Review

Obesity and vulnerability of the CNS

Annadora J. Bruce-Keller *, Jeffrey N. Keller, Christopher D. Morrison

Inflammation and Neurodegeneration Laboratory, Pennington Biomedical Research Center, Louisiana State University, 6400 Perkins Road, Baton Rouge, LA 70808, USA

ABSTRACT

The incidence of obesity is increasing worldwide, and is especially pronounced in developed western countries. While the consequences of obesity on metabolic and cardiovascular physiology are well established, epidemiological and experimental data are beginning to establish that the central nervous system (CNS) may also be detrimentally affected by obesity and obesity-induced metabolic dysfunction. In particular, data show that obesity in human populations is associated with cognitive decline and enhanced vulnerability to brain injury, while experimental studies in animal models confirm a profile of heightened vulnerability and decreased cognitive function. This review will describe findings from human and animal studies to summarize current understanding of how obesity affects the brain. Furthermore, studies aimed at identifying key elements of body–brain dialog will be discussed to assess how various metabolic and adipose-related signals could adversely affect the CNS. Overall, data suggest that obesity-induced alterations in metabolism may significantly synergize with age to impair brain function and accelerate age-related diseases of the nervous system. Thus, enhanced understanding of the effects of obesity and obesity-related metabolic dysfunction on the brain are especially critical as increasing numbers of obese individuals approach advanced age.

© 2008 Elsevier B.V. All rights reserved.

1. Introduction

The epidemic of obesity has become pandemic, defined as an epidemic occurring over a wide geographic area and affecting an exceptionally high proportion of the population. The rise in obesity rates was first noted in the US, but has spread to other industrialized nations and it is even now being documented in developing countries. Indeed, the global extent of the obesity pandemic was formally recognized by the World Health Organization (WHO) in 1997, and worldwide obesity rates are increasing dramatically [1]. Estimates from the WHO indicate that as of 2005, at least 400 million adults (9.8%) were obese. Unlike most global health concerns, the obesity crisis is even more severe in developed nations. From 1960 to 2004, the prevalence of obesity in the US has more than doubled among adults from 13.3% to 32.1%, while the percentage of Americans overweight during the same period has increased from 44.8% to 66%, with most of this rise occurring since 1980 [2]. Obesity is clinically identified based on measurements of body mass index [3], but can be generally defined as the physiological condition in which excess body fat has accumulated to an extent that can negatively affect health. This definition is based on the dramatically enhanced risk for a myriad of disease conditions with obesity, including type 2 diabetes, cardiovascular disease, gastrointestinal and respiratory difficulties, and many types of cancer (reviewed in [4]). Furthermore, obesity is very closely associated with metabolic syndrome, which is characterized by a group of metabolic disorders that can include abdominal obesity, insulin resistance or glucose intolerance, atherogenic dyslipidemia, elevated blood pressure, and increased expression of prothrombotic and proinflammatory markers (reviewed in [5]).

Based on the large body of evidence that strongly indicates that obesity accelerates the onset and exaggerates the severity of a myriad of age-related disorders diseases, including hypertension [6,7], myocardial infarction [8], and stroke [9,10], one could theorize that obesity accelerates age and age-related pathologies. Thus, it is possible that obesity might synergistically interact with the aging process to significantly accelerate the development of age-related disease and speed functional declines in large proportions of the US and global population. The clinical significance of this possibility is amplified by observations that obesity rates among the elderly may be even higher than in the general population, as estimates indicate that 72% of Americans aged 60 and over are overweight with 32.4% obese [11]. Thus, to address this ominous potential public health crisis, it is necessary that clinicians and investigators work together to better understand the etiology of obesity-induced alterations to overall health in both clinical and experimental settings.

One especially costly and debilitating deficit of aging is the loss of cognitive function and the onset of dementia. All cognitive disorders, including dementia, become more common with age. Indeed, it has been estimated that dementia affects as many as 6–10% of people in industrialized nations aged 65 or older, 40–60% of whom may have Alzheimer's disease [12–16]. Despite it's strong association with age, dementia has been proposed as a mainly preventable condition with a large number of modifiable risk factors, including obesity, metabolic

* Corresponding author. Tel.: +1 225 763 2735; fax: +1 225 763 0260.
E-mail address: annadora.bruce-keller@pbrc.edu (A.J. Bruce-Keller).

syndrome, and cardiovascular disease [17]. In light of the 1 billion overweight and 300 million obese individuals worldwide [18], a better understanding of the degree to which, and the mechanisms by which, obesity affects the brain could not only result in significant advances in public health, but could also unmask the pathophysiologic processes that might underlie age-related cognitive dysfunction and dementia.

2. Association of obesity with CNS abnormalities and dysfunction in clinical human studies

As discussed above, the CNS may be one of the more crucial sites at the intersection of age and obesity. This relationship is highlighted by observations of gross abnormalities in overall brain structure and architecture associated with obesity. For example, regression studies in which the effects of age and body mass index (BMI) on brain volume and cognition were measured demonstrated that both age and increased BMI were associated with decreased brain volume [19]. Other studies have confirmed alterations of brain morphology in overweight and obese young adults, and it has been shown that particularly in the frontal lobe, clinical obesity is associated with reductions in focal gray matter volume and enlarged orbitofrontal white matter [20]. Thus, these studies demonstrate that obesity in otherwise healthy middle-aged adults is associated with axonal and/or myelin abnormalities in white matter with decreases in gray matter volumes, which could reflect loss of neurons. Because frontal lobe white matter is more prone to the effects of aging than in other lobes, these data could reflect accelerated aging in obese individuals. Interestingly, these structural abnormalities may be reversible, as it has been reported that structural changes in the brains of obese patients may partially revert with dieting. Specifically, a recent magnetic resonance imaging study has shown that white matter volumes in several basal brain regions are greater in obese subjects compared with lean subjects, with a positive correlation between white matter volume in basal brain structures and waist to hip ratio. More importantly, the detected white matter alterations were partially reversed by dieting [21]. Regional gray matter volumes (which would reflect neuronal cell number and/or expansion) did not differ significantly in obese and lean subjects, and were not affected by dieting [21]. However, it is important to note that these studies were done in non-geriatric populations, indicating that while dieting may reverse some changes, the neurobiological and functional alterations in obese individuals that do not lose weight may be present for decades, and it is not known if they remain reversible with advancing age. In addition to, or possibly because of age-related structural changes, brain aging is associated with enhanced vulnerability to and decreased recovery from injury and/or damage. For example, aging is associated with decreased recovery from traumatic brain injury [22], and likewise, epidemiological data suggests that obese patients suffer more complications and higher mortality than lean patients after traumatic brain injury, an adverse relationship that is further complicated by age [23]. It should be noted, however, that complete consensus regarding the effects of obesity on traumatic injury has not yet been achieved. Indeed, while some studies have shown that obesity is an independent predictor of mortality following blunt trauma [24], other studies have failed to detect increases in mortality following traumatic injury in obese patients, although it was noted that obese individuals had longer hospital stays compared to non-obese patients [25]. In relation to other forms of injury, advanced age is a major risk factor for stroke, and has been reported to increase the severity of stroke-induced brain dysfunction [26]. Elevated adiposity and obesity are also reported to increase the risk of stroke. For example, epidemiological studies have revealed that obesity increases the risk of ischemic stroke [10,27,28]. These studies are also important in that they indicate that the increased risk for stroke in overweight or obese subjects is independent of diabetes, hypertension, or hypercholesterolemia [27]. Additionally, there is evidence indicating that

