enhances the clearance of synaptic glutamate by inducing GLT-1. Additionally, the lateral OFC is disinhibited in obese mice, resulting in impaired reward devaluation during satiety, which can be restored by upregulation of GABAergic signaling. NAC decreases binge eating in rodent models.

- The hippocampus expresses leptin receptors, GLP-1 receptors, and ghrelin receptors to integrate the processing of energy status and memory required for regulating learned aspects of eating behavior. The gut–vagus–hippocampus axis promotes spatial and episodic memory via medial septum cholinergic signaling to the dorsal hippocampus, which increases brain-derived neurotrophic factor (BDNF) signaling to promote neural plasticity.

Roadblocks, Gaps, and Opportunities

- Behavioral measures of food-cue motivation should be improved and standardized.
- The majority of studies related to striatal function and food-seeking behavior have been conducted with male animals. Sex-dependent differences in the pathways have been observed and should be elucidated.
- The effects of feeding-related hormones and peptides (e.g., insulin, GLP1, leptin) on NA function and food-seeking behavior should be determined.
- The role of motivational circuits in the association between food insecurity and obesity is unclear.
- Obesity often is comorbid with psychiatric disorders, and the effects of cognitive changes in obesity should be considered when implementing behavioral therapies.
- Techniques to reduce habit formation might be beneficial in the treatment of obesity.

Cellular Regulators of Neural Plasticity

Emerging Studies

- Brain circuit plasticity during metabolic adaptations often involves interplay between neurons and glia, which are regulated by leptin and are recruited to ARC AgRP and POMC neurons in response to changes in energy balance. AgRP neurons can control feeding behavior by altering circulating lysophospholipid levels, which modulate cortical synapse activity in an astrocyte-dependent manner.
- Glia are regulated by leptin in response to diet-induced obesity. Astrocytic insulin signaling couples brain glucose uptake with nutrient availability.
- Astrocytic BDNF signaling within the ventromedial hypothalamus modulates neuronal activity in response to changes in energy status. Both fasting and BDNF depletion enhance synaptic glutamate clearance by astrocytes and result in increased food intake, reduced energy expenditure, and glucose intolerance.
- Obesity-associated adipocyte hypertrophy/cell death and ectopic fat deposits in non-adipose tissues contribute to pathogenic inflammation. Changes in the permeability of the blood–brain barrier have been observed in mouse models of dietary obesity.

Roadblocks, Gaps, and Opportunities

- The role of communication between glia and neurons in neural circuits related to energy metabolism is understudied.
- Glial regulation of synapse formation, maturation, and deletion might support synaptic remodeling.

- Glial cells should be considered active agents in the regulation of feeding behavior and autonomic functions by the brain.
- The functional heterogeneity of glial cells can be defined using marker genes to identify distinct subpopulations of glia. Regulation of the transcription identity of glia might be cell autonomous or defined by external factors (e.g., association with neuronal subpopulations).
- Models for the propagation of inflammation in obesity can be interrogated at the cellular, system, and spatial level.
- Similar to the development of diabetes following insulin resistance, spatial and temporal regulation of the CNS with chronic obesity might involve compensatory increases in protective factors that are followed by the exhaustion of the compensatory mechanism.

Breakout Discussions: Needed Resources, Model Systems, and Technological Advances

The breakout groups further discussed the following major themes to identify roadblocks to progress and opportunities for translating new insights into more effective strategies to mitigate metabolic conditions. In particular, the groups focused on tools, resources, model organisms, and other technological advances that will be needed for future success in addressing gaps in the field and developing new treatments and therapies for obesity and related conditions.

Plasticity of Chemosensory and Visceral Sensory Signaling (Sessions 1 and 2)

- NIH-funded centers could support imaging modalities that require specialized equipment and training (e.g., electron microscopy).
- CNS research has become increasingly sophisticated. Incorporating these neuroengineering technologies into chemosensory/visceral sensory research will help address fundamental gaps.
- Personnel with appropriate training in chemosensory/visceral sensory research are scarce and difficult to recruit and retain.
- More advanced monitoring methods (e.g., simultaneous monitoring of peripheral and central nervous systems, monitoring of awake animals) would be beneficial.
- NIH-facilitated training workshops could support the exchange of methods and expertise, especially for early career researchers who have not yet established extensive scientific networks.
- Additional organ-specific knockout models of receptors involved in energy homeostasis are needed—especially Flp and Dre recombinase models and rat models.

Plasticity of Autonomic Pathways, Endocrine Signals, and Non-Neural Cells (Sessions 3 and 6)

- Techniques to study the autonomic functions of the brain stem without destroying other areas of the brain are needed.
- Methods to differentiate between the dorsal and ventral cerebellum would be beneficial.
- A central core for telemetric studies (e.g., blood pressure, body temperature, blood glucose) would increase efficiency and measurement standardization in the field.
- Integration of the cardiovascular system with other organ systems and the effects on energy balance are not known.

Plasticity Associated with CNS Circuits and Learning and Memory (Sessions 4 and 5)

- Few studies explore differences in energy homeostasis between the sexes and across the life span.

- Volume transmission in the brain as it relates to peptide signaling is not well understood.
- New technologies are needed for measuring brain function (e.g., simultaneous measurement of several neurotransmitter/neuropeptide types or multiple levels of analysis).
- The importance of outward-facing brain cells (e.g., epithelial cells of the blood–brain barrier) as a site where the brain and body converge was emphasized.
- Animal models and related protocols (e.g., dietary feeding) should be standardized and validated.
- Computational advances in such fields as visual or motor neuroscience should be incorporated into the study of energy homeostasis.
- Interrogating small-scale components of neural circuits while studying their integrated effects on large-scale behaviors is a challenge.
- Big data approaches are promising techniques to interrogate the mechanisms and interactions underlying complex energy systems.

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