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Review

Obesity-Induced Neuroinflammation: Beyond the Hypothalamus

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Obesity is now a worldwide health issue. Far from being limited to weight gain, obesity is generally associated with low-grade inflammation and with a cluster of disorders collectively known as the 'metabolic syndrome'. When considering obesity and the subsequent neuroinflammation, the focus was long set on the hypothalamus. More recently, obesity-derived neuroinflammation has been shown to affect other brain structures such as the hippocampus, cortex, brainstem, or amygdala. Furthermore, obesity has been associated with increased occurrence of central disorders such as depression and impaired cognitive function. We discuss here the effects and mechanisms of obesity-derived neuroinflammation, with a specific emphasis on extra-hypothalamic structures, as well as the repercussions of neuroinflammation for some cerebral functions.

Obesity – A Central Matter

Obesity is now recognized as a worldwide health issue and has reached epidemic proportions affecting both developed and developing countries. The mean global **body-mass index** (BMI; see Glossary) increased from 21.7 kg/m^2 and 22.1 kg/m^2 (for men and women, respectively) in 1975 to 24.2 kg/m^2 and 24.4 kg/m^2 in 2014. If this trend continues, it is projected that the prevalence of global obesity will be 18% for men and 21% for women by 2025 [1]. This pandemic is concomitant with increased incidence of central nervous system (CNS) pathologies such as dementia, stroke, depression, and Alzheimer's disease [2]. Even though these pathologies have different etiologies and pathophysiological manifestations, they share a common neuroinflammatory component [3,4]. Interestingly, obese patients represent a population more prone to develop such central disorders [5].

Far from being limited to weight gain, obesity is generally associated with a cluster of disorders collectively known as the **metabolic syndrome** (**MetS**). The etiology of this metabolic disorder stems from an interplay between genetic predispositions and environmental factors resulting in an immune response and subsequent low-grade inflammation that affects numerous tissues including the liver, the adipose tissue, and the CNS [6]. In this regard, the hypothalamus has naturally attracted the attention because this structure is home to the arcuate nucleus where two distinct neuronal populations (NPY/AgRP neurons and POMC/CART neurons) are involved in body weight regulation and energy balance [7]. Hypothalamic inflammation was shown to be involved in the onset and maintenance of the obese phenotype [7]. The interrelations between inflammation, hypothalamus, and obesity have been extensively reviewed [8,9] (Box 1). However, as we will discuss here, the neuroinflammation derived from obesity is not restricted to the hypothalamus and in fact affects the entire CNS. Indeed, recent evidence supports the presence of neuroinflammation in the amygdala, hippocampus, cortex, and cerebellum during

Trends

Recent evidence supports the presence of an obesity-driven neuroinflammation in the amygdala, hippocampus, and cerebellum.

Based on the numerous studies on the topic it appears that obesity-induced neuroinflammation is dependent on the type of diet and on the duration of the diet.

During diet-induced obesity, neuroinflammation does not develop to the same extent in different brain structures.

Obesity induces neuroinflammation and cognitive dysfunction. However, obesity-induced cognitive dysfunction has been also found in the absence of neuroinflammation.

In obese patients, anthropometric markers (such as waist circumference) have been associated with profound architectural alterations in white and grey matters, and also with microglial activation.

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Box 1. Obesity-Induced Hypothalamic Inflammation

The hypothalamus is central in the regulation of food intake and energy expenditure. It is home to first-order neurons in the arcuate nucleus which, because of their proximity to the third ventricle, circumventricular organs, and mediobasal eminence, are able to sense peripheral cues such as insulin, leptin, or ghrelin. Therefore, these neurons are able to monitor the energy status of the entire organism and are responsible for the overall weight stability of an individual over time. These first-order neurons comprise two different sets that exert opposite effects: the anorexigenic POMC/CART neurons and the orexigenic AgRP/NPY neurons. Obese individuals are characterized by hypothalamic leptin resistance and are therefore no longer able to properly integrate leptin anorexigenic stimulation. This dysregulation in hypothalamic leptin signaling further leads to increased appetite and food consumption, thus aggravating obesity [9,89,90].

The integration of peripheral cues and subsequent neuronal response of arcuate nucleus neurons is delicate and can be easily disrupted. Indeed, a single day of HFD in rodents leads to increased hypothalamic expression of IL-6 and TNF-α as well as activation of microglial cells [91]. Exposure to a HFD for 3 days increased neuroinflammation and gliosis, and increased markers of neuronal injury in rodents [15]. Very interestingly, this neuroinflammation appears long before the onset of obesity or peripheral inflammation [91]. This acute response to a few days of HFD was shown to recede temporarily before returning and becoming chronic upon prolonged HFD feeding [15]. In the obesity context, in addition to the increased levels of proinflammatory cytokines [92], several inflammatory and cellular stress responses including endoplasmic reticulum (ER) stress, SOCS3, and the IKKβ/NF-κB pathways were shown to be upregulated [93]. In this context, astrogliosis and microgliosis are still present and contribute greatly to the neuroinflammatory tone [92,94]. Increased hypothalamic neuroinflammation was identified as a key player in MetS. Indeed, strategies to decrease this process in rats are also able to normalize several hallmarks of obesity and MetS in the periphery [95].

In obese patients, using MRI, it was shown that obese subjects display increased hypothalamic gliosis [15]. This was further confirmed using histology where individuals with a BMI of >30 presented an exacerbated microglia activation compared to individuals with a BMI of <25 [48].

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obesity [10–13]. Hence, it is clear that the hypothalamus is not the only structure affected by obesity, and that the rest of the CNS deserves to be thoroughly studied in this specific setting. Because of the terminology usually used in the field of obesity, we will use the term neuro-inflammation even though it does not completely reflect the inflammatory process classically encountered in the periphery (Box 2).

In light of the ever-increasing obesity epidemic, and the growing incidence of CNS pathologies with a neuroinflammatory component, we will focus on the diet-induced obesity (DIO)-derived neuroinflammation with a specific emphasis on extra-hypothalamic structures. We will discuss the causes of the obesity-induced low-grade inflammatory tone affecting both the CNS and the periphery. We will also detail the impact of obesity on several CNS structures and its patho-physiological consequences. Finally, we will briefly discuss the different attempts aiming at modulating this obesity-induced neuroinflammation.

From Obesity-Induced Inflammation to Neuroinflammation

Causal Factors

Even though genetic obesity can be encountered in some patients, it remains relatively rare and 32 identified BMI-associated loci would only account for about 2–3% of the obese population of European ancestry [14]. Obesity also results from environmental factors such as the diet type or the level of physical activity. Preclinical genetic models (*ob/ob* and *db/db* mice, or the Zucker rat) were pivotal in unraveling many mechanisms involved in obesity. However, DIO models seem to better recapitulate the slow onset of obesity and associated pathologies, allowing time-dependent investigation of several pathophysiological processes. These DIO models also allow direct comparison of **diets** such as high-fat diets (HFD), high-sugar diets (HSD), western diets (WD), cafeteria diets, and high-cholesterol diets, as well as of their potential different impacts.

