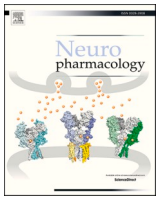
Neuropharmacology 253 (2024) 109951

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm



Rethinking the role of microglia in obesity

G. Cutugno [a,1], E. Kyriakidou [a,1], A. Nadjar [a,b,*]

[a] University of Bordeaux, INSERM, Neurocentre Magendie, Bordeaux, France
[b] Institut Universitaire de France (IUF), France

ARTICLE INFO

Handling Editor: Bruno Frenguelli

ABSTRACT

Microglia are the macrophages of the central nervous system (CNS), implying their role in maintaining brain homeostasis. To achieve this, these cells are sensitive to a plethora of endogenous and exogenous signals, such as neuronal activity, cellular debris, hormones, and pathological patterns, among many others. More recent research suggests that microglia are highly responsive to nutrients and dietary variations. In this context, numerous studies have demonstrated their significant role in the development of obesity under calorie surfeit. Because many reviews already exist on this topic, we have chosen to present the state of our reflections on various concepts put forth in the literature, bringing a new perspective whenever possible. Our literature review focuses on studies conducted in the arcuate nucleus of the hypothalamus, a key structure in the control of food intake. Specifically, we present the recent data available on the modifications of microglial energy metabolism following the consumption of an obesogenic diet and their consequences on hypothalamic neuron activity. We also highlight the studies unraveling the mechanisms underlying obesity-related sexual dimorphism. The review concludes with a list of questions that remain to be addressed in the field to achieve a comprehensive understanding of the role of microglia in the regulation of body energy metabolism.

This article is part of the Special Issue on "Microglia".

1. Introduction

Microglia play an essential role in maintaining brain homeostasis. They actively participate in shaping neuronal circuits during development, clearing debris and dead cells, in modulating neuronal activity, as well as in mounting an inflammatory response in pathophysiological situations. As such, they are highly versatile, capable of rapidly changing phenotype and function to adapt to signals present in their immediate environment. Among the signals capable of modulating microglial function, nutrients appear to be very potent. This has been particularly demonstrated in the arcuate nucleus of the hypothalamus, a structure at the constant interface with the periphery that is crucial in the control of food intake and body energy metabolism. We discuss the available data in this context and provide alternative and/or complementary interpretations whenever relevant.

2. Excess calories prompt microglial response in the arcuate nucleus of the hypothalamus

The response of microglia to an excess of calories has been an area of extensive research, with various detailed reviews covering this topic (Alexaki, 2021; Kim et al., 2023; Mendes et al., 2018; Milanova et al., 2021; Ramírez-Carreto et al., 2023; Salvi et al., 2022; Valdearcos et al., 2019; X.-L. Wang and Li, 2021, among many others). Here, we will focus on summarizing the most crucial information following the temporal progression of events. The microglial response to caloric excess unfolds in three distinct waves within the arcuate nucleus (ARC). The initial response to a high-fat diet (HFD) is rapid, manifesting within hours through the secretion of interleukins (IL-1β, IL-6), tumor necrosis factor alpha (TNF-α), and chemokines (CCL5, CCL2) within 1–3 h post-HFD ingestion, returning to basal levels by 6 h (Cansell et al., 2021). Subsequently, a second wave ensues, occurring within one to seven days of caloric surplus exposure, marked by a resurgence in inflammatory cytokine production. This second phase, although not entirely characterized and subject to differing study results, suggests that these cells

* Corresponding author. University of Bordeaux, INSERM, Neurocentre Magendie, Bordeaux, France.
E-mail address: agnes.nadjar@u-bordeaux.fr (A. Nadjar).
[1] Equal contribution.

https://doi.org/10.1016/j.neuropharm.2024.109951
Received 6 December 2023; Received in revised form 10 April 2024; Accepted 11 April 2024
Available online 12 April 2024

may begin proliferating as early as three days after exposure to the diet (Thaler et al., 2012; Valdearcos et al., 2014, not observed in Baufeld et al., 2016). This coincides with the production of cytokines such as IL-1β, IL-6 and TNF-α in the hypothalamus (Baufeld et al., 2016; Kim et al., 2019; Thaler et al., 2012). This second inflammatory wave subsides after about seven days and then resumes after a month and beyond. During this third phase, microglial density is significantly increased in the ARC (André et al., 2017; Baufeld et al., 2016; Thaler et al., 2012; Valdearcos et al., 2014; Yi et al., 2017), as does the production of inflammatory cytokines in the hypothalamus (Baufeld et al., 2016; De Souza et al., 2005; Thaler et al., 2012; Valdearcos et al., 2014; Yi et al., 2017). Some studies also indicate that these cytokines are specifically produced by microglia (Baufeld et al., 2016; Cansell et al., 2021; Kim et al., 2019; Valdearcos et al., 2014). Moreover, microglia exhibit a change in their phagocytic activity in response to HFD, which partly depends, at least in males, on the EP4 receptor for prostaglandins (Niraula et al., 2023).

While there is no consensus, it is believed that microglia are activated directly by nutrients, specifically palmitate and sugars present in the HFD (Gao et al., 2017; Valdearcos et al., 2014), rather than by body weight gain *per se*. The vagal pathway might also contribute to the early activation of microglia, as reduced inflammation in the hypothalamus is observed after one day of HFD in vagotomised animals (Waise et al., 2015). Although some studies propose that this activation is not related to the humoral pathway (Baufeld et al., 2016), others suggest that hormonal changes could be a relevant factor in microglial response to calorie surfeit (Gao et al., 2014, 2018).

The depletion of microglia using PLX, the transgenic deletion of the main microglial inflammatory pathway NFκB, or the prevention of microglial proliferation, while or before exposing animals to HFD, significantly mitigate weight gain (Valdearcos et al., 2014, 2017; André et al., 2017). All these experiments suggest that the early microglial inflammation plays a critical role in the development of obesity.

Nevertheless, it is necessary to consider certain caveats. Firstly, the evaluation often focuses solely on pro-inflammatory cytokine transcripts in the whole hypothalamus, disregarding the actual proteins synthesized specifically by microglia as well as the levels of anti-inflammatory cytokines. Furthermore, data suggests a potential lack of correlation between cytokine production and the metabolic status of the animals (Wang et al., 2012). Additionally, the term “inflammation” might be somewhat misleading, as the observed elevation in cytokine mRNA production is relatively modest, typically only two to five times higher than controls. This increase stands significantly lower when compared to the robust cytokine production seen in response to a potent inflammatory stimulus, such as exposure to the endotoxin lipopolysaccharide (Buchanan et al., 2010; Layé et al., 1994; Rey et al., 2009, among many others). Some authors have conversely suggested that producing cytokines, particularly TNF-α, is a physiological response of microglia, which allows modulating the activity of ARC neurons (Yi et al., 2017). Another indication of the physiological and adaptive nature of this response is that the early production of cytokines in response to HFD is modulated by the circadian rhythm (Yi et al., 2017).

3. Role of microglial energy metabolism in obesity

In the last two decades, the concept of immunometabolism has developed, i.e. understanding how the activation and functional properties of immune cells are controlled by adapting intracellular metabolic pathways to their needs in energy and in metabolites (Domblides et al., 2018; O’Neill et al., 2016; Pearce and Pearce, 2013). Metabolic reprogramming plays a central role in all immune cells activation, including microglia (Borst et al., 2019; Ghosh et al., 2018; Paolicelli and Angiari, 2019; Volobouéva et al., 2013).

3.1. Microglia are remarkably versatile in their metabolic capabilities

The brain predominantly allocates energy consumption to neurons due to the high energetic expense of synaptic transmission. Nonetheless, a substantial portion of oxygen utilization is linked to non-signaling processes such as actin and microtubule cytoskeleton turnover, or to lipid synthesis (Engl et al., 2017). Microglia, serving as the brain’s resident macrophages, are highly motile cells continuously surveying their surroundings (Nimmerjahn et al., 2005). They repeatedly restructure their cytoskeleton to extend and retract their processes, enabling them to undertake various functions in the brain microenvironment, including phagocytosis, synaptic refinement, and the release of soluble factors (Paolicelli et al., 2022). Consequently, these features of microglia entail a significant energy demand.

Historically, microglia were believed to primarily rely on either glycolysis or oxidative phosphorylation (OXPHOS) to meet their energy requirements and adjust their function in response to environmental conditions (Chénais et al., 2002; Ghosh et al., 2018; Gimeno-Bayón et al., 2014; Moss and Bates, 2001; Vilalta and Brown, 2014; Volobouéva et al., 2013; Wang et al., 2014). According to this binary classification, microglia in a homeostatic or “surveillant” state, or in the presence of anti-inflammatory stimuli, predominantly produce energy through mitochondrial OXPHOS (Holland et al., 2018). This mechanism generates reactive oxygen species (ROS) as a by-product, which are typically counterbalanced by antioxidant systems like glutathione. However, under specific environmental cues demanding microglia to initiate inflammation—such as stress or endotoxin-induced stimulation—these cells shift towards aerobic glycolytic activity (Lynch, 2020). This phenomenon, known as the Warburg effect, was initially described in cancer cells (Warburg et al., 1927) and later identified in immune cells, including macrophages (Liu et al., 2021). Despite glycolysis being less efficient in ATP generation than mitochondrial respiration, its speed in glucose metabolism is 10–100 times faster than that of OXPHOS (Schuster et al., 2015), enabling it to rapidly fuel energy-demanding processes such as proliferation, migration, cytokine secretion and phagocytosis. This is paralleled by excessive mitochondrial fission, which is implicated in the disruption of the electron transport chain, hence of the OXPHOS pathway (Nair et al., 2019; Park et al., 2013). Metabolic reprogramming also facilitates the accumulation of precursor metabolites for neurotrophic or inflammatory molecules and the storage of substrates required to meet the demands of cellular activation and proliferation (Orihuela et al., 2016). While the mechanisms are still poorly described, it has been suggested that the increased glycolytic activity in microglia is associated with the upregulation of the glucose transporter GLUT1, facilitating glucose intake. Blocking this receptor allows microglia to revert to oxidative phosphorylation, thus reducing microglial activation (Wang et al., 2019).

