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Altered brain diagnostic techniques in obesity and related metabolic complications

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ABSTRACT

The prevalence of obesity has been increased in both developed and developing countries during the last decades. Low grade inflammation, insulin and leptin resistance, and endothelial dysfunction are some of obesity-associated metabolic abnormalities, which have proposed to affect the structure and function of brain. The brain alternations in obesity have been recognized using diagnostic methods like EEG, PET and MRI in few studies. Low grade inflammation and increase in pro-inflammatory factors could impact the size and activity of some brain regions. Neurological studies have also proposed that insulin resistance can alter the results of these techniques due to changes of insulin entry to brain. Endothelial dysfunction in blood-brain barrier can result in increased microvascular permeability and impaired microcirculatory blood flow to CNS, which influences the brain activity and structure in obesity. The effect of obesity and related complications such as low grade inflammation, insulin and leptin resistance and endothelial dysfunction on brain structure and function have been reflected by brain diagnostic tests including EEG, structural and functional MRI, and PET. More neurological studies are needed to recognize the relationship between obesity, body fat distribution, and also weight loss with brain structure and function assessed by available techniques. This field of study could also reveal other mechanisms involved in obesity pathogenesis, and potential treatment opportunities.

1. Introduction

Obesity is undoubtedly one of the most outstanding public health concerns of the 21st century. Currently, about 2 billion adults are overweight or obese worldwide (Seidell JCHalberstadt, 2015). Obesity is closely associated with numerous chronic and metabolic diseases, predominantly thorough development of low grade inflammation, insulin resistance and endothelial dysfunction (Van Gaal and Mertens ILDe Block, 2006). There is a significant body of evidence that supports the role of obesity and its complications in pathophysiology of neurodegenerative diseases (NDD) (Gupta et al., 2015; Hafizi et al., 2017). For instance, Alzheimer's disease (AD) and Parkinson's disease (PD), the two most common NDD, are associated with obesity, insulin resistance, neuroinflammation, hyperinsulinemia, dyslipidemia and adipokine imbalance (Gupta et al., 2015). Additionally, it has been stated that obesity and its associated diseases such as diabetes could affect brain endothelial cells, as well as pericyte integrity and specific transporters in blood-brain barrier (BBB) (Banks, 2019). However, little is known about the effects of obesity and its related disorders on diagnostic techniques used to identify brain structural and functional domains. In this study, we briefly reviewed the effects of obesity and its metabolic complications, inflammation, insulin and leptin resistance and endothelial dysfunction on neural system reflected by these techniques.

Abbreviations: ACC, anterior cingulate cortex; AD, Alzheimer's disease; ADC, apparent diffusion coefficient; BBB, Blood-brain barrier; BED, binge eating disorder; CNS, central nervous system; CRP, C-reactive protein; CSF, Cerebrospinal fluid; EEG, electroencephalography; DMN, default mode network; DTI, diffusion tensor imaging; DWI, diffusion weighted imaging; FFAs, free fatty acids; fMRI, functional MRI; ICAM, Intercellular Adhesion Molecule; IL-6, interleukin 6; LBP, lipopolysaccharide binding protein; MCP-1, monocyte chemoattractant protein 1; MRI, magnetic resonance imaging; NDD, Neurodegenerative diseases; OFC, orbitofrontal cortex; PD, parkinson's disease; PET, positron emission tomography; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor α; VCAM, vascular cell adhesion molecule.

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1.1. Obesity and brain diagnostic techniques

Studies using different imaging techniques including electroencephalography (EEG), structural magnetic resonance imaging (MRI), functional MRI (fMRI), and positron emission tomography (PET) have shown that brain systems related to reward, motor function, cognition, control, and attention were altered in obesity (Carnell et al., 2012; Burger KSBerner, 2014).

