Obesity and Brain Positron Emission Tomography

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Abstract Obesity, an increasingly common problem in modern societies, results from energy intake chronically exceeding energy expenditure. This imbalance of energy can be triggered by the internal state of the caloric equation (homeostasis) and non-homeostatic factors, such as social, cultural, psychological, environmental factors or food itself. Nowadays, positron emission tomography (PET) radiopharmaceuticals have been examined to understand the cerebral control of food intake in humans. Using ^{15}O -H₂ PET, changes in regional cerebral blood flow (rCBF) coupled to neuronal activity were reported in states of fasting, satiation after feeding, and sensory stimulation. In addition, rCBF in obese subjects showed a greater increase in insula, the primary gustatory cortex. ^{18}F -fluorodeoxyglucose PET showed higher metabolic activity in postcentral gyrus of the parietal cortex and lower in prefrontal cortex and anterior cingulate cortex in obese subjects. In addition, dopamine receptor (DR) PET demonstrated lower DR availability in obese subjects, which might lead to overeating to compensate. Brain PET has been utilized to reveal

the connectivity between obesity and brain. This could improve understanding of obesity and help develop a new treatment for obesity.

Keywords Obesity · Brain · Positron-emission tomography

Introduction

Obesity rates in Korea are the lowest in the Organization for Economic Co-operation and Development [1]. However, obesity is on the rise and 27.5% of Korean adults are obese according to obesity statistics from National Cancer Information Center [2]. Obesity is a risk factor for malignancies of the colon [3], pancreas [4], thyroid [5], liver [6], and uterus [7] as well as for cardiovascular disease and diabetes mellitus. In addition, obesity is associated with impairment of cognitive functions such as executive function, attention, and memory [8]. Cognition can be affected not only by the comorbidity of cerebrovascular disease, but also by obesity itself [9]. Therefore, obesity causes an economic burden to health care systems [10].

Obesity arises from energy intake chronically exceeding energy expenditure [11]. This imbalance of energy can be triggered by both the internal state of the caloric equation (homeostasis) and non-homeostatic factors, such as social, cultural, psychological, environmental factors or food itself [12–14]. In addition, from the genome-wide association analysis study, 32 loci were associated with body mass index (BMI). However, these loci, genetic factors, could explain only 6–11% of the variance in BMI [15, 16]. In this regard, researchers focused on how the brain regulates human eating behavior [17]. The brain is known to play a central role in controlling the desire to eat [18]. Recently, significant progress has been made in understanding obesity by contributions of

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neuroimaging. Therefore, this review provides an overview of 1) obesity and brain and 2) obesity and brain positron emission tomography (PET).

Obesity and the Brain

Brain areas involved in the regulation of eating behavior are shown in Fig. 1 [17]. The perception of taste is mediated by chemosensory neurons in the oral cavity projecting to the nucleus tractus solitarius (NTS) in the brainstem. The NTS projects to the neurons in the ventral posteromedial nucleus of the thalamus, and then innervates the primary gustatory cortex; the insula and the operculum. The insula (involved in many aspects of eating behaviors including processing information related to the taste and hedonic factors of food) is connected to the orbitofrontal cortex (OFC), the secondary gustatory cortex [19, 20]. The smell of food processed through the olfactory bulb and converges on the insula and OFC [20]. The appearance of food is processed through the visual cortex and then through the inferior temporal visual cortex. Texture is represented independently from taste and smell in the insula. Information related to palatability of food merges with visceral information from the gut such as mechanical distention and nutrient composition, and eventually converges in OFC [21, 22]. This information projects from OFC to striatum, particularly the nucleus accumbens (NAc), modifying neuronal

