Obesity-Induced Neuroinflammation

Subjects: Neurosciences
Contributor: José Luis Marcos , Rossy Olivares-Barraza , Karina Ceballo , Melisa Wastavino , Víctor Ortiz , Julio Riquelme , Jonathan Martínez-Pinto , Pablo Muñoz , Gonzalo Cruz , Ramón Sotomayor-Zárate

Obesity-induced neuroinflammation is a chronic aseptic central nervous system inflammation that presents systemic characteristics associated with increased pro-inflammatory cytokines such as interleukin 1 beta (IL-1β) and interleukin 18 (IL-18) and the presence of microglia and reactive astrogliosis as well as the activation of the NOD-like receptor protein 3 (NLRP3) inflammasome. The obesity pandemic is associated with lifestyle changes, including an excessive intake of obesogenic foods and decreased physical activity. Brain areas such as the lateral hypothalamus (LH), lateral septum (LS), ventral tegmental area (VTA), and nucleus accumbens (NAcc) have been implicated in the homeostatic and hedonic control of feeding in experimental models of diet-induced obesity. A chronic lipid intake triggers neuroinflammation in several brain regions such as the hypothalamus, hippocampus, and amygdala.

diet glia inflammation

1. Introduction

Obesity-induced neuroinflammation is a type of brain aseptic chronic inflammation characterized by high pro-inflammatory cytokines, reactive microglia, and astrogliosis [1][2][3][4]. The intensity of the inflammation induced by obesogenic diets is lower than that caused by infections [5]. However, this neuroinflammation can be evidenced even in normal-weight individuals without insulin resistance or other metabolic disorders [6]. Neuroinflammation induced by a hyperlipidemic diet (lipid, 45 kcal%) was first described in the hypothalamus, evidenced by an increase in c-Jun N-terminal kinase (JNK) and nuclear factor kappa-B (NF-κB) signaling and a reduction in insulin and leptin signaling [1]. Hypothalamic inflammation promotes leptin resistance [7], gliosis, and neuronal death [8]. High-fat diet (HFD)-induced gliosis implicates the activation of astrocytes and microglia [9][10], promoting the release of pro-inflammatory cytokines such as interleukin 1β (IL-1β) and tumor necrosis factor-alpha (TNF-α), resulting in the overexpression of cyclooxygenases and the production of reactive oxygen species [11].

2. Inflammation

2.1. Peripheral Inflammation

Obesity produces a chronic low-grade inflammation within the peripheral tissues; adipose tissue is one of the most sensitive to obesity-induced inflammation [5][12]. In lean individuals, adipose tissue contains multiple immune cells that operate in the T helper 2 (Th2) state, including homeostatic anti-inflammatory macrophages, regulatory T

(Treg) cells, type 2 innate lymphoid cells (ILC2), invariant natural killer T (iNKT) cells, natural killer (NK) cells, and eosinophils [13]. In obesity, this immune profile shifts towards a pro-inflammatory state, hallmarked by the proliferation and recruitment of neutrophils, inflammatory macrophages, B cells, cytotoxic T lymphocytes ($CD8^+$ T) cells, and T helper (Th) 1 and Th17 cells, along with a reduced abundance of eosinophils, Treg cells, iNKT cells, and ILC2 [13]. Saturated fatty acids directly promote inflammation, facilitating the absorption of lipopolysaccharides (LPS) [14] and activating macrophages, microglia, and astrocytes, similar to LPS by binding to toll-like receptor-4 (TLR4), which triggers NF-κB signaling and promotes cytokine release [15]. In the same context, TNF-α decreases the sensitivity of insulin receptor 1 in adipocytes [16], which can be reversed by the inactivation of TNF-α receptors [17]. Similarly, a TLR4 knockout (KO) demonstrated a reduced preference for fat and sugar intake [18]. TLR4 has a critical role in propagating the activation of the NOD-like receptor protein 3 (NLRP3) inflammasome activated by saturated fatty acids [19].

Another aspect that has recently gained interest is the role of microbiota. In this regard, many publications support the involvement of gut microbiota in the pathophysiology of obesity. In rodent models of diet-induced obesity, gut microbiota modifications were associated with increased intestinal permeability, allowing the passage of food or bacterial antigens that contribute to low-grade inflammation and insulin resistance [20]. The perturbation of the intestinal microbiota and changes in intestinal permeability are considered to be a trigger of inflammation in obesity [21]. In the same sense, metabolic endotoxemia originating from dysbiotic gut microbiota has been identified as a primary mediator for triggering the chronic low-grade inflammation responsible for the development of obesity [22]. Animal studies have demonstrated that gut microbiota could promote adiposity and weight gain by altering the host gene expression, the metabolic and inflammatory pathways, and the gut–brain axis [23].