EEG is a non-invasive and efficient method for the assessment of neurophysiological function and functional connectivity through frequency bands in large scale functional networks (Imperatori et al., 2015). This method is used to detect alternations of brain structure and function in several diseases including seizure, stroke and migraine (Varma et al., 2011; Sand, 1991; Tuerxun, 2014). A clinical study using EEG proposed that obese women with binge eating disorder (BED) have greater frontocentral beta activity in different tasks (resting state, visual processing of food and neutral stimuli) compared to obese women without BED (Tammela et al., 2010). PET is a nuclear medicine technique to assess the physiological function of body organs, using a special camera and radiolabelled materials. It is based on the changes in blood flow, metabolism, and neurotransmitters and could analyze the quantitative alterations of brain function during disease progression (Berger, 2003). A case-control study using PET has shown statistically significant differences in regional cerebral blood flow in prefrontal, limbic, and insular cortices in obese compared to lean men (Gautier et al., 2000). Functional MRI is another technique to demonstrate brain activity and regional over-time changes in brain metabolism, by exploring the changes in blood flow and oxygenation (Glover, 2011). In return, structural MRI provides qualitative and quantitative information about the shape, size, and integrity of gray and white matter structures in brain (Symms et al., 2004). Besides, diffusion tensor imaging (DTI) is another type of MRI that detects the directional movement of water molecules on neural pathways and determine micro-structural changes with neuropathology (Alexander et al., 2007). Another kind of MRI is diffusion weighted imaging (DWI), which detects signal contrast generation according to differences in Brownian motion and also assesses the molecular function and micro-architecture (Baliyan et al., 2016). It has been shown that based on fMRI, obese children have lower activity and function of inhibitory control regions, and in return, more response of food reward regions compared to normal weight children (Batterink and Yokum SStice, 2010). Another study using fMRI reported that children with higher BMI exhibited greater functional connectivity between left middle frontal gyrus and the ventromedial prefrontal cortex and orbitofrontal cortex (OFC); the changes that obviously led to less activation of self-control neurocircuitry regions, and decreased restraint when exposed to motivational food advertisements (Black et al., 2014). The fMRI technique also showed that the function of default mode network (DMN) is changed in obese subjects. Following 2 days eucaloric energy intake higher DMN activity was observed in obese participants (with recent weight loss) compared to lean individuals, which was positively associated with appetite (Tregellas et al., 2011). DMN is a brain network reflecting the baseline state of brain function, such as internal mental state, self-relevant mentalizing and interoception (Buckner and Andrews-Hanna JRSchacter, 2008). A study using structural MRI has reported premenopausal obese women, without food stimuli, had significant structural and functional changes within regions of reward-related brain networks, which led to altered ingestive behaviors (Coveleskie et al., 2015). Moreover, another structural MRI study suggested that obesity was contributed to a decrease in gray matter volume in bilateral prefrontal cortex (Mathar et al., 2015). Based on fMRI, overweight and obese subjects exhibited abnormal pattern of neural activation (mediated prominently by insula) when they have experienced negative emotions, which could potentially affect food intake (Steward et al., 2016). Another study investigating potential brain apparent diffusion coefficient (ADC) in obese subjects by DWI, suggested that the ADC of hypothalamus, hippocampal gyrus, amygdala, insula, cerebellum and midbrain were significantly increased in patients with obesity. Also, BMI was directly associated with ADC values of amygdala, insula, orbitofrontal and middle temporal cortex too (Alkan et al., 2008). A DTI study proposed that BMI increase is associated with reduction in myelin, increase in water and reduction in iron content of white matter structures. Besides, substantial changes in mean and axial diffusivity in the corticospinal tract, anterior thalamic radiation and superior longitudinal fasciculus were observed in higher BMI (Kullmann et al., 2016). Another research using diffusion tensor imaging showed that obesity was associated with lower fractional anisotropy and mean diffusivity values and lower volumes of gray and white brain matters. The structural alterations were found in brain regions attributed to reward seeking, inhibitory control, and appetite. In addition, a negative correlation was observed between body fat percentage with fractional anisotropy, mean diffusivity values, gray and white brain matters. Abdominal subcutaneous fat was also inversely linked to gray matter density (Karlsson et al., 2013). The available evidence shows overweight and obesity may affect brain structure and network activity, but the relationship with brain networks contributing to obesity, satiety and hunger should be addressed to improve our understanding of potential mechanisms for treatment of obesity.

1.2. Obesity-associated complications and brain diagnostic techniques

Obesity associated disorders might also affect the specific tests of evaluating brain function.

1.3. Inflammation

Obesity is accompanied with a chronic low-grade inflammation, which differs from usual inflammation and characterized by a modest increase in circulating pro-inflammatory factors without the clinical signs of inflammation (Van Gaal and Mertens ILDe Block, 2006). Obesity-induced inflammation exerts its profound effects on metabolic pathways (Van Gaal and Mertens ILDe Block, 2006). The increased size of adipocytes plays a pivotal role in higher production of pro-inflammatory adipocytokines including tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), and consequently C-reactive protein (CRP) (Vgontzas et al., 1997).

