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PERSPECTIVE

MICROGLIAL ADIPOBIOLOGY: A NEW CONCEPT FOR UNDERSTANDING THE ADIPOSE TISSUE-BRAIN CROSSTALK IN HEALTH AND DISEASE

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Abstract

This article proposes the concept of "microglial adipobiology" as a new theoretical framework for the crosstalk between the adipose tissue and the central nervous system in health and disease. It reviews an important mechanistic link, explaining the neuropsychiatric complications of obesity, including the role of adipose-secreted signaling proteins (adipokines) and adipose-derived stem cells in influencing microglial function and neuroinflammation. An increasing body of evidence suggests that neuroinflammation mediated by microglia, macrophage-like cells in the brain, plays a contributory role in the pathogenesis of various neurodegenerative diseases. The specific positive and negative effects of the major types of dietary fats are also discussed in the case of obesogenic and ketogenic diets. Furthermore, it explores the effects of microglial cells on adipose tissue *via* modulating the central control of energy homeostasis in the hypothalamus and proposes the concept of "transgenerational adipobiology" as a framework explaining the neurological and metabolic complications of the offspring of obese mothers. Finally, potential directions for future therapeutic interventions are considered.

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Introduction

The modern obesity epidemic is associated with significantly increased comorbidity with a variety of other conditions (1), including neurological and psychiatric disease (2). These associations, together with the concurrent mental health crisis (3), raise the question on how does the adipose tissue influence the brain and the pathobiology of neurological disease. Recent studies in adipobiology have shifted the view of adipose tissue as a mere fat-storage depot to a complex endo- and paracrine organ, that can affect systemic physiology and contribute to the pathogenesis of disease (4, 5). Importantly, links have been shown how the adipose tissue can affect the brain in both health and disease (6, 7).

Inflammation of the central nervous system (CNS), termed "neuroinflammation", is currently considered a key mechanism in the pathogenesis of both neurologic and psychiatric conditions (8). A main player in neuroinflammation are microglia, the brain's resident phagocytic cells, which due to their extensive and complex involvement in virtually all CNS conditions are considered

"central players" in brain disease (9).

Could the adipose tissue affect the brain *via* influencing microglial cells either directly or indirectly? The present article reviews the accumulating evidence from both correlational and experimental studies that support this notion, focusing on how microglial function can be altered *via* the contents of an obesogenic diet and signaling proteins (collectively designated adipokines) secreted from adipose cells, as well as, how, in turn, microglial cells can modulate the central control over feeding behavior and energy homeostasis, thus influencing the adipose tissue. Given these findings, we can propose the concept of "microglial adipobiology", establishing the bidirectional adipose-microglial crosstalk as a new theoretical framework, linking the pathobiology of obesity and related neuropsychiatric diseases (see also 10).

Obesity and brain disorders: two linked pandemics

Obesity is a major global health concern, affecting more than 35% of people in the USA (11) and more than 600 million adults worldwide (12). Around 60% of the world's population will reach critical body mass index (BMI) values by 2030 (13). Importantly, obesity is not merely an accumulation of excessive body fat but, rather, a complex systemic pathological state than has been linked with increased risk of several medical conditions, including diabetes (14), hypertension (15), cardiovascular disease, stroke, and even certain cancers (16).

Mounting evidence has shown an association between obesity and cognitive problems. Obese people have diminished cognitive functions on a variety of measures (17–20), including impaired executive functions (18,19). Obesity is associated with reduced brain volume (23), including in key areas for cognition such as the hippocampus (24). Obesity is also linked with cognitive impairments in old age (25) and is considered a risk factor for dementia and Alzheimer's disease (23, 24). The link between obesity and the brain is especially important, given that the prevalence of mood disorders has increased significantly in the West (28,29) to a point where, today, one in five people meet criteria for a common mental disorder (30).

