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Effects of cognitive-behavioral therapy on Eating Disorders: Neurotransmitter secretory response to treatment

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Summary The effects of cognitive-behavioral therapy (CBT) on central dopamine (DA), noradrenaline (NE) and serotonin (5-HT) secretion were studied in a group of 50 female inpatients, of which 14 suffered from anorexia nervosa restricted type (AN-R), 14 from anorexia nervosa bingeing—purging type (AN-BP), and 22 from bulimia nervosa (BN). The aim of the study was to see whether or not CBT modifies the secretion of central DA (blood homovanillic acid = HVA), NE (blood 3-methoxy-4-hydroxy-phenylglycol = MHPG) and the 5-HT transporter (as evaluated by the platelet paroxetine binding = [^{3}H]-Par-binding), if the physical and psychological effects of CBT correlate with changes of the neurotransmitter secretion; and if the biological effects of CBT are linked to specific psychopathological aspect of the disorders. The treatment lasted 20 weeks. Body-mass Index, bingeing and purging, specific AN—BN psychopathological (EDE 12-OD), depression (Beck Inventory), anxiety (STAY Form-Y-1), impulsiveness (Barratt Impulsiveness Scale), self-esteem (Rosenberg Self-Biochemical Scale) and temperament (Temperament and Character Inventory, Cloninger Scale) were assessed at baseline and at the end of the treatment. CBT significantly improved the psychophysical aspects of the diseases. HVA and MHPG concentrations did not change. The [^{3}H]-Par-binding parameters, the maximum binding capacity (B_{max}) and dissociation constant (K_d) values did not change in either AN-R or AN-BP patients, while the [^{3}H]-Par B_{max} (and not the K_d) increased significantly in BN patients. Correlations emerged between basal and final [^{3}H]-Par B_{max} values and psychopathological scores, but not between CBT-induced differences between basal and final values. Our data suggest that only in BN CBT may act through changes in 5-HT system function.

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1. Introduction

Treatments of Eating Disorders (ED), anorexia nervosa (AN), bulimia nervosa (BN) and Binge-Eating Disorder (BED) frequently fail, with chronicization or relapse of the illnesses or even death of patients. Cognitive-behavioral therapy (CBT) seems to be currently the most successful treatment for adults with BN (NICE, 2004) and a promising one in the other ED (Fairburn, 2008). The reason for this is unclear. Equally perplexing is why some patients respond to treatment while others do not, since no clear-cut psychophysical differences exist between responders and non-responders. One possible reason is that the biological mechanism of action of CBT is still unknown; in particular, it is unclear whether or not CBT corrects the brain biochemical pathologies that possibly represent the neurobiological background of the illnesses in AN, BN and BED patients. In other words, does CBT cures in every patient the brain alterations present in AN, BN and BED, and because of that cure these disorders? Or does it only improve some, but not all, the neurotransmitter impairments, thus leaving part of the alterations untreated, ultimately responsible for the partial clinical inefficacy of therapy?

At present, few studies have taken into consideration the neurobiological effects of CBT on phobic, obsessive-compulsive and depressed patients, by using body-imaging techniques (fMRI, PET, SPECT) which have revealed decreases of previous hyperactivity occurring in different brain areas according to the diagnoses (Baxter et al., 1992; Rauch et al., 1994, 1995; Breiter et al., 1996; Schwartz et al., 1996; Brody et al., 2001; Furmark et al., 2002; Paquette et al., 2003; Nakatani et al., 2003; Goldapple et al., 2004; Straube et al., 2006; Linden, 2006). However, no data are available on the effects of CBT in patients with ED. Brain imaging studies are informative of the function of brain circuits whose alterations seem to be linked to specific symptoms of mental disorders, but they provide little information on the biochemical mechanisms through which CBT operates. Studies are needed on the secretion of neurotransmitters, neuropeptides, neurohormones and related receptor function that are known to be impaired in ED and potentially connected with the appearance and maintenance of specific psychopathological symptoms.