obesity not only increases stroke incidence, but also might increase stroke-induced damage, as ischemic events in obese patients are reported to be associated with increased complications and higher mortality rates [29,30].

In terms of brain function, obesity may disrupt cognition, as studies have reported deficits in learning, memory, and executive functioning in obese when compared to non-obese patients [31–33]. Other studies of young and middle-aged healthy adults have confirmed the association of obesity with behavioral declines in executive function [34]. Overall, current evidence suggests that obesity and the consequences of obesity, including midlife hypertension, diabetes, and cerebrovascular disease, contribute significantly to cognitive decline and accelerate the development of dementia [35]. For example, retrospective studies have found that an elevation in BMI of only a single unit associates with a 36% increase in Alzheimer's disease in women [36], while a prospective study of a large cohort of people in New York City revealed that those with low-calorie or low-fat diets had significantly lower risks for Alzheimer's disease than did those with higher calorie intake [37]. Similar studies have reported that abdominal adiposity in the elderly increased the incidence of dementia even after correcting for age [38–40]. It is important to note that in these studies, cognitive decline was determined using established and commonly used cognitive assessments like the mini mental status exam, delayed word-list recall, and coding tasks.

Overall, these reports collectively indicate that obesity in humans is associated with increases in brain injury and decreases in brain function. These studies are important in that they underscore the significant public health concern that is developing as increasing percentages of the population continue to age while carrying the additional physiological burden of obesity. Indeed, brain injury and dementia may be among the most costly clinical conditions to treat, as patients are not able to work and may require institutionalization. However, the relationship between obesity and dementia suggests that a careful and controlled study of obesity in experimental settings could help to unravel the pathophysiological mechanisms of age-related dementia. Elucidation of the physiological mechanisms whereby obesity accelerates the progression of age-related brain dysfunction could lead to a better understanding of, and thus a better clinical management of, unsuccessful brain aging. Thus, there has been considerable research impetus in recent years to put well-developed animal models of obesity to use to understand the pathogenesis of obesity-induced CNS dysfunction.

3. Association of obesity with CNS dysfunction in experimental animal studies

In general, animal models of obesity can be generated with environmental manipulation (diet-induced obesity), spontaneous mutants (*ob/ob* or *db/db* mice, *fa/fa* Zucker rats), genetically engineered transgenic animals (CRF or Agrp transgenic mice) or mechanical intervention (chemical lesion of the ventromedial hypothalamus), and use of these animal models has contributed strongly to the understanding of human obesity (reviewed in [41,42]). Genetic models of obesity have been valuable for their utility in identifying genes linked to human obesity, and for elucidating specific pathways that regulate body weight and the pathogenesis for obesity-related metabolic syndromes. The *ob/ob* leptin deficient mouse gains weight rapidly (recognizable at about 4 weeks of age) and may reach three times the normal weight of wild type controls. In addition to obesity and hyperphagia, mutant mice exhibit transient diabetes-like syndrome of hyperglycemia, glucose intolerance, elevated plasma insulin, and impaired wound healing (reviewed in [43]). Obesity in this model is characterized by an increase in both number and size of adipocytes, and injection of leptin into obese homozygotes sharply reduces body weight, decreases food intake, increases energy expenditure, and restores fertility. This specific model has been used

to measure the effects of obesity on the brain [44,45]. However, it can be questioned whether the results obtained from genetic models of obesity arise from the obese phenotype itself or rather the model's genetic/pharmacological background. Thus, diet-induced models of obesity are thought by some to better model obesity in humans, particularly in Western industrialized nations in which high fat/high calorie diets are commonplace. Studies in which specially formulated high fat or calorie diets were given to experimental animals revealed that such diets promote obesity, hyperglycemia, whole-body insulin resistance, and generalized metabolic syndrome function [41,46,47]. Indeed, dietary manipulation studies in experimental animals have led to important advances in the field, including a better understanding of the relative health benefits of fish-based versus animal-based fats [47]. However, an important downside to this approach is the variability in definition of the term "dietary manipulation". Indeed, while numerous investigators have used this approach, neither the exact content nor composition of the diets employed is standardized. For example, while some investigators employ well-defined, commercially available high fat diets in which the fat component replaces carbohydrate and/or protein components, others have simply added fat to a standard rodent chow, leading to an unbalanced diet composition with respect to nutrient content [47]. Unfortunately, then, various diets with very different fat and/or calorie compositions are summarized under the term "diet-induced obesity" in the literature. While diet-induced models of obesity may thus be better experimental representations of obesity in humans, the wide variation in available diets precludes easy comparisons across studies using different diet formulations. However, observations that remain consistent across both genetic and different diet-induced models of obesity likely highlight a common physiological process that is also likely to accordingly transcend species differences to participate in the human condition, and several excellent reviews are available that systematically describe the currently available animal models of obesity [41,43,47–49].

