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Influence of Obesity on Neurodegenerative Diseases

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1. Introduction

Obesity is one of the greatest public health challenges of the 21st century. Obesity prevalence has been increasing globally at an alarming rate, particularly among children. The progressively increased prevalence of obesity over the past decades among children, as well as adults, is not limited to the US and other industrialized nations but is also evident in developing countries [1]. The World Health Organization (WHO) estimated the prevalence of obesity at more than 1 billion overweight adults, with at least 500 million reaching the level of obese. As this continues to increase, by 2015, WHO estimates the number of overweighted adults will balloon to 2.3 billion with more than 700 million obese. Worldwide, obesity is currently responsible for 2–8% of health care costs and approximately 10–13% of deaths [2].

Fundamental causes of the current obesity epidemic are associated with sedentary lifestyles, increased consumption of energy-dense foods high in saturated fats and sugars and reduced physical activity. All of which correlate with the profound changes occurring in behavioral patterns of communities across societies as a consequence of increased urbanization and industrialization and often the disappearance of traditional lifestyles [3]. However, it is now appreciated that the progression to obesity represents a complex interaction of genetics, metabolism, as well as diet and physical activity level.

Clinically, obesity is defined by measurements of body mass index [4] or waist circumference and waist to hip ratio [5]. Body mass index (BMI) is a simple index weight-to-height defined as a person's weight in kilograms divided by the square of his/her height in meters (kg/m^2). According to WHO guidelines, a BMI $25 \text{ kg}/\text{m}^2$ identifies overweight and a BMI of $30 \text{ kg}/\text{m}^2$ or higher identifies an individual as obese. Physiologically, obesity is an excessive accumulation of fat in adipose tissue in the form of triglycerides, which can negatively affect health. Obesity is associated with number of metabolic disorders, increased expression of

pro-inflammatory markers and elevated risk for various disease including type 2 diabetes, cardiovascular disease, gastrointestinal disorders, respiratory difficulties, and various types of cancer [6]. In a more general nature, it has been suggested that obesity may accelerate the normal process of aging [7] (figure 1).

Figure 1. Obesity accelerates age and age related pathologies. Adapted from [8]

2. Obesity and inflammatory mediators

Adipose tissue has long been regarded as tissue storage of fat in the form of triglycerides; however, it is now recognized as an endocrine tissue producing a number of different factors, including inflammatory-related factors, acting at a physiological level [9].

Two forms of adipose tissues exist in mammals: the brown fat and the white fat (figure 2).

Brown adipose tissue is involved in the regulation of the body temperature. In humans, until recently, it was thought that brown fat was only present in the newborn and infant [12]. The extensive use of positron emission tomography (PET) in cancer medical imaging has changed this dogma. An evaluation of fluorodeoxyglucose PET (FDG PET) data from adult cancer patients indicated a high level of glucose consumption in specific body regions corresponding to brown fat [10], presumably in order to maintain normal body temperature

within an air conditioned room as this was not observed when patients were in a warm environment. White adipose tissue (WAT) is a source of energy involved in heat insulation and mechanical cushion. WAT represents around 15-20% of body weight and in obese individuals it increases up to 50%. WAT is composed of several different cell types, including preadipocytes, mature adipocytes, macrophages, endothelial cells which are involved in WAT homeostasis (Figure 3) [13, 14]. It is worth noting the presence of stem cells in the WAT, which are extensively studied for their potential in therapeutic reparation and even for the treatment of obesity and metabolic disorders [15-17].

Figure 2. Brown fat (A) and white fat (B) tissue distribution in adult from [10, 11]

Different functional properties have been identified for WAT depending upon location in the subcutaneous or visceral areas. For example, a correlation exists between visceral obesity and increased risk of insulin resistance and cardiovascular diseases, while an increase of subcutaneous fat is associated with favorable plasma lipid profiles [11]. Adipose tissue was not usually thought of as an immune or inflammatory organ based upon studies demonstrating that loss of adipose tissue is associated with a decrease in markers of inflammation. It is now well accepted however, that adipose tissue is a key player in the development of inflammation [19]. Excess fat tissue in the obese environment contributes to a low-grade chronic inflammation [20] with elevated production of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF α), interleukin -6 (IL-6) and IL-1 [21, 22]. The visceral adi-

pocytes significantly contribute in this role as they are metabolically active and produce a higher level of pro-inflammatory cytokines [11, 23-25].

