

Childhood abuse, brain-derived neurotrophic factor and psychiatric disorders

Leo SHER^{1,2}, Vanessa LaBODE¹

¹James J. Peters Veterans' Administration Medical Center

²Mount Sinai School of Medicine, New York, USA

Brain-derived neurotrophic factor (BDNF)

Neurotrophins comprise a family of secreted proteins that promote growth, survival, and differentiation of neurons in the central and peripheral nervous systems [1]. Brain-derived neurotrophic factor (BDNF) is a principle mediator in neuronal survival, structure, and function [2, 3]. BDNF modulates the efficacy of synaptic transmission [3]. This effect appears to be presynaptic in origin and to be mediated by the Trk family of receptor tyrosine kinases. The functional importance of the pro region of BDNF was demonstrated in a recent study that investigated the consequences of a single nucleotide polymorphism in this region. This polymorphism is defined by replacement of valine⁶⁶ with methionine and is associated with memory deficits and abnormal hippocampal function in humans [4]. At the cellular level, the Val/Met substitution affects the intracellular trafficking of BDNF to synapses and reduces the regulated activity-dependent release of BDNF. An association between BDNF dysfunction and different psychiatric pathologies has been shown; however, the mechanism of this process is not well understood. Stressors, specifically childhood abuse, have an effect on BDNF levels, making the link between past abuse, BDNF levels, and psychopathology worth investigating [5, 6]. Different psychiatric conditions such as depression, suicide, bipolar disorder, and psychosis have been studied in an attempt to understand the abuse-BDNF relationship [7-10].

Childhood abuse

Early stress is associated with long-term alterations in brain circuits and systems that mediate the stress response [11-16]. Early stressors have lasting effects on the hypothalamic-pituitary adrenal (HPA) axis, norepinephrine, benzodiazepine, opiate, dopaminergic, BDNF and other brain systems. These neurochemical systems modulate function in various brain regions, including the hippocampus, amygdala, and prefrontal cortex. Long-term alterations in these brain regions play a role in the pathophysiology of PTSD, depression, and other symptoms and syndromes related to childhood abuse. Early stress could start a chain reaction of neurohormonal and neurotransmitter effects that would damage brain structure and functions. For example, high levels of cortisol could precipitate hippocampal neurotoxic lesions and excessive stress would act as a toxic agent interfering in the usual neurodevelopment process [15].

Early social experiences and experience-related changes in neural correlates of cognition and emotion play a pivotal role in transgenerational transmission of phenotype [1]. Increased susceptibility to cognitive impairments and psychiatric illnesses in adults with a history of childhood maltreatment may reflect a lasting imprint of early maltreatment on epigenetic mechanisms regulating gene expression [16].

Animal research

A study was performed to investigate the epigenetic effects of childhood maltreatment on the BDNF gene, using infant rats [17]. During their first postnatal week, infant rats were exposed to caretakers with abusive behaviors. Results showed that early-life maltreatment resulted in methylation of BDNF DNA throughout the lifespan, which resulted in reduced BDNF gene expression. The epigenetic effects were, however, reversible with chronic treatment of a DNA methylation inhibitor. Lastly, rats that experienced abuse were more likely to mistreat their own offspring, causing them to have significant DNA methylation, and thus restarting the cycle [16]. It was also found that those rats with early abuse had an increase in methylation of exon IV of the BDNF promoter leading to a decrease in BDNF mRNA in the prefrontal cortex. These differences persisted throughout the lifetime, and analysis showed that the BDNF exon IV methylation was transmitted to the next generation [17].

Depression

Individuals who were abused and neglected during childhood have a higher risk of major depression when they become adults [18, 19]. Child abuse has been linked to depression in clinical populations and community surveys. Any stressful experiences during the childhood may be associated with depression. For example, a follow-up study of 1,658 members of the Helsinki Birth Cohort, born in 1934-1944 (Finland), 410 of whom were evacuated to foster care during World War II has been conducted [20]. More than six decades later, the adults who were evacuated as children had significantly higher depressive symptom scores than the adults who were not evacuated.

Studies were performed to explore the relationship between the BDNF genotype, maltreatment history, and a serotonin transporter gene [10, 21]. After analyzing saliva samples, results showed a significant three-way interaction between these variables. The severity of depression was predicted by the interaction between a functional polymorphism of the promoter region of the serotonin transporter and the BDNF val66met polymorphism. The vulnerability associated with these genotypes was only seen in those children that were mistreated [10].

Childhood abuse also has an effect on adults with Major Depressive Disorder (MDD) [22, 23]. Those with MDD who reported childhood abuse are more likely to have a current episode of MDD, more chronic MDD, increased symptom severity, and comorbid anxiety and alcohol use disorders, compared to those without histories of child abuse. The impact of childhood abuse on serum BDNF levels is dependent on the variation of BDNF polymorphism in those with MDD. In BDNF met carriers, having a history of childhood abuse is associated with reduced BDNF levels [24].