Recent discoveries confront this binary perspective of microglial immunometabolism, highlighting the extraordinary metabolic flexibility of microglial cells (Lauro and Limatola, 2020; Monsorno et al., 2022; Nadjar, 2018). Indeed, recent evidence shows that microglia can switch their metabolic profile to exploit whatever metabolites or nutrients available in their environment, both in physiological states and notably in diseased brains, when glucose accessibility could be reduced. In line with this, transcriptomic data from the mouse cortex demonstrate that microglia express all key enzymes involved in major metabolic pathways (Zhang et al., 2014). This metabolic plasticity was further elucidated *in vitro* by supplying different metabolic fuels - glucose, glutamine, lactate, pyruvate, and ketone bodies - to microglial cultures (primary cultures or BV2 cell line) and assessing basal respiration under starvation conditions. The results show that microglia can utilize these substrates individually, with a pronounced role for glutamine (Nagy et al., 2018). Moreover, in the absence of glucose, cultured microglia retain their ability to proliferate, perform phagocytosis and undergo inflammatory activation. Specifically, microglia deprived of glucose display reduced lipid accumulation in lipid droplets over a 48-h period,

indicating the utilization of scavenged lipids as an alternative energy source during metabolic stress (Churchward et al., 2018). Bernier and colleagues demonstrated *in vivo* and *in situ* that, while microglia primarily depend upon glycolysis, they can rapidly adapt, utilizing alternative sources in conditions of glucose deprivation, primarily supporting mitochondrial respiration through glutaminolysis (Bernier et al., 2020).

Lactate, long considered as a metabolic waste product, is now also recognized as a bioenergetic substrate internalized by the cells, including microglia (Brooks, 2009). It has been recently demonstrated that microglia efficiently import lactate, primarily *via* the transporter MCT4, promoting lysosomal acidification. Notably, microglia lacking MCT4 exhibit impaired synaptic pruning in the early postnatal hippocampus, underlining the substantial impact of microglial lactate metabolism on the brain environment and its homeostasis during neurodevelopment (Monsorno et al., 2023).

3.2. *Microglial metabolic adaptations in obesity*

In obese animals exposed to HFD, microglia within the ARC of the brain experience a substantial surge of energy-rich nutrients, namely saturated fatty acids (palmitate) and glucose. This is likely to lead to a profound reconfiguration of the microglial metabolic pathways, resulting in significant cellular dysfunction. Essentially, we hypothesize that these nutrients may "highjack" the microglial energy metabolic system, thereby modulating their function (cf 1.1) (Fig. 1).

Aligned with this hypothesis, several studies have observed metabolic shifts in microglia provoked by a HFD, which support their functional adaptation to the dietary challenge. For instance, it has been demonstrated that the combination of high fat and high glucose instigates an upsurge in mitochondrial respiration and ATP production, a process reliant on the mitochondrial protein UCP2 (for 'uncoupling protein 2') (Kim et al., 2019). Eliminating microglial UCP2 mitigates HFD-induced inflammation in the ARC and microglia lacking *Ucp2* are unable to utilize fatty acids, thus highlighting the importance of mitochondrial metabolism and lipid metabolism in the microglial response to HFD (Kim et al., 2019). This is concordant with the observation of lipid droplet accumulation in microglia following long-term exposure (6–9 months) to HFD (Zhuang et al., 2022). In a complementary study, Gao et al. elucidated the role of lipid metabolism in the microglial reaction to a surplus of calories. They showed that lipoprotein lipase (LPL) governs microglial phagocytic capability and sustains mitochondrial integrity in response to HFD. Moreover, when the *lpl* gene is knocked down specifically in microglia, the loss of proopiomelanocortin (POMC) neurons accelerates in response to HFD (Gao et al., 2017). This is confirmed by data showing that under HFD, microglia prioritize the use of fatty acids over glucose or glutamine (Milanova et al., 2019). These findings suggest that microglia may potentially safeguard neuronal function by facilitating the uptake of excessive lipids (Gao et al., 2017). It thus also supports a beneficial role for microglia in the response to an obesogenic diet. In line with this hypothesis, a recent paper shows that acute exposure to HFD (3 days) induces profound metabolic changes in microglia, including mitochondrial fission, inhibition of respiratory chain complex II and production of derivatives such as glutamate, succinate, itaconate, and lactate from palmitate β-oxidation. Their data also indicate a beneficial role of these microglial processes on hippocampal function, with improved memory performance in animals (Drougard et al., 2023). Despite all this data, the understanding of HFD effect on microglial lipid metabolism remains sparse. Considering the role of lipid receptors such as CD36, Trem2, or ApoE in controlling microglial functions in various pathophysiological contexts, it would be relevant to also test their role in obesity (Folick et al., 2021).

In the context of obesity, lessons could also be learnt from macrophages. Feng and colleagues showed that lactate produced by adipocytes during the onset of obesity acts as a paracrine signal, enhancing the polarization of adipose tissue macrophages into an inflammatory state, by binding the catalytic domain of PHD2 (for 'prolyl hydroxylase domain') and, thus, stabilizing HIF-1α (Feng et al., 2022). Since microglia are able to import lactate (Monsorno et al., 2023), this evidence leads to the hypothesis that lactate could play a role also in microglial activation during early stages of obesity. Moreover, in the

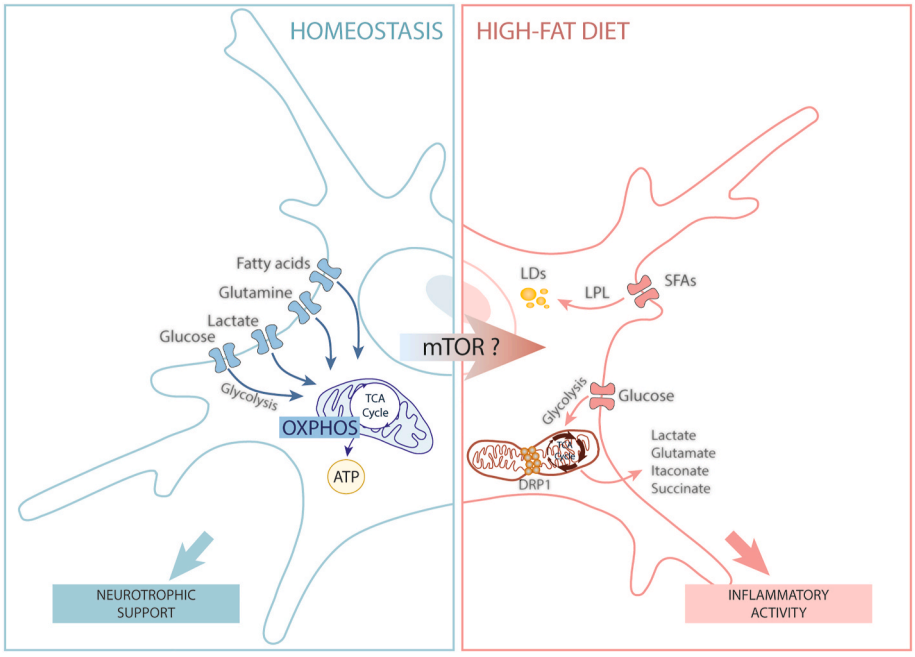


Fig. 1. Obesogenic nutrients hijack the energy metabolism of microglial cells, resulting in a shift in their functional activity. Under homeostatic conditions, microglia function as opportunistic cells, utilizing available nutrients in their environment to generate ATP and neurotrophic metabolites. However, when exposed to a high-fat diet (HFD), obesogenic nutrients have the potential to alter their metabolic activity, resulting in a shift in functionality and subsequent neuronal dysfunction. The mTOR pathway could potentially coordinate the bioenergetic reaction of microglia to a high-fat diet (HFD). OXPHOS: Oxidative Phosphorylation, SFAs: Saturated Fats, TCA cycle: Tricarboxylic Acid cycle, LDs: Lipid Droplets, LPL: Lipoprotein Lipase, DRP1: Dynamin-related protein 1, UCP2: Uncoupling Protein 2, mTOR: Mammalian Target of Rapamycin, ATP: adenosine 5′-triphosphate.

obese epididymal white adipose tissue (eWAT), adipocytes die and release lipids, that trigger the recruitment of eWAT-macrophages (MFs). eWAT-MFs proliferate around dying adipocytes, adopt a pro-inflammatory phenotype to clear those excess extracellular lipids (Wculek et al., 2022), indicating a notable metabolic reprogramming in these cells in a lipid-enriched environment. Finally, the maintenance of these pro-inflammatory macrophages in obesity strictly depends on mitochondrial respiration and not glycolysis, since an impaired OXPHOS is responsible for a decreased presence of pro-inflammatory eWAT-MFs (Wculek et al., 2023).

On the whole, the sparse data in the context of obesity indicates significant metabolic alterations in the microglial response to an excess of saturated lipids, which sustains their functional shift. Additional research is necessary to gain a more comprehensive understanding of the various pathways at play and their interconnections, with the ultimate goal to manipulate these pathways effectively to regulate cellular activity.

4. Role of the mTOR pathway in the control of microglial function

The mammalian target of rapamycin (mTOR) pathway is highly likely to play a role in the microglial metabolic reprogramming. Indeed, it is the principal growth regulator that senses the nutritional cues and, in turn, controls cell metabolism (Baik et al., 2019a; Hu et al., 2020; Mossmann et al., 2018; Saxton and Sabatini, 2017; Sengupta et al., 2010, 2010; Sengupta et al., 2010, 2010; Yang et al., 2021). mTORC1 (for 'complex 1') activation shifts microglial metabolism towards glycolysis upon LPS treatment, increasing the production of ROS and of pro-inflammatory cytokine transcripts (Baik et al., 2019; Hu et al., 2020; Yang et al., 2021). Saturated fatty acids-induced inflammation, mediated via the Toll-like receptor 4 (TLR-4), is completely blocked upon mTOR inhibition (Lancaster et al., 2018). mTORC1 pathway has been shown to impair the autophagic flux resulting in high cytokine levels during brain ischemia (He et al., 2020). The amelioration of LPS-induced neuroinflammation by the mTORC1 inhibitor rapamycin further supports the notion that mTORC1-mediated inhibition of autophagy elevates cytokine levels (Ye et al., 2020). mTORC1 inhibition reduces the levels of CD68 which is highly expressed in inflammatory microglia and, in turn, limits the loss of retinal ganglion cells following optic nerve injury (Mou et al., 2021, p. 1). *In vitro* evidence further confirms that mTORC1 is involved in microglial inflammatory response, since its inhibition hampers the production of nitric oxide (NO) upon LPS-stimulation (Dello Russo et al., 2009).