One evident cause of inflammation in DIO is the diet itself. Indeed, a very short term HFD is able to lead to hypothalamic neuroinflammation in the absence of obesity features [15] (Box 1). The

Glossary

Body mass index (BMI): also known as the Quetelet index. An anthropometric tool used to assess the obesity status of individuals. It is calculated as body mass (kg) divided by the square of body height (m). Normal BMI is in the range 18.5 to 25 kg/m². Individuals are considered to be overweight above 25 kg/m², and obese at >30 kg/m². Even though the BMI is the most widely used anthropometric measurement in the context of obesity, other commonly used measures include waist-to-hip ratio (WHR) and waist circumference (WC).

Diets: a rodent standard diet is generally composed of (in % kcal) 15% protein, 75% carbohydrate, and 10% fat. A Western diet (WD) of 17% protein, 43% carbohydrate, and 41% fat. A high-fat diet (HFD) of 20% protein, 35–20% carbohydrate, and 45–60% fat. Fatty acid (FA) profiles are: standard chow: 17% saturated FAs (SFAs); 24% monounsaturated FAs (MUFAs); 59% polyunsaturated FAs (PUFAs). Lard-based: 32% SFA; 36% MUFA; 32% PUFA. Cocoa butter-based: 64% SFA; 33% MUFA; 3% PUFA. Coconut oil-based: 93% SFA; 3% MUFA; 4% PUFA.

Endotoxemia: the presence of endotoxins (bacterial membrane molecules capable of eliciting an immune response) in the blood.

M1/M2 macrophage polarization: briefly, macrophages can be characterized according to their activation state into M1 'proinflammatory' (or classically activated) or M2 'anti-inflammatory' (or alternatively activated) macrophage subtypes. However, macrophages can be anywhere on the M1–M2 activation state continuum.

Metabolic syndrome (MetS): according to the National Cholesterol Education Program Adult Treatment Panel III, MetS encompasses different metabolic disorders usually associated with obesity. An individual is diagnosed with MetS if they present at least three of the five following criteria: abdominal obesity measured using waist circumference (≥88 cm for women and ≥102 cm for men), plasma triglycerides above 1.7 mM, high-density lipoprotein (HDL) cholesterol below 1.30 mM for women and below 1.04 mM for men,

Box 2. Inflammation and Neuroinflammation

Inflammation is a normal and necessary physiological process aiming at removing the causal agent that led to its initiation and at initiating healing of the wounded tissue(s). It is usually associated by five cardinal signs: redness, heat, swelling, pain, and loss of function, representing the macroscopic manifestations of the cellular processes at play. Briefly, the acute inflammatory process can be divided in two phases. The first, or vascular phase, is characterized by increased permeability of the blood vessels, vasodilation, and increased blood flow in the affected region. The second phase is characterized by the recruitment of circulating immune cells such as monocytes (cellular phase). These phases rely on complex and coordinated crosstalk between cells mediated by pro- and anti-inflammatory cytokines, chemo-attracting signals (chemokines), enzymes (COX2, iNOS, MMPs), and lipids (prostaglandins, resolvins). Acute inflammation is a time-restricted process and recedes with the resolution phase; however, if excessive, inappropriate, or sustained (chronicization), inflammation can lead to severe pathophysiological consequences [96].

The case of the CNS is more complex. Indeed, owing to the presence of the BBB and the blood-to-CSF barrier, the entry of immune cells such as lymphocytes is very limited in the healthy state, and immune surveillance relies mainly on the so-called resident immune cells, the microglia. The definition of neuroinflammation has attracted attention but there is still no clear consensus definition [97–100]. Indeed, if neuroinflammation is considered as the activation of glial cells (microglia and astrocytes), it does not necessarily result in the recruitment of peripheral immune cells. Hence, it does not replicate the usual inflammatory processes seen in the periphery, and some authors would prefer the term 'CNS pseudo-inflammation' [100]. Studies aiming at defining neuroinflammation in several CNS pathologies have used a transcriptomic approach and have drawn a clear distinction between the multiple sclerosis-type of neuroinflammation, where peripheral immune cells are generally recruited in the CNS, and the more-subtle changes in glial cell activation that are seen in Parkinson's and Alzheimer's diseases. Therefore, the latter type of neuroinflammation, which does not rely on an autoimmune reaction, still remains to be thoroughly defined [97]. In any case, the terms inflammation and neuroinflammation define significantly different processes even though they share common signals (e.g., cytokines, chemokines, prostaglandins).
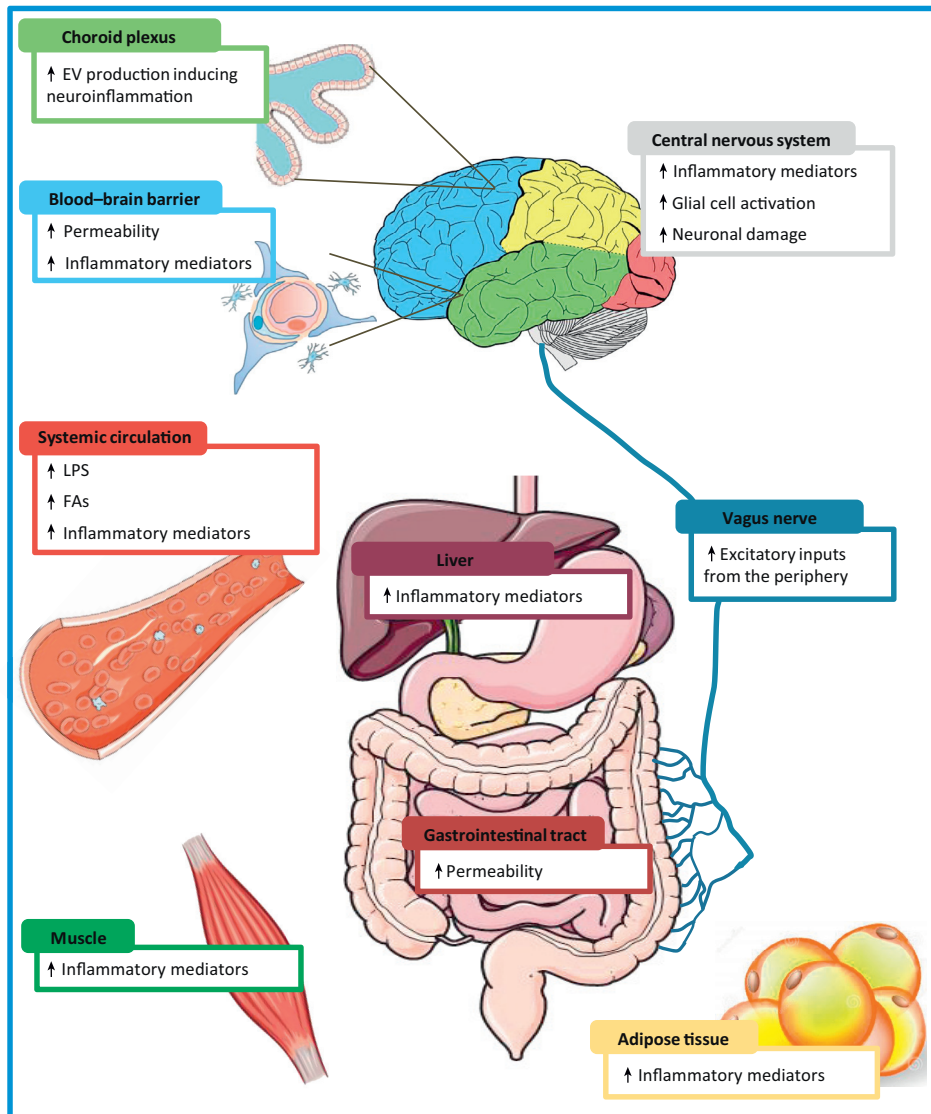
increased fatty acid (FA) intake induces the activation of immune cells and an inflammatory response in many organs including adipose tissue, liver, pancreas, and muscle [6]. FAs are able to activate the innate immune system through Toll-like receptors (TLRs) [16]. For instance, binding of FAs to TLR4 activates two different transcription factors (nuclear factor κB, NF-κB; and activator protein 1, AP-1) that in turn upregulate the expression of proinflammatory mediators such as cytokines [interleukin (IL)-1β, IL-6, and tumor necrosis factor α (TNF-α)] and chemokines (chemokine ligand 2, CCL2; and C-X-C motif chemokine 10, CXCL10). Another proposed mechanism for obesity-induced inflammation relies on the ability of a HFD to modulate the gut microbiota [17]. Indeed, the subsequent changes in microbiota populations result in the permeabilization of the gut barrier leading to increased passage of bacterial endotoxins (e.g., lipopolysaccharides, LPS) into the circulation. The resulting low-grade **endotoxemia**, evidenced both in rodents and humans, can lead to the activation of the innate immune cells [18,19]. The two mechanisms described here illustrate the direct and early impact of the diet as a source of proinflammatory mediators.