Address for correspondence: Leo Sher, M.D. James J. Peters Veterans' Administration Medical Center 130 West Kingsbridge Road Bronx, New York 10468, USA, E-mail: drleosher@gmail.com

Bipolar disorder

A history of childhood abuse also has an effect on bipolar disorder, mediated through BDNF levels. Bipolar patients with a history of traumatic events have lower BDNF levels and a more severe psychopathology compared to those without a history of traumatic events. Bipolar patients with a traumatic history have higher occurrences of alcohol abuse/dependence, anxiety comorbidity, and lower BDNF serum levels compared to those without a traumatic history [25].

Psychotic disorder

Preliminary data in a twin study suggests that BDNF genes may interact with psychosocial stress to create psychosis later on in life. There is an interaction between BDNF Val66Met and social stress [26]. BDNF Met carriers show more stress-induced paranoia, than those that are Val/Val carriers [27].

Suicide

The trauma of childhood physical and sexual abuse has repeatedly been reported as linked with suicidal behavior [28-30]. Adult women with a history of abuse are at an increased risk for developing depression, anxiety, substance abuse and suicidality [28]. In both clinical and community populations of adults who report childhood sexual and/or physical abuse suicidality is higher than in comparison groups who do not have a history of childhood abuse [29]. For example, Briere [31] found that 51% of sexual abuse victims (vs. 34% of non-abused participants) demonstrated a history of suicide attempts, and that 31% of victims (vs. 19% of non-abused individuals) reported self-harm ideation. Gutierrez [32] found that college-

aged women who had been abused as children claimed higher levels of suicidal ideation and felt less repulsion for death and more repulsion for life. Childhood abuse may also increase the likelihood of developing negative beliefs associated with suicide. Hopelessness is a robust predictor of suicide [33] and correlates with a history of childhood abuse [34]. Furthermore, it was found that hopelessness mediated the relation between a childhood abuse history and a history of suicide attempt in a cross-sectional sample [34].

BDNF function and a history of childhood abuse play roles in the frequency and lethality of suicide attempts [35-38]. The frequency of violent suicide attempts is higher in individuals that report severe sexual abuse and that carry the met BDNF allele [39]. The Val66Met allele of BDNF may influence the effects of childhood trauma in relation to the risk of suicide attempts, through its effects on serotonin neurons [40].

CONCLUSION

Multiple lines of evidence suggest that childhood abuse may affect the BDNF function and is associated with the development of psychiatric disorders in childhood, adolescence and adulthood. It is interesting to speculate that certain interventions, such as early exposure to complex environments (enrichment), handling, or treatment with DNA demethylases or histone deacetylase inhibitors, might be useful as treatment strategies for reversing harmful effects of early-life adversity. Further studies of the neurobiological effects of childhood abuse are needed to develop new therapeutic interventions.

REFERENCES:

- Blum R, Konnerth A. Neurotrophin-mediated rapid signaling in the central nervous system: mechanisms and functions *Physiology* (Bethesda) 2005;20:70-78.
- Finkbeiner S, Tavazoie SF, Maloratsky A, et al. CREB: a major mediator of neuronal neurotrophin responses. *Neuron* 1997;19(5):1031-1047.
- Poo MM. Neurotrophins as synaptic modulators. *Nat Rev Neurosci* 2001;2:24-32.
- Egan M, Kojima M, Callicott J, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 2003;112:257-269.
- Brent DA, Oquendo M, Birmaher B, et al. Familial pathways to early-onset suicide attempt: risk for suicidal behavior in offspring of mood-disordered suicide attempters. *Arch Gen Psychiatry* 2002;59:801-807.
- Fergusson DM, Woodward LJ, Horwood LJ. Risk factors and life processes associated with the onset of suicidal behaviour during adolescence and early adulthood. *Psychol Med* 2000;30:23-39.
- Anguelova M, Benkelfat C, Turecki G. A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter: II. Suicidal Behavior. *Mol Psychiatry* 2003;8:646-653.
- Savitz J, van der Merwe L, Stein DJ, et al. Genotype and childhood sexual trauma moderate neurocognitive performance: a possible role for brain-derived neurotrophic factor and apolipoprotein E variants. *Biol Psychiatry* 2007;62:391-399.
- Malberg JE, Eisch AJ, Nestler EJ, et al. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *J Neurosci* 2003;20:9104-9110.
- Kaufman J, Yang B, Douglas-Palumberi H, et al. Brain-derived neurotrophic factor-5-HTTLPR gene interactions and environmental modifiers of depression in children. *Biol Psychiatry* 2006;59:673-680.
- Teicher MH, Glod CA, Surrey J, et al. Early childhood abuse and limbic system ratings in adult psychiatric outpatients. *J Neuropsychiatry Clin Neurosci* 1993;5:301-306.
- De Bellis MD, Keshavan MS, Shifflett H, et al. Brain structures in pediatric maltreatment-related posttraumatic stress disorder: a sociodemographically matched study. *Biol Psych* 2002;52(11):1066-1078.
- Bremner JD, Vythilingam M, Vermetten E, et al. MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. *Am J Psychiatry* 2003;160:924-932.
- Teicher MH, Andersen SL, Polcari A, et al. The neurobiological consequences of early stress and childhood maltreatment. *Neurosci Biobehavioral Rev* 2003;27(1-2):33-44.
- Grassi-Oliveira R, Stein LM. Childhood maltreatment associated with PTSD and emotional distress in low-income adults: the burden of neglect. *Child Abuse and Neglect* 2008;32(12):1089-1094.
- Roth T, Lubin F, Funk A, et al. Lasting epigenetic influence of early-life adversity on the BDNF gene. *Biol Psychiatry* 2009;65:760-769.
- Fagioli M, Jensen C, Champagne F. Epigenetic influences on brain development and plasticity. *Curr Opin Neurobiol* 2009;19(2):207-212.
- Widom CS, DuMont K, Czaja SJ. A prospective investigation of major depressive disorder and comorbidity in abused and neglected children grown up. *Arch Gen Psychiatry* 2007;64(1):49-56.
- Weiss EL, Longhurst JG, Mazure CM. Childhood sexual abuse as a risk factor for depression in women: psychosocial and neurobiological correlates. *Am J Psychiatry* 1999;156:816-828.
- Pesonen AK, Räikkönen K, Heinonen K, Kajantie E, Forsén T, Eriksson JG. Depressive symptoms in adults separated from their parents as children: a natural experiment during World War II. *Am J Epidemiol* 2007;166(10):1126-33.
- Caspi A, Sugden K, Moffitt T, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 2003;301:386-389.
- Charney DS. Psychobiological mechanisms of resilience and vulnerability. *Am J Psychiatry* 2004;161:368-391.
- Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biol Psychiatry* 2001;49:1023-1039.
- Elzinga B, Molendijk M, Voshhaar R, et al. The impact of childhood abuse and recent stress on serum brain-derived neurotrophic factor and the moderating role of BDNF Val 66Met. *Psychopharmacology* 2011;214:319-328.
- Kauer-Sant'Anna M, Tramontina J, Andreazza A, et al. Traumatic life events in bipolar disorder: impact on BDNF levels and psychopathology. *Bipolar Disorders* 2007;9(1):128-135.
- Wichers M, Kenis G, Jacobs N, et al. The BDNF Val(66)<et x 5-HTTLPR x child adversity interaction and depressive symptoms: an attempt at replication. *Am J Med Genet B Neuropsychiatr Genet* 2008;147:120-123.
- Winkel R, Stefanis N, Myin-Germeys I. Psychosocial stress and psychosis. A review of the neurobiological mechanisms and the evidence for gene-stress interaction. *Schizophrenia Bulletin* 2008;34(6):1095-1105.
- Briere J, Runtz M. Suicidal thoughts and behaviors in former sexual abuse victims. *Can J Behav Sci* 1986;18(4):413-423.
- Santa Mina EE, Gallop RM. Childhood sexual and physical abuse and adult self-harm and suicidal behavior: a literature review. *Can J Psychiatry* 1998;43:793-800.
- Makhija N, Sher L. Childhood abuse, adult alcohol use disorders and suicidal behavior. *QJM* 2007;100(5):305-309.
- Briere J. The effects of childhood sexual abuse on later psychological functioning: defining a post-sexual abuse syndrome. *The Third National Conference on Sexual Victimization of Children*. Washington (DC); 1984.
- Gutierrez PM, Thakkar RR, Kuczen C. Exploration of the relationship between physical and/or sexual abuse, attitudes about life and death, and suicidal ideation in young women. *Death Studies* 2000;24:675-688.
- Beck AT, Brown G, Berchick RJ, et al. Relationship between hopelessness and ultimate suicide: a replication with psychiatric outpatients. *Am J Psychiatry* 1990;147(2):190-195.
- Meadows LA, Kaslow NJ. Hopelessness as mediator of the link between reports of a history of child maltreatment and suicidality in African American women. *Cogn Therapy and Res* 2002;26(5):657-674.
- Agerbo E, Nordentoft M, Mortensen PB. Familial, psychiatric, and socioeconomic risk factors for suicide in young people: nested case-control study. *BMJ* 2002;325:1-5.
- Dube SR, Anda RF, Felitti VJ, et al. Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: findings from the Adverse Childhood Experiences Study. *JAMA* 2001;286:3089-3096.
- Dwivedi Y, Rizavi HS, Conley RR, et al. Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects. *Arch Gen Psychiatry* 2003;60:804-815.
- Karege F, Vaudan G, Schwald M, et al. Neurotrophin levels in postmortem brains of suicide victims and the effects of antemortem diagnosis and psychotropic drugs. *Brain Res Mol Brain Res* 2005;136:29-37.
- Iga JI, Ueno SI, Yamauchi K, et al. The Val66Met polymorphism of the brain-derived neurotrophic factor gene is associated with psychotic features and suicidal behavior in Japanese major depressive patients. *Am J Med Genet B Neuropsychiatr Genet* in press.
- Perroud N, Courtet P, Vincze I, et al. Interaction between BDNF Val66Met and childhood trauma on adult's violent suicide attempt. *Genes, Brain and Behavior* 2008;7(3):341-322.