Mental illness is considered the pandemic of the 21st century and the next global health challenge (3). Indeed, obesity has also been associated with psychiatric conditions like depression and anxiety (31–35). There is even evidence that our modern diet may be a key contributing factor to mental health (36,37), hence, the field of "nutritional psychiatry" has been established (38). The association between the two big modern pandemics, obesity and mental illness, raises the need to investigate for possible mechanistic links between the two.

Inflammation as a common mechanism in obesity and brain disease

Accumulating evidence in the past two decades has resulted in several paradigm shifts (5), challenging the classic view of adipose tissue as a mere lipid storage. Currently, adipose tissue is considered a dynamic endocrine and paracrine organ producing over 600 signaling proteins collectively designated adipokines (4, 7, 39). Adipokines have been shown to possess a dazzling array of biological functions, including control over feeding behavior, energy homeostasis, inflammation, immunity, cognition, insulin resistance and the pathogenesis of cardiometabolic and other diseases (4, 6, 40, 41). Since many adipokines have effects in the CNS and can ultimately contribute to the regulation of cognition and behavior, the field of neuroadipocrinology has emerged emerged and the adipose tissue has been considered as "a third brain" (5, 6).

Obesity is not a mere accumulation of the adipose tissue, but is associated with chronic systemic low-grade inflammation due to infiltration and activation of macrophages in adipose tissue. As a consequence, the adipose tissue in obesity is marked by increased secretion of pro-inflammatory adipokines (42) and reduced secretion of anti-inflammatory and metabotrophic ones such as adiponectin (42), nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) (10, 43). This leads to increased levels of inflammatory markers in the serum and multiple metabolically active peripheral tissues and organs, including the brain (44–47). This type of inflammation is considered atypical due to the lack of Galenus' signs such as *rubor et tumor cum calore et dolore* (redness, swelling, heat and pain), which usually are associated with an immune response (48, 49).

On a similar note, the classical neuron-centered views of CNS disease have been challenged with accumulating evidence on the involvement of the immune system in brain pathology (50). Nowadays, inflammation of the nervous system ("neuroinflammation") is considered a leading mechanism in the pathogenesis of CNS conditions, including Alzheimer's and Parkinson disease, stroke, traumatic brain injury, as well as mood disorders (50–53). With respect to the latter, significantly elevated levels of all major kinds of cytokines were detected in blood samples from patients with depression, anxiety, bipolar, and obsessive-compulsive- and posttraumatic stress disorder, schizophrenia, and autism (8). Major molecules involved include soluble interleukin receptors, interleukin antagonists, tumor necrosis factor-alpha (TNF-α), soluble TNF receptor, IFN-γ, chemokines, and matrix metalloproteinases (MMP) (8). Under experimental conditions, animals injected with proinflammatory cytokines like TNF-α have been shown to exhibit sickness behavior in a dose- and time-related manner (54).

Microglia are central players in brain disease

An increasing body of evidence suggests that neuroinflammation mediated by microglia play an important role in the pathobiology of various neurodegenerative diseases. Microglia, the resident phagocytic cells in the brain, are a part of the glial system of non-neuronal elements in the CNS and account for around 10% of all cells in the brain (55). During development, microglia arise from erythromyeloid precursors in the yolk sac which migrate and colonize the embryonic brain (56–60). Under physiological conditions, microglia possess numerous highly-branched elongated fine processes (61), which they use to actively survey their cell-specific territory, monitoring the CNS environment for infection or injury.

Accumulating evidence in recent years has revealed crucial microglial functions beyond the immune response to pathology, namely, involvement in the regulation of cognitive processes like learning and memory. During development, microglia regulate neurogenesis, as well as synaptogenesis and neural network formation (62, 63). Postnatally, they have been shown to contact presynaptic and postsynaptic neuronal elements and contribute to synapse regulation, including synaptogenesis and pruning (64, 65). Microglia monitor neuronal activity and neurotransmitter release (66, 67), especially in the context of sensory deprivation and stimulation, as well as specific learning and memory tasks (68, 69).