One of the earliest reports of adverse effects of experimental obesity on brain pathology described alterations to the lipid composition of myelin in genetically obese mice. While dysfunction of peripheral myelin and sensory neuropathy is a well established characteristic of type 2 diabetes [50,51], this study reported that genetically obese (*ob*/*ob*) mice had decreased overall levels of myelin and marked alterations to the fatty acid composition of the myelin as compared to wild type mice [52]. The use of a genetic model for these studies is significant in that it suggests that increased adiposity, rather than increase in dietary lipids, is sufficient to alter the composition of brain myelin. This study is supported by more recent imaging studies in humans that also have revealed changes in white matter and myelin abnormalities in association with obesity [53,54]. While the human studies have not been followed up by pathology studies to characterize the actual molecular and biochemical changes to human myelin in obese patients, an obvious consequence of altered myelination would be altered synaptic transmission, and indeed, animal studies have confirmed that experimental obesity is associated with a wide array of cognitive abnormalities [55,56]. For example, diet-induced obesity and insulin resistance have both been shown by several groups to decrease spatial learning skills in rats [57–59]. Other studies have likewise shown that diet-induced obesity is able to synergize with traumatic brain injury in decreasing hippocampal plasticity and learning [60]. Studies have also examined biochemical and histological indices of synaptic dysfunction and reported that obesity is associated with decreases in dendritic spine density [57] and in the expression of synaptic marker proteins such as synapsin and GAP-43 [59–61]. Interestingly, these studies of synaptic markers also reported decreases in local levels of the neurotrophic factor BDNF, suggesting that brain regulation of growth factor synthesis could be regulated by obesity and/or metabolic syndromes. As it is well established that BDNF supports synaptic plasticity and neuronal excitability [62], and appears to be important for maintaining learning and memory function, particularly in aging [63–65], these studies again support the hypothesis that obesity is able to accelerate the physiological indices of brain aging.

Studies have also documented that experimental obesity can synergize with other pathophysiological conditions related to brain aging. For instance, obesity-induced by a high calorie diet has been shown to increase insoluble amyloid burden and decrease cognitive performance in a transgenic mouse model of Alzheimer's disease [66]. Complementary studies have also demonstrated that the obesity-related peptide leptin (see Section 4 below) is able to regulate the secretion and uptake of amyloid beta peptides in vitro [67]. In relation to stroke, studies have shown that blood–brain barrier dysfunction and infarct volume following middle cerebral artery occlusion is increased in genetically obese mice compared to non-obese wild type mice [45]. Finally, it has also been established that neurodegeneration induced by specific neurotoxins is increased by both genetic [68] and diet-induced obesity [69].

Although the physiologic mechanisms whereby obesity adversely affects the brain are not understood (see Section 4, below), both experimental and human studies have shown that obesity is associated with increased oxidative stress, which has been implicated in cognitive declines seen in neurodegenerative diseases [70,71], and indeed has been suggested to be altered by diet [72]. For example, several studies have shown that administration of high fat or high calorie diets to rodents increases free radical generation [73] and protein oxidation [74] in the brain. Furthermore, it has been shown in the Zucker genetic model of rat obesity that endothelial cell dysfunction in this model is caused by oxidative stress secondary to overactivation of NADPH oxidase, which in turn is caused by circulating free fatty acids [75]. Interestingly, NADPH oxidase has also been shown in human studies to mediate obesity-induced oxidative stress in both blood mononuclear cells [76] and endothelial cells [77]. Finally, it should be noted that it has been demonstrated that administration of the lipid-soluble antioxidant Vitamin E not only reverses oxidative modification to proteins in the brains of rats given a high-fat diet, but also normalizes levels of BDNF, synapsin I and cyclic AMP-response element-binding protein (CREB), and prevents obesity-induced alterations to cognitive function [61]. It should be noted, however, that it is not clear at this point if oxidative stress in genetic or diet-induced animal models of obesity are a result of obesity *per se*, or more related to obesity-related metabolic syndrome. Thus, available data from animal models indicates that obesity and/or metabolic syndrome can induce neuropathology and cognitive dysfunction and can also synergize with pathological conditions and/or environmental toxins to accelerate CNS dysfunction. Thus, investigation into the dialog of peripheral signals of adiposity with the CNS is necessary to dissect out the mechanisms of obesity-induced brain pathology.

4. Potential mediators of obesity-related CNS dysfunction

The mechanism(s) by which obesity results in brain injury and/or dysfunction are uncertain and subject to extensive speculation. While postulated indirect mechanisms include the effects of hyperglycemia on brain energetics and/or vascular damage to the central nervous system [78], it is well known that consumption of a high fat diet and/or increased adiposity causes dramatic changes in the profile of bioactive serum lipids, including cholesterol. While an association between cholesterol and cognitive function could be explained based on increased risk stroke or cerebrovascular hypoperfusion, many studies have examined the role of serum cholesterol in brain function independent of vascular effects. In general, results are mixed, with some studies noting a correlation between lipid levels and cognitive function, whereas other studies do not [79–81]. Positive studies related to the role of cholesterol in dementia have primarily related to effects of statin drug use, but these studies have also yielded mixed results, with a generally diminished risk for dementia although some of the tests did not achieve statistical significance [82].

Interestingly, there is compelling evidence that triglycerides and/or free fatty acids might mediate CNS alterations in obese individuals. In

general, triglycerides are good candidates to study the pathogenesis of obesity as other lipid mediators, particularly cholesterol, are subject to complex genetic control. Recent studies have indeed highlighted a potentially important role for triglycerides in the cognitive and pathological alterations in obesity. For example, it has been shown that direct administration of triglycerides can impair hippocampal long-term potentiation, and that lowering of triglycerides pharmacologically with gemfibrozil reduces the expression of markers of oxidative stress in the brains of obese mice [83]. These studies are further supported by clinical studies in which it has been shown that elevated triglycerides are associated with poor cognitive performance in patients with type 2 diabetes [84], and by studies in which the reduction of hypertriglyceridemia with gemfibrozil improved cerebral blood flow and function on the cognitive capacity screening examination [80]. Finally, triglycerides have been shown to impair leptin transport through the blood–brain barrier [85], indicating that the well-characterized phenomena of leptin resistance may be related in part to the action of triglycerides at the blood–brain barrier. Another potential means whereby triglycerides could adversely affect the brain is through their breakdown into free fatty acids, which can also be formed and released directly from adipocytes. Indeed, there is abundant evidence that alterations in free fatty acid metabolism play a key role in many of the local and systemic manifestations of obesity, including insulin resistance, pancreatic beta cell injury, and dyslipidemia [86–88]. In specific relation to the brain, GPR40, a putative free fatty acid receptor, has been localized to the hippocampus [89], and the saturated free fatty acids palmitic acid and lauric acid have both been shown to cause inflammatory signaling in cultured macrophages [90,91], and also to modulate astrocytic and microglial signaling [92]. Conversely, oleic acid has been shown to be ineffective at inducing an inflammatory phenotype in immunocompetent cells [90]. Finally, circulating glucocorticoids have also been studied in terms of their ability to perturb brain function in models of obesity. Obesity is strongly associated with elevated circulating endogenous glucocorticoids, possibly through chronic activation of the sympathetic nervous system [93], and a recent series of elegant studies has provided evidence that elevated glucocorticoids could mediate the effects of diabetes on hippocampal neurogenesis, synaptic plasticity, and cognitive performance [94,95].

