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Serotonin transporter gene polymorphisms and platelet [³H]paroxetine binding in premenstrual dysphoria

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Abstract

The purpose of this study was to investigate if women with premenstrual dysphoria differ from controls with respect to the number of platelet serotonin transporters, and with respect to three polymorphisms in the gene coding for the serotonin transporter: a 44 base pair insertion/deletion in the promoter region, a variable number of tandem repeats in the second intron, and a single nucleotide polymorphism in the 3' untranslated region. Also, the possible relationship between the three polymorphisms and platelet serotonin transporter density was analyzed. The density of platelet [³H]paroxetine binding sites was significantly lower in women with premenstrual dysphoria than in controls, but patients and controls did not differ with respect to allele or genotype frequency for any of the three polymorphisms examined. A significant association between the number of platelet serotonin transporters and the promoter polymorphism was observed, subjects being homozygous for the short (deletion) variant having higher platelet serotonin transporter density than subjects carrying the long (insertion) allele. The results support the assumption that serotonin-related psychiatric disorders—such as premenstrual dysphoria—may be associated with a reduction in platelet [³H]paroxetine binding.

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but argue against the notion that this reduction is due to certain variants of the serotonin transporter gene being more common in patients than in controls.

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1. Introduction

Five to 10 percent of fertile-aged women suffer from premenstrual dysphoria (PMD) (Angst et al., 2001). Animal experiments and clinical studies suggest that serotonin exerts an inhibitory influence on symptoms such as irritability, affect lability and depressed mood (Eriksson and Humble, 1990; Ho et al., 2001); since these are the most prominent symptoms in women with PMD (Freeman and Halbreich, 1998; Endicott et al., 1999; Yonkers, 1999; Steiner and Born, 2000), the notion that this condition is related to brain serotonergic transmission is not farfetched (Rapkin, 1992; Halbreich and Tworek, 1993; Steiner and Pearlstein, 2000; Parry, 2001). Supporting this assumption, women with PMD are reported to differ from symptom-free controls with respect to various serotonin-related biological markers (Rapkin et al., 1987; Ashby et al., 1988; Rojansky et al., 1991; Steege et al., 1992); moreover, it is well established that serotonin reuptake inhibitors, but not non-serotonergic antidepressants, exert an impressive symptom-reducing effect in PMD, with a short onset of action (Eriksson et al., 1995; Steiner et al., 1995; Yonkers, 1997; Wikander et al., 1998; Eriksson, 1999; Freeman et al., 1999). Further reinforcing an influence of serotonin on the symptoms characterizing PMD, a reduction in premenstrual complaints has been reported upon treatment with the serotonin releasing agents fenfluramine (Brzezinski et al., 1990) and mCPP (Su et al., 1997), as well as with the serotonin precursor tryptophan (Steinberg et al., 1999); conversely, tryptophan depletion is reported to aggravate premenstrual irritability (Menkes et al., 1994; Bond et al., 2001).

Evidence from family and twin studies suggests that the genetic contribution to the etiology of premenstrual dysphoria is considerable (Wilson et al., 1991; Kendler et al., 1992; Condon, 1993), but as yet none of the genes involved has been identified. Given the marked efficacy of serotonin reuptake inhibitors for PMD, the gene coding for the serotonin transporter (SLC6A4), located on chromosome 17q12 (Ramamoorthy et al., 1993), would be one reasonable candidate in this context. So far, three common polymorphisms of this gene have been identified, a 44 base pair insertion/deletion in the promoter region (Heils et al., 1995; Lesch et al., 1996), a variable number of tandem repeats (VNTR) in the second intron (Ogilvie et al., 1996), and a single nucleotide polymorphism (SNP) in the 3'-untranslated region (Battersby et al., 1999).

The serotonin transporter expressed in platelets is identical to that expressed in brain (Ozaki et al., 1994). In an attempt to achieve an indirect measure of brain serotonergic transmission, many researchers have studied platelet serotonin trans-

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