Obesity as a Risk Factor for Alzheimer’s Disease: Implication of Leptin and Glutamate

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Obesity is known to induce leptin and insulin resistance. Leptin is a peptide hormone synthesized in adipose tissue that mainly regulates food intake. It has been shown that insulin stimulates the production of leptin when adipocytes are exposed to glucose to encourage satiety; while leptin, via a negative feedback, decreases the insulin release and enhances tissue sensitivity to it, leading to glucose uptake for energy utilization or storage. Therefore, resistance to insulin is closely related to leptin resistance. Obesity in middle age has also been related to Alzheimer’s disease (AD). In recent years, the relation between impaired leptin signaling pathway and the onset of AD has been studied. In all this context the role of the blood brain barrier (BBB) is crucial. Slow excitotoxicity happens in AD due to an excess of the neurotransmitter glutamate. Since leptin has been shown to regulate N-methyl-d-aspartate (NMDA) receptors, we want to review the link between these pathological pathways, and how they are affected by other AD triggering factors and its role in the onset of AD.

Keywords: leptin-resistance, dementia, overweight, excitotoxicity, LTP

INTRODUCTION

In the last years obesity has changed from a mere aesthetic problem to become into a serious health problem worldwide. Nowadays it is considered by medical authorities as a genuine epidemic, consuming enormous technical, human, and economic resources. Obesity and also overweight affect near than 300 million people from child to elderly, and it is not related with the development level of the country (World Health Organization [WHO], 2003). Moreover, research has shown that obese children are more likely to be overweight or obese as adults (Sahoo et al., 2015). The growing incidence caused by a change in eating habits, by an increased consumption of fat and also by a substantial reduction in physical activity. This nutritional disorder implicates a number of conditions associated with excess weight, such as heart diseases, type 2 diabetes, high blood pressure, different types of cancer, and even neurodegeneration (Friedemann et al., 2012; Odegard and Chawla, 2013; Hotamisligil, 2017). All these chronic pathologies associated with obesity, englobe the main causes of death and also monopolize 80% of healthcare expense (The World Health Organization [WHO], 2019).
The body mass index (BMI) is the most widely used method to classify a person in relation to his/her weight. In adults a BMI of 18.5 to 24.9 stands for a healthy, normal weight, while a value between 25 and 29.9 means is considered overweight. From values from 30 to 39.9 implies you are obese and from 40 to above means you are severely obese. A BMI lower than 18.5 is considered underweight and may indicate an eating disorder or malnutrition. However, BMI is not representative of overweight in the case of people with high percentage of muscle mass. In these populations a high BMI would not indicate excess of fat. Perhaps a more accurate method to assess excess fat is waist circumference, which can be used as an additional measure in people who are overweight or moderately obese. Usually, men with a waist circumference of 94 cm (37 in) or more and women with a waist circumference of 80 cm (31.5 in) or more are in risk of obesity-related diseases.

In the last 15 years, obesity and dementia risk have been related (Whitmer et al., 2005). An increase in adipose tissue could promote a decrease in the blood flow to the brain, leading to vascular injury. In fact, obesity is related to changes in cerebral vascularization, because perivascular adipose tissue is not found around the cerebral arteries (Dorrance et al., 2014). A decrease in blood flow to the brain causes ischemia in vulnerable brain areas. The most sensitive areas, specifically vulnerable, are neurons located in the hippocampal regions CA1, CA3, and CA4, portions of the caudate nucleus, cerebellum, and layers III, V, VI of the neocortex (Payavash et al., 2011). The hippocampal areas, due to its high baseline metabolic activity, are extremely susceptible to reduced oxygen and glucose intake and it is believed that it can be one of the causes of increased memory loss (Kivipelto et al., 2005). Chronic peripheral inflammation caused by the release of adipokines as leptin and other cytokines, may spread to the brain and the neuroinflammation is linked to a decrease in the brain white matter, leading to impair neuronal connections (Arnoldussen et al., 2014; Kiliaan et al., 2014). Moreover, neuroinflammation could be triggered by an imbalance in the gut microbiota due to the consumption of diets high in fats and sugars (Solás et al., 2017), which could provoke an alteration in the “gut-brain axis.”

In this review, we are going to discuss the role of the cytokine leptin in brain function and specially in the memory decline associated with Alzheimer’s disease (AD).

