Published in final edited form as:
Eur Neuropsychopharmacol. 2014 December ; 24(12): 1982–1999. doi:10.1016/j.euroneuro.2014.03.002.

Obesity and dementia:

Adipokines interact with the brain

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Abstract

Obesity is a pandemic and a serious global health concern. Obesity is a risk factor for multiple conditions and contributes to multi-morbidities, resulting in increased health costs and millions of deaths each year. Obesity has been associated with changes in brain structure, cognitive deficits, and dementia and Alzheimer's disease. Adipokines, defined as hormones, cytokines and peptides secreted by adipose tissue, may have more widespread influence and functionality in the brain than previously thought. In this review, six adipokines, and their actions in the obese and non-obese condition will be discussed. Included are: plasminogen activator inhibitor-1 (PAI-1), interleukin-6 (IL-6), tumor necrosis factors alpha (TNF-α), angiotensinogen (AGT), adiponectin and leptin. Their functionality in the periphery, their ability to cross the blood brain barrier (BBB) and their influence on dementia processes within the brain will be discussed.

Keywords

Obesity; adipokines; brain; leptin; Alzheimer; dementia

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Conflict of interest: The authors declare no conflicts of interest.

Contributors: Deborah R. Gustafson was invited to submit this review. Subsequently, all contributors, Ilse AC Arnoldussen, Amanda J Kiliaan, and Deborah R Gustafson, participated equally in the drafting of this review manuscript.

1. Introduction

Each year, obesity or obesity-related conditions lead to the death of 2.8 million adults around the world (WHO, 2012). This epidemic in Western societies, and burgeoning epidemic in non-Western societies, increase the risk for multiple adverse health conditions and contributes to multiple morbidities (Olde Dubbelink et al., 2008). Obesity has an obscure etiology but it is generally ascribed to an imbalance of energy intake versus energy output and a complex interplay between genes and environment, (Doherty, 2011) leading to the highest prevalence of overweight and obesity ever observed in the world's history (Bray and Popkin, 1998). Adipose tissue, mainly white adipose tissue (WAT), functions as the largest endocrine organ by secreting hundreds of hormones, peptides and cytokines which are collectively referred to as adipokines. These adipokines affect processes in the periphery and the central nervous system (CNS).

Obesity has been associated with alterations in brain structure and function, cognitive deficits and even dementia and Alzheimer's disease (AD) (Businaro et al., 2012; Delgado et al., 2011; Gustafson, 2008, 2010; Gustafson et al., 2004; Haltia et al., 2007). In 2003, the first association was reported between AD and being more overweight, (defined within the overweight category of body mass index (BMI) between 25-29.99 kg/m2) in women (Gustafson et al., 2003). Thus, the year 2013, marks 10 years of published epidemiologic reports relating higher mid-life and late-life BMI to dementia (Fitzpatrick et al., 2009; Gustafson et al., 2009; Gustafson et al., 2003; Hayden et al., 2006; Kivipelto et al., 2005; Whitmer et al., 2007; Whitmer et al., 2008). Levels of mid-life and late-life BMI associated with AD are in overweight and obese ranges based on traditional cutpoints used for cardiovascular disease and overall mortality. While higher levels of adult BMI may increase risk for chronic neurodegenerative diseases of aging, some studies show that the direction of the BMI-AD relationship changes direction, and BMI declines in association with AD, later in life (Besser, 2013, in press; Gustafson et al., 2012; Gustafson et al., 2009). Higher BMI in middle adult life could be reflecting higher vascular risk and declining BMI reflecting more neurodegenerative events in latest life. This theory is illustrated by observations of both higher absolute level of baseline BMI and more body weight decline among those with Mild Cognitive Impairment (MCI) being associated with clinical dementia progression (CDR-Sum of Boxes) (Besser, 2013, in press).

Accompanying the literature on dementia and AD, are observed alterations in brain structure and function including decreased total and gray matter volumes, increased white matter lesions and reduced white matter integrity (Brooks et al., 2012; Gustafson et al., 2004; Pannacciulli et al., 2006; Raji et al., 2010; Stanek et al., 2011). More specifically, abnormalities in brain regions such as the amygdala, hippocampus and frontal cortex (Cazettes et al., 2011; Widya et al., 2011); decreased cortical thickness (Haltia et al., 2007; Hassenstab et al., 2012); axonal degradation (Mueller et al., 2011); and decreased functional connectivity in the brain (Nummenmaa et al., 2012; Stoeckel et al., 2009) have been observed.

It is known that adipokines, secretory products of adipose tissue such as leptin, interact directly with specific nuclei in certain areas of the brain such as the hippocampus. This

results inregulation of not only feeding behavior, but also neurodegeneration, synaptic plasticity, neurogenesis and memory consolidation (Doherty, 2011). Reviewed herein are the adipokines, plasminogen activator inhibitor-1 (PAI-1), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), angiotensinogen (AGT), adiponectin and leptin. These adipokines are not exclusively secreted by adipose tissue, nor is adipose tissue the only or primary source of these compounds. However, the adipokines selected for review have been associated with obesity-related morbidities that have also been implicated in dementia and AD, such as chronic low levels of inflammation, hypertension, and direct impaired in regulation of energy metabolism (Gustafson, 2006; Harrison, 2013; Iadecola and Davisson, 2008; Jequier, 2002; Rocha and Folco, 2011; Xu et al., 2011). More specifically, AGT is an important mediator of hypertension; TNF-α, IL-6 and PAI-1 are involved in chronic inflammation and fibrinolysis; and leptin and adiponectin regulate several processes including energy metabolism (Diez and Iglesias, 2003; Gardes et al., 1982; Guerre-Millo, 2004; Jequier, 2002; Ouchi et al., 2003a; Rocha and Folco, 2011; Villarreal-Molina and Antuna-Puente, 2012). Before circulating peripheral adipokines are able to interact with the brain, they must cross the blood brain barrier (BBB) to enter the central nervous system (CNS). This large neurovascular interface controls the transport of a variety of blood-borne factors such as amino acids, peptides, polypeptides and proteins, as well as many other molecules, such as adipokines, into the CNS (Banks, 2006; Kastin et al., 1999a; Pan and Kastin, 2007).

To better understand the epidemiologic associations between obesity and dementia and AD, we focus this review on how adipose tissue may influence the brain via adipokine action, the biology of each adipokine in the periphery, as well as its ability to cross the BBB and influence brain processes. First will be described how adipokine levels are altered in the obese versus non-obese condition. Second will be described possible pathways and processes by which these adipokines might affect the BBB and brain in obesity. Because very little literature is available regarding detailed molecular pathways in humans, these last descriptions are mainly based on findings from *in vitro (cell culture) studies* and *in vivo* experiments using animal models.

2. Leptin

Leptin is a protein hormone that has drawn the most attention in obesity research since its discovery in 1994 (Zhang et al., 1994). Leptin was discovered as a hormone involved in long-term regulation of energy intake and expenditure, body weight, and neuroendocrine functions in mammals (Jequier, 2002). Furthermore, it has significantly broadened our understanding of the mechanisms underlying the development of obesity and its complications. In the non-obese condition, energy intake increases leptin secretion, and in the brain leptin induces a negative feedback on energy intake via stimulating the expression of anorexigenic neuropeptides. In children, plasma levels of leptin are positively correlated with body weight, thus a higher body weight is associated with a higher leptin level (Fleisch et al., 2007; Salbe et al., 2002). Obese adolescents show higher plasma leptin concentrations in comparison with non-obese adolescents (Foschini et al., 2008; Salbe et al., 2002). Similar positive correlations are observed between body weight or BMI in adults and elderly (Ahima, 2006; Considine et al., 1996; Gustafson, 2012; Zeki Al Hazzouri et al., 2012). Despite these positive correlations, levels of adipokines such as leptin are highly variable in

adults (Gustafson, 2012). Moreover, leptin production is influenced by sex and BMI in humans (Wiesner et al., 1999).