However, mTOR appears to play a regulatory role in key microglial functions across various pathological conditions. Suppressing microglial mTORC1 has been shown to decrease microglial viability in primary cultures (Lisi et al., 2015) and microglial mTORC1 deficiency *in vivo* has been linked to increased neuronal loss in a mouse model of epilepsy (Zhao et al., 2020). Microglial mTORC1 activation in tumor microenvironments creates an immunosuppressive environment favoring tumor growth (Lisi et al., 2023). Specifically, it reduces iNOS expression and the production of pro-inflammatory cytokines by downregulating the NF-κB pathway, while it upregulates the anti-inflammatory cytokine IL-10 by upregulating the STAT-3 pathway, which favours tumour growth (Dumas et al., 2020; Lisi et al., 2014, 2019). Additionally, mTORC1 activation has been linked to increased phagocytic activity (Zhao et al., 2018), by upregulating Trem2 and lysosomal biogenesis. This ultimately leads to better clearance of amyloid plaques in Alzheimer's disease models (Shi et al., 2022, p. 202). The first step of the mTORC1 signaling pathway that mediates microglial response is the upregulation of glycolysis and it is necessary for the induction of phagocytic activity and, in turn, the reduction of amyloid plaques (Baik et al., 2019b).

All these data demonstrate the central role of the mTORC1 pathway in the regulation of microglia energy metabolism and associated functions. However, the intricacies of the system warrant further investigation. Indeed, it has been observed that genetic inhibition of the mTORC1 pathway in aged mice, despite elevating transcript levels of pro-inflammatory cytokines via the NFκB pathway following LPS treatment, concurrently results in decreased protein levels (Keane et al., 2021). Furthermore, the mTORC1 pathway occupies a strategic position between the amount of energy available in the local environment and the modulation of microglial inflammatory and phagocytic function. Therefore, it would be interesting to investigate its role in the microglial response to a calorie-rich diet, when the available energy is high (Fig. 1).

5. Microglia-neuron interactions in the context of obesity

Within the ARC, there are two functionally opposite neuronal populations: the orexigenic agouti-related peptide (AgRP) and neuropeptide Y (NPY) neurons, and on the other hand the anorexigenic POMC and cocaine- and amphetamine-regulated transcript (CART) neurons. HFD consumption induces profound and time-dependent neuronal remodeling in the arcuate nucleus of the hypothalamus, including significant changes in the activity of all ARC neurons, and, in their intra-ARC and extra-ARC connectivity, as well as in their sensitivity to peripheral cues (hormones, nutrients) (for review, see e.g. Jais and Brüning, 2022; Quarta et al., 2021). This imbalance in metabolic neuronal networks leads to the generation of disproportionate hunger and food intake signals. Since microglia triggers an inflammatory response in the ARC following consumption of a HFD (see above), one could hypothesize that neurons and microglia engage in a detrimental crosstalk, ultimately leading to compromised neuronal function and ensuing metabolic dysregulation. Nonetheless, we lack knowledge about the molecules and pathways involved in the cross-talk between microglia and neurons in the ARC under HFD. Moreover, whether this communication prevents or promotes diet-induce obesity is mostly unknown.

Upon HFD, microglia release pro-inflammatory molecules such as chemokines and cytokines (Valdearcos et al., 2017). The chemokine CX3CL1, also referred to as fractalkine, is released by neurons and maintains microglial homeostatic activity via the receptor CX3CR1, located on microglial surface (Arnoux and Audinat, 2015). Following HFD, the CX3CL1-CX3CR1 signaling decreases in vulnerable male mice, whereas resilient females (not gaining weight on HFD) maintain high CX3CL1-CX3CR1 tone. Knock-down of CX3CR1 in females induces a male-like phenotype (increase in body weight), whereas it has no effect on the metabolism of males (Dorfman et al., 2017). However, one study using siRNA found the opposite, showing that inhibiting hypothalamic CX3CL1 protects against diet-induced hypothalamic inflammation and the development of diet-induced obesity (Morari et al., 2014). These findings imply the essential role of fractalkine-mediated microglia-neuron interactions in obesity development, although further experiments are necessary to elucidate the precise processes involved.

Banerjee and colleagues have subsequently proposed a potential mechanism elucidating how fractalkine signalling protects against body weight gain. Specifically, they showed that CX3CL1 treatment of HFD-fed mice restores POMC neuronal excitability and increased *pomc* expression, leading to reduced body weight and food intake, thus indicating fractalkine as a link between microglial activation and neuronal dysfunction (Banerjee et al., 2022). The prostaglandin PGE2 is a lipid mediator which acts as a key inflammatory factor (Smyth et al., 2009). This latter can affect microglial inflammatory activity through the receptor EP4, highly expressed in microglia (Shi et al., 2010). Remarkably, PGE2 expression reaches elevated levels in the ARC of HFD-fed mice (Lee et al., 2021). A recent study showed that mice with EP4-deficient microglia exhibit a defective microglial phagocytic activity, associated with lower number of microglia-neuron cell-cell contacts and a higher density of POMC neuron fibres in the paraventricular nucleus of the hypothalamus (Niraula et al., 2023).

As specialized phagocytes, microglia are responsible for the elimination of excess synapses, a process called synaptic pruning, which is

critical during neurodevelopment (Paolicelli et al., 2011). However, ample evidence across various pathological contexts suggests that any dysregulation of these mechanisms (reduction or exacerbation of pruning) contributes to disease exacerbation (Henstridge et al., 2019). But what about obesity? HFD-induced obesity is associated with the long-term synaptic reorganization of hypothalamic POMC and AgRP neurons, which present fewer total synapses on their perikarya (Horvath et al., 2010). Moreover, already after 3 days of HFD, there is a significant increase in the excitatory inputs on POMC neurons, consistent with the progressive decrease in energy intake observed after HFD introduction (Benani et al., 2012). Since microglia are proliferating and producing inflammatory factors at 3 days post-HFD, they may be directly implicated in the rapid refinement of neuronal circuits, albeit no direct causal evidence supporting this model is yet available. Interestingly, microglia isolated from mice fed with a HFD show a higher internalization of synaptosomes compared to controls *in vitro* (Hao et al., 2016). Obesity is also associated with cognitive deficits in the prefrontal cortex (Bocarsly et al., 2015) and in the hippocampus (Hao et al., 2016; Valladolid-Acebes et al., 2013), that goes along with synapse loss, suggesting a potential role for microglial synaptic pruning under HFD. Additional studies showed that the inhibition of the phagocytic activity of microglia, and thus of the potential premature engulfment of functional synaptic material, is sufficient to prevent obesity-associated cognitive decline (Cope et al., 2018). Interestingly, they also demonstrated that the partial knock-down of the microglial fractalkine receptor is capable of disrupting obesity-associated cognitive deficits and of dampening microglial activation in the hippocampus, indicating again a key role for this microglia-neuron signalling in the context of diet-induced obesity (Cope et al., 2018).

In a model of obesity and type 2 diabetes characterized by impaired hypothalamic neuronal synaptic plasticity (Horvath et al., 2010; Mizuno et al., 1998), hypothalamic microglial cells show reduced expression of the phagocytic marker CD68 (Gao et al., 2014). Similarly, transgenic mice with a specific leptin receptor deficiency in myeloid cells (including microglia) display an obesity-like phenotype, a reduced number of hypothalamic ARC POMC-expressing neurons and signs of impaired microglial phagocytic capacity in the hypothalamus (Gao et al., 2018). It has to be remarked that microglial cells not only prune synapses, but they also promote synapse formation (Miyamoto et al., 2016). However, no studies have investigated whether changes in microglial-mediated synaptogenesis occur during diet-induced metabolic stress, which represents an interesting angle for future investigations. It is also worth noting that microglia continuously engulf and rapidly degrade apoptotic neurons and synaptic material (Peri and Nüsslein-Volhard, 2008). The HFD-triggered loss of synapses is likely to take place gradually over several days or even weeks. Moreover, the time window between the phagocytosis of synapses and their degradation is short, potentially impeding the detection of synaptic material inside microglia, even though there is eventually an effective reduction in spine numbers. It is also plausible that under conditions of obesity, the degradation rate of synaptic proteins by microglia could be accelerated, or conversely defective, leading to a, respectively, reduced or increased accumulation of synapses in microglial lysosomes. More experiments are needed to understand whether and how a high-calorie diet exacerbates microglia-mediated synaptic pruning, leading to the disruption of the AgRP/NPY and POMC neurons activity, and thus contributing to the development of obesity.

6. Do microglia play a role in the sexual dimorphism observed in obesity?

Females and males show differential susceptibility to body weight gain under HFD, and many obesity-related comorbidities, such as type 2 diabetes, show sex-specific pathways (Casimiro et al., 2021; Cooper et al., 2021; Dorfman et al., 2017; Hong et al., 2009; Oraha et al., 2022; Pettersson et al., 2012). However, most of the aforementioned studies have investigated the role of microglia in diet-induced obesity, focusing almost exclusively on male mice (Gao et al., 2014; Thaler et al., 2012; Valdearcos et al., 2014). When exposed to HFD, both male and female mice reduce their caloric intake, but this phenomenon is less pronounced in females, resulting in higher energy expenditure in females than in males (Casimiro et al., 2021; Oraha et al., 2022). This correlates with a faster and greater decline in respiratory quotient in females, suggesting a greater ability to use fatty acids as a primary fuel source. In addition, females experience a less pronounced decline in physical activity than males, and they sleep less than males. As a result, females accumulate less body fat than males and are protected from excessive weight gain induced by calorie overload (Casimiro et al., 2021; Oraha et al., 2022).

Exposure of females to HFD does not induce microglial morphological changes, microglial expansion and macrophage infiltration in the ARC and does not alter levels of pro-inflammatory cytokines in the whole hypothalamus (Dorfman et al., 2017; Lainez et al., 2018). Conversely, female mice express high levels of the anti-inflammatory cytokine IL-10, which likely serves as a defense against diet-induced inflammation (Lainez et al., 2018). This sexually dimorphic phenotype appears to rely on two distinct mechanisms: an estrogen-mediated process (Hong et al., 2009; Morselli et al., 2016; Xu et al., 2011) and the CX3CR1-CX3CL1 signaling cascade (Dorfman et al., 2017). HFD induces the CX3CR1-CX3CL1 signaling and in turn attenuates microglial inflammation in females (Dorfman et al., 2017). Accordingly, CX3CR1-CX3CL1 deficiency in males after HFD exacerbates inflammation, body weight gain, and glucose and insulin intolerance (Dorfman et al., 2017; Kawamura et al., 2022; Nagashimada et al., 2021). Interestingly, the protective role of estrogens appears to be facilitated by a different mechanism, as ovariectomized female mice are susceptible to weight gain (Hong et al., 2009; Lainez et al., 2018), but without stimulation of CX3CR1-CX3CL1 signalling (Dorfman et al., 2017; Lainez et al., 2018).