LEPTIN AND ITS ROLE IN THE BRAIN

Leptin was discovered in Zhang et al. (1994) by Friedman and co-workers using modern molecular biology tools such as positional cloning. After cloning the ob gene in mice and its homolog in humans, the gene product was purified and called leptin (Maffei et al., 1995). Leptin is a hormone mainly produced by adipose tissue which is released to the bloodstream and circulates throughout the body proportionally to the body fat mass (Friedman and Halaas, 1998). Moreover, leptin is expressed either in subcutaneous and visceral adipose tissue (Lieb et al., 2009), and also in placenta, skeletal muscle, ovaries, mammary epithelial cells, (Margetic et al., 2002), or even in the gastrointestinal tract with both endocrine and exocrine actions (Cammisotto et al., 2005). Leptin can be found into the bloodstream either associated to binding proteins or in a free, bioactive form (Sinha et al., 1996). Obese individuals show a higher proportion of the free circulating leptin form and in contrast, in lean subjects leptin circulates mainly bound to its soluble receptor (Sinha et al., 1996). This is in line with the fact that one of the functions attributed to leptin is to regulate food intake and energy expenditure. When adipose tissue decreases plasma leptin levels also decrease, and when adipose tissue increases leptin levels increase and suppresses appetite (Maffei et al., 1995). But we know today that the functions of leptin are many others: it is a growth factor, a permissive factor for puberty, controls metabolism and immune system and is also implicated in memory (Margetic et al., 2002; Kelesidis et al., 2010; McGregor and Harvey, 2018a). All these effects are mediated by binding to specific leptin receptors (LepR) expressed in the central nervous system (CNS) as well as in peripheral tissues.

The LepR has six different isoforms: five of them (LepRa, LepRc, LepRd, LepRf, and LepRb) show transmembrane domain, whereas LepRe only presents an extracellular domain and acts as a soluble receptor. LepRb is the long form of the receptor while the others isoforms are shorter (Chua et al., 1997; Tartaglia, 1997; Cui et al., 2017). LepRs are widely expressed all along the body, but focusing in the brain, both short and long isoforms are broadly expressed. LepR is found in the hypothalamus (specifically, in the arcuate, ventromedial, paraventricular, and ventral premammillary nuclei) but LepRs are also present in other areas primarily non-associated with energy balance such as the neocortex, hippocampus, thalamus, leptomeninges, choroid plexus (Mercer et al., 1996; Fei et al., 1997; De Matteis and Cinti, 1998), entorhinal cortex, amygdala, and rostral medulla (Savioz et al., 1997; Burguera et al., 2000).

LEPTIN AND OBESITY

To reach the CNS, leptin crosses the blood-brain barrier (BBB) through a saturable transport system (Banks et al., 1996). Brain microvessels express short leptin receptors which bind and internalize leptin (Karlsson et al., 1997; Björback et al., 1998). It has been proposed that leptin enters via cerebrospinal fluid (CSF) from plasma because the choroid plexus contains many leptin receptors (Schwartz et al., 1996; Golden et al., 1997). In the hypothalamus, a very specific type of cell, the tanycyte has a remarkable role conducting leptin. Tanycytes are ependymal cells located in the third ventricle and also in the floor of the fourth ventricle. They have cellular extensions that communicate deep into the hypothalamus, and thank to these cellular prolongations, the leptin is conducted to its target areas through transcytosis (Balland et al., 2014). When leptin binds to its receptor it activates several signaling cascades such as the Janus tyrosine kinase 2 (JAK2), the signal transducer activator of transcription 3 (STAT3), the phosphatidylinositol 3-kinase (PI3 kinase), and the AKT pathways (Flak and Myers, 2016) that culminates in the modification of neurons releasing three hormone-derived peptides: neuropeptide Y (NPY), pro-opiomelanocortin and also in placenta, skeletal muscle, ovaries, mammary epithelial cells, (Margetic et al., 2002), or even in the gastrointestinal tract with both endocrine and exocrine actions (Cammisotto et al., 2005). Leptin can be found into the bloodstream either associated to binding proteins or in a free, bioactive form (Sinha et al., 1996). Obese individuals show a higher proportion of the free circulating leptin form and in contrast, in lean subjects leptin circulates mainly bound to its soluble receptor (Sinha et al., 1996). This is in line with the fact that one of the functions attributed to leptin is to regulate food intake and energy expenditure. When adipose tissue decreases plasma leptin levels also decrease, and when adipose tissue increases leptin levels increase and suppresses appetite (Maffei et al., 1995). But we know today that the functions of leptin are many others: it is a growth factor, a permissive factor for puberty, controls metabolism and immune system and is also implicated in memory (Margetic et al., 2002; Kelesidis et al., 2010; McGregor and Harvey, 2018a). All these effects are mediated by binding to specific leptin receptors (LepR) expressed in the central nervous system (CNS) as well as in peripheral tissues.