Under pathological conditions, microglia "activate" and undergo a series of changes, including adopting an amoeboid morphology with enlargement of the soma and shortening and thickening of primary processes, moving toward the site of injury, increased proliferation and phagocytic ability, as well as secretion of pro-inflammatory molecules (70).

However, microglial activation has implications beyond normal immunological defense and can become neurotoxic (71, 72). Disruptions in neuronal networks during development due to perturbations in synaptic pruning and modification by microglia has been linked to diseases such as autism and schizophrenia (73). A staggering amount of evidence has elucidated multiple mechanisms of microglial involvement in conditions such as Alzheimer's disease, amyotrophic lateral sclerosis, multiple sclerosis, glaucoma, and neuropathic pain (9,74). As key players in neuroinflammation, microglia have been associated with virtually all neurological conditions (75) and are now considered "central players" in brain disease (9).

It should be noted that, although, ramified microglia have been classically termed "resting", however, this is confusing and does not reflect their physiological roles. Indeed, with the growing body of evidence about the physiological effects of ramified microglia, they have been termed "never resting" (76). By "resting" it should be understood not a lack of activity but, rather, a current lack of involvement in neuroinflammation. Thus, analyzing microglial morphology is a way to assess their activation during neuroinflammation. Ramified cells are correlated with anti-inflammatory processes (77) while amoeboid cells are associated with CNS inflammation or injury (78–80).

Peripheral inflammation can activate microglia and inflame the brain

It is well established that peripheral inflammation can reach the brain, activate microglia (54, 81) and contribute to the pathogenesis of neurological and psychiatric disorders (51). Among commonly studied markers contributing to this process are the pro-inflammatory cytokines IL-1β, TNF-α, and IL-6 (51). These molecules can reach the brain via several routes (51).They can enter in areas of the CNS missing blood-brain barrier (BBB) such as the circumventricular organs, choroid plexus, and parts of the hypothalamus (82, 83). The BBB itself is made leaky by pro-inflammatory cytokines, including TNF-α, and in turn, becomes permeable to them (84). Moreover, these molecules can enter the brain *via* the vagus nerve projecting to the nucleus of the solitary tract which is connected with the hypothalamus and amygdala (85). Given that inflammatory cytokines in the periphery can stimulate microglia and cause neuroinflammation and that obesity is associated with a systemic inflammatory state, the logical question arises about the possibility of microglia mediating the obesity-associated neurological and cognitive damage.

One possible mechanism, by which microglial cells can impact cognition in obesity is dysregulation of synaptic plasticity. In rats, obesity leads to cognitive deficits, accompanied with changes in microglial morphology and synapse loss in the medial prefrontal cortex (86). It has also been shown that microglia from obese mice are activated and internalize synaptosomes at higher rates compared to non-obese controls (87). However, it is not clear which process comes first: does obesity itself damage synapses which are then phagocytosed by microglia, or does obesity activate microglia which, in turn, engulf otherwise functional synapses (46). Several studies have attempted to address this question.

Cope *et al* have demonstrated that partial knockdown of the fractalkine receptor prevented both microglial activation and cognitive decline in diet-induced obesity in male rats. Moreover, pharmacological inhibition of microglial activation prevented dendritic spine loss and cognitive degradation. Obesity-associated cognitive decline was ameliorated via pharmacological blockade of microglial phagocytosis (46). Hao *et al* have demonstrated that dietary obesity reversibly induces synaptic stripping

by microglia and impairs hippocampal plasticity. Interestingly, only a partial attenuation of obesity via diet-reversal was needed for a complete normalization of hippocampal function and the spatial relationships between microglia and synapses, showing a non-linear relationship between total body adiposity and neuroinflammation (87).