Peripheral leptin is able to enter cerebrospinal fluid (CSF) and the central nervous system (CNS crossing the BBB and choroid plexus,), and subsequently in the CNS leptin interacts with specific areas of the brain such as the hypothalamus and hippocampus (Peiser et al., 2000; Zlokovic et al., 2000). However, besides leptin transport into the CNS and CSF, several studies indicated that leptin can also be produced in human and rodent brains, for example in the hypothalamus, cortex and cerebellum (Brown et al., 2007; Brown et al., 2008; Morash et al., 1999; Wiesner et al., 1999; Wilkinson et al., 2007). Leptin transport across the BBB occurs via a mechanism involving leptin receptor a (LepRa), and a second, not yet characterized, transport mechanism (Schulz et al., 2010). This transport system for leptin has been demonstrated to be diurnal, both *in vivo* in mice and *in vitro* in cell culture studies (Banks et al., 1996; Maresh et al., 2001; Pan and Kastin, 2001).

Within the brain, leptin regulates energy intake and expenditure via suppression and induction of the expression of selected neuropeptides (Ahima, 2006; Jequier, 2002). Within the hypothalamus leptin binds to leptin receptors located on two populations of hypothalamic neurons. One population of neurons produces orexigenic neuropeptides (neuropeptide Y (NPY) and the agouti-related peptide (AGRP)). The second population of neurons produces anorexigenic neuropeptides (α-melanocyte-stimulating hormone (α-MSH) & pro-opiomelanocortin (POMC)) (Jequier, 2002). Leptin inhibits the expression of orexigenic neuropeptides and stimulates the expression of anorexigenic neuropeptides, which results in inhibition of energy intake (Jequier, 2002). An important functional leptin receptor in the brain is leptin receptor b (LepRb), which is highly expressed in the specific brain regions as the neocortex, hypothalamus, medulla and cerebellum (Burguera et al., 2000b). LepRb is the full-length isoform of the leptin receptor, and *in vivo* and *in vitro* experiments have revealed that it is the only receptor that contains intracellular motifs required for activation of the janus kinase 2 and signal transducer and activator of transcription 3 (JAK-2/STAT-3) pathway (Baumann et al., 1996; Bjorbaek and Kahn, 2004; Bjorbaek et al., 1997; Fruhbeck, 2006; Myers, 2004; Tartaglia et al., 1995; White et al., 1997).

Besides a role in energy intake, the presence of leptin receptors in specific regions of the brain illustrates its potential for being involved in multiple mechanisms related to brain function and structure in many rodent models (Banks, 2006; Banks et al., 2000; Grill et al., 2002; Guan et al., 1997; Huang et al., 1996; Shioda et al., 1998). Thus, the multiple effects of leptin in experimental models on various aspects of memory, neurogenesis, neuroprotection and brain structure are not surprising (See Figure 2/Table 1) (Ahima et al., 1999; Farr et al., 2006). Mainly in experimental rodent models, these effects of leptin on brain structure are determined by its influence on neurogenesis, axon growth, synaptogenesis and dendritic morphology, which occur during both pre-and postnatal life, and are important for the establishment of hypothalamic, hippocampal and cortical pathways (Bouret, 2010; Paz-Filho et al., 2010). The effects of leptin on axonal growth are not restricted to the hippocampus, but are also evident in the cortex (Valerio et al., 2006). Leptin effects on memory are facilitated by the conversion of short term potentiation into long term

potentiation (LTP). Leptin enhances N-methyl-D-aspartate (NMDA) receptor function and subsequently enhances LTP formation at hippocampal CA1 synapses and rapidly remodels dendrites, which partially explains its effect on improvement of hippocampal memory formation (Farr et al., 2006; Harvey, 2007; Oomura et al., 2006; Paz-Filho et al., 2010). In addition, several *in vitro* experiments and *in vivo* rodent studies suggest that leptin has neuroprotective actions by inhibiting apoptotic cell death, attenuating cell death, improving cell survival, protecting against glutametergic cytotoxicity, protecting against oxidative stress and promoting the proliferation of hippocampal progenitor cells (Morrison, 2009; Zhang et al., 2007). Thus, within the brain, leptin regulates energy intake and affects memory processes, neurogenesis, neuroprotection and brain structure.

In contrast, rodent studies have shown that leptin often does not reach the CNS due to impaired transport across the BBB (Banks et al., 1999; Banks and Lebel, 2002; Burguera et al., 2000a; Kastin et al., 1999b). Leptin-resistance at the BBB decreases the transport of peripheral leptin into the brain. However, whether this leads to a decrease in total brain leptin levels also depends on leptin production within the brain. Impaired transport could contribute, in part, to the development of leptin-resistance observed in obesity (Caro et al., 1996; Friedman and Halaas, 1998). Additionally, animal research shows that leptin-resistance also develops in the brain and is associated with an impaired leptin receptor such as LepRb, tyrosine residues, and downstream neuronal circuitry via the JAK-2/STAT-3 pathway (Banks et al., 1999; El-Haschimi et al., 2000; Hileman et al., 2002; Wilsey et al., 2003; Yamashita et al., 1997). Tyrosine residues, Tyr985 and Tyr1138 are directly autophosphorylated after activation of LepRb in the acurate nucleus of the hypothalamus. Phosphorylated Tyr1138 mediates the activation of the transcription factor STAT3 (Munzberg and Myers, 2005). Among other targets, STAT-3 induces the transcription of suppressor of cytokine signaling 3 (SOCS-3) during LepRb signaling (See Figure 1) (Munzberg and Myers, 2005). Furthermore, Tyr985 plays a dual role in LepRb signaling, first binding tyrosine-protein phosphatase non-receptor type 11 (SHP-2) and second also providing an important site of interaction for SOCS-3 (Munzberg and Myers, 2005). SOCS-3 binding to the LepRb-JAK-2 complex attenuates LepRb-mediated signalling, and thereby LepRb-mediated signalling via the JAK-2/STAT-3 pathway (See Figure 1) (Bjorbaek et al., 1998; Munzberg and Myers, 2005). At high levels of circulating leptin as observed in obesity, LepRbs are highly activated and subsequently tyrosine residues are intensely phosphorylated. In case of LepRb this will lead to increased ‘leptin signalling’ via the JAK-2/STAT-3 pathway, while phosphorylation of the tyrosine residues will lead to increased expression of SOCS-3 which inhibits LepRb-mediated signalling (See Figure 1) (Munzberg and Myers, 2005). This inhibition could attenuate most of the expected increase in LepRb signalling (Munzberg and Myers, 2005). It is hypothesized that this inhibitory mechanism of SOCS-3 could be an underlying mechanism of leptin resistance in obesity (Munzberg and Myers, 2005). Moreover, rodent studies reveal that in the hypothalamus of rodents with diet-induced obesity, SOCS-3 expression is upregulated, while the leptin response via the JAK-2/STAT-3 signaling is attenuated (El-Haschimi et al., 2000; Munzberg and Myers, 2005).

If assumed that obesity induces lower brain leptin levels or an attenuated leptin response, it could evoke a disrupted negative feedback loop in energy intake, impairments in memory processes, neurogenesis, neuroprotection and brain structure (See Figure 2/Table 1). However, leptin resistance within the CNS combined with impaired leptin transport at the BBB is not a waterproof explanation for all cases of human obesity. Leptin resistance is found in some animal models of obesity (Banks et al., 1999; El-Haschimi et al., 2000; Hileman et al., 2002; Yamashita et al., 1997), while for sporadic human obesity, there is often no evidence that leptin transport or response is impaired or deficient enough to be the primary cause of obesity (Arch et al., 1998; van Rossum et al., 2003).

