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Nitric Oxide Branch of Arginine Metabolism in Depression: Effect of Venlafaxine

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ABSTRACT

Objectives

Major Depressive Disorder is an established independent risk factor for cardiovascular disease, but the precise pathophysiological mechanism remains obscure. The nitric oxide branch of arginine metabolism has been linked to vascular homeostasis.

Methods

Five plasma biomarkers of the nitric oxide branch of arginine metabolism were quantified in depressed patients (n = 22) and healthy controls (n = 17): total nitrite, nitrotyrosine, asymmetric dimethylarginine, agmatine, and myeloperoxidase. Thirteen of the depressed patients were restudied after 4-8 weeks of mood normalization with venlafaxine, a mixed serotonin/norepinephrine reuptake blocker.

Results

None of the biomarkers were altered in depressed patients compared to controls. However, treatment reduced agmatine and myeloperoxidase levels (p=0.02 each). A clear but non-significant rise in total nitrite and nitrotyrosine was also observed at week-4.

Conclusions

Despite no changes at pre-treatment, the reductions in agmatine and myeloperoxidase may result from serotonin and/or noradrenaline changes occurring with venlafaxine antidepressant therapy.

Keywords: Nitric oxide, Arginine, Nitrotyrosine, Agmatine, Depression, Antidepressants, Venlafaxine, Cardiovascular Disease

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INTRODUCTION

Major Depressive Disorder (MDD) is recognized as an independent risk factor for cardiovascular disease (CVD).[1] The cardiovascular burden that depression imposes towards CVD is clear, documented by every long-term prospective study we could find (now numbering more than 25 studies) where psychological predictors have been investigated[2-6], as well as by most retrospective studies[7] (for complete review see Lett et al, 2004[1]). A relative risk of approximately 2.0 has been established for developing cardiac disease in those patients carrying a diagnosis of major depression.[8] Patients who experience clinical depression following myocardial infarction have an even higher relative risk for subsequent myocardial infarction and cardiac mortality within 6-12 months (RR = 1.7 - 3.5+).[9, 10] No unifying biological mechanism has yet been able to fully explain the link of MDD leading to CVD. Platelet hyperactivity, endothelial damage, and hypothalamic-pituitary-adrenal axis dysregulation have all been suggested as contributing factors.[11, 12]

Arginine (arg) is a nutritionally essential amino acid of critical importance to vascular tone and hemodynamics.[13] *Arg* metabolism is highly regulated and follows co-expressed competitive metabolic branches in humans.[13] The bulk of *arg* is normally metabolized by arginases, leading to ornithine and its downstream products (principally the polyamines).[14] Additional branches of *arg* metabolism are mediated by: (a) nitric oxide synthases (NOSs) leading to production of nitric oxide (NO) and downstream nitrogenous compounds, (b) *arg* decarboxylase leading to agmatine and its related byproducts, and (c) *arg*:glycine amidinotransferase leading to guanidinoacetic acid, the immediate precursor of creatine. Each enzyme is highly regulated under physiological or pathological conditions.[13] The production of NO is often placed "center stage" due its key role in vascular homeostasis[15] (Fig. 1). Decreased metabolism of arg to form NO (plus forming citrulline as byproduct) has also been associated with cardiovascular risk.[16] Rising NO and nitrate levels are the main actions of the therapeutic agent, nitroglycerine.[17] Two stable NO metabolites, nitrite and nitrate, collectively designated NOx, also have healthy vascular properties. However, a further downstream product, peroxynitrite, is a reactive metabolite that is cytotoxic.[18] Myeloperoxidase is the main plasma enzyme that oxi-