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associated with hippocampal affection. But some pathological changes related to obesity, such as neuroinflammation, insulin resistance, or mitochondrial dysfunction, also occur in AD pathological progression (O’Brien et al., 2017).

The number of studies relating an increase in fat body mass and the risk of suffer AD has increased in the last years. However, the results are controversial and many times inconclusive. It seems that it is important to differentiate between mid-life and late-life overweight (Xu et al., 2011). Specifically, obesity in midlife and a weight loss in the preclinical phase characterizes dementia (Singh-Manoux et al., 2018). In fact, in a recent meta-analysis of 21 studies, the authors conclude that obesity below the age of 65 years (midlife obesity) correlates with the incident of dementia, but not the late-life obesity (over 65 years) (Pedditizi et al., 2016). Very recently, Kivimäki et al. (2018) analyzed 1,349,857 people from 39 different cohorts with BMI data assessed at baseline. The authors find that 20 years before dementia diagnosis, higher BMI is associated with increased dementia risk in mid-life. Moreover, they describe that this risk is reversed in late-life and a higher BMI could even be protective (Kivimäki et al., 2018).

Furthermore, a meta-analysis of 15 prospective studies including more than 72000 participants used BMI measures and the authors found that both underweight and obese are related to an increased risk of AD but only in mid-life; high BMI in late-life was not associated with any dementia (Anstey et al., 2011). Moreover, the authors conclude that underweight could be a useful marker for identifying mild cognitive impairment (MCI) subjects at increased risk to convert to AD (Joo et al., 2018). Another very large retrospective cohort study with two million people analyzed, concludes that underweight in both middle and old age increases the risk of dementia over two decades (Qizilbash et al., 2015), although this study is not focused specifically in AD. In spite of these publications, the hypothesis that being overweight in mid-life is linked to dementia in late-life seems to be widely accepted by scientific community. A recent analysis explains that the duration of the preclinical weight loss phase could be a negative confounding parameter and a plausible explanation of this paradox (Pegueroles et al., 2018).

THE ROLE OF LEPTIN IN AD

Since obesity and dementia were related, many studies tried to find a link between brain leptin activity and AD development. In this line, Bonda et al. (2014) show that leptin is increased in the CSF and also in the hippocampus of AD patients, but leptin receptor mRNA is decreased within degenerating neurons and this could suggest a novel neuronal leptin resistance in AD. On the other hand, Maioli et al. (2015) show no changes in leptin concentration in CSF, but LepR also diminishes in post-mortem brains of AD patients, confirming that leptin resistance occurs. LepR decreased expression related to age, is also shown in an animal model of AD (King et al., 2018).

Brain leptin resistance is proposed as part of the neurodegenerative process. Leptin has both neurotrophic and neuroprotective properties therefore, leptin signaling deficits may lead to susceptibility to AD-related neurotoxic conditions.
In fact, leptin is able to modify the levels of Aβ peptide by limiting its production in neurons via reducing β-secretase activity (Fewlass et al., 2004; Marwarha et al., 2010). Likewise, leptin protects hippocampal neurons in primary cell culture from Aβ derived insults such as oxidative stress (Martins et al., 2013). Moreover, leptin enhances the removal of Aβ by promoting its clearance and degradation and activating the insulin degrading enzyme (Patterson et al., 2008). Furthermore, in neurons treated with Aβ, leptin prevents glycogen synthase kinase 3β (GSK3β) activation (Greco et al., 2009; Marwarha et al., 2010; Martins et al., 2013). This is very significant for AD pathogenesis since GSK3β is a kinase of tau and is implicated in the formation of neurofibrillary tangles. Besides, development of leptin resistance is linked with higher tau pathology in transgenic mouse models of AD suggesting that a defect in LepR-mediated signaling cascade could increase p-tau levels (Platt et al., 2016).

An important target of leptin action is the hippocampus, where it has a role in synaptic plasticity process, in memory preservation, and has pro-cognitive effects (Harvey, 2007, 2013). All these effects seem to be mediated by modulating glutamate receptors: the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-d-aspartate (NMDA). These receptors are involved in long-term potentiation (LTP) and in long-term depression (LTD). Leptin enhances LTP and decreases LTD, increasing the efficacy of excitatory synaptic transmission (Shanley et al., 2001; Wayner et al., 2004; Moult and Harvey, 2011; McGregor and Harvey, 2018b; McGregor et al., 2018). Moreover, leptin resistance is determinant for hippocampal dysfunction (Mainardi et al., 2017). In AD models,
leptin prevents the anomalous effects of Aβ on hippocampal LTP and LTD, restoring normal hippocampal synaptic function (Doherty et al., 2013), and also increasing the synaptic density and rescuing memory deficits (Perez-Gonzalez et al., 2014).