3. Adiponectin

Adiponectin is a protein hormone, most well-described for modulating inflammatory responses, energy expenditure (CNS and periphery), food intake (CNS) and a number of metabolic processes, including glucose regulation and fatty acid catabolism in the periphery (See Figure 2) (Diez and Iglesias, 2003; Holland et al., 2013; Ouchi et al., 2003a; Qi et al., 2004; Villarreal-Molina and Antuna-Puente, 2012). In the periphery, adiponectin is released from adipose tissue into the blood circulation as full-length trimers, hexamers, high molecular weight (>500kDA, HMW) multimers and a globular fraction called globular adiponectin (Beltowski, 2003; Ouchi et al., 2003b). The two functional receptors of adiponectin, adipoR1 and adipoR2, contain seven transmembrane domains that serve as receptors for the multiple forms of globular and full length adiponectin. Activation of adiponectin receptors stimulates acetyl coenzyme-A carboxylase (ACC) phosphorylation and increases 5′ adenosine monophosphate-activated protein kinase (AMPK) in skeletal muscle and liver in animal models (Villarreal-Molina and Antuna-Puente, 2012). In humans, plasma adiponectin levels are, in contrast to most adipokines, inversely correlated to an increase in WAT, as well as to surrogate measures such as percentage body fat, waist-to-hip ratio and BMI (Cnop et al., 2003; Weyer et al., 2001). These correlations are less clear in children, adolescents and elderly (Ukkola and Santaniemi, 2002). In children, low adiponectin has been suggested to predict insulin resistance (Makni et al., 2012).

Adiponectin inhibits production of proinflammatory signals like TNF-α and IL-6. Adiponectin and TNF-α inhibit each other's production in adipose tissue, and adiponectin counteracts the proinflammatory effects of TNF-α in the vascular endothelium (Maeda et al., 2002; Matsuda et al., 2002; Ouchi et al., 1999; Ouchi et al., 2003a; Yokota et al., 2000). However, in contrast to IL-6, there is no evidence that plasma adiponectin levels are correlated with TNF-α levels in human plasma (Ouchi et al., 2003a). At the BBB, adiponectin affects proinflammatory signals by suppressing IL-6 release from endothelial cells in brain microvessels in mice(Spranger et al., 2006). Thus, interactions of adiponectin with the BBB seem to suppress proinflammatory signals, which is evidenced by decreased IL-6 production in rodent studies (Pan and Kastin, 2007). By inhibiting the production of IL-6 and TNF-α, adiponectin may indirectly affect inflammatory signalling across the BBB and within the brain. Thus, fewer proinflammatory cytokines might be able to cross the BBB due to high levels of circulating adiponectin. Peripheral plasma adiponectin levels are very low In human obesity (Cnop et al., 2003; Weyer et al., 2001). Thus, according to the afore mentioned hypothesis, more proinflammatory cytokines can cross the BBB, because of low

circulating levels of adiponectin which result in an attenuation of the inhibitory effect on proinflammatory cytokine expression (Maeda et al., 2002; Matsuda et al., 2002; Ouchi et al., 1999; Ouchi et al., 2003a; Spranger et al., 2006; Yokota et al., 2000).

Based on rodent studies, it has been proposed that adiponectin has a neuroprotective function and may induce weight loss centrally by increasing energy expenditure (Qi et al., 2004; Qiu et al., 2011). Both adipoR1 and adipoR2 receptors are functional and widely found throughout the CNS in brain microvessels, hippocampus, hypothalamus and brainstem in humans and rodent models (Fry et al., 2006; Kos et al., 2007; Kubota et al., 2007; Qiu et al., 2011; Wilkinson et al., 2007). However, in humans the influx of adiponectin into the CNS is not sufficient to represent an active transport mechanism for adiponectin across the BBB. The observed 1000-fold lower cerebrospinal fluid (CSF)/serum adiponectin concentration implies the presence of an effective barrier (Kos et al., 2007). Thus, it is still a matter of debate from whence the adiponectin in the brain originates. Is it secreted within the brain after a trigger of peripheral adipokines such as leptin, or can the small functional forms of peripheral adiponectin also cross the BBB? Remarkably, the clinical study mentioned above did not determine which isoforms of adiponectin enter the CSF (Kos et al., 2007). Other studies have shown that the trimeric and low molecular weight adiponectin forms are detectable in the CSF of humans and rodents (Kubota et al., 2007; Kusminski et al., 2007; Qi et al., 2004). Lack of HMW adiponectin in CSF may imply that only smaller forms of adiponectin are able to cross the BBB (Kubota et al., 2007; Kusminski et al., 2007; Schulz et al., 2010).

Neuroprotective effects of adiponectin are emphasized by a study showing that adiponectin-knockout mice exhibit larger brain infarctions and more neurological deficits after ischemia reperfusion compared to wild-type mice, while adenovirus-mediated supplementation of adiponectin significantly reduces cerebral infarction size in both wild-type and adiponectin-deficient mice (Nishimura et al., 2008). Furthermore, preloading of adiponectin centrally via lateral ventricle injection in mice attenuates subsequent neuronal damage from kainic acid-induced seizure activity in hippocampal neurons (Jeon et al., 2009). These results emphasize that adiponectin has a neuroprotective function (See Figure 2/Table 1).

Low plasma levels of adiponectin commonly observed in human obesity may also disrupt blood glucose regulation and fatty acid catabolism, and attenuate inhibition of inflammatory signals in the periphery(Villarreal-Molina and Antuna-Puente, 2012). Rodent studies reveal that, in the brain, deficient levels of adiponectin disrupt the normal regulation of energy expenditure, decrease neuroprotective effects, and increase the risk of cerebral infarctions (Nishimura et al., 2008; Qi et al., 2004; Qiu et al., 2011). However, it remains a matter of debate if peripheral adiponectin is able to cross the BBB to affect brain processes.

4. Angiotensinogen

Almost every tissue in the human body, including adipose tissue and the brain contain a fully functional renin-angiotensin system (RAS) (Grobe et al., 2010; Weiland and Verspohl, 2008; Yvan-Charvet and Quignard-Boulange, 2011). Initially, the role of peripheral RAS in blood pressure regulation was described, but RAS is now recognized to regulate a variety of

tissue-specific functions (Crowley and Coffman, 2012; Gonzalez-Villalobos et al., 2013). In the periphery, angiotensinogen (AGT), is the only known precursor for the production of the vasoconstriction-active peptide angiotensin II (ANG II). AGT is converted into angiotensin I by renin which is secreted by the kidneys, and subsequently converted into angiotensin II (ANG II) by angiotensin converting enzyme (ACE). Via binding to angiotensin receptor 2, ANG II increases blood pressure by increasing peripheral vascular resistance, increasing sympathetic nervous system activity, and controlling sodium homeostasis. Increased levels of ANG II are therefore associated with a higher risk for hypertension (Yiannikouris et al., 2012b). A positive correlation between blood pressure and circulating levels of AGT is consistently reported (Gardes et al., 1982; Kim et al., 1995; Ohkubo et al., 1990; Walker et al., 1979; Watt et al., 1992). The primary source of AGT is the liver, but WAT is considered as the major extrahepatic source of AGT which explains higher circulating plasma levels of AGT found in obese adults (Guerre-Millo, 2004; Van Harmelen et al., 2000a; van Harmelen et al., 2000b).

