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Obesity and Neuroinflammation: Mechanisms, Evidence, and Implications for Health

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ABSTRACT

Obesity represents a growing global health crisis, characterized by excessive adiposity and associated with multiple metabolic, cardiovascular, and neuropsychiatric comorbidities. Recent evidence indicates that obesity is strongly linked to neuroinflammation, mediated through peripheral and central immune mechanisms. Excess adipose tissue contributes to chronic low-grade systemic inflammation, with elevated pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β crossing the blood–brain barrier and activating microglia and astrocytes in the central nervous system (CNS). These neuroinflammatory processes impact cognitive function, mood regulation, and the hypothalamic control of energy homeostasis, potentially accelerating neurodegenerative disorders and psychiatric conditions. Lifestyle interventions, including dietary modification and physical activity, as well as pharmacological strategies targeting inflammation, show promise in mitigating obesity-related neuroinflammation. Nevertheless, current research is limited by cross-sectional designs, incomplete mechanistic understanding, and insufficient translation from animal models to human populations. Future studies integrating multi-omics approaches, longitudinal designs, and precision medicine strategies are needed to clarify the causal pathways linking obesity and neuroinflammation, improve early interventions, and reduce the burden of obesity-related neuropsychiatric and cognitive disorders.

Keywords: Obesity, Neuroinflammation, Blood–brain barrier, Microglial activation, and Cognitive decline.

INTRODUCTION

Obesity constitutes a significant contemporary health challenge, affecting a substantial proportion of the global population and representing one of the major drivers of preventable morbidity and mortality [1-5]. Classically defined as an excessive accumulation of body fat, obesity is generally estimated in humans by using the body mass index (BMI) the body mass index (BMI) (mass in kilograms divided by the squared height in meters a simple and widely accepted clinical measure of body composition [6-9]. At the levels commonly termed "overweight" (BMI ≥ 25 kg/m^2) and "obesity" (BMI ≥ 30 kg/m^2), obesity is associated with increased risk of a range of diseases, including type 2 diabetes, cardiovascular disease, chronic kidney disease, certain cancers, and osteoarthritis, among others. Such "co-morbidities" are major morbidity and mortality drivers associated with obesity, and currently, it is estimated that at least 2.8 million people die every year as a consequence of being overweight and obese [10-14]. Obesity is also associated with substantial 'mental health' costs and is classically associated with an increased prevalence of anxiety disorders and depression [15-19]. However, it is a complex disorder characterized by a number of physiological, metabolic, genetic, psychological, and social factors, and accounting for many of the related 'comorbidity' and psychological issues is key to addressing obesity [20-25]. Obesity is currently a growing global epidemic, with elevated levels worldwide, particularly in economically advanced countries and especially in adolescents and children. In the United States, 66.3% of the population was overweight or obese according to an assessment undertaken between 2015 and 2016, with 32.7% officially classified as obese (Body Mass Index, 2016). To help control this epidemic, new lifestyle and pharmacological-based strategies are warranted, and one possible answer is to treat the inflammatory component of obesity, which has been suggested to play a role in the various co-morbidities and associated mental health issues [26-29].

Overview of Obesity: Definitions, Epidemiology, and Pathophysiology

Obesity is defined as extensive and/or excessive adiposity that varies by population, sex, and method of assessment [30]. Body mass index (BMI) has long been the standard metric in public health research. The World Health Organization (WHO) considers overweight as ≥25 kg/ m^2 and obesity as ≥30 kg/m^2. The United States National Institutes of Health (NIH) classifies BMI 25–29.9 kg/m^2 as overweight, 30–34.9 kg/m^2 as class I (moderate) obesity, 35–39.9 kg/m^2 as class II (severe) obesity, and ≥40 kg/m^2 as class III (very severe or morbid) obesity [31-36]. Increasingly, waist circumference (WC) is being adopted as a complementary metric. Taken as a risk factor for metabolic syndrome and type 2 diabetes, it exceeds 94 cm in men and 80 cm in women, while metrics of atrophy also focus on ratios between visceral and total fat or between the abdominal area and other body areas [37-44]. Unfortunately, the prevalence of obesity has risen markedly since the late 20th century in Europe, North America, and many parts of East and Near Asia [45-48]. Despite public awareness of this growing epidemic and its metabolic consequences, chronic obesity remains undiagnosed and untreated [49-53]. There is no health condition with such a wide range of biological, behavioral, environmental, genetic, psychological, and social risk factors; although primary obesity is recognized as a disorder of the neuroendocrine control of body-weight homeostasis, it does often require lifestyle changes to mitigate [54-61].