Of particular interest are the inflammatory changes in the brain's center of metabolic control, the hypothalamus, especially the arcuate nucleus of the mediobasal hypothalamus (MBH). Due to its leaky BBB, this nucleus serves as a sensor of circulating signals, allowing direct microglial exposure to blood-borne molecules (88, 89). De Souza *et al* were the first to show an association between diet-induced obesity and hypothalamic inflammation (90). The study demonstrated that in rats, a 4-month period of high-fat diet (HFD) feeding leads to activation of inflammatory pathways such as NF-κB and JNK in the MBH with the production of pro-inflammatory cytokines TNF-α, IL-1β, and IL-6. These findings were later replicated and extended in rodents, humans, and non-human primates (89,91–98).

Interestingly, HFD leads to hypothalamic inflammation due to over-expression of pro-inflammatory cytokines with activation and proliferation of microglia rapidly, even within the course of 24h (91), weeks before the onset of obesity and the associated metabolic disturbances (91,99), suggesting that hypothalamic inflammation is a response to nutrients rather than peripheral inflammation. Importantly, the gliosis observed in the hypothalamus under HFD feeding is reversible for a short time (2-3 weeks) and it has been suggested that it serves a protective role against "injury" induced by overload of dietary fat (49,91).

Dietary fats can modulate microglial function

Evidence suggest that, in respect to macronutrient content, diets high in fat, especially, saturated fats, lead to obesity and metabolic syndrome (100,101), as well as hypothalamic inflammation (102). Moreover, under obese conditions, the adipose tissue releases large amounts of non-esterified saturated fatty acid in the circulation (103), which can cross the blood brain barrier (BBB) (104) and stimulate both neurons and glial cells (105). The direct and indirect effects of different lipids on microglial function have been extensively reviewed by Leyrolle *et al* (106).

Based on the number of double bonds, three main families of fatty acids can be distinguished, namely the saturated (SFA), monounsaturated (MUFA) or polyunsaturated (PUFA) fatty acids (106). Differences in the effects of each family on microglial function have been demonstrated.

Microglia and saturated fatty acids

Obesity-inducing diets are high in SFA, particularly palmitate (106). After ingestion, SFA can reach the brain, where they are taken up by microglia and induce hypothalamic inflammation (93). This is supported by in vitro studies, showing increased pro-inflammatory activity of cultured microglial cells (93, 107–110). Saturated fatty acids activate microglia via various toll-like receptors (TLRs) (111). In particular, after palmitic acid stimulation, the TLR4-initiated signaling pathway induces cytokine release from microglia with subsequent neuronal damage in the hypothalamus, which, in turn, disrupts the circuitry controlling homeostatic eating (48, 112). Microglial depletion cancels SFA-induced inflammation in hypothalamic slices, and, remarkably, enhances leptin signaling and reduces food intake (93).

Microglia and monounsaturated fatty acids

In contrast to SFA, MUFA such as oleate does not trigger the release of pro-inflammatory cytokines of cultured microglia (93). Oleate has also been shown to prevent 7-ketocholesterol-induced cytotoxicity (113). The anti-inflammatory effects of oleate can be partially explained by the higher affinity of MUFA compared to SFA for the transcription factor peroxisome proliferator-activated receptor, that is involved in anti-inflammatory processes (114).

Microglia and polyunsaturated fatty acids

The two main PUFA families are n-3 and n-6 PUFA (115). It is considered that n-3 PUFA and their derivatives are rather anti-inflammatory while n-6 PUFA and their derivatives are pro-inflammatory (116). An important hallmark of the modern Western diet is a decrease of the n-3/n-6 PUFA ratio (117). This is of practical importance, since it has been shown that diet enriched with n-3 PUFA may be able to inhibit neuroinflammation (118). Linoleic acid, a n-6 PUFA has been shown to reverse the inflammatory responses induced by palmitic acid treatment in microglial cells (119). In mice, lifelong dietary n-3 PUFA deficiency leads to alterations in microglia composition (120). Several n-3 PUFA have been shown to attenuate microglial activation due to various challenges (121–130), possibly due to inhibition of the inflammatory signaling cascades NFκB, and MAPK and activation of the anti-inflammatory factors PPAR, retinoid X receptor (RXR) and the G-protein coupled receptor 120 (GPR120) (106,116,131–133). PUFA have also been shown to modulate microglial phagocytic activity against Aβ particles, myelin debris, synaptic elements and apoptotic neurons (67, 106, 134, 135). Deficiency of n-3 PUFAs during development has been shown to increase pro-inflammatory gene expression in the hippocampus and decrease microglial motility (130). Furthermore, n-3 PUFA inhibit LPS-stimulated cytokine production by microglia *in vitro* (132, 136).

