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Research report

Serum methylarginines and incident depression in a cohort of older adults

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ABSTRACT

Background: Methylarginines are endogenous nitric oxide synthase inhibitors that have been implicated in depression. This study measured serum concentrations of L-arginine, asymmetric (ADMA) and symmetric (SDMA) dimethylarginine in a representative sample of older community-dwelling adults and determined their association with incident depression over 6-years of follow-up.
Methods: Data on clinical, lifestyle, and demographic characteristics, methylated arginines, and L-arginine (measured using LC–MS/MS) were collected from a population-based sample of older Australian adults (Median age=64 years; IQR=60–70) from the Hunter Community Study. Clinical depression was defined as a Centre for Epidemiological Studies Depression Scale (CES-D) score ≥16 or use of antidepressant medications.
Results: In adjusted analyses ADMA (Q3), SDMA (Q2), L-arginine (Q2), gender, and asthma remained statistically significant predictors of incident depression at follow-up. Quartile 3 of ADMA concentration was associated with 3.5 times the odds of developing depression compared with Q1 (OR=3.54; 95% CI: 1.25–9.99).
Limitations: Limitations of our study include the use of a subjective self-reported questionnaire tool using a dichotomous cut-off, together with use of antidepressant medications, as proxies for clinical depression. Moreover, similarly to most population studies on methylated arginines, the measurement of ADMA and SDMA from blood does not necessarily reflect intracellular concentrations of these compounds. Finally, there

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were no measures of nitric oxide metabolites to determine if these levels were altered in the presence of elevated methylarginines and depression.
Conclusions: After adjusting for clinical, demographic, biochemical, and pharmacological confounders, higher serum ADMA was independently associated with incident depression at 6-years follow-up.

1. Introduction

Depression contributes significantly to the global burden of disease with the lifetime prevalence of major depressive disorder reported to vary from 3% in Japan to 17% in the USA (World Health Organisation, 2001). It is estimated that by the year 2020 it will be the second leading cause of disability worldwide (World Health Organisation, 2012). Interventions for depression include psychotherapy, or pharmacotherapy, which is costly and may carry significant side-effects. Furthermore, current estimates suggest that these therapies are ineffective in >30% of cases (Souery et al., 2006). Hence, there is a need to identify new modifiable risk factors and prevention strategies.

Nitric oxide (NO) plays an important role in neurotransmission, neuromorphogenesis, neurosecretion, synaptic plasticity, and regulation of gene expression, as well as modulating sexual and aggressive behaviours, learning, appetite, and perception of pain (Calabrese et al., 2007). NO has also been shown to exert permissive or preventive effects on the hypothalamic–pituitary–adrenal (HPA) axis (stress axis) in response to the type of stressor (Mancuso et al., 2010). In the circulatory system NO induces vasodilation, thereby regulating vascular tone and blood flow and also inhibits platelet aggregation and monocyte adhesion to the endothelial surface (Cannon, 1998).

In human endothelial cells, NO is synthesised from the conversion of the amino acid L-arginine to L-citrulline by the constitutive enzyme, endothelial NO synthase (eNOS) (Cannon, 1998). Endothelial NOS is also expressed by vascular endothelial cells in the brain where it regulates cerebral blood flow; however eNOS immunoreactivity has also been detected in the cerebellum, olfactory bulb, cerebellar cortex, dentate gyrus of the hippocampus, and the bed nucleus of the stria terminalis (Bredt et al., 1990). In the central and peripheral nervous systems the synthesis of NO is predominantly accomplished by neuronal NO synthase (nNOS). nNOS has been found in neuronal populations of the cerebral cortex, striatum, hippocampus (CA1 region and dentate gyrus), the lateral dorsal and pedunculopontine tegmental nuclei, the cerebellum (granule cells), and the hypothalamic paraventricular nucleus (PVN) and supraoptic nucleus (SON) (Dawson and Snyder, 1994). Neuronal NOS immunoreactivity has also been detected in astrocytes, cerebral blood vessels, and the posterior pituitary (Dawson and Snyder, 1994; Guix et al., 2005). An inducible nitric oxide synthase (iNOS) is also expressed in nervous tissue in response to inflammation, viral infection, or trauma producing large amounts of NO relative to that produced by eNOS and nNOS (Dawson and Dawson, 1996).