Studies in animal models provide evidence that production of AGT by WAT increases circulating AGT levels in obesity, thereby inducing hypertension (Yiannikouris et al., 2012a; Yiannikouris et al., 2012b). In wild-type mice, overexpression of AGT mRNA in WAT results in elevated plasma AGT and hypertension (Massiera et al., 2001). When overexpression of AGT is induced in AGT-knockout mice, which are hypotensive and lean, re-expression of AGT mRNA in WAT is sufficient to restore WAT mass and normal blood pressure (Massiera et al., 2001). However, some human studies report that plasma concentrations of AGT are similar in obese and lean humans (Goossens et al., 2007). These unaltered plasma AGT levels could alternatively be explained by β-adrenergic stimulation, which is shown to cause release of AGT from adipose tissue and increase plasma ANG II levels (Goossens et al., 2007). It is proposed that peripheral RAS is under control of the sympathetic nervous system (Hsueh et al., 1985). In the previous described study, the control of the sympathetic nervous system was mimicked by (3-adrenergic stimulation (Goossens et al., 2007). Plasma AGT levels are unaltered in obese individuals, but the effect of increased production of AGT by the WAT on peripheral RAS stays the same through an increase in plasma ANG II in obese individuals, which is in line with the results of the previous described animal studies.

Neither renin nor angiotensin peptides are able to cross the BBB (See Figure 2) (McKinley et al., 2003; Pardridge, 1983; Reid, 1979; Severs et al., 1978). Nevertheless, the brain contains an intrinsic brain RAS (Bader and Ganten, 2002; McKinley et al., 2003). The circumventricular organs are excluded from the brain RAS, because these organs lack a BBB and are directly influenced by the peripheral RAS (McKinley et al., 2003). All RAS components are produced within the brain, for example AGT is produced in most regions of the brain by glial cells, mainly astrocytes (Stornetta et al., 1988). Within the human brain AGT can also be converted into ANG I via renin and into ANG II via ACE. ANG II influences arterial pressure at a number of brain sites (Allen et al., 1988; Andreatta et al., 1988; Averill et al., 1987; Jensen et al., 1992; McKinley et al., 2003; Severs and Daniels-Severs, 1973; Simpson, 1981; Thornton and Nicolaidis, 1993). Moreover, ANG II can be converted into angiotensin III (ANG III) and angiotensin IV (ANG IV) by aminopeptidase A and N. When ANG IV interacts with angiotensin receptor 4 it influences learning and

memory mechanisms within the brain (McKinley et al., 2003). AGT, the only precursor of angiotensin peptides, has a protective role in maintaining the integrity of the BBB (Goossens et al., 2007; Pan and Kastin, 2007; Yanai et al., 2000). A study in AGT knockout mice revealed that deletion of the AGT gene is involved in impairment of BBB function (Kakinuma et al., 1998). Impairment of the BBB results in movement of peptides and proteins into and out of the brain via leaky tight junctions between endothelial cells comprising the BBB (Janzer and Raff, 1987). In response to BBB impairment, reactive astrocytes migrate to the injured area, where they proliferate, produce extracellular matrix and reconstitute the BBB (Laywell et al., 1992; Ludwin, 1985). These astrocytes express AGT, suggesting that AGT also contributes to BBB reconstitution from the CNS (Kakinuma et al., 1998; Milsted et al., 1990; Stornetta et al., 1988).

In the periphery, increased AGT production by adipose tissue leads to higher plasma ANG II levels inducing hypertension in obese individuals. Subsequently, the vascular risk factor, hypertension, damages the vasculature (Novak et al., 2003). Higher levels of BMI are also associated with disrupted BBB integrity (Gustafson et al., 2007). Thus, increased AGT production in the periphery could result in increased ANG II levels, leading to hypertension (Yiannikouris et al., 2012b), which may impair BBB permeability (Youssef et al., 2012). On the other hand, peripheral AGT may protect BBB integrity, and AGT produced by astrocytes may contribute to BBB reconstruction (Goossens et al., 2007; Pan and Kastin, 2007; Yanai et al., 2000). Thus, AGT may be an important mediator in directly regulating BBB integrity in obesity, or indirectly increasing BBB permeability via elevated ANG II levels.

Overall, whether the effects of higher AGT levels in the periphery and at the BBB are advantageous among obese individuals should be a focus of future research. In the brain's RAS, the only precursor of angiotensin peptides, AGT, induces learning and memory processes via ANG IV.

5. Plasminogen activator inhibitor-1

Plasminogen activator inhibitor-1 (PAI-1) is a member of the serpin gene family. PAI-1 influences vascular health via inhibition of fibrinolysis, a process that prevents blood clots that clog arteries (Guerre-Millo, 2004). PAI-1 causes inhibition of fibrinolysis via inhibition of tissue type plasminogen activator (tPA) and urokinase plasminogen activator (uPA) (Guerre-Millo, 2004; Loskutoff et al., 1989). However, the biological role of PAI-1 extends beyond the regulation of inflammation and fibrinolysis, since PAI-1 has been shown to influence cell migration and angiogenesis by competing with integrin binding on the extracellular matrix (Guerre-Millo, 2004). In humans, the adipokine, PAI-1, is elevated in plasma of obese children, adolescents and adults (Giordano et al., 2011; Greenberg and Obin, 2006; Mantovani et al., 2011; Singh et al., 2012). Adipocytes are a main contributor to the elevated levels of PAI-1 seen in obesity. Furthermore, excess adipose tissue and especially central obesity in adults has been associated with decreased fibrinolysis, possibly via an elevated production of PAI-1 (Skurk and Hauner, 2004).

PAI-1 transport mechanisms across the BBB are still unknown. PAI-1 produced within the brain by microglia and astrocytes may regulate apoptosis, survival of neurites and migration

of microglia(Ahn et al., 1999; Jeon et al., 2012; Soeda et al., 2008; Soeda et al., 2001). *In vitro* experiments examining the role of PAI-1 show that sufficient PAI-1 in the extracellular environments of neurons prevents apoptotic changes (Soeda et al., 2008; Soeda et al., 2001). Thus, PAI-1 inhibits apoptosis in neurons. PAI-1 in extracellular environments may be produced by neighbouring astrocytes (Soeda et al., 2001). Moreover, *in vitro* studies show that PAI-1 contributes to the survival of neurites, axons and/or dendrites. PAI-1 prevents the disintegration of formed neuronal networks by maintaining or promoting neuroprotective signalling through the MAPK/ERK pathway (Soeda et al., 2008). Furthermore, PAI-1 promotes the migration of microglial cells in culture via the low-density lipoprotein receptor-related protein (LRP) 1/Janus kinase (JAK)/signal transducer and activator of transcription (STAT)1 axis (Jeon et al., 2012). Several other cell culture studies indicate that glia-derived PAI-1 may regulate microglial migration in an autocrine or paracrine manner (Ahn et al., 1999; Jeon et al., 2012). Microglia, the resident macrophages of the CNS, constitute the brain's innate immune system and play a pivotal role in neuroinflammation and host defense against microbial agents (Block et al., 2007; Garden and Moller, 2006; Graeber and Streit, 2010; Jeon et al., 2012; Mallat et al., 2005; Woo et al., 2008). Thus, PAI-1 is an important adipokine involved in the regulation of microglial migration, thereby affecting neuroinflammation and the immune system in the brain.

Considering a function for PAI-1 in a non-obese hypothalamus, it is interesting to mention that transgenic mice overexpressing urokinase-type plasminogen activator (uPA) in several brain regions, including the paraventricular nucleus of the hypothalamus, also exhibit reduced energy intake, and body weight and size (Masos and Miskin, 1997; Miskin and Masos, 1997). PAI-1 is considered as the primary inhibitor of uPA (Masos and Miskin, 1997). Thus, overexpression of PAI-1 within the hypothalamus could attenuate uPA expression and thereby increase energy intake, and body weight and size, which are all three important parameters in obesity.