DIO also leads to long-term alterations in many organs (Figure 1). For instance, the adipose tissue must cope with increased triglyceride (TG) levels. In this context, pre-adipocytes differentiate and adipocytes increase in size, leading to enhanced storage capabilities. This is accompanied by immune changes because the resident macrophages, which in lean adipose tissue display **M2-like polarization**, will switch to **M1-like polarization**, resulting in the expression of proinflammatory mediators and the recruitment of circulating monocytes. Moreover, in a healthy environment, **type 2 T helper (Th2) cells** and **regulatory T cells** (T_reg) are the T cell subsets present in adipose tissue but, in obesity settings, **type 1 T helper (Th1) cells** represent the dominant subtype, further leading to a proinflammatory environment [20]. The liver is also affected and, with time, steatosis is often observed because triglycerides accumulate in hepatocytes and alter their metabolic function (e.g., glucose and lipid metabolism), leading to further obesity-associated disorders (hypertriglyceridemia, increased low-density lipoprotein cholesterol, glucose intolerance, etc). Here again the resident macrophages, known as Kupffer cells, are skewed towards a proinflammatory phenotype, further aggravating inflammation. Together, the diet and the alterations to hepatic homeostasis lead to

blood pressure higher than 130/85 mm Hg, and finally fasting glucose greater than 6.1 mM. Moreover, most patients with MetS are at greater risk of developing cardiovascular diseases and type 2 diabetes.

NLRP3 inflammasome: a complex protein oligomer involved in inflammatory processes. Its activation depends on a priming event such as the activation of the NF-κB pathway that leads to transcriptional upregulation of inactive forms of NLRP3, pro-IL-1β, or pro-IL-18. Following a second event, NLRP3 forms a complex oligomer with ASC and pro-caspase-1 that activates pro-caspase-1 into its active form, caspase-1. Finally, caspase-1 cleaves pro-IL-1β and pro-IL-18 into their active forms, IL-1β and IL-18.

Type 1 and type 2 T helper (Th1/2) cells; regulatory T cells (T_reg): depending on the cytokines present in their environment, T cells can acquire different phenotypes that are classified based on the mediators they specifically produce. Th1 cells produce IFN-γ and IL-2, whereas Th2 cells produce IL-4 and IL-13. T_reg cells represent another activation state of T cells and are implicated in decreasing the amplitude of immune responses.

Figure 1. Obesity Induces Metabolic Inflammation throughout the Organism. Obesity results in increased levels of circulating FAs, endotoxins (e.g., LPS) and inflammatory mediators, leading to altered homeostasis in many organs. Activation of immune cells in tissues such as liver (e.g., Kupffer cells) and adipose tissue (e.g., adipose tissue resident macrophages) induces the production of inflammatory mediators the further amplify tissue stress and the levels of circulating proinflammatory mediators. The CNS can be affected through different communication pathways including the vagus nerve, the choroid plexus, and the blood–brain barrier. This will lead to neuroinflammation, although to a varying extent depending on numerous factors such as obesity stage, the age of the subject, diet, and CNS structure examined (see text). Abbreviations and symbols: ↑, increased; CNS, central nervous system; EVs, extracellular vesicles; FAs, fatty acids; LPS, lipopolysaccharide.

the production of circulating proinflammatory mediators resulting in obesity-induced metabolic inflammation. Hence, obesity is usually characterized, in humans and murine models, by altered levels of LPS, FAs, adipokines, and cytokines [6,21].

Blood–Brain Barrier (BBB) Alterations in the Context of Obesity

As discussed, obesity is characterized by a low-grade inflammation affecting the whole organism. The CNS is considered to be an immune-privileged organ owing to the presence

of the BBB, a barrier tightly controlling exchanges with the periphery [22]. However, the BBB, the choroid plexus, the vagus nerve, CNS lymphatic vessels [23], and even direct cell entry represent multiple channels of communication between the periphery and the CNS (Figure 1) that allow the CNS to physiologically adapt to peripheral cues (e.g., insulin, leptin) and to respond accordingly. Furthermore, the BBB is not a passive structure because it can react to stimuli by modifying its permeability and uptake capabilities, as well as by secreting mediators into both the circulation and the CNS. However, when chronically challenged, CNS homeostasis is profoundly altered, potentially leading to neuroinflammation and/or behavioral and cognitive alterations. Hence, disruption of the barriers between the periphery and the CNS can represent an important and deleterious mechanism leading to neuroinflammation. As an example, a recent study using *db/db* mice (*Lepr*db) as a genetic model of obesity directly implicated BBB leakage as a contributing factor to obesity-induced neuroinflammation and cognitive deficits. Indeed, by reducing BBB leakage (using a PKCβ inhibitor), neuroinflammation and cognitive deficits in *db/db* mice were rescued [24].

Several studies have assessed the consequences of DIO on BBB permeability. For instance, a HFD (60% kcal from fat, lard-based) for 14 weeks led to decreased protein levels of claudin-5 and occludin in the frontal cortex, while no changes were found for ZO-1 [25]. BBB permeability can also be directly/functionally assessed. Using Evans blue dye, Nerurkar and colleagues found increased passage of the dye into the CNS of mice fed a HFD (60% kcal from fat, coconut oil-based) for 16 weeks [26]. The impact of both age and obesity was also addressed in this context using 7- and 24-month-old mice fed a HFD (60% kcal from fat, lard-based) for 20 weeks. In this study no diet-induced difference was measured for immunoglobulin G (IgG) extravasation in the hippocampus of young mice. However, both diet and age induced IgG extravasation in the hippocampus of elderly mice [27].

The impact of a HFD (40% kcal from fat) on the BBB was also assessed [28–30]. Both 10 weeks and 36 weeks of HFD (cocoa butter-based) resulted in increased BBB permeability (measured by IgG extravasation) in the cortex and hippocampus [28,29]. The expression of tight and adherens junction (occludin, claudin-5 and -12) mRNA in the thalamus and midbrain was also decreased after 13 weeks of HFD (lard-based) in rats. Interestingly, the authors found, using sodium fluorescein (NaFl), increased BBB permeability in the hippocampus but not in either the prefrontal cortex or the striatum [30].