Taken together, the studies described above indicate that brain leptin resistance could be central in AD pathophysiology, including the regulation of glutamatergic connections involved in hippocampal LTP and LTD. A schematic view is shown in Figure 1.

GLUTAMATE, OBESITY AND AD ARE LINKED VIA LEPTIN-RESISTANCE

Mild cognitive impairment and AD patients show an increase in plasma glutamate and glutamine (Miulli et al., 1993; Trushina et al., 2013). This increment is also reflected in brain, since some studies identify an increase in glutamate and glutamine levels in CSF from AD (Pomara et al., 1992; Jimenez-Jimenez et al., 1998; Kaiser et al., 2010; Madeira et al., 2018) and from MCI patients (D’Aniello et al., 2005). If this increase comes directly from the arise in the peripheral levels of glutamate and glutamine or if it is an indirect phenomenon is not yet known in AD. Curiously, glutamine levels increase in hippocampus from mice fed with a high-fat diet during 6 months (Lizarbe et al., 2019). Moreover, the BBB is disrupted in early phases of the disease and the consequences of this disruption in the amino acid transport are not yet studied in depth (Montagne et al., 2017). In any case, a slow excitotoxicity is shown in AD and this consist of an overexcitation of NMDA receptors by glutamate (Beal, 1992; Ong et al., 2013). Glutamate overexcite the NMDA receptors in a tonic manner and a good evidence of this, is that memantine, an uncompetitive NMDA receptor antagonist, is a well-established treatment of AD (Parsons et al., 2007). In fact, Aβ causes the increase of glutamate (Fuchsberger et al., 2016) and the intraneuronal Ca2+ levels (Kuchibhotla et al., 2008). A pathological signaling cascade is triggered, involving an increase of Cdk5-p35 levels, a decrease of Cdh1 and finally glutaminase increase, causing a positive feedback loop of excitotoxicity (Fuchsberger et al., 2016). Interestingly, Cdk5-p35 also modulates signaling induced by leptin (He et al., 2009). Cdk5-p35 causes SOCS3 activation, a negative feedback regulator which inhibits leptin-induced signal transduction and causes leptin resistance (He et al., 2009). So, the excess of glutamate levels can cause a cascade of events that also induce leptin-resistance.

Interestingly, in AD the aforementioned overactivation is produced in extrasynaptic NMDA receptors rather than in synaptic NMDA receptors (Zhang et al., 2016). Overstimulation of synaptic NMDA receptors is considered neuroprotective and in contrast, the overstimulation of extrasynaptic NMDA receptors induces tau hyperphosphorylation (Sun et al., 2016) and cell death (Hardingham and Bading, 2010). In fact, memantine blocks preferentially extrasynaptic over synaptic NMDA receptors (Xia et al., 2010) as part of its action as AD treatment. NR2-A is a subunit mainly present in synaptic NMDA receptors and it has shown that leptin mediates neuroprotection activating them (O’Malley et al., 2007), and this is critical for the induction of LTP and LTD (Muller et al., 2009). When leptin binds to its receptor, activates JAK2, which in turn promotes the activation of STAT3, and then, PI3K-Akt signaling pathways are induced. Activation of synaptic NR2A-containing NMDARs by glutamate also induces the PI3K-dependent pathway (Lee et al., 2002), so both common signals are highly potentiated. The signal cascade will induce AMPA exocytosis and LTP (Moult et al., 2010) but also neuronal survival by promoting expression of mitochondrial antioxidant enzymes and anti-apoptotic proteins such as Bcl-xl (Guo et al., 2008), and by inhibiting Foxo (Al-Mubarak et al., 2009) and GSK3β (Greco et al., 2009). In contrast, in AD extrasynaptic NMDA receptors are overstimulated and this leads to neuronal death. Extrasynaptic NMDAR induces the pro-apoptotic transcription factor Foxo (Dick and Bading, 2010) and also mitotoxicity. The consequences are mitochondrial calcium sustained increase, compromised ATP production and mitochondrial dysregulation finally inducing cell death (Bading, 2017). A global scheme is shown in Figure 2.

CONCLUSION

Leptin is a hormone secreted by adipose tissue that matters for the correct functioning of the brain, including the memory, and learning processes in the hippocampus. Leptin is neuroprotective and increase LTP, potentiating the activity of synaptic NMDA receptors of glutamate. We discussed how in AD both leptin resistance, LTP dysfunction, and also an increase in glutamate levels (Kuchibhotla et al., 2008). When leptin binds to its receptor, activates JAK2, which in turn promotes the activation of STAT3, and then, PI3K-Akt signaling pathways are induced. Activation of synaptic NR2A-containing NMDARs by glutamate also induces the PI3K-dependent pathway (Lee et al., 2002), so both common signals are highly potentiated. The signal cascade will induce AMPA exocytosis and LTP (Moult et al., 2010) but also neuronal survival by promoting expression of mitochondrial antioxidant enzymes and anti-apoptotic proteins such as Bcl-xl (Guo et al., 2008), and by inhibiting Foxo (Al-Mubarak et al., 2009) and GSK3β (Greco et al., 2009). In contrast, in AD extrasynaptic NMDA receptors are overstimulated and this leads to neuronal death. Extrasynaptic NMDAR induces the pro-apoptotic transcription factor Foxo (Dick and Bading, 2010) and also mitotoxicity. The consequences are mitochondrial calcium sustained increase, compromised ATP production and mitochondrial dysregulation finally inducing cell death (Bading, 2017). A global scheme is shown in Figure 2.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

This work was supported by SAF2016-75508-R (Ministerio de Economía y Competitividad), CB16/10/00435 (CIBERFESISCIII), PROMETEOIIH2014/056 (Conselleria de Educación, Investigación, Cultura y Deporte).
REFERENCES

Al-Mubarak, B., Soriano, F. X., and Hardingham, G. E. (2009). Synaptic NMDAR activity suppresses FOXO1 expression via a cis-acting FOXO binding site: FOXO1 is a FOXO target gene. Channels 3, 233–238.

Amitani, M., Asakawa, A., Amitani, H., and Inui, A. (2013). The role of leptin in the control of insulin-glucose axis. Front. Neurosci. 7:51. doi: 10.3389/fnins.2013.00051

Anstey, K., Cherbuin, N., Budge, M., and Young, J. (2011). Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. Obes. Rev. 12, e426–e437. doi: 10.1111/j.1467-789X.2010.00825.x

Arnoldussen, I. A., Kiliaan, A. J., and Gustafson, D. R. (2014). Obesity and diabetes: adipokines interact with the brain. Neuropsychopharmacol. 24, 1982–1999. doi: 10.1002/euro.2014.03.002

Bading, H. (2017). Therapeutic targeting of the pathological triad of extrasynaptic NMDA receptor signaling in neurodegenerations. J. Exp. Med. 214, 569–578. doi: 10.1084/jem.20161673

Balland, E., Dam, J., Langlet, F., Caron, E., Steculorum, S., Messina, A., et al. (2014). Peptides induces excitotoxicity mediated by APC/C-Cdh1 depletion that can be prevented by glutaminase inhibition promoting neuronal survival. Sci. Rep. 4, 5309. doi: 10.1038/srep05309

Golden, P. L., Maccagnan, T. J., and Partridge, W. M. (1997). Human blood-brain barrier leptin receptor. Binding and endocytosis in isolated human brain microvessels. J. Clin. Invest. 99, 14–18. doi: 10.1172/jci119125

Greco, S. J., Sarkar, S., Casadesus, G., Zhu, X., Smith, M. A., Ashford, J. W., et al. (2009). Leptin inhibits glycogen synthase kinase-3β to prevent tau phosphorylation in neuronal cells. Neurosci. Lett. 455, 191–194. doi: 10.1016/j.neulet.2009.03.066

Guo, Z., Jiang, H., Xu, X., Duan, W., and Mattson, M. P. (2008). Leptin-mediated cell survival signaling in hippocampal neurons mediated by JAK STAT3 and mitochondrial stabilization. J. Biol. Chem. 283, 1754–1763. doi: 10.1074/jbc.m703753200

Hardingham, G. E., and Bading, H. (2010). Synaptic versus extrasynaptic NMDA receptor signaling: implications for neurodegenerative disorders. Nat. Rev. Neurosci. 11, 682–696. doi: 10.1038/nrn2911

Harvey, J. (2007). Leptin regulation of neuronal excitability and cognitive function. Curr. Opin. Pharmacol. 7, 643–647. doi: 10.1016/j.coph.2007.10.006

Harvey, J. (2013). Leptin regulation of neuronal morphology and hippocampal synaptic function. Front. Syn. Neurosci. 5:3. doi: 10.3389/fnsyn.2013.00003

He, Y., Kastin, A. J., Hsuhou, H., and Pan, W. (2009). The Gsk3β/35 kinases modulate leptin-induced STAT3 signaling. J. Mol. Neurosci. 39, 49–58. doi: 10.1007/s12031-008-9174-3

