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Eating as a motivated behavior: modulatory effect of high fat diets on energy homeostasis, reward processing, and neuroinflammation.

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Abstract

Eating is a basic motivated behavior that provides fuel for the body and supports brain function. To ensure survival, the brain's feeding circuits are tuned to monitor peripheral energy balance and promote food-seeking behavior when energy stores are low. The brain's bias toward a positive energy state, which is necessary to ensure adequate nutrition during times of food scarcity, is evolutionarily conserved across mammalian species and is likely to drive overeating in the presence of a palatable, energy-dense diet. Animal models of diet-induced overeating have played a vital role in investigating how the drive to consume palatable food may override the homeostatic processes that serve to maintain energy balance. These animal models have provided valuable insights into the neurobiological mechanisms underlying homeostatic and non-homeostatic eating, motivation and food reward, and the development of obesity and related comorbidities. Here, we provide a brief review of this literature and discuss how diet-induced inflammation in the central nervous system impacts the neural control of food intake and regulation of body weight. The connection between diet and the immune system provides an exciting new direction for the study of ingestive behavior and the pathophysiology of obesity.

Keywords

obesity; high fat diet; inflammation

Introduction

Although the act of eating is a basic motivated behavior that is necessary to fuel the body and support brain function, deciding how much to eat within a given meal is a more complex process. This is because meal size is influenced by a myriad of signals arising from within the body, which can be further modulated by circadian, social and environmental factors. To ensure survival, the neural circuits that regulate food intake are exquisitely tuned to monitor peripheral energy balance and promote food-seeking behavior when energy stores are low.

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Because these neural circuits evolved during times of food scarcity and unpredictability, our inherent motivation to obtain food can become over-engaged in the presence of highly palatable foods and thus override the homeostatic processes that regulate energy balance. As a result, the abundance of food in our current environment can increase the motivation to seek out and consume excess calories, resulting in unhealthy weight gain and related comorbidities.

At the most basic level, our drive to eat is governed by homeostatic and nonhomeostatic processes within the body. Homeostatic regulation is mediated by our body's ability to monitor energy stores and activate or inhibit feeding circuits within the brain in an attempt to maintain energy balance. For example, the adipocyte-derived hormone leptin is secreted in proportion to body adiposity and acts on leptin-responsive neurons in the brain to suppress feeding in response to positive energy balance (Balthasar *et al.*, 2004). In this way, leptin functions as a "lipostat", continually informing the brain about peripheral energy stores. However, there are times when homeostatic signals are disregarded, and we engage in nonhomeostatic eating that is driven by the sensory and/or hedonic properties of food. This form of non-homeostatic eating, often referred to as hedonic eating, is typically driven by palatable foods that are high in fat and/or sugar content. Hedonic eating activates reward pathways in the brain, which result in increased motivation to consume food and increased energy consumption (Leigh & Morris, 2016a). More recently, the consumption of high-fat foods has also been shown to induce a state of inflammation in the hypothalamus (Kälin *et al.*, 2015), a brain region critical for the control of food intake (Ziotopoulou *et al.*, 2000). Over time, chronic hypothalamic inflammation can disrupt the activity of brain circuits that control homeostatic eating, allowing for increased hedonic eating and associated weight gain (Jais & Brüning, 2017).

Understanding the neural circuits that control food intake is prerequisite to understanding how disruptions in these circuits may promote overeating. In this regard, animal models of diet-induced obesity have been used extensively to study the neural control of both homeostatic and hedonic eating, as well as the pathophysiology of dysregulated eating behavior (Lutz *et al.*, 2012; Speakman *et al.*, 2008). In these animal studies, the discovery of several genetic mutations, either spontaneous or engineered, has helped shed light on multiple genes that are necessary for the control of food intake and regulation of energy balance (Speakman *et al.*, 2008). Interestingly, single gene mutations that promote overeating in obese laboratory animals are also associated with hyperphagia and excess weight gain in humans who express the same mutations. For example, null mutation of the gene that encodes leptin promotes profound overeating and weight gain in both mice and humans (Aberman, Ward & Salamone, 1998; Drel *et al.*, 2006). Although gene mutations can certainly promote sustained overeating and associated weight gain, the rapid escalation in the prevalence of obesity in the past few decades suggests that environmental factors, including the high abundance of energy-dense foods, play a critical role in our current state of overnutrition. Indeed, chronic exposure to energy-dense foods has been shown to be a primary trigger for overeating that is most pronounced in genetically vulnerable individuals. This suggests that eating behavior is ultimately regulated by a complex interplay between environmental and genetic factors.

