Neuroendocrinology

Neuroendocrinology , DOI: 10.1159/000524059
Received: December 22, 2021
Accepted: March 2, 2022
Published online: March 11, 2022

Insulin resistance in the brain: Evidence supporting a role for inflammation, reactive microglia, and the impact of biological sex

Doust YV, Sumargo N, Ziebell JM, Premilovac D

ISSN: 0028-3835 (Print), eISSN: 1423-0194 (Online)
https://www.karger.com/NEN
Neuroendocrinology

Insulin resistance in the brain: Evidence supporting a role for inflammation, reactive microglia, and the impact of biological sex

Yasmine V. Doust[a], Nicole Sumargo[b], Jenna M. Ziebell[a]* and Dino Premilovac[b]*

*To be considered as co-senior authors.

[a] Wicking Dementia Research and Education Centre, College of Health and Medicine, University of Tasmania, Hobart, Tasmania, Australia
[b] Tasmanian School of Medicine, College of Health and Medicine, University of Tasmania, Hobart, Tasmania, Australia

Short Title: Inflammation in the development of obesity and insulin resistance

Corresponding Author:
Full name: Dino Premilovac
Department: Tasmanian School of Medicine
Institute/University/Hospital: University of Tasmania
Street Name & Number: 17 Liverpool Street
City, State, Postal code, Country: Hobart, Tasmania, 7001, Australia.
Tel: +61 3 6226 2701
E-mail: dino.premilovac@utas.edu.au

Number of Tables: 0
Number of Figures: 2
Word count: 4504
Keywords: obesity, microglia, inflammation, sex differences, insulin, insulin resistance

Abstract
Increased intake of highly processed, energy-dense foods combined with a sedentary lifestyle are helping fuel the current overweight and obesity crisis, which is more prevalent in women than in men. Although peripheral organs such as adipose tissue contribute to the physiological development of obesity, emerging work aims to understand the role of the central nervous system to whole body energy homeostasis and development of weight gain and obesity. The present review discusses the impact of insulin, insulin resistance, free fatty acids, and inflammation on brain function and how these differ between the males and females in the context of obesity. We highlight the potential of microglia, the resident immune cells in the brain, as mediators of neuronal insulin resistance that drive reduced satiety, increased food intake and thus, obesity.

The silent obesity crisis

It is estimated that 2.1 billion people around the world are overweight or obese [1]. Although genetic predisposition makes individuals and/or ethnicities more prone to obesity, weight gain is promoted by overconsumption of highly processed, energy-dense foods, increasingly sedentary lifestyle as well as physiological changes in whole body function [2]. Although obesity can occur at any age, studies report that obesity prevalence has increased in adults and children of all ages, indiscriminate of geographical location, ethnicity, or socioeconomic status [2][3]. Worldwide, the proportion of overweight individuals between the biological sexes is similar [2], but obesity is more prevalent in females (15%) than males (11%). Currently, it is projected that one-fifth of adults around the world will be obese by 2025 [4]. This is concerning as obesity adversely affects nearly all physiological functions in the body and is a major risk factor for developing diabetes, cardiovascular disease, and neurological diseases such as dementia [4]. We know that environmental factors such as socioeconomic status influence the prevalence of obesity, but the underlying pathophysiological mechanisms that drive continued weight gain in obesity remain to be fully understood, particularly with respect to impact of biological sex. Understanding the biological mechanisms that promote weight gain and how these differ between males and females is pivotal to developing ways of reducing the burden of obesity and associated disorders.

Biological sex differences in metabolism and insulin sensitivity

It is not clear why biological sex determines susceptibility to obesity, but differences in body morphology as well as the site and storage of energy within adipose tissue have been identified as potential factors. Epidemiological and clinical studies show that despite a lower percentage of overall obesity, the prevalence of abdominal adiposity and insulin resistance is higher in males [5, 6]. Differences in the susceptibility to insulin resistance between sexes may be due to higher whole-body insulin sensitivity in females thus providing a larger buffer before insulin resistance manifests [7, 8]. Clinical data are consistent with rodent studies and demonstrate greater insulin sensitivity and reduced effectiveness of high fat diet-induced insulin resistance in females [9, 10]. The exact mechanisms responsible for biological sex differences in insulin sensitivity are not understood but some have linked this to differences in the absolute amount and pattern of insulin secretion in response to stimulation (e.g., following a meal) [11]. Although some studies report no differences in insulin secretion between young males and females [11], others demonstrate females have higher first-phase insulin secretion [12, 13]. An increase in post-prandial insulin secretion and subsequent nutrient uptake into insulin-sensitive tissues may account for some of the discrepancies in metabolism between males and females. Different levels of glucose-mediated insulin secretion between males and females may be due to differences in beta cells mitochondrial function or dimorphic effects of sex hormones on beta cell function [14]. Studies using aged rats on a high-fat diet have shown that there is an increase in mitochondrial biogenesis (numbers) and function (ATP and O_2 consumption) in females, but not males, which can enhance insulin secretion [14]. This additional insulin-producing capacity may explain why females are more likely to have improved glucose handling despite increased fat intake compared with males. Sex hormones are also known modulators of insulin release from beta cells (reviewed in [15]). In females, estrogen acts via Src or ERK signalling hubs to enhance insulin secretion and promote pancreatic beta cell survival [15]. In addition, variations in pancreatic insulin mRNA levels and serum insulin levels have been observed during the estrous cycle, suggesting that sex steroid hormones could modulate insulin secretion. In males, testosterone acts on beta cell (via the androgen receptor) to enhance glucose-stimulated insulin secretion by potentiating the insulinotropic action of glucagon-like peptide-1[16]. These studies indicate that even though males and females both release insulin after a meal, the underlying mechanisms differ depending on the status of testosterone and estrogen in males and females. Although a growing body of literature is emerging in this space, the exact mechanisms that determine differences in insulin sensitivity between the biological sexes remain to be determined.

Obesity, insulin resistance and inflammation – biological sex matters

Once released into the blood stream, insulin acts as a master-metabolic regulator that stimulates nutrient uptake and storage within insulin-sensitive tissues such as skeletal muscles, the liver and adipose tissue via the IRS-1/PI3K/Akt pathway (reviewed in [17]). How much insulin is released into the blood stream is tightly coupled to blood glucose concentrations, thus enabling exquisite control of glucose homeostasis at any given time. Obesity is the major risk factor for developing insulin resistance – a condition where the body becomes less sensitive to the actions of insulin [18-21, 17, 22]. From a metabolic perspective, insulin resistance leads to reduced insulin-mediated suppression of hepatic glucose output as well as reduced insulin-mediated glucose uptake by skeletal muscle and adipose tissue [18, 21]. To compensate for this, the pancreatic beta cells produce more insulin to achieve glucose homeostasis [19, 17]. The need for additional insulin leads to a state of chronic hyperinsulinemia and if allowed to continue, eventually leads to pancreatic beta cell exhaustion, loss of insulin production and thus chronic hyperglycaemia – the characteristic feature of type 2 diabetes [19, 17]. Although this pathophysiological process is generally accepted in the literature (reviewed here [19, 17]), the specific mechanisms that contribute to the initiation and progression of insulin resistance in obesity remain a point of contention [23, 17, 24]. Despite this, the role of increased circulating free fatty acids and altered adipose tissue physiology appear to be common threads linking obesity with multi-organ insulin resistance, including the central nervous system (CNS) [25]. Importantly, the location of adipose tissue depot that expands during obesity confers either protection or deterioration of insulin sensitivity.

It is generally well accepted that accumulation of visceral adipose tissue is detrimental, and that subcutaneous adipose expansion is protective with respect to insulin sensitivity (reviewed in [26]). Subcutaneous and visceral adipose depots display an array of differences including developmental lineage [27, 28] and metabolic characteristics [29, 30]. An increase in expression of pro-inflammatory genes is also evident in visceral adipose tissue compared with subcutaneous depots along with a reduction in genes related to insulin signalling and lipid synthesis [31, 30]. Additionally, adipokine secretion profiles differ between visceral and subcutaneous depots [32, 33]. Visceral adipose secretes a greater amount of pro-inflammatory cytokines (IL-6 and IL-8) as well as a lower amount of adiponectin and leptin compared with subcutaneous adipose tissue which contributes toward a reduction in insulin sensitivity and lipid metabolism [32, 33]. Males preferentially accumulate visceral adipose tissue, while premenopausal females accumulate more subcutaneous adipose tissue [34]. Experimental models support this dichotomy and report that female mice gain weight when fed a high fat diet, however, males gain more weight and fat mass compared to their female counterparts on the same high fat diet [35-37]. Studies have shown male mice develop hyperinsulinaemia, hyperglycaemia, and hypercholesterolaemia after 8 – 11 months on high fat diet, whereas female mice showed little to no evidence of the same metabolic disturbances [38]. However, others have shown that risk of developing cardiovascular consequences after high fat diet for 6 months is similar between male and female mice suggesting that obesity impairs cardiovascular function in both males and females but the underlying mechanisms are likely to be sex-specific [39]. In humans, these patterns of adipose distribution result in characteristically female pear-shaped obesity and male apple-shaped obesity (shown in Fig. 1) [40]. In postmenopausal females, adipose distribution shifts toward a male-like pattern, implicating sex hormones in maintaining a balance between subcutaneous and visceral depot mass [34]. Importantly, the cellular and molecular mechanisms underlying differential adipose distribution in males and females remain to be determined. However, the differences in adipose distribution between males and females have been correlated with sex hormones (reviewed in [41]). Estrogen has been reported to increase on high fat diet which promotes the accumulation of subcutaneous adipose tissue [41]. Whilst testosterone has been documented to become reduced in males on high fat diet which promotes visceral adipose deposition [41]. In addition to this, genes expressed on the X chromosome are also associated with adiposity control between sexes [42]. Studies using mouse models have also shown that visceral adipocyte proliferation, known as hyperplasia, occurs in male mice after 8-weeks on high fat diet,

whilst female mice exhibit both visceral and subcutaneous adipocyte hyperplasia [43]. However, in ovariectomised female mice, 8-weeks of high fat diet feeding leads to primarily visceral adipocyte hyperplasia, similar to male mice. Transplant of visceral or subcutaneous adipose tissue from male mice on high fat diet into visceral adipose depot of recipient male mice on high fat diet induces adipocyte hyperplasia of both the visceral and subcutaneous adipose that had been transplanted [43]. These results indicate that intrinsic cellular differences in adipocytes between visceral or subcutaneous depots may not influence how adipocytes respond to high fat diet, but rather, the microenvironment and thus function of the distinct depots.