Neuroinflammation: Concepts, Cells, and Mediators

Neuroinflammation, Concepts, Cells, and Mediators. Neuroinflammation is defined as an inflammatory response occurring in the central nervous system (CNS) and involves activation of resident glial cells, mainly microglia and astrocytes [5]. Inflammatory processes in the brain could be triggered by various factors, including the invasion of pathogens, mechanical injuries, and the release of pro-inflammatory factors by peripheral immune cells [9]. It is well established that obesity is associated with chronic sterile low-grade inflammation. Consequently, individuals exhibiting metabolic disorders or obesity show increased levels of pro-inflammatory cytokines such as IL1-β, IL-6, TNF-α, and chemokines (CCL2, CCL5) in the circulation [8]. A growing body of evidence indicates that elevated plasma levels of pro-inflammatory mediators can cross the blood-brain barrier (BBB) and activate microglia and astrocytes in the CNS [5]. These immune cells secrete other pro-inflammatory mediators that propagate neuroinflammation and exacerbate metabolic dysfunction [1].

Interplay Between Obesity and Neuroinflammation

Obesity is characterized by an excessive accumulation of body fat, established to have adverse effects on health (World Health Organization, 2020) [4]. Worldwide obesity has nearly tripled since 19751[1]. Obesity is a primary driver of non-communicable diseases such as diabetes, cardiovascular diseases, musculoskeletal disorders, and certain cancers, significantly reducing life expectancy (World Health Organization, 2020)[3]. In 2022, 36% of men and 40% of women worldwide were considered overweight. 29% of the population is classified as obese (World Health Organization, 2020). Obesity is estimated to have contributed to the premature death of at least 2.8 million adults globally in 2022 [5]. Obesity has been linked to a wide range of disease processes, including neuroinflammation and diseases of the central nervous system (CNS) [1]. Adiposity is of particular interest since it appears to provoke signalling processes within the CNS and alter blood-brain-barrier (BBB) integrity. Adiposity has been associated with the remodelling of many organ systems and pathological consequences in non-adipose sites [4]. The normal physiological functions of an organism require that organs and systems communicate with one another, and adiposity disrupts organ crosstalk and the physiological state, leading to multi-system alterations [6]. Apprehension of and communication with the external environment is a fundamental requirement of any organism, which connects the state of the internal environment to the external world [7]. Thus, the precise mechanisms whereby adiposity connects to local and remote organs and the hypothalamus, the CNS, and the environment are under intense investigation [5].

Adipose Tissue Inflammation and Central Nervous System Signaling

The fundamental notion that excess caloric intake from a rich diet leads to overweight and subsequently to obesity, a condition recognized as an epidemic in contemporary society, has been fundamentally revised to include the perspective that a diet rich in calories but low in micronutrients could induce the same pathological outcome [4]. Such an oft-ignored diet constitutes a diet leading to neuroinflammation in the precursor stage of obesity, which is generally referred to as the obesogenic diet [1]. In line with the current knowledge, accumulating evidence indicates that obesity augments inflammation within and outside the central nervous system (CNS) [5]. Accumulation of excessive body weight during life under all kinds of obesogenic environments is indeed an alarming risk factor for many chronic pathological conditions in the life span of individuals [6].

