



HAL
open science

Influence of Obesity on Neurodegenerative Diseases

Rana Awada, Avinash Parimisetty, Christian Lefebvre d'Hellencourt

► **To cite this version:**

Rana Awada, Avinash Parimisetty, Christian Lefebvre d'Hellencourt. Influence of Obesity on Neurodegenerative Diseases. Neurodegenerative Diseases, InTech, pp.381-401, 2013, 10.5772/53671 . hal-02304316

HAL Id: hal-02304316

<https://hal.univ-reunion.fr/hal-02304316>

Submitted on 3 Oct 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

Influence of Obesity on Neurodegenerative Diseases

Rana Awada, Avinash Parimisetty, Christian Lefebvre D'Hellencourt

► **To cite this version:**

Rana Awada, Avinash Parimisetty, Christian Lefebvre D'Hellencourt. Influence of Obesity on Neurodegenerative Diseases. Neurodegenerative Diseases, InTech ,pp.381-401, 2013, 10.5772/53671 . hal-02304316

HAL Id: hal-02304316

<https://hal.univ-reunion.fr/hal-02304316>

Submitted on 3 Oct 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Influence of Obesity on Neurodegenerative Diseases

Rana Awada , Avinash Parimisetty and
Christian Lefebvre d'Hellencourt

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/53671>

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).

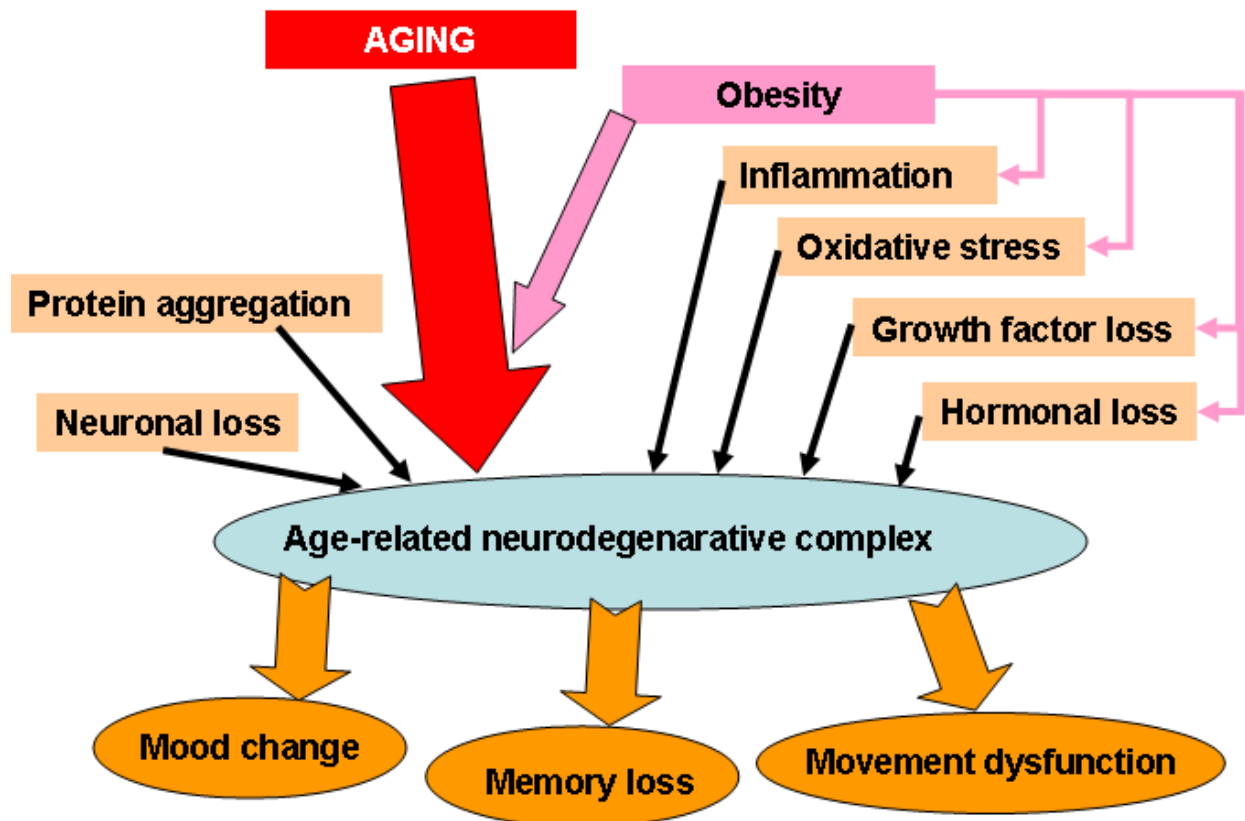


Figure 1. Obesity accelerates age and age related pathologies. Adapted from [8]

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].