In addition to bioactive lipids, serum factors related to adiposity could adversely affect the brain. Indeed, adipose tissue is no longer considered to be an inert tissue functioning solely as an energy store, but is emerging as an important factor in the regulation of many pathological processes [96,97]. Numerous secreted products of adipose tissue have been identified and characterized, and given the moniker "adipokines". Over 50 adipokines have been identified, and generally function as hormones to influence energy homeostasis and feeding behavior [98]. Furthermore, some adipokines, particularly adiponectin and leptin may provide an important link between obesity, insulin resistance and related inflammatory disorders [99,100]. Leptin, originally identified in 1994 as the 16 kDa product of the *ob* gene [101] may also be important in CNS responses to obesity. Leptin is best known for its action as an afferent adiposity signal to the brain that suppresses appetite and increases energy expenditure [102]. Leptin enters the brain via a saturable transport mechanism [103] and while it is known that leptin acts on hypothalamic centers to regulate feeding behavior, leptin receptors (OBR) are widely expressed in numerous extra-hypothalamic regions of the brain, including the hippocampus, cerebellum, amygdale, and brain stem [104–106]. While the full extant of leptin's actions on the brain have not been characterized, the past decade of research has not only revealed that leptin receptors are widely expressed in the CNS, but has also identified numerous additional functions for this hormone in the brain [107]. In particular, there is evidence that leptin influences neuronal excitability via the activation and trafficking of potassium channels in several brain regions, which may be important in regulation of food intake, cognition, and also anti-convulsant effects

[108]. A number of studies have also identified a role for leptin in cognitive processes [109]. For example, it has been shown that direct administration of leptin into the dentate gyrus enhances long-term potentiation [110], and that intravenous administration of leptin to rats facilitates behavioral performance in passive avoidance and Morris water-maze tasks [111]. Finally, leptin has been shown to modulate the inflammatory signaling in microglia [112,113] which could affect brain inflammatory and oxidative pathways.

As a final note, there is a body of data that suggests a potential scenario whereby the sensory perception (generally via olfaction or taste) of calories or nutrients might significantly influence the activity of metabolic hormones and modulate lifespan [114,115]. For example, studies in both *Drosophila melanogaster* and *Caenorhabditis elegans* have shown that genetic mutations that cause defects in sensory cilia or their support cells, or in sensory signal transduction, significantly extend lifespan [116,117]. Furthermore, exposure of *Drosophila* to food-derived odorants has been shown to partially reverse the longevity-extending effects of dietary restriction [117]. While the mechanisms whereby sensory perception regulates lifespan is not entirely clear, effects on insulin/IGF (insulin-like growth factor) signaling are thought to be involved [118]. Overall, these data indicate that a perceived lack of nutritional resources (via defects in olfaction) can increase lifespan via a physiologic stress response similar to caloric restriction [115]. It should be noted that the converse – the perception of adequate or excess resources via exposure to food-related odorants – does not appear to decrease lifespan in animals that are not calorically restricted [117]. However, other studies have indicated that gustatory perception can be sufficient to modulate plasma insulin and glucose turnover, as saccharin was shown to induce cephalic-phase insulin release, and to increase hepatic glucose production in rats [119]. Thus, the potential exists for modulation of longevity and metabolism via environmental sensing, although the degree to which this potential scenario might participate in the physiologic complications of obesity in humans is not at all resolved.

5. Conclusions and unanswered questions

It is now very clear that nutrition, as an integral component of human physiology, has the ability to modulate cognitive function and CNS responses to injury. There is a great concern therefore, to critically evaluate and understand the mechanisms by which nutrition and particularly obesity can affect neuroplasticity and cognitive function. As summarized in this review, there is compelling evidence that obesity modulates brain responses, and may in particular accelerate brain aging and age-related neurodegeneration. While it is not currently known how obesity disrupts brain homeostasis during aging, numerous clinical and rodent studies strongly link diet-induced metabolic disturbances to the development of dementia. The progressive nature by which diet-induced obesity promotes brain disturbances raises the possibility that the careful implementation and study of this model will lead to better understanding of the linkages between metabolism and the brain, and might also unravel the complex relationship between brain function and measurable aspects of brain pathology. An additional key issue to resolve relates to the role of maternal obesity in the cognitive strength and health of offspring and the further predisposition of the offspring to obesity and/or enhanced CNS responses to obesity.

References

[1] B. Caballero, The global epidemic of obesity: an overview, Epidemiol. Rev. 29 (2007) 1–5.
[2] National Center for Health Statistics, Chartbook on Trends in the Health of Americans, Public Health Service, Hyattsville, MD, 2006.
[3] Z. Mei, L.M. Grummer-Strawn, A. Pietrobelli, A. Goulding, M.I. Goran, W.H. Dietz, 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. 75 (2002) 978–985.