Blood-Brain Barrier Alterations in Obesity

The blood–brain barrier (BBB) is a specialized structure formed by brain endothelial cells and astrocytes, which maintains central nervous system homeostasis by restricting the entry of molecules into the brain and regulating the transport of non-permeant substances [4]. Physiological alterations to the BBB occur during different metabolic states, and obesity is associated with marked modifications of its composition and transport mechanisms

[3]. A high-fat diet enhances the passage of peripheral inflammatory mediators into the CNS and alters the expression of transporters such as glucose transporter type 1 (GLUT-1), insulin receptor, low-density lipoprotein receptor-related protein 1 (LRP-1), and the transferrin receptor, which are involved in the transport of systemic signals critically regulating the brain's homeostasis [7]. Increased blood insulin levels, characteristic of obesity and type 2 diabetes, affect the brain regions involved in energy balance and glucose homeostasis by down-regulating insulin receptor expression at the BBB [4]. Impaired transport and access of insulin to the brain already occur during the early stages of metabolic syndrome in experimental and clinical conditions [6]. The consequent increase in plasma levels of brain-derived neurotrophic factor (BDNF), des-acyl BDNF, and free fatty acids has also been reported [7].

Microglial Activation and Neuronal Consequences

Neuroinflammation, defined as an acute or persistent immune response mediated by the central nervous system (CNS), has gained increasing interest due to its implication in numerous pathologies, including obesity [5]. The immune system of the brain is composed of a wide variety of cells; however, microglia are the primary resident immune cells and thus play a pivotal role in brain homeostasis [6]. Under healthy conditions, microglia have a ramified morphology and continuously remodel their dendrites to monitor tissue and neuronal integrity. Acute or chronic perturbations, such as obesity, affect microglia and drive a switch from surveillance to an activated state [3]. The impact of diet and obesity on the morphology, activity, and phenotype of microglia, as well as the underlying pathways, is therefore crucial for establishing the link between obesity and neuroinflammation [7]. A multitude of microglial-activation triggers act synergistically in obesity, including peripheral hormone and metabolic dysregulation, changes in the gut microbiome, and alterations in the blood–brain barrier (BBB) (Moser et al., 2018; Léon et al., 2021)[8]. Obesity induces chronic low-grade inflammation at the systemic and central levels, contributing to the development of metabolic syndrome and cognitive decline [1]. Microglial feasibility for sensing and integration of multiple stimuli provides a central mechanism through which these insults promote brain-inflammation networks that are activated in obesity [7]. The presence of fat in the vasculature activates diverse immune-system components and micromodules linked to the status of peripheral metabolic organs. Activation of the inflammatory response is characterized by increased expression of pro-inflammatory cytokines and activation of downstream signaling pathways [5].

Systemic Inflammation and Neurodegenerative Risk

Chronic, sterile, low-grade systemic inflammation is a common feature of obesity, significantly contributing to various comorbidities [7]. This condition is typified by the increased presence of pro-inflammatory cytokines such as interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP) in circulation. Elevated levels of these molecules correlate with the development of vascular pathologies and are frequently measured as biomarkers in Alzheimer's disease [6]. Furthermore, obesity fosters an orchestrated accumulation of immune cell populations in peripheral tissues, culminating in a progressive state of organ dysfunction. Studies indicate that the levels of systemic pro-inflammatory biomarkers and the recruitment of circulating leukocyte populations escalate in a coordinated manner during the early stages of both diet-induced and genetic obesity in mice [8]. Specific pro-inflammatory mediators secreted from peripheral tissues are now recognized as significant contributors to the onset and advancement of CNS disorders. Adipose tissue emerges as a particularly influential peripheral organ in the metabolic–inflammatory interplay between the periphery and the brain [4]. The adiposity-induced propagation of peripheral inflammation intimately influences hypothalamic micromilieu, illustrating the iterative nature of the bodily-wide neuro–metabolic–inflammatory communication loop. Elevated levels of circulating leptin and insulin are also indicative of peripheral pro-inflammatory action [5]. Data from longitudinal, cross-species, and human studies establish a compelling link between obesity-associated peripheral inflammation and evolving neurodegenerative processes [5]. Key regions implicated in the neurobiological and behavioral regulation of food intake and metabolic homeostasis, such as the hypothalamus, hippocampus, and mesolimbic circuit, are particularly compromised [7]. Such alterations occur alongside the advent of a broader-spectrum, systemic metabolic syndrome that includes dyslipidemia, hyperleptinemia, and hypertension. Consequently, early-stage obesity is associated with a unique and thus far poorly characterized set of peripheral pro-inflammatory mediators and time-dependent neurophysiological fluctuations [6].