2.2. Central Inflammation or Neuroinflammation

Obesity-induced neuroinflammation was first described in the hypothalamus, evidenced by the upregulation of JNK and NF-κB signaling and a reduced insulin and leptin profile caused by exposure to an HFD [1]. Hypothalamic inflammation leads to leptin resistance [7] and changes in neural projections as well as gliosis and neuronal death [8]. In neuroinflammation, gliosis is characterized by reactive astrocytes and microglia [10][24]. Activated microglia can release various pro-inflammatory cytokines such as IL-1β and TNF-α as well as cyclooxygenases and reactive oxygen species [11]. The deletion of adapter proteins for toll-like receptors protected mice from weight gain and the development of leptin resistance when fed an HFD [25].

2.2.1. Neuroinflammatory Mechanisms

Blood-Brain Barrier

The functionality of the BBB depends on a strict architecture. In the ventromedial hypothalamus, the barrier specializes in admitting the dynamic passage of hormones and nutrients from the blood to the energy-sensing arcuate nucleus of the hypothalamus (ARC) and the export of newly synthesized hormones to the pituitary. At the median eminence (ME) level, the barrier has fenestrated capillaries that allow the faster transport of substances into the nutrient-sensing hypothalamic nuclei adjacent to it. However, ME tanycytes, specialized radial glia cells

lining the walls of the third ventricle, form a physical barrier to control the correct transport of nutrients and metabolic hormones into the brain parenchyma [26][27][28].

Several mechanisms have been proposed to explain how diet-induced inflammation occurs. One possible mechanism is the alteration of the blood–brain barrier (BBB). A Western Diet (WD) (high fat/high sucrose) consumption increases the BBB permeability, thus allowing immune cell infiltration and leading to hypothalamic inflammation [29]. In this sense, the interactions between the C-reactive protein and the BBB increase the paracellular permeability and induce reactive gliosis [30]. In leptin receptor-deficient (db/db) mice, inflammatory changes in the BBB participated in obesity-related cognitive alterations; rescued cognitive deficits were achieved by reducing the BBB permeability [31]. In this sense, an Evans blue stain entered the central nervous system (CNS) of mice fed with an HFD [32][33][34]; a possible explanation of the mechanism arose from the reduction of tight junction transcripts such as occludin, claudin-5, and claudin-12 in the thalamus and midbrain, increasing the permeability of the BBB in the hippocampus [33][35].

Fatty Acids

High-fat and high-sugar diets upregulate the inflammatory NF-κB pathway in the hypothalamus, which is a binding site for regulating energy homeostasis [36]. An inflammatory phenotype was visualized when microglia were treated with saturated fatty acids in vitro [37]. Hypothalamic inflammation contributes to developing and maintaining the obese phenotype; exposure to an HFD for three days produced neuroinflammation, gliosis, and the markers of neuronal injuries in rodents [2]. Furthermore, just one day of an HFD could increase the expression of IL-6 and TNF-α as well as microglial activation [4]. Lipids in the hypothalamus play a potential role in the development of obesity and related metabolic diseases, suggesting that the WD affects lipid accumulation and synthesis in the brain [38], leading to an onset of an increase in inflammatory cytokines, oxidative stress, transcription factor changes, neuron malfunctions, or cell death [39]. A WD drives the inflammatory responses in the hypothalamus, eventually leading to metabolic disorders [40].

2.2.2. Role of Glial Cells in Obesity

Microglia sense their surrounding environment and express pro-inflammatory (M1) or anti-inflammatory (M2) phenotypes [41] in response to the presence of pathogen-associated molecular patterns (PAMPs) [42]. Microglia cells have been proposed to be a critical target of obesity-related inflammation [43]. In this context, systemic injection of lipopolysaccharide (LPS) promoted microglial activation in the hypothalamus [44]. LPS induces a greater expression of the primary histocompatibility complex class 1 (MHC-I), pro-inflammatory cytokines (TNF-α, IL-1, and IL-6), and the activation of cyclooxygenase 1 (COX-1) and NF-κB [45][46]. In a mouse model of diet-induced obesity, a partial substitution of the fatty acid composition of a diet of flax seed oil (rich in C18:3) or olive oil (rich in C18:1) corrected hypothalamic inflammation, which was evaluated by a JNK and NF-κB activity reduction [47]. At the hypothalamic level, metabolic inflammation increased the activation of IKKb/NF-κB up to two times compared to a chronic HFD, and up to five or six times in the case of hyperphagic obese animals [25]. Similarly, microglial cell cultures treated with palmitic acid (a long-chain saturated fatty acid) have a rapid TLR4-dependent microglial activation [48]. Investigations into the ARC observed that microglia activation was critical for altering the energy

balance and inducing weight gain during long-term HFD exposure in mice [49], leading to enhanced susceptibility to obesity and a possible suitable pharmacological target. On the other hand, diet-induced microgliosis in the hippocampus has been identified in patients and experimental models of Alzheimer's disease, providing a potential mechanistic link between obesity/type 2 diabetes and cognitive impairments [50]. A high-caloric diet also increases NLRP3 expression, indicating inflammasome activation and IL-1β production in the hippocampus and amygdala-derived microglia [51] (**Figure 1**). Interestingly, minocycline (a second-generation tetracycline) is considered to be an inhibitor of microglia-induced neuroinflammation [52], inhibiting intracellular signaling pathways such as p38, ERK1/2, and NF-κB and the release of pro-inflammatory factors, including IL-1β, IL-18, IL-6, and NOS2 [53]. Several studies have shown that treatment with minocycline improves depressive symptoms, decreases the expression of pro-inflammatory cytokines associated with the hyperactivity of the hypothalamic–pituitary–adrenal axis (HPA) [54], and the administration of drugs of abuse in the reward system [55]. Minocycline, an FDA-approved tetracyclic antibiotic with anti-inflammatory properties [56], has been associated with a reduction in HFD-induced weight gain as well as an improvement in insulin sensitivity, a decline in active microglia, and the restoration of alterations in autophagy-related gene networks in the PVN [57]. Microglial activation could influence the energy balance, but the promotion of leptin resistance and impairments in adipose thermogenesis are not yet clear [58].

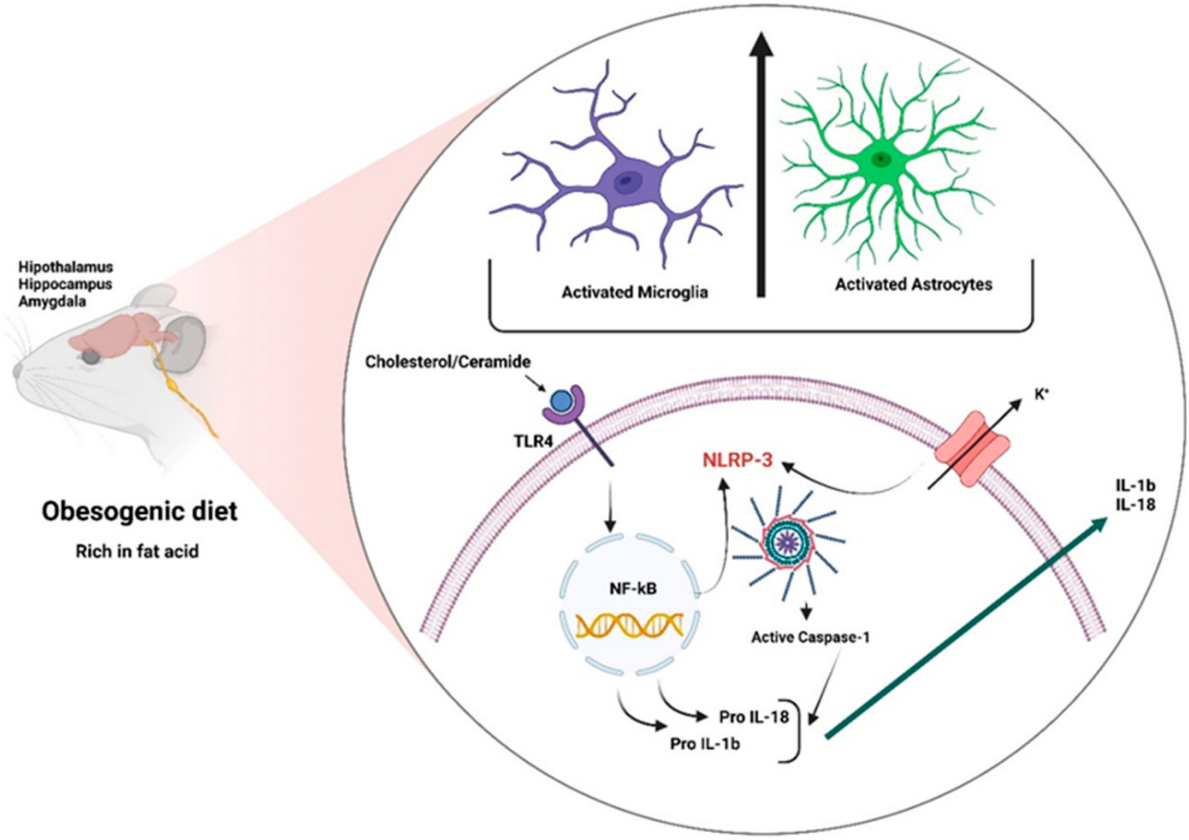

Figure 1. Activating the NLR family pyrin domain-containing 3 (NLRP3) inflammasome signaling pathway requires two signals. Signal 1 or priming is provided by pathogen-associated molecular patterns (PAMPs), danger-associated molecular patterns (DAMPs), cholesterol, or the activation of toll-like receptors (TLRs) or cytokine receptors, leading to the nuclear factor kappa-B NF-κB activation that upregulates the levels of several inflammasome components such as the protein NLRP3, pro-IL-1β, and pro-IL-18. Signal 2 or activation is provided

by numerous PAMPs or DAMPs, including viruses, cholesterol, potassium efflux, reactive oxygen species (ROS), extracellular ATP, and lysosomal dysfunctions, among others. ASC, an adaptor protein, recruits NLRP3 and pro-caspase-1 to form the NLRP3 inflammasome complex. Caspase-1 promotes the processing of interleukins for their subsequent release. This figure was created with BioRender.com under a subscription and has a license from BioRender to use the figure in journal publications.

2.2.3. Inflammasomes

The NLRP3 inflammasome is part of the innate immune system activating caspase-1, promoting the release of pro-inflammatory cytokines IL-1β/IL-18 in response to microbial infections and cell damage [59]. At the molecular level, inflammasomes comprise three components: (1) a sensor such as a NOD-like receptor (NLR) or an AIM-2-like receptor (ALR); (2) an apoptosis-associated adapter protein (ASC) containing a caspase recruitment domain; and (3) cysteine inflammatory caspase-1 aspartate [59]. Inflammasomes are also involved in the cleavage of gasdermin-D (GSDM-D), the induction of pyroptosis [60], and obesity-induced inflammation [61]. The NLRP3 inflammasome is one of the most extensively studied inflammasomes [62]. This complex belongs to the nucleotide-binding oligomerization domain-like receptor family (NOD-like) pyrin domain-containing 3 (NLRP3) [61][63]. The NLRP3 inflammasome is activated by molecular patterns associated with cell damage (DAMPS) and favors the proteolytic cleavage of pro-interleukin 1β and 18 through caspase-1, generating the respective active proteins (IL-1β and IL-18), which tend to the inflammatory response [64]. In this context, the NLRP3 inflammasome can be activated by cholesterol crystals and ceramides [65] due to the exacerbation of lipolysis in obesity [66], but can also be activated by bacteria, fungi, and viruses; however, NLRP3 is associated with metabolic and inflammatory conditions such as obesity [67][68]. Unlike other inflammasome complexes, NLRP3 is unique. It mediates the recognition of DAMPs directly involved in cellular metabolism [69]; NLRP3 expression is dependent on NF-κB and, therefore, can be regulated by the components of a diet.

Astrogliosis is characterized by an increase in glial fibrillar acid protein (GFAP), promoting a pro-inflammatory phenotype and hypertrophic morphology. An HFD increases the expression of astrocytic and microglial markers such as GFAP and ionized calcium-binding adapter 1 (Iba-1), respectively, in the hypothalamus [42].

References

1. De Souza, C.T.; Araujo, E.P.; Bordin, S.; Ashimine, R.; Zollner, R.L.; Boschero, A.C.; Saad, M.J.; Velloso, L.A. Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus. Endocrinology 2005, 146, 4192–4199.
2. Thaler, J.P.; Guyenet, S.J.; Dorfman, M.D.; Wisse, B.E.; Schwartz, M.W. Hypothalamic inflammation: Marker or mechanism of obesity pathogenesis? Diabetes 2013, 62, 2629–2634.
3. Buckman, L.B.; Thompson, M.M.; Moreno, H.N.; Ellacott, K.L. Regional astrogliosis in the mouse hypothalamus in response to obesity. J. Comp. Neurol. 2013, 521, 1322–1333.

4. Waise, T.M.Z.; Toshinai, K.; Naznin, F.; NamKoong, C.; Md Moin, A.S.; Sakoda, H.; Nakazato, M. One-day high-fat diet induces inflammation in the nodose ganglion and hypothalamus of mice. Biochem. Biophys. Res. Commun. 2015, 464, 1157–1162.
5. Lee, B.C.; Lee, J. Cellular and molecular players in adipose tissue inflammation in the development of obesity-induced insulin resistance. Biochim. Biophys. Acta 2014, 1842, 446–462.
6. Lee, T.J.; Hargrave, S.L.; Kinzig, K.P. Dual functions of CNS inflammation in food intake and metabolic regulation. Brain Res. 2020, 1740, 146859.
7. Pan, W.; Allison, M.B.; Sabatini, P.; Rupp, A.; Adams, J.; Patterson, C.; Jones, J.C.; Olson, D.P.; Myers, M.G., Jr. Transcriptional and physiological roles for STAT proteins in leptin action. Mol. Metab. 2019, 22, 121–131.
8. Dorfman, M.D.; Thaler, J.P. Hypothalamic inflammation and gliosis in obesity. Curr. Opin. Endocrinol. Diabetes Obes. 2015, 22, 325–330.
9. Cai, M.; Wang, H.; Li, J.J.; Zhang, Y.L.; Xin, L.; Li, F.; Lou, S.J. The signaling mechanisms of hippocampal endoplasmic reticulum stress affecting neuronal plasticity-related protein levels in high fat diet-induced obese rats and the regulation of aerobic exercise. Brain Behav. Immun. 2016, 57, 347–359.
10. Seong, J.; Kang, J.Y.; Sun, J.S.; Kim, K.W. Hypothalamic inflammation and obesity: A mechanistic review. Arch. Pharm. Res. 2019, 42, 383–392.
11. Shabab, T.; Khanabdali, R.; Moghadamtousi, S.Z.; Kadir, H.A.; Mohan, G. Neuroinflammation pathways: A general review. Int. J. Neurosci. 2017, 127, 624–633.
12. Unamuno, X.; Gomez-Ambrosi, J.; Rodriguez, A.; Becerril, S.; Fruhbeck, G.; Catalan, V. Adipokine dysregulation and adipose tissue inflammation in human obesity. Eur. J. Clin. Invest. 2018, 48, e12997.
13. Trim, W.V.; Lynch, L. Immune and non-immune functions of adipose tissue leukocytes. Nat Rev Immunol 2022, 22, 371–386.
14. Fritsche, K.L. The science of fatty acids and inflammation. Adv. Nutr. 2015, 6, 293S–301S.
15. Wang, Z.; Liu, D.; Wang, F.; Liu, S.; Zhao, S.; Ling, E.A.; Hao, A. Saturated fatty acids activate microglia via Toll-like receptor 4/NF-kappaB signalling. Br. J. Nutr. 2012, 107, 229–241.
16. Hotamisligil, G.S.; Peraldi, P.; Budavari, A.; Ellis, R.; White, M.F.; Spiegelman, B.M. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. Science 1996, 271, 665–668.
17. Uysal, K.T.; Wiesbrock, S.M.; Marino, M.W.; Hotamisligil, G.S. Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. Nature 1997, 389, 610–614.