[4] D.W. Haslam, W.P. James, Obesity, Lancet Neurol. 366 (2005) 1197–1209.
[5] R. Olufadi, C.D. Byrne, Clinical and laboratory diagnosis of the metabolic syndrome, J. Clin. Pathol. 61 (2008) 697–706.
[6] H.B. Hubert, M. Feinleib, P.M. McNamara, W.P. Castelli, Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study, Circulation 67 (1983) 968–977.
[7] R. Stamler, J. Stamler, W.F. Riedlinger, G. Algera, R.H. Roberts, Weight and blood pressure. Findings in hypertension screening of 1 million Americans, JAMA 240 (1978) 1607–1610.
[8] L.S. Piegas, A. Avezum, J.C. Pereira, Risk factors for myocardial infarction in Brazil, Am. Heart J. 146 (2003) 331–338.
[9] S.P. Walker, E.B. Rimm, A. Ascherio, I. Kawachi, M.J. Stampfer, W.C. Willet, Body size and fat distribution as predictors of stroke among U.S. men, Am. J. Epidemiol. 144 (1996) 1143–1150.
[10] K.M. Rexrode, C.H. Hennekens, W.C. Willett, A prospective study of body mass index, weight change, and risk of stroke in women, JAMA 277 (1997) 1539–1545.
[11] Y. Wang, M.A. Beydoun, The obesity epidemic in the United States-gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis, Epidemiol. Rev. 29 (2007) 6–28.
[12] H.C. Hendrie, Epidemiology of dementia and Alzheimer's disease, Am. J. Geriatr. Phychiatry 6 (1998) S3–S18.
[13] S.G. Riedel-Heller, A. Busse, C. Aurich, H. Matschinger, M.C. Angermeyer, Incidence of dementia according to DSM-III-R and ICD-10: results of the Leipzig Longitudinal Study of the Aged (LEILA75+), Part 2, Br. J. Psychiatry 179 (2001) 255–260.
[14] A. Wimo, B. Winblad, H. Aguero-Torres, E. von Strauss, The magnitude of dementia occurrence in the world, Alzheimer Dis. Assoc. Disord. 17 (2003) 63–67.
[15] C.P. Ferri, M. Prince, C. Brayne, H. Brodaty, L. Fratiglioni, M. Ganguli, K. Hall, K. Hasegawa, H. Hendrie, Y. Huang, A. Jorm, C. Mathers, P.R. Menezes, E. Rimmer, M. Scazufca, Global prevalence of dementia: a Delphi consensus study, Lancet 366 (2005) 2112–2117.
[16] H. Brunnström, L. Gustafson, U. Passant, E. Englund, Prevalence of dementia subtypes: A 30-year retrospective survey of neuropathological reports, Arch. Gerontol. Geriatr. (2008) Electronic publication ahead of print.
[17] M.N. Haan, R. Wallace, Can dementia be prevented? Brain aging in a population-based context, Ann. Rev. Public Health 25 (2004) 1–24.
[18] P.T. James, R. Leach, E. Kalamara, M. Shayeghi, The worldwide obesity epidemic, Obes. Res. 9 (2001) 228S–233S.
[19] M.A. Ward, C.M. Carlsson, M.A. Trivedi, M.A. Sager, S.C. Johnson, The effect of body mass index on global brain volume in middle-aged adults: a cross sectional study, BMC Neurol. (2005) 23.
[20] N. Pannacciulli, A. Del Parigi, K. Chen, D.S. Le, E.M. Reiman, P.A. Tataranni, Brain abnormalities in human obesity: a voxel-based morphometric study, Neuro-Image 31 (2006) 1419–1425.
[21] L.T. Haltia, A. Viljanen, R. Parkkola, N. Kemppainen, J.O. Rinne, P. Nuutila, V. Kaasinen, Brain white matter expansion in human obesity and the recovering effect of dieting, J. Clin. Endocrinol. Metab. 92 (2007) 3278–3284.
[22] T.R. Bashore, K.R. Ridderinkhof, Older age, traumatic brain injury, and cognitive slowing: some convergent and divergent findings, Psychol. Bull. 128 (2002) 151–198.
[23] C.V. Brown, P. Rhee, A.L. Neville, B. Sangthong, A. Salim, D. Demetriades, Obesity and traumatic brain injury, J. Trauma 61 (2006) 572–576.
[24] A.L. Neville, C.V. Brown, J. Weng, D. Demetriades, G.C. Velmahos, Obesity is an independent risk factor of mortality in severely injured blunt trauma patients, Arch. Surg. 139 (2004) 983–987.
[25] T.M. Duane, T. Dechert, M.B. Aboutanos, A.K. Malhotra, R.R. Ivatury, Obesity and outcomes after blunt trauma, J. Trauma. 61 (2006) 1218–1221.
[26] A. Popa-Wagner, S.T. Carmichael, Z. Kokaia, C. Kessler, L.C. Walker, The response of the aged brain to stroke: too much, too soon? Curr. Neurovasc. Res. 4 (2007) 216–227.
[27] T. Kurth, J.M. Gaziano, K. Berger, C.S. Kase, K.M. Rexrode, N.R. Cook, J.E. Buring, J.E. Manson, Body mass index and the risk of stroke in men, Arch. Intern. Med. 162 (2002) 2557–2562.
[28] R.D. Abbott, G.R. Behrens, D.S. Sharp, B.L. Rodriguez, C.M. Burchfiel, G.W. Ross, K. Yano, J.D. Curb, Body mass index and thromboembolic stroke in nonsmoking men in older middle age. The Honolulu Heart Program, Stroke 25 (1994) 2370–2376.
[29] L.C. Clavijo, T.L. Pinto, P.K. Kuchulakanti, R. Torguson, W.W. Chu, L.F. Satler, K.M. Kent, W.O. Suddath, A.D. Pichard, R. Waksman, Metabolic syndrome in patients with acute myocardial infarction is associated with increased infarct size and in-hospital complications, Cardiovasc. Revasc. Med. 7 (2006) 7–11.
[30] W.U. Weitbrecht, D. Kirchhoff, Long-term prognosis of cerebral infarct in comparison with a normal population, Versicherungsmedizin 47 (1995) 46–49.
[31] M.F. Elias, P.K. Elias, L.M. Sullivan, P.A. Wolf, R.B. D, Agostino, Lower cognitive function in the presence of obesity and hypertension: the Framingham Heart Study, Int. J. Obes. Relat. Metab. Disord. 27 (2003) 260–268.
[32] M.F. Elias, P.K. Elias, L.M. Sullivan, P.A. Wolf, R.B. D, Agostino, Obesity, diabetes and cognitive deficit: the Framingham Heart Study, Neurobiol. Aging 26 (2005) 11–16.
[33] S.R. Waldstein, L.I. Katzel, Interactive relations of central versus total obesity and blood pressure to cognitive function, Int. J. Obes. (Lond.) 30 (2006) 201–207.
[34] J. Gunstad, R.H. Paul, R.A. Cohen, D.F. Tate, M.B. Spitznagel, E. Gordon, Elevated body mass index is associated with executive dysfunction in otherwise healthy adults, Compr. Psychiatry 48 (2007) 57–61.
[35] C. Qiu, D. De Ronchi, L. Ratiglioni, The epidemiology of the dementias: an update, Curr. Opin. Psychiatry 4 (2007) 380–385.