A key driver of obesity-driven pathophysiology may be altered immune system function in both the periphery and CNS [44]. Visceral adipose tissue, which occurs predominantly in males, secretes large amounts of pro-inflammatory cytokines and free fatty acids and has been linked to the development of obesity-induced cardiovascular events [45, 44]. Dietary factors such as free fatty acids can activate toll-like receptor 4 (TLR4) on peripheral immune cells and initiate inflammatory cascades [45, 44]. Adipose tissue expansion, particularly visceral, causes macrophage recruitment and release of pro-inflammatory cytokines into the bloodstream [46] leading to low-grade systemic inflammation [47, 48]. Increased pro-inflammatory cytokines can have downstream effects on the liver and muscle insulin signalling, thus, contributing to systemic insulin resistance [19]. Free fatty acids have also been shown to induce endothelial "nod-like" receptor protein 3 (NLRP3) inflammasome activation along with the release of pro-inflammatory cytokines and production of reactive oxygen species that are reported to disrupt the blood brain barrier (BBB) and thus contribute to altered CNS function [49-53]. Furthermore, immune cells and adipose tissue have been shown to share intracellular signalling pathways, such as peroxisome proliferator-activated receptors (PPARs), which act to modulate the expression of genes related to glucose and lipid metabolism as well as proliferation and inflammation (reviewed in [54, 55]). Activation of PPARs promotes secretion of adiponectin by adipose as well as anti-inflammation by immune cells which acts to promote insulin sensitivity and lipid metabolism. A reduction in PPARs has been reported in obese children [56] and treatment with PPAR agonists in obese adult males [57] and mouse models has shown to improve lipid and glucose metabolism as well as resolve insulin resistance but enhances subcutaneous weight gain [58]. These results indicate that both immune cells and adipose tissue share intracellular signalling pathways that may be underlying obesity pathophysiology. Increasing literature demonstrates sexual dichotomy in the immune response to stimuli, such as exposure to lipopolysaccharide (LPS), in both the periphery and CNS, which may also influence the obesity-induced inflammatory response [59, 60]. During development, males tend to have greater immune reactivity compared with females, however, the opposing trend occurs in adulthood where females exhibit greater immune reactivity compared with males ([59, 60]). The expression of PPARs in T cells also has sex-specific functions in humans and mouse models, where interferon gamma production was promoted in males and the production of IL-17a was promoted in females [61]. Overall, these results suggest that sex differences in the immune system could be driving the sex differences in obesity pathophysiology and, thus, incidence of obesity. The amount of pro-inflammatory cytokines and chemokines in the brain has been shown in mouse models to be most strongly correlated with the amount of LPS in the blood, compared with peripheral cytokines and chemokines [60], suggesting that immune cells in the CNS can drive the systemic inflammatory response to LPS, which has implications for systemic inflammation that occurs in obesity. Recent work also demonstrates the presence of both afferent and efferent neural innervation of adipose tissue [62-64], suggesting the control of adipose tissue expansion and function may be linked to changes in the CNS and vice-versa. Whether this adipose-CNS crosstalk is influenced by inflammation, how this differs between the biological sexes and how this contributes to obesity and insulin resistance is not well understood.

Insulin and insulin resistance in the CNS

In the cerebrospinal fluid, insulin concentrations are ~25% of those in the blood and increase proportionally after eating or with peripheral insulin infusion [65]. This suggests that a fraction of

plasma insulin can cross the BBB via a saturable transport process, likely through interactions with the insulin receptor on the microvascular endothelium [66] and/or other saturable transport processes [67]. In rodents, insulin receptor distribution is widespread throughout the CNS with the highest expression in the olfactory bulb, cortex, hippocampus, hypothalamus and cerebellum and relatively lower levels in the midbrain, striatum, and brainstem [68-70]. Although insulin access to the brain parenchyma is tightly controlled by the BBB in almost all regions of the brain, sensory circumventricular organs that surround the third and fourth ventricles lack a classic BBB and allow more passive movement of bloodborne factors such as insulin into the brain [71-73]. This is critical because it allows agouti-related protein (AgRP) and proopiomelanocortin (POMC) neurons in the nucleus tractus solitarii (NTS) and hypothalamus to have privileged access to detect nutrient and insulin concentrations in the blood at any given time [74]. Indeed, studies have shown rapid activation of IRS-1/PI3K/Akt signalling in AgRP/POMC neurons after peripheral insulin injection [75]. Although the exact neuronal circuitry and glial cell contributions remain to be determined, recent advances in the field highlight the complex interplay between insulin and leptin (adipose tissue derived hormone) in the regulation of feeding behaviour and metabolic homeostasis in otherwise healthy or obese male mice [76, 77]. Furthermore, the activation of NMDA receptors on NTS neurons by insulin has been demonstrated to feed input into the hypothalamus which is required to lower glucose production by the liver as well as reduce feeding behaviour [78, 79]. Therefore, current literature indicates that NTS and hypothalamic neurons appear to mediate insulin's ability to control whole body energy homeostasis and feeding behaviour.

Beyond hypothalamic neurons, it is becoming increasingly recognised that almost all neurons are insulin sensitive and neuronal insulin signalling primarily involves the phosphorylation and activation of the IRS-1/PI3K/Akt cascade in addition to MAPK/ERK pathways [80]. In turn, these cascades targets multiple downstream pathways, including mammalian target of rapamycin complex 1 (mTORC1), glycogen synthase kinase 3 beta (GSK3b), and the forkhead box protein O1 (FoxO) family of transcription factors [80] – pathways that play pivotal roles in normal brain function. For instance, mTORC1-mediated protein synthesis is important for synaptic plasticity [81] and the regulation of autophagy, a major mechanism to degrade misfolded proteins and damaged organelles in neurons [82]. Dysregulation of mTORC1-dependent autophagy in neurons results in neuronal cell death and the onset of neurodegenerative diseases, which can occur as a consequence of obesity [82]. GSK3b regulates multiple aspects of neuronal functioning, including neural progenitor cell proliferation, neuronal polarity, and neuroplasticity [83]. GSK3b can also phosphorylate tau proteins, a process involved in the pathogenesis of Alzheimer disease [84, 85]. Brain-specific knockout of the insulin receptor or IRS-2 results in decreased GSK3b activity and increased tau phosphorylation [86, 87]. FoxO transcription factors also play diverse and important roles in the CNS, including controlling energy homeostasis and leptin sensitivity, as well as locomotor activity [88, 89]. In addition to the IRS-1/PI3K/Akt cascade, insulin also stimulates activation of the MAPK pathway in neurons which contributes to neuronal function and survival in addition to playing a direct role in proliferation, differentiation, gene expression, and cytoskeletal reorganization [90]. Therefore, mounting evidence suggests that insulin may act on most neurons and can have a diverse array of effects beyond metabolism alone.

As in peripheral tissues, it is now widely appreciated that neurons, in particular hypothalamic neurons, develop insulin resistance [91-93]. However, the extent to which CNS insulin resistance contributes to the systemic perturbations in glucose metabolism in humans has remained contentious and whether this is different between the biological sexes remains unknown [94, 95]. In rodent studies, high fat diet feeding drives sex-dependent changes in hypothalamic genes where female mice exhibit changes in expression of epithelial cell related genes such as Epcam, Cldn5 and claudin 5, whilst males exhibited an increase in pro-inflammatory genes including COX2, MerTK, CD86 and CD163 [96]. Evidence from such rodent studies suggests that hypothalamic inflammation, unlike peripheral inflammation, occurs within hours of high-fat diet prior to any weight gain [97]. Beyond the hypothalamus, studies in mice have demonstrated that high fat diet-driven inflammation

occurs across multiple regions of the brain including the cortex and hippocampus which can impact many CNS functions including cognitive function and memory [98, 99]. Therefore, brain inflammation and neuronal insulin resistance appear to manifest early after high fat diet intake and occur before any changes in body weight/composition are evident. While the mechanisms that cause neuronal changes remain to be determined, emerging research indicates glial cells as potential mediators of CNS inflammation and insulin resistance during high fat diet intake.

Insulin and insulin resistance in astrocytes

While most of the work thus far has focussed on insulin's effects in neurons, insulin signalling in glial cells is an emerging area of research with a predominant focus on astrocytes and microglia. Astrocytes perform numerous vital functions such as the regulation of synaptic transmission and their location at the interface between blood vessels and neurons makes them essential for the supply of blood-derived metabolic cues into the parenchyma [100, 101]. In the hypothalamus, astrocytes express insulin receptors and control glucose-induced activation of POMC neurons via the IRS-1/PI3K/Akt cascade [100]. Hypothalamic astrocytes are also regulators of both central and peripheral response to glucose availability and play a key role in glucose transport through the BBB [102, 100]. Both female and male mice constitutively lacking insulin receptors in astrocytes exhibit delayed puberty, hypothalamic-pituitary-gonadotropin axis dysfunction and reduced fertility [103]. Mice with postnatal ablation of the insulin receptor in astrocytes show excessive re-feeding after an overnight fast [104]. In addition, female mice lacking the insulin receptor specifically in astrocytes exhibit reduced preference for sucrose [105]. These findings suggest insulin has multiple CNS effects mediated by astrocytes that are important in many homeostatic functions. Recent work highlights that the release of saturated free fatty acids by astrocytes following CNS damage or disease can cause neuronal death [106]. Why astrocytes release neurotoxic free fatty acids into the brain parenchyma is not clear but appears to involve TLR4-mediated microglial activation [107]. Whether release of toxic free fatty acids from astrocytes is exacerbated in the obese, insulin resistant brain to drive chronic microglial activation is not known.

Insulin and insulin resistance in microglia

Microglia are the resident immune cell in the CNS and have long processes, which they continuously extend and retract to scan their environment. Beyond immune activities in the CNS, microglia also have important functions in brain physiology and contribute to learning and memory [108], trophic neuronal support, synaptic pruning and homeostatic support for living neurons, which is crucial for the neural circuit remodelling and synaptic plasticity [109]. Loss of these homeostatic microglial functions is commonly reported with ageing and in neurodegenerative disease, such as Alzheimer's Disease and this is proposed to be further disturbed by obesity [110]. Recent evidence indicates that microglia also express insulin receptors and are insulin responsive, *in vitro,* such that insulin induces the activation of IRS-1/PI3K/Akt signalling pathway to increase the phagocytic activity of microglia when exposed to a pro-inflammatory stimulus such as lipopolysaccharide (LPS) [102, 111]. *In vivo*, insulin persistently activates microglia and increases COX-2/ IL-1β expression in the hippocampus of young, but not aged male rats [112]. These data suggest that insulin is able to alter microglial physiology and that excessive insulin signalling may lead to a pro-inflammatory microglial phenotype. Insulin's effects in the CNS may become even more important in presence of obesity and peripheral inflammation since these alter BBB permeability and thus enhance insulin transport into the brain [113]. This sustained influx of insulin into the brain in obesity may be contributing toward insulin resistance in neurons (potentially via insulin receptor desensitization), which has been recently proposed to occur with aging [114, 115]. Lastly, peripheral immune cells chronically exposed to insulin can become insulin-resistant and exhibit altered inflammatory profiles [116]. Whether microglia become insulin resistant and how a loss of normal insulin action impacts microglial activity is now known.

In a diet-induced model of obesity in rodents, systemic low-grade inflammation was reported to be associated with increased microglial synaptic pruning and thus reduced cognitive function [117, 118]. Whether microglial-mediated synaptic pruning contributes to the specific hypothalamic neuronal dysfunction observed in obesity is not known. However, observations in the *db*/*db* mouse model (leptin receptor mutation leading to obesity) suggest that neuronal synaptic plasticity in the hypothalamus [119, 120], and hypothalamic microglia present with reduced expression of phagocytic marker CD68 [121]. Furthermore, microglial activation in the arcuate nucleus (ARC) of the hypothalamus has been observed as early as 3-days on high fat diet [122]. This occurred prior to weight gain and as accompanied with an increase in uncoupling protein 2 (UCP2) mRNA, a reduction in synapses on ARC POMC neurons and astrogliosis [122]. When UCP2 was genetically deleted in mice using an inducible model, microglial activation was attenuated with an increase in excitatory inputs on POMC neurons. In turn, this protected against diet-induced obesity in both male and female mice despite the continued presence of astrogliosis in these mice [122]. Therefore, microglia and astrocytes become activated in the hypothalamus during diet-induced obesity, even prior to weight gain. However, only microglial activation was associated with changes to neuronal circuitry organisation involved with feeding behaviour and energy homeostasis. These findings suggest that aberrant microglial activity is an early driver of hypothalamic dysfunction and has implications for feeding behaviour and whole-body energy homeostasis.

Under homeostatic conditions microglia dynamically interact with various components of the CNS including neurons, astrocytes, blood vessels and other glia [123, 124]. When homeostasis is disturbed, microglia become reactive and produce inflammatory cascades to allow for microglial proliferation and migration, recruitment of additional immune cells, and increased phagocytotic activity [125-127]. Importantly, ablation of microglia leads to dramatic weight loss largely accounted for by an acute reduction in food intake in otherwise healthy male rats [128]. Similarly, treating male mice with an inhibitor of microglia (PLX5622) or deleting inhibitor of NF-κB kinase subunit b (IKβKβ) in microglia reduces diet-induced obesity susceptibility [129]. It should be noted, however, that the beneficial effects of genetic and pharmacological manipulation of microglial functions in obesity were demonstrated in male rodents only and whether these effects are also present in females needs to be determined. This is important to highlight given that microglia possess sexually dimorphic roles in the developing, adult, and aged brain as well as in neurological conditions such as autism and traumatic brain injury [130-132]. Thus, biological sex may influence the microglial response to various stimuli and, hence, how microglia respond to insulin, insulin resistance and obesity. Increasing research indicates that microglia are sensitive to changes in lipid profile in the CNS. Therefore, differences in adipose tissue expansion between males and females may alter the species of lipids present in the CNS and thus account for some of the different microglial activities and thus inflammation observed between the sexes.

Could increased fatty acids and insulin be the trigger for microglial dysfunction that drives obesity?

Obesity is associated with chronic dyslipidaemia and hyperinsulinaemia [19, 133]. Circulating fatty acids are increased in obesity due to expansion of adipose tissue and increased rates of lipolysis due to adipocyte insulin resistance [133]. Certain species of fatty acids, such as palmitic and stearic acids, are immunogenic and can trigger peripheral inflammatory cascades initiated by TLR4 stimulation, releasing pro-inflammatory cytokines such as TNF-α as well as interleukin (IL)-1β and IL-6 [134, 135]. Chronic exposure to free fatty acids on high fat diet promotes endothelial dysfunction which increases BBB permeability [49, 50, 52, 53], allowing increased access of circulating factors, such as fatty acids and insulin to the brain parenchyma. Increased fatty acids in the CNS have been shown to cause insulin resistance [136] and activate microglia in a TLR4-dependent manner leading to increased production of proinflammatory cytokines (e.g., TNF-α) and reactive oxygen species [137-140] (shown in Fig. 2). Increased BBB permeability also increases access of circulating proinflammatory cytokines to the CNS thus forming a chronic, toxic environment for neurons [141-145]. Indeed, studies show that acute high fat feeding in rodents quickly activates inflammatory

responses in the CNS and these impairs CNS insulin signalling prior to any weight gain [146, 97, 147, 139]. It is worth noting that studies have reported increased expression of pro-inflammatory genes specifically in male mice given a high fat diet with no changes noted in female mice [96]. The discrepancy in immune system activation between the biological sexes may partially explain the accelerated metabolic dysfunction seen in obese males compared with obese females.
As noted previously, insulin has also been demonstrated to induce microglia reactivity and trigger the release of pro-inflammatory cytokines [112]. Hyperinsulinaemia, as seen following high fat diet intake [18, 148], may provide another stimulus to further drive microglia toward a proinflammatory state in obesity. In turn, increased microglial production of cytokines such as TNF-α, which inhibits insulin receptor signalling at very low concentrations [149], provides a mechanism where microglia can directly inhibit neuronal insulin signalling. The impact of reduced insulin signalling on brain function as a whole is poorly understood but has been linked with cognitive impairment and Alzheimer's disease [87, 150, 139, 145]. In the hypothalamus, insulin resistance in AgRP and POMC neurons leads to loss of whole-body energy homeostasis and obesity by driving alterations in feeding behaviour and glucose metabolism in addition to increased lipolysis in adipose tissue as a result of insulin resistance in POMC, but not AgRP neurons [151]. These important studies indicate that CNS insulin resistance can drive changes in whole body energy homeostasis to fuel increased weight gain (shown in Fig. 2), which in turn can drive further CNS insulin resistance.

Summary

To better deal with the growing obesity epidemic and associated metabolic disorders such as insulin resistance, there is an urgent need to better understand the role of the CNS in the regulation and dysregulation of energy homeostasis. The evidence above suggests microglia are highly sensitive to changes in whole body metabolism, becoming activated when exposed to increased free fatty acids and/or increased insulin. Thus, the combined effect of increased fatty acids and hyperinsulinaemia during obesity provides a mechanism where aberrant microglial activity impacts neuronal function in the hypothalamus, leading to impaired regulation of appetite/satiety and loss of energy homeostasis leading to further food intake (shown in Fig. 2). This results in further dysregulation of whole-body metabolism and promotes a positive feedback cycle where peripheral changes drive CNS changes that in turn drive further peripheral changes. Thus, modulation of microglial function could offer new approaches to interrupt this cycle to restore metabolic homeostasis and help mitigate obesity and its pathophysiological consequences.

Statements

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

Authors must give full details about the funding of any research relevant to their study, including sponsor names and explanations of the roles of these sources in the preparation of data or the manuscript.

Author Contributions

Dino Premilovac and Jenna Ziebell devised the concept of review. All authors contributed to a review of the current literature through database searches. Yasmine Doust, Nicole Sumargo, Jenna Ziebell and Dino Premilovac were responsible for the initial draft of manuscript. Dino Premilovac critically revised the draft. Yasmine Doust, Nicole Sumargo created the figures.

All authors have approved the final version of this manuscript.

References

1. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014 Aug 30;384(9945):766-81.
2. Chooi YC, Ding C, Magkos F. The epidemiology of obesity. Metabolism. 2019 Mar;92:6-10.
3. Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, Moodie ML, et al. The global obesity pandemic: shaped by global drivers and local environments. Lancet. 2011 Aug 27;378(9793):804-14.
4. Collaboration NCDRF. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet. 2016 Apr 2;387(10026):1377-96.
5. Kuhl J, Hilding A, Ostenson CG, Grill V, Efendic S, Bavenholm P. Characterisation of subjects with early abnormalities of glucose tolerance in the Stockholm Diabetes Prevention Programme: the impact of sex and type 2 diabetes heredity. Diabetologia. 2005 Jan;48(1):35-40.
6. Kautzky-Willer A, Harreiter J, Pacini G. Sex and Gender Differences in Risk, Pathophysiology and Complications of Type 2 Diabetes Mellitus. Endocr Rev. 2016 Jun;37(3):278-316.
7. Boyns DR, Crossley JN, Abrams ME, Jarrett RJ, Keen H. Oral glucose tolerance and related factors in a normal population sample. I. Blood sugar, plasma insulin, glyceride, and cholesterol measurements and the effects of age and sex. Br Med J. 1969 Mar 8;1(5644):595-8.
8. Hale PJ, Wright JV, Nattrass M. Differences in insulin sensitivity between normal men and women. Metabolism. 1985 Dec;34(12):1133-8.
9. Zierath JR, Houseknecht KL, Gnudi L, Kahn BB. High-fat feeding impairs insulin-stimulated GLUT4 recruitment via an early insulin-signaling defect. Diabetes. 1997 Feb;46(2):215-23.
10. Corsetti JP, Sparks JD, Peterson RG, Smith RL, Sparks CE. Effect of dietary fat on the development of non-insulin dependent diabetes mellitus in obese Zucker diabetic fatty male and female rats. Atherosclerosis. 2000 Feb;148(2):231-41.
11. Basu R, Dalla Man C, Campioni M, Basu A, Klee G, Toffolo G, et al. Effects of age and sex on postprandial glucose metabolism: differences in glucose turnover, insulin secretion, insulin action, and hepatic insulin extraction. Diabetes. 2006 Jul;55(7):2001-14.
12. Flanagan DE, Holt RI, Owens PC, Cockington RJ, Moore VM, Robinson JS, et al. Gender differences in the insulin-like growth factor axis response to a glucose load. Acta Physiol (Oxf). 2006 Jul;187(3):371-8.
13. Bock G, Dalla Man C, Campioni M, Chittilapilly E, Basu R, Toffolo G, et al. Effects of nonglucose nutrients on insulin secretion and action in people with pre-diabetes. Diabetes. 2007 Apr;56(4):1113-9.
14. Li T, Jiao W, Li W, Li H. Sex effect on insulin secretion and mitochondrial function in pancreatic beta cells of elderly Wistar rats. Endocr Res. 2016 Aug;41(3):167-79.
15. Ortiz-Huidobro RI, Velasco M, Larque C, Escalona R, Hiriart M. Molecular Insulin Actions Are Sexually Dimorphic in Lipid Metabolism. Front Endocrinol (Lausanne). 2021;12:690484.
16. Xu W, Morford J, Mauvais-Jarvis F. Emerging role of testosterone in pancreatic β cell function and insulin secretion. Journal of Endocrinology. 2019;240(3):R97-R105.
17. James DE, Stockli J, Birnbaum MJ. The aetiology and molecular landscape of insulin resistance. Nat Rev Mol Cell Biol. 2021 Nov;22(11):751-71.
18. Premilovac D, Bradley EA, Ng HL, Richards SM, Rattigan S, Keske MA. Muscle insulin resistance resulting from impaired microvascular insulin sensitivity in Sprague Dawley rats. Cardiovasc Res. 2013 Apr 1;98(1):28-36.
19. DeFronzo RA, Ferrannini E, Groop L, Henry RR, Herman WH, Holst JJ, et al. Type 2 diabetes mellitus. Nat Rev Dis Primers. 2015 Jul 23;1:15019.
20. Keske MA, Premilovac D, Bradley EA, Dwyer RM, Richards SM, Rattigan S. Muscle microvascular blood flow responses in insulin resistance and ageing. J Physiol. 2016 Apr 15;594(8):2223-31.
21. Russell RD, Hu D, Greenaway T, Blackwood SJ, Dwyer RM, Sharman JE, et al. Skeletal Muscle Microvascular-Linked Improvements in Glycemic Control From Resistance Training in Individuals With Type 2 Diabetes. Diabetes Care. 2017 Sep;40(9):1256-63.
22. Russell RD, Roberts-Thomson KM, Hu D, Greenaway T, Betik AC, Parker L, et al. Impaired postprandial skeletal muscle vascular responses to a mixed meal challenge in normoglycaemic people with a parent with type 2 diabetes. Diabetologia. 2021 Sep 29.

23. Defronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009 Apr;58(4):773-95.
24. Sylow L, Tokarz VL, Richter EA, Klip A. The many actions of insulin in skeletal muscle, the paramount tissue determining glycemia. Cell Metab. 2021 Apr 6;33(4):758-80.
25. Beddows CA, Dodd GT. Insulin on the brain: The role of central insulin signalling in energy and glucose homeostasis. J Neuroendocrinol. 2021 Apr;33(4):e12947.
26. Mittal B. Subcutaneous adipose tissue & visceral adipose tissue. Indian J Med Res. 2019 May;149(5):571-73.
27. Chau YY, Bandiera R, Serrels A, Martinez-Estrada OM, Qing W, Lee M, et al. Visceral and subcutaneous fat have different origins and evidence supports a mesothelial source. Nat Cell Biol. 2014 Apr;16(4):367-75.
28. Sanchez-Gurmaches J, Guertin DA. Adipocytes arise from multiple lineages that are heterogeneously and dynamically distributed. Nat Commun. 2014 Jun 19;5:4099.
29. Tran TT, Yamamoto Y, Gesta S, Kahn CR. Beneficial effects of subcutaneous fat transplantation on metabolism. Cell Metab. 2008 May;7(5):410-20.
30. Cohen P, Levy JD, Zhang Y, Frontini A, Kolodin DP, Svensson KJ, et al. Ablation of PRDM16 and beige adipose causes metabolic dysfunction and a subcutaneous to visceral fat switch. Cell. 2014 Jan 16;156(1-2):304-16.
31. Grove KL, Fried SK, Greenberg AS, Xiao XQ, Clegg DJ. A microarray analysis of sexual dimorphism of adipose tissues in high-fat-diet-induced obese mice. Int J Obes (Lond). 2010 Jun;34(6):989-1000.
32. Shi H, Seeley RJ, Clegg DJ. Sexual differences in the control of energy homeostasis. Front Neuroendocrinol. 2009 Aug;30(3):396-404.
33. Lagana AS, Vitale SG, Nigro A, Sofo V, Salmeri FM, Rossetti P, et al. Pleiotropic Actions of Peroxisome Proliferator-Activated Receptors (PPARs) in Dysregulated Metabolic Homeostasis, Inflammation and Cancer: Current Evidence and Future Perspectives. Int J Mol Sci. 2016 Jun 24;17(7).
34. Palmer BF, Clegg DJ. The sexual dimorphism of obesity. Mol Cell Endocrinol. 2015 Feb 15;402:113-9.
35. Yang Y, Smith DL, Jr., Keating KD, Allison DB, Nagy TR. Variations in body weight, food intake and body composition after long-term high-fat diet feeding in C57BL/6J mice. Obesity (Silver Spring). 2014 Oct;22(10):2147-55.
36. Dorfman MD, Krull JE, Douglass JD, Fasnacht R, Lara-Lince F, Meek TH, et al. Sex differences in microglial CX3CR1 signalling determine obesity susceptibility in mice. Nat Commun. 2017 Feb 22;8:14556.
37. Lainez NM, Jonak CR, Nair MG, Ethell IM, Wilson EH, Carson MJ, et al. Diet-Induced Obesity Elicits Macrophage Infiltration and Reduction in Spine Density in the Hypothalami of Male but Not Female Mice. Front Immunol. 2018;9:1992.
38. Hwang LL, Wang CH, Li TL, Chang SD, Lin LC, Chen CP, et al. Sex differences in high-fat diet-induced obesity, metabolic alterations and learning, and synaptic plasticity deficits in mice. Obesity (Silver Spring). 2010 Mar;18(3):463-9.
39. Bruder-Nascimento T, Ekeledo OJ, Anderson R, Le HB, Belin de Chantemele EJ. Long Term High Fat Diet Treatment: An Appropriate Approach to Study the Sex-Specificity of the Autonomic and Cardiovascular Responses to Obesity in Mice. Front Physiol. 2017;8:32.
40. Gesta S, Tseng YH, Kahn CR. Developmental origin of fat: tracking obesity to its source. Cell. 2007 Oct 19;131(2):242-56.
41. Fuente-Martin E, Argente-Arizon P, Ros P, Argente J, Chowen JA. Sex differences in adipose tissue: It is not only a question of quantity and distribution. Adipocyte. 2013 Jul 1;2(3):128-34.
42. Chen X, McClusky R, Chen J, Beaven SW, Tontonoz P, Arnold AP, et al. The number of x chromosomes causes sex differences in adiposity in mice. PLoS Genet. 2012;8(5):e1002709.
43. Jeffery E, Wing A, Holtrup B, Sebo Z, Kaplan JL, Saavedra-Pena R, et al. The Adipose Tissue Microenvironment Regulates Depot-Specific Adipogenesis in Obesity. Cell Metab. 2016 Jul 12;24(1):142-50.
44. Alexopoulos N, Katritsis D, Raggi P. Visceral adipose tissue as a source of inflammation and promoter of atherosclerosis. Atherosclerosis. 2014 Mar;233(1):104-12.
45. Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. J Clin Invest. 2011 Jun;121(6):2111-7.
46. Odegaard JI, Chawla A. Pleiotropic actions of insulin resistance and inflammation in metabolic homeostasis. Science. 2013 Jan 11;339(6116):172-7.