Previous neurological studies have shown the effect of inflammation on brain structure and function. Greater levels of CRP were linked to cortical thinning in left hemisphere in healthy adult men (Krishnadas et al., 2013; Taki et al., 2013). Peripheral IL-6 level was inversely associated with gray-matter volume in hippocampus and also greater IL-6 responses were linked to more neural activity within substantia nigra in elderly (Brydon et al., 2008; Marsland et al., 2008). Furthermore, greater levels of TNF-α in umbilical cord blood was correlated with decreased amplitude-integrated EEG in preterm infants (Wikstrom et al., 2008). Other experimental studies have found that the activity of brain structures with pleiotropic functions like the substantia nigra (Brydon et al., 2008), the dorsal anterior cingulate cortex (ACC) (associated with self-reported feelings of social distress) (Slavich et al., 2010) and anterior insula (linked to emotional awareness) (Slavich et al., 2010) were altered by inflammation. It has been shown that lipopolysaccharide binding protein (LBP) concentration is raised in obesity (Sun et al., 2010). A longitudinal study found that circulating LBP was associated with DTI-metrics axial diffusivity (L1) and fractional anisotropy values of several white matter regions in obese subjects (Moreno-Navarrete et al., 2017).

Additionally, patients with malignant melanoma receiving interferon-α therapy have shown greater glucose metabolism in the basal ganglia and cerebellum and lower glucose metabolism in the dorsal prefrontal cortex (Capuron et al., 2007). Few studies have reported the effect of inflammation on brain imaging tests. PET studies have demonstrated that lipopolysaccharide administration by activation the

innate immune system could increase microglial activation in brain (Sandiego et al., 2015; Hannestad et al., 2012). Experimental studies have shown that the activity of the amygdala, hypothalamus and hippocampus, the regions that are respectively responsible for emotions, physiologic functions, and memory, were noticeably influenced by inflammatory processes (Frenois et al., 2007). A clinical study using fMRI technique proposed an association between the activity of the ACC (including information of physiological condition) and insula with peripheral inflammation in patients with asthma (Rosenkranz et al., 2005). Besides, another clinical fMRI study in a chronically stressed population has stated that local inflammation was directly associated with activation of brain regions responsible for functions such as inflammation homeostasis, decision-making, and other regions related to emotional tasks such as noun retrieval and visual processing (O'Connor et al., 2009). Furthermore, prior studies have suggested that inflammation may occur in the hypothalamus of obese animals (De Souza et al., 2005). A retrospective study of brain MRI of 34 individuals with BMI range of 17.7–44.1 kg/m^2 showed a hyper-intensity in MRI transverse relaxation time (T2) of the mediobasal hypothalamus in obese subjects, which has been attributed to BMI (Thaler et al., 2012). To the best of our knowledge, currently the number of studies investigating the effect of inflammation on changes of brain structure and function, detected by neuroimaging techniques, distinctively between normal weight and obese subjects or considering the body fat mass is limited and results are inconsistent.

1.4. Insulin and leptin resistance

Central obesity negatively affects insulin sensitivity in many organs including brain. It causes brain insulin resistance in cerebral cortex (Tschritter et al., 2009), and more particularly in hypothalamus (Kullmann et al., 2015). Fat accumulation is associated with higher production of mediators such as free fatty acids (FFAs), TNF-α, IL-6, resistin and leptin, which impair insulin action (Bergman RNMittelman, 1998), and lower production of the insulin sensitizing peptide adiponectin (Yamauchi et al., 2003). Insulin and leptin signaling could regulate energy homeostasis and appetite in the central nervous system (CNS) (Baskin et al., 1999). Additionally, insulin and leptin play numerous roles in cognitive function like learning and memory and their receptors are expressed in several regions of brain (Cholerton and Baker LDCraft, 2013; Morrison, 2009).