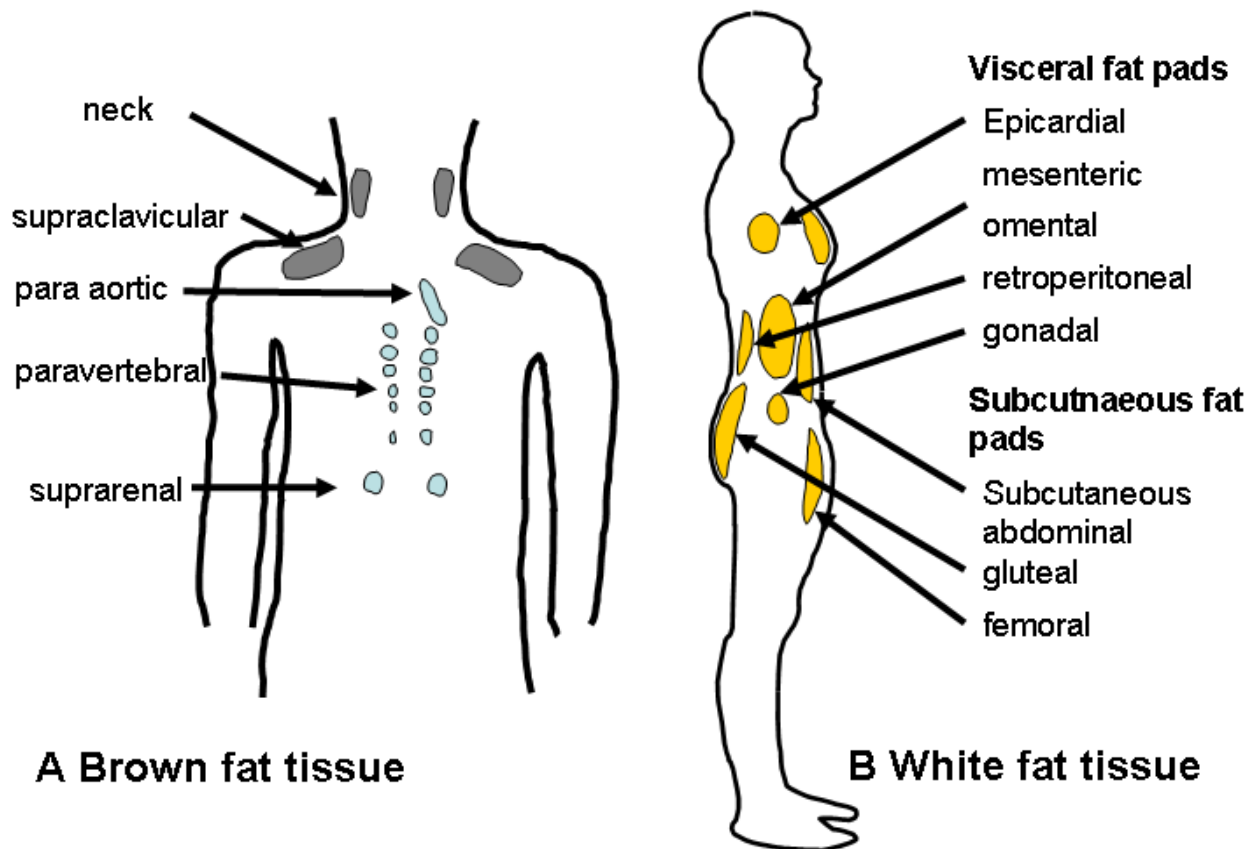


Figure 2. Brown fat (A) and white fat (B) tissue distribution in adult from [10, 11]

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].

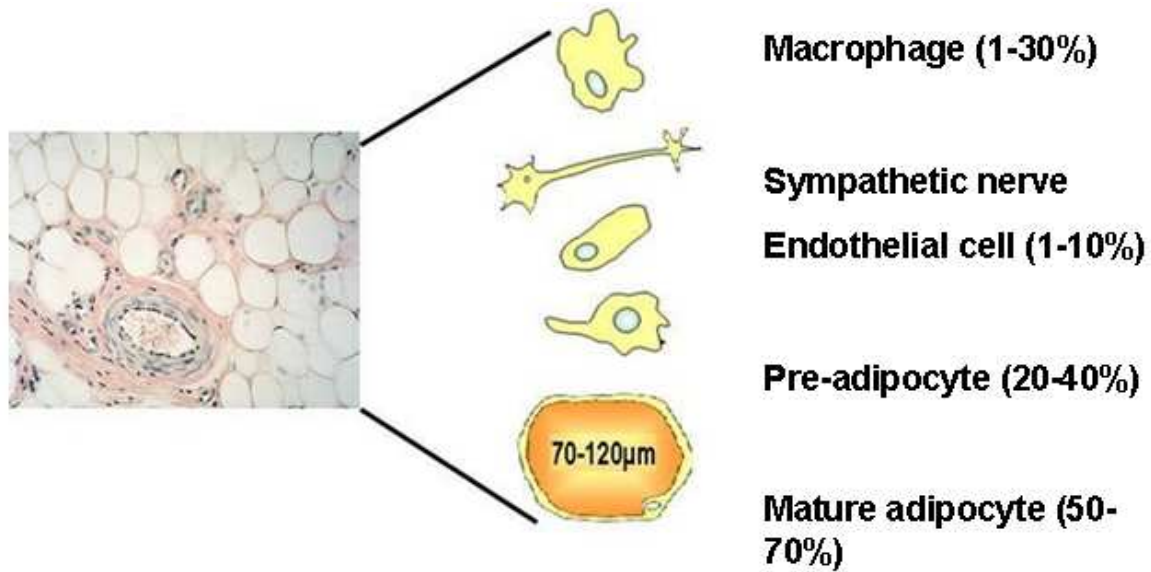


Figure 3. Cells present in the fat tissue adapted from [13, 18]

