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Plasma concentrations of three methylated arginines, endogenous nitric oxide synthase inhibitors, in schizophrenic patients undergoing antipsychotic drug treatment

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ABSTRACT

Plasma concentration of three methylated arginines, endogenous nitric oxide synthase inhibitors, is not studied in schizophrenic patients. The purpose of this study was to determine plasma concentrations of N^G-monomethyl-L-arginine (L-NMMA), N^G,N^G-dimethyl-L-arginine (ADMA), N^G,$N^{G'}$-dimethyl-L-arginine (SDMA), and L-arginine in 56 male and 45 female schizophrenic patients undergoing antipsychotic drug treatment versus those of 39 male and 24 female healthy controls. Plasma concentrations of methylated arginines and L-arginine were measured using newly developed high performance liquid chromatography with fluorescence detection which we previously reported. Methylated arginine levels were slightly but significantly higher in schizophrenic patients. L-Arginine levels and the L-arginine/(ADMA+L-NMMA) ratio were higher in schizophrenic patients than in healthy controls. It is considered that pharmacological treatment of schizophrenic patients may lower methylated arginine levels that are increased by the disease, and increase L-arginine levels, eliciting an improvement in nitric oxide (NO) bioavailability.

1. Introduction

N^G-Monomethyl-L-arginine (L-NMMA), N^G,N^G-dimethyl-L-arginine (ADMA), and N^G,$N^{G'}$-dimethyl-L-arginine (SDMA) are methylated derivatives of L-arginine that are present in the human body in small amounts (Vallance et al., 1992). L-NMMA and ADMA inhibit all isoforms of nitric oxide synthase (NOS). ADMA is present at much higher plasma concentrations than L-NMMA; thus it presumably exerts a greater influence on NOS activity (Vallance et al., 1992; Leiper and Vallance, 1999). SDMA does not directly inhibit NOS; however, it inhibits cellular uptake of L-arginine (Closs et al., 1997), a substrate of NOS, thereby indirectly inhibiting nitric oxide (NO) production. L-NMMA and ADMA are metabolized by dimethylarginine dimethylaminohydrolase (DDAH), while the main metabolic pathway of SDMA is renal excretion (Caplin and Leiper, 2012).

NO, which is generated by endothelial cells, smooth muscle cells, and neurons (Moncada and Higgs, 1995), plays an important role in the control of systemic and cerebral blood flow by regulating vascular tone (Faraci and Brian, 1994), and is also involved in neurotransmission (Prast and Philippu, 2001). Increased plasma concentrations of ADMA have been reported in circulatory dysfunctions of the heart (Bouras et al., 2013), liver (Nicković et al., 2012; Wnuk et al., 2012), and kidney (Wang et al., 2007), as well as in diabetes mellitus (Fogarty et al., 2012; Tousoulis et al., 2012). Recently, many studies have shown that oxidative stress increases plasma AMDA concentrations (Böger et al., 2000; Sydow et al., 2003), which might be related to decreased DDAH expression resulting from oxidative stress (Lin et al., 2002; Scalera et al., 2004). Elevated ADMA concentrations have also been observed in several psychiatric disorders such as Alzheimer's disease (Abe et al., 2001; Selley, 2003, 2004a; Arlt et al., 2008, 2012; Chen et al., 2010; Asif

