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Reduced plasma levels of asymmetric Di-Methylarginine (ADMA) in patients with alcohol dependence normalize during withdrawal

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Abstract
Asymmetric Di-Methylarginine, an endogenous inhibitor of nitric oxide synthase, is increasingly recognized as vascular risk factor. Elevated ADMA levels have been described not only in 'typical' vascular diseases like congestive heart failure, artherosclerosis and diabetes but also for major depression and Alzheimer's disease.
As homocysteine increases ADMA levels and elevated homocysteine serum levels are present in patients with alcohol dependence, the aim of the present study was to examine plasma ADMA levels in patients with alcohol dependence during withdrawal.
ADMA and homocysteine levels were measured in the plasma from 42 patients drawn at baseline, on day 1, day 3 and day 7–10 of inpatient detoxification treatment. Measurements were compared against 32 healthy controls. We found significantly lower levels of ADMA in patients at baseline and on day 1 and 3, while no differences were present at the end of treatment. Plasma ADMA levels significantly increased during withdrawal. We found no association between homocysteine and ADMA levels.
Our finding of reduced ADMA levels in actively drinking alcohol dependent patients is in apparent contrast to other findings regarding cardiovascular risk factors in alcoholism. However an influence of alcohol on arginine metabolism may help explain the so called 'French paradox'.

1. Introduction

Recent years have witnessed an ongoing controversy about possible beneficial effects of alcohol consumption on the cardiovascular system. This debate was initiated by

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epidemiological data linking elevated consumption of red wine in France with reduced cardiovascular mortality, which also named this effect "French paradox" (Renaud and de Lorgeril, 1992). Several hypotheses on the mechanism behind a potential cardioprotective effect of alcohol in general, or red wine specifically have been discussed (Gronbaek and Sorensen, 1996; Mukamal et al., 2006). These findings were not undisputed. Among others, serious doubts about the hypothesis of cardioprotective properties of alcohol consumption have been raised by studies showing that moderate alcohol consumption increases the plasma levels of the amino-acid homocysteine, which is known to be a risk factor for artherosclerosis (Bleich and Bleich, 2002; Bleich et al., 2001). Even though matter of debate in social drinkers, the increased cardiovascular risk associated with alcohol dependence and heavy drinking is unanimously accepted among researchers and supported by clinical data (e.g. alcoholism associated hypertension and congestive heart disease, etc.).

The metabolism of the amino-acid arginine, which is closely related to the homocysteine metabolism, is also involved in the (patho-) physiology of the vascular system: the most potent vasorelaxing substance, nitric oxide (NO), is synthesized from arginine by the NO-synthase (NOS). This enzyme is blocked by asymmetric Di-Methylarginine (ADMA), which is released during proteolysis. Elevated levels of ADMA have been reported in coronary heart disease (CHD) and several other vasculopathies, but were also found in patients suffering from depression, schizophrenia and Alzheimer's disease (Das et al., 1996; Selley, 2003, 2004b). ADMA is degraded by the isoenzymes of the dimethyldiarginine hydrolase (DDAH-1 and -2), which hydrolyzes it to L-citrulline and methylamine. DDAH-1 is primarily found in tissues expressing the neuronal form of NOS (nNOS), while DDAH-2 is mostly expressed in tissues also expressing the endothelial form of NOS (eNOS) (Selley, 2004a). Disturbances of the NO pathway have been related to impaired neuronal plasticity (Kleppisch and Feil, 2009). In opiate dependence, adaptions of the NO pathway are believed to mediate development of tolerance towards the drug and loss of the antinociceptive effects (Kielstein et al., 2007).

Homocysteine leads to increased ADMA levels in cultured neuronal cells and it is believed that this effect is mainly due to a blockade of DDAH (Selley, 2004a). The complex interaction between ADMA-/, NO- and homocysteine-metabolism is depicted in Fig. 1.

As we have shown that patients suffering from alcohol dependence have strongly elevated homocysteine plasma levels (Bleich et al., 2005), we hypothesized, that these patients would also have elevated ADMA levels. The present pilot study was performed to analyze homocysteine and ADMA plasma levels in a sample of alcohol dependent patients during alcohol withdrawal and to compare these with healthy controls.

2. Experimental procedures

2.1. Patients and design

The present investigation was part of a large prospective research project on neurobiological mechanisms in alcohol dependence (FARS: Franconian Alcoholism Research Studies (Bleich et al., 2005)) and was approved by the local ethics committee. The study was carried out in complete accordance with the ethical standards of the declaration of Helsinki in 1975. All patients suffered from alcohol dependence according to DSM-IV and ICD-10 and were admitted for in-patient detoxification treatment. Participants included in the study gave written informed consent after the procedures had been fully explained to them. Patients with concomitant psychiatric illnesses, other substance abuse apart from alcohol or nicotine and existence of a current or a history of cardiovascular disease or any severe somatic illness were excluded. Therefore, all patients underwent a detailed physical examination, a routine laboratory testing and urine drug screening. In the present analysis we included 42 male patients with alcohol dependence and 32 healthy men as control group.

We measured alcohol craving using the Obsessive Compulsive Drinking Scale (OCDS), which provides a well validated and reliable measurement (Anton et al., 1995). The severity of alcohol withdrawal was assessed with the withdrawal syndrome scale for alcohol and related psychoactive drugs (WSA) (Kristensen et al., 1986) and the Clinical Institute Withdrawal Assessment (CIWA-Ar) (Sullivan et al., 1989). In addition, we obtained personal and sociodemographic data like age, the previous daily intake of alcohol in grams and the volume intake of alcoholic beverages in liters using a structured interview according to the protocol of the FARS (Bleich et al., 2005).

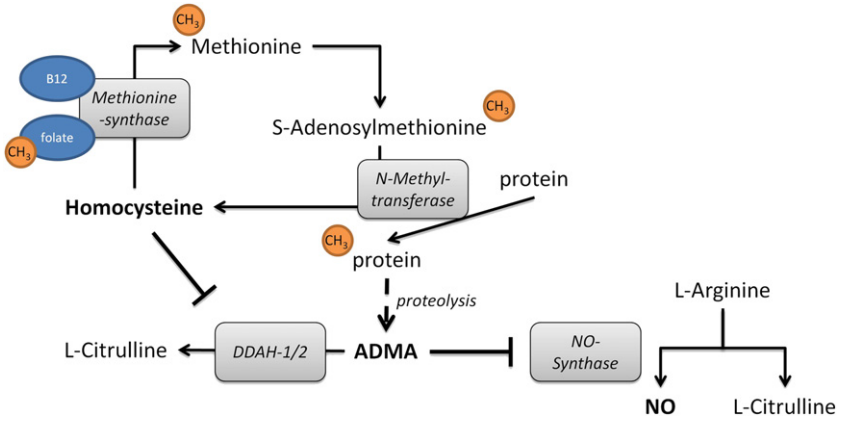

Fig. 1 Overview of the homocysteine and the NO metabolism. Further explanations are provided in the introduction. CH_3: methyl groups.