Please cite this article in press as: Ignácio ZM et al. Epigenetic and epistatic interactions between serotonin transporter and brain-derived neurotrophic factor genetic polymorphism: Insights in depression. Neuroscience (2014), http://dx.doi.org/10.1016/j.neuroscience.2014.06.036

Neuroscience xxx (2014) xxx–xxx

REVIEW

EPIGENETIC AND EPISTATIC INTERACTIONS BETWEEN SEROTONIN TRANSPORTER AND BRAIN-DERIVED NEUROTROPHIC FACTOR GENETIC POLYMORPHISM: INSIGHTS IN DEPRESSION

Q1 Z. M. IGNÁCIO,[a,c] G. Z. RÉUS,[a,b]* H. M. ABELAIRA[a] AND J. QUEVEDO[a,b]

[a] *Laboratório de Neurociências, Programa de Pós-Graduação em Ciências da Saúde, Unidade Acadêmica de Ciências da Saúde, Universidade do Extremo Sul Catarinense, Criciúma, SC, Brazil*

[b] *Center for Experimental Models in Psychiatry, Department of Psychiatry and Behavioral Sciences, Medical School, The University of Texas Health Science Center at Houston, Houston, TX, USA*

[c] *Laboratório de Fisiologia, Farmacologia, Patologia e Psicopatologia, Campus Chapecó, Universidade Federal da Fronteira Sul – UFFS, Chapecó, SC, Brazil*

Abstract—Epidemiological studies have shown significant results in the interaction between the functions of brain-derived neurotrophic factor (BDNF) and 5-HT in mood disorders, such as major depressive disorder (MDD). The latest research has provided convincing evidence that gene transcription of these molecules is a target for epigenetic changes, triggered by stressful stimuli that starts in early childhood and continues throughout life, which are subsequently translated into structural and functional phenotypes culminating in depressive disorders. The short variants of 5-HTTLPR and BDNF-Met are seen as forms which are predisposed to epigenetic aberrations, which leads individuals to a susceptibility to environmental adversities, especially when subjected to stress in early life. Moreover, the polymorphic variants also feature epistatic interactions in directing the functional mechanisms elicited by stress and underlying the onset of depressive disorders. Also emphasized are works which show some mediators between stress and epigenetic changes of the 5-HTT and BDNF genes, such as the hypothalamic–pituitary–adrenal (HPA) axis and the cAMP response element-binding protein (CREB), which is a cellular transcription factor. Both the HPA axis and CREB are also involved in epistatic interactions between polymorphic variants of 5-HTTLPR and Val66Met. This review highlights some research studying changes in the epigenetic patterns intrinsic to genes of 5-HTT and BDNF, which are related to lifelong environmental adversities, which in turn increases the risks of developing MDD. © 2014 Published by Elsevier Ltd. on behalf of IBRO.

Key words: lifelong stress, BDNF, serotonin transporter, polymorphism, epigenetic, depression.

Contents

INTRODUCTION

Major depressive disorder (MDD) is a serious and recurrent illness linked to diminished role functioning and quality of life, medical morbidity, and mortality (Hays et al., 1995; Spijker et al., 2004; Üstün et al., 2004). In addition, the pathogenesis of depression and the action mechanisms of antidepressant drugs currently available are not yet clearly understood (Wong and Licinio, 2001; Leuchter et al., 2010).

Multiple episodes of maltreatment during childhood, such as sexual abuse, physical neglect and family violence were correlated with an increased vulnerability to depression in adulthood (Vranceanu et al., 2007). Nevertheless, MDD seems to result from a complex interaction between multiple inherited genetic factors and

*Correspondence to: G. Z. Réus, Department of Psychiatry and Behavioral Sciences, Center for Experimental Models in Psychiatry, Medical School, The University of Texas Health Science Center at Houston, Houston, TX, USA.
E-mail address: gislainezilli@hotmail.com (G. Z. Réus).

Q2 *Abbreviations:* 5-HT, serotonin; ACTH, adrenocorticotropic hormone; BDNF, brain-derived neurotrophic factor; BLA, basolateral amygdala; CpG, cytosine phosphate guanosine; CREB, cAMP response element-binding protein; GR, glucocorticoid receptor; HAT, histone acetyltransferase enzymes; HDAC, histone deacetylase enzyme; HPA, hypothalamic–pituitary–adrenal; LTP, long-term potentiation; MDD, major depressive disorder; mPFC, medial prefrontal cortex; PFC, prefrontal cortex; SERT, serotonin transporter; SNP, single-nucleotide polymorphism; SSRI, selective serotonin reuptake inhibitor; trkB, tyrosine kinase B.

http://dx.doi.org/10.1016/j.neuroscience.2014.06.036
0306-4522/© 2014 Published by Elsevier Ltd. on behalf of IBRO.

subsequent exposure to a wide variety of lifelong adverse environmental events (aan het Rot et al., 2009).