In this review, we discuss the merits and limitations of animal models of diet-induced obesity, and how such models have been used to provide a better understanding of the homeostatic and hedonic processes that regulate appetite. We provide an overview of the neural circuits that govern homeostatic and hedonic eating and discuss recent work revealing a novel mechanism by which the consumption of a high fat diet can impair homeostatic eating by inducing a state of chronic hypothalamic inflammation. We end by highlighting future directions in the field.

Animal models of diet-induced obesity

Animal models of diet-induced obesity are simple in concept and design – they involve switching animals from a nutritionally complete chow diet, one that is low in fat and refined sugar but high in complex carbohydrates and fiber, to a more palatable, energy-dense diet. While the macronutrient content of these energy-dense diets can vary across studies, most are high in fat and the bulk of the carbohydrate content is in the form of sucrose. Similar to that observed in humans, laboratory animals will overconsume a highly palatable, energy-dense diet and, if the diet is constantly available, gradually accrue excess adiposity (Buettner, Schölmerich & Bollheimer, 2007). Once obesity is established, switching the animal back to a standard chow diet typically has minimal impact in terms of weight loss. This suggests that the excess calories consumed through this reward-driven process can override the processes that promote homeostatic regulation (Yu, 2017). It also confirms that weight loss is difficult to achieve and even harder to maintain, similar to that observed in obese humans. As such, these animal models of diet-induced weight gain, the bulk of which are conducted in rats and mice, offer a good model system by which to study diet-induced overeating and the associated weight gain in humans.

Some of the earliest laboratory studies of the diet induced obesity model utilized “cafeteria” or “junk food” diets consisting of a wide array of sweet and savory high-fat/high-sugar solid foods that are regularly consumed by humans, or a choice of processed foods, snacks and lard/chow mixtures. These cafeteria diets have been shown to drive the overconsumption of calories and accrual of body fat in multiple rodent strains and both sexes (Barrett *et al.*, 2016; Ong *et al.*, 2013). Within days, these diets can adversely affect metabolic function (Williams *et al.*, 2014) and over weeks to months, promote binge-like eating through alterations in feeding and reward circuits in the brain (Johnson & Kenny, 2010; Martire, Westbrook & Morris, 2015). Interestingly, perinatal exposure to a cafeteria diet has been shown to increase the preference for, and consumption of, high fat diet from the time of weaning, and lead to changes in gene expression in the mesolimbic reward system (Ong & Muhlhauser, 2011; Ong *et al.*, 2013).

While cafeteria diets clearly aim to recapitulate the obesogenic Western diet, they lack standardization. This is problematic as diets that differ in energy density, texture, flavor, and palatability can lead to vast differences in energy intake and weight gain across studies and thereby contribute to inconsistent or non-reproducible findings (Mercer & Archer, 2008). Moreover, the physically heterogeneous diet composition makes it difficult to calculate the energy and macronutrient intake of individual animals (Barrett *et al.*, 2016). This has led many researchers to utilize a more defined diet, such as a commercially available 45% or

60% high fat diet. Like cafeteria diets, these defined high fat diets have been shown to promote reliable increases in food intake and adiposity in both mice and rats (Barrett *et al.*, 2016). The main limitation of the defined high fat diet is that it eliminates dietary choice, which is known to be a primary driving factor in excess weight gain in humans (Barrett *et al.*, 2016). As such, the overeating and weight gain associated with exposure to a defined high fat diet is most pronounced during the first few weeks, before the novelty of the diet begins to dissipate (Buettner *et al.*, 2007).

The prognosis of obesity is generally poor, with current treatments often failing to achieve long-term maintenance of a reduced body weight. This poor prognosis is related, at least in part, to a failure to recognize that a leading cause of obesity is dysregulated feeding behavior (Woods *et al.*, 2004). Studies involving the diet induced obesity rodent model have revealed that overconsumption of high fat diets is predominantly the result of an increase in meal size that, over time, can lead to the development of binge-like eating (Farley *et al.*, 2003). This suggests that high fat feeding can actually impair the functioning of brain circuits implicated in the physiological control of meal size. In addition to increasing consummatory behaviors, long-term exposure to high fat diets in laboratory animals has been shown to increase appetitive behaviors such as the motivation to seek out palatable food. For example, when rats are maintained on a high fat/high sugar diet, they display increased motivation to consume sucrose pellets as measured by a behavioral test of motivation in which the animal must press a lever to gain access to the sucrose pellets (la Fleur *et al.*, 2007). Thus, exposure to highly palatable, energy-dense diets affects both the ability to regulate the amount of calories consumed in an individual meal (i.e., homeostatic eating) and the motivation to seek out food even in the absence of caloric need (i.e., hedonic eating). The following sections provide brief overviews of the neural circuits regulating homeostatic and hedonic eating, and discuss the evidence that both of these circuits are affected by high fat feeding.

Hypothalamic control of food intake: homeostatic eating

Advances in mouse genetics, coupled with electrophysiology, pharmacology, optogenetics, and chemogenetics, has provided considerable detail about the hypothalamic control of food intake. From this work, the arcuate nucleus (Arc) has emerged as a key regulator of homeostatic eating, which is classically defined as eating in response to deficits in peripheral energy stores. The Arc resides within the mediobasal hypothalamus, adjacent to the median eminence that receives a rich blood supply and has a semi-permeable blood brain barrier (Sohn, 2015). As such, neurons within the Arc are optimally positioned to receive and act upon endocrine signals and metabolites in the bloodstream. Critical to this process are two interconnected groups of Arc neurons. One group expresses proopiomelanocortin (POMC), which undergoes posttranslational modification to yield the anorexigenic peptide α -melanocyte-stimulating hormone (α -MSH). The second group co-expresses the orexigenic peptides neuropeptide Y (NPY) and agouti gene-related peptide (AgRP). As described below, these anorexigenic POMC and orexigenic NPY/AgRP neurons play opposing but coordinated roles in the control of food intake, and comprise the first-order neurons of what is commonly referred to as the hypothalamic melanocortin system.

The anorexigenic effect of POMC neurons was discovered through POMC knockout mice, which are hyperphagic and obese (Yaswen *et al.*, 1999). Studies using optogenetic stimulation have shown that direct activation of POMC neurons leads to a suppression in food intake (Aponte, Atasoy & Sternson, 2011a; Zhan *et al.*, 2013). When activated, POMC neurons release α -MSH, which binds to melanocortin receptors (MC4R), which are expressed on second-order anorexigenic neurons in the paraventricular nucleus (PVN) of the hypothalamus (Balthasar *et al.*, 2005). As expected, MC4R deletion, both in transgenic mice and humans with point mutations in the *Mcr4* gene, are hyperphagic and obese (Huszar *et al.*, 1997; Vaisse *et al.*, 1998). This provides further evidence for the necessity of POMC signaling in the physiological control of food intake.

POMC neurons receive input from a variety of signals from the periphery that regulate their activity. One such signal is leptin, an anorexigenic hormone that is synthesized and secreted by adipocytes in proportion to body adiposity (Park & Ahima, 2015). Leptin binds to leptin receptors on POMC neurons, resulting in an increase in POMC neuronal activity (Elmqvist *et al.*, 1997; Balthasar *et al.*, 2004; Berglund *et al.*, 2012). Research has shown that leptin's anorexigenic effect appears to be mediated, at least in part, via activation of the JAK-STAT pathway in POMC neurons (Håkansson & Meister, 1998; Dodd *et al.*, 2015).

Another hormone that plays a role in modulating POMC neuronal activity is the steroid hormone estradiol. In the context of energy homeostasis, estradiol is an anorexigenic hormone, and estrogen receptors are highly expressed in the ventromedial hypothalamic nucleus (VMH), PVN, and Arc, including POMC neurons (Malyala, Kelly & Rønnekleiv, 2005; Eckel, 2011). Electrophysiological recordings have shown that estradiol modulates the activity of G protein-linked inwardly rectifying potassium channels in POMC neurons, resulting in increased anorexigenic POMC signaling and thus likely contributing to estradiol's anorexigenic effect (Kelly *et al.*, 2002).

The Arc neurons that co-expresses NPY and AgRP are likely the best characterized orexigenic population of neurons in the central nervous system. Pharmacological or optogenetic stimulation of these NPY/AgRP neurons in rodents promotes a robust increase in food intake that can persist for hours to days (Aponte, Atasoy & Sternson, 2011b; Krashes *et al.*, 2011). It is surprising, therefore, that studies involving the selective ablation of NPY neurons in 1-day-old neonatal mice were found to have no significant effect on feeding behavior in adolescence/adulthood, and failed to alter the normal trajectory of weight gain (Luquet, 2005; Luquet, Phillips & Palmiter, 2007). However, other studies have shown that chemical ablation of NPY neurons in adulthood does have a detrimental effect on feeding behavior (Gropp *et al.*, 2005; Wu, Boyle & Palmiter, 2009; Wu, Clark & Palmiter, 2012). This suggests that the failure of early postnatal ablation of NPY neurons to affect feeding and weight gain is secondary to developmental compensation, which may be driven by the need for a strong orexigenic signaling pathway in order to promote survival.

When stimulated, Arc NPY/AgRP neurons release NPY, which activates Y1 and Y5 receptors on orexigenic neurons in the PVN and lateral hypothalamus (LH). These Arc NPY/AgRP neurons also release AgRP upon stimulation. Interestingly, AgRP acts as an inverse agonist at melanocortin receptors (MC4R) that are expressed on the same second-

order, anorexigenic PVN neurons that are stimulated by α -MSH (Sohn, Elmquist & Williams, 2013). These orexigenic NPY/AgRP neurons also synapse directly on POMC neuronal cell bodies within the Arc and release the inhibitory neurotransmitter GABA, which serves to silence POMC neuron signaling (Sohn *et al.*, 2013). This dual action of NPY/AgRP neurons ultimately results in an increase in feeding behavior, through both the activation of orexigenic neurons in the LH and the suppression of anorexigenic neurons in the PVN.

Like POMC neurons, NPY/AgRP neurons express leptin and estrogen receptors but these peripheral hormones exert the opposite effect in that they inhibit NPY and AgRP signaling (Wang *et al.*, 1997; Elias *et al.*, 1999; Kelly & Rønnekleiv, 2008). These same NPY/AgRP neurons are also responsive to ghrelin. Ghrelin is an appetite-stimulating hormone that is released from the gastric mucosa in response to negative energy balance and thus plays an important role in meal initiation (Cowley *et al.*, 2003). Arc NPY/AgRP neurons express the ghrelin receptor, and increases in circulating ghrelin have been shown to increase NPY and AgRP signaling (Cowley *et al.*, 2003; Kohno *et al.*, 2003).

In summary, the neural circuitry underlying the homeostatic control of food intake is essential for maintenance of energy balance and stability of body weight. Critical to this process of homeostatic regulation is the ability to detect and respond to changes in peripheral signals of energy balance. Together, Arc POMC and NPY/AgRP neurons, with input from peripheral metabolic signals including leptin and insulin, play coordinated roles in keeping daily fluxes in energy stores balanced. As such, any structural or molecular changes along these signaling cascades, including the development of leptin or insulin resistance, may disrupt the homeostatic regulation of appetite and, thereby, promote undesired weight gain over time. It should be evident, therefore, that these homeostatic processes are most important for regulating feeding behavior over the long-term, as opposed to the amount of food consumed in an individual meal, which is heavily influenced by non-homeostatic factors as described in the next section.

Reward circuitry and food intake: hedonic eating

From an evolutionary perspective, the feeding system is biased toward positive energy balance to enhance survival in times of food scarcity. While this was once adaptive, it works against us in the current obesogenic food environment we now inhabit. Given that eating is essential for survival, it has evolved to be an intrinsically rewarding behavior. The taste and consumption of palatable foods is known to activate the brain's reward system (Berridge, 1996), which plays a critical role in generating motivated behaviors, including feeding. Because the brain's reward circuitry has evolved to increase an organism's probability of performing behaviors that will increase its chance of survival (Leigh & Morris, 2016b), the rewarding aspects of palatable food can lead to compulsive overeating. This provides a mechanism by which the homeostatic control of food intake can be overridden by the motivation to consume highly palatable food. Indeed, the prevailing notion is that homeostatic signals, which modify food intake over extended periods of time in an attempt to maintain energy homeostasis, are often weaker than hedonic signals, which are processed

by different neural circuits that often do not respect energy balance and thus promote storage of excess calories (Alonso-Alonso *et al.*, 2015).

Hedonic eating, defined as the consumption of food for pleasure in the absence of an energy deficit (Berridge, 2009), activates reward circuitry in the brain to promote both mesolimbic dopamine and opioid signaling. Palatable food, like other natural and synthetic reinforcers, stimulates the release of dopamine into the nucleus accumbens (NAc) from dopaminergic neurons originating in the ventral tegmental area (VTA). Increased dopamine neurotransmission within this mesolimbic pathway has been shown to increase the amount of palatable food consumed in a behavioral test of motivation in which animals must press a lever in their cage to obtain palatable food rewards (Zhang, Balmadrid & Kelley, 2003). Moreover, the infusion of dopamine antagonists directly into the NAc attenuates how hard an animal will work to obtain palatable food rewards (Aberman *et al.*, 1998; Hamill *et al.*, 1999). Taken together, these studies provide clear evidence that dopamine signaling is involved in motivation and food seeking behavior (Berridge, 2009), and that palatable foods activate this specific reward pathway.

While dopamine plays an important role in driving our desire or “wanting” to consume palatable food, there is little evidence to suggest that it enhances food palatability (Berridge & Kringelbach, 2015), which is typically driven by the sensory qualities of food. Rather, hedonic assessment or “liking” of palatable food appears to be driven by opioid signaling in the brain (Berridge & Kringelbach, 2015; Steidl *et al.*, 2017). Peripheral or central administration of μ -opioid receptor agonists has been shown to increase the consumption of sweet and fatty foods, and opioid receptor antagonists preferentially decrease the consumption of palatable, energy-dense foods in comparison to healthier, less-preferred food (Glass *et al.*, 1996; Lowe & Butryn, 2007; Taha, 2010).

One of the main sites of action for opioids in the regulation of hedonic eating is the central amygdala. Infusion of opioid receptor antagonists into this brain region decreases the consumption of preferred food, but has no effect on non-preferred food (Glass, Billington & Levine, 2000). Another brain region involved in opioid-driven feeding is the NAc, as local infusions of μ -opioid receptor agonists into this specific brain region increase the consumption of palatable foods (Zhang & Kelley, 1997; Zhang, Gosnell & Kelley, 1998; Katsuura, Heckmann & Taha, 2011). Thus, the NAc serves as a site of integration for increased dopamine and opioid signaling, and available data suggest that increased mesolimbic opioid signaling can augment dopamine release (Berridge & Kringelbach, 2015; Steidl *et al.*, 2017). Although the dopamine and opioid systems appear to have distinct functional roles in hedonic eating, processing the “wanting” and “liking” of palatable food, respectively, it is clear that these two systems can interact to drive the consumption of palatable, preferred foods.

Integration of homeostatic and hedonic signals

While the neural circuits that process homeostatic and hedonic signals were once thought to be independent of each other, it is now clear that these two circuits are integrated and each one can inform the other (Lutter & Nestler, 2009). This integration is facilitated, in part, by

dopamine neurons in the VTA that are responsive to changes in circulating endocrine signals, including leptin and ghrelin, which play an important role in the homeostatic control of food intake. For example, the anorexigenic hormone leptin inhibits the activity of VTA dopamine neurons, resulting in a decrease in food-seeking behavior and food intake (Hommel *et al.*, 2006; Domingos *et al.*, 2011). Additionally, the orexigenic hormone ghrelin, a gut peptide that is released in response to a negative energy state, stimulates VTA dopamine neurons and thereby increases food-seeking behavior and palatable food intake (Naleid *et al.*, 2005).

The LH is another key nucleus involved in the integration of hedonic and homeostatic signals. Subpopulations of LH neurons are involved in homeostatic feeding but can also act as modulators of motivational reward circuits. The LH sends heterogeneous projections of glutamate or GABA and various homeostatic peptides, such as orexin and neurotensin, to the VTA (Harris, Wimmer & Aston-Jones, 2005; Opland *et al.*, 2013). Activation of this pathway can reinforce compulsive sucrose-seeking behavior (Nieh *et al.*, 2015). Specifically, it has been shown that the GABAergic projections from the LH to the VTA act to disinhibit dopamine neurons, thus enhancing dopamine release resulting in an increase in food-seeking behavior (Nieh *et al.*, 2016).

When there is a need to replenish energy, for example when one is hungry after skipping a meal, homeostatic and hedonic signals are well aligned and work together to drive food intake. Anyone who has engaged in dieting for weight loss will understand the power of these combined regulatory systems in stimulating the desire to eat. On the other hand, when one is in a state of positive energy balance, these two systems can operate in a discordant manner with the anticipated pleasure of eating a dessert driving further intake despite a feeling of fullness after having just consumed a satiating meal. As the extra calories are consumed, increased activity within the hedonic system can actually dampen the strength of homeostatic signals. Unfortunately, we find that these two regulatory systems are often discordant in today's obesogenic environment.

High fat diet feeding promotes inflammation

Peripheral inflammation

It is well established that obesity is associated with chronic, low-grade inflammation in metabolically active peripheral tissues (Gregor & Hotamisligil, 2011). This inflammatory response occurs in the absence of systemic or local microbial infection, and is considered atypical in that it is not associated with signs of swelling, redness, or pain, which usually accompany an immune response. As such, this form of chronic peripheral inflammation is commonly referred to as metabolic inflammation (Le Thuc *et al.*, 2017).

The primary trigger of metabolic inflammation is the chronic consumption of a high fat diet. In animal models of diet induced obesity, chronic overeating of a high fat diet has been shown to promote high levels of free-fatty acids that exceed the storage capacity of lipocytes and thus spill over to metabolically active tissues causing a state of lipotoxicity and glucotoxicity. These free-fatty acids interact with toll like receptors on immune cells to activate inflammatory pathways and impair normal cell signaling in the liver, pancreas,

skeletal muscle and white adipose tissue (Lumeng & Saltiel, 2011). This inflammatory response is typically characterized by the release of pro-inflammatory cytokines and chemokines, increased cellular stress, and macrophage infiltration of adipocytes (Valdearcos, Xu & Koliwad, 2015). Together, these changes in cellular activity and function drive aspects of metabolic dysfunction, including impaired insulin signaling, insulin resistance, and impaired glucose homeostasis (Gregor & Hotamisligil, 2011; Le Thuc *et al.*, 2017). Over time, this metabolic dysfunction can lead to the development of insulin resistance and type 2 diabetes. Because the genetic deletion of key elements of the inflammatory signaling pathway has been shown to protect mice from diet-induced insulin resistance (Zhang *et al.*, 2008), peripheral metabolic inflammation is believed to play a causal role in the development of type 2 diabetes and related metabolic dysfunction.

Central nervous system inflammation

It is now well accepted that the same inflammatory pathways that can become activated in peripheral, metabolic tissue can also be activated in brain regions that regulate energy homeostasis. This is an emerging field of study since, for many years, the brain was thought to be an immune-privileged organ based on its separation from most peripheral pathogens by the blood brain barrier, and on the belief that the brain lacked antigen-presenting cells (APCs) and lymphatic vessels providing a connection to the peripheral immune system (Wekerle, 2002; Kaplan & Niederkorn, 2007). However, with the recent discovery that the brain does, in fact, have lymphatic vessels, and therefore a lymphatic drainage system, the idea that the brain is an immunologically-privileged organ has faded (Louveau *et al.*, 2015). The discovery that lymphocytes function to survey the central nervous system and help mediate the brain's immune response has further overturned the notion of the brain as an immunologically isolated organ (Ransohoff & Brown, 2012).

In addition to its adverse effects on metabolically active peripheral tissues, high fat diet consumption can also promote inflammation in the central nervous system. The first report of diet-induced inflammation in the brain appeared in 2005 (De Souza *et al.*, 2005). In this study, rats that were fed a high fat diet for 16 weeks had higher concentrations of pro-inflammatory markers in the hypothalamus, and impaired insulin signaling in hypothalamic neurons, in comparison to chow fed control rats. Moreover, this cellular response was reversible as insulin sensitivity was restored by inhibiting c-Jun N-terminal kinase signaling (De Souza *et al.*, 2005).

Cellular mediators of metabolic inflammation

An organism's innate immune system is its first line of defense against the invasion of pathogens or other stimuli, like dietary fats, that have pathogenic effects. Activation of the immune system, resulting in a pro-inflammatory response, can be classified in two ways: (1) acute inflammation characterized by a time window of minutes to hours and by the presence of neutrophils; and (2) chronic inflammation, like that induced by a high fat diet, which extends from days to years and is marked by the accumulation of lymphocytes in the inflamed tissue (Maldonado-Ruiz, Fuentes-Mera & Camacho, 2017). The diet-induced, chronic inflammatory response is coordinated by various cell types and involves the recruitment of macrophages and leukocytes and the release of cytokines including tumor

necrosis factor alpha (TNF- α) and multiple interleukins (Maldonado-Ruiz *et al.*, 2017). In the context of metabolic inflammation, experimental evidence suggests that the accumulation of ceramides, diacylglycerols, and saturated fatty acids cause tissue damage to metabolically important organs including the brain (Pewzner-Jung *et al.*, 2010; Ginkel *et al.*, 2012; Chakraborty & Jiang, 2013). In addition to input from the peripheral immune system, one of the biggest mediators of the brain's immune response is its own innate immune cells.

Microglia are the brain's resident immune cells and are thought to be of mesodermal origin and enter the nervous system during early embryonic development (Ransohoff & Brown, 2012). Microglia can rapidly transition from a resting state to an activated state in response to various immunological challenges, including exposure to saturated fatty acids (Ransohoff & Brown, 2012). However, regardless of the triggering stimulus, microglia activation occurs in a stereotyped manner that involves proliferation and migration to the site of injury followed by morphological and functional changes (Gehrmann *et al.*, 1992; Gehrmann, Matsumoto & Kreutzberg, 1995; Dickson *et al.*, 1993). As a result of these cellular changes, microglia release pro-inflammatory cytokines (e.g., TNF- α), interleukins (e.g., IL-1 β and IL-6), and free radicals (e.g. nitric oxide). Together, these pro-inflammatory cytokines interact with neighboring neurons, inducing a state of endoplasmic reticulum stress that ultimately decreases neuronal health and promotes changes in neuropeptide expression (Giulian & Baker, 1985, 1986; Banati *et al.*, 1993; Jais & Brüning, 2017).