Hotamisligil, G. S. (2017). Foundations of immunometabolism and implications for metabolic health and disease. Immunity 47, 406–420. doi: 10.1016/j.immuni.2017.08.009

Jimenez-Jimenez, F. J., Molina, J. A., Gomez, P., Vargas, C., de Bustos, F., Benito-Leon, J., et al. (1998). Neurotransmitter amino acids in cerebrospinal fluid of patients with Alzheimer’s disease. J. Neural. Transm. 105, 269–277. doi: 10.1007/s10976-005-5056-6

Joo, S. H., Yun, S. H., Kang, D. W., Hahn, C. T., Lim, H. K., and Lee, C. U. (2018). Body mass index in mild cognitive impairment according to age, sex, cognitive intervention and hypertension and risk of progression to alzheimer’s disease. Front. Psychiatry 9:142.

Kahn, B. B., and Flier, J. S. (2000). Obesity and insulin resistance. J. Clin. Invest. 106, 473–481.

Kaiser, E., Schonkecht, P., Kassner, S., Hildebrandt, W., Kinscherf, R., and Schroeder, J. (2010). Cerebrospinal fluid concentrations of functionally important amino acids and metabolic compounds in patients with mild cognitive impairment and Alzheimer’s disease. Neurodegener. Dis. 7, 251–259. doi: 10.1159/000287933

Karlsson, C., Lindell, K., Svensson, E., Bergh, C., Lind, P., Billig, H., et al. (1997). Expression of functional leptin receptors in the human ovary. J. Clin. Endocrinol. Metab. 82, 4144–4148. doi: 10.1210/jc.82.12.4144
Lloret et al. Obesity and AD Risk

Kelesidis, T., Kelesidis, I., Chou, S., and Mantzoros, C. S. (2010). Narrative review: the role of leptin in human physiology: emerging clinical applications. Annu. Intern. Med. 152, 93–100. doi: 10.7326/0003-4819-152-2-20100119-00008

Kiliaan, A. J., Arnoldussen, I. A., and Gustafson, D. R. (2014). Adipokines: a link between obesity and dementia? Lancet Neurol. 13, 913–923. doi: 10.1016/S1474-4422(14)70057-5

King, A., Brain, A., Hanson, K., Dittmann, J., Vickers, J., and Fernandez-Martos, C. (2018). Disruption of leptin signalling in a mouse model of Alzheimer's disease. Metab. Brain Dis. 33, 1097–1110. doi: 10.1007/s11011-018-0203-9

Kivimäki, M., Luukkonen, R., Batty, G. D., Ferrie, J. E., Pentti, J., Nyberg, S. T., et al. (2018). Body mass index and risk of dementia: analysis of individual-level data from 1.3 million individuals. Alzheimers Dem. 14, 601–609. doi: 10.1016/j.jalz.2017.09.016

Kivipelto, M., Ngandu, T., Fratiglioni, L., Viitanen, M., Kääriäinen, H., Winblad, B., et al. (2005). Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch. Neurol. 62, 1556–1560.

Kuchibhotla, K. V., Goldman, S. T., Lattarulo, C. R., Wu, H. Y., Hyman, B. T., and Bacskai, B. J. (2008). Abeta plaques lead to aberrant regulation of calcium homeostasis in vivo resulting in structural and functional disruption of neuronal networks. Neuron 59, 214–225. doi: 10.1016/j.neuron.2008.06.008

Kulkarni, R. N., Wang, Z. L., Wang, R. M., Hurley, J. D., Smith, D. M., Ghatei, M. A., et al. (1997). Leptin rapidly suppresses insulin release from insulinoma cells, rat and human islets and, in vivo, in mice. J. Clin. Invest. 100, 2729–2736. doi: 10.1172/jci199818

Lee, F. J. S., Xue, S., Pei, J., Vukusic, B., Chéry, N., Wang, Y., et al. (2002). Dual regulation of NMDA receptor functions by direct protein-protein interactions with the dopamine D1 receptor. Cell 111, 219–230. doi: 10.1002/0096-8674(20020409)111:3<219::AID-CYL21>3.0.CO;2-Q

Lieber, W., Beiser, A. S., Vasan, R. S., Tan, Z. S., Au, R., Harris, T. B., et al. (2009). Association of plasma leptin levels with incident Alzheimer disease and MRI measures of brain aging. JAMA 302, 2565–2572. doi: 10.1001/jama.2009.1836

Lizarbe, B., Soares, A. F., Larsson, S., and Duarte, J. M. N. (2019). Neurochemical Frontiers in Neuroscience | www.frontiersin.org 9