Cognitive and Behavioral Implications

In addition to neurodegeneration, the associated cognitive decline, depression, and loss of motivation also seem related to obesity-induced inflammation [6]. Some studies have found that lesions in areas involved in appetite regulation, such as the hypothalamus or the brain stem, affect associative memory and executive functions. Furthermore, lesions in the lateral hypothalamus have been linked to alterations in mood and motivation [7]. Memory deficits in animals with obesity can still be observed after controlling for sensory deficits or acute food shortage and may involve alterations in the brain itself, rather than simply being a consequence of the effects on peripheral systems or behavior [5]. There is evidence that peripheral inflammation affects learning and memory

processes by modulating synaptic plasticity. Pro-inflammatory cytokines, besides being present in the circulation during metabolic disease, may also influence learning and memory processes, and some cytokines released into the circulation can act on the brain through the induction of fever or an acute-phase response [5]. Research with human participants suggests that the relationship between obesity and cognition is regulated by other risk factors. A large body of literature indicates that chronic low-grade inflammation is related to cognitive decline and neurodegenerative diseases [6]. Some studies found increased levels of pro-inflammatory cytokines and markers of systemic inflammation associated with poorer performance in certain cognitive tests [5]. However, an increase in the number of tests administered may result in the significance of the relationship between cognitive decline and inflammation disappearing [7]. Future studies that examine the temporal relationship between these biomarkers and cognitive decline are needed in order to confirm the role of systemic inflammation as a risk factor for cognitive decline, as well as to determine the regions of the brain involved in cognition more affected by these processes. Nevertheless, it seems reasonable to assume that the association between obesity and alterations in cognition is influenced by the levels of the pro-inflammatory mediator IL-6[4].

Metabolic Syndromes and Neuropsychiatric Outcomes

Obesity is associated with a greater risk of brain injury and neurodegeneration [1]. Consistent with the extensive morbidity and mortality associated with obesity, blood levels of proinflammatory cytokines, chemokines, and neurodegenerative biomarkers are elevated, systemic inflammation is greater, and cerebrospinal fluid levels of proinflammatory cytokines and brain biomarkers of Alzheimer's disease pathology are increased [2]. Experimental studies show that restrictions in caloric intake, polyunsaturated fatty acid enrichment, intermittent fasting, omega-3 supplementation, and regular physical activity reduce neuroinflammatory signaling, lower the production of biological markers of Alzheimer's disease, protect cerebrovascular function, and slow the accumulation of amyloid-β and tau in the brains of obese rodents[6].

Therapeutic Perspectives and Intervention Strategies

Obesity increases the risk of developing several neuropsychological disorders, including depression, anxiety, attention deficit hyperactivity disorder, and cognitive impairment [2]. A broad sentiment, according to the authors, postulates that an alteration of the functions of the central nervous system (CNS) accompanies the endocrine disorder known as obesity [4]. Minimal neuroinflammation that commonly accompanies obesity remains correlated with the range, severity, and evolution of anxiety, depression, and cognitive impairment occurring in conjunction with obesity. Changes in the white matter content of the brain regions involved in a learning process, memory storage, and processing trigger cognitive alteration in converted rats fed a hypercaloric diet [2]. Neufeld and co-authors assert that alteration of the gut microbiota originating from an industrialized diet intervenes in the learning process by a microbiota-brain axis associated with neuroinflammation [3].