[36] A.M. Kanaya, E. Barrett-Connor, G. Gildengorin, K. Yaffe, Change in cognitive function by glucose tolerance status in older adults: a 4-year prospective study of the Rancho Bernardo study cohort, Arch. Intern. Med. 164 (2004) 1327–1333.
[37] J.A. Luchsinger, M.X. Tang, S. Shea, R. Mayeux, Caloric intake and the risk of Alzheimer disease, Arch. Neurol. 59 (2002) 1258–1263.
[38] S.K. Jeong, H.S. Nam, M.H. Son, E.J. Son, K.H. Cho, Interactive effect of obesity indexes on cognition, Dement. Geriatr. Cogn. Disord. 19 (2005) 91–96.
[39] K. Yaffe, M.N. Haan, T. Blackwell, E. Cherkasova, R.A. Whitmer, N. West, Metabolic syndrome and cognitive decline in elderly latinos: findings from the SALSA Study, J. Am. Geriatr. Soc. 55 (2007) 758–762.
[40] V.H. Taylor, G.M. MacQueen, Cognitive dysfunction associated with metabolic syndrome, Obes. Rev. 8 (2007) 409–418.
[41] M. Tschöp, M.L. Heiman, Rodent obesity models: an overview, Exp. Clin. Endocrinol. Diabetes 109 (2001) 307–319.
[42] R.C. Casper, E.L. Sullivan, L. Tecott, Relevance of animal models to human eating disorders and obesity, Psychopharmacology (Berl) 199 (2008) 313–329.
[43] P. Lindström, The physiology of obese-hyperglycemic mice [ob/ob mice], Sci. World J. 7 (2007) 666–685.
[44] E. Itateyama, S. Chiba, T. Sakata, H. Yoshimatsu, Hypothalamic neuronal histamine in genetically obese animals: its implication of leptin action in the brain, Exp. Biol. Med. (Maywood) 228 (2003) 1132–1137.
[45] S. Terao, G. Yilmaz, K.Y. Stokes, M. Ishikawa, T. Kawase, D.N. Granger, Inflammatory and injury responses to ischemic stroke in obese mice, Stroke 39 (2008) 943–950.
[46] N.D. Oakes, G.J. Cooney, S. Camilleri, D.J. Chisholm, E. Kraegen, Mechanisms of liver and muscle insulin resistance induced by chronic high-fat feeding, Diabetes 46 (1997) 1768–1774.
[47] R. Buettner, J. Schölmerich, L.C. Bollheimer, High-fat diets: modeling the metabolic disorders of human obesity in rodents, Obesity (Silver Spring) 15 (2007) 798–808.
[48] R. Buettner, K.G. Parhofer, M. Woenckhaus, C.E. Wrede, L.A. Kunz-Schughart, J. Schölmerich, L.C. Bollheimer, Defining high-fat-diet rat models: metabolic and molecular effects of different fat types, J. Mol. Endocrinol. 36 (2006) 485–501.
[49] B. Dziedzic, J. Szemraj, J. Bartkowiak, A. Walczewska, Various dietary fats differentially change the gene expression of neuropeptides involved in body weight regulation in rats, J. Neuroendocrinol. 19 (2007) 364–373.
[50] G. Said, Diabetic neuropathy—a review, Nat. Clin. Pract. Neurol. 3 (2007) 331–340.
[51] J.A. Tracy, P.J. Dyck, The spectrum of diabetic neuropathies, Phys. Med. Rehabil. Clin. North Am. 19 (2008) 1–26.
[52] A. Sena, L.L. Sarliève, G. Rebel, Brain myelin of genetically obese mice, J. Neurol. Sci. 68 (1985) 233–243.
[53] W. Jagust, What can imaging reveal about obesity and the brain? Curr. Alzheimer Res. 4 (2007) 135–139.
[54] S. Gazdzinski, J. Kornak, M.W. Weiner, D.J. Meyerhoff, Body mass index and magnetic resonance markers of brain integrity in adults, Ann. Neurol. 63 (2008) 652–657.
[55] C.E. Greenwood, G. Winocur, High-fat diets, insulin resistance and declining cognitive function, Neurobiol. Aging 26 (2005) 42–45.
[56] G. Winocur, C.E. Greenwood, Studies of the effects of high fat diets on cognitive function in a rat model, Neurobiol. Aging 26 (2005) 46–49.
[57] A.M. Stranahan, E.D. Norman, K. Lee, R.G. Cutler, R.S. Telljohann, J.M. Egan, M.P. Mattson, Diet-induced insulin resistance impairs hippocampal synaptic plasticity and cognition in middle-aged rats, Hippocampus 18 (2008) 1085–1088.
[58] N. Jurdak, A.H. Lichtenstein, R.B. Kanarek, Diet-induced obesity and spatial cognition in young male rats, Nutr. Neurosci. 11 (2008) 48–54.
[59] R. Molteni, R. Barnard, Z. Ying, C. Roberts, F. Gómez-Pinilla, A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning, Neuroscience 112 (2002) 803–814.
[60] A. Wu, R. Molteni, Z. Ying, F. Gomez-Pinilla, A saturated-fat diet aggravates the outcome of traumatic brain injury on hippocampal plasticity and cognitive function by reducing brain-derived neurotrophic factor, Neuroscience 119 (2003) 365–375.
[61] A. Wu, Z. Ying, F. Gomez-Pinilla, The interplay between oxidative stress and brain-derived neurotrophic factor modulates the outcome of a saturated fat diet on synaptic plasticity and cognition, Eur. J. Neurosci. 19 (2004) 1699–1707.
[62] J.N. Jovanovic, A.J. Czernik, A.A. Fienberg, P. Greengard, T.S. Sihra, Synapsins as mediators of BDNF-enhanced neurotransmitter release, Nat. Neurosci. 3 (2000) 323–329.
[63] S.D. Croll, N.Y. Ip, R.M. Lindsay, S.J. Wiegand, Expression of BDNF and trkB as a function of age and cognitive performance, Brain Res. 812 (1998) 200–208.
[64] Y. Kovalchuk, E. Hanse, K.W. Kafitz, A. Konnerth, Postsynaptic induction of BDNF-mediated long-term potentiation, Science 295 (2002) 1711–1729.
[65] Y. Kovalchuk, E. Hanse, K.W. Kafitz, A. Konnerth, Postsynaptic induction of BDNF-mediated long-term potentiation, Science 295 (2002) 1729–1734.
[66] D. Cao, H. Lu, T. Lewis, L. Li, Intake of sucrose-sweetened water induces insulin resistance and exacerbates memory deficits and amyloidosis in a transgenic mouse model of Alzheimer disease, J. Biol. Chem. 282 (2007) 36275–36282.
[67] D.C. Fewlass, K. Noboa, F.X. Pi-Sunyer, J.M. Johnston, S.D. Yan, N. Tezapsidis, Obesity-related leptin regulates Alzheimer's Abeta, FASEB J. 18 (2004) 1870–1878.
[68] K. Sriram, S.A. Benkovic, D.B. Miller, J.P. O, Callaghan, Obesity exacerbates chemically induced neurodegeneration, Neuroscience 115 (2002) 1335–1346.
[69] J.Y. Choi, E.H. Jang, C.S. Park, J.H. Kang, Enhanced susceptibility to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine neurotoxicity in high-fat diet-induced obesity, Free Radic. Biol. Med. 38 (2005) 806–816.