WD was also shown to affect the BBB permeability. For instance, after 8 weeks of WD, mice displayed decreased immunoreactivity for both occludin and ZO-1 that was associated with increased passage of Evans blue into the CNS [31]. Another experiment assessed the impact of WD duration on BBB permeability. No changes in permeability were found after 1 or 6 weeks of diet. However, after 13 weeks, both dorsal and ventral hippocampus displayed increased leakage (NaFl), and this was also the case for the dorsal striatum. Conversely, BBB permeability in the cerebellum was not affected after 1, 6, or 13 weeks of WD [32]. Another interesting finding in this study revolves around the potential link between DIO resistance and BBB permeability. They assessed the effects of a WD on the BBB permeability after 1, 6, or 13 weeks in DIO-resistant and DIO-susceptible rats. The DIO-resistant rats fed a WD displayed no modification in BBB permeability (NaFl), compared to control rats fed a standard chow, in dorsal and ventral hippocampus, the striatum, or the cerebellum at the different times tested [32].

In another study, DIO-resistant rats displayed the same BBB hippocampal permeability (NaFl) when fed a standard chow compared to control rats, whereas DIO-susceptible rats fed a standard chow displayed increased BBB permeability in the hippocampus. Conversely, in the prefrontal cortex, DIO-susceptible rats had the same permeability as control rats, whereas

DIO-resistant rats displayed increased BBB permeability [33]. In the striatum, however, no difference was found between the groups [33].

The choroid plexus, the blood to cerebrospinal fluid (CSF) barrier, has been less studied than the BBB with regards to obesity-induced alterations. The choroid plexus epithelial cells are responsible for the synthesis of CSF, but it has recently been proposed that they also play a role in mediating the ingress of inflammatory cues (e.g., miRNA, proteins, lipids) from the periphery in the context of systemic inflammation [34]. The barrier was also found to display decreased mRNA expression for claudin-5 and -12 in rats fed a WD for ∼13 weeks [30].

As discussed, the BBB is susceptible to DIO but is not affected in the same manner in different CNS structures. Indeed, in the same study, DIO led to increased BBB permeability in the hippocampus while both prefrontal cortex and striatal BBB were unaffected [30]. Are these changes linked to a different BBB 'composition' according to the structure considered, or could astrocytes, pericytes, endothelial cells composing the BBB determine differential susceptibility to DIO insults? For instance, the role of endothelial cells has been recently highlighted as they were able to control cortical and hippocampal neuroinflammation and neurodegeneration [35]. Furthermore, a 3 day HFD (60% kcal from fat, lard-based) led to decreased glucose transporter GLUT1 mRNA expression in endothelial cells of specific CNS structures that translated into decreased glucose uptake by these structures [36]. This underlines, when considering different CNS structures, that the BBB is not 'homogenous' in its response. Finally, because the BBB is not the only barrier separating the CNS from the periphery, additional studies to further unravel the effects of DIO on the choroid plexus are needed.

Cellular Players

In response to changes in levels of peripheral mediators such as leptin, insulin, FAs, LPS, or cytokines, several cell types in the CNS undergo phenotypic changes leading to their activation.

Glial cells play a central role in the context of neuroinflammation. In this regard, microglial cells are considered to be the resident immune cells of the CNS. In their 'quiescent' state these cells continuously monitor their territory using thin processes with multiple branches. As the 'immune cells' of the CNS, microglia can be activated and undergo phenotypic and morphological changes when homeostatic disruption is detected. Microglial cells are able to produce several inflammatory mediators, are capable of phagocytosis, and can present antigens [37]. In the context of obesity, saturated fatty acids (SFAs) and mono-unsaturated fatty acids (MUFAs) were shown, in BV-2 cells and primary microglia, to activate in a TLR4-dependent way the NF-κB pathway, leading to increased levels of proinflammatory cytokines and reactive oxygen species (ROS) [38,39]. Moreover, the FA-activated BV-2 cell culture medium was shown to be cytotoxic for neurons [39]. Importantly, not all FAs induce proinflammatory responses. For instance, polyunsaturated fatty acids (PUFAs), either ω-3 or ω-9, following intracerebroventricular administration, were shown in a rat DIO model to reduce the number of activated microglial cells in the hypothalamus in a GPR120-dependent manner [40].

Astrocytes are the most abundant cell type in the CNS. They are involved in the control and regulation of multiple mechanisms in the CNS, including modulation of BBB permeability and blood flow as well as CNS metabolism [37]. These cells are also important in a pathophysiological context. Indeed, reactive astrocytes are encountered during CNS trauma, ischemic shock, and neuroinflammation [37]. Similarly to microglia, primary astrocytes can also be activated *in vitro* by SFAs, leading to the production of IL-6 or TNF-α. Conversely, unsaturated FAs were not able to elicit such changes [41]. Moreover, SFA-induced astrocyte activation was TLR4-dependent and was not dependent on the presence of microglial cells. Furthermore,

the ω-3 PUFA docosahexaenoic acid was shown to dose-dependently prevent unsaturated FA activation of astrocytes [41].

In vitro experiments indicate that both microglia and astrocytes are activated by FAs and more specifically by SFAs. However, *in vivo* and in the hypothalamus, it seems that microglia are the key players. Indeed, microglia were specifically activated by SFAs (administered by enteric gavage) whereas astrocytes were not. Moreover, microglia depletion rescued hypothalamic neuroinflammation and decreased food intake [42]. Therefore, microglia would be, in this context, an essential player mediating the detrimental effects of SFAs on hypothalamic function.

Pericytes are well known for their active role in BBB homeostasis. Upon activation by immune stimuli they can produce proinflammatory mediators (cytokines, ROS) that will in turn disrupt the BBB permeability by destabilizing tight junction proteins [43,44]. These cells are also responsible for helping peripheral immune cell transmigration across the BBB [45]. Other cell types potentially involved in the context of obesity-induced neuroinflammation and BBB integrity, such as polydendrocytes and tanycytes, have mainly been studied in the hypothalamus because of their roles in energy homeostasis [46].

Finally, the potential infiltration of peripheral immune cells into the CNS during obesity has been investigated. Buckman *et al.*, using mice transplanted with bone marrow from GFP+ mice, showed that 15 and 30 weeks of HFD (60% kcal from fat, lard-based) increased the recruitment of bone marrow-derived monocytes into the brain relative to chow-fed controls. This increased monocyte derived cell population was found in the septum, hypothalamus, and cortex of the HFD mice [47]. However, in another study using a similar model, mice fed a HFD (60% kcal from fat, lard-based) for 20 weeks did not display increased GFP+ myeloid cells in the brain [48]. The reasons for these discrepancies are not yet clear, but could be explained by differences in the cell sorting methods employed. Baufeld and colleagues [48] further suggest that meningeal and perivascular macrophages could also have been sorted in the other study, hence including other myeloid cells.