The need for females to manage weight fluctuations during pregnancy and lactation may rationalize their metabolic flexibility based on resource availability (Tinius et al., 2020). Another notable aspect that may contribute to the sex-specific phenotype in diet-induced obesity is the sex-specific phenotype of microglia themselves, including their metabolic characteristics (Bobotis et al., 2023; Guillot-Sestier et al., 2021; Lynch, 2022; Maes et al., 2023; Villa et al., 2018). Finally, microglia show differential expression of a significant number of genes independent of sex steroids, and this pattern persists even after transplantation into the opposite sex (Villa et al., 2018).

7. Is the microglial reaction to excess calories truly not adapted?

Let's reflect now on the role of the early response of microglia to calorie excess. These cells, as resident macrophages, function to maintain brain homeostasis. In this context, their immediate response to any changes in the environment aims to preserve neuron integrity and thus ensure organism's survival (Paolicelli et al., 2022). In response to HFD, the proliferation and inflammatory activation of microglia are implicated in exacerbated weight gain and could therefore be defined as detrimental and maladaptive for the organism.

To comprehend this apparent contradiction, evolutionary constraints shaping the development of energy balance-regulating mechanisms must be considered. The regulation of energy balance is overseen by two conventionally termed systems: the homeostatic and non-homeostatic systems (Berthoud, 2003; De Castro and Plunkett, 2002). While the homeostatic system reacts to a decline in the organism's internal energy status by stimulating hunger and food consumption, conversely, the non-homeostatic system is engaged simply by the presence of food in the environment (Berthoud, 2003, 2011; De Castro and Plunkett, 2002). Thus, individuals may eat even when satiated if presented with new and/or attractive foods.

The adaptive value of this system is challenging to grasp in the

current environmental conditions of developed Western countries, where food availability is virtually unlimited. However, humans have been hunters and gatherers for approximately four million years (Harari, 2015). In conditions where food presence was inconsistent and could not be stored, having a system capable of addressing immediate needs and increasing energy storage to endure forthcoming periods of scarcity was vital for survival. Individuals who better controlled motivational forces gained a clear advantage in species preservation (for review, Piazza et al., 2017). In this context, the early effects of microglia on calorie intake when high-calorie food is available may be viewed as a perfectly physiological and adaptive response, which allows the animals to ingest higher amount of food and save energy for periods of starvation to come. This hypothesis aligns with recent findings from the Thaler's group (Douglass et al., 2023), indicating that the suppression of the HFD-triggered microglial inflammatory response not only diminishes weight gain but also exacerbates glucose intolerance in mice. Hence, the microglial response to HFD positively influences the regulation of glucose metabolism in mice while concurrently contributing to weight gain. In accordance with our hypothesis, the concurrent effects of increased body weight and restriction of glucose intolerance bolster the proposition that the microglial response might have a beneficial role in situations marked by limited environmental caloric intake.

Changing the conceptual framework into which we study the role of microglia in obesity, especially in the early phase of exposure to HFD, could thus provide a different approach to apprehend and understand the response of these cells.

8. Unresolved questions

There are still many questions to be answered in this field before we have a clear idea of the role of microglia in the development of obesity. Here is a non-exhaustive list:

1. What is the exact nature and timing of microglia-neuron interactions in response to calorie surfeit? The production of inflammatory cytokines by microglia has been the focus of most studies. However, it is very likely that other mechanisms, such as the refinement of synapses or the control of neuronal excitability, could also be at play in this context. Furthermore, all these mechanisms are likely to be time-dependent. Therefore, further comparative studies will be necessary for an understanding of the early and late microglial response to calorie excess.
2. Role of lipid mediators in the microglial response to HFD? Most if not all studies focus on the production of inflammatory proteins (cytokines) by microglia, in response to HFD. However, it is highly likely that due to the lipid surfeit, microglia predominantly produce inflammatory mediators derived from lipids, such as prostaglandins. This lipid landscape of the microglial inflammatory response has never been comprehensively studied. Lipidomics experiments would be necessary to assess these mechanisms.
3. What triggers the microglial response to HFD? Some studies suggest that saturated fat and glucose may have a direct effect on microglial inflammatory activity in ARC. Others have shown that microglia respond to hormones such as leptin or insulin. Further studies are therefore needed to understand the different signals that trigger microglial reactivity and to look at other potentially relevant pathways, such as the vagus nerve.
4. Interactions with other glial cells. Astrocytes and tanycytes are also active players in the brain's response to HFD, but almost no study is available on how all the glial cells combine their efforts to modulate neuronal activity in this context, if they do.
5. Role of macrophages vs microglia? Although there is no clear consensus on their origin (local progenitors or periphery), macrophages infiltrate the ARC in response to HFD and are likely to play a role in modulating the activity of local neurons. It would therefore be very interesting to develop approaches to distinguish between the role of macrophages and microglia in response to HFD, and to assess the relative importance of these two cell types in the development of obesity. Are their actions complementary or opposite remains an open question.
6. Understanding the role of microglial in the obesity-related sexual dimorphism. Few studies have addressed the question of sexual dimorphism in the response of ARC to HFD. This is all the more important as men and women are not equal in terms of obesity and related metabolic complications. Whether microglia, which are sexually dimorphic cells, play a role in this remains to be investigated.

CRediT authorship contribution statement

G. Cutugno: Writing – review & editing, Writing – original draft. **E. Kyriakidou:** Writing – review & editing, Writing – original draft. **A. Nadjar:** Writing – review & editing, Writing – original draft, Validation, Supervision.

Declaration of competing Interest

All authors declare that they have no conflicts of interest.

Data availability

No data was used for the research described in the article.

Acknowledgments

AN is supported by the Institut Universitaire de France (IUF), the University of Bordeaux, the French Foundation for Brain Research (FRC), the GLN (Lipid-Nutrition Group), the National Research Agency (ANR, PRC 2023-MicroNRJ). This project has received funding from the European Union's Horizon Europe research and innovation program under the MSCA Doctoral Networks 2021, No. 101072759 (FuElThE-bRaiNIn healtThYaging and age-related diseases, ETERNITY.

References

Alexaki, V.I., 2021. The impact of obesity on microglial function: immune, metabolic and endocrine perspectives. Cells 10, 1584. https://doi.org/10.3390/cells10071584.

André, C., Guzman-Quevedo, O., Rey, C., Rémus-Borel, J., Clark, S., Castellanos-Jankiewicz, A., Ladeveze, E., Leste-Lasserre, T., Nadjar, A., Abrous, D.N., Laye, S., Cota, D., 2017. Inhibiting microglia expansion prevents diet-induced hypothalamic and peripheral inflammation. Diabetes 66, 908–919. https://doi.org/10.2337/db16-0586.

Arnoux, I., Audinat, E., 2015. Fractalkine signaling and microglia functions in the developing brain. Neural Plast. 1–8. https://doi.org/10.1155/2015/689404, 2015.

Baik, S.H., Kang, S., Lee, W., Choi, H., Chung, S., Kim, J.-I., Mook-Jung, I., 2019a. A breakdown in metabolic reprogramming causes microglia dysfunction in Alzheimer's disease. Cell Metabol. 30, 493–507.e6. https://doi.org/10.1016/j.cmet.2019.06.005.

Baik, S.H., Kang, S., Lee, W., Choi, H., Chung, S., Kim, J.-I., Mook-Jung, I., 2019b. A breakdown in metabolic reprogramming causes microglia dysfunction in Alzheimer's disease. Cell Metabol. 30, 493–507.e6. https://doi.org/10.1016/j.cmet.2019.06.005.

Banerjee, J., Dorfman, M.D., Fasnacht, R., Douglass, J.D., Wyse-Jackson, A.C., Barria, A., Thaler, J.P., 2022. CX3CL1 action on microglia protects from diet-induced obesity by restoring POMC neuronal excitability and melanocortin system activity impaired by high-fat diet feeding. Int. J. Mol. Sci. 23, 6380. https://doi.org/10.3390/ijms23126380.

Baufeld, C., Osterloh, A., Prokop, S., Miller, K.R., Heppner, F.L., 2016. High-fat diet-induced brain region-specific phenotypic spectrum of CNS resident microglia. Acta Neuropathol. 132, 361–375. https://doi.org/10.1007/s00401-016-1595-4.

Benani, A., Hryhorczuk, C., Gouazé, A., Fioramonti, X., Brenachot, X., Guissard, C., Krezymon, A., Duparc, T., Colom, A., Nédélec, E., Rigault, C., Lemoine, A., Gascuel, J., Gerardy-Schahn, R., Valet, P., Knauf, C., Lorsignol, A., Pénicaud, L., 2012. Food intake adaptation to dietary fat involves PSA-dependent rewiring of the arcuate melanocortin system in mice. J. Neurosci. 32, 11970–11979. https://doi.org/10.1523/JNEUROSCI.0624-12.2012.

Bernier, L.-P., York, E.M., Kamyabi, A., Choi, H.B., Weilinger, N.L., MacVicar, B.A., 2020. Microglial metabolic flexibility supports immune surveillance of the brain parenchyma. Nat. Commun. 11, 1559. https://doi.org/10.1038/s41467-020-15267-z.

