

## Low density and high affinity of platelet [<sup>3</sup>H]paroxetine binding in women with bulimia nervosa

Agneta Ekman <sup>a,\*</sup>, Charlotta Sundblad-Elverfors <sup>a</sup>, Mikael Landén <sup>b</sup>,  
Tomas Eriksson <sup>c</sup>, Elias Eriksson <sup>a</sup>

<sup>a</sup> Department of Pharmacology, Göteborg University, 405 30 Göteborg, Sweden

<sup>b</sup> Department of Clinical Neuroscience, Section of Psychiatry, S:t Görans Hospital, Karolinska Institutet, 112 28 Stockholm, Sweden

<sup>c</sup> Department of General and Forensic Psychiatry, Lund University, Malmö University Hospital, 205 02 Malmö, Sweden

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### Abstract

Impaired serotonin transmission has been suggested to be implicated in the pathophysiology of bulimia nervosa. As an indirect measure of brain serotonergic activity, the binding of tritiated ligands to platelet serotonin transporters has been studied in bulimia nervosa as well as in other putatively serotonin-related psychiatric disorders. In this study, the density and affinity of platelet serotonin transporters were assessed in 20 women meeting the DSM-IV criteria for bulimia nervosa and in 14 controls without previous or ongoing eating disorder using [<sup>3</sup>H]paroxetine as a ligand. In comparison to controls, women with bulimia nervosa had a significantly reduced number of platelet binding sites ( $B_{\max}=721\pm 313$  vs.  $1145\pm 293$  fmol/mg protein) and an increase in the affinity for the ligand demonstrated by a lower dissociation constant ( $K_d=33\pm 10$  vs.  $44\pm 10$  pM). A significant correlation between  $B_{\max}$  and  $K_d$  values was found in patients but not in controls. Our results support the notion that bulimia nervosa is associated with a reduction in platelet serotonin transporter density. In addition, our study is the first to report that this reduced transporter density in women with bulimia nervosa is accompanied by an increase in the affinity of the transporter for the ligand.

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### 1. Introduction

Bulimia nervosa is characterised by recurrent episodes of binge eating and compensatory behaviour to prevent weight gain, e.g. self-induced vomiting. The disorder is much more common in women than in men

(Halmi, 2002; Mehler, 2003). An involvement of serotonin in this condition gains support mainly from the fact that treatment with serotonin reuptake inhibitors leads to a symptom reduction (Kaye et al., 1998; McElroy et al., 2000; Arnold et al., 2002) but also from reports suggesting that subjects with bulimia display decreased concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid in cerebrospinal fluid (Jimerson et al., 1992) and blunted prolactin responses to a variety of serotonergic agents (for references, see Brewerton, 1995).

\* Corresponding author. Department of Pharmacology, Göteborg University, P.O. Box 431, SE 405 30 Göteborg, Sweden. Tel.: +46 31 773 34 47; fax: +46 31 82 10 85.

E-mail address: [agneta.ekman@pharm.gu.se](mailto:agneta.ekman@pharm.gu.se) (A. Ekman).

The serotonin transporter expressed in platelets is identical to that found in brain (Lesch et al., 1993; Ozaki et al., 1994). The binding of tritiated serotonin reuptake inhibitors to platelets has been studied in patients suffering from putative serotonin-related psychiatric disorders as an indirect measure of brain serotonergic activity. In contrast to the notorious difficulty in finding biological markers that are consistently aberrant in groups of psychiatric patients, a majority of these studies have in fact revealed a reduced density of platelet serotonin transporter binding sites in patients with, for example, depression (Briley et al., 1980; Nemeroff et al., 1994; Alvarez et al., 1999), obsessive–compulsive disorder (Marazziti et al., 1996; Sallee et al., 1996), premenstrual dysphoria (Rojansky et al., 1991; Melke et al., 2003), and panic disorder (Marazziti et al., 1999; Neuger et al., 2000).

The purpose of this study was to determine if it is possible to replicate that women with bulimia nervosa differ from controls with respect to the number and affinity of platelet serotonin transporters using the tritiated selective serotonin reuptake inhibitor paroxetine as ligand.