It is expected that, *in vivo*, all cell types will be affected by DIO to some extent. However, their respective contributions to neuroinflammation remain to be fully addressed. Regarding the infiltration of peripheral immune cells, the actual extent of recruitment of myeloid cells in the hypothalamus and cortex, their fate, and their potential role in DIO-induced neuroinflammation is not clear yet and needs to be clarified.

Obesity-Induced Neuroinflammation in Extra-Hypothalamic Structures

During obesity the levels of numerous mediators (including not only gut-derived LPS and FAs but also adiponectin, leptin, and resistin) are chronically altered, resulting in neuroinflammatory responses in many CNS structures (Figure 2) [6,21]. Other than the hypothalamus (Box 1), the best-studied CNS structure in the context of obesity-induced neuroinflammation is the hippocampus (Table 1). In this structure, after 16 weeks of HFD, TLR4 protein levels were found to be increased [49] (the type of diet is described in Table 1). Consistently, Lu *et al.* found enhanced IKKB/NF-κB-mediated inflammatory signaling in the HFD animals [10]. Moreover, obesity-driven neuroinflammation in the hippocampus is characterized by increased expression of cytokines (e.g., IL-1β, IL-6, and TNF-α) and enzymes (e.g., cyclooxygenase 2, COX2; and inducible nitric oxide synthase, iNOS) that are involved in proinflammatory processes [10,49–54]. HFD-fed rats also display increased protein levels of NLRP3 (NOD-like receptor family, pyrin domain-containing 3) compared to rats fed a standard chow, indicating activation of the **NLRP3 inflammasome** [53].

As mentioned, glial cells undergo phenotypic changes depending on their environment. In the hippocampus, HFD (40% and 60% kcal from fat) was shown to induce the activation of
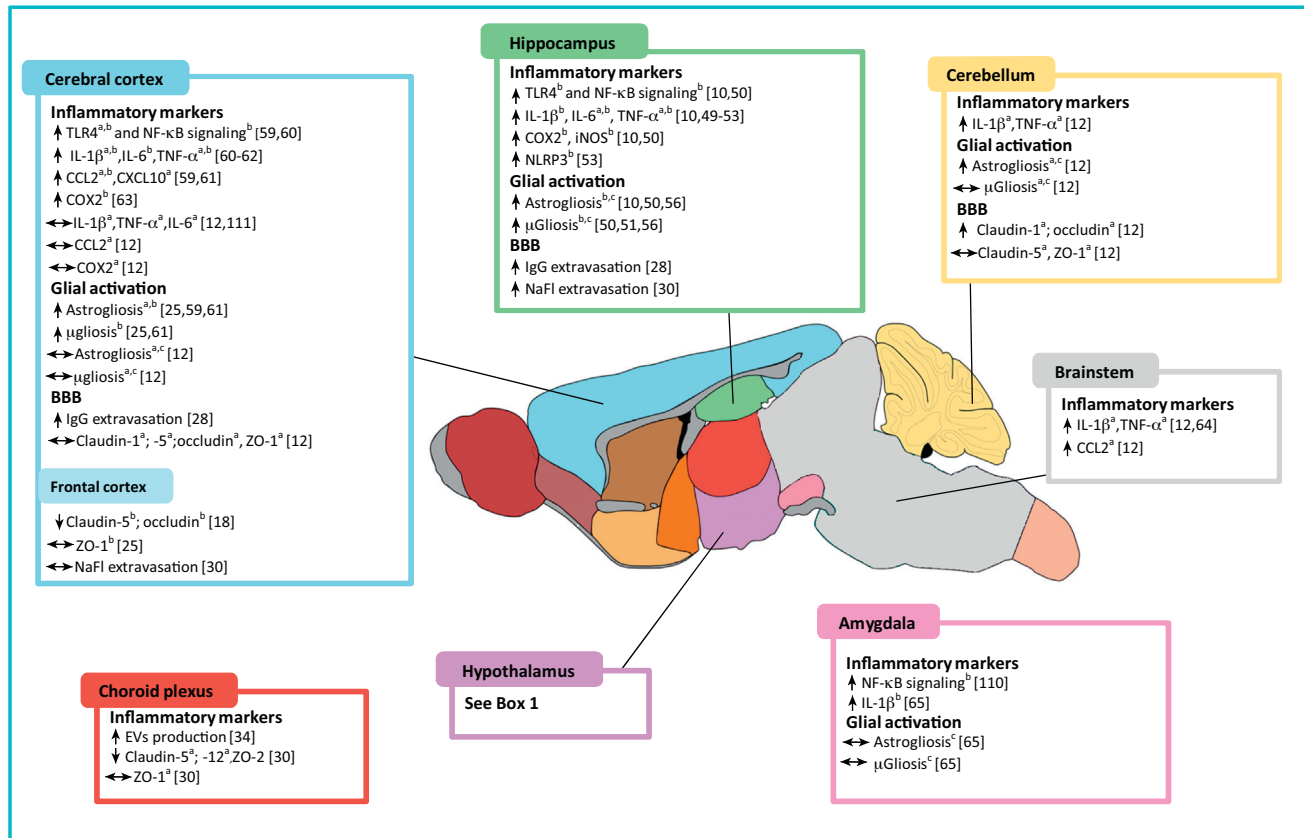
Figure 2. Long-Term Impact of Diet-Induced Obesity on Neuroinflammation. Several markers of inflammation have been studied in rodent models of diet-induced obesity. These include the expression of proinflammatory cytokines/chemokines and the activation of microglia (μGliosis) and astrocytes (astrogliosis). The extent of blood–brain barrier (BBB) alteration can be studied either via the expression of tight junction proteins or by the extravasation of non-permeant molecules/proteins (e.g., IgG and sodium fluorescein, NaFl). The sagittal brain scheme is adapted from the Gene Expression Nervous System Atlas (GENSAT) Project (www.gensat.org). Symbols: ↓, decrease; ↔, no change; ↑, increase; [a]mRNA expression; [b]protein expression (ELISA or western blot); [c]immunohistology.

astrocytes (astrogliosis) as well as the activation of microglia (microgliosis) [10,51,55,56] (Figure 2). Neurons were also shown to be affected during obesity. For instance, mice fed a HFD for 8 weeks displayed a decreased number of newly generated neurons (decreased neurogenesis) in the dentate gyrus as well as in the dorsal and ventral regions of the hippo-campus [57]. Hippocampal neurons of HFD mice fed for 20 weeks were also shown to display less dendritic complexity and length compared to control mice [51].

DIO-induced alterations appear to be time-dependent (Table 1). This is supported by studies where different periods of HFD feeding have been tested. For instance, Hao *et al.* showed that IL-1β levels were increased after 12 weeks of HFD feeding, but not before (i.e., at 4 and 8 weeks). This was also accompanied by an alteration of neuronal synapses and more specifically by microglial synapse internalization [58].

Even though HFD remains the most widely used model of DIO, the impact of sugar intake has also been studied in the context of neuroinflammation. Beilharz *et al.* showed that a standard diet supplemented by sucrose in drinking water induces the activation of the NF-κB pathway and subsequent expression of proinflammatory mediators in the hippocampus after only 8 days, but not in the hypothalamus or cortex [11].