In the periphery, PAI-1 inhibits fibrinolysis and regulates cell migration and angiogenesis (See Figure 1/Table 1). Even today, PAI-1 transport mechanisms across the BBB are unknown, so only PAI-1 produced by microglia has been shown to regulate apoptosis, energy intake, survival of neurites, microglia migration, neuroinflammation and the brain's immune system (Ahn et al., 1999; Jeon et al., 2012; Masos and Miskin, 1997; Miskin and Masos, 1997; Soeda et al., 2008; Soeda et al., 2001). Although, it should be mentioned that these results are primarily obtained from *in vitro* experiments, thus it is still questionable if these processes are affected in human obesity. In the plasma of obese individuals, high levels of PAI-1 are found, which could lead to decreased fibrinolysis. If the effects of excessive PAI-1 levels within the brain in obesity are neuroprotective or even damaging is still under debate. Additionally, peripheral PAI-1 among other proteins produced by adipose tissue is not capable of affecting brain processes, since no transport mechanism for PAI-1 across the BBB has been discovered. However, PAI-1 produced by microglia may be modified by obesity. Therefore, more research is needed on the effects of obesity on PAI-1 levels in the brain.

6. Interleukin-6

The inflammatory cytokine, IL-6, is produced by adipocytes, macrophages and T-cells, and is involved in the acute phase reaction in inflammation (See Figure 2). In the liver, IL-6 stimulates the production of acute phase proteins such as C-reactive protein and fibrinogen. Obesity is marked by a peripheral chronic low inflammation state partly mediated via production of inflammatory adipokines such as IL-6 and TNF-α (Das, 2001). This chronic low inflammation state is already observed in obese children, manifested especially by elevated concentrations of IL-6 (Stelzer et al., 2012; Tam et al., 2010; Visser, 2001), which persist during adolescence and into adulthood (Stelzer et al., 2012). Furthermore, another inflammatory state is found in obese individuals, as examination of their brains via magnetic resonance imaging (MRI) showed increased gliosis in the mediobasal hypothalamus (Thaler et al., 2012).

Radioactively labelled IL-6 has been shown to cross the BBB by a saturable transport mechanism, entering both CSF and brain parenchyma. Approximately 50% of IL-6 in the CSF and 16% in brain parenchyma represent intact peripheral cytokine in male mice (Banks et al., 1994). However, excessive degradation of IL-6 is observed in the brain, thus the relative contribution of peripheral IL-6 on actions in the CNS is not clear. Nevertheless, relatively small amounts of intact IL-6 may be sufficient to produce biological effects (Banks et al., 1994). Rodent studies show that within the brain IL-6 is produced by glial cells, astrocytes and endothelial cells of the brain's microvessels (Fabry et al., 1993; Frei et al., 1989; Lieberman et al., 1989). A association exits between higher peripheral plasma IL-6 levels and lower hippocampal grey matter volume in middle-aged adults (Marsland et al., 2008; Yaffe et al., 2007). These findings possibly indicate that peripheral IL-6 mediates cognitive decline (Marsland et al., 2008). In addition, animal models show that peripheral inflammation increases the production of IL-6 in the brain, activating glial cells in the hippocampus, which in turn, inhibit neurogenesis and decrease synaptic plasticity, thereby disrupting learning and memory processes (Balschun et al., 2004; Gibertini et al., 1995; Monje et al., 2003; Poluektova et al., 2005).

Normally, IL-6 is expressed at relatively low levels within the brain (Gadient and Otten, 1997). When overexpression of IL-6 is stimulated in granule cells in a mouse hippocampus, the modulatory role of IL-6 on synaptic plasticity is revealed (Wei et al., 2012). IL-6 overexpression stimulates the formation of granule cell excitatory synapses, without affecting inhibitory synapses (Wei et al., 2012). Moreover, these cells are affected in granule cell adhesion and migration, suggesting that IL-6 is involved in the regulation of cell adhesion molecules that critically modulate excitatory synaptic formation (Wei et al., 2011). In mouse hippocampus, IL-6 elevation caused alterations in excitatory and inhibitory synaptic formations and disrupted the balance of excitatory/inhibitory synaptic transmissions, causing abnormal changes in the shape, length and distribution of dendritic spines (Wei et al., 2012). Another rodent study demonstrated that high IL-6 levels are neurotoxic and associated with maternal infection and neurodevelopmental damage (Samuelsson et al., 2006). It was even demonstrated that excessive prenatal exposure to IL-6 is noxious for CNS function, as it may play a role in the origin of neurodevelopmental and neurodegenerative diseases (Samuelsson et al., 2006).

Exercise in rodents increases the central anti-inflammatory response in the hypothalamus. IL-6 induces an anti-inflammatory environment by inducing the production of interleukin-10 (IL-10) (Ropelle et al., 2010). This phenomenon is crucial for restoring hypothalamic insulin and leptin signaling, and reorganizing the set point of energy (Ropelle et al., 2010). Moreover, another rodent study revealed that in the hypothalamus saturated fatty acids trigger the intracellular signaling network that induces an inflammatory response which includes IL-6, and determines resistance to anorexigenic signals (Milanski et al., 2009). Thus, in obesity IL-6 production is triggered by lack of exercise and monounsaturated fat-rich diets, which can lead to resistance to anorexigenic signals in the hypothalamus (Milanski et al., 2009; Ropelle et al., 2010). It remains to be seen what the influence of other dietary components and exercise may be.

The hippocampus is particularly vulnerable to the adverse effects of IL-6. IL-6 originating from the periphery, as well as glial and endothelial cells in the brain's microvessels, affects brain functions like synaptic plasticity and neurogenesis. In the hypothalamus, IL-6 is able to modify leptin signaling and other anorexic signals. Although it should be mentioned that peripheral IL-6 is quickly degraded in the brain. An early onset of IL-6 elevation and its persistence in aging obese individuals have been proposed to negatively affect brain functioning by inhibiting neurogenesis, decreasing synaptic plasticity and subsequently disrupting learning and memory processes (See Figure 2/Table 1) particularly in the hippocampus, which increases the risk of cognitive deficits in obese individuals (Yaffe et al., 2004).

7. TNF-α

TNF-α regulates the acute phase reaction of inflammation (See Figure 2), and is therefore an important mediator of the chronic inflammation found in obesity in the periphery and hypothalamus (Das, 2001; Thaler et al., 2012). In obese adults, elevated plasma levels of TNF-α have been observed when compared to normal weight adults (Mousa, 2005). In the periphery, TNF-α is produced by adipocytes and macrophages, and binds to two receptors, TNF-R1 and TNF-R2. TNF-R1 is expressed in most peripheral tissues and is activated via membrane bound soluble trimeric forms of TNF-α. Meanwhile, TNF-R2 is only expressed on cells of the immune system and is activated by the membrane bound homotrimer, TNF-α. In obese children, no increase in plasma TNF-α levels was observed as in obese adults, but obese children evidenced higher levels of TNF-R2, when compared to non-obese children (Schipper et al., 2012).

Rodent studies reveal that TNF-α is transported across the BBB (Di Simone et al., 2006), and can also be produced by astrocytes, microglia and some neurons within the brain (Chung and Benveniste, 1990; Lieberman et al., 1989; Morganti-Kossman et al., 1997). TNF-α receptors are expressed on neurons and glial cells throughout the CNS and can trigger processes like apoptosis (Montgomery and Bowers, 2012; Pickering et al., 2005). Within the brain TNF-α regulates synaptic transmission, synaptic plasticity and neurogenesis. As a result, it has a broad range of actions which can be either neuroprotective or neurotoxic.