47. Hermsdorff HH, Angeles Zulet M, Bressan J, Alfredo Martinez J. Effect of diet on the low-grade and chronic inflammation associated with obesity and metabolic syndrome. Endocrinol Nutr. 2008 Oct;55(9):409-19.
48. Cooke AA, Connaughton RM, Lyons CL, McMorrow AM, Roche HM. Fatty acids and chronic low grade inflammation associated with obesity and the metabolic syndrome. Eur J Pharmacol. 2016 Aug 15;785:207-14.
49. Wang L, Chen Y, Li X, Zhang Y, Gulbins E, Zhang Y. Enhancement of endothelial permeability by free fatty acid through lysosomal cathepsin B-mediated Nlrp3 inflammasome activation. Oncotarget. 2016 Nov 8;7(45):73229-41.
50. Ghosh A, Gao L, Thakur A, Siu PM, Lai CWK. Role of free fatty acids in endothelial dysfunction. J Biomed Sci. 2017 Jul 27;24(1):50.
51. Rhea EM, Salameh TS, Logsdon AF, Hanson AJ, Erickson MA, Banks WA. Blood-brain barriers in obesity. The AAPS journal. 2017;19(4):921-30.
52. Van Dyken P, Lacoste B. Impact of Metabolic Syndrome on Neuroinflammation and the Blood-Brain Barrier. Front Neurosci. 2018;12:930.
53. Salameh TS, Mortell WG, Logsdon AF, Butterfield DA, Banks WA. Disruption of the hippocampal and hypothalamic blood-brain barrier in a diet-induced obese model of type II diabetes: prevention and treatment by the mitochondrial carbonic anhydrase inhibitor, topiramate. Fluids Barriers CNS. 2019 Jan 8;16(1):1.
54. Vitale SG, Lagana AS, Nigro A, La Rosa VL, Rossetti P, Rapisarda AM, et al. Peroxisome Proliferator-Activated Receptor Modulation during Metabolic Diseases and Cancers: Master and Minions. PPAR Res. 2016;2016:6517313.
55. Le Menn G, Neels JG. Regulation of Immune Cell Function by PPARs and the Connection with Metabolic and Neurodegenerative Diseases. Int J Mol Sci. 2018 May 25;19(6).
56. Akyurek N, Aycan Z, Cetinkaya S, Akyurek O, Yilmaz Agladioglu S, Ertan U. Peroxisome proliferator activated receptor (PPAR)-gamma concentrations in childhood obesity. Scand J Clin Lab Invest. 2013;73(4):355-60.
57. Riserus U, Sprecher D, Johnson T, Olson E, Hirschberg S, Liu A, et al. Activation of peroxisome proliferator-activated receptor (PPAR)delta promotes reversal of multiple metabolic abnormalities, reduces oxidative stress, and increases fatty acid oxidation in moderately obese men. Diabetes. 2008 Feb;57(2):332-9.
58. Shiomi Y, Yamauchi T, Iwabu M, Okada-Iwabu M, Nakayama R, Orikawa Y, et al. A Novel Peroxisome Proliferator-activated Receptor (PPAR)alpha Agonist and PPARgamma Antagonist, Z-551, Ameliorates High-fat Diet-induced Obesity and Metabolic Disorders in Mice. J Biol Chem. 2015 Jun 5;290(23):14567-81.
59. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. 2016 Oct;16(10):626-38.
60. Erickson MA, Liang WS, Fernandez EG, Bullock KM, Thysell JA, Banks WA. Genetics and sex influence peripheral and central innate immune responses and blood-brain barrier integrity. PLoS One. 2018;13(10):e0205769.
61. Zhang MA, Rego D, Moshkova M, Kebir H, Chruscinski A, Nguyen H, et al. Peroxisome proliferator-activated receptor (PPAR)alpha and -gamma regulate IFNgamma and IL-17A production by human T cells in a sex-specific way. Proc Natl Acad Sci U S A. 2012 Jun 12;109(24):9505-10.
62. Bartness TJ, Liu Y, Shrestha YB, Ryu V. Neural innervation of white adipose tissue and the control of lipolysis. Front Neuroendocrinol. 2014 Oct;35(4):473-93.
63. Gautron L, Elmquist JK, Williams KW. Neural control of energy balance: translating circuits to therapies. Cell. 2015 Mar 26;161(1):133-45.
64. Caron A, Lee S, Elmquist JK, Gautron L. Leptin and brain-adipose crosstalks. Nat Rev Neurosci. 2018 Feb 16;19(3):153-65.
65. Woods SC, Seeley RJ, Baskin DG, Schwartz MW. Insulin and the blood-brain barrier. Curr Pharm Des. 2003;9(10):795-800.
66. Meijer RI, Gray SM, Aylor KW, Barrett EJ. Pathways for insulin access to the brain: the role of the microvascular endothelial cell. Am J Physiol Heart Circ Physiol. 2016 Nov 1;311(5):H1132-H38.
67. Rhea EM, Rask-Madsen C, Banks WA. Insulin transport across the blood–brain barrier can occur independently of the insulin receptor. The Journal of physiology. 2018;596(19):4753-65.
68. Havrankova J, Roth J, Brownstein M. Insulin receptors are widely distributed in the central nervous system of the rat. Nature. 1978 Apr 27;272(5656):827-9.
69. Baron-Van Evercooren A, Olichon-Berthe C, Kowalski A, Visciano G, Van Obberghen E. Expression of IGF-I and insulin receptor genes in the rat central nervous system: a developmental, regional, and cellular analysis. J Neurosci Res. 1991 Feb;28(2):244-53.