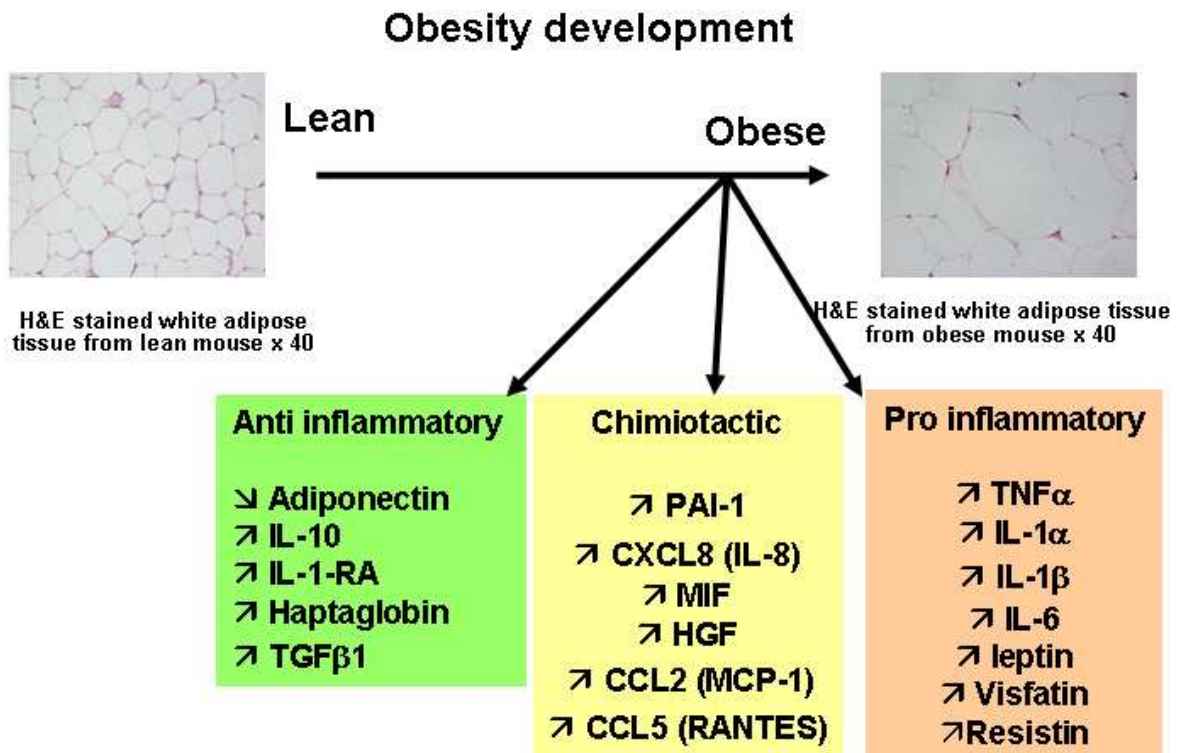


Figure 4. Inflammatory factors produced by WAT in obese situations. [26-35]

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).

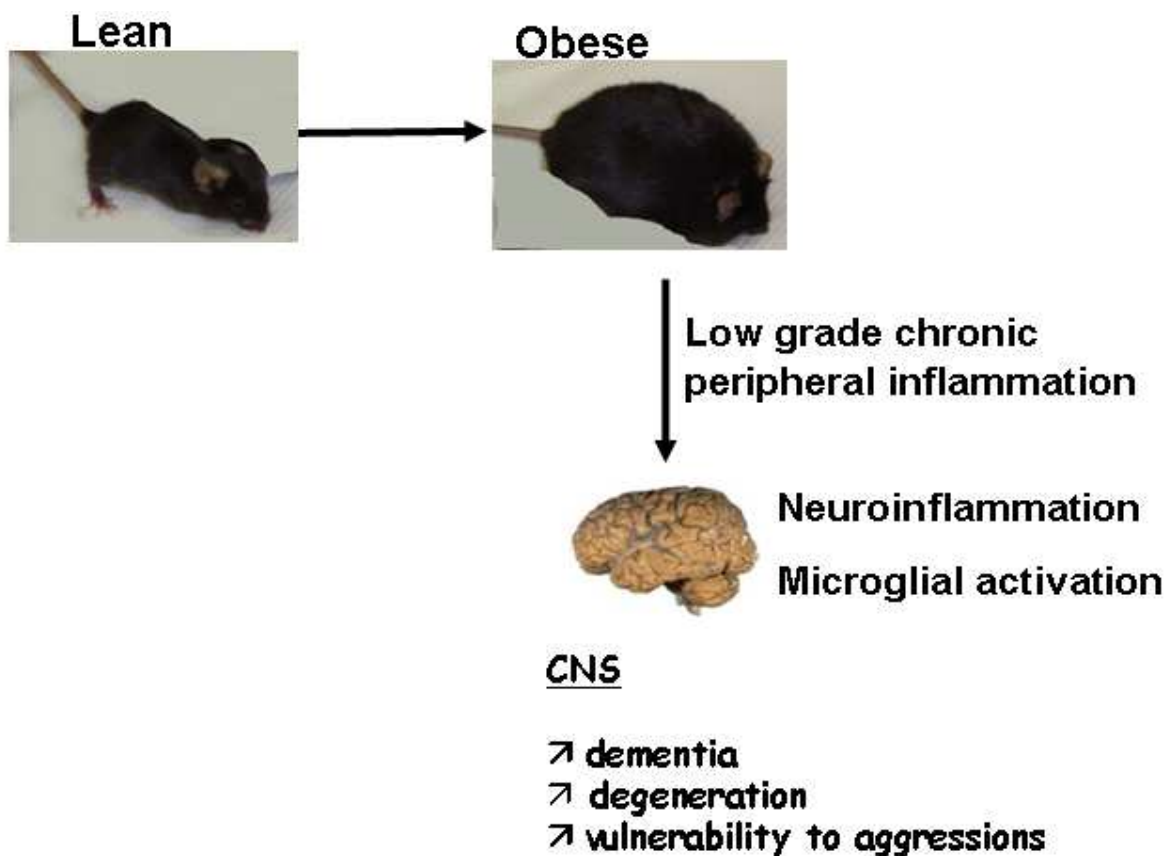


Figure 5. low grade chronic inflammation affect the response of the brain to later injury.

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, pentylentetrazol (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.

Acknowledgements

We would like to thank Dr. G. Jean Harry (NTP/NIEHS/NIH) for her comments and edition. We would like to thank the 'Region La Reunion', Europe (CPER/FEDER) for its funding supports. AP is funded by fellowships from 'Conseil Régional de La Réunion'.

