

A Cys23–Ser23 substitution in the 5-HT_{2C} receptor gene influences body weight regulation in females with seasonal affective disorder: An Austrian–Canadian collaborative study [☆]

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Abstract

Most females with seasonal affective disorder (SAD) exhibit atypical vegetative symptoms such as overeating, and weight gain when depressed. The serotonin 2C receptor (5-HT_{2C}) plays a key role in control of appetite and satiety. A 5-HT_{2C} Cys23Ser substitution, coded for by a single nucleotide polymorphism (Cys23Ser) within the 5-HT_{2C} gene, has been shown to influence 5-HT_{2C} function. We hypothesized that Cys23Ser influences weight regulation in females with SAD. Two independent samples from Austria (162 females with SAD, 119 controls), and Canada (90 females with SAD, 42 controls) were genotyped for Cys23Ser. Influence on weight regulation was analyzed within patients with atypical features. In Austrians, genotype distribution differed between patients and controls ($p = 0.044$) and Cys23Ser was associated with weight ($p = 0.039$), body mass index (BMI; $p = 0.038$), and seasonal appetite change ($p = 0.031$). All values were highest in Cys/Cys, intermediate in Cys/Ser, and lowest in Ser/Ser carriers. In Canadian patients, Cys23Ser was associated with minimum lifetime BMI ($p = 0.046$), with lowest values in Ser/Ser carriers. Our data provide evidence that Cys23Ser mediates severity of weight regulation disturbances in females with SAD, and the gene-dose effect-like differences suggest a direct functional role of Cys23Ser in the behavioral regulation of body weight.

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Keywords: Serotonin; 5-HT_{2C} receptor gene; Cys23Ser; Genetic polymorphism; Seasonal affective disorder; Body weight regulation

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1. Introduction

Seasonal affective disorder/winter type (SAD) is characterized by recurrent depressive episodes of DSM IV major depressive or bipolar disorder in fall and winter (Rosenthal et al., 1984). Most patients with SAD, particularly females, meet DSM-IV criteria for atypical depression subtype as they exhibit atypical vegetative

symptoms such as carbohydrate craving, increased appetite, weight gain, fatigue, and hypersomnia when depressed (Rosenthal et al., 1984; Partonen and Lonnqvist, 1998). These seasonal changes in mood, eating behavior, energy, and sleep, termed seasonality, have a heritable component (Jang et al., 1997; Madden et al., 1996), and have been associated with alterations in brain serotonin (5-HT) receptor function (Levitan et al., 1998; Schwartz et al., 1997). Multiple lines of evidence suggest a genetic link between SAD and eating disorders, possibly involving a number of serotonin-related genes with small interactive and additive effects (Collier et al., 1997; Enoch et al., 1999; Levitan et al., 2004; Sher, 2001; Sorbi et al., 1998). Receptor genes within the 5-HT system that play a role in eating behavior and weight regulation are thus excellent candidates to study SAD and seasonality.

The 5-HT_{2C} receptor gene is of special interest in SAD and other disorders associated with disturbed body weight regulation, as this receptor subtype is expressed predominantly in the medial hypothalamus, a brain region known to be a regulator of food intake and energy metabolism (Lentes et al., 1997). Animal studies give evidence for an important role of 5-HT_{2C} in the control of appetite: 5-HT_{2C} knockout mice develop hyperphagia and midlife obesity (Chou-Green et al., 2003; Tecott et al., 1995), while 5-HT_{2C} receptor mutant mice show higher food intake (Nonogaki et al., 1998), and a decreased satiety response to D-fenfluramine, a releaser of 5-HT (Vickers et al., 1999). In humans, the 5-HT_{2C} agonist mCPP leads to both hypophagia and weight loss (Sargent et al., 1997), while the 5-HT_{2C} antagonist clozapine is associated with increased eating and weight gain (Leadbetter et al., 1992). The functional state of 5-HT_{2C} receptors in SAD has been examined in vivo, revealing abnormal hormonal and behavioral responses to the nonselective 5-HT_{2C} agonist mCPP in patients compared to normal controls (Garcia-Borreguero et al., 1995; Joseph-Vanderpool et al., 1993; Levitan et al., 1998; Schwartz et al., 1997).

A functional Cys23Ser substitution has been identified in the first hydrophobic region of the 5-HT_{2C} receptor (Lappalainen et al., 1995). It is coded by a single nucleotide polymorphism within the 5-HT_{2C} receptor gene on the X-chromosome (Xq24). Male subjects are therefore either hemizygous for Cys23, or hemizygous for Ser23. Frequencies of the Cys23 and Ser23 alleles in unrelated Caucasians are 0.87 and 0.13, respectively. A recent study has shown that the Cys23Ser substitution influences 5-HT_{2C} receptor function, with the Ser23 variant being constitutively more active than Cys23 in the absence of the endogenous ligand, 5-HT (Okada et al., 2004). An association study investigating several 5-HT-related polymorphisms in patients with SAD found no association of Cys/Ser genotype with the diagnosis of SAD, but higher seasonal variation in

mood and eating behavior in Cys/Ser heterozygous women as expressed by the Global Seasonality Score (GSS) (Johansson et al., 2001). In addition, there is significant evidence that the Cys23Ser polymorphism plays a role in body weight regulation per se. The Ser23 allele was found to be associated with weight loss in teenage girls (Westberg et al., 2002). Ser23 was also associated with the diagnosis of anorexia nervosa, and the severity of illness, as expressed by low body mass index (BMI) values (Hu et al., 2003; Westberg et al., 2002). Another study in late onset Alzheimer's disease found an association between Cys23Ser and the presence of hyperphagia (Holmes et al., 1998). These various studies suggest that at least in certain populations, the Cys23Ser polymorphism plays an important role in body weight regulation.

The current study examined the influence of the Cys23Ser polymorphism on both the overall diagnosis of SAD as well as body weight regulation parameters in two independent female samples from Austria, and Canada, respectively. Our first hypothesis was that 5-HT_{2C} Cys23Ser genotype distribution would differ between female patients with SAD and female healthy controls. Our second hypothesis was that in patients with SAD, atypical subtype – a patient collective with a high degree of seasonal changes in energy, appetite and weight – there would be an association between Cys23Ser genotype and disturbances in appetite and weight regulation (body weight, BMI, BMI fluctuations, seasonal changes in appetite, seasonal overeating and weight gain).

2. Materials and methods

2.1. Study sample

All 252 Austrian and Canadian patients were recruited from respective outpatient clinics for SAD of the Medical University of Vienna, Austria, and the Centre of Addiction and Mental Health, University of Toronto. All 161 Austrian and Canadian controls were recruited through standard advertising protocols. Study samples were partially overlapping with samples from previous association studies (Levitan et al., 2004; Willeit et al., 2003). Patients and controls were free of major past and current medical illness, and substance abuse. Patients were diagnosed according to Rosenthal and DSM-IV criteria for SAD (Rosenthal et al., 1984). Of 162 Austrian patients, 121 fulfilled criteria for atypical depression subtype, 41 for melancholic depression subtype. All 90 Canadian patients met criteria for atypical depression subtype. Controls were free of DSM-IV Axis I psychiatric disorders. Subject selection and clinical information obtained were slightly different in the two samples: In Austrian probands (162 Caucasian

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