Berthoud, H.-R., 2003. Neural systems controlling food intake and energy balance in the modern world. Curr. Opin. Clin. Nutr. Metab. Care 6, 615–620. https://doi.org/10.1097/00075197-200311000-00002.
Berthoud, H.-R., 2011. Metabolic and hedonic drives in the neural control of appetite: who is the boss? Curr. Opin. Neurobiol. 21, 888–896. https://doi.org/10.1016/j.conb.2011.09.004.
Bobotis, B.C., Braniff, O., Gargus, M., Akinluyi, E.T., Awogbindin, I.O., Tremblay, M.-È., 2023. Sex differences of microglia in the healthy brain from embryonic development to adulthood and across lifestyle influences. Brain Res. Bull. 202, 110752 https://doi.org/10.1016/j.brainresbull.2023.110752.
Bocarsly, M.E., Fasolino, M., Kane, G.A., LaMarca, E.A., Kirschen, G.W., Karatsoreos, I.N., McEwen, B.S., Gould, E., 2015. Obesity diminishes synaptic markers, alters microglial morphology, and impairs cognitive function. Proc. Natl. Acad. Sci. USA 112, 15731–15736. https://doi.org/10.1073/pnas.1511593112.
Borst, K., Schwabenland, M., Prinz, M., 2019. Microglia metabolism in health and disease. Neurochem. Int. 130, 104331 https://doi.org/10.1016/j.neuint.2018.11.006.
Brooks, G.A., 2009. Cell–cell and intracellular lactate shuttles. J. Physiol. 587, 5591–5600. https://doi.org/10.1113/jphysiol.2009.178350.
Buchanan, J.B., Sparkman, N.L., Johnson, R.W., 2010. A neurotoxic regimen of methamphetamine exacerbates the febrile and neuroinflammatory response to a subsequent peripheral immune stimulus. J. Neuroinflammation 7, 82. https://doi.org/10.1186/1742-2094-7-82.
Cansell, C., Stobbe, K., Sanchez, C., Le Thuc, O., Mosser, C., Ben-Fradj, S., Leredde, J., Lebeaupin, C., Debayle, D., Fleuriot, L., Brau, F., Devaux, N., Benani, A., Audinat, E., Blondeau, N., Nahon, J., Rovère, C., 2021. Dietary fat exacerbates postprandial hypothalamic inflammation involving glial fibrillary acidic protein-positive cells and microglia in male mice. Glia 69, 42–60. https://doi.org/10.1002/glia.23882.
Casimiro, I., Stull, N.D., Tersey, S.A., Mirmira, R.G., 2021. Phenotypic sexual dimorphism in response to dietary fat manipulation in C57BL/6J mice. J. Diabet. Complicat. 35, 107795 https://doi.org/10.1016/j.jdiacomp.2020.107795.
Chénais, B., Morjani, H., Drapier, J., 2002. Impact of endogenous nitric oxide on microglial cell energy metabolism and labile iron pool. J. Neurochem. 81, 615–623. https://doi.org/10.1046/j.1471-4159.2002.00864.x.
Churchward, M.A., Tchir, D.R., Todd, K.G., 2018. Microglial function during glucose deprivation: inflammatory and neuropsychiatric implications. Mol. Neurobiol. 55, 1477–1487. https://doi.org/10.1007/s12035-017-0422-9.
Cooper, A.J., Gupta, S.R., Moustafa, A.F., Chao, A.M., 2021. Sex/gender differences in obesity prevalence, comorbidities, and treatment. Curr. Obes. Rep. 10, 458–466. https://doi.org/10.1007/s13679-021-00453-x.
Cope, E.C., LaMarca, E.A., Monari, P.K., Olson, L.B., Martinez, S., Zych, A.D., Katchur, N. J., Gould, E., 2018. Microglia play an active role in obesity-associated cognitive decline. J. Neurosci. 38, 8889–8904. https://doi.org/10.1523/JNEUROSCI.0789-18.2018.
De Castro, J.M., Plunkett, S., 2002. A general model of intake regulation. Neurosci. Biobehav. Rev. 26, 581–595. https://doi.org/10.1016/S0149-7634(02)00018-0.
De Souza, C.T., Araujo, E.P., Bordin, S., Ashimine, R., Zollner, R.L., Boschero, A.C., Saad, M.J.A., Velloso, L.A., 2005. Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus. Endocrinology 146, 4192–4199. https://doi.org/10.1210/en.2004-1520.
Dello Russo, C., Lisi, L., Tringali, G., Navarra, P., 2009. Involvement of mTOR kinase in cytokine-dependent microglial activation and cell proliferation. Biochem. Pharmacol. 78, 1242–1251. https://doi.org/10.1016/j.bcp.2009.06.097.
Domblides, C., Lartigue, L., Faustin, B., 2018. Metabolic stress in the immune function of T cells, macrophages and dendritic cells. Cells 7, 68. https://doi.org/10.3390/cells7070068.
Dorfman, M.D., Krull, J.E., Douglass, J.D., Fasnacht, R., Lara-Lince, F., Meek, T.H., Shi, X., Damian, V., Nguyen, H.T., Matsen, M.E., Morton, G.J., Thaler, J.P., 2017. Sex differences in microglial CX3CR1 signalling determine obesity susceptibility in mice. Nat. Commun. 8, 14556 https://doi.org/10.1038/ncomms14556.
Douglass, J.D., Ness, K.M., Valdearcos, M., Wyse-Jackson, A., Dorfman, M.D., Frey, J.M., Fasnacht, R.D., Santiago, O.D., Niraula, A., Banerjee, J., Robblee, M., Koliwad, S.K., Thaler, J.P., 2023. Obesity-associated microglial inflammatory activation paradoxically improves glucose tolerance. Cell Metabol. 35, 1613–1629.e8. https://doi.org/10.1016/j.cmet.2023.07.008.
Drougard, A., Ma, E.H., Wegert, V., Sheldon, R., Panzeri, I., Vatsa, N., Apostle, S., Fagnocchi, L., Schaf, J., Gossens, K., Völker, J., Pang, S., Bremser, A., Dror, E., Giacona, F.Sagar, Henderson, M.X., Prinz, M., Jones, R.G., Pospisilik, J.A., 2023. A rapid microglial metabolic response controls metabolism and improves memory. https://doi.org/10.7554/eLife.87120.1.
Dumas, A.A., Pomella, N., Rosser, G., Guglielmi, L., Vinel, C., Millner, T.O., Rees, J., Aley, N., Sheer, D., Wei, J., Marisetty, A., Heimberger, A.B., Bowman, R.L., Brandner, S., Joyce, J.A., Marino, S., 2020. Microglia promote glioblastoma via mTOR-mediated immunosuppression of the tumour microenvironment. EMBO J. 39, e103790 https://doi.org/10.15252/embj.2019103790.
Engl, E., Jolivet, R., Hall, C.N., Attwell, D., 2017. Non-signalling energy use in the developing rat brain. J. Cerebr. Blood Flow Metabol. 37, 951–966. https://doi.org/10.1177/0271678X16648710.
Feng, T., Zhao, X., Gu, P., Yang, W., Wang, C., Guo, Q., Long, Q., Liu, Q., Cheng, Y., Li, J., Cheung, C.K.Y., Wu, D., Kong, X., Xu, Y., Ye, D., Hua, S., Loomes, K., Xu, A., Hui, X., 2022. Adipocyte-derived lactate is a signalling metabolite that potentiates adipose macrophage inflammation via targeting PHD2. Nat. Commun. 13, 5208. https://doi.org/10.1038/s41467-022-32871-3.
Folick, A., Koliwad, S.K., Valdearcos, M., 2021. Microglial lipid biology in the hypothalamic regulation of metabolic homeostasis. Front. Endocrinol. 12, 668396 https://doi.org/10.3389/fendo.2021.668396.
Gao, Y., Ottaway, N., Schriever, S.C., Legutko, B., García-Cáceres, C., De La Fuente, E., Mergen, C., Bour, S., Thaler, J.P., Seeley, R.J., Filosa, J., Stern, J.E., Perez-Tilve, D., Schwartz, M.W., Tschöp, M.H., Yi, C., 2014. Hormones and diet, but not body weight, control hypothalamic microglial activity. Glia 62, 17–25. https://doi.org/10.1002/glia.22580.
Gao, Y., Vidal-Itriago, A., Kalsbeek, M.J., Layritz, C., García-Cáceres, C., Tom, R.Z., Eichmann, T.O., Vaz, F.M., Houtkooper, R.H., Van Der Wel, N., Verhoeven, A.J., Yan, J., Kalsbeek, A., Eckel, R.H., Hofmann, S.M., Yi, C.-X., 2017. Lipoprotein lipase maintains microglial innate immunity in obesity. Cell Rep. 20, 3034–3042. https://doi.org/10.1016/j.celrep.2017.09.008.
Gao, Y., Vidal-Itriago, A., Milanova, I., Korpel, N.L., Kalsbeek, M.J., Tom, R.Z., Kalsbeek, A., Hofmann, S.M., Yi, C.-X., 2018. Deficiency of leptin receptor in myeloid cells disrupts hypothalamic metabolic circuits and causes body weight increase. Mol. Metabol. 7, 155–160. https://doi.org/10.1016/j.molmet.2017.11.003.
Ghosh, S., Castillo, E., Frias, E.S., Swanson, R.A., 2018. Bioenergetic regulation of microglia. Glia 66, 1200–1212. https://doi.org/10.1002/glia.23271.
Gimeno-Bayón, J., López-López, A., Rodríguez, M.J., Mahy, N., 2014. Glucose pathways adaptation supports acquisition of activated microglia phenotype. J. Neurosci. Res. 92, 723–731. https://doi.org/10.1002/jnr.23356.
Guillot-Sestier, M.-V., Araiz, A.R., Mela, V., Gaban, A.S., O'Neill, E., Joshi, L., Chouchani, E.T., Mills, E.L., Lynch, M.A., 2021. Microglial metabolism is a pivotal factor in sexual dimorphism in Alzheimer's disease. Commun. Biol. 4, 711. https://doi.org/10.1038/s42003-021-02259-y.
Hao, S., Dey, A., Yu, X., Stranahan, A.M., 2016. Dietary obesity reversibly induces synaptic stripping by microglia and impairs hippocampal plasticity. Brain Behav. Immun. 51, 230–239. https://doi.org/10.1016/j.bbi.2015.08.023.
Harari, Yuval Noah, 2015. Sapiens : A Brief History of Humankind. HarperColinsPublishers, New York.
He, T., Li, W., Song, Y., Li, Z., Tang, Y., Zhang, Z., Yang, G.-Y., 2020. Sestrin2 regulates microglia polarization through mTOR-mediated autophagic flux to attenuate inflammation during experimental brain ischemia. J. Neuroinflammation 17, 329. https://doi.org/10.1186/s12974-020-01987-y.
Henstridge, C.M., Tzioras, M., Paolicelli, R.C., 2019. Glial contribution to excitatory and inhibitory synapse loss in neurodegeneration. Front. Cell. Neurosci. 13, 63. https://doi.org/10.3389/fncel.2019.00063.
Holland, R., McIntosh, A.L., Finucane, O.M., Mela, V., Rubio-Araiz, A., Timmons, G., McCarthy, S.A., Gun'ko, Y.K., Lynch, M.A., 2018. Inflammatory microglia are glycolytic and iron retentive and typify the microglia in APP/PS1 mice. Brain Behav. Immun. 68, 183–196. https://doi.org/10.1016/j.bbi.2017.10.017.
Hong, J., Stubbins, R.E., Smith, R.R., Harvey, A.E., Núñez, N.P., 2009. Differential susceptibility to obesity between male, female and ovariectomized female mice. Nutr. J. 8, 11. https://doi.org/10.1186/1475-2891-8-11.
Horvath, T.L., Sarman, B., García-Cáceres, C., Enriori, P.J., Sotonyi, P., Shanabrough, M., Borok, E., Argente, J., Chowen, J.A., Perez-Tilve, D., Pfluger, P.T., Brönneke, H.S., Levin, B.E., Diano, S., Cowley, M.A., Tschöp, M.H., 2010. Synaptic input organization of the melanocortin system predicts diet-induced hypothalamic reactive gliosis and obesity. Proc. Natl. Acad. Sci. USA 107, 14875–14880. https://doi.org/10.1073/pnas.1004282107.
Hu, Y., Mai, W., Chen, L., Cao, K., Zhang, B., Zhang, Z., Liu, Y., Lou, H., Duan, S., Gao, Z., 2020. mTOR-mediated metabolic reprogramming shapes distinct microglia functions in response to lipopolysaccharide and ATP. Glia 68, 1031–1045. https://doi.org/10.1002/glia.23760.
Jais, A., Brüning, J.C., 2022. Arcuate nucleus-dependent regulation of metabolism—pathways to obesity and diabetes mellitus. Endocr. Rev. 43, 314–328. https://doi.org/10.1210/endrev/bnab025.
Kawamura, N., Katsuura, G., Yamada-Goto, N., Nakama, R., Kambe, Y., Miyata, A., Furuyashiki, T., Narumiya, S., Ogawa, Y., Inui, A., 2022. Brain fractalkine-CX3CR1 signalling is anti-obesity system as anorexigenic and anti-inflammatory actions in diet-induced obese mice. Sci. Rep. 12, 12604 https://doi.org/10.1038/s41598-022-16944-3.
Keane, L., Antignano, I., Riechers, S.-P., Zollinger, R., Dumas, A.A., Offermann, N., Bernis, M.E., Russ, J., Graelmann, F., McCormick, P.N., Esser, J., Tejera, D., Nagano, A., Wang, J., Chelala, C., Biederbick, Y., Halle, A., Salomoni, P., Heneka, M. T., Capasso, M., 2021. mTOR-dependent translation amplifies microglia priming in aging mice. J. Clin. Invest. 131 https://doi.org/10.1172/JCI132727.
Kim, J.D., Yoon, N.A., Jin, S., Diano, S., 2019. Microglial UCP2 mediates inflammation and obesity induced by high-fat feeding. Cell Metabol. 30, 952–962.e5. https://doi.org/10.1016/j.cmet.2019.08.010.
Kim, J.D., Copperi, F., Diano, S., 2023. Microglia in central control of metabolism. Physiology physiol, 00021. https://doi.org/10.1152/physiol.00021.2023, 2023.
Lainez, N.M., Jonak, C.R., Nair, M.G., Ethell, I.M., Wilson, E.H., Carson, M.J., Coss, D., 2018. Diet-induced obesity elicits macrophage infiltration and reduction in spine density in the hypothalami of male but not female mice. Front. Immunol. 9, 1992. https://doi.org/10.3389/fimmu.2018.01992.
Lancaster, G.I., Langley, K.G., Berglund, N.A., Kammoun, H.L., Reibe, S., Estevez, E., Weir, J., Mellett, N.A., Pernes, G., Conway, J.R.W., Lee, M.K.S., Timpson, P., Murphy, A.J., Masters, S.L., Gerondakis, S., Bartonicek, N., Kaczorowski, D.C., Dinger, M.E., Meikle, P.J., Bond, P.J., Febbraio, M.A., 2018. Evidence that TLR4 is not a receptor for saturated fatty acids but mediates lipid-induced inflammation by reprogramming macrophage metabolism. Cell Metabol. 27, 1096–1110.e5. https://doi.org/10.1016/j.cmet.2018.03.014.
Lauro, C., Limatola, C., 2020. Metabolic reprograming of microglia in the regulation of the innate inflammatory response. Front. Immunol. 11, 493. https://doi.org/10.3389/fimmu.2020.00493.

Layé, S., Parnet, P., Goujon, E., Dantzer, R., 1994. Peripheral administration of lipopolysaccharide induces the expression of cytokine transcripts in the brain and pituitary of mice. Mol. Brain Res. 27, 157–162. https://doi.org/10.1016/0169-328X(94)90197-X.

Lee, M.-L., Matsunaga, H., Sugiura, Y., Hayasaka, T., Yamamoto, I., Ishimoto, T., Imoto, D., Suematsu, M., Iijima, N., Kimura, K., Diano, S., Toda, C., 2021. Prostaglandin in the ventromedial hypothalamus regulates peripheral glucose metabolism. Nat. Commun. 12, 2330. https://doi.org/10.1038/s41467-021-22431-6.

Lisi, L., Laudati, E., Navarra, P., Dello Russo, C., 2014. The mTOR kinase inhibitors polarize glioma-activated microglia to express a M1 phenotype. J. Neuroinflammation 11, 125. https://doi.org/10.1186/1742-2094-11-125.

Lisi, L., Aceto, P., Navarra, P., Dello Russo, C., 2015. mTOR kinase: a possible pharmacological target in the management of chronic pain. BioMed Res. Int., 394257 https://doi.org/10.1155/2015/394257, 2015.

Lisi, L., Ciotti, G.M.P., Chiavari, M., Pizzoferrato, M., Mangiola, A., Kalinin, S., Feinstein, D.L., Navarra, P., 2019. Phospho-mTOR expression in human glioblastoma microglia-macrophage cells. Neurochem. Int. 129, 104485 https://doi.org/10.1016/j.neuint.2019.104485.

Lisi, L., Pizzoferrato, M., Ciotti, G.M., Martire, M., Navarra, P., 2023. mTOR inhibition is effective against growth, survival and migration, but not against microglia activation in preclinical glioma models. Int. J. Mol. Sci. 24 https://doi.org/10.3390/ijms24129834.

Liu, Y., Xu, R., Gu, H., Zhang, E., Qu, J., Cao, W., Huang, X., Yan, H., He, J., Cai, Z., 2021. Metabolic reprogramming in macrophage responses. Biomark. Res. 9, 1. https://doi.org/10.1186/s40364-020-00251-y.

Lynch, M.A., 2020. Can the emerging field of immunometabolism provide insights into neuroinflammation? Prog. Neurobiol. 184, 101719 https://doi.org/10.1016/j.pneurobio.2019.101719.

Lynch, M.A., 2022. Exploring sex-related differences in microglia may Be a game-changer in precision medicine. Front. Aging Neurosci. 14, 868448 https://doi.org/10.3389/fnagi.2022.868448.

Maes, M.E., Colombo, G., Schoot Uiterkamp, F.E., Sternberg, F., Venturino, A., Pohl, E.E., Siegert, S., 2023. Mitochondrial network adaptations of microglia reveal sex-specific stress response after injury and UCP2 knockout. iScience 26, 107780. https://doi.org/10.1016/j.isci.2023.107780.

Mendes, N.F., Kim, Y.-B., Velloso, L.A., Araújo, E.P., 2018. Hypothalamic microglial activation in obesity: a mini-review. Front. Neurosci. 12, 846. https://doi.org/10.3389/fnins.2018.00846.

Milanova, I.V., Kalsbeek, M.J.T., Wang, X.-L., Korpel, N.L., Stenvers, D.J., Wolff, S.E.C., De Goede, P., Heijboer, A.C., Fliers, E., La Fleur, S.E., Kalsbeek, A., Yi, C.-X., 2019. Diet-induced obesity disturbs microglial immunometabolism in a time-of-day manner. Front. Endocrinol. 10, 424. https://doi.org/10.3389/fendo.2019.00424.

Milanova, I.V., Correa-da-Silva, F., Kalsbeek, A., Yi, C.-X., 2021. Mapping of microglial brain region, sex and age heterogeneity in obesity. Int. J. Mol. Sci. 22, 3141. https://doi.org/10.3390/ijms22063141.

Miyamoto, A., Wake, H., Ishikawa, A.W., Eto, K., Shibata, K., Murakoshi, H., Koizumi, S., Moorhouse, A.J., Yoshimura, Y., Nabekura, J., 2016. Microglia contact induces synapse formation in developing somatosensory cortex. Nat. Commun. 7, 12540 https://doi.org/10.1038/ncomms12540.

Mizuno, T.M., Kleopoulos, S.P., Bergen, H.T., Roberts, J.L., Priest, C.A., Mobbs, C.V., 1998. Hypothalamic pro-opiomelanocortin mRNA is reduced by fasting in *ob/ob* and *db/db* mice, but is stimulated by leptin. Diabetes 47, 294–297. https://doi.org/10.2337/diab.47.2.294.

Monsorno, K., Buckinx, A., Paolicelli, R.C., 2022. Microglial metabolic flexibility: emerging roles for lactate. Trends Endocrinol. Metab. 33, 186–195. https://doi.org/10.1016/j.tem.2021.12.001.

Monsorno, K., Ginggen, K., Ivanov, A., Buckinx, A., Lalive, A.L., Tchenio, A., Benson, S., Vendrell, M., D'Alessandro, A., Beule, D., Pellerin, L., Mameli, M., Paolicelli, R.C., 2023. Loss of microglial MCT4 leads to defective synaptic pruning and anxiety-like behavior in mice. Nat. Commun. 14, 5749. https://doi.org/10.1038/s41467-023-41502-4.

Morari, J., Anhe, G.F., Nascimento, L.F., De Moura, R.F., Razolli, D., Solon, C., Guadagnini, D., Souza, G., Mattos, A.H., Tobar, N., Ramos, C.D., Pascoal, V.D., Saad, M.J., Lopes-Cendes, I., Moraes, J.C., Velloso, L.A., 2014. Fractalkine (CX3CL1) is involved in the early activation of hypothalamic inflammation in experimental obesity. Diabetes 63, 3770–3784. https://doi.org/10.2337/db13-1495.