Do dietary fats really cause brain damage?

The interpretation that dietary fats, particularly saturated fats, are an adverse stimulus, leading to brain damage should be taken with caution (137). Why would the brain be vulnerable to injury by such an acute and common stimulus (137)? Many mammals evolved to thrive on diets high in pro-inflammatory saturated fat as early as the newborn stage due to the high-fat content of mother's milk (137). Hypothalamic microgliosis is increased by higher consumption of saturated fats but this is not the case with unsaturated or short-chain fatty acids even when calories and fat content are held constant (93). This, plus the reversibility of saturated fat-induced hypothalamic microgliosis, suggests that this is a response to the overconsumption of specific nutrients, rather than "injury" (137). Furthermore, Gao *et al* have shown that a high-carbohydrate HFD induced hypothalamic inflammation but this is not the case in a low-carbohydrate, high-fat diet (101). Baufeld *et al* have demonstrated that the pro-inflammatory reaction of microglia to HFD reverses after 8 weeks, suggesting a switch to an anti-inflammatory phenotype (138). Similar observations have been reported previously (139). Importantly, there was no excessive reaction of microglia when stimulated by plasma from HFD-fed animals (138). These differences in observations can be accounted by variations in the experimental design (138), particularly in terms of using neonatal *versus* adult microglia, which are considered functionally different populations (140). Furthermore, postmortem analysis of human brains revealed significant microglial alterations in the hypothalamus of obese subjects, however, no such changes were observed in the cortex (138).

The picture gets even more complicated when we take the ketogenic diet into account.

The ketogenic diet is high in fat but also neuroprotective

The ketogenic diet has been originally used in the treatment of epilepsy since the beginning of the 20th century (141). It has a very high fat content with low carbohydrate and protein levels, thus shifting the metabolism to producing ketone bodies from fatty acids stored in the adipose tissue, as an energy source. Acetoacetate (ACA) and beta-hydroxybutyrate (BHB) are the main ketone bodies and can pass the BBB (141). The ketogenic diet has been shown to exert effects beyond covering the energy needs, including the regulation of synaptic transmission, neurotransmitter concentration, and optimization of mitochondrial function (141). As such, it has been considered neuroprotective in the context of many neurological disorders (142).

Suppression of microglial activation has been associated with the neuroprotective effects of the ketogenic diet (143–145). Indeed, microglia have the ability to metabolize both ACA and BHB (146), and several mechanisms have been proposed regarding the anti-inflammatory effects of ketones on these cells. Beta-hydroxybutyrate can increase the ramification of microglia both *in vitro* and *in vivo* (141, 147).

Moreover, high BHB levels can decrease proinflammatory cytokine release (148). Beta-hydroxybutyrate can activate the hydroxy-carboxylic acid receptor 2 (HCA2), expressed by microglia (149) and inhibit neuroinflammation (150), possibly *via* inhibition of NF-kB activation (150). Beta-hydroxybutyrate activates G-protein-coupled receptors 109A (GPR109A) and inhibits histone deacetylases (146, 147, 150, 151). This attenuates the NF-kB pathway, resulting in reduced pro-inflammatory cytokine production (152).