18. Camandola, S.; Mattson, M.P. Toll-like receptor 4 mediates fat, sugar, and umami taste preference and food intake and body weight regulation. Obesity 2017, 25, 1237–1245.
19. Reynolds, C.M.; McGillicuddy, F.C.; Harford, K.A.; Finucane, O.M.; Mills, K.H.; Roche, H.M. Dietary saturated fatty acids prime the NLRP3 inflammasome via TLR4 in dendritic cells-implications for diet-induced insulin resistance. Mol. Nutr. Food Res. 2012, 56, 1212–1222.
20. Genser, L.; Poitou, C.; Brot-Laroche, E.; Rousset, M.; Vaillant, J.C.; Clement, K.; Thenet, S.; Leturque, A. Alteration of intestinal permeability: The missing link between gut microbiota modifications and inflammation in obesity? Med. Sci. (Paris) 2016, 32, 461–469.
21. Cox, A.J.; West, N.P.; Cripps, A.W. Obesity, inflammation, and the gut microbiota. Lancet Diabetes Endocrinol 2015, 3, 207–215.
22. Kang, C.; Wang, B.; Kaliannan, K.; Wang, X.; Lang, H.; Hui, S.; Huang, L.; Zhang, Y.; Zhou, M.; Chen, M.; et al. Gut Microbiota Mediates the Protective Effects of Dietary Capsaicin against Chronic Low-Grade Inflammation and Associated Obesity Induced by High-Fat Diet. MBio 2017, 8, e00470-17.
23. Bauer, K.C.; Huus, K.E.; Finlay, B.B. Microbes and the mind: Emerging hallmarks of the gut microbiota-brain axis. Cell Microbiol. 2016, 18, 632–644.
24. Cai, Z.; Hussain, M.D.; Yan, L.J. Microglia, neuroinflammation, and beta-amyloid protein in Alzheimer’s disease. Int. J. Neurosci. 2014, 124, 307–321.
25. Zhang, X.; Zhang, G.; Zhang, H.; Karin, M.; Bai, H.; Cai, D. Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energy imbalance and obesity. Cell 2008, 135, 61–73.
26. Ganong, W.F. Circumventricular organs: Definition and role in the regulation of endocrine and autonomic function. Clin. Exp. Pharm. Physiol. 2000, 27, 422–427.
27. Mullier, A.; Bouret, S.G.; Prevot, V.; Dehouck, B. Differential distribution of tight junction proteins suggests a role for tanycytes in blood-hypothalamus barrier regulation in the adult mouse brain. J. Comp. Neurol. 2010, 518, 943–962.
28. Rodriguez, E.M.; Blazquez, J.L.; Guerra, M. The design of barriers in the hypothalamus allows the median eminence and the arcuate nucleus to enjoy private milieus: The former opens to the portal blood and the latter to the cerebrospinal fluid. Peptides 2010, 31, 757–776.
29. Buckman, L.B.; Hasty, A.H.; Flaherty, D.K.; Buckman, C.T.; Thompson, M.M.; Matlock, B.K.; Weller, K.; Ellacott, K.L. Obesity induced by a high-fat diet is associated with increased immune cell entry into the central nervous system. Brain Behav. Immun. 2014, 35, 33–42.
30. Hsuchou, H.; Kastin, A.J.; Mishra, P.K.; Pan, W. C-reactive protein increases BBB permeability: Implications for obesity and neuroinflammation. Cell Physiol. Biochem. 2012, 30, 1109–1119.

31. Stranahan, A.M.; Hao, S.; Dey, A.; Yu, X.; Baban, B. Blood-brain barrier breakdown promotes macrophage infiltration and cognitive impairment in leptin receptor-deficient mice. J. Cereb. Blood Flow Metab. 2016, 36, 2108–2121.
32. Nerurkar, P.V.; Johns, L.M.; Buesa, L.M.; Kipyakwai, G.; Volper, E.; Sato, R.; Shah, P.; Feher, D.; Williams, P.G.; Nerurkar, V.R. Momordica charantia (bitter melon) attenuates high-fat diet-associated oxidative stress and neuroinflammation. J. Neuroinflammation 2011, 8, 64.
33. Chang, H.C.; Tai, Y.T.; Cherng, Y.G.; Lin, J.W.; Liu, S.H.; Chen, T.L.; Chen, R.M. Resveratrol attenuates high-fat diet-induced disruption of the blood-brain barrier and protects brain neurons from apoptotic insults. J. Agric. Food Chem. 2014, 62, 3466–3475.
34. Elahy, M.; Lam, V.; Pallebage-Gamarallage, M.M.; Giles, C.; Mamo, J.C.; Takechi, R. Nicotine Attenuates Disruption of Blood-Brain Barrier Induced by Saturated-Fat Feeding in Wild-Type Mice. Nicotine Tob. Res. 2015, 17, 1436–1441.
35. Kanoski, S.E.; Zhang, Y.; Zheng, W.; Davidson, T.L. The effects of a high-energy diet on hippocampal function and blood-brain barrier integrity in the rat. J. Alzheimers Dis. 2010, 21, 207–219.
36. Douglass, J.D.; Dorfman, M.D.; Fasnacht, R.; Shaffer, L.D.; Thaler, J.P. Astrocyte IKKbeta/NF-kappaB signaling is required for diet-induced obesity and hypothalamic inflammation. Mol. Metab. 2017, 6, 366–373.
37. Valdearcos, M.; Robblee, M.M.; Benjamin, D.I.; Nomura, D.K.; Xu, A.W.; Koliwad, S.K. Microglia dictate the impact of saturated fat consumption on hypothalamic inflammation and neuronal function. Cell Rep. 2014, 9, 2124–2138.
38. Borg, M.L.; Omran, S.F.; Weir, J.; Meikle, P.J.; Watt, M.J. Consumption of a high-fat diet, but not regular endurance exercise training, regulates hypothalamic lipid accumulation in mice. J. Physiol. 2012, 590, 4377–4389.
39. Thaler, J.P.; Choi, S.J.; Schwartz, M.W.; Wisse, B.E. Hypothalamic inflammation and energy homeostasis: Resolving the paradox. Front. Neuroendocr. 2010, 31, 79–84.
40. Andre, C.; Guzman-Quevedo, O.; Rey, C.; Remus-Borel, J.; Clark, S.; Castellanos-Jankiewicz, A.; Ladeveze, E.; Leste-Lasserre, T.; Nadjar, A.; Abrous, D.N.; et al. Inhibiting Microglia Expansion Prevents Diet-Induced Hypothalamic and Peripheral Inflammation. Diabetes 2017, 66, 908–919.
41. Tang, Y.; Le, W. Differential Roles of M1 and M2 Microglia in Neurodegenerative Diseases. Mol. Neurobiol. 2016, 53, 1181–1194.
42. Kigerl, K.A.; de Rivero Vaccari, J.P.; Dietrich, W.D.; Popovich, P.G.; Keane, R.W. Pattern recognition receptors and central nervous system repair. Exp. Neurol. 2014, 258, 5–16.