[70] B.N. Ames, M.K. Shigenaga, T.M. Hagen, Oxidants, antioxidants, and the degenerative diseases of aging, Proc. Natl. Acad. Sci. U. S. A. 90 (1993) 7915–7922.

[71] J. Liu, E. Head, A.M. Gharib, W. Yuan, R.T. Ingersoll, T.M. Hagen, C.W. Cotman, B.N. Ames, Memory loss in old rats is associated with brain mitochondrial decay and RNA/DNA oxidation: partial reversal by feeding acetyl-L-carnitine and/or R-alpha-lipoic acid, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 2356–2361.

[72] M.P. Mattson, W. Duan, Z. Guo, Meal size and frequency affect neuronal plasticity and vulnerability to disease: cellular and molecular mechanisms, J. Neurochem. 84 (2003) 417–431.

[73] X. Zhang, F. Dong, J. Ren, M.J. Driscoll, B. Culver, High dietary fat induces NADPH oxidase-associated oxidative stress and inflammation in rat cerebral cortex, Exp. Neurol. 191 (2005) 318–325.

[74] C.G. Souza, J.D. Moreira, I.R. Siqueira, A.G. Pereira, D.K. Rieger, D.O. Souza, T.M. Souza, L.V. Portela, M.L. Perry, Highly palatable diet consumption increases protein oxidation in rat frontal cortex and anxiety-like behavior, Life Sci. 81 (2007) 198–203.

[75] I. Chinen, M. Shimabukuro, K. Yamakawa, N. Higa, T. Matsuzaki, K. Noguchi, S. Ueda, M. Sakanashi, N. Takasu, Vascular lipotoxicity: endothelial dysfunction via fatty-acid-induced reactive oxygen species overproduction in obese Zucker diabetic fatty rats, Endocrinology 148 (2007) 160–165.

[76] C. Patel, H. Ghanim, S. Ravishankar, C.L. Sia, P. Viswanathan, P. Mohanty, P. Dandona, Prolonged reactive oxygen species generation and nuclear factor-kappaB activation after a high-fat, high-carbohydrate meal in the obese, J. Clin. Endocrinol. Metab. 92 (2007) 4476–4479.

[77] A.E. Silver, S.D. Beske, D.D. Christou, A.J. Donato, K.L. Moreau, I. Eskurza, P.E. Gates, D.R. Seals, Overweight and obese humans demonstrate increased vascular endothelial NAD(P)H oxidase-p47(phox) expression and evidence of endothelial oxidative stress, Circulation 115 (2007) 627–637.

[78] J.E. Morley, The metabolic syndrome and aging, J. Gerontol. Med. Sci. 59A (2004) 139–142.

[79] C. Reitz, J. Luchsinger, M. Tang, J. Manly, R. Mayeux, Impact of plasma lipids and time on memory performance in healthy elderly without dementia, Neurology 64 (2005) 1378–1383.

[80] R.L. Rogers, J.S. Meyer, K. McClintic, K.F. Mortel, Reducing hypertriglyceridemia in elderly patients with cerebrovascular disease stabilizes or improves cognition and cerebral perfusion, Angiology 40 (1989) 260–269.

[81] G. Atzmon, I. Gabriely, W. Greiner, D. Davidson, C. Schechter, N. Barzilai, Plasma HDL levels highly correlate with cognitive function in exceptional longevity, J. Gerontol. Med. Sci. 57 (2002) M712–M715.

[82] D.L. Sparks, M.N. Sabbagh, D.J. Conner, J. Lopez, L.J. Launer, P. Browne, D. Wasser, S. Johnson-Traver, J. Lochhead, C. Ziolwolski, Atorvastatin for the treatment of mild to moderate Alzheimer disease preliminary results, Arch. Neurol. 62 (2005) 753–757.

[83] S.A. Farr, K.A. Yamada, D.A. Butterfield, H.M. Abdul, L. Xu, N.E. Miller, W.A. Banks, J.E. Morley, Obesity and hypertriglyceridemia produce cognitive impairment, Endocrinology 149 (2008) 2628–2636.

[84] L.C. Perlmuter, D.M. Nathan, S.H. Goldfinger, P.A. Russo, J. Yates, M. Larkin, Triglyceride levels affect cognitive function in non-insulin-dependent diabetes, J. Diabetes Complicat. 2 (1998) 210–213.

[85] W.A. Banks, A.B. Coon, S.M. Robinson, A. Moinuddin, J.M. Shultz, R. Nakaoke, J.E. Morley, Triglycerides induce leptin resistance at the blood–brain barrier, Diabetes 53 (2004) 1253–1260.

[86] G. Boden, P. She, i.M. Mozzol, P. Cheung, K. Gumireddy, P. Reddy, X. Xiang, Z. Luo, N. Ruderman, Free fatty acids produce insulin resistance and activate the proinflammatory nuclear factor-B pathway in rat liver, Diabetes 54 (2005) 3458–3465.

[87] Y. Lee, H. Hirose, M. Ohneda, J.H. Johnson, J.D. McGarry, R.H. Unger, Beta-cell lipotoxicity in the pathogenesis of non-insulin-dependent diabetes mellitus of obese rats: impairment in adipocyte-beta-cell relationships, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 10878–10882.

[88] M. Petruzzelli, G. Lo Sasso, P. Portincasa, G. Palasciano, A. Moschetta, Targeting the liver in the metabolic syndrome: evidence from animal models, Curr. Pharm. Des. 13 (2007) 2199–2207.

[89] D. Ma, L. Lu, N.B. Boneva, S. Warashina, D.B. Kaplamadzhiev, Y. Mori, M.A. Nakaya, M. Kikuchi, A.B. Tonchev, H. Okano, T. Yamashima, Expression of free fatty acid receptor GPR40 in the neurogenic niche of adult monkey hippocampus, Hippocampus 18 (2008) 326–333.

[90] P.S. Laine, E.A. Schwartz, Y. Wang, W.Y. Zhang, S.K. Karnik, N. Musi, P.D. Reaven, Palmitic acid induces IP-10 expression in human macrophages via NF-kappaB activation, Biochem. Biophys. Res. Commun. 358 (2007) 150–155.

[91] A. Aronis, Z. Madar, O. Tirosh, Lipotoxic effects of triacylglycerols in J774.2 macrophages, Nutrition 24 (2008) 167–176.