## 2. Methods

### 2.1. Participants

Women ( $n=20$ , age  $25.3\pm 4.6$  years, mean value  $\pm$  S.D.) ( $>18$  years of age) fulfilling the DSM-IV (American Psychiatric Association, 1994) criteria for bulimia nervosa, purging type, were recruited by means of newspaper advertisements for a drug trial. Criteria for bulimia nervosa, as well as the absence of other common psychiatric Axis I disorders, were confirmed by means of a structured interview conducted by an MD or a PhD. Absence of depression was also confirmed by means of the Montgomery–Åsberg Depression Rating Scale (MADRS). Episodes of purging and binge eating per week during a 3-week period of daily rating were  $11.0\pm 14.7$  and  $7.7\pm 4.3$ , respectively. All participants reported that they were free from somatic illness and that they did not take any medication (the occasional use of mild pain killers and antiallergic drugs being disregarded). Thirty percent reported irregular menstruations. As a control group, 14 healthy women ( $26.9\pm 4.9$  years) were recruited by local advertisements, e.g. within the hospital and university; that these subjects were free from bulimia nervosa as well as other common psychiatric Axis I disorders was confirmed by means of a structured interview and the MADRS. All participants gave written informed consent after having received a complete

description of the study. The study protocol was approved by the institutional review board of Göteborg University.

### 2.2. Membrane preparation

Preparation of membranes from platelets and the [ $^3\text{H}$ ]paroxetine radioligand binding experiments were performed essentially as described by Plenge and Mellerup (1991). Blood samples (total volume: 30 ml) were taken before the start of the drug trial using evacuated 10-ml tubes (Venoject containing EDTA) from fasting patients and controls between 0800 and 1000 h on days 6 to 10 of the menstrual cycle (day 1 = the first day of menstrual bleeding). All samples were collected from October to January to avoid seasonal effects on platelet transporter sites (Klompener et al., 1990). Plasma was obtained by low-speed centrifugation ( $200\times g$ , 10 min,  $4^\circ\text{C}$ ) and centrifuged again ( $3000\times g$ , 20 min,  $4^\circ\text{C}$ ); the resulting pellet was homogenized using a dounce glass teflon homogenizer in 10 ml buffer A (50 mM Tris–HCl, 120 mM NaCl, 5 mM KCl, pH 7.5) and recentrifuged at high speed ( $30000\times g$ , 15 min,  $4^\circ\text{C}$ ). After the membrane pellet had been washed once in 10 ml of the same buffer and centrifuged again, the membranes were lysed and rehomogenized in 5 mM Tris–HCl containing 5 mM EDTA (pH 7.5) and centrifuged at high speed as above. Thereafter the membrane pellet was washed once in 20 ml of buffer A, and recentrifuged. Finally, the membranes were resuspended in 1 ml of buffer A and stored at  $-70^\circ\text{C}$  until use.

### 2.3. [ $^3\text{H}$ ]paroxetine binding

Each membrane preparation was resuspended in 26 ml buffer A. In the saturation experiments, 1 ml membrane suspension (corresponding to approximately 40  $\mu\text{g}$  protein) was incubated (total volume of 1.2 ml) in duplicates with six different concentrations (0.035–1.2 nM) of [ $^3\text{H}$ ]paroxetine (NEN, Boston, MA, USA; specific activity 14.8 Ci/mmol) for 2 h at  $20^\circ\text{C}$ . Non-specific binding was determined by the addition of 10  $\mu\text{M}$  citalopram (H. Lundbeck A/S, Copenhagen, Denmark). The reaction was terminated by addition of 4 ml of buffer A ( $20^\circ\text{C}$ ) and the suspension was filtered rapidly through GB/B glass-fiber filters coated by 0.5% polyethyleneimine using a cell harvester (Brandel, Gaithersburg, MD, USA) followed by three washes (4 ml) using buffer A ( $20^\circ\text{C}$ ). The radioactivity trapped on the filters was assessed using conventional liquid scintillation techniques. Protein concentration was

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