activity in striatohypothalamic and striatopallidal circuits which are influenced by mesolimbic and nigrostriatal dopaminergic inputs [23, 24] and the lateral hypothalamus [22]. In industrialized countries where foods are plentiful, the palatability of food increases food intake by a positive-feedback reward mechanism [25]. Dopamine is a neurotransmitter modulating reward, which processes information related to food reward influenced by metabolic and hormonal signals [26]. The reward circuits include mesolimbic neurons from the ventral tegmental area (VTA), which increases the firing of dopamine neurons after exposure to food into NAc of the ventral striatum [27, 28]. However, with repeated exposure to a food reward, activation of dopamine neurons lessens as a habituation [29]. This blunted activation can trigger overeating to compensate for the reward response [30]. Therefore, a decreased sensitivity to the rewarding effects of actual food consumption in dopaminergic neurons develops in obesity [31]. However, it is an open question whether obesity is caused by the difference in dopaminergic systems or causes differences of dopaminergic system. As dopamine is pivotal in rewarding and conditioning of both food and drugs, obesity and drug addiction share a significant overlap of striatal connectivity patterns [32]. A network model of four interacting circuits underlying addiction was proposed by Volkow et al.: 1) reward/saliency (NAc, VTA, ventral pallidum), 2) motivation/drive (OFC, ventral anterior cingulate gyrus, subcallosal cortex), 3) conditioning/habits (amygdala,

Fig. 1 Brain areas involved in the regulation of eating behavior: amygdala (behavioral salience and stress responses), anterior cingulate cortex (regulation of autonomic function of the body, reward anticipation, and decision making), brainstem (blood–brain barrier crossing of peripheral peptide hormones and binding to intracerebral receptors), dorsolateral prefrontal cortex (goal-directed behavior), fusiform gyrus (visual association cortex), hypothalamus (integration of homeostatic information from the body), insula (interoception, homeostasis, and

integration of sensory signals across modalities), nucleus accumbens (reward prediction and conditioning), nucleus caudatus (feedback processing), and the orbitofrontal cortex (valuation and secondary gustatory cortex). Reprinted from Functional neuroimaging in obesity and the potential for development of novel treatments, *Lancet Diabetes Endocrinology*, 4(8), Schlögl H et al., 695–705, 2016, with permission from Elsevier

Table 1 Summary of previous studies

Author	Year of publication	Country	Radiopharmaceuticals	No. and characteristics of subjects	Study design	Brain regions
Tataranni et al. [43]	1999	USA	$^{15}\text{O}-\text{H}_2$	11 healthy, normal-weight men	hunger vs. satiation	hunger, increased activity: hypothalamus, insular cortex, orbitofrontal cortex, anterior cingulate cortex, parahippocampal, hippocampal formation, thalamus, caudate, putamen, cerebellum satiation: ventromedial prefrontal cortex, dorsolateral prefrontal cortex, inferior parietal lobule
Gautier et al. [44]	2000	USA	$^{15}\text{O}-\text{H}_2$	11 obese and 11 lean men	hunger vs. satiation obese vs. lean	satiation, increased activity: ventromedial/dorsolateral prefrontal cortex obese, increased activity: prefrontal cortex
DelParigi et al. [45]	2005	USA	$^{15}\text{O}-\text{H}_2$	21 obese and 20 lean subjects	hunger vs. sensory stimulation obese vs. lean	obese, increased activity: middle-dorsal insula, midbrain
Le et al. [47]	2006	USA	$^{15}\text{O}-\text{H}_2$	9 obese and 9 lean men	hunger vs. fixed amount of liquid meal obese vs. lean	lean, increased activity: left dorsolateral prefrontal cortex
DelParigi et al. [48]	2007	USA	$^{15}\text{O}-\text{H}_2$	9 successful dieters and 20 non-dieters	hunger vs. sensory stimulation successful dieters vs. non-dieters	successful dieter, increased activity: dorsal prefrontal cortex, dorsal striatum, anterior cerebellar lobe non-dieter, increased activity: orbitofrontal cortex
DelParigi et al. [49]	2002	USA	$^{15}\text{O}-\text{H}_2$	22 men and 22 women	hunger vs. satiation men v.s women	hunger, men, increased activity: frontotemporal, paralimbic area satiation, women, increased activity: occipital, parietal sensory association area, dorsolateral prefrontal cortex
Stephan et al. [50]	2003	USA	$^{15}\text{O}-\text{H}_2$	18 normal-weight women	hunger vs. stomach distention	satiation, men, increased activity: ventromedial prefrontal cortex stomach distention, increased activity: dorsal brainstem, left inferior frontal gyrus, bilateral insula, right subgenual, anterior cingulate cortex
Wang et al. [52]	2004	USA	$^{18}\text{F}-\text{FDG}$	12 healthy, normal-weight subjects	neutral stimulation vs. food stimulation	food stimulation, increased activity: whole brain (especially in superior temporal, anterior insula, orbitofrontal cortex)
Wang et al. [53]	2002	USA	$^{18}\text{F}-\text{FDG}$	10 obese and 20 lean subjects	obese vs. lean	obese, increased activity: bilateral parietal somatosensory cortex
Volkow et al. [54]	2009	USA	$^{18}\text{F}-\text{FDG}$	21 healthy subjects	correlation with BMI	negative correlation: prefrontal cortex, cingulate gyrus
Wang et al. [55]	2009	USA	$^{18}\text{F}-\text{FDG}$	23 healthy subjects	food stimulation with/without inhibition men vs. women	food stimulation with inhibition, men, decreased activity: amygdala, hippocampus, insula, orbitofrontal cortex, striatum
Wang et al. [57]	2001	USA	$^{11}\text{C}-\text{raclopride}$	10 obese and 10 normal-weight subjects	obese vs. normal-weight	obese, decreased activity: striatum
Small et al. [58]	2003	USA	$^{11}\text{C}-\text{raclopride}$	7 healthy subjects	hunger vs. satiation	hunger, decreased activity: dorsal putamen, caudate nucleus