Lifestyle Interventions: Diet and Exercise

The anti-inflammatory effects of lifestyle interventions such as caloric restriction, dietary modifications, and physical activity have been the subject of numerous studies at both peripheral and central levels [5]. Two interventions emerge with consistent evidence across different experimental conditions: adherence to a pattern of nutrient-rich, minimally processed foods and sufficient physical activity, particularly when adapting to energy intake [3]. Both interventions have also been shown to mitigate neuroinflammatory mechanisms in the central nervous system [8]. It is worth noting that, while these anti-inflammatory effects represent a potential common mechanism through which lifestyle interventions support brain health, not all dietary patterns confer such protection. Interactions between dietary, physical activity, and other lifestyle practices either enhance or attenuate the associated neuroinflammation-protective influence. In humans, evidence remains suggestive rather than confirmatory [6]. Longitudinal studies with larger cohorts, alongside metabolomic and enteric microbiota temporal monitoring, could elucidate how alterations in nutrient intake or exercise influence these neuroinflammatory mechanisms [4]. Likewise, generating standardized, long-term dietary patterns in controlled dietary intake laboratory studies, combined with metabolic monitoring, could clarify how specific nutrients exert effects on the brain in parallel with dietary pattern interventions [1].

Pharmacological Approaches Targeting Inflammation

Although lifestyle modifications effectively reduce central nervous system (CNS) inflammation associated with obesity, strategies targeting the inflammatory process may offer additional therapeutic benefits [1]. As previously mentioned, anti-inflammatory agents (such as non-steroidal anti-inflammatory drugs [NSAIDs]) exert health-promoting effects in population studies, animal models, and clinical trials [6]. Cytokine inhibition represents a second pharmacological approach, with blockade of specific cytokines yielding CNS-targeted effects [2]. Finally, metabolic agents (such as antidiabetic and antiobesity medications) can indirectly regulate inflammatory pathways while exerting their primary metabolic action [4].

Emerging Therapies and Precision Medicine

Although dietary and lifestyle interventions remain the cornerstones of obesity management, emerging therapies are beginning to modify the field of obesity treatment for certain selected patients [7]. Efforts in precision medicine stratify treatment based on discrete obesity pathways such as neurotransmitter signalling, energy expenditure, and lipoprotein metabolism [6]. Other approaches target multiple aspects of the obesity phenotype simultaneously. Individualised, obesity biomarkers remain a goal to further refine patient stratification and enhance therapeutic responses [6]. Recent work outlining the precise pathways by which obesity-related inflammation engages and promotes neuroinflammation in the central nervous system (CNS) has reshaped postulations on which patients are more vulnerable to obesity-associated cognitive deficits and emotional disturbances [8]. Vulnerability to one or several of these neuropsychiatric problems, collectively termed 'sick brain syndrome', seems partly determined by obesity phenotype, and emerging preliminary evidence suggests that many anti-obesity medications exert direct effects on CNS inflammation, potentially enabling simultaneous body weight reduction and dampening of neuroinflammation[7]. Deciphering which therapeutic approaches produce CNS and peripheral anti-inflammatory effects is therefore gaining traction. Current pharmacological anti-inflammatory interventions with established CNS permeability and anti-inflammatory properties include Aspirin (Acetylsalicylic Acid), KineretTM (Anakinra), OrenciaTM (Abatacept), HumiraTM (Adalimumab), EnbrelTM (Etanercept), Consilient Health (Infiximab), LantusTM (Insulin Glargine), DexilantTM (Dexlansoprazole), NexiumTM (Esomeprazole), PantozolTM (Pantoprazole), Prium (Lansoprazole), AdnaGen AG Holds (Apremilast), Pappas et al. [9].

