Association of central serotonin transporter availability and body mass index in healthy Europeans

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1. Introduction

Obesity rates have reached epidemic proportions worldwide, and might become the number one preventable public health threat for the 21st century (Sturm, 2002) with high socio-economic impact due to serious medical sequelae, e.g. an increase in type II diabetes mellitus. Despite rapid progress in identifying the social, environmental and genetic causes of overeating, the mechanisms by which these factors result in obesity are not resolved. Regarding the central mechanism thought to be relevant for obesity, the monoaminergic systems seem to play a pivotal role in reward processing (i.e. the dopaminergic pathways of the ventral tegmental area, nucleus accumbens, and frontal cortex) (Volkow et al., 2011), stress-mediation (in particular norepinephrine; Hainer et al., 2006), and the homoeostatic control of feeding. With respect to this, the modulation by serotonin of eating behaviour integrates homoeostatic and hedonic aspects as well as reward regulation at the intersection of the mesolimbic system, hypothalamus and brainstem (Hoebel, 1985). Changes in serotonergic functioning, as a main factor in the regulation of eating behaviour and energy balance, were shown in a variety of animal and clinical studies. Recently, a study in genetically engineered mice showed that knocking out the serotonin transporter (SERT) leads not only to hypophagia and hyperleptinemia but also to insulin resistance, hepatic steatosis, and obesity independent of food intake (Chen et al., 2012). Other studies on SERT knock-out mice also showed increased levels of abdominal fat and susceptibility to obesity (Homberg et al., 2010; Učeýler et al., 2010). In addition, selectively bred polygenic obese rats had lower SERT binding when compared to polygenic diet-resistant rats (Ratner et al., 2012), whereas no change in SERT was seen in diet-induced obesity in outbred rats. This was not the case in a mouse model: diet resistant mice have lower SERT binding than diet-induced obese mice (Huang et al., 2004). Also, a recent imaging study showed that obesity is associated with high serotonin-4 receptor availability in the brain reward system (Haahr et al., 2012). Evidence for a serotonergic involvement in the pathophysiology of satiety and overeating also came from the efficacy of anorectic drugs. For example, sibutramine (Reductil) targeting the SERT as well as the norepinephrine transporter (NET) has an appetite-suppressing, anorexogenic effect (Hainer et al., 2006). Hence, both monoaminergic systems, and in particular the presynaptically located transporters, are likely to represent key biochemical substrates in the intrinsic control of eating, and their failure in function, or compensatory change in expression, are thought to underlie overeating.

Only few studies have been performed that applied single-photon emission computed tomography (SPECT) or positron emission tomography (PET) with radiotracers for the SERT to unravel altered SERT availability in vivo in obesity or that looked into the association between BMI and SERT. Talbot et al. (2010) reported on a PET study with the highly SERT-selective radiotracer [11C]DASB, which was initiated to investigate mechanisms underlying the clinical efficacy of sibutramine. They found SERT occupancy, by clinical doses of sibutramine, of modest magnitude

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**Abstract**

Serotonin-mediated mechanisms, in particular via the serotonin transporter (SERT), are thought to have an effect on food intake and play an important role in the pathophysiology of obesity. However, imaging studies that examined the correlation between body mass index (BMI) and SERT are sparse and provided contradictory results. The aim of this study was to further test the association between SERT and BMI in a large cohort of healthy subjects. **Methods:** 127 subjects of the ENC DAT database (58 females, age 52±18 years, range 20–83, BMI 25.2±3.8 kg/m², range 18.2–41.1) were analysed using region-of-interest (ROI) and voxel-based approaches to calculate [123I]FP-CIT specific-to-nonspecific binding ratios (SBR) in the hypothalamus/thalamus and midbrain/brainstem as SERT-specific target regions. **Results:** In the voxel-based analysis, SERT availability and BMI were positively associated in the thalamus, but not in the midbrain. In the ROI-analysis, the interaction between gender and BMI showed a trend with higher correlation coefficient for men in the midbrain albeit not significant (0.033 SBR m²/kg, p = 0.1). **Conclusions:** The data are in agreement with previous PET findings of an altered central serotonergic tone depending on BMI, as a probable pathophysiologic mechanism in obesity, and should encourage further clinical studies in obesity targeting the serotonergic system.