70. Kleinridders A, Ferris HA, Cai W, Kahn CR. Insulin action in brain regulates systemic metabolism and brain function. Diabetes. 2014 Jul;63(7):2232-43.
71. van Houten M, Posner BI, Kopriwa BM, Brawer JR. Insulin binding sites localized to nerve terminals in rat median eminence and arcuate nucleus. Science. 1980 Mar 7;207(4435):1081-3.
72. Blasberg RG, Patlak CS, Fenstermacher JD. Selection of experimental conditions for the accurate determination of blood--brain transfer constants from single-time experiments: a theoretical analysis. J Cereb Blood Flow Metab. 1983 Jun;3(2):215-25.
73. Siso S, Jeffrey M, Gonzalez L. Sensory circumventricular organs in health and disease. Acta Neuropathol. 2010 Dec;120(6):689-705.
74. Wang D, He X, Zhao Z, Feng Q, Lin R, Sun Y, et al. Whole-brain mapping of the direct inputs and axonal projections of POMC and AgRP neurons. Front Neuroanat. 2015;9:40.
75. Kleinridders A, Lauritzen HP, Ussar S, Christensen JH, Mori MA, Bross P, et al. Leptin regulation of Hsp60 impacts hypothalamic insulin signaling. J Clin Invest. 2013 Nov;123(11):4667-80.
76. Dodd GT, Xirouchaki CE, Eramo M, Mitchell CA, Andrews ZB, Henry BA, et al. Intranasal Targeting of Hypothalamic PTP1B and TCPTP Reinstates Leptin and Insulin Sensitivity and Promotes Weight Loss in Obesity. Cell Rep. 2019 Sep 10;28(11):2905-22 e5.
77. Dodd GT, Kim SJ, Mequinion M, Xirouchaki CE, Bruning JC, Andrews ZB, et al. Insulin signaling in AgRP neurons regulates meal size to limit glucose excursions and insulin resistance. Sci Adv. 2021 Feb;7(9).
78. Lam CK, Chari M, Su BB, Cheung GW, Kokorovic A, Yang CS, et al. Activation of N-methyl-D-aspartate (NMDA) receptors in the dorsal vagal complex lowers glucose production. J Biol Chem. 2010 Jul 16;285(29):21913-21.
79. Lam CK, Chari M, Rutter GA, Lam TK. Hypothalamic nutrient sensing activates a forebrain-hindbrain neuronal circuit to regulate glucose production in vivo. Diabetes. 2011 Jan;60(1):107-13.
80. Fernandez AM, Torres-Aleman I. The many faces of insulin-like peptide signalling in the brain. Nat Rev Neurosci. 2012 Mar 20;13(4):225-39.
81. Stoica L, Zhu PJ, Huang W, Zhou H, Kozma SC, Costa-Mattioli M. Selective pharmacogenetic inhibition of mammalian target of Rapamycin complex I (mTORC1) blocks long-term synaptic plasticity and memory storage. Proc Natl Acad Sci U S A. 2011 Mar 1;108(9):3791-6.
82. Son JH, Shim JH, Kim KH, Ha JY, Han JY. Neuronal autophagy and neurodegenerative diseases. Exp Mol Med. 2012 Feb 29;44(2):89-98.
83. Salcedo-Tello P, Ortiz-Matamoros A, Arias C. GSK3 Function in the Brain during Development, Neuronal Plasticity, and Neurodegeneration. Int J Alzheimers Dis. 2011;2011:189728.
84. Rankin CA, Sun Q, Gamblin TC. Tau phosphorylation by GSK-3beta promotes tangle-like filament morphology. Mol Neurodegener. 2007 Jun 28;2:12.
85. Ponce-Lopez T, Hong E, Abascal-Díaz M, Meneses A. Role of GSK3β and PP2A on Regulation of Tau Phosphorylation in Hippocampus and Memory Impairment in ICV-STZ Animal Model of Alzheimer's Disease. Advances in Alzheimer's Disease. 2017;6(1):13-31.
86. Schubert M, Brazil DP, Burks DJ, Kushner JA, Ye J, Flint CL, et al. Insulin receptor substrate-2 deficiency impairs brain growth and promotes tau phosphorylation. J Neurosci. 2003 Aug 6;23(18):7084-92.
87. Schubert M, Gautam D, Surjo D, Ueki K, Baudler S, Schubert D, et al. Role for neuronal insulin resistance in neurodegenerative diseases. Proc Natl Acad Sci U S A. 2004 Mar 2;101(9):3100-5.
88. Kim KW, Donato J, Jr., Berglund ED, Choi YH, Kohno D, Elias CF, et al. FOXO1 in the ventromedial hypothalamus regulates energy balance. J Clin Invest. 2012 Jul;122(7):2578-89.
89. Ren H, Plum-Morschel L, Gutierrez-Juarez R, Lu TY, Kim-Muller JY, Heinrich G, et al. Blunted refeeding response and increased locomotor activity in mice lacking FoxO1 in synapsin-Cre-expressing neurons. Diabetes. 2013 Oct;62(10):3373-83.
90. Adams JP, Sweatt JD. Molecular psychology: roles for the ERK MAP kinase cascade in memory. Annu Rev Pharmacol Toxicol. 2002;42:135-63.
91. Anthony K, Reed LJ, Dunn JT, Bingham E, Hopkins D, Marsden PK, et al. Attenuation of insulin-evoked responses in brain networks controlling appetite and reward in insulin resistance: the cerebral basis for impaired control of food intake in metabolic syndrome? Diabetes. 2006 Nov;55(11):2986-92.

92. Tschritter O, Preissl H, Hennige AM, Stumvoll M, Porubska K, Frost R, et al. The cerebrocortical response to hyperinsulinemia is reduced in overweight humans: a magnetoencephalographic study. Proc Natl Acad Sci U S A. 2006 Aug 8;103(32):12103-8.
93. Hirvonen J, Virtanen KA, Nummenmaa L, Hannukainen JC, Honka MJ, Bucci M, et al. Effects of insulin on brain glucose metabolism in impaired glucose tolerance. Diabetes. 2011 Feb;60(2):443-7.
94. Deem JD, Muta K, Scarlett JM, Morton GJ, Schwartz MW. How Should We Think About the Role of the Brain in Glucose Homeostasis and Diabetes? Diabetes. 2017 Jul;66(7):1758-65.
95. Ruud J, Steculorum SM, Bruning JC. Neuronal control of peripheral insulin sensitivity and glucose metabolism. Nat Commun. 2017 May 4;8:15259.
96. Chen KE, Lainez NM, Nair MG, Coss D. Visceral adipose tissue imparts peripheral macrophage influx into the hypothalamus. J Neuroinflammation. 2021 Jun 21;18(1):140.
97. Thaler JP, Yi CX, Schur EA, Guyenet SJ, Hwang BH, Dietrich MO, et al. Obesity is associated with hypothalamic injury in rodents and humans. J Clin Invest. 2012 Jan;122(1):153-62.
98. Pistell PJ, Morrison CD, Gupta S, Knight AG, Keller JN, Ingram DK, et al. Cognitive impairment following high fat diet consumption is associated with brain inflammation. Journal of neuroimmunology. 2010;219(1-2):25-32.
99. Biessels GJ, Reagan LP. Hippocampal insulin resistance and cognitive dysfunction. Nature Reviews Neuroscience. 2015;16(11):660-71.
100. Garcia-Caceres C, Quarta C, Varela L, Gao Y, Gruber T, Legutko B, et al. Astrocytic Insulin Signaling Couples Brain Glucose Uptake with Nutrient Availability. Cell. 2016 Aug 11;166(4):867-80.
101. Clasadonte J, Prevot V. The special relationship: glia-neuron interactions in the neuroendocrine hypothalamus. Nat Rev Endocrinol. 2018 Jan;14(1):25-44.
102. Spielman LJ, Bahniwal M, Little JP, Walker DG, Klegeris A. Insulin Modulates In Vitro Secretion of Cytokines and Cytotoxins by Human Glial Cells. Curr Alzheimer Res. 2015;12(7):684-93.
103. Manaserh IH, Chikkamenahalli L, Ravi S, Dube PR, Park JJ, Hill JW. Ablating astrocyte insulin receptors leads to delayed puberty and hypogonadism in mice. PLoS Biol. 2019 Mar;17(3):e3000189.
104. MacDonald AJ, Holmes FE, Beall C, Pickering AE, Ellacott KLJ. Regulation of food intake by astrocytes in the brainstem dorsal vagal complex. Glia. 2020 Jun;68(6):1241-54.
105. Cai W, Xue C, Sakaguchi M, Konishi M, Shirazian A, Ferris HA, et al. Insulin regulates astrocyte gliotransmission and modulates behavior. J Clin Invest. 2018 Jul 2;128(7):2914-26.
106. Guttenplan KA, Weigel MK, Prakash P, Wijewardhane PR, Hasel P, Rufen-Blanchette U, et al. Neurotoxic reactive astrocytes induce cell death via saturated lipids. Nature. 2021 Nov;599(7883):102-07.
107. Oishi Y, Spann NJ, Link VM, Muse ED, Strid T, Edillor C, et al. SREBP1 Contributes to Resolution of Pro-inflammatory TLR4 Signaling by Reprogramming Fatty Acid Metabolism. Cell Metab. 2017 Feb 7;25(2):412-27.
108. Parkhurst CN, Yang G, Ninan I, Savas JN, Yates JR, 3rd, Lafaille JJ, et al. Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. Cell. 2013 Dec 19;155(7):1596-609.
109. Salter MW, Beggs S. Sublime microglia: expanding roles for the guardians of the CNS. Cell. 2014 Jul 3;158(1):15-24.
110. Tabassum S, Misrani A, Yang L. Exploiting Common Aspects of Obesity and Alzheimer's Disease. Frontiers in Human Neuroscience. 2020;14.
111. Brabazon F, Bermudez S, Shaughness M, Khayrullina G, Byrnes KR. The effects of insulin on the inflammatory activity of BV2 microglia. PLoS One. 2018;13(8):e0201878.
112. Haas CB, de Carvalho AK, Muller AP, Eggen BJL, Portela LV. Insulin activates microglia and increases COX-2/IL-1beta expression in young but not in aged hippocampus. Brain Res. 2020 Aug 15;1741:146884.
113. Xaio H, Banks W, Niehoff ML, Morley J. Effect of LPS on the permeability of the blood–brain barrier to insulin. Brain research. 2001;896(1-2):36-42.
114. Kurauti MA, Ferreira SM, Soares GM, Vettorazzi JF, Carneiro EM, Boschero AC, et al. Hyperinsulinemia is associated with increasing insulin secretion but not with decreasing insulin clearance in an age-related metabolic dysfunction mice model. J Cell Physiol. 2019 Jun;234(6):9802-09.
115. Janssen J. Hyperinsulinemia and Its Pivotal Role in Aging, Obesity, Type 2 Diabetes, Cardiovascular Disease and Cancer. Int J Mol Sci. 2021 Jul 21;22(15).

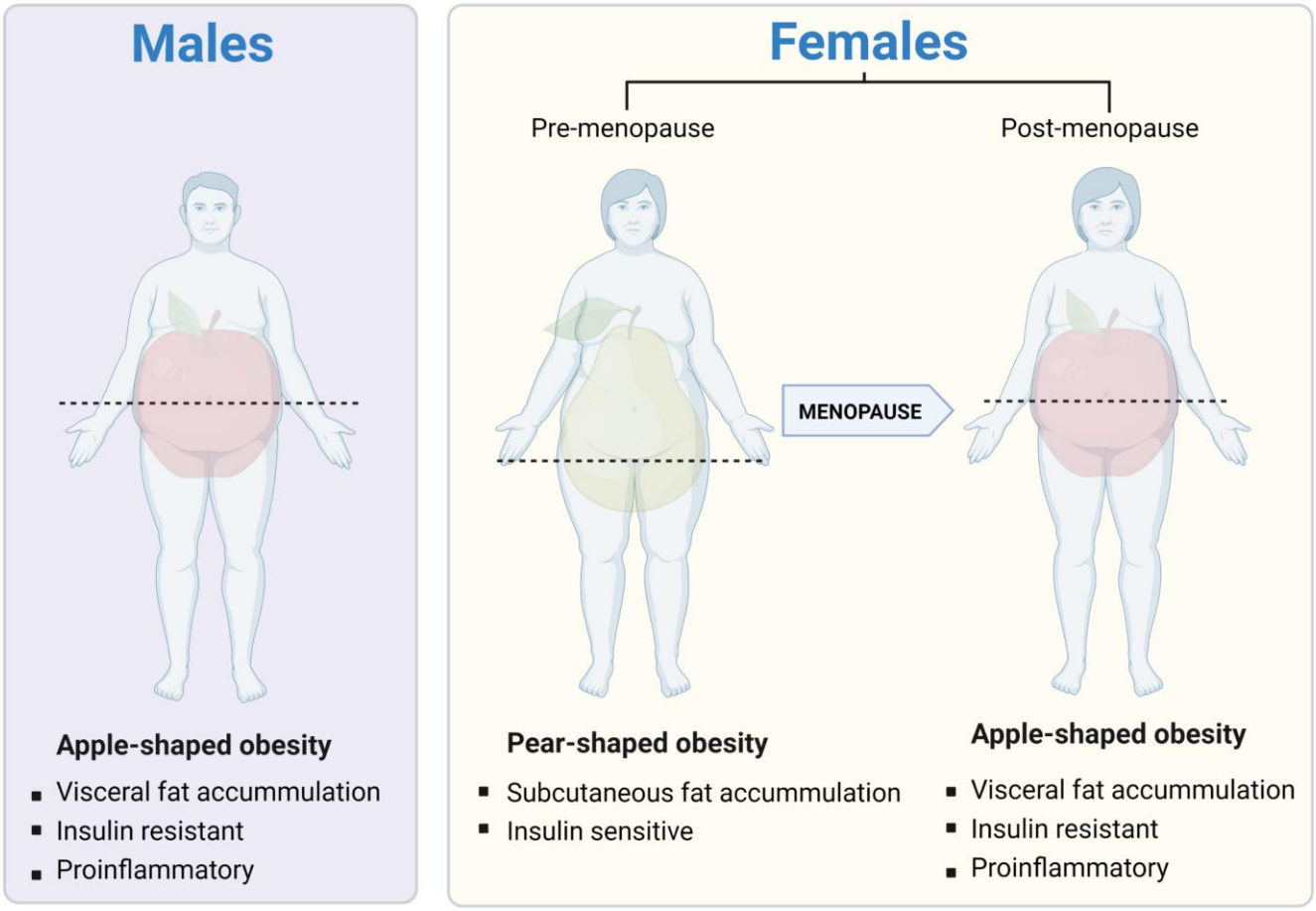
116. Ieronymaki E, Theodorakis EM, Lyroni K, Vergadi E, Lagoudaki E, Al-Qahtani A, et al. Insulin resistance in macrophages alters their metabolism and promotes an M2-like phenotype. The Journal of Immunology. 2019;202(6):1786-97.
117. Hao S, Dey A, Yu X, Stranahan AM. Dietary obesity reversibly induces synaptic stripping by microglia and impairs hippocampal plasticity. Brain Behav Immun. 2016 Jan;51:230-39.
118. Cope EC, LaMarca EA, Monari PK, Olson LB, Martinez S, Zych AD, et al. Microglia Play an Active Role in Obesity-Associated Cognitive Decline. J Neurosci. 2018 Oct 10;38(41):8889-904.
119. Mizuno TM, Kleopoulos SP, Bergen HT, Roberts JL, Priest CA, Mobbs CV. Hypothalamic pro-opiomelanocortin mRNA is reduced by fasting and [corrected] in ob/ob and db/db mice, but is stimulated by leptin. Diabetes. 1998 Feb;47(2):294-7.
120. Horvath TL. Synaptic plasticity in energy balance regulation. Obesity (Silver Spring). 2006 Aug;14 Suppl 5:228S-33S.
121. Gao Y, Ottaway N, Schriever SC, Legutko B, Garcia-Caceres C, de la Fuente E, et al. Hormones and diet, but not body weight, control hypothalamic microglial activity. Glia. 2014 Jan;62(1):17-25.
122. Kim JD, Yoon NA, Jin S, Diano S. Microglial UCP2 Mediates Inflammation and Obesity Induced by High-Fat Feeding. Cell Metab. 2019 Nov 5;30(5):952-62 e5.
123. Nimmerjahn A, Kirchhoff F, Helmchen F. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science. 2005 May 27;308(5726):1314-8.
124. Li Q, Barres BA. Microglia and macrophages in brain homeostasis and disease. Nat Rev Immunol. 2018 Apr;18(4):225-42.
125. Gehrmann J, Matsumoto Y, Kreutzberg GW. Microglia: intrinsic immuneffector cell of the brain. Brain Res Brain Res Rev. 1995 Mar;20(3):269-87.
126. Kofler J, Wiley CA. Microglia: key innate immune cells of the brain. Toxicol Pathol. 2011 Jan;39(1):103-14.
127. Bachiller S, Jimenez-Ferrer I, Paulus A, Yang Y, Swanberg M, Deierborg T, et al. Microglia in Neurological Diseases: A Road Map to Brain-Disease Dependent-Inflammatory Response. Front Cell Neurosci. 2018;12:488.
128. De Luca SN, Sominsky L, Soch A, Wang H, Ziko I, Rank MM, et al. Conditional microglial depletion in rats leads to reversible anorexia and weight loss by disrupting gustatory circuitry. Brain Behav Immun. 2019 Mar;77:77-91.
129. Valdearcos M, Douglass JD, Robblee MM, Dorfman MD, Stifler DR, Bennett ML, et al. Microglial Inflammatory Signaling Orchestrates the Hypothalamic Immune Response to Dietary Excess and Mediates Obesity Susceptibility. Cell Metab. 2017 Jul 5;26(1):185-97 e3.
130. Villapol S, Loane DJ, Burns MP. Sexual dimorphism in the inflammatory response to traumatic brain injury. Glia. 2017 Sep;65(9):1423-38.
131. Villa A, Gelosa P, Castiglioni L, Cimino M, Rizzi N, Pepe G, et al. Sex-Specific Features of Microglia from Adult Mice. Cell Rep. 2018 Jun 19;23(12):3501-11.
132. Villa A, Della Torre S, Maggi A. Sexual differentiation of microglia. Front Neuroendocrinol. 2019 Jan;52:156-64.
133. Saltiel AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. J Clin Invest. 2017 Jan 3;127(1):1-4.
134. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW, Jr. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest. 2003 Dec;112(12):1796-808.
135. Shu CJ, Benoist C, Mathis D. The immune system's involvement in obesity-driven type 2 diabetes. Semin Immunol. 2012 Dec;24(6):436-42.
136. Banks W, Farr S, Salameh T, Niehoff M, Rhea E, Morley J, et al. Triglycerides cross the blood–brain barrier and induce central leptin and insulin receptor resistance. International journal of obesity. 2018;42(3):391-97.
137. Wang Z, Liu D, Wang F, Liu S, Zhao S, Ling EA, et al. Saturated fatty acids activate microglia via Toll-like receptor 4/NF-kappaB signalling. Br J Nutr. 2012 Jan;107(2):229-41.
138. Button EB, Mitchell AS, Domingos MM, Chung JH, Bradley RM, Hashemi A, et al. Microglial cell activation increases saturated and decreases monounsaturated fatty acid content, but both lipid species are proinflammatory. Lipids. 2014 Apr;49(4):305-16.
139. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, Koenig AM, Wang HY, Ahima RS, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. Nat Rev Neurol. 2018 Mar;14(3):168-81.

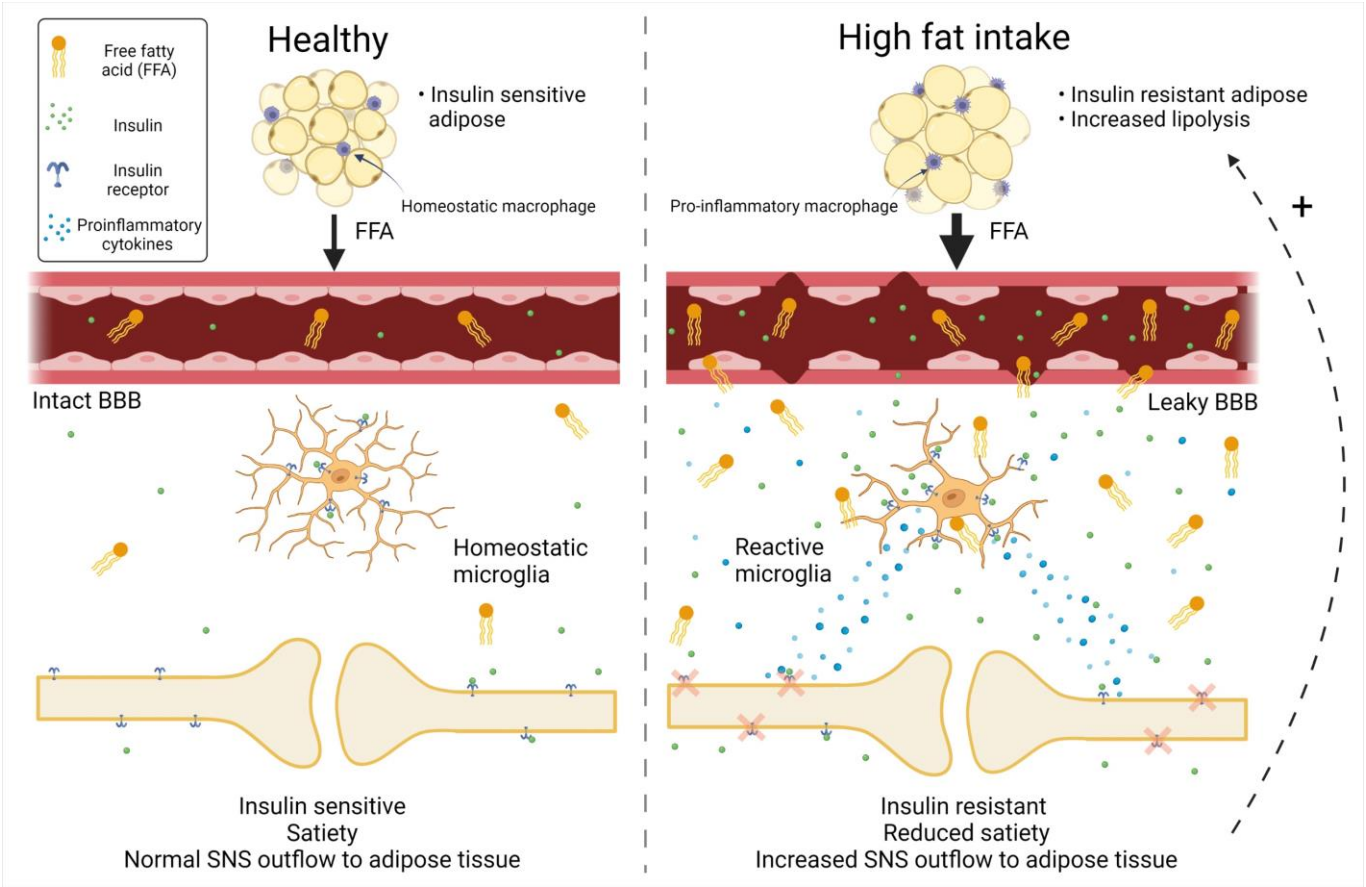
140. Carroll RG, Zaslona Z, Galvan-Pena S, Koppe EL, Sevin DC, Angiari S, et al. An unexpected link between fatty acid synthase and cholesterol synthesis in proinflammatory macrophage activation. J Biol Chem. 2018 Apr 13;293(15):5509-21.
141. Bomfim TR, Forny-Germano L, Sathler LB, Brito-Moreira J, Houzel JC, Decker H, et al. An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease- associated Abeta oligomers. J Clin Invest. 2012 Apr;122(4):1339-53.
142. Gupta S, Knight AG, Gupta S, Keller JN, Bruce-Keller AJ. Saturated long-chain fatty acids activate inflammatory signaling in astrocytes. J Neurochem. 2012 Mar;120(6):1060-71.
143. Lourenco MV, Clarke JR, Frozza RL, Bomfim TR, Forny-Germano L, Batista AF, et al. TNF-alpha mediates PKR-dependent memory impairment and brain IRS-1 inhibition induced by Alzheimer's beta-amyloid oligomers in mice and monkeys. Cell Metab. 2013 Dec 3;18(6):831-43.
144. Kiernan EA, Smith SM, Mitchell GS, Watters JJ. Mechanisms of microglial activation in models of inflammation and hypoxia: Implications for chronic intermittent hypoxia. J Physiol. 2016 Mar 15;594(6):1563-77.
145. Vieira MNN, Lima-Filho RAS, De Felice FG. Connecting Alzheimer's disease to diabetes: Underlying mechanisms and potential therapeutic targets. Neuropharmacology. 2018 Jul 1;136(Pt B):160-71.
146. Lu J, Wu DM, Zheng YL, Hu B, Cheng W, Zhang ZF, et al. Ursolic acid improves high fat diet-induced cognitive impairments by blocking endoplasmic reticulum stress and IkappaB kinase beta/nuclear factor-kappaB-mediated inflammatory pathways in mice. Brain Behav Immun. 2011 Nov;25(8):1658-67.
147. Almeida-Suhett CP, Graham A, Chen Y, Deuster P. Behavioral changes in male mice fed a high-fat diet are associated with IL-1beta expression in specific brain regions. Physiol Behav. 2017 Feb 1;169:130-40.
148. Bradley EA, Premilovac D, Betik AC, Hu D, Attrill E, Richards SM, et al. Metformin improves vascular and metabolic insulin action in insulin-resistant muscle. J Endocrinol. 2019 Nov;243(2):85-96.
149. Hotamisligil GS, Murray DL, Choy LN, Spiegelman BM. Tumor necrosis factor alpha inhibits signaling from the insulin receptor. Proceedings of the National Academy of Sciences. 1994;91(11):4854-58.
150. Salameh TS, Rhea EM, Banks WA, Hanson AJ. Insulin resistance, dyslipidemia, and apolipoprotein E interactions as mechanisms in cognitive impairment and Alzheimer's disease. Experimental Biology and Medicine. 2016;241(15):1676-83.
151. Shin AC, Filatova N, Lindtner C, Chi T, Degann S, Oberlin D, et al. Insulin Receptor Signaling in POMC, but Not AgRP, Neurons Controls Adipose Tissue Insulin Action. Diabetes. 2017 Jun;66(6):1560-71.

Figure Legends

Fig. 1. Schematic depicting differences in adipose distribution between females and males. In males, apple-shaped obesity is more prevalent where visceral fat accumulation occurs. In apple-shaped obesity, systemic inflammation and insulin resistance are typical consequences of obesity. In pre-menopausal females, pear-shaped obesity is more prevalent where subcutaneous fat accumulation, particularly on the thighs, is favoured and this is associated with normal insulin sensitivity. In contrast, adipose distribution in post-menopausal females shifts towards a male-like, apple-shaped pattern where visceral fat accumulation is favoured promoting insulin resistance and inflammation.

Fig. 2. Schematic depicting the role microglia may play in the CNS during obesity to drive neuronal insulin resistance and loss of whole-body metabolic homeostasis. (A) In healthy people, adipose tissue is insulin sensitive and releases low amounts of free fatty acids into the circulation as needed for homeostasis. The BBB is intact and free fatty acid and insulin access to the brain parenchyma is tightly controlled by transport mechanisms. Microglia are performing homeostatic roles and neuronal insulin activation promotes satiety. (B) In response to increased dietary fat intake adipose tissue expands and becomes insulin resistant. Loss of insulin action in adipose tissue leads to lipolysis and increased release of free fatty acids into the blood stream. At the same time, insulin secretion is increased to compensate for the developing insulin resistance driving hyperinsulinaemia. Free fatty acids increase the permeability of the BBB leading to increased access of fatty acids and insulin to the brain parenchyma and activation of microglia. Activated microglia release proinflammatory cytokines, such as TNF-α, which further increase BBB permeability and inhibit insulin signalling in neurons leading to reduced satiety and thus increased feeding behaviour. Together, a lack of satiety promoted increased food intake coupled with increased sympathetic nervous system (SNS outflow to adipose tissue driving more lipolysis creates a positive feedback cycle to drive weight gain and insulin resistance as seen in obesity.


Males
Apple-shaped obesity
Visceral fat accummulation
Insulin resistant
Proinflammatory
Females
Pre-menopause
Post-menopause
MENOPAUSE
Pear-shaped obesity
Subcutaneous fat accummulation
Insulin sensitive
Apple-shaped obesity
Visceral fat accummulation
Insulin resistant
Proinflammatory


Free fatty acid (FFA)
Insulin
Insulin receptor
Proinflammatory cytokines
Healthy
• Insulin sensitive adipose
Homeostatic macrophage
FFA
Intact BBB
Homeostatic microglia
Insulin sensitive
Satiety
Normal SNS outflow to adipose tissue
High fat intake
• Insulin resistant adipose
• Increased lipolysis
Pro-inflammatory macrophage
FFA
Leaky BBB
Reactive microglia
+
Insulin resistant
Reduced satiety
Increased SNS outflow to adipose tissue