Saturated fats and neuroinflammation

Saturated fatty acids activate immune cells, including microglia, via various toll-like receptors (TLRs) (Maldonado-Ruiz *et al.*, 2017). Both lauric acid and palmitic acid have been shown to induce TLR migration to lipid rafts and initiate dimerization of TLR1 and TLR2 receptors in peripheral macrophages (Wong *et al.*, 2009; Huang *et al.*, 2012). In the brain, palmitic acid stimulation of neurons induces the release of cytokines from microglia via a TLR4-initiated signaling pathway, resulting in decreased hypothalamic cell viability, which can lead to disruptions in the neural circuits that control homeostatic eating (Delint-Ramirez *et al.*, 2015). Chronic hypothalamic inflammation can also contribute to both leptin and insulin resistance, and this would serve to further weaken the hypothalamic circuits that signal satiation and thereby favor overeating and weight gain. Specifically, the development of insulin and leptin resistance appears to be mediated by increases in TNF- α and IL-6 in the hypothalamus, which promote an increase in suppressor of cytokine signaling 3 (SOCS3) protein, leading to phosphorylation of insulin resistance substrate and suppression of the leptin receptor mediated activation of the JAK-STAT pathway (Howard & Flier, 2006).

As might be expected, diet composition influences the magnitude of the hypothalamic inflammatory response. For example, diets high in saturated fats result in greater hypothalamic inflammation after 8 weeks than diets high in unsaturated fats (Maric, Woodside & Luheshi, 2014). Moreover, fats obtained from different sources can produce different hypothalamic inflammatory responses in that saturated fats from butter produce greater neuroinflammation than saturated fats derived from coconut oil (Maric *et al.*, 2014).

Modulators of inflammation: hypothalamic peptides and hormones

The location of the Arc in the mediobasal hypothalamus makes it highly sensitive to peripheral signals in the blood and cerebral spinal fluid allowing Arc POMC and NPY/AgRP neurons to react to the nutrient and energy state of the organism (Sohn, 2015). This also makes these Arc neurons particularly susceptible to the detrimental effects of elevated circulating free fatty acids and subsequent neuroinflammation (De Souza *et al.*, 2005). Indeed, diet-induced inflammation has been shown to impair the functioning of these Arc neurons leading to reduced anorexigenic signaling in the brain circuit that controls homeostatic eating. Interestingly, the same peptides and hormones regulating homeostatic feeding circuits in the hypothalamus can also modulate neuroinflammation (Maldonado-Ruiz *et al.*, 2017).

α -MSH

Systemic administration of α -MSH, an anorexigenic peptide released by Arc POMC neurons, has been shown to reduce cytokine expression during cerebral ischemia and decrease hippocampal inflammation (Bertolini, Tacchi & Vergoni, 2009). It has also been shown to reduce nitric oxide levels in the hypothalamus (Cragnolini *et al.*, 2006). A reduction in hypothalamic nitric oxide could reduce oxidative stress associated with free radical exposure from chronic inflammation, thus improving neuronal health in circuits critical for the control of food intake. A proposed mechanism for the anti-inflammatory effects of α -MSH is through a direct action on microglia. Available data suggest that MC4R activation in microglia cells by α -MSH inhibits the transcription factor NF κ B, which is a critical regulator of cytokine production in microglia (Ichiyama *et al.*, 1999).

Leptin

Leptin is an anorexigenic hormone with high levels of leptin receptor expression in the Arc and is released from adipocytes in proportion to body adiposity (Balthasar *et al.*, 2004). Interestingly, leptin has been shown to activate signaling pathways associated with inflammation, including the JAK-STAT and MAPK-PI3K pathways, which regulate IL-6 production in Th1 lymphocytes (Pérez-Pérez *et al.*, 2017). Leptin also reduces production of the anti-inflammatory cytokine IL-10 (Pérez-Pérez *et al.*, 2017). In the brain, leptin has been shown to stimulate the release of IL-1 β and IL-6 from microglia (Lafrance *et al.*, 2010; Larsen *et al.*, 2016). Given that leptin levels would be increased in animals fed a high fat diet and it has pro-inflammatory effects, understanding how endogenous leptin is aiding the development of hypothalamic inflammation in response to high fat diet could be of value.

Estradiol

Estradiol is another hormone with significant anorexigenic effects in the hypothalamus (Eckel, 2011). Specifically, site-specific infusion of estradiol into the Arc or medial preoptic area of the hypothalamus is sufficient to decrease food intake in ovariectomized rats (Santollo, Torregrossa & Eckel, 2011). In regards to immune function, estradiol has been shown to have a potent anti-inflammatory effect in the peripheral immune system. In the brain, estradiol also has an anti-inflammatory effect, likely mediated through a direct mechanism on microglia cells, which express multiple ERs including ER α , ER β , and G

protein-coupled estrogen receptor (GPER-1) (Mor *et al.*, 1999; Zhao *et al.*, 2016). Application of estradiol to primary cultures of rat microglia or N9 microglia cell lines has been shown to attenuate LPS-induced superoxide release and iNOS protein expression (Bruce-Keller *et al.*, 2000). Estradiol treatment in these cells phosphorylated mitogen-activated protein kinase (MAP kinase), and the anti-inflammatory effect was blocked with a MAP kinase inhibitor (Bruce-Keller *et al.*, 2000). While the specific estrogen receptor mechanism mediating the effect in this study is unknown, recent work suggests that GPER-1 may play a vital role in estradiol's anti-inflammatory effect. Primary rat microglia treated with a GPER-1 agonist attenuated LPS-induced IL-1 β and TNF- α release. Furthermore, a GPER-1 antagonist blocked estradiol's anti-inflammatory response, as did GPER-1 knockdown in mice (Zhao *et al.*, 2016).