43. Valdearcos, M.; Xu, A.W.; Koliwad, S.K. Hypothalamic inflammation in the control of metabolic function. Annu. Rev. Physiol. 2015, 77, 131–160.
44. Buttini, M.; Limonta, S.; Boddeke, H.W. Peripheral administration of lipopolysaccharide induces activation of microglial cells in rat brain. Neurochem. Int. 1996, 29, 25–35.
45. Garcia-Bueno, B.; Serrats, J.; Sawchenko, P.E. Cerebrovascular cyclooxygenase-1 expression, regulation, and role in hypothalamic-pituitary-adrenal axis activation by inflammatory stimuli. J. Neurosci. 2009, 29, 12970–12981.
46. Shih, R.H.; Wang, C.Y.; Yang, C.M. NF-kappaB Signaling Pathways in Neurological Inflammation: A Mini Review. Front. Mol. Neurosci. 2015, 8, 77.
47. Cintra, D.E.; Ropelle, E.R.; Moraes, J.C.; Pauli, J.R.; Morari, J.; Souza, C.T.; Grimaldi, R.; Stahl, M.; Carvalheira, J.B.; Saad, M.J.; et al. Unsaturated fatty acids revert diet-induced hypothalamic inflammation in obesity. PLoS ONE 2012, 7, e30571.
48. Wang, Y.; Qian, Y.; Fang, Q.; Zhong, P.; Li, W.; Wang, L.; Fu, W.; Zhang, Y.; Xu, Z.; Li, X.; et al. Saturated palmitic acid induces myocardial inflammatory injuries through direct binding to TLR4 accessory protein MD2. Nat. Commun. 2017, 8, 13997.
49. 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.; et al. Microglial Inflammatory Signaling Orchestrates the Hypothalamic Immune Response to Dietary Excess and Mediates Obesity Susceptibility. Cell Metab. 2017, 26, 185–197 e3.
50. Cope, E.C.; LaMarca, E.A.; Monari, P.K.; Olson, L.B.; Martinez, S.; Zych, A.D.; Katchur, N.J.; Gould, E. Microglia Play an Active Role in Obesity-Associated Cognitive Decline. J. Neurosci. 2018, 38, 8889–8904.
51. Butler, M.J.; Cole, R.M.; Deems, N.P.; Belury, M.A.; Barrientos, R.M. Fatty food, fatty acids, and microglial priming in the adult and aged hippocampus and amygdala. Brain Behav. Immun. 2020, 89, 145–158.
52. Hahm, J.R.; Jo, M.H.; Ullah, R.; Kim, M.W.; Kim, M.O. Metabolic Stress Alters Antioxidant Systems, Suppresses the Adiponectin Receptor 1 and Induces Alzheimer's Like Pathology in Mice Brain. Cells 2020, 9, 249.
53. Jin, S.; Kim, K.K.; Park, B.S.; Kim, D.H.; Jeong, B.; Kang, D.; Lee, T.H.; Park, J.W.; Kim, J.G.; Lee, B.J. Function of astrocyte MyD88 in high-fat-diet-induced hypothalamic inflammation. J. Neuroinflammation 2020, 17, 195.
54. Shi, H.; Wang, Q.; Zheng, M.; Hao, S.; Lum, J.S.; Chen, X.; Huang, X.F.; Yu, Y.; Zheng, K. Supplement of microbiota-accessible carbohydrates prevents neuroinflammation and cognitive decline by improving the gut microbiota-brain axis in diet-induced obese mice. J. Neuroinflammation 2020, 17, 77.

55. Kim, J.D.; Yoon, N.A.; Jin, S.; Diano, S. Microglial UCP2 Mediates Inflammation and Obesity Induced by High-Fat Feeding. Cell Metab. 2019, 30, 952–962 e5.
56. Robison, L.S.; Gannon, O.J.; Thomas, M.A.; Salinero, A.E.; Abi-Ghanem, C.; Poitelon, Y.; Belin, S.; Zuloaga, K.L. Role of sex and high-fat diet in metabolic and hypothalamic disturbances in the 3xTg-AD mouse model of Alzheimer's disease. J. Neuroinflammation 2020, 17, 285.
57. Shi, H.; Yu, Y.; Lin, D.; Zheng, P.; Zhang, P.; Hu, M.; Wang, Q.; Pan, W.; Yang, X.; Hu, T.; et al. beta-glucan attenuates cognitive impairment via the gut-brain axis in diet-induced obese mice. Microbiome 2020, 8, 143.
58. Park, J.H.; Ahn, J.H.; Song, M.; Kim, H.; Park, C.W.; Park, Y.E.; Lee, T.K.; Lee, J.C.; Kim, D.W.; Lee, C.H.; et al. A 2-Min Transient Ischemia Confers Cerebral Ischemic Tolerance in Non-Obese Gerbils, but Results in Neuronal Death in Obese Gerbils by Increasing Abnormal mTOR Activation-Mediated Oxidative Stress and Neuroinflammation. Cells 2019, 8, 1126.
59. Kelley, N.; Jeltema, D.; Duan, Y.; He, Y. The NLRP3 Inflammasome: An Overview of Mechanisms of Activation and Regulation. Int. J. Mol. Sci. 2019, 20, 3328.
60. He, W.T.; Wan, H.; Hu, L.; Chen, P.; Wang, X.; Huang, Z.; Yang, Z.H.; Zhong, C.Q.; Han, J. Gasdermin D is an executor of pyroptosis and required for interleukin-1beta secretion. Cell Res. 2015, 25, 1285–1298.
61. Lamkanfi, M.; Dixit, V.M. Inflammasomes and their roles in health and disease. Annu. Rev. Cell Dev. Biol. 2012, 28, 137–161.
62. de Rivero Vaccari, J.P.; Dietrich, W.D.; Keane, R.W. Activation and regulation of cellular inflammasomes: Gaps in our knowledge for central nervous system injury. J. Cereb. Blood Flow Metab. 2014, 34, 369–375.
63. Jorquera, G.; Russell, J.; Monsalves-Alvarez, M.; Cruz, G.; Valladares-Ide, D.; Basualto-Alarcon, C.; Barrientos, G.; Estrada, M.; Llanos, P. NLRP3 Inflammasome: Potential Role in Obesity Related Low-Grade Inflammation and Insulin Resistance in Skeletal Muscle. Int. J. Mol. Sci. 2021, 22, 3254.
64. Man, S.M.; Kanneganti, T.D. Regulation of inflammasome activation. Immunol. Rev. 2015, 265, 6–21.
65. Rajamaki, K.; Lappalainen, J.; Oorni, K.; Valimaki, E.; Matikainen, S.; Kovanen, P.T.; Eklund, K.K. Cholesterol crystals activate the NLRP3 inflammasome in human macrophages: A novel link between cholesterol metabolism and inflammation. PLoS ONE 2010, 5, e11765.
66. Giordano, A.; Murano, I.; Mondini, E.; Perugini, J.; Smorlesi, A.; Severi, I.; Barazzoni, R.; Scherer, P.E.; Cinti, S. Obese adipocytes show ultrastructural features of stressed cells and die of pyroptosis. J. Lipid Res. 2013, 54, 2423–2436.

67. Rheinheimer, J.; de Souza, B.M.; Cardoso, N.S.; Bauer, A.C.; Crispim, D. Current role of the NLRP3 inflammasome on obesity and insulin resistance: A systematic review. Metabolism 2017, 74, 1–9.
68. Barra, N.G.; Henriksbo, B.D.; Anhe, F.F.; Schertzer, J.D. The NLRP3 inflammasome regulates adipose tissue metabolism. Biochem. J. 2020, 477, 1089–1107.
69. Schroder, K.; Zhou, R.; Tschopp, J. The NLRP3 inflammasome: A sensor for metabolic danger? Science 2010, 327, 296–300.