TNF-α *in vitro* may protect neurons against metabolic, excitotoxic or oxidative insults by promoting maintenance of intracellular calcium homeostasis and suppression of reactive oxygen species (Barger et al., 1995; Cheng et al., 1994). TNF-α has direct effects on glutamate transmission by increasing the expression of AMPA receptors on synapses (Beattie et al., 2002). Furthermore, TNF-α originating from glial cells causes an increase in surface expression of neuronal AMPA receptors (Beattie et al., 2002). Thus, TNF-α is able to increase glutamate transmission by increasing the expression of AMPA receptors.

Examples of neurotoxic effects of TNF-α are its involvement in damage to myelin and oligodendrocytes (Selmaj and Raine, 1988). It also plays a facilitating role in glutamate excitotoxicity both directly as described above, and indirectly by inhibiting glial glutamate transporters on astrocytes. Decreased expression of glutamate transporters was caused by TNF-α inducing the classical I kappa B (IκB) degradation pathway to trigger NF-κB nuclear translocation and DNA binding to repress EAAT2 expression (Sitcheran et al., 2005). In this situation, the presence of elevated TNF-α concentrations led to an elevated extracellular glutamate concentration, thereby increasing the risk of glutamate excitotoxicity (Pickering et al., 2005). It was demonstrated that the combination of glutamate and TNF-α provoked an amplified neurotoxic effect on the AMPA receptor (Hermann et al., 2001). Furthermore, TNF-α mediates synaptic plasticity by inhibiting long-term potentiation (LTP) during the early phase of LTP by activation of TNF-R1 depending on p38 activation (Pickering et al., 2005). TNF-α also inhibits LTP in the CA1 and dentate gyrus regions of the rat hippocampus at pathophysiological levels (Butler et al., 2004; Cunningham et al., 1996; Tancredi et al., 1992). In humans and mice, differences in cognitive performance have been associated with TNF-α gene polymorphisms and TNF-α knockout mice display cognitive dysfunctions (Baune et al., 2008a; Baune et al., 2008b; Beste et al., 2010). Furthermore, TNF-α levels are elevated in several potential neuropathological states, and are associated with learning and memory deficits. In rodent models, it has been revealed that TNF-alpha, in a dose-dependent manner, modulates leptin signaling and action in the hypothalamus (Romanatto et al., 2007). Thus, in the hypothalamus, TNF-α produces a potent anorexic effect.

TNF-α may also have an anti-neurogenic effect during adult neurogenesis. In culture, microglia secreting TNF-α were found to be detrimental to hippocampal progenitor cells (HPC) by abruptly halting cell division which led to progenitor cell death (Cacci et al., 2005). Nevertheless, others have shown that striatal and hippocampal neurogenesis is compromised when an antibody to TNF-α is transiently infused into the lateral ventricle of a rat stroke model, indicating that TNF-α encourages the survival of neural progenitor cells (Hermann et al., 2001; Marchetti et al., 2004). These neuroprotective effects of TNF-α could be mediated through the TNF-R2 (Hermann et al., 2001; Marchetti et al., 2004). These findings demonstrate that TNF-α has positive and negative effects during adult neurogenesis as described above. Positive effects occur via encouraging survival of neural progenitor cells in a rat stroke model and negative effects occur via abruptly halting hippocampal progenitor cell division. These different effects could be triggered and dependent upon induction context and receptor sub-type engagement (Montgomery and Bowers, 2012).

The actions of TNF- α on neurons may be either neuroprotective or neurotoxic via its receptors and fluctuations in TNF- α levels. In obese individuals, excessive production of TNF-α by WAT could give onset to decreased adult neurogenesis by halting cell division of hippocampal progenitor cells, impaired LTP facilitation with subsequent memory and learning deficits, increased glutamate excitotoxicity and damaged myelin and oligodendrocytes (See Figure 2/Table 1).

8. Conclusion

After a decade of research on overweight and obesity in AD, a research focus on the endocrine aspects of adipose tissue and the brain has been birthed and escalated. Of the adipokines reviewed herein, it is known that peripheral leptin, TNF-α and IL-6 are able to cross the BBB and affect brain function (See Figure 2/Table 1). However, the other adipokines discussed including adiponectin, AGT and PAI-1, are either not able to cross the BBB, or possible transport mechanisms have not been identified. In obesity, excessive adipokine production by WAT mediates characteristic peripheral pathological processes like imbalanced energy metabolism, inflammation and hypertension. Several effects of adipokines on the brain increase vulnerability to the development of pathological processes in the brain. Adipose tissue secretes a multitude of compounds other than those discussed here, including for example, visfatin, resistin, apelin and chemerin (Adeghate, 2008; Guo et al., 2009; Lehr et al., 2012; Leivo-Korpela et al., 2011; MacDougald and Burant, 2007), for which even less is known about interactions with the brain. While epidemiologic studies have already shown a higher risk of dementia and brain-associated events in association with overweight and obesity during mid-life and to some extent late-life, the endocrine aspects of adipose tissue in relation to these outcomes are virtually unexplored, and could be useful for refining the adipose tissue exposure. Given secular increases in the prevalence of overweight and obesity due to a rise in the proportion obese (≥ 30 kg/m^2) in particular(Ogden and Carroll, 2010), it remains to be seen whether the continued increasing occurrence of obesity continues to lead to impaired processes within the brain such as impaired neurogenesis and LTP. This would lead to more severe cognitive impairments and decline and perhaps even higher risk of dementia (Gustafson, 2008; Gustafson et al., 2007). Alternatively, improvements in health and care, education, and other social factors may dilute future observations of the influence of obesity on the brain. Further research must focus on the crosstalk between WAT-secreted adipokines and the brain to elucidate when and via which mechanisms brain processes become affected by these important endocrine mediators. In addition, whether the mechanisms associating these hormones in the obese condition with brain health, are protective or detrimental, remains to be further elucidated.

Acknowledgments

This study was supported by the EU 7th framework LipiDiDiet project (FP7/2007-2013) under grant agreement no211696; in part by grants NIH/NIAID 1R01MH076537, 1R01MH079880, and U01 318345; Swedish Research Council Diarienummer: 523-2005-8460, and the State University of New York Research Foundation.

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Highlights

- Adipokines from periphery and brain interact with obesity processes.
- Obesity is associated with changes in brain structure, function and even dementia.
- Adipokines have a widespread influence and function on brain health.
- Adipokines may form a potential mechanism, which links obesity with brain health.