Methodological Considerations in Obesity–Neuroinflammation Research

Obesity constitutes a significant global burden, with its recognition as a disease further stimulating research into associated risks [8]. During the past decades, obesity has witnessed a proliferation of studies, including its association with neuroinflammation, yet the scientific community continues to address various concerns to delineate this relationship. Most of the published literature relies on cross-sectional designs, which may impede firm conclusions regarding the causality of the associations reported [7]. Furthermore, since very few imaging biomarkers targeting neuroinflammation have been developed for human studies, the understanding of the responsible mechanisms remains incomplete [6]. Taking into account the involvement of adipose tissue in the modulation of various neuroactive molecules and substances linked with the peripheral state of the body, many studies have emphasized the measurement of peripheral molecules related to neuroinflammation, while others did not get to determine whether these substances cross the blood–brain barrier, leaving a gap in knowledge regarding their action into the central nervous system [8]. Finally, the literature accumulates evidence linking neuroinflammation and various factors worsening the neuropsychiatric condition of individuals suffering from obesity, yet the mechanisms establishing the action of obesity-associated inflammation on cognitive and behavioral outcomes largely remain unclear [2]. Unraveling the relationship between obesity and neuroinflammation thus constitutes a challenge for the future. Addressing these worries by means of long-term studies able to assess a larger number of individuals across the lifespan, fostering the use of translational models employing diets inducing similar metabolic syndrome alterations as those suffered by humans, and developing multi-omics approaches to characterize the metagenomic and metabolomic alterations induced by the obesogenic environment in parallel with the transcriptomic adaptations and their consequences on the interplay between neuroinflammation and the neuropsychiatric marks of obesity would prove beneficial for clarifying the nature of the association and its precise influence on the pathology [1].

Gaps in Knowledge and Future Directions

Neuroinflammatory mechanisms triggered by obesity have been thoroughly dissected yet remain insufficiently explored [8]. Unraveling the relevant processes is crucial to the understanding of obesity per se and it's associated risks of neuropsychiatric disorders and cognitive decline [7]. Elucidation of the pathways through which obesity alters central nervous system (CNS) function would also yield insights into when, during the progression of obesity, the onset of neuroinflammation occurs and how to intervene to obstruct potential negative consequences [1]. Furthermore, a more comprehensive mapping of the CNS endpoints impacted by excess adiposity could inform the selection of imaging biomarkers that would facilitate the rigorous examination of the obesity–neuroinflammation connection in human studies [2]. Many of the investigations conducted thus far have established only correlations between obesity and neuroinflammatory signalers either measured in a peripheral compartment or imputed to a CNS response [9-12]. Future research would benefit from both longitudinal designs and the incorporation of experimental rodent models that closely approximate dietary and metabolic patterns in the human population [9]. The translation of knowledge derived from preclinical approaches would be aided by multi-omics approaches, genomics, proteomics, transcriptomics, and lipidomics that permit a greater

understanding of how metabolic disturbances precipitate further changes in metabolism and neuroinflammatory signalling that progressively disrupt the function of mnemonic circuits in both physiology and disease [13, 14].

CONCLUSION

Obesity is not merely a metabolic disorder but a complex condition with profound implications for central nervous system function. Chronic low-grade systemic inflammation associated with obesity extends to the brain, activating neuroinflammatory pathways that contribute to cognitive decline, mood disorders, and neurodegenerative risk. Lifestyle interventions and pharmacological strategies targeting inflammatory mechanisms offer potential avenues to mitigate these effects, yet research gaps remain, particularly in understanding causality, CNS-specific effects, and translational relevance from preclinical models to humans. Addressing these gaps through longitudinal studies, multi-omics analyses, and precision medicine approaches will be critical to developing effective strategies for preventing and managing obesity-associated neuroinflammation and its neuropsychiatric consequences.

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