Table 1. Diet Composition and Neuroinflammatory Outcome for Different CNS Structures

Diet type	Composition	CNS structure	Neuroinflammation[a]	Diet duration
High-fat diet	60% kcal from fat (lard-based)	Cerebral cortex	↔ Proinflammatory cytokines, chemokines	1 Week [12]; 16 weeks [12]; 18 weeks [65]
			↑ Proinflammatory cytokines, chemokines, and other mediators	14 Weeks [60]; 16 weeks [61,62]
		Cerebellum	↑ Proinflammatory cytokines	1 Week [12]; 16 weeks [12]
		Brainstem	↑ Proinflammatory cytokines, chemokines	1 Week [12]; 16 weeks [12]
		Hippocampus	↔ Proinflammatory cytokines	8 Weeks [58]
			↑ Proinflammatory cytokines, nuclear factor signaling, and other mediators	12 Weeks [52,58]; 16 weeks [49]; 20 weeks [10,50,51,54]
		Amygdala	↑ Proinflammatory cytokines and other mediators	8 Weeks [110]; 18 weeks [65]
	40–45% kcal from fat (lard-based)	Cerebral cortex	↔ Proinflammatory cytokines	16 Weeks [111]
			↑ Other mediators	10 Weeks[b] [28]; 20 weeks [63]
		Hippocampus	↔ Proinflammatory cytokines and other mediators	1 Week [84]
			↑ Proinflammatory cytokines and other mediators	10 Weeks[b] [28]; 17 weeks[c] [53]
Western diet	40% kcal from fat (milk, corn oil) and 40% carbohydrate (maltodextrin, sucrose, corn starch)	Cerebral cortex	↔ Proinflammatory cytokines and chemokines	21 Weeks [61]
			↑ Proinflammatory cytokines, nuclear factor signaling and other mediators	8 Weeks [59]
		Brainstem	↑ Proinflammatory cytokines	10 Weeks [64]
Sugar	Sucrose in drinking water (10%)	Hippocampus	↑ Proinflammatory cytokines and other mediators	2 Weeks [11]
			↔ Proinflammatory cytokines	4 Weeks [79]
	Fructose corn syrup in drinking water (11%)		↔ Proinflammatory cytokines	4 Weeks [79]

[a]Symbols: ↔, no change; ↑, increase.
[b]Fat from cocoa butter.
[c]Fat source not specified.

The cortex is another CNS structure that has attracted attention. Again, cortical TLR4 and NF-κB are activated in the context of HFD [59–62]. This leads to the expression of proinflammatory cytokines (e.g., IL-1β, IL-6, TNF-α) and chemokines (e.g., CCL2 and CXCL10) [59,60,62]. Zhang *et al.* took a closer look at the prostanoid system and reported increased COX2 expression leading to higher prostaglandin E$_2$ levels [63]. Activation of cortical astrocytes and microglia was evidenced in several experiments [25,59,61]. Finally, synaptic density has been found to be decreased after 14 weeks on a HFD [25]. However, depending on the study, and even though similar diets were used, cortical neuroinflammation has not been

systematically evidenced because no changes in the levels of IL-1β, TNF-α, or IL-6, or of glial cell activation, were found in several studies [12,60,61].

In the brainstem, our group found increased IL-1β and CCL2 mRNA expression after only 1 week of HFD diet. This neuroinflammatory environment was still present after 16 weeks of HFD, with an additional increase of TNF-α expression [12]. In the nucleus tractus solitarius of the medulla oblongata, a 10 weeks WD was also found to increase mRNA expression levels of IL-1β and TNF-α, and to decrease IL-10 expression [64]. Increased neuroinflammation was also found in the cerebellum after 1 week of HFD, with increased expression of IL-1β, TNF-α, CCL2, and COX2. After 16 weeks of HFD, mice displayed increased expression of IL-1β and TNF-α as well as increased astrogliosis but no activation of microglia [12]. In the amygdala, mice fed a HFD display increased levels of IL-1β but glial cells were not activated [65].

Other studies did not look at specific cerebral structures and assessed whole-brain neuro-inflammation in the context of DIO. They found increased NF-κB, cytokine, and COX2 expression together with activation of microglia and astrocytes [26,29,31]. Finally, in a more translational perspective, rhesus monkeys fed a WD for 2 years were shown to display activation of pathways leading to neuroinflammation (e.g., NF-κB, ROS) in their cortex compared to control-fed monkeys [66].

These different studies did not necessarily assess the effects of the diet duration on specific CNS structures. However, from the data gathered from the different studies (Table 1), we can see that the duration of the diet is an important factor to take into account when studying DIO-derived neuroinflammation. Indeed, in the hippocampus and for similar types of diet (in terms of kcal from fat and FA profiles), short-term HFD (1 and 8 weeks) does not elicit the production of proinflammatory mediators. However, when the duration of the diet exceeds 10–12 weeks, production of proinflammatory mediators was consistently found in independent studies. In this regard, different CNS structures also seem to be differentially affected by DIO. For instance, production of proinflammatory mediators in the cerebral cortex was not systematically observed with a HFD of more than 16 weeks (Table 1). This could underline a differential susceptibility of specific CNS structures to DIO. Finally, all diets are not equal with regards to their consequences for neuroinflammation. For instance, Pistell *et al.* used both a HFD and a WD during the same experiment, and they found that only the HFD elicited a neuroinflammatory reaction in the cortex while the WD did not [61]. This would suggest that the most deleterious diet when studying neuroinflammation is the HFD. Other factors may also influence DIO-induced neuroinflammation; for example, the different sources of fat in the diet (e.g., lard or cocoa butter) lead to different FA proportions (i.e., different proportions of SFAs, MUFAs, and PUFAs). Although the effects of these changes seem to be less marked, they deserve to be studied further.

Consequences of Obesity-Driven Neuroinflammation

Obesity not only induces neuroinflammation but can also alter several other mechanisms, some of which have been implicated in deficits in cognitive function. For instance, 10 days WD induced a decrease in the hippocampal GLUT1 glucose transporter that supports glucose transport into the CNS, and this was associated with learning and memory deficits [36,67]. Several reviews have addressed the link between obesity and cognitive impairment [68,69]. Different mechanisms were identified as being able to alter cognitive function, including reduced levels of brain-derived neurotrophic factor, altered glutamatergic signaling, and impaired insulin regulation [69,70].

In rodents, there is good evidence that neuroinflammation impacts on cognition. For instance, adenovirus-mediated TNF-α overexpression in the lateral ventricle results in increased anxiety,

whereas its overexpression in the hippocampus led to anxiety and poor memory consolidation. Finally, in the amygdala, overexpression of TNF-α led to anxiety and anhedonia [71]. Because obesity can be considered as a neuroinflammatory pathology, we have chosen to discuss studies where the effects of DIO on both behavioral outcome and neuroinflammation were assessed.

In rodents, three main sets of outputs have been assessed: (i) recognition memory, spatial learning, and spatial memory, (ii) anxiety, and (iii) depression and anhedonia.

Regarding the specific effects of a HFD, they seem to be mainly dependent on the duration of diet exposure. Indeed, mice fed a HFD (60% kcal from fat, lard-based) for 5 weeks performed similarly to control mice in the novel object recognition (NOR) test [72]. However, in a similar NOR test (assessing short-term recognition memory), mice fed a HFD (60% kcal from fat, lard-based) for 21 weeks clearly displayed impaired recognition memory [73].