Lloret et al. Obesity and AD Risk

McGregor, G., and Harvey, J. (2018b). Regulation of hippocampal synaptic function by the metabolic hormone, leptin: Implications for health and neurodegenerative disease. Front. Cell. Neurosci. 12:340. doi: 10.3389/fncel.2018.00340

Mercer, J. G., Hoggard, N., Williams, L. M., Lawrence, C. B., Hannah, L. T., and Trayhurn, P. (1996). Localization of leptin receptor mRNA and the long form splice variant (Ob-Rb) in mouse hypothalamus and adjacent brain regions in situ hybridization. FEBS Lett. 387, 113–116. doi: 10.1016/0014-5793(96)04735-3

Mulli, D. E., Norwell, D. Y., and Schwartz, F. N. (1993). Plasma concentrations of glutamate and its metabolites in patients with Alzheimer's disease. J. Am. Osteopath. Assoc. 93, 670–676.

Montagne, A., Zhao, Z., and Zlokovic, B. V. (2017). Alzheimer's disease: a matter of blood-brain barrier dysfunction? J. Exp. Med. 214, 3151–3169. doi: 10.1084/jem.20171406

Moutl, P. R., Cross, A., Santos, S. D., Carvalho, A. L., Lindsay, Y., Connolly, C. N., et al. (2010). Leptin regulates AMPA receptor trafficking via PTEN inhibition. J. Neurosci. 30, 4088–4101. doi: 10.1523/JNEUROSCI.3614-09.2010

Moutl, P. R., and Harvey, J. (2011). NMDA receptor subunit composition determines the polarity of leptin-induced synaptic plasticity. Neuropharmacology 61, 924–936. doi: 10.1016/j.neuropharm.2011.06.021

Müller, T., Albrecht, D., and Gebhardt, C. (2009). Both NR2A and NR2B subunits of the NMDA receptor are critical for long-term potentiation and long-term depression in the lateral amygdala of horizontal slices of adult mice. Learn. Mem. 16, 395–405. doi: 10.1101/lm.1398709

Mysers, M. G. Jr. (2015). Leptin keeps working, even in obesity. Cell Metab. 21, 791–792. doi: 10.1016/j.cmet.2015.05.017

Mysers, M. G. Jr., Leibl, R. L., Seeley, R. J., and Schwartz, M. W. (2010). Obesity and leptin resistance: distinguishing cause from effect. Trends Endocrinol. Metab. 21, 643–651. doi: 10.1016/j.tem.2010.08.002

Myers, M. G., Cowley, M. A., and Münzherr, B. (2008). Mechanisms of leptin action and leptin resistance. Annu. Rev. Physiol. 70, 537–556. doi: 10.1146/annurev.physiol.70.113006.100707

O'Brien, P. D., Hinder, L. M., Callaghan, B. C., and Feldman, E. L. (2017). Neurological consequences of obesity. Lancet Neurol. 16, 465–477.

Odegaard, J. I., and Chawla, A. (2013). Pliotropic actions of insulin resistance and inflammation in metabolic homeostasis. Science 339, 172–177. doi: 10.1126/science.1230721

O'Malley, D., MacDonald, N., Mizielinska, S., Connolly, C. N., Irving, A. J., and Harvey, J. (2007). Leptin promotes rapid dynamic changes in hippocampal dendritic morphology. Mol. Cell. Neurosci. 35, 559–572. doi: 10.1016/j.mcn.2007.05.001

Ong, W. Y., Tanaka, K., Dawe, G. S., Ittner, L. M., and Farooqui, A. A. (2013). Slow excitotoxicity in Alzheimer's disease. J. Alzheimers Dis. 35, 643–668. doi: 10.3233/JAD-121990

Pallett, A. L., Morton, N. M., Cawthorne, M. A., and Emilsson, V. (1997). Leptin inhibits insulin secretion and reduces insulin mRNA levels in rat isolated pancreatic islets. Biochem. Biophys. Res. Commun. 238, 267–270. doi: 10.1006/ bbrc.1997.7274

Parsons, C. G., Stöffler, A., and Danyts, W. (2007). Memantine: A NMDA receptor antagonist that improves memory by restoration of homeostasis in the glutamatergic system-too little activation is bad, too much is even worse. Neuropharmacology 53, 699–723. doi: 10.1016/j.neuropharm.2007.07.013