In a group of anorexic and bulimic patients we monitored dopamine (DA) and noradrenaline (NE) secretions before and after CBT therapy, by measuring the plasma levels of the two neurotransmitters main metabolites, homovanillic acid (HVA) for DA and 3-methoxy-4-hydroxy-phenylglycol (MHPG) for NE. Although plasma HVA and MHPG values include the peripheral secretion of DA and NE, it has been repeatedly demonstrated that these metabolites closely mimic central secretion of the two neurotransmitters and can be used as a correct peripheral mirror of the neurotransmitter function (Pickar et al., 1990; Zhang et al., 2001). To measure the peripheral expression of serotonin (5HT) brain secretion, we evaluated the 5-HT transporter as assessed through the specific binding of tritiated paroxetine ([^{3}H]-Par) to platelet membranes. Platelet function has been found to be a reliable peripheral model of central presynaptic 5-HT neuron activity, in particular of the 5-HT transporter one, which corresponds to that in brain synaptosomes. It has been demonstrated that the binding of [^{3}H]-paroxetine to platelet membranes represents a simple, scarcely invasive technique that provides an indirect significant measure of central 5-HT function that can be used routinely (Briley et al., 1979; Marazziti et al., 1988; Ramacciotti et al., 2003; Rausch et al., 2005).

The aim of our study was to see whether or not in AN and BN patients CBT modifies central DA, NE and 5-HT secretions, as measured by their peripheral parameters, if the positive physical and psychological effects of CBT correlate with changes in neurotransmitter secretion, and if the biological effects of treatment are linked to specific psychopathological aspects of ED.

2. Materials and methods

2.1. Patients

The study population comprised 50 female patients, 28 suffering from AN [14 restricted type (AN-R) and 14 bingeing/purging type (AN-BP)] and 22 from BN. All probands were inpatients in the ED unit of the Villa Garda Hospital, randomly recruited without operating any specific set of selection criteria, in particular not stratified for age, age of onset and duration of the diseases, weight, frequency of bingeing and purging and particular psychopathological symptoms. All the patients were admitted after a mean waiting list of 12 weeks. The diagnosis of AN and BN were made according to the Diagnostic and Statistical Manual of Mental Disorders IV criteria (DSM-IV, American Psychiatric Association, 1994), based on the Eating Disorder Examination Interview (EDE 12.0D, Fairburn and Cooper, 1993). Exclusion criteria from the study were general medical, endocrine, metabolic, immune alterations other than those linked to AN and BN, cerebral trauma, epilepsy, active substance abuse, psychiatric disorders other than ED. All the patients had been previously treated in an outpatient setting with various types of psychotherapies (50% with psychodynamic psychotherapy, 30% with support psychotherapy, 20% with CBT), with no therapeutic benefit. Pharmacotherapies were previously administered to 16 of the 50 patients for variable period of time, and consisted of sertraline or paroxetine (from 20 to 40 mg/day in AN, and from 20 to 100 mg/day in BN), again with no therapeutic benefit.

Written informed consent to participate to the study according to the Helsinki declaration was obtained from all subjects. The study protocol was approved by the Institutional Review Board of Villa Garda Hospital, Verona.

2.2. Treatment protocol

The treatment protocol was derived from the new transdiagnostic cognitive-behavior theory and treatment of ED (Fairburn and Harrison, 2003), adapted to make it suitable for an inpatient setting by Dalle Grave (2005). The treatment is manual-based (Dalle Grave, 2005), lasts 20 weeks (13 for inpatient therapy followed by 7 weeks of residential day-hospital), and is divided into three stages. In stage 1 (from week 1 to 4) the focus is on engaging and educating the patients to obtain maximal early behavior change, including in underweight patients the initiation of weight regain, and to create a personalized formulation of the disorder. In stage 2 (from week 5 to 17) the content is dictated by the extended