Genetic epidemiological studies have assembled convincing evidence that depression and other psychiatric disorders are substantially influenced by genetic factors, and that the genetic component is highly complex, polygenic and epistatic. The idea that genetic traits are a liability factor to disease also supports the hypothesis that a genetic predisposition to stress in critical stages of development may result in a neurobiological phenotype which is vulnerable to stress and may lower the threshold of an individual to the development of depression when exposed to additional stress (Lesch, 2004). The interaction between gene and environment as predictors for the development of MDD has been the subject of many recent studies, taking into account that the adversities of life increase the risk of psychiatric disorders in people with certain polymorphic variants of genes involved in the control of mood (Hariri and Holmes, 2006).

5-HTTLPR, a genetic polymorphism in humans, is associated with changes in the expression and function of the serotonin transporter (SERT), and implicated in some psychiatric disorders, as well as in MDD (Ramasubbu, 2003). Besides the reduced transcriptional activity, researches have observed that the short variant of the polymorphism is related to a phenotype with increased anxiety and increased amygdala response to fearful stimuli (Hariri et al., 2002, 2005). In addition, the research showed a high activation of the amygdala and hippocampus in individuals who experienced lifelong stress (Canli et al., 2006), compared with those homozygous for the "L" allele.

Another genetic polymorphism that confers differences in the reactions of individuals to aversive environmental stimuli is the single-nucleotide polymorphism (SNP) of the human BDNF (brain-derived neurotrophic factor) gene, which substitutes a valine for a methionine at position 66 in the prodomain of BDNF (Val66Met) (Sarchiapone et al., 2008). Studies have shown that homozygous and heterozygous humans and other animals, which have a Met allele, are more susceptible to lifelong adverse environmental effects and are resistant to treatment with antidepressants (Jiang et al., 2005; Chen et al., 2006). The Met-BDNF variant is known to have lower mRNA transcription and a smaller release of BDNF protein in the hippocampus and other brain structures (Egan et al., 2003). Moreover, the underlying structural and functional mechanisms and antidepressant therapy appears to depend, at least in part, on the brains' plasticity promoted by BDNF (Lyons et al., 1999; Sairanen et al., 2005; Bath et al., 2012). Although the effects of various classes of antidepressants are acute in their sites of action, their therapeutic benefits require chronic drug administration. These drug characteristics suggest that the response to chronic treatment with antidepressants requires structural and functional adaptations in the affected nervous system regions, notably in the hippocampus. Structural plasticity, neurogenesis and increases in the numbers of mossy fibers within the hippocampus may be involved in responses to chronic treatment, as well as with electroconvulsive therapy and drugs (Gombos et al., 1999; Vaidya et al., 1999a,b; Malberg et al., 2000).

A noteworthy point is that 5-HTTLPR and Val66Met polymorphisms have epistatic effects, and variant BDNF-Met and S-5-HTTLPR exhibit synergism in directing the behavioral phenotype associated with MDD in patients undergoing environmental adversities throughout life (Kaufman et al., 2006; Clasen et al., 2011). The interaction of genetic polymorphisms and environmental factors suggest that some polymorphic variants are more susceptible to epigenetic changes, and therefore more prone to developing psychiatric disorders, such as MDD. For example, S-5-HTTLPR exhibited a tendency toward increased methylation of CpG islands associated with the 5-HTT gene and also MDD (Philibert et al., 2008). Another feature that makes the interpretation of the results complex and challenging is that epigenetic patterns undergo changes according to the differing brain regions, and thus confer differences in the expression of mRNA and proteins between the limbic structures involved in behaviors that are influenced by stress (Lagopoulos and Bennett, 2014).

The aim of this review is to analyze the survey data that show epigenetic alterations involved in the structural and functional variations of SERT and BDNF in humans and other animals subjected to lifelong environmental adversities. A special focus will be given to the epistatic interactions between 5-HTT and BDNF genes, and more so to the polymorphic variants, 5-HTTLPR and Val66Met. In addition, this review also includes a consideration for the involvement of the hypothalamic–pituitary–adrenal (HPA) axis and other mechanisms that mediate the functions of SERT and serotonin, as well as to BDNF in the limbic structures involved in the manifestations of anxiety and depression.

SEROTONIN (5-HT) AND SERT POLYMORPHISM

5-HT is a major neurotransmitter in the mammalian central nervous system, and is released in various central nervous system areas from specific neurons whose cell bodies are almost exclusively located in the raphe nuclei of the brainstem, and in the innervate multiple cortical regions. 5-HT modulates various physiological activities, including; thermoregulation, cardiovascular and respiratory functions, food intake, the sleep–wake cycle, nociception, cognition and sexual behavior, as well as a wide repertoire of emotional behaviors (Hoyer et al., 2002). In addition to their prominent role as a neurotransmitter, 5-HT plays an important role in brain development by regulating cell survival and synaptogenesis (Gaspar et al., 2003).

The removal of 5-HT from the synaptic cleft is mediated by a single protein, the SERT, which determines the magnitude and duration of the serotonergic responses, and therefore plays a key role in 5-HT neurotransmission (Lesch and Mossner, 1998). SERT is a membrane protein that is responsible for serotonin uptake from the extracellular medium in synaptic clefts, into the pre-sympathetic neuronal terminal,

Please cite this article in press as: Ignácio ZM et al. Epigenetic and epistatic interactions between serotonin transporter and brain-derived neurotrophic factor genetic polymorphism: Insights in depression. Neuroscience (2014), http://dx.doi.org/10.1016/j.neuroscience.2014.06.036