Earliest studies showed that insulin action in brain may decrease or entirely cease in obese individuals (Tschritter et al., 2006). In healthy people, plasma insulin levels are correlated with insulin concentration in Cerebrospinal fluid (CSF). However, with increasing body weight and consequently insulin resistance, plasma insulin increases while the CSF:plasma insulin ratio is decreased. It may be hypothesized that the entry rate of plasma insulin into the brain is reduced in obesity, which may lead to peripheral insulin resistance and weight gain (Kern et al., 2006). The association between increased body weight and insulin action has been assessed by fMRI and PET techniques (Kullmann et al., 2015; Anthony et al., 2006). A clinical study using PET scan has shown that insulin could significantly increase metabolism in ventral striatum and prefrontal cortex of healthy individuals; while this effect was less in patients with systemic insulin resistance. It has been shown that brain insulin resistance exists in these patients, particularly in regions controlling appetite and reward, which might disturb energy balance and consequently contribute to development of obesity and associated disorders (Anthony et al., 2006). Although, another study using fMRI have reported that intranasal insulin could cause significant cerebral blood fluid reduction in the hypothalamus in both lean and obese participants. But the intensity of this response was positively associated with visceral adipose tissue. Additionally, a different response of prefrontal cortex and consequently an insulin-induced CBF reduction was observed only in lean compared to overweight/obese subjects, which contributed to lower craving of sweet foods after insulin application. This response was remarkably correlated to peripheral insulin sensitivity (Kullmann et al., 2015). Brain insulin action was selectively impaired in prefrontal cortex of overweight and obese adults, and in hypothalamus of participants with high visceral adipose tissue, which promoted an altered homeostatic set point and reduced inhibitory control related to overeating behavior (Kullmann et al., 2015). In addition, a clinical study has shown that patients with insulinoma developed early EEG changes during intensive hypoglycemia, while EEG did not alter at moderate levels of hypoglycemia (Blaabjerg LJuhl, 2016). Another clinical study in adolescents with type 1 diabetes, reported that hypoglycemia is linked to decrease in alpha band (showing a state of wakeful relaxation) EEG signals (Nguyen et al., 2013). Additionally, EEG abnormalities were observed in these patients underwent multiple insulin injection therapy. Poor metabolic control (long-term high HbA1c levels) contributed to a global increase in delta power (known as slow-wave sleep), particularly in the frontal regions (Hyllienmark et al., 2005). Although it has been observed that insulin resistance and induced-hypoglycemia are associated with changes in brain diagnostic techniques more studies should be carried out to explore the distinctive alterations of these methods in obese compared to lean subjects in response to hypo- or hyper-glycemia.

In addition to insulin resistance, leptin resistance is also prevalent in obesity. Leptin circulating concentration is near four-fold higher in obese compared to lean individuals. Hyperleptinemia is accompanied with decreased dietary intake and increased energy expenditure. However, most obese people are not as sensitive as those with normal weight to the effect of endogenous leptin. One possible mechanism of leptin resistance is attributed to leptin-specific binding in the choroid plexus. Since the choroid plexus is accountable for the synthesis of CSF and is part of the barrier between blood and brain, one of the roles of leptin receptor may be transporting leptin across the blood-CSF barrier (Caro et al., 1996). When serum leptin levels exceed 25–30 ng/mL, the concentration of leptin does not increase in brain tissues and CSF (Holtkamp et al., 2004). In other words, excessive circulating leptin in blood causes a reduction in leptin transportation trough BBB and consequently leptin resistance (Mantzoros, 1999). Moreover, leptin resistance increases the predisposition of patients to diet-induced obesity, which in turn contributes to higher leptin levels and deterioration of leptin resistance. In addition, hypothalamic inflammation, endoplasmic reticulum stress, and autophagy disorders account for development of obesity-associated leptin resistance (de Git KCAdan, 2015).

It has been reported that serum leptin concentration was noticeably higher in obese than lean people. While CSF/serum leptin ratio was 4.3-fold higher in lean than obese individuals. There was a strong positive correlation between serum leptin and BMI, but a negative correlation between CSF/serum leptin ratio and BMI (Caro et al., 1996). Additionally, leptin CSF concentration was strongly and inversely correlated to plasma levels and BMI, which confirmed the hypothesis that circulating leptin can enter CSF proportional to excess weight. Leptin entrance to CSF was lower among obese subjects with higher concentration of plasma leptin (Schwartz et al., 1996). Accordingly, a saturable mechanism was proposed to regulate leptin transport to CSF. The capacity of leptin transport is limited in obese individuals, which may partly explain leptin resistance in this group (Schwartz et al., 1996). Interestingly, it was observed that the efficacy of leptin transport to CSF was reduced through 10 weeks administration of a high fat diet in diet-induced obese minipigs (Chmielewski et al., 2019). Leptin can modulate food intake through changes in neuronal activity in the mediobasal hypothalamus (MBH). Leptin transport by tanycytes has a vital role in the pathophysiology of leptin resistance (Balland et al., 2014). Tanycytes are specialized glial cell type lining the wall of the third ventricle in the hypothalamus. These cells mediate the release of neuropeptides to the portal vasculature by hypothalamus cells and regulate blood-brain and blood-CSF exchanges (Prevot et al., 2018). These processes rely on the ability of these cells to adapt their morphology to the physiological state of the animal (Langlet, 2014; Prevot