Author details

Rana Awada , Avinash Parimisetty and Christian Lefebvre d'Hellencourt*

*Address all correspondence to: Christian.Lefebvre-d-Hellencourt@univ-reunion.fr

Groupe d'Etude sur l'Inflammation Chronique et l'Obésité (GEICO), EA 4516, Plateforme CYROI, UFR Santé, Université de La Réunion, Ile de La Réunion, France

References

- [1] Prentice AM. The emerging epidemic of obesity in developing countries. *Int J Epidemiol* 2006; 35(1) 93-9
- [2] World Health Organisation (WHO). Obesity in Europe. <http://www.euro.who.int/obesity>. 2008
- [3] Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000; 894(i-xii, 1-253

- [4] Mei Z, Grummer-Strawn LM, Pietrobelli A, Goulding A, Goran MI and Dietz WH. Validity of body mass index compared with other body-composition screening indexes for the assessment of body fatness in children and adolescents. *Am J Clin Nutr* 2002; 75(6) 978-85
- [5] Eckel RH, Grundy SM and Zimmet PZ. The metabolic syndrome. *Lancet* 2005; 365(9468) 1415-28
- [6] Haslam DW and James WP. Obesity. *Lancet* 2005; 366(9492) 1197-209
- [7] Tzanetakou IP, Katsilambros NL, Benetos A, Mikhailidis DP and Perrea DN. "Is obesity linked to aging?": adipose tissue and the role of telomeres. *Ageing Res Rev* 2012; 11(2) 220-9
- [8] Granholm AC, Boger H and Emborg ME. Mood, memory and movement: an age-related neurodegenerative complex? *Curr Aging Sci* 2008; 1(2) 133-9
- [9] Harwood HJ, Jr. The adipocyte as an endocrine organ in the regulation of metabolic homeostasis. *Neuropharmacology* 2012; 63(1) 57-75
- [10] Nedergaard J, Bengtsson T and Cannon B. Unexpected evidence for active brown adipose tissue in adult humans. *Am J Physiol Endocrinol Metab* 2007; 293(2) E444-52
- [11] Wronska A and Kmiec Z. Structural and biochemical characteristics of various white adipose tissue depots. *Acta Physiol (Oxf)* 2012; 205(2) 194-208
- [12] Cannon B and Nedergaard J. Brown adipose tissue: function and physiological significance. *Physiol Rev* 2004; 84(1) 277-359
- [13] Hauner H. Secretory factors from human adipose tissue and their functional role. *Proc Nutr Soc* 2005; 64(2) 163-9
- [14] Hauner H. The new concept of adipose tissue function. *Physiology & Behavior* 2004; 83(4) 653-8
- [15] Cawthorn WP, Scheller EL and MacDougald OA. Adipose tissue stem cells meet preadipocyte commitment: going back to the future. *J Lipid Res* 2011; 53(2) 227-46
- [16] Tran TT and Kahn CR. Transplantation of adipose tissue and stem cells: role in metabolism and disease. *Nat Rev Endocrinol* 2010; 6(4) 195-213
- [17] Roche R, Hoareau L, Mounet F and Festy F. Adult stem cells for cardiovascular diseases: the adipose tissue potential. *Expert Opin Biol Ther* 2007; 7(6) 791-8
- [18] Palaniyandi R, Awada R, Harry GJ and Lefebvre d'Hellencourt C. White fat tissue, obesity and possible role in neurodegeneration in Harry GJ and Tilson HA (ed) *White fat tissue, obesity and possible role in neurodegeneration*. Book 2010
- [19] Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL and Ferrante AW, Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 2003; 112(12) 1796-808

- [20] Greenberg AS and Obin MS. Obesity and the role of adipose tissue in inflammation and metabolism. *Am J Clin Nutr* 2006; 83(2) 461S-5S
- [21] Moschen AR, Kaser A, Enrich B, Mosheimer B, Theurl M, Niederegger H and Tilg H. Visfatin, an adipocytokine with proinflammatory and immunomodulating properties. *J Immunol* 2007; 178(3) 1748-58
- [22] Tilg H and Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol* 2006; 6(10) 772-83
- [23] Van Harmelen V, Reynisdottir S, Eriksson P, Thorne A, Hoffstedt J, Lonnqvist F and Arner P. Leptin secretion from subcutaneous and visceral adipose tissue in women. *Diabetes* 1998; 47(6) 913-7
- [24] Fain JN, Madan AK, Hiler ML, Cheema P and Bahouth SW. Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. *Endocrinology* 2004; 145(5) 2273-82
- [25] Lafontan M and Langin D. Lipolysis and lipid mobilization in human adipose tissue. *Prog Lipid Res* 2009; 48(5) 275-97
- [26] Tilg H and Moschen AR. Role of adiponectin and PBEF/visfatin as regulators of inflammation: involvement in obesity-associated diseases. *Clin Sci (Lond)* 2008; 114(4) 275-88
- [27] Berndt J, Kloting N, Kralisch S, Kovacs P, Fasshauer M, Schon MR, Stumvoll M and Bluher M. Plasma visfatin concentrations and fat depot-specific mRNA expression in humans. *Diabetes* 2005; 54(10) 2911-6
- [28] Azuma K, Katsukawa F, Oguchi S, Murata M, Yamazaki H, Shimada A and Saruta T. Correlation between serum resistin level and adiposity in obese individuals. *Obes Res* 2003; 11(8) 997-1001
- [29] Sartipy P and Loskutoff DJ. Monocyte chemoattractant protein 1 in obesity and insulin resistance. *Proc Natl Acad Sci U S A* 2003; 100(12) 7265-70
- [30] Madani R, Karastergiou K, Ogston NC, Miheisi N, Bhome R, Haloob N, Tan GD, Karpe F, Malone-Lee J, Hashemi M, Jahangiri M and Mohamed-Ali V. RANTES release by human adipose tissue in vivo and evidence for depot-specific differences. *Am J Physiol Endocrinol Metab* 2009; 296(6) E1262-8
- [31] Chiellini C, Santini F, Marsili A, Berti P, Bertacca A, Pelosini C, Scartabelli G, Pardini E, Lopez-Soriano J, Centoni R, Ciccarone AM, Benzi L, Vitti P, Del Prato S, Pinchera A and Maffei M. Serum haptoglobin: a novel marker of adiposity in humans. *J Clin Endocrinol Metab* 2004; 89(6) 2678-83