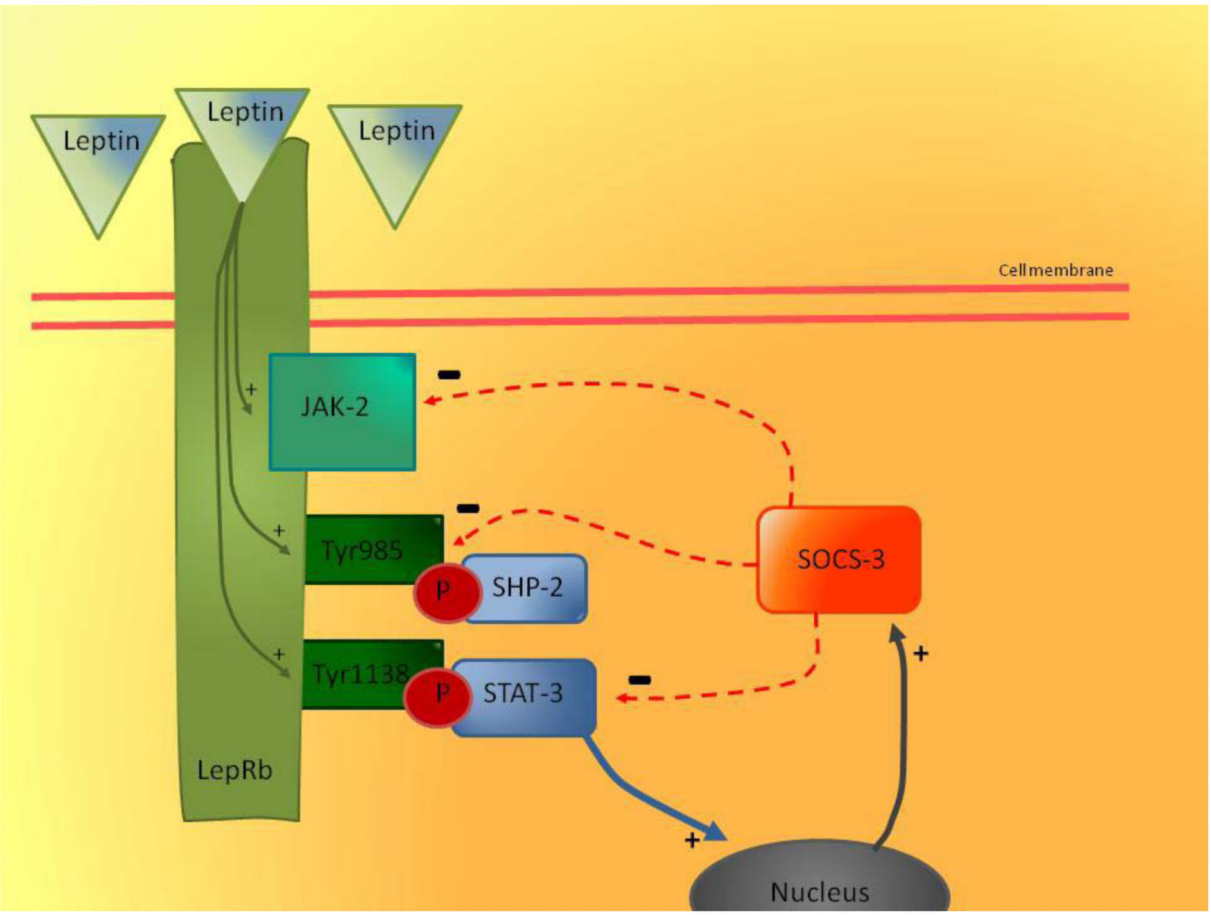

Figure 1. Leptin resistance in obesity via SOCS-3 and JAK-2/STAT-3 pathway acurate nucleus of the hypothalamus

Leptin binding to LepRb activates the LepRb-associated JAK-2 tyrosine kinase (green arrows), leading to the autophosphorylation of tyrosine residues on JAK-2 and the phosphorylation of Tyr985 and Tyr1138 on the intracellular tail of LepRb (green arrows). Tyr985 and Tyr1138 are directly autophosphorylated after activation of LepRb, and phosphorylated Tyr1138 mediates the activation of the transcription factor STAT-3, and phosphorylated Tyr985 binds to SHP-2. Among other targets, STAT-3 induces the transcription of SOCS-3 during LepRb signalling in the nucleus (blue arrow). SOCS-3 is produced and released from the nucleus (grey arrow). The binding of phosphorylated Tyr985 to SHP-2 provides an important site of inhibition for SOCS-3 (red arrow). Furthermore, SOCS-3 inhibits STAT-3 and via binding to the LepRb-JAK-2 complex it attenuates LepRb-mediated signalling, and thereby LepRb-mediated signalling via the JAK-2/STAT-3 pathway. At high levels of circulating leptin as observed in obesity, LepRbs are highly activated and subsequently tyrosine residues are intensely phosphorylated. In case of LepRb this will lead to increased ‘leptin signalling’ via the JAK-2/STAT-3 pathway, while phosphorylation of the tyrosine residues will lead to increased expression of SOCS-3 which inhibits LepRb-mediated signalling. This inhibition could attenuate most of the expected increase in LepRb signalling, and explain leptin resistance in obesity. (Munzberg and Myers, 2005)

Abbreviations: LepRb: Leptin receptor Rb; JAK-2: janus kinase 2; Tyr985/Tyr1138: tyrosine residues 985 and 1138; STAT-3: signal transducer and activator of transcription 3; P: phosphorylation; SHP-2: tyrosine-protein phosphatase non-receptor type 11; SOCS-3: suppressor of cytokine signaling 3; +: stimulation; -: inhibition

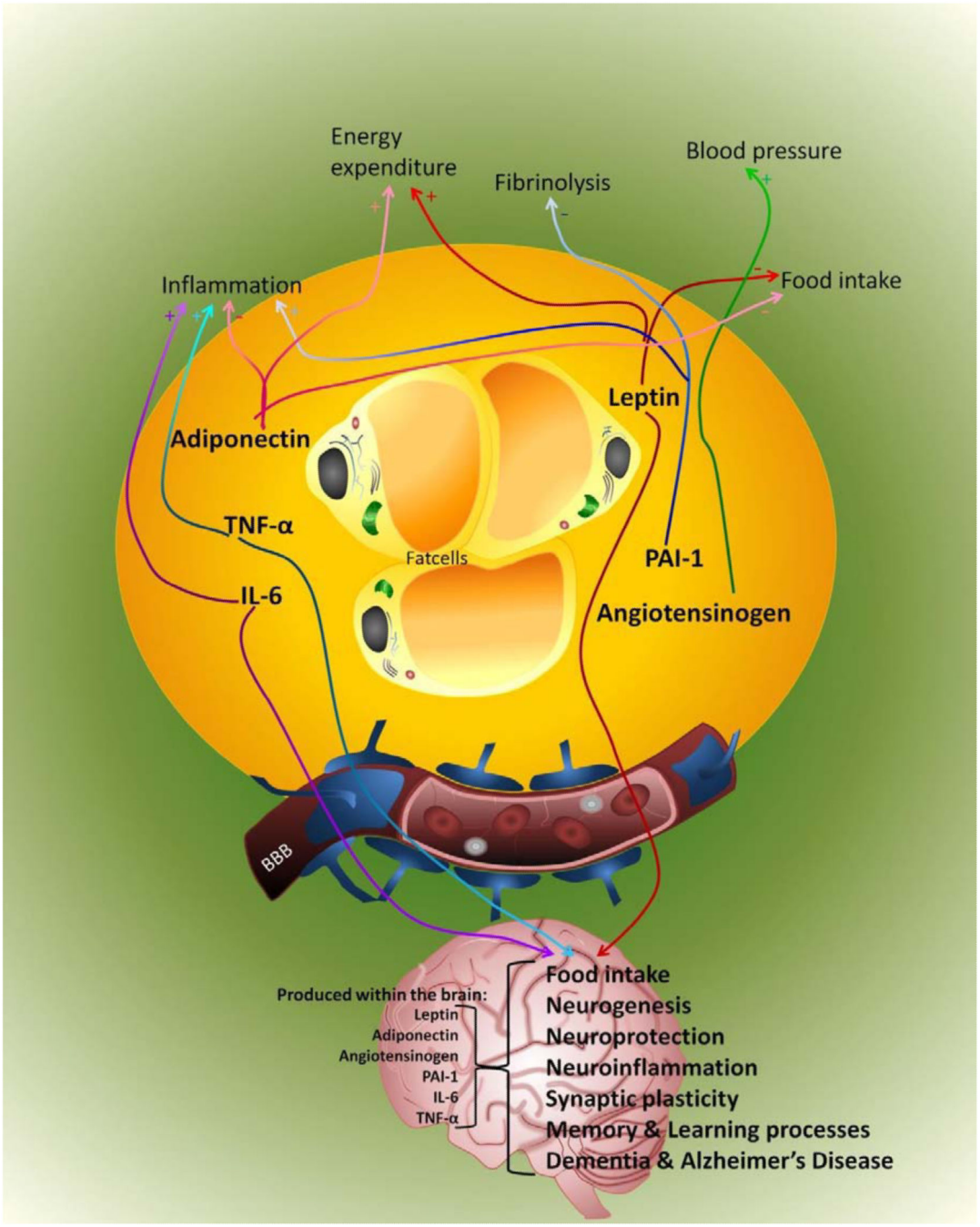

Figure 2. Effects of reviewed adipokines in the periphery and brain in obesity

Fat cells produce and secrete adipokines like, leptin (red), PAI-1 (blue), angiotensinogen (green), adiponectin (pink), TNF-α (turquoise) and IL-6 (purple). In the periphery, TNF-α and IL-6 stimulate inflammation; these adipokines trigger the liver to produce acute phase proteins. Adiponectin attenuates the inflammatory response by inhibiting the production of TNF-α and IL-6. Furthermore, adiponectin modulating inflammatory responses, energy expenditure (CNS and periphery), food intake (CNS) and a number of metabolic processes, including glucose regulation and fatty acid catabolism. Angiotensinogen increases blood