Interestingly, a high fat diet has been shown to induce greater hypothalamic inflammation in males, compared to females (Morselli *et al.*, 2014). Consumption of a high fat diet for 16 weeks was associated with decreased expression of hypothalamic ER α levels in male, but not female, mice, suggesting this sex difference is regulated by ER α expression in the hypothalamus (Morselli *et al.*, 2014). In the same study, estradiol pretreatment attenuated palmitic acid induced inflammation in cultured hypothalamic neurons that express ER α , but failed to modulate palmitic acid-induced inflammation in the BV2 microglial cell line that does not express ER α . Furthermore, knockdown of ER α prevented estradiol's protective effects in cultured hypothalamic neurons. These data led the authors to conclude that ER α is critical for estradiol's anti-inflammatory effects. However, BV2 microglia cells express ER β and estradiol has been shown to be anti-inflammatory in BV2 cells via ER β in response to oxygen deprivation (Habib *et al.*, 2013). Thus, the inability of estradiol to attenuate palmitic acid-induced inflammation in BV2 cells suggests that the neuroprotective effects of estradiol are stimulus-specific. Interestingly, mouse genetics utilizing receptor knockout models and pharmacological studies using selective estrogen receptor agonists have revealed estradiol's inhibitory effects on feeding to be primarily mediated via ER α , not ER β (Eckel, 2011).

Perspectives and future directions

The high level of dietary-induced weight gain in today's society, combined with ineffective treatments for sustained weight loss, highlight the need for continued research into the neural mechanisms underlying the homeostatic and non-homeostatic processes that affect the motivation to eat, type of food selected, and amount consumed. While much progress has been made in understanding the neurobiological mechanisms that control food intake, most of this work has utilized male subjects. Thus, sex differences in eating behavior and the neurobiological mechanisms contributing to those differences are understudied. Given that declining levels of estradiol in peri-menopausal women are associated with overeating and weight gain (Carr, 2003), it is important to investigate the mechanisms by which estradiol modulates the homeostatic and non-homeostatic controls of food intake, dietary choice, motivation to consume food, and vulnerability to metabolic inflammation.

A primary distinction between diet-induced inflammation of peripheral tissues and that occurring in the hypothalamus is the time course. Inflammatory responses to high fat feeding develop much more rapidly in the hypothalamus in comparison to peripheral tissues.

Studies in rats have shown that hypothalamic inflammation can occur within 24 – 72 hours of high fat feeding (Thaler *et al.*, 2012). Thus, while obesity appears to be a causal factor in the development of peripheral inflammation, hypothalamic inflammation actually precedes weight gain, suggesting that it plays a causal role in the development of diet-induced overeating (Thaler *et al.*, 2012; Jais & Brüning, 2017). Additional studies investigating the time course of metabolic inflammation and its impacts on the development of obesity would be valuable in understanding the pathophysiology of obesity.

As is reflected in our review, the focus of most investigations of central metabolic inflammation has been on the hypothalamus. This is likely due to its unique position and function as a sensor of peripheral metabolic signals, which render it critical to the neural control food intake. That said, many other brain areas are involved in controlling food intake (Schwartz *et al.*, 2000), and this highlights a pressing need to investigate the effects of high fat diet on inflammation in other brain regions. Such studies would provide an important next step in understanding the full impact of diet-induced metabolic inflammation on ingestive behavior and how it may increase the risk of developing obesity and related health problems. Targeted areas might include the NAc and VTA for their known roles in processing food reward (Berridge, 1996), and regions of the hindbrain, specifically the nucleus of the solitary tract (NTS). Like the Arc, the NTS expresses anorexigenic POMC neurons (Zhan *et al.*, 2013), and it is ideally situated to monitor peripheral metabolic signals due to its location in the hindbrain, adjacent to the area postrema and its compromised blood-brain barrier.

The connection between diet and the immune system provides an exciting new direction for the study of ingestive behavior and the pathophysiology of obesity. While much of the available data has focused on the adverse effects of a high fat diet, it will be important to investigate the impact of other diets, especially those high in sugar content, on dietary-induced inflammation of metabolically-sensitive tissues both in the periphery and in the central nervous system.

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