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Possible role of adrenomedullin and nitric oxide in major depression

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ABSTRACT

Adrenomedullin (ADM) and nitric oxide (NO) have been implicated in the pathogenesis of certain psychiatric disorders such as schizophrenia and bipolar disorder. ADM induces vasorelaxation by activating adenylate cyclase and stimulating the release of NO. These two molecules are known to influence cerebral activity. In this study, we aimed to examine the serum levels of ADM and NO in patients with major depression (MD). We enrolled 50 patients with MD and 50 healthy control subjects. The diagnosis of MD was established on the basis of a structured clinical interview using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). The severity of depressive symptoms was evaluated using Hamilton's 17-item Depression Rating Scale. The mean serum levels of ADM and NO in patients with MD were significantly higher than those in healthy subjects ($p = 0.001$, for both). The severity of psychomotor retardation in patients with MD was significantly correlated with the ADM ($r = 0.37$, $p = 0.007$) and NO levels ($r = 0.29$, $p = 0.038$). The patients with obvious psychomotor retardation had significantly higher levels of ADM and NO than did the patients with no psychomotor retardation ($p = 0.025$, $p = 0.030$). A significantly positive correlation was found between ADM and NO levels in patients with MD ($r = 0.79$, $p = 0.001$). Serum levels of ADM and NO levels were not correlated with the severity or duration of depression or depressive symptoms (except psychomotor retardation). In conclusion, our study indicates that serum levels of ADM and NO are elevated in patients with MD and that increased serum levels of ADM and NO may be associated with psychomotor retardation. The ADM–NO system may serve as a new target in the treatment of patients with MD and psychomotor retardation.

1. Introduction

Major depression (MD) is a biopsychosocial disorder. Monoamine neurotransmission is hypothesized to play a significant role in the pathogenesis of depression (Chopra et al., 2011). However, the potential role of other possible factors such as nitric oxide (NO) and adrenomedullin (ADM) are under investigation. NO is suggested to play a role in this pathogenesis since it was found that interferon induces depression by evoking type II NO synthase (NOS) gene expression (McDonald et al., 1987). Similarly, NOS inhibitors exhibit antidepressant-like properties (Joca and Guimarães, 2006). In addition, paroxetine (Finkel et al., 1996), venlafaxine and bupropion (Dhir and Kulkarni, 2011) affect the signaling pathway of L-arginine-NO-cyclic guanosine monophosphate (cGMP).

NO is synthesized from L-arginine by an NOS enzyme. NO is a highly diffusible gas that can easily penetrate the biological membranes, and it is present in peripheral–central tissues and neurons (Akyol et al., 2004). The levels of NO in the cerebrospinal fluid (CSF) and serum were found to be moderately correlated in patients with acute brain injury (Rejdak et al., 2003). NO is the only endogenous molecule that functions as a cytoprotective and cytotoxic molecule (Akyol et al., 2004). It also plays a role in regulating neurotransmitter release by Ca^{2+} dependent processes (Ohkuma and Katsura, 2001) and -methyl-D-aspartate receptor stimulation (Lin et al., 1995).

Previous studies have reported increased levels of NO (Kim et al., 2006; Suzuki et al., 2001; Talarowska et al., 2012), while others have shown decreased (Chrapko et al., 2004; García et al., 2011; Selley, 2004) or similar (Herken et al., 2007; Kim et al., 2006) levels of NO in patients with MD as compared to healthy groups. Decreased plasma level of NO might increase the risk of coronary heart disease (Chrapko et al., 2004), influence the release of neurotransmitters (Selley, 2004), and reflect a decreased NO production in central nervous system (CNS) (García et al., 2011). On the other hand, increased plasma level of NO might be associated with suicide attempts (Kim et al., 2006) or with the severity of depressive symptoms, impairment of visual–spatial working memory (Talarowska et al., 2012), and reflect an increased NO production in CNS (Suzuki et al., 2001) in patients

Abbreviations: ADM, adrenomedullin; NO, nitric oxide; MD, major depression; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; NOS, nitric oxide synthase; cGMP, cyclic guanosine monophosphate; CSF, cerebrospinal fluid; CNS, central nervous system; HDRS, Hamilton's 17-item Depression Rating Scale; SE, standard error; HPA, hypothalamus pituitary adrenal.