Another possible mechanism for the beneficial effects of ketogenic diets can be the lower formation of advanced glycation end products (AGEs) due to low dietary glucose levels. AGEs are non-enzymatic modifications of proteins and lipids from reactions with sugars (146). Microglia have been shown to express receptors for AGEs (146), which stimulate pro-inflammatory signaling pathways (153, 154).

Adipose tissue can influence microglia via adipokines

When discussing the interplay between the adipose tissue and microglia in the regulation of metabolism and the mechanisms of obesity-related complications, it is of interest whether microglia can sense blood-borne molecules other than nutrients, especially adipose-derived signals. Indeed, such molecules exist, enabling the adipose-microglia crosstalk.

Leptin

Leptin is the prototypic adipokine, which has multiple functions including the regulation of appetite, body weight and energy homeostasis (155); and can enter the brain (156). Elevated levels of leptin reduce appetite and body weight (3). Obesity is associated with leptin resistance due to either a defect in leptin receptor's intracellular signaling or decreased leptin transport across the BBB (155, 157–159).

The mutant strain of mice (ob^-/ob^-) are genetically deficient in leptin, suffer from extreme obesity (155) and are often used as an experimental model for obesity research. Leptin has been shown to exert effects on microglia (137, 160). Mice lacking leptin or its receptor have lower microglial density in the MBH (99), which is reversible to wild-type levels when restoring the leptin signal (99). In both obesity and experimental leptin resistance, leptin levels are elevated also in the hippocampus, a key structure involved in cognition, which is associated with microglial activation (161). Interestingly, voluntary exercise increases

leptin sensitivity and, in turn, decreases microglial activation and pro-inflammatory signaling in the hippocampus (161). In both obesity and experimental leptin resistance, leptin levels are elevated in the hippocampus (161). Mice lacking leptin have defective neurite growth in the hypothalamus (162), which can be possibly attributed to impaired microglial activity (82). Indeed, leptin has been shown to regulate microglial phagocytosis (163).

However, some studies have challenged the existence of a direct action of leptin on microglia (137). Possible indirect mechanisms involve neuron-glial interactions in the MBH (137) and activation of astrocytes by leptin, which, in turn, activate microglia (161).

Adiponectin

Adiponectin is the most abundant adipokine (164,165), involved in a variety of physiological processes, including the regulation of energy metabolism, vascular physiology, and inflammation (166, 167). It is generally considered an anti-inflammatory molecule, and its low plasma levels have been linked to chronic inflammation (168,169). Adiponectin can cross the BBB and reach the brain, where it can exert actions on both neurons and glia, including microglia (167) *via* its receptors, AdipoR1 and AdipoR2 (166,170,171). Adiponectin has anti-depressant (172) and anti-inflammatory (173) properties in mice. It has also been shown to be a candidate mediator of the positive effects of exercise and environmental enrichment on neurogenesis, mood, and cognition (174). Nicolas *et al* have shown that elevated adiponectin levels in the brain regulate microglial phenotype and activation, leading to reduction in neuroinflammation and depressive-like behavior in mice (167). These effects are possibly mediated by the AdipoR1/NF-kB signaling pathway and reduction of IL-1β, IL-6, and TNF-α synthesis by globular adiponectin in particular (167). On the other hand, adiponectin deficiency enhances microglial responsiveness to pro-inflammatory challenges, thus increasing brain susceptibility to inflammation (167). Furthermore, adiponectin has been shown to be a major contributor to the antidepressant effects of enriched environment *via* its actions on microglia (174)

Adipose-derived stem cells can influence microglia

Adult stem cell therapy involves the transplantation of either embryonic stem cells or induced pluripotent stem cells, hoping that these can rejuvenate damaged tissue by differentiating into other viable cell types (175). However, this method is associated with high costs, methodological difficulties, and ethical challenges (176).

A proposed alternative are adult stem cells, which, despite their more limited multipotentiality and self-renewal capabilities, can be obtained from all tissues (175). The adipose tissue is an abundant source of such cells, termed adipose-derived stem cells (ADSC), containing over 500 times more mesenchymal stem cells than bone marrow (177). These cells have been shown to be able to differentiate into multiple other cell types (175,178,179) and are able to modulate inflammation (180–182).

Huang *et al* have shown that ADSC can survive a long time after transplantation and are able to suppress microglial activation induced by LPS, which prevented dopaminergic neuron loss in the substantia nigra in a Parkinson's disease model. Interestingly, the anti-inflammatory modulatory effects of ADSC on microglia took a long time to manifest, which in the case of the study was around 4-6 months (178).

The importance of such studies is that they show how the adipose tissue can influence microglial function via mechanisms beyond molecular signaling.

The other direction: microglia can influence adipose tissue

The idea of adipose tissue's influence on microglia, although unintuitive, makes sense in light of the current systemic inflammatory concept of obesity. However, the adipose-microglia crosstalk becomes even more interesting if we consider the other direction: can microglia influence the adipose tissue? In light of the current evidence, we can imagine how microglia can modulate neuroinflammation in the hypothalamus and, in turn, affect feeding behavior and energy homeostasis.

The adipose tissue signals the current availability of nutrients via adipokines to the hypothalamus, which, in turn, controls energy homeostasis, feeding behavior and metabolic rate (183). Hypothalamic inflammation, particularly in the MBH, has been shown to modulate the control of insulin resistance, as well as energy intake and expenditure (184,185). Surprisingly, homeostatic feeding circuits in the hypothalamus are regulated by peptides and hormones which can also modulate neuroinflammation (48, 111). If microglia are either depleted or their activation is suppressed pharmacologically, mice fed a HFD show decreased food intake and gain less weight. A possible mechanism is that reducing inflammation enhances leptin signaling (93). Interestingly, the opposite has also been shown: activating microglia leads to stimulation of food intake and weight gain in mice fed a normal non-obesogenic diet (186). Microglia of mice fed a high-carbohydrate high-fat diet secrete TNF-α which disrupts pro-opiomelanocortin-producing anorexigenic neurons in the MBH (187). Obesity is associated with dysfunction of these neurons (188,189). Moreover, in rats, Cx3cr1-driven microglia and monocyte ablation leads to disruption of the gustatory circuitry at the hypothalamic paraventricular nucleus, which, in turn, re-

sults in anorexia and weight loss (190).

Central application of an antimitotic agent inhibits microglial expansion in the hypothalamic arcuate nucleus, restores leptin sensitivity and limits food intake and consequent weight gain (191). Disruption of hypothalamic microglia *via* subcutaneous application of liraglutide or canagliflozin in obese insulin-resistant mice improves insulin resistance, glucose homeostasis, and decreases fat and triglyceride content (192, 193).

Transgenerational microglial adipobiology

There is accumulating evidence that maternal obesity can affect the long-term health of the offspring (194–197). Maternal nutrition as well can influence the energy homeostasis of offspring even into adulthood (198, 199). Can microglial activation explain this "metabolic programming"?

Exposure to HFD in both rodents and non-human primates activates the maternal immune system, leading to increased brain inflammatory markers in the offspring (96, 200-202). Furthermore, the offspring of mice fed a HFD during both pregnancy and lactation have increased microglial activation (200, 203), despite the lack of any challenges in their diet. Maternal programming by exposure to a cafeteria diet induced a plasma lipotoxic profile in the offspring. This lead to microglial activation and disrupted ghrelin sensitivity which was associated with overfeeding behavior after fasting (204).

Interestingly, n-3 PUFA supplementation from the onset of pregnancy until weaning has been shown to modify the fatty acid content and phospholipid class distribution in the offspring's microglia (120).

Summary and future directions

This article introduces the concept of "microglial adipobiology" as a framework, explaining how the bidirectional adipose-to-microglia crosstalk can account for the neuropsychiatric complications seen in obesity, as well as, how microglial function can affect food intake, energy homeostasis, and, ultimately, adipose tissue function (Fig. 1). Several mechanistic links have been reviewed. First, obesity leads to inflammation of the adipose tissue, which releases pro-inflammatory cytokines, which cross the BBB, activate microglia and induce neuroinflammation. Second, dietary fatty acids have been shown to affect microglial function in both positive and negative ways, depending on the fat's quantity and type. Third, due to obesity, the adipose tissue alters its secretory profile of several important adipokines, including leptin, adiponectin, NGF and BDNF, which too can enter the brain and change microglial function. Fourth, under experimental conditions, adipose-derived stem cells can affect microglia, not only showing a possible adipose-to-microglia mechanism for

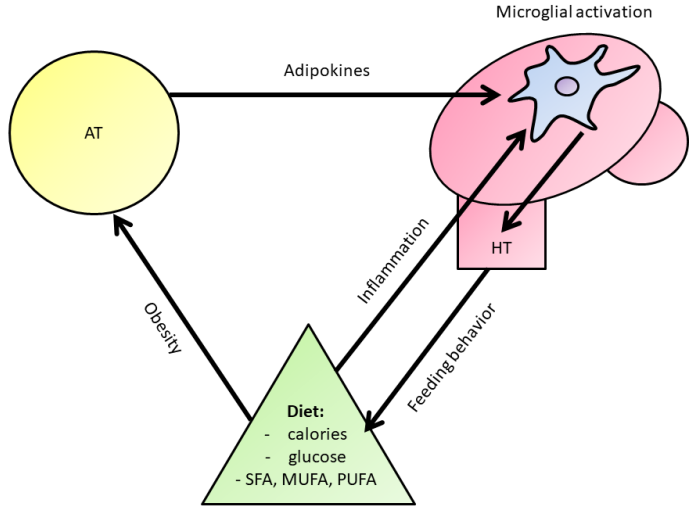

Figure 1. Schematic presentation of a summary of microglial adipobiology. Diet can modulate microglial activation either directly *via* the specific effects of certain dietary components, or indirectly *via* inducing obesity and the associated adipose tissue inflammation, which favors a pro-inflammatory adipokine secretory profile, causing neuroinflammation. Microglia, in turn, can influence the central control over energy homeostasis in the hypothalamus, thus affecting feeding behavior and, ultimately, adipose tissue function. AT, adipose tissue; HT, hypothalamus; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

communication but also opening a new possibility for stem cell-based neurotherapies. Fifth, microglia can affect obesity and adipose tissue function *via* modulating the hypothalamic control over feeding behavior and energy metabolism. Finally, the concept of "transgenerational microglial adipobiology" is proposed as a way of explaining how maternal obesity and high-fat feeding can activate the offspring's microglia and, in turn, their neurodevelopment, behavior, and metabolism.

The proposed framework reveals several possibilities for therapeutic applications. First, the pro-inflammatory adipose-to-microglia signaling, including specific adipokines such as leptin, adiponectin, NGF and BDNF is a potential target for pharmacological interventions, aimed at reducing neuropsychiatric complications in obesity. Second, understanding how the different types of dietary fatty acids specifically affect microglia can lead to relatively easy ways to control neuroinflammation *via* targeted nutritional interventions. Third, considering the other direction, namely the microglia-to-adipose signaling, we can propose a new method for the management of obesity *via* targeting microglia in the MBH, thus, affecting the central control of energy

homeostasis. Finally, all future interventions can be used to prevent the adverse cognitive and metabolic outcomes seen in the offspring of obese mothers.

As evidence for the associations between obesity, adipose tissue and the brain continues to accumulate, our knowledge expands rapidly and we risk losing the forest for the trees, thus, we need a theoretical framework that can help organize the "big data" in the field. The concept of microglial adipobiology is such a perspective aiming to clarify at least one line of reasoning, and may, hopefully, provide a basis for future hypotheses.

Conflict of interest

None

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