Table 1 (continued)

Author	Year of publication	Country	Radiopharmaceuticals	No. and characteristics of subjects	Study design	Brain regions
Volkow et al. [61]	2002	USA	¹¹ C-raclopride	10 healthy subjects	hunger vs. sensory stimulation placebo vs. methylphenidate correlation with BMI	sensory stimulation, methylphenidate: dorsal striatum
Guo et al. [62]	2014	USA	¹⁸ F-fallypride	20 obese and 23 normal-weight subjects	correlation with BMI and neuropeptides	positive correlation: dorsal/lateral striatum negative correlation: ventromedial striatum
Dunn et al. [63]	2012	USA	¹⁸ F-fallypride	14 obese and 8 lean women	correlation with BMI and neuropeptides	positive correlation, BMI: caudate negative correlation, ghrelin: caudate, putamen, ventral striatum, amygdala, temporal lobes
Eisenstein et al. [64]	2013	USA	¹¹ C-NMB	15 obese and 15 normal-weight subjects	correlation with BMI	none

*No, number; FDG, fluorodeoxyglucose; NMB, N-methyl benperidol; BMI, body mass index

hippocampus, dorsal striatum), and 4) inhibitory control/executive functions (dorsolateral prefrontal cortex, anterior cingulate gyrus, inferior frontal cortex, and lateral OFC) [33, 34]. During addiction, these circuits are imbalanced with the enhanced value in circuits of reward/saliency, motivation/drive, and conditioning/habits overcoming that of inhibitory control/executive [33, 34]. There is evidence that neuropeptide hormones also regulate the eating behavior [35–38]. Leptin from adipose tissue, insulin from pancreas, and cholecystokinin/glucagon-like peptide-1 from gut act to reduce food intake [26], while ghrelin from stomach is secreted before meal onset and can stimulate feeding [39]. Neurons in NTS and hypothalamus sense and response to peripheral energy signals to promote energy homeostasis [26]. In addition, neurons in VTA and NAc express receptors of neuropeptide hormones [35–38], which influence the reward responses to food.

Obesity and Brain PET

Neuroimaging has been utilized to reveal the connectivity between obesity and brain which regulates human eating behavior [17]. PET and functional magnetic resonance imaging studies have become increasingly common in obesity research [40]. Using PET, information at the molecular level can be investigated and specific molecules can be labeled to detect the target [41]. In addition, PET scanning can be performed repeatedly over time with minimal invasiveness and strong reproducibility [41]. However, PET is limited by low resolution and nonspecific binding of radiopharmaceuticals. Restricted availability, exposure to radiation, and high cost are other challenges in using PET [42]. Moreover, a controlled experimental activation of the neural system in a laboratory setting might differ from real-life eating behavior [17, 41].