- [32] Hillenbrand A, Knippschild U, Weiss M, Schrezenmeier H, Henne-Bruns D, Huber-Lang M and Wolf AM. Sepsis induced changes of adipokines and cytokines - septic patients compared to morbidly obese patients. *BMC Surg* 2010; 10(26)
- [33] Bell LN, Ward JL, Degawa-Yamauchi M, Bovenkerk JE, Jones R, Cacucci BM, Gupta CE, Sheridan C, Sheridan K, Shankar SS, Steinberg HO, March KL and Considine RV. Adipose tissue production of hepatocyte growth factor contributes to elevated serum HGF in obesity. *Am J Physiol Endocrinol Metab* 2006; 291(4) E843-8
- [34] Fain JN. Release of inflammatory mediators by human adipose tissue is enhanced in obesity and primarily by the nonfat cells: a review. *Mediators Inflamm* 2010; 2010(513948)
- [35] Meier CA, Bobbioni E, Gabay C, Assimacopoulos-Jeannet F, Golay A and Dayer JM. IL-1 receptor antagonist serum levels are increased in human obesity: a possible link to the resistance to leptin? *J Clin Endocrinol Metab* 2002; 87(3) 1184-8
- [36] Panee J. Monocyte Chemoattractant Protein 1 (MCP-1) in obesity and diabetes. *Cytokine* 2012;
- [37] Clement S, Juge-Aubry C, Sgroi A, Conzelmann S, Pazienza V, Pittet-Cuenod B, Meier CA and Negro F. Monocyte chemoattractant protein-1 secreted by adipose tissue induces direct lipid accumulation in hepatocytes. *Hepatology* 2008; 48(3) 799-807
- [38] Gonzalez-Castejon M and Rodriguez-Casado A. Dietary phytochemicals and their potential effects on obesity: a review. *Pharmacol Res* 2011; 64(5) 438-55
- [39] Hotamisligil GS, Shargill NS and Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. *Science* 1993; 259(5091) 87-91
- [40] Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H and Flier JS. TLR4 links innate immunity and fatty acid-induced insulin resistance. *J Clin Invest* 2006; 116(11) 3015-25
- [41] Strowig T, Henao-Mejia J, Elinav E and Flavell R. Inflammasomes in health and disease. *Nature* 481(7381) 278-86
- [42] Stienstra R, Tack CJ, Kanneganti TD, Joosten LA and Netea MG. The inflammasome puts obesity in the danger zone. *Cell Metab* 2012; 15(1) 10-8
- [43] Stienstra R, van Diepen JA, Tack CJ, Zaki MH, van de Veerdonk FL, Perera D, Neale GA, Hooiveld GJ, Hijmans A, Vroegrijk I, van den Berg S, Romijn J, Rensen PC, Joosten LA, Netea MG and Kanneganti TD. Inflammasome is a central player in the induction of obesity and insulin resistance. *Proc Natl Acad Sci U S A* 2011; 108(37) 15324-9
- [44] Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM and Burcelin R. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* 2008; 57(6) 1470-81

- [45] Nicholson JK, Holmes E, Kinross J, Burcelin R, Gibson G, Jia W and Pettersson S. Host-gut microbiota metabolic interactions. *Science* 2012; 336(6086) 1262-7
- [46] Bes-Houtmann S, Roche R, Hoareau L, Gonthier MP, Festy F, Caillens H, Gasque P, Lefebvre d'Hellencourt C and Cesari M. Presence of functional TLR2 and TLR4 on human adipocytes. *Histochem Cell Biol* 2007; 127(2) 131-7
- [47] Meijer K, de Vries M, Al-Lahham S, Bruinenberg M, Weening D, Dijkstra M, Kloosterhuis N, van der Leij RJ, van der Want H, Kroesen BJ, Vonk R and Rezaee F. Human primary adipocytes exhibit immune cell function: adipocytes prime inflammation independent of macrophages. *PLoS ONE* 2011; 6(3) e17154
- [48] Ahima RS and Osei SY. Adipokines in obesity. *Front Horm Res* 2008; 36(182-97)
- [49] Zhang Y, Proenca R, Maffei M, Barone M, Leopold L and Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994; 372(6505) 425-32
- [50] Loffreda S, Yang SQ, Lin HZ, Karp CL, Brengman ML, Wang DJ, Klein AS, Bulkley GB, Bao C, Noble PW, Lane MD and Diehl AM. Leptin regulates proinflammatory immune responses. *Faseb J* 1998; 12(1) 57-65
- [51] Friedman JM and Halaas JL. Leptin and the regulation of body weight in mammals. *Nature* 1998; 395(6704) 763-70
- [52] Banks WA, Kastin AJ, Huang W, Jaspan JB and Maness LM. Leptin enters the brain by a saturable system independent of insulin. *Peptides* 1996; 17(2) 305-11
- [53] Elmquist JK, Bjorbaek C, Ahima RS, Flier JS and Saper CB. Distributions of leptin receptor mRNA isoforms in the rat brain. *J Comp Neurol* 1998; 395(4) 535-47
- [54] Buettner C, Poci A, Muse ED, Etgen AM, Myers MG, Jr. and Rossetti L. Critical role of STAT3 in leptin's metabolic actions. *Cell Metab* 2006; 4(1) 49-60
- [55] Gautron L and Elmquist JK. Sixteen years and counting: an update on leptin in energy balance. *J Clin Invest* 2011; 121(6) 2087-93
- [56] Ohashi K, Ouchi N and Matsuzawa Y. Anti-inflammatory and anti-atherogenic properties of adiponectin. *Biochimie* 2012;
- [57] Ouchi N and Walsh K. Adiponectin as an anti-inflammatory factor. *Clin Chim Acta* 2007; 380(1-2) 24-30
- [58] Robinson K, Prins J and Venkatesh B. Clinical review: adiponectin biology and its role in inflammation and critical illness. *Crit Care* 2011; 15(2) 221
- [59] Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, Hotta K, Shimomura I, Nakamura T, Miyaoka K, Kuriyama H, Nishida M, Yamashita S, Okubo K, Matsubara K, Muraguchi M, Ohmoto Y, Funahashi T and Matsuzawa Y. Paradoxical

- decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* 1999; 257(1) 79-83
- [60] Venkatesh B, Hickman I, Nisbet J, Cohen J and Prins J. Changes in serum adiponectin concentrations in critical illness: a preliminary investigation. *Crit Care* 2009; 13(4) R105
- [61] Uji Y, Yamamoto H, Tsuchihashi H, Maeda K, Funahashi T, Shimomura I, Shimizu T, Endo Y and Tani T. Adiponectin deficiency is associated with severe polymicrobial sepsis, high inflammatory cytokine levels, and high mortality. *Surgery* 2009; 145(5) 550-7
- [62] Teoh H, Quan A, Bang KW, Wang G, Lovren F, Vu V, Haitisma JJ, Szmítko PE, Al-Omran M, Wang CH, Gupta M, Peterson MD, Zhang H, Chan L, Freedman J, Sweeney G and Verma S. Adiponectin deficiency promotes endothelial activation and profoundly exacerbates sepsis-related mortality. *Am J Physiol Endocrinol Metab* 2008; 295(3) E658-64
- [63] Vachharajani V, Cunningham C, Yoza B, Carson J, Jr., Vachharajani TJ and McCall C. Adiponectin-deficiency exaggerates sepsis-induced microvascular dysfunction in the mouse brain. *Obesity (Silver Spring)* 2012; 20(3) 498-504
- [64] Umezū-Goto M, Kishi Y, Taira A, Hama K, Dohmae N, Takio K, Yamori T, Mills GB, Inoue K, Aoki J and Arai H. Autotaxin has lysophospholipase D activity leading to tumor cell growth and motility by lysophosphatidic acid production. *J Cell Biol* 2002; 158(2) 227-33
- [65] Ishii I, Fukushima N, Ye X and Chun J. Lysophospholipid receptors: signaling and biology. *Annu Rev Biochem* 2004; 73(321-54)
- [66] Simon MF, Daviaud D, Pradere JP, Gres S, Guigne C, Wabitsch M, Chun J, Valet P and Saulnier-Blache JS. Lysophosphatidic acid inhibits adipocyte differentiation via lysophosphatidic acid 1 receptor-dependent down-regulation of peroxisome proliferator-activated receptor gamma2. *J Biol Chem* 2005; 280(15) 14656-62
- [67] Valet P, Pages C, Jeanneton O, Daviaud D, Barbe P, Record M, Saulnier-Blache JS and Lafontan M. Alpha2-adrenergic receptor-mediated release of lysophosphatidic acid by adipocytes. A paracrine signal for preadipocyte growth. *J Clin Invest* 1998; 101(7) 1431-8
- [68] Fan H, Zingarelli B, Harris V, Tempel GE, Halushka PV and Cook JA. Lysophosphatidic acid inhibits bacterial endotoxin-induced pro-inflammatory response: potential anti-inflammatory signaling pathways. *Mol Med* 2008; 14(7-8) 422-8
- [69] Ferry G, Tellier E, Try A, Gres S, Naime I, Simon MF, Rodriguez M, Boucher J, Tack I, Gesta S, Chomarot P, Dieu M, Raes M, Galizzi JP, Valet P, Boutin JA and Saulnier-Blache JS. Autotaxin is released from adipocytes, catalyzes lysophosphatidic acid

- synthesis, and activates preadipocyte proliferation. Up-regulated expression with adipocyte differentiation and obesity. *J Biol Chem* 2003; 278(20) 18162-9
- [70] Gesta S, Simon MF, Rey A, Sibrac D, Girard A, Lafontan M, Valet P and Saulnier-Blache JS. Secretion of a lysophospholipase D activity by adipocytes: involvement in lysophosphatidic acid synthesis. *J Lipid Res* 2002; 43(6) 904-10
- [71] Boucher J, Quilliot D, Praderes JP, Simon MF, Gres S, Guigne C, Prevot D, Ferry G, Boutin JA, Carpenne C, Valet P and Saulnier-Blache JS. Potential involvement of adipocyte insulin resistance in obesity-associated up-regulation of adipocyte lysophospholipase D/autotaxin expression. *Diabetologia* 2005; 48(3) 569-77
- [72] Whitmer RA. The epidemiology of adiposity and dementia. *Curr Alzheimer Res* 2007; 4(2) 117-22
- [73] Bruce-Keller AJ, Keller JN and Morrison CD. Obesity and vulnerability of the CNS. *Biochim Biophys Acta* 2009; 1792(5) 395-400
- [74] Taki Y, Kinomura S, Sato K, Inoue K, Goto R, Okada K, Uchida S, Kawashima R and Fukuda H. Relationship between body mass index and gray matter volume in 1,428 healthy individuals. *Obesity (Silver Spring)* 2008; 16(1) 119-24
- [75] Ward MA, Carlsson CM, Trivedi MA, Sager MA and Johnson SC. The effect of body mass index on global brain volume in middle-aged adults: a cross sectional study. *BMC Neurol* 2005; 5(23)
- [76] Gustafson D, Lissner L, Bengtsson C, Bjorkelund C and Skoog I. A 24-year follow-up of body mass index and cerebral atrophy. *Neurology* 2004; 63(10) 1876-81
- [77] Jagust W, Harvey D, Mungas D and Haan M. Central obesity and the aging brain. *Arch Neurol* 2005; 62(10) 1545-8
- [78] DeBette S, Beiser A, Hoffmann U, Decarli C, O'Donnell CJ, Massaro JM, Au R, Himali JJ, Wolf PA, Fox CS and Seshadri S. Visceral fat is associated with lower brain volume in healthy middle-aged adults. *Ann Neurol* 2010; 68(2) 136-44
- [79] Pannacciulli N, Del Parigi A, Chen K, Le DS, Reiman EM and Tataranni PA. Brain abnormalities in human obesity: a voxel-based morphometric study. *Neuroimage* 2006; 31(4) 1419-25
- [80] Walther K, Birdsill AC, Glisky EL and Ryan L. Structural brain differences and cognitive functioning related to body mass index in older females. *Hum Brain Mapp* 2010; 31(7) 1052-64
- [81] Raji CA, Ho AJ, Parikshak NN, Becker JT, Lopez OL, Kuller LH, Hua X, Leow AD, Toga AW and Thompson PM. Brain structure and obesity. *Hum Brain Mapp* 2010; 31(3) 353-64
- [82] Ho AJ, Stein JL, Hua X, Lee S, Hibar DP, Leow AD, Dinov ID, Toga AW, Saykin AJ, Shen L, Foroud T, Pankratz N, Huentelman MJ, Craig DW, Gerber JD, Allen AN,

- Corneveaux JJ, Stephan DA, DeCarli CS, DeChairo BM, Potkin SG, Jack CR, Jr., Weiner MW, Raji CA, Lopez OL, Becker JT, Carmichael OT and Thompson PM. A commonly carried allele of the obesity-related FTO gene is associated with reduced brain volume in the healthy elderly. *Proc Natl Acad Sci U S A* 2010; 107(18) 8404-9
- [83] Ristow M. Neurodegenerative disorders associated with diabetes mellitus. *J Mol Med* 2004; 82(8) 510-29
- [84] Gustafson D. Adiposity indices and dementia. *Lancet Neurol* 2006; 5(8) 713-20
- [85] Gustafson D, Rothenberg E, Blennow K, Steen B and Skoog I. An 18-year follow-up of overweight and risk of Alzheimer disease. *Arch Intern Med* 2003; 163(13) 1524-8
- [86] Naderali EK, Ratcliffe SH and Dale MC. Obesity and Alzheimer's disease: a link between body weight and cognitive function in old age. *Am J Alzheimers Dis Other Demen* 2009; 24(6) 445-9
- [87] Myers MG, Jr., Heymsfield SB, Haft C, Kahn BB, Laughlin M, Leibel RL, Tschop MH and Yanovski JA. Challenges and opportunities of defining clinical leptin resistance. *Cell Metab* 2012; 15(2) 150-6
- [88] St-Pierre J and Tremblay ML. Modulation of leptin resistance by protein tyrosine phosphatases. *Cell Metab* 2012; 15(3) 292-7
- [89] Shimizu H, Oh IS, Okada S and Mori M. Leptin resistance and obesity. *Endocr J* 2007; 54(1) 17-26
- [90] Doherty GH. Obesity and the ageing brain: could leptin play a role in neurodegeneration? *Curr Gerontol Geriatr Res* 2011; 2011(708154)
- [91] Awada R, Rondeau P, Gres S, Saulnier-Blache JS, Lefebvre d'Hellencourt C and Bourdon E. Autotaxin protects microglial cells against oxidative stress. *Free Radic Biol Med* 2012; 52(2) 516-26
- [92] Hu E, Liang P and Spiegelman BM. AdipoQ is a novel adipose-specific gene dysregulated in obesity. *J Biol Chem* 1996; 271(18) 10697-703
- [93] Chen B, Liao WQ, Xu N, Xu H, Wen JY, Yu CA, Liu XY, Li CL, Zhao SM and Campbell W. Adiponectin protects against cerebral ischemia-reperfusion injury through anti-inflammatory action. *Brain Res* 2009; 1273(129-37)
- [94] Nishimura M, Izumiya Y, Higuchi A, Shibata R, Qiu J, Kudo C, Shin HK, Moskowitz MA and Ouchi N. Adiponectin prevents cerebral ischemic injury through endothelial nitric oxide synthase dependent mechanisms. *Circulation* 2008; 117(2) 216-23
- [95] Lee EB, Warmann G, Dhir R and Ahima RS. Metabolic dysfunction associated with adiponectin deficiency enhances kainic acid-induced seizure severity. *J Neurosci* 2012; 31(40) 14361-6