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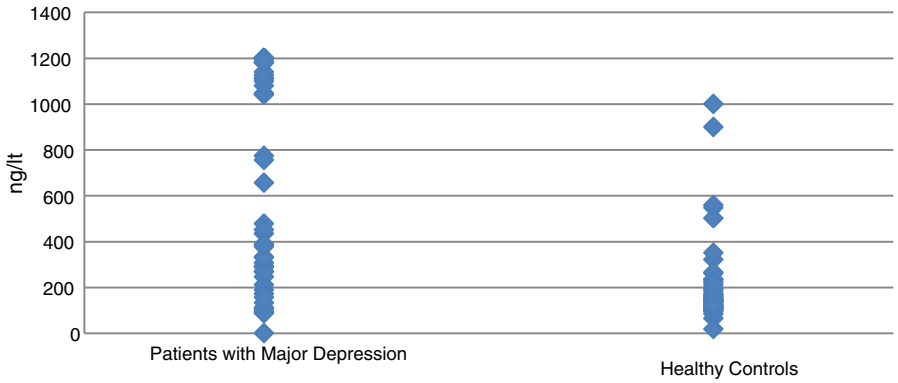

Fig. 1. Scatter graph of individual variables for serum level of ADM in patients with major depression compared with healthy control subjects.

with MD. These conflicting results can be explained by methodological differences of the aforementioned studies.

ADM is a recently characterized hormone that is produced by many different cell types in almost all tissues of the body (Hinson et al., 2000; Kitamura et al., 1993). It is present in the peripheral circulation, the CSF and the CNS and its cellular components (Díaz et al., 2003; Ichiki et al., 1994). It is able to cross the intact blood–brain barrier (Kastin et al., 2001). ADM binding sites and ADM gene have been identified in the brain (Díaz et al., 2003). Its functions in the brain under normal physiological conditions include maintenance of the blood brain barrier, autoregulation, and regulation of the hypothalamus–pituitary–adrenal (HPA) axis (Armstead et al., 2010; Honda et al., 2006; Yuksel et al., 2002).

ADM induces vasorelaxation by activating adenylate cyclase and by stimulating the release of NO (Richards et al., 1996). Both NO and ADM are involved in the regulation of the HPA axis and central autonomic functions (Bernstein et al., 1998; Shan and Krukoff, 2001). MD is associated with HPA axis dysregulation (Brown et al., 1999) and reduced hippocampal volumes (MacQueen and Frodl, 2011). NO participates in synaptic plasticity in the hippocampus (Bartus et al., 2013), and ADM reduces intracellular calcium concentration in cultured hippocampal neurons that may have cytoprotective roles in the hippocampus (Ji et al., 2005).

Increased plasma levels of NO and ADM were found in patients with schizophrenia, bipolar disorder, and autism; (Savas et al., 2002; Zoroglu et al., 2002; Zoroğlu et al., 2003) however, no clear causal relationship between levels of NO or ADM and schizophrenia, autism and bipolar disorder have been suggested.

This is the first study in which ADM and NO levels were assessed in patient with MD. The significance of ADM and NO in the first episode of MD is unclear. The present study aimed to investigate the levels of ADM and NO in patients who had their first episode of MD. In addition, we aimed to determine the possible association of between the depressive symptoms and the duration of depression with ADM and NO levels. We also aimed to examine the relation between ADM and NO in MD.

2. Materials and methods

The study was performed in accordance with the Declaration of Helsinki. It was approved by the ethics committee of Suleyman Demirel University Medical Faculty. A complete description of the study was given to each participant, and written informed consents were obtained from all.

2.1. Patients

The study group included 50 patients who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for major depressive disorder and 50 healthy controls between April 2012 and October 2012. The age of all participants ranged from 25 to 55 years. All subjects were recruited from a psychiatry outpatient clinic

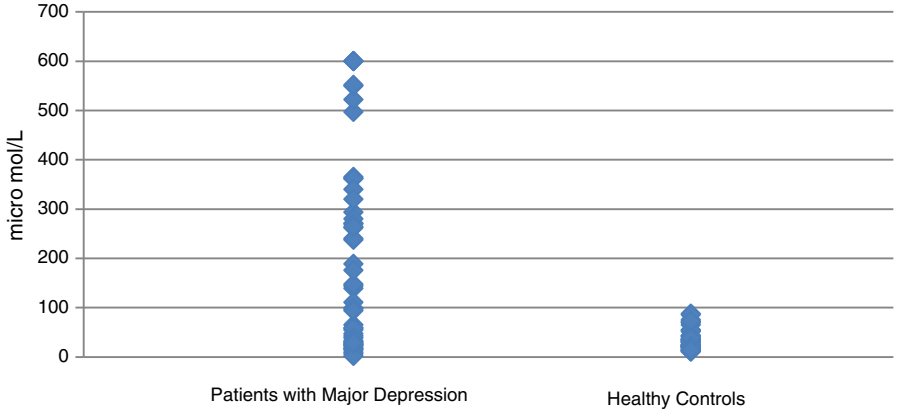

Fig. 2. Scatter graph of individual variables for serum level of NO in patients with major depression compared with healthy control subjects.