and Langlet FDehouck, 2013). Changes in tanycytes has been shown to modify the tortuosity of the extracellular space. In this context, it was observed that semaphorin7A mediates neuroglial plasticity in hypothalamic median eminence of adult rodents (Parkash et al., 2015). Moreover, two studies using MRI showed that the diffusivity of water molecules was changed in the hypothalamus during the artificial menstrual cycle (Baroncini et al., 2010) and puberty (Denis et al., 2018). Tanycytes are able to sense blood glucose levels and play a fundamental and active role in entrance of circulating metabolic signals to hypothalamus that regulate food intake. Moreover, tanycytes may respond to dietary or reproductive signals by regulating hypothalamic neurogenesis. (Prevot et al., 2018). A study on diet-induced obese mice showed that peripheral administration of leptin activates its receptor in median eminence tanycytes followed by MBH neurons; a process that requires tanycytic ERK signaling and transition of leptin through the CSF. ERK signaling in these cells mediates leptin transport, increases MBH neuron activity and energy expenditure in obese animals, and enhances leptin sensitivity upon return to a normal-fat diet (Balland et al., 2014). Microglia also exerts a neuroprotective effect via releasing factors such as brain-derived neurotrophic factor and engulfing cellular debris. Although, generation of extra debris and metabolic waste by neurons in obesogenic settings, evokes the production of pro-inflammatory cytokines such as TNF by microglia, which in turn could lead to neural damage. Ultimately, the formation of a defective cycle between the reactive microglia and hypothalamic neurons, cause disruption in brain control of systemic energy metabolism (Garcia-Caceres et al., 2019). Similar to insulin resistance, leptin resistance could potentially affect the results of brain diagnostic techniques or even might be detected with these methods especially in obese individuals.

1.5. Endothelial dysfunction

Endothelial dysfunction occurs when there is a failure in vasodilation, fibrinolysis, anticoagulation, and other physiological functions of endothelium (Avogaro Ade Kreutzenberg, 2005). Obesity and its related disorders including insulin resistance, hyperglycemia, hypertension, dyslipidemia and altered fibrinolysis can contribute to endothelial dysfunction (Avogaro Ade Kreutzenberg, 2005). Adipocyte hypertrophy in obesity, leads to increased production of pro-inflammatory adipocytokines and chemokines, and consequently higher production of vascular and intercellular adhesion molecules (VCAM and ICAM), by local endothelium, and increased vascular permeability. Other adipose tissue derived factors involved in endothelial function are leptin, resistin, IL-6, monocyte chemoattractant protein (MCP)-1, adiponectin and the proteins of the renin–angiotensin system (Kershaw EEFlier, 2004).

Cerebrovascular endothelium keeps the balance between pro- and anti-inflammatory cytokines that could influence the vascular cells. For example, TNF-α has been shown to up-regulate the expression of adhesion molecules in cerebrovascular endothelial cells, whereas transforming growth factor-β (TGF-β) exerts the opposite effect (Park et al., 2000).

Structural and functional alterations of BBB endothelial cells, along with inflammation, have been linked to increased microvascular permeability and impaired microcirculatory blood flow (Abbott NJFriedman, 2012). Vascular permeability allows macromolecules to infiltrate into the CNS and lead to transient opening of the BBB, which plays a role in brain infarction, specifically the lacunar subtype (Pretnar-Oblak et al., 2006). A clinical study using PET technique in hypertensive individuals showed that cerebral blood flow was reduced in the frontal cortex and basal ganglia (Fujishima et al., 1995). It has been proposed that the circulating products of endothelial cells including ICAM-1, thrombomodulin, tissue factor, and tissue factor pathway inhibitor increase when the endothelium is activated, damaged or under repair (Poggesi et al., 2016). Only few studies have investigated the link between EEG, PET or MRI abnormalities with endothelial dysfunction and they did not consider body weight status and adiposity.

2. Conclusion

Obesity is associated with low grade inflammation, insulin and leptin resistance, endothelial dysfunction and other metabolic complications. There is growing evidence suggesting profound associations between obesity, its complications and alternations in brain structure and function. Although it has been interestingly shown that brain diagnostic tests including EEG, structural and functional MRI, and PET will change in obesity and related disorders, this field of study is just starting to develop and could open new insight to understand other mechanisms involved in obesity, and potential treatment opportunities. Experimental and clinical studies are required to understand the effect of obesity, body fat distribution, and weight loss on different aspects of brain structure and function reflected by available techniques. The effect of endocrine and metabolic disorders associated with obesity should also be investigated distinctively in obese and normal weight individuals.

Conflicts of interest

We wish to confirm that there are no known conflicts of interest associated with this manuscript and there has been no significant financial support for this work that could influence the results.

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