- [96] Jeon BT, Shin HJ, Kim JB, Kim YK, Lee DH, Kim KH, Kim HJ, Kang SS, Cho GJ, Choi WS and Roh GS. Adiponectin protects hippocampal neurons against kainic acid-induced excitotoxicity. *Brain Res Rev* 2009; 61(2) 81-8
- [97] Speakman J, Hambly C, Mitchell S and Krol E. Animal models of obesity. *Obes Rev* 2007; 8 Suppl 1(55-61)
- [98] Dickies MM. A new viable yellow mutation in the house mouse. *J Hered* 1962; 53(84-6)
- [99] Yen TT, Gill AM, Frigeri LG, Barsh GS and Wolff GL. Obesity, diabetes, and neoplasia in yellow A(vy)/- mice: ectopic expression of the agouti gene. *Faseb J* 1994; 8(8) 479-88
- [100] Dietrich HM. Housing, breeding and selecting chickens of the Obese strain (OS) with spontaneous autoimmune thyroiditis. *Lab Anim* 1989; 23(4) 345-52
- [101] Hen G, Yosefi S, Simchaev V, Shinder D, Hrubby VJ and Friedman-Einat M. The melanocortin circuit in obese and lean strains of chicks. *J Endocrinol* 2006; 190(2) 527-35
- [102] Keller JN. Special issue: Reciprocal interactions between diet, metabolism, and the nervous system. Foreword. *Biochim Biophys Acta* 2009; 1792(5) 393-4
- [103] Zhang L, Bruce-Keller AJ, Dasuri K, Nguyen AT, Liu Y and Keller JN. Diet-induced metabolic disturbances as modulators of brain homeostasis. *Biochim Biophys Acta* 2009; 1792(5) 417-22
- [104] Kalmijn S. Fatty acid intake and the risk of dementia and cognitive decline: a review of clinical and epidemiological studies. *J Nutr Health Aging* 2000; 4(4) 202-7
- [105] Hida K, Wada J, Eguchi J, Zhang H, Baba M, Seida A, Hashimoto I, Okada T, Yasuhara A, Nakatsuka A, Shikata K, Hourai S, Futami J, Watanabe E, Matsuki Y, Hiramatsu R, Akagi S, Makino H and Kanwar YS. Visceral adipose tissue-derived serine protease inhibitor: a unique insulin-sensitizing adipocytokine in obesity. *Proc Natl Acad Sci U S A* 2005; 102(30) 10610-5
- [106] Bousquet M, St-Amour I, Vandal M, Julien P, Cicchetti F and Calon F. High-fat diet exacerbates MPTP-induced dopaminergic degeneration in mice. *Neurobiol Dis* 2012; 45(1) 529-38
- [107] Choi JY, Jang EH, Park CS and Kang JH. Enhanced susceptibility to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine neurotoxicity in high-fat diet-induced obesity. *Free Radic Biol Med* 2005; 38(6) 806-16
- [108] Morris JK, Bomhoff GL, Stanford JA and Geiger PC. Neurodegeneration in an animal model of Parkinson's disease is exacerbated by a high-fat diet. *Am J Physiol Regul Integr Comp Physiol* 299(4) R1082-90
- [109] Thaler JP, Yi CX, Schur EA, Guyenet SJ, Hwang BH, Dietrich MO, Zhao X, Sarruf DA, Izgur V, Maravilla KR, Nguyen HT, Fischer JD, Matsen ME, Wisse BE, Morton

- GJ, Horvath TL, Baskin DG, Tschop MH and Schwartz MW. Obesity is associated with hypothalamic injury in rodents and humans. *J Clin Invest* 2012; 122(1) 153-62
- [110] Sriram K, Benkovic SA, Miller DB and O'Callaghan JP. Obesity exacerbates chemically induced neurodegeneration. *Neuroscience* 2002; 115(4) 1335-46
- [111] Erbayat-Altay E, Yamada KA, Wong M and Thio LL. Increased severity of pentylene-tetrazol induced seizures in leptin deficient ob/ob mice. *Neurosci Lett* 2008; 433(2) 82-6
- [112] Ming GL and Song H. Adult neurogenesis in the mammalian brain: significant answers and significant questions. *Neuron* 2011; 70(4) 687-702
- [113] Anderson MF, Aberg MA, Nilsson M and Eriksson PS. Insulin-like growth factor-I and neurogenesis in the adult mammalian brain. *Brain Res Dev Brain Res* 2002; 134(1-2) 115-22
- [114] Ciaroni S, Cuppini R, Cecchini T, Ferri P, Ambrogini P, Cuppini C and Del Grande P. Neurogenesis in the adult rat dentate gyrus is enhanced by vitamin E deficiency. *J Comp Neurol* 1999; 411(3) 495-502
- [115] Valente T, Hidalgo J, Bolea I, Ramirez B, Angles N, Reguant J, Morello JR, Gutierrez C, Boada M and Unzeta M. A diet enriched in polyphenols and polyunsaturated fatty acids, LMN diet, induces neurogenesis in the subventricular zone and hippocampus of adult mouse brain. *J Alzheimers Dis* 2009; 18(4) 849-65
- [116] van Praag H, Christie BR, Sejnowski TJ and Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc Natl Acad Sci U S A* 1999; 96(23) 13427-31
- [117] Kokoeva MV, Yin H and Flier JS. Neurogenesis in the hypothalamus of adult mice: potential role in energy balance. *Science* 2005; 310(5748) 679-83
- [118] Bachner D, Ahrens M, Betat N, Schroder D and Gross G. Developmental expression analysis of murine autotaxin (ATX). *Mech Dev* 1999; 84(1-2) 121-5
- [119] Bengzon J, Kokaia Z, Elmer E, Nanobashvili A, Kokaia M and Lindvall O. Apoptosis and proliferation of dentate gyrus neurons after single and intermittent limbic seizures. *Proc Natl Acad Sci U S A* 1997; 94(19) 10432-7
- [120] Harry GJ, McPherson CA, Wine RN, Atkinson K and Lefebvre d'Hellencourt C. Trimethyltin-induced neurogenesis in the murine hippocampus. *Neurotox Res* 2004; 5(8) 623-7
- [121] McNay DE, Briancon N, Kokoeva MV, Maratos-Flier E and Flier JS. Remodeling of the arcuate nucleus energy-balance circuit is inhibited in obese mice. *J Clin Invest* 2012; 122(1) 142-52
- [122] Dias GP, Cavegn N, Nix A, do Nascimento Bevilaqua MC, Stangl D, Zainuddin MS, Nardi AE, Gardino PF and Thuret S. The role of dietary polyphenols on adult hippo-

campal neurogenesis: molecular mechanisms and behavioural effects on depression and anxiety. *Oxid Med Cell Longev* 2012; 2012(541971)

- [123] Stangl D and Thuret S. Impact of diet on adult hippocampal neurogenesis. *Genes Nutr* 2009; 4(4) 271-82
- [124] Zainuddin MS and Thuret S. Nutrition, adult hippocampal neurogenesis and mental health. *Br Med Bull* 2012;
- [125] Jeon BT, Jeong EA, Shin HJ, Lee Y, Lee DH, Kim HJ, Kang SS, Cho GJ, Choi WS and Roh GS. Resveratrol attenuates obesity-associated peripheral and central inflammation and improves memory deficit in mice fed a high-fat diet. *Diabetes* 2012; 61(6) 1444-54
- [126] Lu J, Wu DM, Zheng YL, Hu B, Cheng W, Zhang ZF and Shan Q. 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; 25(8) 1658-67