NO synthesis and/or availability appears to be altered in depression, however the evidence is conflicting (Dhir and Kulkarni, 2011). Some studies have reported reduced concentrations of the NO metabolites, nitrate and nitrite, in the plasma of depressed patients (Chrapko et al., 2005, 2004; Srivastava et al., 2002) compared with healthy controls while other studies have demonstrated higher concentrations (Kim et al., 2006; Lee et al., 2006; Suzuki et al., 2001). However, the validity of these studies has been questioned since patients were either receiving drug therapy that may have altered the synthesis of NO or they had comorbid psychiatric conditions (e.g. anxiety, post-traumatic stress disorder) that may have affected per se the synthesis of NO and its metabolites. In addition, laboratory methods used to measure plasma nitrate and nitrite differed across studies.

Immunohistochemical studies have revealed increased levels of nNOS mRNA and protein and enhanced nNOS activity in the PVNs of rats exposed to stressful conditions, such as forced swimming, immobilisation, and endotoxin administration (Lee et al., 1995; Kishimoto et al., 1996; Tsuchiya et al., 1997; Kostoglou-Athanassiou et al., 1998; Sanchez et al., 1999). Hence, alteration of brain nNOS (and possibly eNOS) activity and NO synthesis within this axis may be linked with an impaired response to stress and the development of depression.

Given the importance of NO in vascular function, neurotransmission, and the HPA axis, a disturbed synthesis and/or availability of NO might contribute to the development of affective disorders such as depression. The methylarginine asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of NOS that inhibits the activity of all three NO synthase isoforms, and has been shown to reduce NO concentrations in numerous cell types (Fliser, 2005; Segarra et al., 2001, 1999; Selley, 2004; Cardounel et al., 2005). Elevated plasma ADMA concentrations have been consistently demonstrated in individuals with traditional vascular risk factors and those with existing cardiovascular disease (Caplin and Leiper, 2012). Symmetric dimethylarginine (SDMA) is a related molecule that has been reported to competitively inhibit arginine uptake in vitro (Caplin and Leiper, 2012), potentially implicating it in vascular disease and other conditions dependent on adequate NO availability (Mangoni, 2009).

Vascular disease and risk factors are associated with an increased risk of developing depression (Celano and Huffman, 2011). ADMA-induced endothelial dysfunction may play a causal role in mediating this association. A number of studies report decreased endothelial function in patients with depression (Pinto et al., 2008). Furthermore, there is growing evidence that impaired cerebral blood flow may contribute to the pathology of depression (Pinto et al., 2008). More than a decade ago Faraci et al. showed that ADMA constricts cerebral blood vessels and inhibits vasodilation in response to acetylcholine (Guix et al., 2005). Hence, inhibition of eNOS and/or nNOS by ADMA may contribute to the development of depression through vascular mechanisms and/or effects on neurotransmission and neurosecretion.

Given that only one small cross-sectional study has examined the association of ADMA with depression (Selley, 2004), the primary aim of this research is to measure serum concentrations of the methylarginines ADMA and SDMA in a representative sample of older community-dwelling adults and determine their ability to predict incident depression over 6-years of follow-up. As L-arginine is a NOS-dependent substrate for synthesis of NO a secondary aim is to determine if serum L-arginine and/or L-arginine/ADMA ratio is associated with depressive symptoms. We hypothesise that in a sample of older community-dwelling adults, increased serum ADMA and SDMA will be associated with increased risk of depression as measured by the Centre for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977) or use of antidepressant medications over 6 years of follow-up.

2. Methods

Data for this study was obtained from the Hunter Community Study (HCS), a cohort of community-dwelling men and women