Morselli, E., Frank, A.P., Palmer, B.F., Rodriguez-Navas, C., Criollo, A., Clegg, D.J., 2016. A sexually dimorphic hypothalamic response to chronic high-fat diet consumption. Int. J. Obes. 40, 206–209. https://doi.org/10.1038/ijo.2015.114.

Moss, D.W., Bates, T.E., 2001. Activation of murine microglial cell lines by lipopolysaccharide and interferon-γ causes NO-mediated decreases in mitochondrial and cellular function. Eur. J. Neurosci. 13, 529–538. https://doi.org/10.1046/j.1460-9568.2001.01418.x.

Mossmann, D., Park, S., Hall, M.N., 2018. mTOR signalling and cellular metabolism are mutual determinants in cancer. Nat. Rev. Cancer 18, 744–757. https://doi.org/10.1038/s41568-018-0074-8.

Mou, Q., Yao, K., Ye, M., Zhao, B., Hu, Y., Lou, X., Li, H., Zhang, H., Zhao, Y., 2021. Modulation of sirt1-mTORC1 pathway in microglia attenuates retinal ganglion cell loss after optic nerve injury. J. Inflamm. Res. 14, 6857–6869. https://doi.org/10.2147/JIR.S338815.

Nadjar, A., 2018. Role of metabolic programming in the modulation of microglia phagocytosis by lipids. Prostaglandins Leukot. Essent. Fatty Acids 135, 63–73. https://doi.org/10.1016/j.plefa.2018.07.006.

Nagashimada, M., Sawamoto, K., Ni, Y., Kitade, H., Nagata, N., Xu, L., Kobori, M., Mukaida, N., Yamashita, T., Kaneko, S., Ota, T., 2021. CX3CL1-CX3CR1 signaling deficiency exacerbates obesity-induced inflammation and insulin resistance in male mice. Endocrinology 162, bqab064. https://doi.org/10.1210/endocr/bqab064.

Nagy, A.M., Fekete, R., Horvath, G., Koncsos, G., Kriston, C., Sebestyen, A., Giricz, Z., Kornyei, Z., Madarasz, E., Tretter, L., 2018. Versatility of microglial bioenergetic machinery under starving conditions. Biochim. Biophys. Acta BBA - Bioenerg 1859, 201–214. https://doi.org/10.1016/j.bbabio.2017.12.002.

Nair, S., Sobotka, K.S., Joshi, P., Gressens, P., Fleiss, B., Thornton, C., Mallard, C., Hagberg, H., 2019. Lipopolysaccharide-induced alteration of mitochondrial morphology induces a metabolic shift in microglia modulating the inflammatory response in vitro and in vivo. Glia 67, 1047–1061. https://doi.org/10.1002/glia.23587.

Nimmerjahn, A., Kirchhoff, F., Helmchen, F., 2005. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science 308, 1314–1318. https://doi.org/10.1126/science.1110647.

Niraula, A., Fasnacht, R.D., Ness, K.M., Frey, J.M., Cuschieri, S.A., Dorfman, M.D., Thaler, J.P., 2023. Prostaglandin PGE2 receptor EP4 regulates microglial phagocytosis and increases susceptibility to diet-induced obesity. Diabetes 72, 233–244. https://doi.org/10.2337/db21-1072.

Oraha, J., Enriquez, R.F., Herzog, H., Lee, N.J., 2022. Sex-specific changes in metabolism during the transition from chow to high-fat diet feeding are abolished in response to dieting in C57BL/6J mice. Int. J. Obes. 46, 1749–1758. https://doi.org/10.1038/s41366-022-01174-4.

Orihuela, R., McPherson, C.A., Harry, G.J., 2016. Microglial M1/M2 polarization and metabolic states. Br. J. Pharmacol. 173, 649–665. https://doi.org/10.1111/bph.13139.

O'Neill, L.A.J., Kishton, R.J., Rathmell, J., 2016. A guide to immunometabolism for immunologists. Nat. Rev. Immunol. 16, 553–565. https://doi.org/10.1038/nri.2016.70.

Paolicelli, R.C., Angiari, S., 2019. Microglia immunometabolism: from metabolic disorders to single cell metabolism. Semin. Cell Dev. Biol. 94, 129–137. https://doi.org/10.1016/j.semcdb.2019.03.012.

Paolicelli, R.C., Bolasco, G., Pagani, F., Maggi, L., Scianni, M., Panzanelli, P., Giustetto, M., Ferreira, T.A., Guiducci, E., Dumas, L., Ragozzino, D., Gross, C.T., 2011. Synaptic pruning by microglia is necessary for normal brain development. Science 333, 1456–1458. https://doi.org/10.1126/science.1202529.

Paolicelli, R.C., Sierra, A., Stevens, B., Tremblay, M.-E., Aguzzi, A., Ajami, B., Amit, I., Audinat, E., Bechmann, I., Bennett, M., Bennett, F., Bessis, A., Biber, K., Bilbo, S., Blurton-Jones, M., Boddeke, E., Brites, D., Brône, B., Brown, G.C., Butovsky, O., Carson, M.J., Castellano, B., Colonna, M., Cowley, S.A., Cunningham, C., Davalos, D., De Jager, P.L., De Strooper, B., Denes, A., Eggen, B.J.L., Eyo, U., Galea, E., Garel, S., Ginhoux, F., Glass, C.K., Gokce, O., Gomez-Nicola, D., González, B., Gordon, S., Graeber, M.B., Greenhalgh, A.D., Gressens, P., Greter, M., Gutmann, D.H., Haass, C., Heneka, M.T., Heppner, F.L., Hong, S., Hume, D.A., Jung, S., Kettenmann, H., Kipnis, J., Koyama, R., Lemke, G., Lynch, M., Majewska, A., Malcangio, M., Malm, T., Mancuso, R., Masuda, T., Matteoli, M., McColl, B.W., Miron, V.E., Molofsky, A.V., Monje, M., Mracsko, E., Nadjar, A., Neher, J.J., Neniskyte, U., Neumann, H., Noda, M., Peng, B., Peri, F., Perry, V.H., Popovich, P.G., Pridans, C., Priller, J., Prinz, M., Ragozzino, D., Ransohoff, R.M., Salter, M.W., Schaefer, A., Schafer, D.P., Schwartz, M., Simons, M., Smith, C.J., Streit, W.J., Tay, T.L., Tsai, L.-H., Verkhratsky, A., Von Bernhardi, R., Wake, H., Wittamer, V., Wolf, S.A., Wu, L.-J., Wyss-Coray, T., 2022. Microglia states and nomenclature: a field at its crossroads. Neuron 110, 3458–3483. https://doi.org/10.1016/j.neuron.2022.10.020.

Park, J., Choi, H., Min, J., Park, S., Kim, J., Park, H., Kim, B., Chae, J., Yim, M., Lee, D., 2013. Mitochondrial dynamics modulate the expression of pro-inflammatory mediators in microglial cells. J. Neurochem. 127, 221–232. https://doi.org/10.1111/jnc.12361.

Pearce, E.L., Pearce, E.J., 2013. Metabolic pathways in immune cell activation and quiescence. Immunity 38, 633–643. https://doi.org/10.1016/j.immuni.2013.04.005.

Peri, F., Nüsslein-Volhard, C., 2008. Live imaging of neuronal degradation by microglia reveals a role for v0-ATPase a1 in phagosomal fusion in vivo. Cell 133, 916–927. https://doi.org/10.1016/j.cell.2008.04.037.

Pettersson, U.S., Waldén, T.B., Carlsson, P.-O., Jansson, L., Phillipson, M., 2012. Female mice are protected against high-fat diet induced metabolic syndrome and increase the regulatory T cell population in adipose tissue. PLoS One 7, e46057. https://doi.org/10.1371/journal.pone.0046057.

Piazza, P.V., Cota, D., Marsicano, G., 2017. The CB1 receptor as the cornerstone of exostasis. Neuron 93, 1252–1274. https://doi.org/10.1016/j.neuron.2017.02.002.

Quarta, C., Claret, M., Zeltser, L.M., Williams, K.W., Yeo, G.S.H., Tschöp, M.H., Diano, S., Brüning, J.C., Cota, D., 2021. POMC neuronal heterogeneity in energy balance and beyond: an integrated view. Nat. Metab. 3, 299–308. https://doi.org/10.1038/s42255-021-00345-3.

Ramírez-Carreto, R.J., Rodríguez-Cortés, Y.M., Torres-Guerrero, H., Chavarría, A., 2023. Possible implications of obesity-primed microglia that could contribute to stroke-associated damage. Cell. Mol. Neurobiol. 43, 2473–2490. https://doi.org/10.1007/s10571-023-01329-5.

Rey, A.D., Randolf, A., Wildmann, J., Besedovsky, H.O., Jessop, D.S., 2009. Re-exposure to endotoxin induces differential cytokine gene expression in the rat hypothalamus and spleen. Brain Behav. Immun. 23, 776–783. https://doi.org/10.1016/j.bbi.2009.02.009.

Salvi, J., Andreoletti, P., Audinat, E., Balland, E., Ben Fradj, S., Cherkaoui-Malki, M., Heurtaux, T., Liénard, F., Nédélec, E., Rovère, C., Savary, S., Véjux, A., Trompier, D., Benani, A., 2022. Microgliosis: a double-edged sword in the control of food intake. FEBS J. febs 16583. https://doi.org/10.1111/febs.16583.

Saxton, R.A., Sabatini, D.M., 2017. mTOR signaling in growth, metabolism, and disease. Cell 168, 960–976. https://doi.org/10.1016/j.cell.2017.02.004.
Schuster, S., Boley, D., Möller, P., Stark, H., Kaleta, C., 2015. Mathematical models for explaining the Warburg effect: a review focussed on ATP and biomass production. Biochem. Soc. Trans. 43, 1187–1194. https://doi.org/10.1042/BST20150153.
Sengupta, S., Peterson, T.R., Sabatini, D.M., 2010. Regulation of the mTOR complex 1 pathway by nutrients, growth factors, and stress. Mol. Cell 40, 310–322. https://doi.org/10.1016/j.molcel.2010.09.026.
Shi, J., Johansson, J., Woodling, N.S., Wang, Q., Montine, T.J., Andreasson, K., 2010. The prostaglandin E2 E-prostanoid 4 receptor exerts anti-inflammatory effects in brain innate immunity. J. Immunol. 184, 7207–7218. https://doi.org/10.4049/jimmunol.0903487.
Shi, Qian, Chang, Cheng, Saliba, Afaf, Bhat, Manzoor A., 2022. Microglial mTOR activation upregulates Trem2 and enhances β-amyloid plaque clearance in the 5XFAD Alzheimer's disease model. J. Neurosci. 42, 5294. https://doi.org/10.1523/JNEUROSCI.2427-21.2022.
Smyth, E.M., Grosser, T., Wang, M., Yu, Y., FitzGerald, G.A., 2009. Prostanoids in health and disease. J. Lipid Res. 50, S423–S428. https://doi.org/10.1194/jlr.R800094-JLR200.
Thaler, J.P., Yi, C.-X., Schur, E.A., Guyenet, S.J., Hwang, B.H., Dietrich, M.O., Zhao, X., Sarruf, D.A., Izgur, V., Maravilla, K.R., Nguyen, H.T., Fischer, J.D., Matsen, M.E., Wisse, B.E., Morton, G.J., Horvath, T.L., Baskin, D.G., Tschöp, M.H., Schwartz, M.W., 2012. Obesity is associated with hypothalamic injury in rodents and humans. J. Clin. Invest. 122, 153–162. https://doi.org/10.1172/JCI59660.
Tinius, R.A., Blankenship, M.M., Furgal, K.E., Cade, W.T., Pearson, K.J., Rowland, N.S., Pearson, R.C., Hoover, D.L., Maples, J.M., 2020. Metabolic flexibility is impaired in women who are pregnant and overweight/obese and related to insulin resistance and inflammation. Metabolism 104, 154142. https://doi.org/10.1016/j.metabol.2020.154142.
Valdearcos, M., Robblee, M.M., Benjamin, D.I., Nomura, D.K., Xu, A.W., Koliwad, S.K., 2014. Microglia dictate the impact of saturated fat consumption on hypothalamic inflammation and neuronal function. Cell Rep. 9, 2124–2138. https://doi.org/10.1016/j.celrep.2014.11.018.
Valdearcos, M., Douglass, J.D., Robblee, M.M., Dorfman, M.D., Stifler, D.R., Bennett, M. L., Gerritse, I., Fasnacht, R., Barres, B.A., Thaler, J.P., Koliwad, S.K., 2017. Microglial inflammatory signaling orchestrates the hypothalamic immune response to dietary excess and mediates obesity susceptibility. Cell Metabol. 26, 185–197.e3. https://doi.org/10.1016/j.cmet.2017.05.015.
Valdearcos, M., Myers, M.G., Koliwad, S.K., 2019. Hypothalamic microglia as potential regulators of metabolic physiology. Nat. Metab. 1, 314–320. https://doi.org/10.1038/s42255-019-0040-0.
Valladolid-Acebes, I., Fole, A., Martín, M., Morales, L., Victoria Cano, M., Ruiz-Gayo, M., Olmo, N.D., 2013. Spatial memory impairment and changes in hippocampal morphology are triggered by high-fat diets in adolescent mice. Is there a role of leptin? Neurobiol. Learn. Mem. 106, 18–25. https://doi.org/10.1016/j.nlm.2013.06.012.
Vilalta, A., Brown, G.C., 2014. Deoxyglucose prevents neurodegeneration in culture by eliminating microglia. J. Neuroinflammation 11, 58. https://doi.org/10.1186/1742-2094-11-58.
Villa, A., Gelosa, P., Castiglioni, L., Cimino, M., Rizzi, N., Pepe, G., Lolli, F., Marcello, E., Sironi, L., Vegeto, E., Maggi, A., 2018. Sex-specific features of microglia from adult mice. Cell Rep. 23, 3501–3511. https://doi.org/10.1016/j.celrep.2018.05.048.
Voloboueva, L.A., Emery, J.F., Sun, X., Giffard, R.G., 2013. Inflammatory response of microglial BV-2 cells includes a glycolytic shift and is modulated by mitochondrial glucose-regulated protein 75/mortalin. FEBS Lett. 587, 756–762. https://doi.org/10.1016/j.febslet.2013.01.067.
Waise, T.M.Z., Toshinai, K., Naznin, F., NamKoong, C., Md Moin, A.S., Sakoda, H., Nakazato, M., 2015. One-day high-fat diet induces inflammation in the nodose ganglion and hypothalamus of mice. Biochem. Biophys. Res. Commun. 464, 1157–1162. https://doi.org/10.1016/j.bbrc.2015.07.097.
Wang, X.-L., Li, L., 2021. Microglia regulate neuronal circuits in homeostatic and high-fat diet-induced inflammatory conditions. Front. Cell. Neurosci. 15, 722028 https://doi.org/10.3389/fncel.2021.722028.
Wang, X., Ge, A., Cheng, M., Guo, F., Zhao, M., Zhou, X., Liu, L., Yang, N., 2012. Increased hypothalamic inflammation associated with the susceptibility to obesity in rats exposed to high-fat diet. Exp. Diabetes Res. 1–8. https://doi.org/10.1155/2012/847246, 2012.
Wang, B., Liu, T., Lai, C.-H., Rao, Y., Choi, M.-C., Chi, J.-T., Dai, J., Rathmell, J.C., Yao, T.-P., 2014. Glycolysis-dependent histone deacetylase 4 degradation regulates inflammatory cytokine production. Mol. Biol. Cell 25, 3300–3307. https://doi.org/10.1091/mbc.e13-12-0757.
Wang, L., Pavlou, S., Du, X., Bhuckory, M., Xu, H., Chen, M., 2019. Glucose transporter 1 critically controls microglial activation through facilitating glycolysis. Mol. Neurodegener. 14, 2. https://doi.org/10.1186/s13024-019-0305-9.
Warburg, O., Wind, F., Negelein, E., 1927. The metabolism of tumors in the body. J. Gen. Physiol. 8, 519–530. https://doi.org/10.1085/jgp.8.6.519.
Wculek, S.K., Dunphy, G., Heras-Murillo, I., Mastrangelo, A., Sancho, D., 2022. Metabolism of tissue macrophages in homeostasis and pathology. Cell. Mol. Immunol. 19, 384–408. https://doi.org/10.1038/s41423-021-00791-9.
Wculek, S.K., Heras-Murillo, I., Mastrangelo, A., Mañanes, D., Galán, M., Miguel, V., Curtabbi, A., Barbas, C., Chandel, N.S., Enríquez, J.A., Lamas, S., Sancho, D., 2023. Oxidative phosphorylation selectively orchestrates tissue macrophage homeostasis. Immunity 56, 516–530.e9. https://doi.org/10.1016/j.immuni.2023.01.011.
Xu, Y., Nedungadi, T.P., Zhu, L., Sobhani, N., Irani, B.G., Davis, K.E., Zhang, X., Zou, F., Gent, L.M., Hahner, L.D., Khan, S.A., Elias, C.F., Elmquist, J.K., Clegg, D.J., 2011. Distinct hypothalamic neurons mediate estrogenic effects on energy homeostasis and reproduction. Cell Metabol. 14, 453–465. https://doi.org/10.1016/j.cmet.2011.08.009.
Yang, S., Qin, C., Hu, Z.-W., Zhou, L.-Q., Yu, H.-H., Chen, M., Bosco, D.B., Wang, W., Wu, L.-J., Tian, D.-S., 2021. Microglia reprogram metabolic profiles for phenotype and function changes in central nervous system. Neurobiol. Dis. 152, 105290 https://doi.org/10.1016/j.nbd.2021.105290.
Ye, X., Zhu, M., Che, X., Wang, H., Liang, X.-J., Wu, C., Xue, X., Yang, J., 2020. Lipopolysaccharide induces neuroinflammation in microglia by activating the MTOR pathway and downregulating Vps34 to inhibit autophagosome formation. J. Neuroinflammation 17, 18. https://doi.org/10.1186/s12974-019-1644-8.
Yi, C.-X., Walter, M., Gao, Y., Pitra, S., Legutko, B., Kälin, S., Layritz, C., García-Cáceres, C., Bielohuby, M., Bidlingmaier, M., Woods, S.C., Ghanem, A., Conzelmann, K.-K., Stern, J.E., Jastroch, M., Tschöp, M.H., 2017. TNFα drives mitochondrial stress in POMC neurons in obesity. Nat. Commun. 8, 15143 https://doi.org/10.1038/ncomms15143.
Zhang, Y., Chen, K., Sloan, S.A., Bennett, M.L., Scholze, A.R., O'Keeffe, S., Phatnani, H.P., Guarnieri, P., Caneda, C., Ruderisch, N., Deng, S., Liddelow, S.A., Zhang, C., Daneman, R., Maniatis, T., Barres, B.A., Wu, J.Q., 2014. An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. J. Neurosci. 34, 11929–11947. https://doi.org/10.1523/JNEUROSCI.1860-14.2014.
Zhao, X., Liao, Y., Morgan, S., Mathur, R., Feustel, P., Mazurkiewicz, J., Qian, J., Chang, J., Mathern, G.W., Adamo, M.A., Ritaccio, A.L., Gruenthal, M., Zhu, X., Huang, Y., 2018. Noninflammatory changes of microglia are sufficient to cause epilepsy. Cell Rep. 22, 2080–2093. https://doi.org/10.1016/j.celrep.2018.02.004.
Zhao, Xiao-Feng, Liao, Yuan, Alam, Mahabub Maraj, Mathur, Ramkumar, Paul, Feustel, Mazurkiewicz, Joseph E., Adamo, Matthew A., Zhu, Xinjun C., Huang, Yunfei, 2020. Microglial mTOR is neuronal protective and antiepileptogenic in the pilocarpine model of temporal lobe epilepsy. J. Neurosci. 40, 7593. https://doi.org/10.1523/JNEUROSCI.2754-19.2020.
Zhuang, H., Yao, X., Li, H., Li, Q., Yang, C., Wang, C., Xu, D., Xiao, Y., Gao, Y., Gao, J., Bi, M., Liu, R., Teng, G., Liu, L., 2022. Long-term high-fat diet consumption by mice throughout adulthood induces neurobehavioral alterations and hippocampal neuronal remodeling accompanied by augmented microglial lipid accumulation. Brain Behav. Immun. 100, 155–171. https://doi.org/10.1016/j.bbi.2021.11.018.