ELSEVIER

Archives of Medical Research 38 (2007) 247–252

Archives of Medical Research

ORIGINAL ARTICLE

Adenosine Deaminase, Nitric Oxide, Superoxide Dismutase, and Xanthine Oxidase in Patients with Major Depression: Impact of Antidepressant Treatment

Hasan Herken,[a,b] Ahmet Gurel,[c] Salih Selek,[a] Ferah Armutcu,[c] Murat Eren Ozen,[d] Mahmut Bulut,[a] Ozlem Kap,[a] Mehmet Yumru,[a] Haluk Asuman Savas,[a] and Omer Akyol[e,f]

[a]*Department of Psychiatry, School of Medicine, Gaziantep University, Gaziantep, Turkey*
[b]*Department of Psychiatry, School of Medicine, Pamukkale University, Denizli, Turkey*
[c]*Department of Clinical Biochemistry, School of Medicine, Karaelmas University, Zonguldak, Turkey*
[d]*Department of Psychiatry, Nobel Private Medical Center, Adana, Turkey*
[e]*Department of Clinical Biochemistry, School of Medicine, Inonu University, Malatya, Turkey*
[f]*Department of Clinical Biochemistry, School of Medicine, Hacettepe University, Ankara, Turkey*

Received for publication March 8, 2006; accepted October 4, 2006 (ARCMED-D-06-00093).

Background. There has been much evidence in recent years that free oxygen radicals and nitric oxide (NO) may play an important role in the pathophysiology of neuropsychiatric disorders. In this study, we aimed to investigate whether NO, xanthine oxidase (XO), superoxide dismutase (SOD), and adenosine deaminase (ADA) levels are associated with major depression (MD) and to evaluate the impact of antidepressant treatments on NO, SOD, ADA and XO levels in MD.

Methods. Thirty-six patients who were diagnosed as MD according to DSM-IV criteria and 20 healthy controls were included. The serum levels of NO, XO, SOD, and ADA were measured by spectrophotometric methods both in patients and controls. Patients were treated with antidepressant drugs for 8 weeks. All patients were assessed by Hamilton Depression Rating Scale (HDRS) both before and after antidepressant treatment.

Results. ADA and XO levels of the patients were significantly higher than the controls. SOD level of the patients was significantly lower than the controls. Although NO levels of the patients were higher than the controls, the difference was not statistically significant. There was no correlation between HDRS and the parameters studied (SOD, ADA, XO, and NO) of the patients. After 8 weeks of antidepressant treatment, ADA and SOD activities were increased, whereas NO and, XO levels decreased significantly.

Conclusions. ADA, XO, and SOD activity may have a pathophysiological role in MD and may predict prognosis of MD. Activity of these enzymes may be used to monitor effects of the antidepressant treatment. © 2007 IMSS. Published by Elsevier Inc.

Key Words: Depression, Adenosine deaminase, Xanthine oxidase, Nitric oxide, Superoxide dismutase, Antidepressant.

Introduction

There is mounting evidence that reactive oxygen species (ROS) are involved in initiation and development of many different forms of human pathologies. Recently, ROS have been suggested to play a role in major depression (MD) (1). Predominantly superoxide, hydroxyl ion and nitric oxide are produced under physiological conditions during aerobic metabolism (2). ROS are produced by many different ways, such as activation of phagocytes and the general immune system, lipid peroxidation, electron transport system in mitochondria, ischemia and trauma (3). ROS can be evaluated

Address reprint requests to: Hasan Herken, M.D., Department of Psychiatry, Medical Faculty of Pamukkale University, Doktorlar Caddesi No. 42, 20100 Denizli, Turkey; E-mail: drhasanherken@yahoo.com

0188-4409/07 $–see front matter.
doi: 10.1016/j.arcmed.2006.10.005

indirectly by the measurement of some antioxidant enzyme levels such as superoxide dismutase (SOD), catalase (CAT) or glutathione peroxidase (GSH-Px).

A major source of radicals in biological systems is dioxygen (O_2). The radicals originated from molecular oxygen are generally named as ROS. One of the most important enzymatic sources of superoxide anion radical (O_2^-) is xanthine oxidase (XO). This enzyme is located in all of the nucleated cells and catalyzes the conversion of hypoxanthine and xanthine to uric acid, the rate-limiting step in purine nucleotide catabolism. Current interest focused on XO stems from its proposed role in postischemic reperfusion injury (4); in such cases, the activity of this O_2^- producer enzyme may increase through the proteolytic conversion of xanthine dehydrogenase to XO and produce an enormous amount of O_2^-.

Adenosine deaminase (ADA) has been accepted as an important enzyme in the maturation and function of T lymphocytes. Its main physiological activity is related to lymphocytic proliferation and differentiation. The enzyme activity increases substantially during mitogenic and antigenic responses of lymphocytes, and conversely, lymphocyte blastogenesis is inhibited by ADA inhibitors. It is, therefore, known that ADA activity is higher in T cells than B lymphocytes. As an indicator of cellular immunity, plasma activity of this enzyme has been suggested to be increased in inflammatory diseases, which causes a cell-mediated immune response (5). XO plays a role in purine metabolism, particularly in the last reactions of the pathway. Thus, it may be useful to evaluate serum activities of both enzymes in MD (6).

Nitric oxide (NO) is a soluble gas produced by the activity of an enzyme that is present in peripheral tissues and in neurons. The generation of NO following NMDA or norepinephrine receptor activation seems to be important in the context of central nervous system (CNS) pathology. NO is known to be both a ROS and neurotransmitter in the CNS and peripheral nervous system. Although NO is described as an atypical neurotransmitter in the nervous system, it seems more appropriate to consider it a second messenger (7) or hormone (8). Most of the effects of NO are mediated through activation of the enzyme guanylate cyclase, which produces guanosine 3′,5′-cyclic monophosphate (cGMP) (8). Elevation of cGMP then triggers a cascade of intracellular events that eventually cause decreased intracellular free calcium. It has been implicated in a number of physiological functions such as noradrenaline and dopamine release, memory and learning, regulation of the cerebrovascular system, modulation of wakefulness, modulation of nociception, olfaction, food intake and drinking, and also in certain pathologies like Alzheimer's and Huntington's diseases, cerebral ischemia and stroke. The involvement of NO in depression has also been proposed (9,10).

Bilici et al. (1) suggested that free radical-mediated neuronal damage has a role in the pathophysiology of depression. Oxidation of catecholamines such as dopamine and norepinephrine (NE) by monoamine oxidase (MAO) may result in increased radical burden. Controlled studies show that especially platelet MAO enzyme activity increases in patients with MD (36). It is also known that some patients with MD respond to MAO inhibitory treatment. An association between increased monoamine oxidation and overproduction of ROS has been suggested (35). Inhibition of MAO activity seems to have neuroprotective actions (37). Bilici et al. (1) also suggested that antioxidative enzyme activities might be used to monitor antidepressant treatment.

In some brain diseases some metabolic parameters are used for diagnose. Prolactin and/or creatine kinase levels may be increased just after convulsions in epilepsy. Yet, there are no diagnostic blood tests for psychiatric disorders. Therefore, in the present study, we aimed to assess whether plasma levels of nitrite (a metabolite of NO), XO, SOD, and ADA levels were associated with MD and to also evaluate the effect of antidepressant treatment on these free radicals in MD. Not only a brain disease but also a syndrome, MD may be involved with other systems such as oxidative metabolism.

Materials and Methods

The study was comprised of 36 patients (19 females, 17 males; age range: 17–62 years) who had applied to Gaziantep University School of Medicine, Department of Psychiatry, and were diagnosed as MD according to DSM-IV criteria (11). Written informed consent to participate in the study was obtained from the subjects after they were thoroughly informed about the research details. Approval of the study was given by the ethics committee of the Gaziantep University Hospital. Subjects had ceased all medications for at least the previous 2 weeks. Each patient underwent diagnostic evaluation by one psychiatrist on the basis of a semi-structured interview to determine any pathology according to DSM-IV. Patients with any kind of axis I comorbidity were excluded. All subjects were evaluated by a semi-structured questionnaire, which was arranged in accordance with the clinical experience and available information sources. Gender, age, marital status, educational condition, socioeconomic status and duration of illness were noted. Additionally, the course of the treatment was evaluated by Hamilton Depression Rating Scale (HDRS) (12).

Exclusion criteria were alcohol and substance abuse or dependence, presence of severe organic disorders, use of any antioxidants like vitamin E or C, presence of epilepsy or severe neurological disorder, presence of infectious and viral disease, and excessive obesity.

Selective serotonin reuptake inhibitors were given to all patients. MD patients were treated with fluoxetine 20 mg/day ($n = 11$); citalopram 20 mg/day ($n = 10$); sertraline 50 mg/day ($n = 8$); fluvoxamine 150 mg/day ($n = 7$). HDRS