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

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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 investigated2-6, as well as by most retrospective studies7 (for complete review see Lett et al, 20041). 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+).8,9 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.15 The production of NO is often placed “center stage” due its key role in vascular homeostasis15 (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-