[92] S. Patil, C. Chan, Palmitic and stearic fatty acids induce Alzheimer-like hyperphosphorylation of tau in primary rat cortical neurons, Neurosci. Lett. 384 (2005) 288–293.

[93] M.F. Dallman, N.C. Pecoraro, S.E. La Fleur, J.P. Warne, A.B. Ginsberg, S.F. Akana, K.C. Laugero, H. Houshyar, A.M. Strack, S. Bhatnagar, M.E. Bell, Glucocorticoids, chronic stress, and obesity, Prog. Brain Res. 153 (2006) 75–105.

[94] A.M. Stranahan, T.V. Arumugam, R.G. Cutler, K. Lee, J.M. Egan, M.P. Mattson, Diabetes impairs hippocampal function through glucocorticoid-mediated effects on new and mature neurons, Nat. Neurosci. 11 (2008) 309–317.

[95] A.M. Stranahan, K. Lee, P.J. Pistell, C.M. Nelson, N. Readal, M.G. Miller, E.L. Spangler, D.K. Ingram, M.P. Mattson, Accelerated cognitive aging in diabetic rats is prevented by lowering corticosterone levels, Neurobiol. Learn. Mem. 90 (2008) 479–483.

[96] G. Frühbeck, Overview of adipose tissue and its role in obesity and metabolic disorders, Methods Mol. Biol. 456 (2008) 1–22.

[97] V.Z. Rocha, P. Libby, The multiple facets of the fat tissue, Thyroid 18 (2008) 175–183.

[98] R.S. Ahima, S.Y. Osei, Adipokines in obesity, Front. Horm. Res. 36 (2008) 182–197.

[99] G. Fantuzzi, Adipose tissue, adipokines, and inflammation, J. Allergy Clin. Immunol. 115 (2005) 911–919.

[100] B. Antuna-Puente, B. Feve, S. Fellahi, J.P. Bastard, Adipokines: the missing link between insulin resistance and obesity, Diabetes Metab. 34 (2008) 2–11.

[101] Y. Zhang, R. Proenca, M. Maffei, M. Barone, L. Leopold, J.M. Friedman, Positional cloning of the mouse obese gene and its human homologue, Nat. Neurosci. 372 (1994) 425–432.

[102] J.M. Friedman, J.L. Halaas, Leptin and the regulation of body weight in mammals, Nature 395 (1998) 763–770.

[103] W.A. Banks, A. Kastin, W. Huang, J. Jaspan, L.M. Maness, Leptin enters the brain by a saturable system independent of insulin, Peptides 17 (1996) 305–311.

[104] J.K. Elmquist, C. Bjorbaek, R.S. Ahima, J.S. Flier, C.B. Saper, Distributions of leptin receptor mRNA isoforms in the rat brain, J. Comp. Neurol. 395 (1998) 535–547.

[105] L.A. Tartaglia, M. Dembski, X. Weng, N. Deng, J. Culpepper, R. Devos, G.J. Richards, L.A. Campfield, F.T. Clark, J. Deeds, C. Muir, S. Sanker, A. Moriarty, K.J. Moore, J.S. Smutko, G.G. Mays, E.A. Wool, C.A. Monroe, R.I. Tepper, Identification and expression cloning of a leptin receptor, OB-R, Cell 83 (1995) 1263–1271.

[106] H. Fei, H.J. Okano, C. Li, G.H. Lee, C. Zhao, R. Darnell, J.M. Friedman, Anatomic localization of alternatively spliced leptin receptors (Ob-R) in mouse brain and other tissues, Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 7001–7005.

[107] J. Harvey, Leptin regulation of neuronal excitability and cognitive function, Curr. Opin. Pharmacol. 7 (2007) 643–647.

[108] S. Diano, T.L. Horvath, Anticonvulsant effects of leptin in epilepsy, J. Clin. Invest. 118 (2008) 26–28.

[109] J. Harvey, L.J. Shanley, D. O, Malley, A.J. Irving, Leptin: a potential cognitive enhancer? Biochem. Soc. Trans. 33 (2005) 1029–1032.

[110] M.J. Wayner, D.L. Armstrong, C.F. Phelix, Y. Oomura, Orexin-A (Hypocretin-1) and leptin enhance LTP in the dentate gyrus of rats in vivo, Peptides 25 (2004) 991–996.

[111] Y. Oomura, N. Hori, T. Shiraishi, K. Fukunaga, H. Takeda, M. Tsuji, T. Matsumiya, M. Ishibashi, S. Aou, X. Li, D. Kohno, K. Uramura, H. Sougawa, T. Yada, M. Wayner, K. Sasaki, Leptin facilitates learning and memory performance and enhances hippocampal CA1 long-term potentiation and CaMK II phosphorylation in rats, Peptides 11 (2006) 2738–2749.

[112] E. Pinteaux, W. Inoue, L. Schmidt, F. Molina-Holgado, N.J. Rothwell, G.N. Luheshi, Leptin induces interleukin-1beta release from rat microglial cells through a caspase 1 independent mechanism, J. Neurochem. 102 (2007) 826–833.

[113] C.H. Tang, D.Y. Lu, R.S. Yang, H.Y. Tsai, M.C. Kao, W.M. Fu, Y.F. Chen, Leptin-induced IL-6 production is mediated by leptin receptor, insulin receptor substrate-1, phosphatidylinositol 3-kinase, Akt, NF-kappaB, and p300 pathway in microglia, J. Immunol. 179 (2007) 1292–1302.

[114] C.A. Wolkow, Life span: getting the signal from the nervous system, Trends Neurosci. 25 (2002) 212–216.

[115] S. Libert, S.D. Pletcher, Modulation of longevity by environmental sensing, Cell 131 (2007) 1231–1234.

[116] J. Apfeld, C. Kenyon, Regulation of lifespan by sensory perception in *Caenorhabditis elegans*, Nature 402 (1999) 804–809.

[117] S. Libert, J. Zwiener, X. Chu, W. Vanvoorhies, G. Roman, S.D. Pletcher, Regulation of *Drosophila* life span by olfaction and food-derived odors, Science 315 (2007) 1133–1137.

[118] J. Alcedo, C. Kenyon, Regulation of *C. elegans* longevity by specific gustatory and olfactory neurons, Neuron 41 (2004) 45–55.

[119] E. Ionescu, F. Rohner-Jeanrenaud, J. Proietto, R.W. Rivest, B. Jeanrenaud, Taste-induced changes in plasma insulin and glucose turnover in lean and genetically obese rats, Diabetes 37 (1988) 773–779.