Nowadays, PET radiopharmaceuticals have been examined to understand the cerebral control of food intake in humans. This review focused on three main radiopharmaceuticals of PET; ¹⁵O-H₂, ¹⁸F-fluorodeoxyglucose (FDG), and radiopharmaceuticals of dopamine receptor (Table 1).

¹⁵O-H₂ PET

In ¹⁵O-H₂ PET studies, regional cerebral blood flow (rCBF) coupled to neuronal activity is measured to estimate brain activity [43]. After 36 h of fasting, rCBF increased in hypothalamus and thalamus (regulates feeding behavior); paralimbic and limbic areas (involved in affect and motivation); caudate nucleus, precuneus, putamen, insula, and cerebellum [44]. However, with satiation after feeding, rCBF increased in the ventromedial/dorsolateral prefrontal cortex and the inferior parietal cortex (exerts inhibitory effects to hunger and promotes the termination of a meal) [44]. In response to

satiation, obese men had greater increases in rCBF of the prefrontal cortex and greater decreases in rCBF of the limbic, paralimbic areas, temporal and occipital cortex than lean men, raising the possibility of different brain response to feeding stimuli between obese and lean [45]. To investigate the response after sensory stimulation, 21 obese and 20 lean subjects underwent PET scans following oral administration of 2 ml of a liquid formula meal after a 36 h fast [46]. In obese subjects compared with lean, a greater increase of rCBF in insula which integrates information of food, and a greater decrease of rCBF in posterior cingulate cortex, temporal lobe, and medial OFC which implicates in monitoring the changing reward of primary and learned reinforcement were observed [46, 47]. Perfusion in the left dorsolateral prefrontal cortex significantly decreased in response to a liquid meal in obese men, possibly important in regulation of eating behavior to terminate a meal [48]. In successful dieters who kept their weight stable for at least three months, activation in dorsal prefrontal cortex increased significantly after a satiating amount of the meal compared with non-dieters [49]. The response in the prefrontal cortex was inversely correlated with that in OFC [49]. Therefore, there might be inhibitory feedback circuit links between the prefrontal cortex and OFC [49]. Between men and women, extensive similarities in the brain responses to hunger and satiation was reported [50]. However, men had higher activity in the frontotemporal lobes, posterior cingulate cortex, and parahippocampal gyrus (mainly involved in processing emotion) in response to hunger [50]. Women had higher activity in the frontal lobe, precuneus, parietal lobe, occipito-temporal cortex (involved in sensorial

association and behavioral planning) in response to satiation [50]. The effect of short-term satiety was investigated using gastric balloon inflation [51]. rCBF in the parabrachial nucleus of the brainstem (integrates vagal afferent information on food intake), lateral inferior frontal, OFC, insula, and anterior cingulate cortex (processes a visceral sensation with a negative affective component) [51].

¹⁸F-FDG PET

¹⁸F-FDG PET provides functional maps in vivo related to both body region and submodality of sensory information in the human brain [52]. After exposure to food stimuli, subjects' metabolism increased significantly in the postcentral gyrus of the parietal cortex (involved in taste perception), anterior insula, superior temporal lobe, and OFC [53] (Fig. 2). Metabolism in the OFC was positively associated with ratings of hunger and desire for consuming the food, which might reflect downstream effects from dopamine stimulation [53]. Obese subjects showed higher metabolic activity than lean subjects in postcentral gyrus of the parietal cortex (where somatosensory maps of the mouth, lips, and tongue are located even at baseline condition), which might reflect the enhanced sensitivity to food palatability in obese subjects [54]. Negative association between BMI and baseline cerebral metabolism was reported in the prefrontal cortex and anterior cingulate cortex [55]. As the prefrontal cortex is involved in regulating impulse control, self-monitoring, and goal-directed behaviors, decreased glucose metabolism in the prefrontal cortex may reflect vulnerability to overeating [55]. Wang et al.