Dutheil and colleagues assessed the effect of 8 and 16 weeks of HFD (60% kcal from fat, lard-based) on several behavioral outcomes including the NOR test for assessment of long-term recognition memory. They found that rats fed a HFD for 8 weeks performed similarly to the controls whereas rats fed a HFD for 16 weeks performed less successfully than the controls in the same test [49]. Finally, rodents fed a HFD (60% kcal from fat, lard-based) for a longer period of time (20–21 weeks) displayed a deterioration in spatial memory and spatial learning, evidenced using the Morris water maze [10,51], the T-maze [61], and the Y-maze [58], that were accompanied by neuroinflammation (e.g., increased TNF-α, IL-6, CCL2, iNOS, and COX2) and glial cell activation.

The weaning period is suggested to be important in the context of obesity and memory. For instance, Boitard *et al.* found that 3 months of HFD (45% kcal from fat, lard-based) initiated upon weaning (3 weeks of age) induced impaired relational memory, accompanied by decreased neurogenesis in the hippocampus, that were absent if the same diet was started at 12 weeks of age [74]. Interestingly, they found that reverting to a control diet for 3 months rescued the alterations induced by HFD feeding (45% kcal from fat, lard-based) started at weaning [75].

The second outcome studied in obesity-driven changes in behavior is anxiety. Mice fed a HFD (60% kcal from fat, lard-based) for 5 weeks displayed increased anxiety levels (assessed using the marble-burying test) compared to chow-fed control mice [72]. Here again, the exposure period seems to be of importance because rats fed a HFD for 8 weeks performed similarly to the controls in the open field test (OFT) whereas rats fed a HFD (60% kcal from fat, lard-based) for a longer period (10 and 16 weeks) displayed alterations in their behavior and increased anxiety using the OFT [49,76]. This was accompanied by increased proinflammatory cytokine levels in the hippocampus. Interestingly, rats displaying obesity-induced anxiety using the OFT or light–dark transition tests after 10 and 16 weeks of HFD (60% kcal from fat, lard-based) performed similarly to controls in another test, namely the elevated plus-maze (EPM) [49,76]. These discrepancies could be explained by the outcome measured by these specific tests. Indeed, the EPM is still considered to be the gold standard behavioral test for measuring anxiety. Conversely, the OFT is primarily a behavioral test measuring global motor activity, although it has also been used in some instances to measure anxiety. However, the use of the OFT in the anxiety context remains controversial [77,78].

For anhedonia/depression, diet duration also seems to be the main driver of the obesity-induced alterations. Indeed, in the same study, rats fed a HFD (60% kcal from fat, lard-based) for 8 weeks behaved as the chow-fed controls in the novelty-suppressed feeding test, sucrose

preference test, and female urine sniffing test [49]. However, rats fed for 16 weeks displayed evident signs of anhedonia/depression compared to chow-fed controls in the same tests. These behavioral changes were accompanied by increased levels and expression of hippocampal IL-1β, IL-6, and TNF-α [49].

It seems that, given sufficient exposure time to HFD, obese rodents display dramatic changes in their behaviors: decreased spatial learning ability, deficits in spatial memory and recognition memory, and increased anxiety, anhedonia, and depressive-like symptoms. Apart from the early effects of a cafeteria diet and a high-sugar diet (after only 8 days) on the NOR test [11], no significant changes in behavior (spatial learning and memory or anxiety) were found in rats fed a HSD for 4 weeks [79]. However, the age of the rats seems to be a factor to take into consideration because adolescent rats fed a HSD for 4 weeks performed poorly in the Barnes maze compared to adult rats fed the same diet for 4 weeks [79].

In humans, peripheral inflammation (evaluated using IL-6 and C reactive protein, CRP) plasma levels) was associated with changes in brain morphology (e.g., decreased hippocampal volume and cortical surface area) (Box 3) as well as with impaired learning and memory [80]. In the context of obesity, low-grade inflammation was specifically identified as being linked to impaired cognitive function and especially attention. Indeed, obese patients with high plasma CRP levels displayed poor cognitive flexibility whereas obese patient with lower CRP levels performed similarly to non-obese patients [81]. Furthermore, this acute-phase protein was associated with cerebral microstructural defects mainly affecting frontal pathways identified by magnetic resonance imaging (MRI). These defects also correlated with poor executive function [82]. Another study showed an association between high CRP peripheral levels and reduced volume of the left medial temporal lobe as well as with poor recognition memory [83]. This

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Box 3. Obesity-Induced Brain Architectural Alterations in Humans

Several morphometric factors can be used to assess obesity and its extent, such as **body mass index** (**BMI**), waist-to-hip ratio (WHR), and waist circumference (WC). However, the assessment of the impact of obesity on the CNS in human is only possible post-mortem or through imaging techniques. Using diffusion tensor imaging or MRI, the activation state of glial cells can be studied in obese individuals, allowing translational comparison with rodent models. Indeed, using MRI of the mediobasal hypothalamus in patients, Schur and colleagues identified the presence of gliosis which was further associated with insulin resistance, one parameter of the MetS [101]. These techniques also enabled changes occurring in global CNS architecture to be studied, such as modifications in white matter (WM), grey matter (GM), or overall brain volumes.

Early adulthood obesity, and specifically increased BMI, was associated with decreased ventral diencephalon and brainstem volumes [102]. In older adults, WHR and WC (but not BMI) were positively associated with decreased overall brain volume [103]. Interestingly, the association between increased BMI and decreased overall brain volume seems to be only valid in elderly subjects [104].

In a study of 2344 individuals, WC was positively associated with decreased GM volume [105]. This was also the case for both WC and WHR in another study [103]. In both morbidly obese and elderly subjects, BMI was positively correlated with decreased GM volume [106,107]. This decrease in GM volume was more specifically defined as a decrease in cortical GM thickness but not in the surface occupied or GM folding, and was further associated with increased BMI [102,108]. Finally, aging has also been associated with cortical thinning [108].

The WM is also affected by obesity. Normoglycemic obese patients tend to display reduced WM volume compared to healthy subjects. WM atrophy was also identified in morbidly obese patients in several brain structures [106]. Finally, the structural integrity of WM connections between the frontal and temporal lobes negatively correlated with increased BMI in older adults [109].

These modifications in brain structures and architecture induced by obesity reinforce links between obesity and CNS pathologies. Indeed, modifications of specific brain structures can lead to alterations of associated functions (anxiety, memory).

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further emphasizes, in human, the importance of peripheral inflammation in the context of obesity and its functional repercussions for the CNS.

From these studies assessing both DIO-driven neuroinflammation and cognitive outcome, it clearly appears that that duration is pivotal. As discussed, recognition and spatial memory as well as spatial learning do not seem to be altered after 5 or 8 weeks of HFD; however, after 16 weeks of HFD or more, cognitive deficits were found. Interestingly, DIO does not always result in neuroinflammation (Table 1) and neuroinflammation does not seem to be a prerequisite for DIO-disrupted cognitive functions. Indeed, a short-term HFD (2 weeks) led to deterioration of hippocampus-dependent functions in the absence hippocampal neuroinflammation [84]. To clarify these elements, further studies could aim at assessing the impact of DIO on both neuroinflammation and cognitive function in a time-dependent manner. The other factor identified as being central to susceptibility to DIO-induced cognitive deficits is the age of the animal. Indeed, the weaning period seems to be crucial because a HFD started at this period led to cognitive disturbances after 3 months of diet, but this was not the case for older animals fed the same diet. In humans, peripheral inflammation has been clearly associated with cognitive deficits. However, gliosis should be assessed in this context and evaluated against both anthropometric factors and peripheral inflammatory markers to further link CNS neuro-inflammation with cognitive outcome during obesity.