Payabvash, S., Souza, L. C., Wang, Y., Schaefer, P. W., Furie, K. L., Halpern, E. F., et al. (2011). Regional ischemic vulnerability of the brain to hypoperfusion: the need for location specific computed tomography perfusion thresholds in acute stroke patients. Stroke 42, 1255–1260. doi: 10.1161/STROKEAHA.110.60940

Pedditizi, E., Peters, R., and Beckett, N. (2016). The risk of overweight/obesity in mid-life and late life for the development of dementia: a systematic review and meta-analysis of longitudinal studies. Age Ageing 45, 14–21. doi: 10.1093/ageing/afv151

Pequerolles, J., Jiménez, A., Villalpanda, E., Montal, V., Carmona-Iragui, M., Pané, A., et al. (2018). Obesity and Alzheimer's disease, does the obesity paradox
真的存在吗？磁共振成像研究。*Oncotarget* 9, 34691–34698. doi: 10.18632/oncotarget.26162

Perez-Gonzalez, R., Alvarez-Botero, M. X., Robayo, O., Antequera, D., Garzon, M., Martin-Moreno, A. M., et al. (2014). Leptin gene therapy attenuates neuronal damages evoked by amyloid-β and rescue memory deficits in APP/PS1 mice. *Gene Ther.* 21, 298–308. doi: 10.1038/gt.2013.85

Platt, T. L., Reckett, T. L., Kohler, K., Niedowicz, D. M., and Murphy, M. P. (2016). Obesity, diabetes, and leptin resistance promote tau pathology in a mouse model of disease. *Neuroscience* 315, 162–174. doi: 10.1016/j.neuroscience.2015.12.011

Pomara, N., Singh, R., Dextula, D., Chou, J. C., Schwartz, M. B., and LeWitt, P. A. (1992). Glutamate and other CSF amino acids in Alzheimer’s disease. *Am. J. Psychiatry* 149, 251–254. doi: 10.1176/ajp.149.2.251

Qizilbash, N., Gregson, J., Johnson, M. E., Pearce, N., Douglas, I., Wing, K., et al. (2015). BMI and risk of dementia in two million people over two decades: a retrospective cohort study. *Lancet Diabetes Endocrinol.* 3, 431–436. doi: 10.1016/S2213-8587(15)00033-9

Sahoo, K., Sahoo, B., Choudhury, A. K., Sofi, N. Y., Kumar, R., and Bhadoria, A. S. (2015). Childhood obesity: causes and consequences. *J. Fam. Med. Prim. Care* 4:187.

Savioz, A., Charnay, Y., Huguenin, C., Graviou, C., Greggio, B., and Bouras, C. (1997). Expression of leptin receptor mRNA (long form splice variant) in the human cerebellum. *Neuroreport* 8, 3123–3126. doi: 10.1097/00001756-199709290-00023

Schwartz, M. W., Peskind, E., Raskind, M., Boyko, E. J., and Porte, D., Jr. (1996). Cerebrospinal fluid leptin levels: relationship to plasma levels and to adiposity in humans. *Nat. Med.* 2, 589–593. doi: 10.1038/nm05 96-589

Shanley, L. J., Irving, A. J., and Harvey, J. (2001). Leptin enhances NMDA receptor function and modulates hippocampal synaptic plasticity. *J. Neurosci.* 21:24CR186.

Singh-Manoux, A., Dougrovot, A., Shipley, M., Brunner, E. J., Elbaz, A., Sabia, S., et al. (2018). Obesity trajectories and risk of dementia: 28 years of follow-up in the Whitehall II study. *Alzheimers Dem.* 21:24RC186.

Sinha, M. K., Opentanova, L., Ohanessian, J. P., Kolacynski, J. W., Heiman, M. L., Hale, J., et al. (1996). Evidence of free and bound leptin in human circulation. Studies in lean and obese subjects and during short-term fasting. *J. Clin. Invest.* 98, 1277–1282. doi: 10.1172/jci118913

Solías, M., Milagro, F. I., Ramírez, M. J., and Martínez, J. A. (2017). Inflammation and gut-brain axis link obesity to cognitive dysfunction: plausible pharmacological interventions. *Curr. Opin. Pharmacol.* 37, 87–92. doi: 10.1016/j.coph.2017.10.005

Sun, X. Y., Tuo, Q. Z., LiuYang, Z. Y., Xie, A. J., Feng, X. L., Yan, X., et al. (2016). Extrasynaptic NMDA receptor-induced tau overexpression mediates neuronal death through suppressing survival signaling ERK phosphorylation. *Cell Death Dis.* 7:e2449. doi: 10.1038/cddis.2016.329

Tartaglia, L. A. (1997). The leptin receptor. *J. Biol. Chem.* 272, 6093–6096.