Figure 3. Cells present in the fat tissue adapted from [13, 18]

Figure 4. Inflammatory factors produced by WAT in obese situations. [26-35]

WAT is considered as an important organ in the regulation of many pathological processes by producing several inflammatory factors including, chemokines, cytokines and adipokines (also named adipocytokines). During the development of obesity expression of these factors is modified (figure 4).

Adipocytes secrete various chemo-attractants that recruit monocytes into the WAT. Obese adipose tissue exhibits an increased expression of Monocyte Chemoattractant Protein 1 (MCP-1) and of its receptor CCR2. The signaling of MCP1 / CCR2 has a direct impact on the development of obesity (for review see [36]). CCL-2, another chemokine with capability to recruit macrophages, has also a high level of expression in obese adipose tissue; however, it does not appear to be critical for adipose tissue macrophage recruitment [37]. Several other chemokines are also likely to play a role in the recruitment of monocytes/macrophages into the adipose tissue, such as MCP2, MCP4, migration inhibitory factor (MIF), macrophage inflammatory protein-1 α (MIP-1 α), MIP-1 β , or MIP2- α [26, 38]. The adipocytes are not alone in the elevated inflammatory condition of obesity in that the number of macrophages is also higher in the obese environment thus, providing an additional cellular source of inflammatory factors [19].

Experimental animal studies have served a critical role in advancing our knowledge with regards to the biological relationship between adipose tissue, obesity, and inflammation. The first study to show a link between obesity and inflammation was the work of Hotamisligil and colleagues in 1993 in which they demonstrated that TNF α expression was up-regulated in adipose tissue of genetically obese mice [39]. Additional work reported that the number of bone-marrow derived macrophages present in white adipose tissue directly correlated with obesity [19]. In addition to macrophages, it has been demonstrated that pre-adipocytes and mature adipocytes also produce inflammatory factors. The mechanisms that initiate and trigger the inflammation are not yet totally elucidated, but different hypothesis have been proposed. A number of factors could trigger an inflammatory response and among them the saturated fatty acids may play a contributing role. For example, palmitate, an abundant nutritional fatty acid, could bind to the inflammation-related toll like receptors (TLR) leading to activation of a signalling cascade and the activation of the transcription factor NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) [40]. NF- κ B is involved in many cellular processes including immune and inflammatory responses. Upon activation and nuclear translocation, NF- κ B can further induce the production of inflammatory cytokines, including TNF and IL-1. An alternative, but as relevant a process, is the recognition of a diverse range of stress and damage signals by inflammasomes. These are a group of protein complexes including the Nod-Like Receptor (NLR) proteins that can directly activate caspase-1 leading to the secretion of pro-inflammatory cytokines and pyroptotic cell death (for review see [41]).

Recently inflammasomes and their activation of down-stream events have been shown to play a major role in the development of obesity, insulin resistance, and diabetes [42, 43]. Another hypothesis linking inflammation and obesity is supported by Burcelin's group and involves the intestinal flora equilibrium. In this model, a high fat diet is proposed to

increase the gram-negative bacteria proportion in the intestine; this increases intestine permeability and the absorption of lipopolysaccharide (LPS; the wall component of the gram-negative bacteria). Upon this increased absorption, TLR activation leads to an up-regulation of the inflammatory response [44, 45]. These two hypotheses are not mutually exclusive but rather it is likely that the two mechanisms coexist. While the classic localization of TLRs is on macrophages our laboratory and others have shown the presence of functional Toll-like receptors (TLRs) on human adipocytes including the expression of TLR type 2 (TLR2) and TLR type 4 (TLR4) [46, 47] providing evidence for the potential of an adipocyte receptor-mediated response.

Adipokines are defined as soluble mediators that are mainly, but not exclusively, produced by adipocytes and exert their biological function in an autocrine, paracrine or systemic manner. Over 50 adipokines have been identified, and they generally function as hormones to influence energy homeostasis and feeding [22, 48]. The following sections will focus on a review of two specific adipokines (leptin and adiponectin) and an additional factor (autotaxin) produced by WAT. Information is presented supporting that these factors and their activation may provide an important link between obesity and related inflammatory disorders.