Potential Treatment Options

The demonstration of a link between obesity and neuroinflammation has prompted research into strategies to reduce obesity-driven neuroinflammation. Four main types of interventions have been considered: (i) pharmacological treatments, (ii) caloric restriction, (iii) exercise, and (iv) surgery. Some examples are discussed below.

Mice fed a HFD (60% kcal from fat) for 20 weeks and receiving daily administration of the triterpenoid ursolic acid displayed decreased activation of glial cells in the hippocampus compared to HFD-fed mice. Ursolic acid was also able to decrease neuroinflammatory markers such as TNF-α, COX2, and iNOS in the same structure, and rescued spatial memory and learning impairments [10]. Nicotine given in the drinking water rescued BBB permeability induced by 10 weeks of HFD (40% kcal from fat, cocoa butter-derived) in both cortex and hippocampus (IgG extravasation). Nicotine also reduced glial cell activation in both zones, but did not prevent the increase in COX2 protein expression [28]. In both medium- and long-term studies using either a HFD (60% kcal from fat, lard-based) or a WD, the polyphenol resveratrol was shown to reduce BBB permeability (Evans blue), to normalize TNF-α levels in the hippocampus, and to rescue hippocampal neuronal degeneration and cognitive function [31,51]. In the long-term HFD (60% kcal from fat, lard-based) study, resveratrol was also able to decrease peripheral markers of inflammation [51].

Another approach to tackling obesity-induced neuroinflammation and accompanying cognitive or mood disorders is dietary intervention. A 24 h fasting period after 11 weeks of HFD decreased F4/80 and CD11d markers in the whole brain and decreased IL-1α in cortex but not in hippocampus. However, the mice still displayed memory impairments after this fasting period [85]. In another study, a 10 days switch to standard chow after a 3 week period of high-cholesterol diet did not change behavioral components associated with anxiety and depression [86]. However, caloric restriction in rats for a longer period rescued hippocampal microgliosis and improved spatial learning and memory function compared to rats still fed a HFD [55]. In another study, rats were fed a HFD (60% kcal from fat, lard- and soybean oil-based) for 8 weeks and were then fed for another 8 weeks with the same HFD enriched with 10, 20, and 30% (g/kg) of either flaxseed oil (FA profile of the diet: SFA 27%, MUFA 38%, PUFA 35%) or olive oil (FA profile of the diet: SFA 31%, MUFA 49%, PUFA 20%). These

supplementations led to decreased hypothalamic protein levels of iNOS, IL-6, and TNF-α compared to HFD-fed rats [40]. However, the direct impact of FAs has not been studied in other structures in the course of obesity. Finally, intentional weight loss and the potential effects on cognitive function were also studied in patients diagnosed with mild cognitive impairment. Caloric restriction for 12 months led to a mean decrease of 1.7 kg/m^2 in BMI and was associated with improvements in memory, executive function, and global cognition [87].

Increasing physical activity is often advised to promote weight loss and increase quality of life for patients. Mandatory treadmill running showed interesting outcomes with regards to neuroinflammation, glial cell activation, and memory for rats fed a HFD (60% kcal from fat, lard-based). Indeed, running decreased protein levels of the TLR4 and NF-κB pathways as well as proinflammatory markers in the hippocampus. In both hippocampus and cortex, forced treadmill exercise normalized glial cell activation [50]. Finally, it also rescued working memory and spatial learning [50,88]. On the other hand, voluntary exercise was not as efficient as mandatory physical activity for mice fed a WD. Voluntary running led to decreased expression of CCL2 and CXCL10 in the prefrontal cortex but had no effect on glial cell activation [59].

Finally, one of the last options to decrease weight for morbidly obese patients remains surgery. One study compared the effects of two different surgeries using either Roux-en-Y gastric bypass (ReY) or vertical sleeve gastrectomy in rats. Strikingly, the latter did not rescue obesity-altered spatial learning and memory functions nor hippocampal microgliosis despite similar reductions in body weight. However, the ReY procedure had a positive impact on these cognitive parameters [55].

In both humans and rodents, despite the effectiveness of weight loss (either through restrictive diets or surgical procedures) to rescue some aspects of neuroinflammation and defects in cognition and behavior, it remains to be seen whether these interventions and their beneficial effects are due to a direct central effect or to decreased peripheral inflammation.

Concluding Remarks

From the elements discussed above it appears that the consequences of obesity for neuro-inflammation are highly dependent on the type of diet, its duration, and age. Another key element to consider is that, while neuroinflammation affects structures well beyond the hypothalamus, they are not all affected in the same manner by a HFD (see Outstanding Questions). This stresses the importance of studying specific and defined structures as opposed to 'the brain''. An important question that should be investigated in the same study is to assess different DIO-induced neuroinflammation kinetics to assess the specific susceptibility of different CNS structures to DIO.

As discussed here, another key element to move the field forward would be to set up studies allowing the simultaneous assessment of both neuroinflammation and cognitive function alterations in DIO.

The obesity epidemic coupled to the aging population constitutes a major threat to CNS homeostasis in terms of both neuroinflammation and function. Thus, future studies will need to further address the mechanisms linking obesity and neuroinflammation as well as potential treatments to restore CNS homeostasis despite the presence of obesity.

Outstanding Questions

Whether peripheral immune cells actually enter the CNS during obesity still needs clarification. If they are, what is the fate of recruited peripheral immune cells? What type of phenotype would they acquire and what would be their relevance for obesity-driven neuroinflammation? Would preventing their migration into the CNS be in any way beneficial in the context of obesity-induced neuroinflammation?

The choroid plexus has recently been put forward as an important relay of peripheral inflammatory cues to the CNS via extracellular vesicles. What is the relevance of this pathway in the context of obesity-induced neuro-inflammation? Furthermore, could the use of exosome secretion inhibitors prove beneficial in this context and rescue the brain functions that are classically impaired by obesity?

A lymphatic system located in dural sinuses and connected to deep cervical lymph nodes has been uncovered in the CNS. This adds further complexity to the communication network between the CNS and the periphery. What is its exact role in CNS homeostasis, and what would be its potential relevance in the context of obesity and subsequent inflammatory insults?

Why do some structures (e.g., hippocampus) appear to be more sensitive to obesity-induced neuroinflammation compared to others (e.g., amygdala)?

In the hypothalamus and hippocampus, neurons are affected by the obesity-induced inflammation. Are neurons also affected in other structures, and what would be the pathophysiological consequences of such alterations?

How does diet composition, in terms of the proportions of specific lipids and sugar, affect the onset and extent of neuroinflammation? Furthermore, to date it remains unclear whether the differential effects of HFD and WD on neuroinflammation are only due to a different total percentage of fat in the diet.

Do the architectural changes observed in white and grey matters of obese patients translate into cognitive and behavioral alterations?

The use of targeted imaging techniques, such as positron emission tomography (PET)-based measures using translocator protein (TSPO) ligands, is being developed to assess glial cell activation more specifically. Could these methods reveal more-subtle changes in CNS structures between obese patients and non-obese subjects?

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