Fig. 2 Transaxial FDG PET images of a subject during food presentation and during neutral intervention at levels of postcentral gyrus, superior temporal cortex, insula, and orbitofrontal cortex. Reprinted from

Exposure to appetitive food stimuli markedly activates the human brain, *Neuroimage*, 21(4), Wang GJ et al., 1790–1797, 2004, with permission from Elsevier

Fig. 3 Group average images of ^{11}C -Raclopride (distribution volume image) PET for controls (left) and obese (right) individuals at the level of the basal ganglia. Reprinted from Brain dopamine and obesity, Lancet, 357(9253), Wang GJ et al., 354–357, 2001, with permission from Elsevier

investigated the gender differences in the ability to inhibit brain activation by food stimulation [56]. During food presentation with cognitive inhibition, glucose metabolism in amygdala, hippocampus, insula, OFC, and striatum was suppressed in men, but not in women, which may reflect gender differences in the prevalence of obesity and other eating disorders [56].

Dopamine Receptor PET

Most studies on the dopaminergic system concentrated on dopamine receptors. However, there are several inconsistencies between studies, possibly due to radiopharmaceuticals used and small sample sizes [18]. Lower dopamine receptor (DR) availability of striatum in obese subjects was observed using ^{11}C -raclopride [57] (Fig. 3). In addition, DR availability was negatively correlated with BMI [57]. Feeding increases extracellular dopamine release similar to a drug reward [57, 58]. Therefore, individuals with lower DR availability might overeat to compensate [57, 59]. However, the alternative hypothesis is that individuals with lower DR availability may be more vulnerable to addictive behaviors including compulsive food intake [57, 59]. Lower DR availability in the striatum is associated with decreased glucose metabolism in the OFC (involved in salience attribution), the cingulate gyrus, and the dorsolateral prefrontal cortex (implicates in inhibitory control) [60]. Therefore, dysregulation of food consumption mediated by reward signals of DR could underlie a mechanism for loss of control and compulsive behavior [60]. Although functional abnormalities in food addiction tend to occur in brain regions functionally connected to both dorsal and ventral striatum, the dorsal and ventral striatum have a distinct role in food motivation. After consumption of a favorite meal [58] and non-hedonic food motivation [61], DR availability decreased in the dorsal striatum, but not in the ventral striatum [32]. ^{18}F -fallypride studies found that BMI is positively associated with D2R availability of dorsal/lateral striatum [62] and caudate [63], possibly contributing to the development of obesity by potentiating a habitual susceptibility to opportunistic overeating [62]. DR availability of ventromedial striatum is negatively associated with BMI, which may be a reflection of reward hypofunction leading to compensatory overeating

[62]. However, no difference in striatal DR availability was observed between obese and normal weight subjects by ^{11}C -N-methyl-benperidol (NMB) PET [64]. ^{11}C -NMB is more than 200 times selective for D2R than D3R, and is not displaceable by endogenous dopamine, different from ^{11}C -raclopride or ^{18}F -fallypride [64]. Therefore, reduced DR availability measured by ^{11}C -raclopride or ^{18}F -fallypride might be derived from the extracellular release of dopamine [64], not from the decrease of number or affinity of D2R. This inconsistency between studies may be related not only with the radiopharmaceuticals, but also with the experimental settings such as the time of the day, and food restriction [63]. For example, D2R mediated neurotransmission and dopamine clearance vary diurnally and ^{18}F -fallypride is less sensitive to competition with endogenous dopamine than ^{11}C -raclopride, which may be influenced by the duration of food restriction [62]. DR availability measured by ^{11}C -raclopride increased in patients who lose weight after bariatric surgery, proportional to the amount of weight loss in five female patients [65]. However, a decrease [66] or no change [67] of DR availability was reported in a small number of patients.

Conclusions

The brain has an important role in maintaining energy balance by regulating eating behavior. Neuroimaging has been utilized to reveal the connectivity between obesity and brain. Therefore, brain PET could improve understanding of obesity and help develop a new treatment for obesity.

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Compliance with Ethical Standards

Conflict of Interest Kyoungjune Pak, Seong-Jang Kim, and In Joo Kim declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants performed by any of the authors.

Informed Consent This article does not contain any studies with human participants performed by any of the authors.

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