

# Arginine vasopressin and adrenocorticotropin secretion in response to psychosocial stress is attenuated by ethanol in sons of alcohol-dependent fathers

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## Abstract

Familial risk and environmental stress promote the development of alcohol dependence. We investigated whether a positive family history of alcoholism affects the neuroendocrine response to a standardized laboratory stress test in healthy subjects without alcohol use disorders. Twenty-four high-risk subjects with a paternal history of alcoholism (PHA) and 16 family history negative (FHN) controls were evaluated. Psychosocial stress was induced by having subjects deliver a 5-min speech and mental arithmetics in front of an audience on separate days, after drinking either placebo or ethanol (0.6 g/kg) in a randomized sequence. Adrenocorticotropin (ACTH) was measured in 10 plasma samples covering up to 75 min after the stress test. Plasma arginine vasopressin (AVP) was determined before the stressor, at the time of maximum ACTH secretion, and at 75 min after stress onset. The stress test induced a phasic increase in ACTH secretion. At the time of maximum ACTH, AVP was significantly increased in relation to baseline. Compared to placebo, alcohol administration significantly attenuated maximum ACTH concentration in PHA but not FHN subjects, and decreased AVP measured in the same samples in PHA but not FHN subjects. We conclude that activation of the hypothalamic–pituitary–adrenal system by psychosocial stress is accompanied by an increase in peripheral plasma AVP levels. Secretion of both ACTH and AVP suggest that alcohol attenuates the stress response selectively in PHA but not FHN subjects. This might imply some short-term positive alcohol effect in sons of alcoholics, but also constitute a mechanism by which their risk to develop alcohol use disorders is increased.

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## 1. Introduction

Alcoholism runs in families (Cotton, 1979), and twin studies suggest that a substantial part of the associated risk is conveyed by genetic factors (Prescott and Kendler, 1999). The social environment is also long known to contribute to development and maintenance of alcoholism. Stress appears to be a particularly rele-

vant mechanism (for review, see Sinha, 2001), possibly by interacting with genetic risk factors (Madrid et al., 2001). One possibility to study how the genetic risk manifests itself is to investigate offspring of alcohol-dependent parents who themselves have not yet developed alcohol use disorders (for review, see Newlin and Thomson, 1990). Using this approach, several authors found that offspring of alcoholics had increased autonomic reactivity to aversive electrical shocks and public speaking, and that alcohol had a stronger stress response-dampening effect compared to family history negative controls (Levenson et al., 1987; Finn et al., 1990; Conrod et al., 1998; Sinha et al., 1998).

We were recently able to extend these findings by investigating adrenocorticotropin (ACTH) and cortisol

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secretion in response to psychosocial stress, which was exaggerated in healthy males with a paternal history of alcoholism (PHA) compared to control subjects with a negative family history (FHN). In this study, alcohol administration significantly attenuated the endocrine stress response in PHA but not in FHN subjects, while pre-stress hormone levels did not differ between groups (Zimmermann et al., in press). However, while ACTH and cortisol are the core parameters defining a stress response, they provide only indirect information about central nervous control of the hypothalamic–pituitary–adrenal (HPA) system since they are secreted by peripheral endocrine glands. In an effort to complement these data by a parameter which is more closely related to the central nervous processes that elicit the HPA activation, this paper reports on arginine vasopressin (AVP) secretion in a subgroup of the same subjects.

Release of ACTH from the anterior pituitary lobe is stimulated by corticotropin releasing hormone (CRH) and AVP. In rodents, the pattern of stress-induced ACTH secretagogue activity depends on the type of stressor. The HPA activation elicited by physical stress is mainly caused by CRH, while other stressors such as novelty, social isolation, restraint, or fear are believed to predominantly result in AVP secretion in animals (Romero and Sapolsky, 1996).