Leptin was identified in 1994 as the 16 kDa protein product of the obese (*ob*) gene [49]. It displays immune-regulatory effects by increasing the production of pro-inflammatory cytokines by macrophages [50]. It is best known as an important regulator of energy balance through its actions in the brain to suppress appetite and increase energy expenditure [51]. Leptin in the blood enters the brain via a transport mechanism that can be saturated [52]. Upon entry it is believed to act primarily on the hypothalamic centers thus possibly providing a target for its effects upon appetite. In addition to the hypothalamus, leptin receptors (OBR) are widely expressed in numerous extra-hypothalamic regions of the brain, including the hippocampus, cerebellum, amygdala, and brain stem [53]. There are many splice variants of the receptor; those with short cytoplasmic domains are expressed in multiple tissues while the one with long cytoplasmic domains (OB-Rb) are expressed in specific brain regions. OB-Rb stimulates the JAK/STAT3 pathway and PI3K which are necessary for the leptin effects on food intake and hepatic glucose metabolism [54, 55].

Adiponectin, a prototypic adipocytokine is an anti-inflammatory adipokine secreted by adipocytes [56-58]. It plays a major role in regulation of insulin sensitivity and in obesity the levels of adiponectin are diminished due to a decreased release from WAT [59]. A deficiency in adiponectin is associated with exaggerated inflammatory response in patients with critical illness, including sepsis [32, 60] and with the development of a proinflammatory phenotype in animal models of polymicrobial sepsis [61, 62]. Further studies demonstrated that adiponectin deficiency is associated with increased leukocyte and platelet adhesion as well as blood brain barrier dysfunction with cecal ligation and puncture induced sepsis in mice [63].

Autotaxin (ATX), also known as ectonucleotide pyrophosphatase phosphodiesterase-2 (ENPP2), is a secreted enzyme with lysophospholipase D (lysoPLD) activity involved in hydrolysis of lysophosphatidylcholine (LPC) into lysophosphatidic acid (LPA) [64]. LPA is bioactive phospholipid involved in numerous biological activities, including cell proliferation,

differentiation, and migration acting via specific G-protein coupled receptors [65]. The LPA strongly influences proliferation and differentiation of pre-adipocytes *via* the activation of LPA1 receptor [66, 67]. Anti-inflammatory properties for LPA have been suggested based upon the ability to inhibit, in mice, the LPS-induced inflammatory response of macrophages [68]. The expression of ATX is up-regulated during adipogenesis [69, 70] as well as in adipocytes from obese-diabetic db/db mice and in adipose tissue obtained from glucose-intolerant obese women subjects [69, 71]. The role of ATX in inflammation is less clear, but LPA seems to demonstrate some anti-inflammatory properties as it inhibits LPS-induced inflammation in cultured macrophages and in mice. Based upon these findings, it has been suggested that in addition to its role in cancer and LPA production, ATX may be involved in adipose tissue development and/or obesity-associated pathologies such as diabetes.

3. Influence of obesity on CNS

It is only relatively recently that the concept that obesity could have an effect on the brain has been emerging. Associations between obesity and various neurological disorders have been reported including sleep apnea, anxiety, manic depressive disorders, increased risk of developing cerebrovascular accident (CVA), and other neurological disorders [18, 72]. Additional consideration has been raised that obesity may be linked to various progressive and aging-related neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease (AD), and autoimmune nervous system diseases like multiple sclerosis.

Over the last decade, a number of magnetic resonance imaging (MRI) and computed tomography (CT) studies have reported alterations in brain morphology of overweight/obese individuals. Initial studies demonstrated a higher BMI and/or waist-to-hip ratio in middle-aged individuals associated with a reduction in whole brain volume [73-75]. A similar association was observed with temporal lobe atrophy in elderly women [76] with additional evidence of hippocampal atrophy [77]. Debette et al. [78] reported a link between abdominal fat and reduced brain volume in otherwise healthy middle-aged adults. This study reported an inverse association between various obesity indicators (BMI, waist circumference, waist-to-hip ratio, and abdominal fat) and brain volume as determined by structural MRI of 733 participants. Independent of other obesity indicators, waist-to-hip ratio was found to be associated with increased temporal horn volume. Pannacciulli et al., 2006 reported gray matter reductions in the left postcentral gyrus, bilateral putamen, and right cerebellar regions in obese individuals as detected using voxel-based morphometry [79]. Gender differences have been suggested with a male-specific association between increasing BMI and smaller cerebellum, midbrain, frontal, temporal, and parietal cortex [74]. In a cohort of 95 obese women between the ages of 52 and 92, gray matter reductions were reported in the left orbitofrontal, right inferior frontal, right precentral gyri, and right cerebellar regions [80]. In contrast, increased volumes in white matter in the frontal, temporal, and parietal lobes were also reported [80]. In a cross-sectional study of normal elderly individuals showing no sign of

cognitive deficit, tensor-based morphometry unveiled atrophy in the white and gray matter of the frontal lobes, anterior cingulate gyrus, hippocampus, and thalamus in both male and female subjects with a high BMI (BMI > 30) as compared to individuals with a normal BMI (18.5–25) [81]. Upon further investigation, the brain volume reduction in gray and white matter was found to be associated with a common variant of the fat mass and obesity associated (*FTO*) gene [82]. Three-dimensional MRI brain maps of 206 healthy elderly participants showed an association between brain volume and the risk allele of the *FTO* gene known to be strongly associated with higher body-mass index. Participants who carried at least one copy of the allele had marked reductions in the volume of various brain structures compared to average volumes in non-carriers and in the general population. Carriers of the allele had, on average, an 8% deficit in the frontal lobe, 12% deficit in the occipital lobe (percentage units are expressed in terms of the average volumes seen in the general population of carriers and non-carriers). A reduction in temporal lobe volume was observed in participants with a higher BMI, but not in carriers of the risk allele. A pronounced effect of BMI was seen in carriers of the *FTO* allele showing volume deficits in all the other lobes of the brain, as well as in the brain stem and cerebellum. The authors proposed as a strong hypothesis that “BMI affects brain structure and that *FTO* exerts some additive detectable effect over and above whatever the BMI of the person happens to be” [82].

The possible relationship between neurodegeneration and obesity in animal models and in humans has been studied now for over a decade with a primary focus on the possibility that obesity and related metabolic disorders exacerbate neurodegeneration and thereby, promote cognitive decline and increase vulnerability to brain injury [73]. Based upon the identification of hereditary neurodegenerative disorders associated with obesity such as Alstrom, Bardet-Biedl or Prader-Willi syndromes, some studies have addressed the possibility that neurodegeneration in the brain may be a causal factor for obesity [83]. A more recent association between obesity and neurological function is based upon correlations with biological processes of oxidative stress and inflammation. While the causal nature of these processes to neurodegeneration has not been definitively established, it is widely accepted that neuroinflammation and oxidative stress responses occur with clinical manifestation of the disease. Given the recent reports of adipokines within the body fat and the elevation of these inflammatory factors with stimulation, a more direct linkage between obesity and various human diseases, including neurodegenerative disease, has been hypothesized. In the past decade, a linkage has been demonstrated between being overweight in middle age and increased risk for AD and other forms of dementia [84, 85]. However, as to date, the exact nature of the elevated risk has not been identified and characterized. There however, have been a number of hypotheses put forth, many including a role for inflammation. As previously stated, WAT can produce an array of inflammatory-related factors, for which expression levels may be modified in obesity. It has been proposed that an obesity-related chronic low-grade inflammation can serve to change the environment leading to a priming the brain for subsequent insults leading to a heightened inflammatory response and possibly exacerbation of the damage (figure 5).

Figure 5. low grade chronic inflammation affect the response of the brain to later injury.

Obesity has a major negative impact on cognitive function due to vascular defects, impaired insulin metabolism and signaling pathway or a defect in glucose transport mechanisms in brain [86]. As shown in figure 4, leptin level is increased in obesity but there is also evidence that leptin signaling may become less effective in obesity, provoking a leptin-resistance status [87-89]. Thus, obesity, as it relates to leptin, may be due to a lack of leptin or of its receptor(s) but may also be a consequence of a signaling defect. Interestingly, leptin has protective effects in the brain both *in vitro* and *in vivo* and thus, has been suggested to be a good candidate as a link between obesity and neurodegeneration [90]. Similar to leptin, ATX is increased in obesity. LPA receptors are present in the CNS but the potential effect of ATX on oxidative stress or neuroinflammation was not known. In a recent study, Awada et al. [91] demonstrated that ATX synthesis and secretion by the brain immune cell, the microglia, have a protective effect by mitigating intracellular oxidation. These data suggests a novel anti-oxidant role for ATX in the brain. In contrast, adiponectin level is lowered with obesity [92]. In the CNS, adiponectin has been shown to improve cerebrovascular injury in mice [93, 94]. A deficiency in adiponectin in the mouse increases the severity of seizure activity [95] while presence of adiponectin provides a level of protection to hippocampal neurons against kainic acid-induced excitotoxicity [96]. It is likely that other factors produced by the WAT could have some effects on the CNS and further investigations are needed to decipher this complex network.

4. Susceptibility of the CNS to obesity in animal studies

Animal models of obesity have been very useful and important for understanding the regulation of food intake and imbalance in energy expenditure. The initial models examined spontaneous single gene mutations leading to the loss of the gene function [97]. The first of these models described is the agouti mouse [98, 99]. In addition to rats, other species have been used to study obesity related issues. These include, pigs, chicken, and even bats [97, 100, 101]. As several genes have been found to be involved in energy balance regulation, the advancement of methods for the overexpression or silencing of genes has allowed for a dramatic increase in the number of mouse models of obesity.

There is a growing body of evidence that nutrition could affect the inflammatory status of the brain [102, 103]. High dietary fat is a significant risk for cerebral oxidative stress development, neuronal inflammation, vascular dementia, AD, and Parkinson disease [104-108]. High fat diet induces a rapid (24 hours) temporary inflammation in the CNS, which can potentially progress to a chronic condition in obese mice as well as in human and leads to gliosis and mediobasal hypothalamus neuronal injury [109].

In genetic murine model of obesity, an increased susceptibility of CNS to trauma has been observed; obesity is an aggravating factor in chemical-induced neurodegeneration. In mice deficient for the leptin gene (*ob/ob*), the effects of two neurotoxicants are exacerbated, methamphetamine (METH), which affects dopaminergic neurons and kainic acid (KA), affecting the hippocampus [110]. The *ob/ob* mice are also more susceptible to seizure induced by the gamma-aminobutyric acid A receptor (GABAAR) antagonist, pentylenetetrazol (PTZ) [111].

It is now known that in distinct neurogenic sites of the brain the presence of stem/progenitor cells allows for the generation of new neurons over the full lifespan [112]. This process is influenced by a number of factors including cytokines, hormones, growth factors, and exercise [112-116]. The regulatory effects of growth factors demonstrate a level of specificity for brain regions with brain-derived neurotrophic factor (BDNF) showing prominent effects in the hippocampus while ciliary neurotrophic factor (CNTF) induces neurogenesis in the hypothalamus. In this case the neurogenesis occurs in the satiety centers inducing a persistent weight loss [117]. More importantly, with regards to inflammatory factors, injury to the brain such as ischemia [118], epilepsy [119], or chemically induced neurodegeneration [120] induce an increase in neurogenesis. This induction has been termed "injury-induced neurogenesis". A relationship between adult neurogenesis and obesity has been demonstrated in the decrease in the turnover of new neurons in the hypothalamic arcuate nucleus (region playing a key role in body weight regulation) in obese mice (high fat diet or *ob/ob*) [121]. While the research effort targeted toward this area of the effects of nutrition or obesity on adult neurogenesis is in its infancy, it is likely that a link similar to what has been found with neurodegeneration, may be found for molecules such as Omega 3 fatty acids, flavonoids, and polyphenols [122-124].

5. Conclusion

It is now well accepted that obesity is associated with several pathologies including neuropathies and the ability of the nervous system to repair following injury. While further research is needed in characterizing the nature of the effect of obesity on the nervous system there are current studies suggesting that such effects can be modified. For example, resveratrol or ursolic acid have been shown to attenuate obesity-associated nervous system inflammation resulting in an improvement of memory deficits in mice fed a high-fat diet. [125, 126]. Given the accelerated increase in obesity and neurodegenerative diseases as well as the influence of childhood health status and adult disease, there is a critical need to better understand the relationship between obesity and the nervous system. Identification of the critical factors underlying the various changes seen in the brain and its response to injury as a function of age, nutritional status, and body mass, i.e., obesity will lay the foundation for developing therapeutic interventions that will be applicable to the human population.

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