pressure. PAI-1 inhibits fibrinolysis and also stimulates the inflammatory response. Leptin increases energy expenditure and decreases food intake. Only three adipokines discussed in this review are able to cross the BBB and affect, positively or negatively depending on concentration and environment, brain processes such as food intake, synaptic plasticity, learning and memory, and development of dementia. Furthermore, angiotensinogen, PAI-1, IL-6, TNF-α are also produced within the brain by neurons, astrocytes and microglia, and several theories exist that leptin and adiponectin might also be produced in the brain. Several studies reported that, within the brain, adiponectin can be involved in regulating food intake and neuroprotection, while angiotensinogen is involved in learning and memory processes and PAI-1 regulates among other neuroinflammation. Il-6 and TNF-α produced by astrocytes and microglia are involved in neurogenesis, neuroinflammation, synaptic plasticity and learning and memory processes.

In obesity, the amount and function of adipokines are excessive, except for adiponectin and leptin. Adiponectin levels are decreased and it is hypothesized that leptin functionality could be decreased via leptin resistance. Therefore, obesity increases inflammation, increases blood pressure, and decreases fibrinolysis, energy expenditure and food intake in the periphery. In the brain, obesity results in impaired food intake, neurogenesis, synaptic plasticity and memory and learning processes possibly mediated through leptin, TNF-α and IL-6. Abbreviations: PAI-1: plasminogen activator inhibitor-1; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha; CNS: central nervous system; BBB: blood brain barrier; +: increases/stimulates; -: decreases/inhibits

Table 1

Overview of reviewed adipokines: level in obesity, ability to cross the BBB, and roles in the periphery, non-obese and obese brain

Adipokine	Obesity	BBB	Role in Periphery	Role in non-Obese brain	Role in Obese brain
Leptin	↑	Y	Long term regulation food intake(Jequier, 2002)	Inhibition of food intake(Jequier, 2002)	Leptin resistance(Banks et al., 1999; Caro et al., 1996; El-Haschimi et al., 2000; Friedman and Halaas, 1998; Hileman et al., 2002; Wilsey et al., 2003; Yamashita et al., 1997)
			Body weight(Jequier, 2002)	Memory formation(Farr et al., 2006; Harvey, 2007; Oomura et al., 2006; Paz-Filho et al., 2010)	Deficits in negative feedback loop food intake
			Energy expenditure(Jequier, 2002)	Neurogenesis(Bouret, 2010; Paz-Filho et al., 2010)	Impairs memory
				Neuroprotective(Morrison, 2009; Zhang et al., 2007)	Impairs neurogenesis
				Brain structure(Fulton et al., 2006; Hayes et al., 2010; Hommel et al., 2006; Lu et al., 2006)	Impairs neuroprotection
					Abnormal brain structure
Adiponectin	↓	N	Glucose regulation(Diez and Iglesias, 2003; Ouchi et al., 2003a; Villarreal-Molina and Antuna-Puente, 2012)	Neuroprotective(Qiu et al., 2011)	Decreases neuroprotection
			Fatty acid metabolism(Diez and Iglesias, 2003; Ouchi et al., 2003a; Villarreal-Molina and Antuna-Puente, 2012)	Energy expenditure(Qi et al., 2004)	Decreases energy expenditure
			Less inhibition of inflammatory signals(Diez and Iglesias, 2003; Ouchi et al., 2003a; Villarreal-Molina and Antuna-Puente, 2012)		
Angiotensinogen	↑	N	Blood pressure regulation(Gardes et al., 1982; Kim et al., 1995; Ohkubo et al., 1990; Walker et al., 1979; Watt et al., 1992; Yiannikouris et al., 2012b)	Protects BBB(Banks, 2006; Pan and Kastin, 2007; Yanai et al., 2000)	Alters CBF (due to high blood pressure) (Yiannikouris et al., 2012b; Youssef et al., 2012)
				Regulates arterial blood pressure(Allen et al., 1988; Andreatta et al., 1988; Averill et al., 1987; Jensen et al., 1992; McKinley et al., 2003; Simpson, 1981; Thornton and Nicolaidis, 1993)	
				Enhances learning & memory(McKinley et al., 2003)	
Plasminogen activator inhibitor-1	↑	N	Fibrinolysis(Guerre-Millo, 2004)	Regulates apoptosis(Soeda et al., 2008; Soeda et al., 2001)	Inhibit BBB fibrinolysis
			Cell migration(Guerre-Millo, 2004)	Survival of neurites(Soeda et al., 2008)	Increase energy expenditure

Adipokine	Obesity	BBB	Role in Periphery	Role in non-Obese brain	Role in Obese brain
			Angiogenesis(Guerre-Millo, 2004)	Microglial migration(Jeon et al., 2012)	Increase energy intake
				Neuroinflammation(Block et al., 2007; Garden and Moller, 2006; Graeber and Streit, 2010; Jeon et al., 2012; Mallat et al., 2005; Woo et al., 2008)	
				Brain immune system(Block et al., 2007; Garden and Moller, 2006; Graeber and Streit, 2010; Jeon et al., 2012; Mallat et al., 2005; Woo et al., 2008)	
				Energy intake(Miskin and Masos, 1997)	
Interleukin-6	↑	Y	Inflammation(Rocha and Folco, 2011)	Neuroprotection(Samuelsson et al., 2006)	Inhibits neurogenesis(Balschun et al., 2004; Gibertini et al., 1995; Monje et al., 2003; Poluektova et al., 2005)
				NeuroInflammation(Balschun et al., 2004; Gibertini et al., 1995; Monje et al., 2003; Poluektova et al., 2005)	Decreases synaptic plasticity(Balschun et al., 2004; Gibertini et al., 1995; Monje et al., 2003; Poluektova et al., 2005)
				Synaptic formation(Wei et al., 2011)	Disrupts learning & memory processes(Balschun et al., 2004; Gibertini et al., 1995; Monje et al., 2003; Poluektova et al., 2005)
				Differentiation of neurons and astrocytes(Wei et al., 2012)	
				Leptin signaling(Milanski et al., 2009; Ropelle et al., 2010)	
Tumor necrosis factor- α	↑	Y	Inflammation(Rocha and Folco, 2011)	Synaptic transmission(Barger et al., 1995; Beattie et al., 2002)	Inhibits neurogenesis(Cacci et al., 2005)
				Synaptic plasticity(Pickering et al., 2005)	Disrupts learning & memory processes(Butler et al., 2004; Tancredi et al., 1992)
				Neuroinflammation	Increases glutamate excitotoxicity(Pickering et al., 2005)
				Leptin signaling(Romanatto et al., 2007)	Damages myelin & oligodendrocytes(Selmaj and Raine, 1988)

↑; Plasma levels of adipokine are upregulated in obesity. ↓; Plasma levels of adipokine are downregulated in obesity. Y; Adipokine is able to cross the BBB. N; Adipokine is not able to cross the BBB.