The nonapeptides AVP and oxytocin (OXT) are synthesized in, transported by, and secreted from two distinct classes of neurons. Magnocellular vasopressinergic and oxytocinergic neurons of the hypothalamic paraventricular (PVN), supraoptic, and accessory nuclei constitute the hypothalamic–neurohypophyseal system (Hatton, 1990), whereas parvocellular vasopressinergic neurons are found in the hypothalamus within the suprachiasmatic nucleus (SCN) and the parvocellular part of the PVN (De Vries et al., 1985). The neurons of SCN and PVN project predominantly to the median eminence (Alonso and Assenmacher, 1981), where AVP and CRH are secreted into the portal blood to act synergistically as secretagogues of ACTH at the adenohypophysis (Plotsky, 1991). The parvocellular vasopressinergic system originating from the PVN appears to be activated in depressive syndromes (for review, see Holsboer and Barden, 1996; for animal model see Wigger et al., 2004), which suggests that increased secretion of AVP might contribute to the hyperactivity of the HPA system in major depression. This notion is supported by one study reporting increased plasma AVP in depressive patients compared to healthy controls (van Londen et al., 1997), while other studies found no difference in plasma (Brunner et al., 2002) or cerebrospinal fluid AVP (Heuser et al., 1998; Brunner et al., 2002).

In recent years, evidence has been accumulated that both AVP and CRH act not only as hormones, but also as neuromodulators and neurotransmitters within the central nervous system. Following its central release (Landgraf,

1995) and independent of HPA system regulation, AVP appears to be critically involved in a variety of brain functions including learning, memory, and emotionality (de Wied et al., 1993; Landgraf, 2001; Engelmann et al., 1996).

AVP measured in peripheral blood predominantly originates from the magnocellular system and is secreted in response to osmotic stimuli, its main function being regulation of osmolality (for review, see Lightman, 1990; Hussy et al., 2000). On the other hand, psychological stress activates the parvocellular system to release ACTH secretagogues into the hypophyseal portal vein system (Herman, 1995; for review, see Romero and Sapolsky, 1996). This was associated with an increase in peripheral blood AVP in various animal models (Romero and Sapolsky, 1996), and in humans preparing for their first parachute jump (Dugue et al., 1993). Pain due to injuries was also associated with increased peripheral AVP levels (Kendler et al., 1978), while milder stressors such as noise combined with mental arithmetics and cold stress (Ehrenreich et al., 1997) did not stimulate AVP secretion.

Several studies investigated alcohol effects on peripheral AVP in humans. Oral dosages of 0.25 (Gianoulakis et al., 1997), 0.5 (Chiodera and Coiro, 1990; Gianoulakis et al., 1997), or 0.88 g/kg (Inder et al., 1995) did not alter basal AVP levels, while two studies found a decrease after 0.8 g/kg (Eisenhofer and Johnson, 1982) or approximately 0.4 g/kg (Leppaluoto et al., 1992). Even a low dosage of approximately 0.5 g/kg almost abolished the rise in AVP induced by insulin hypoglycemia (Chiodera and Coiro, 1990). On the other hand, if alcohol induced nausea, this was associated with a marked increase of peripheral AVP and ACTH (Inder et al., 1995).

These observations lead us to investigate plasma AVP levels in response to a standardized laboratory psychosocial stress test that was performed twice in males with a PHA and in FHN controls, once being sober and once being moderately alcohol-intoxicated. We hypothesized that the stress-induced HPA activation might be accompanied by an increase in peripheral blood AVP levels, which might be attenuated by prior alcohol administration. According to our findings on ACTH secretion, we expected the AVP response to be higher in PHA subjects, and the alcohol effect to be more pronounced in PHA than FHN subjects. In an exploratory design, we also investigated whether AVP levels are influenced by potentially confounding factors such as plasma osmolality, individual psychiatric comorbidity, or personality trait variables.

## 2. Methods

### 2.1. Subjects

Recruitment of participants based on a prospective longitudinal epidemiological survey investigating a rep-

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