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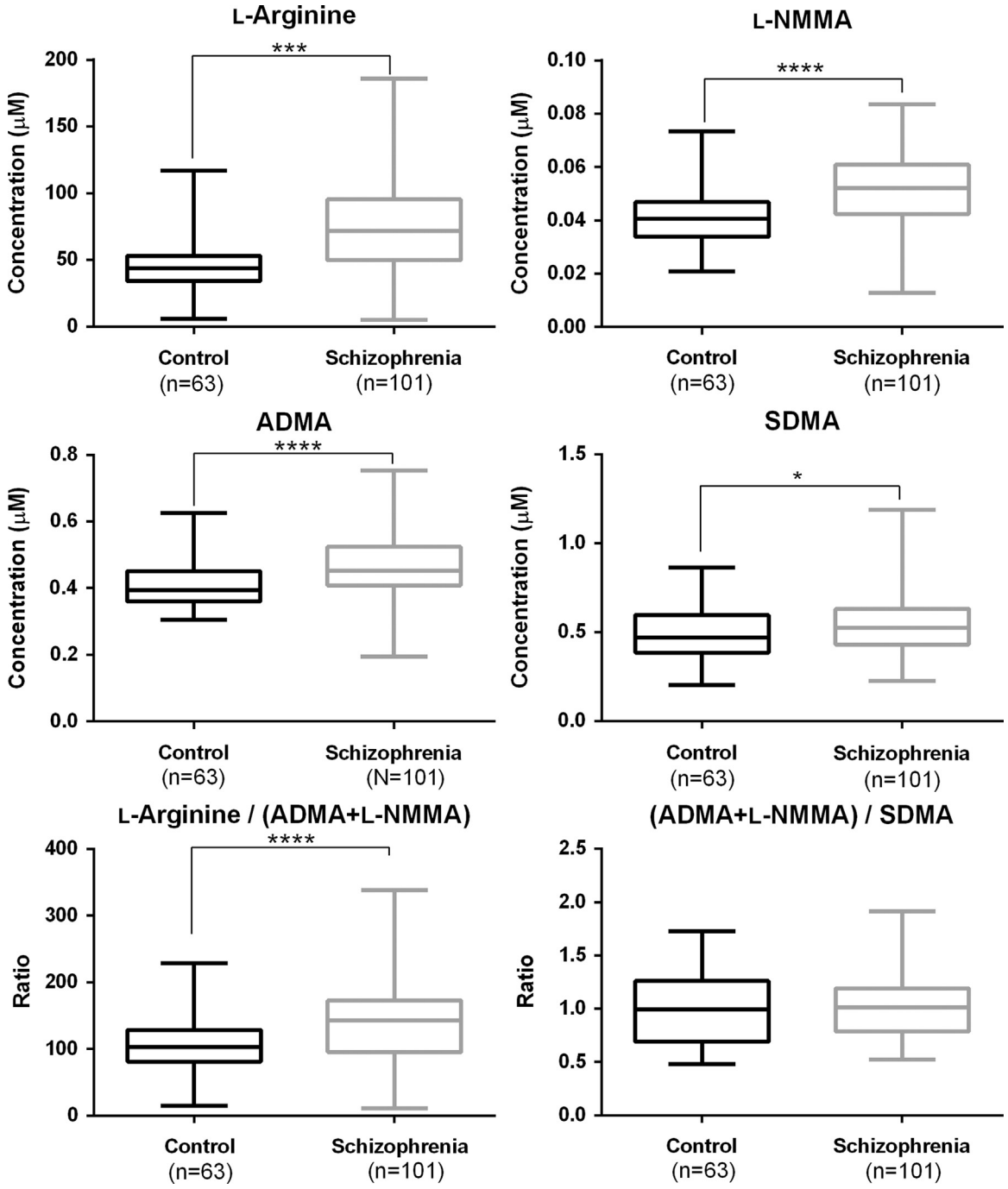

Fig. 1. Levels of methylated arginines and L-arginine in control and schizophrenic groups (*$p < 0.05$,**$p < 0.01$,***$p < 0.001$,****$p < 0.0001$).

et al., 2013; McEvoy et al., 2014) and bipolar depression (Selley, 2004b; McEvoy et al., 2013). Since bipolar depression shares common symptoms, e.g., auditory hallucinations and delusions, with schizophrenia (Tanaka, 2013), methylated arginines are also likely associated with the pathogenesis of schizophrenia. Methylated arginines are naturally occurring substances within the brain (Nakajima et al., 1971; Kotani et al., 1992). Therefore, they may regulate brain NOS activity and modulate NO metabolism in schizophrenia.

In this study, we determined the plasma concentrations of L-NMMA, ADMA, SDMA, and L-arginine in schizophrenic patients who were undergoing antipsychotic drug therapy in a hospital setting and were not in the active or acute phase of schizophrenia. In addition, using our previously reported method (Nonaka et al., 2014), we successfully measured plasma L-NMMA concentrations, which are much lower than ADMA levels. We also measured plasma concentrations in matched control subjects. In addition, we evaluated ratios of L-arginine/(ADMA+L-NMMA) and (ADMA+L-NMMA)/SDMA, which may reflect NO bioavailability and DDAH expression (Bode-Böger et al., 2007), respectively.

2. Methods

2.1. Subjects

Plasma samples were obtained from 101 schizophrenic patients (56 males and 45 females, age range: 20–81 years, mean: