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Peripheral Brain Derived Neurotrophic Factor (BDNF) in Bulimia Nervosa: A Systematic Review

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A B S T R A C T

Introduction: Currently, there is limited understanding of the etiology of BN. While multifaceted etiology is likely, several neurobiological factors may play a role. Brain derived neurotrophic factor (BDNF), a potential biomarker linked to eating and weight disorders, is one factor of recent investigation. This paper examined studies comparing BDNF blood levels in BN to healthy control (HC) subjects.
Methods: A systematic review of the literature was conducted utilizing five databases (PubMed, CINAHL, EMBASE, PsycINFO, and Medline). Key terms included eating disorders, BDNF, and bulimia nervosa.
Conclusions: BDNF blood levels appear lower in BN than in HC subjects; however, studies are needed to examine the influence of possible correlates including symptom severity, mood, medications, exercise, and substance use.

Bulimia nervosa (BN) is an eating disorder characterized by episodes of eating a large amount of food in a short period of time with a subjective experience of loss of control (American Psychiatric Association [APA], 2013). The caloric content resulting from the binge episodes is then compensated in some way such as self-induced vomiting or laxative misuse (APA, 2013). The onset of the disorder typically occurs during adolescence or young adulthood and affects more women than men (Hudson, Hiripi, Pope, & Kessler, 2007). BN is associated with significant medical morbidity including electrolyte imbalances, dental erosion, and arrhythmias (Mehler, 2011). Currently there is limited understanding of the etiology of BN. Several biomarkers have been implicated in the etiology of BN, including brain derived neurotrophic factor (BDNF) (Nakazato, Hashimoto, Shimizu, Niitsu, & Iyo, 2012). The purpose of this review is to examine investigations to date to further elucidate the possible role of BDNF in BN.

BDNF

Compound Characteristics

BDNF is a member of the neurotrophin family, a group of proteins with similar amino acid structures (Lewin & Barde, 1996). The group includes nerve growth factor (NGF), the prototype, neurotrophin-3 (NT-3), neurotrophin-4 (NT-4/5) and BDNF (Lewin & Barde, 1996). Neurotrophins selectively bind to one of the tyrosine kinase receptors (Trk A, B, or C), and all neurotrophins bind to the tumor necrosis factor receptor p75NTR (Huang & Reichardt, 2003). BDNF is widely distributed in the brain (Conner, Lauterborn, Yan, Gall, & Varon, 1997), including areas associated with eating behavior (Bariohay, Lebrun, Moyse, & Jean, 2005).

Synthesis

Chromosome 11 band p13 is the location of the gene that codes for BDNF (Maisonpierre et al., 1991). The creation of the BDNF protein begins with preproBDNF, a protein 240–260 amino acids long, which is formed from BDNF mRNA inside the endoplasmic reticulum of a cell (Lessmann, Gottmann, & Malcangio, 2003). Prior to leaving the endoplasmic reticulum, the "pre" section is removed, and the protein is sent as proBDNF to the Golgi apparatus for sorting (Lessmann et al., 2003). The cell can release either proBDNF, the immature form of BDNF, or remove the "pro" section to release the mature form of BDNF (Lessmann et al., 2003).

Circulation and Measurement

BDNF freely crosses the blood brain barrier (Pan, Banks, Fasold, Bluth, & Kastin, 1998). Pre-clinical evidence from mammalians found positive associations between brain levels of BDNF and that circulating in blood samples (Klein et al., 2011). A human study measuring BDNF in the internal jugular vein during exercise and at rest showed that the brain contributes approximately 72% of

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circulating BDNF at rest and 84% during exercise (Rasmussen et al., 2009). Other sources of circulating BDNF include muscles (Sakuma & Yamaguchi, 2011), vascular endothelial cells (Nakahashi et al., 2000), and platelets (Fujimura et al., 2002).

Measurement of BDNF in the periphery can be done through serum or plasma blood samples using an enzyme-linked immunoassay (ELISA). Several studies provide evidence of reliability with little variability for BDNF measurement in serum or plasma with an ELISA (Elfving, Plougmann, & Wegener, 2010; Trajkovska et al., 2007). While serum and plasma samples both provide reliable ELISA measures, serum samples of BDNF are estimated to be higher than levels in plasma, which may be due to the release of BDNF from platelets (Fujimura et al., 2002; Rosenfeld et al., 1995). Despite these differences researchers generally find serum and plasma BDNF levels to follow a similar pattern as, for example, evidenced by studies indicating individuals with depression have lower levels of serum and plasma BDNF than healthy control subjects (Brunoni, Lopes, & Fregni, 2008).

Function

A primary function of neurotrophins is to promote peripheral and central nervous system (CNS) neuronal growth, differentiation, and survival (Porter & Kaplan, 2011). Immature proBDNF has been found to prune existing neurons by binding to the p75NTR and initiating cell death (Teng et al., 2005). Mature BDNF activates cell growth, survival and regeneration through the TrkB receptor (Teng et al., 2005). BDNF's function in helping to grow new neurons is the reason for antidepressants' effect according to the neurotrophic hypothesis of depression (Duman & Monteggia, 2006).

Role in Eating Behavior

Pre-clinical studies have indicated that BDNF may be implicated in eating and weight disorders. Research on animal models identified BDNF in areas of the brain known to influence eating, such as the hypothalamus, dorsal vagal complex (DVC) and paraventricular nucleus (PVN) (Bariohay et al., 2005; Wang, Bomberg, Billington, Levine, & Kotz, 2007). BDNF and the TrkB receptor are involved in eating and weight disorders as evidenced by animal models where lack of either is associated with hyperphagia and obesity (Rios et al., 2001; Tsao et al., 2008). Mice with only one copy of the BDNF gene show increased food intake in addition to increased activity levels compared to mice that are homozygous for the BDNF gene (Kernie, Liebl, & Parada, 2000). When BDNF is administered to genetically homozygous BDNF mice, decreases in food intake and body weight were seen (Kernie et al., 2000).

A study by Bariohay et al. (2005) indicated that fasting rats showed decreased BDNF in the DVC compared to those fed ad libitum. When the fasting rats were refed, the levels of BDNF in the DVC were increased significantly compared to those fed ad libitum (Bariohay et al., 2005). Levels of BDNF in the hypothalamus of fasting rats did not change compared to ad libitum controls throughout the study, indicating that BDNF levels in the hypothalamus were not affected by food intake while levels in the DVC were (Bariohay et al., 2005).

Because of the possible corollary of hyperphagia to clinical symptoms of binge eating (the cardinal feature of BN), several investigations have begun to explore the role of BDNF and BN. Thus, the purpose of this paper is to review and summarize the findings to date comparing peripheral blood levels of BDNF in individuals with

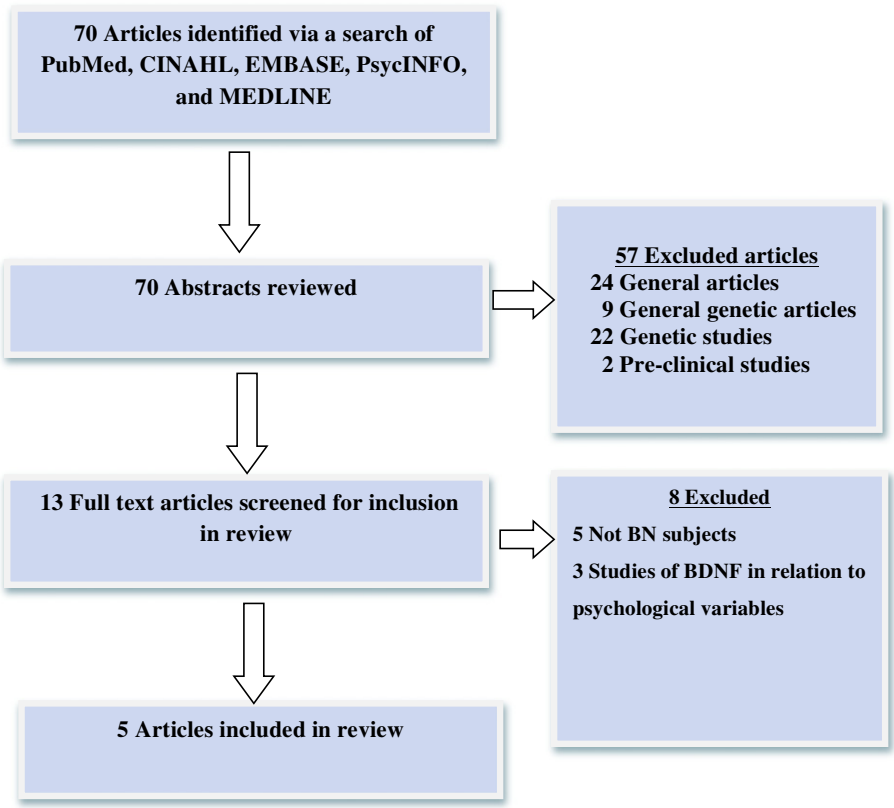

Fig. 1. Findings. Subject Characteristics. To date, five studies have compared blood levels of BDNF in BN subjects with levels of HCs. Sample size of individuals with BN ranged from 16 to 29 participants (Yamada et al., 2012; Mercader et al., 2007; Table 1). Four studies included an HC comparison group ranging from 10–24 participants (Monteleone et al., 2005; Saito et al., 2009; Yamada et al., 2012). One additional study utilized healthy siblings of the BN participant as the control group (Mercader et al., 2007). Studies were conducted in Italy, Japan, and Spain.