Psychoneuroendocrinology (2009) 34, 996–1003

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Ethanol administration dampens the prolactin response to psychosocial stress exposure in sons of alcohol-dependent fathers

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Received 26 September 2008; received in revised form 16 December 2008; accepted 27 January 2009

KEYWORDS
Stress;
Alcoholism;
Prolactin;
Ethanol;
Administration

Summary Genetic predisposition and exposure to alcohol and stress increase the risk for alcoholism, possibly by forming a threefold interaction. This is suggested by various aspects of alcohol-induced stress response dampening in offspring of alcoholics. We tested whether such an interaction is also revealed by prolactin secretion, which is predominantly controlled by hypothalamic dopamine.

Plasma prolactin was measured during four experimental days in 26 young males with a paternal history of alcoholism (PHA) and in 22 family history negative (FHN) controls. A public speaking stress paradigm was applied on the first 2 days, and a non-stress acoustic startle experiment on the others. Before the tests, subjects drank alcohol (0.6 g/kg) or placebo in a randomized, double-blind crossover design.

During placebo experiments, prolactin levels significantly increased after stress, but not after startle, and did not differ between risk groups. Alcohol administration significantly increased prolactin before stress and during startle in both groups, did not alter stress-induced prolactin stimulation in FHN, but significantly attenuated the prolactin stress response in PHA subjects. The alcohol effects on prolactin, cortisol, and adrenocorticotropin stress response were positively interrelated with each other.

These data confirm that alcohol specifically dampens the stress response in PHA but not FHN subjects. Since prolactin responses to stress alone and alcohol alone were normal in PHA, we conclude that this genetic effect is not related to altered physiology of the hypothalamic dopaminergic system, but to risk-group specific alcohol effects on hierarchically higher brain areas controlling the stress response in general.

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doi:10.1016/j.psyneuen.2009.01.015

1. Introduction

Offspring of alcohol-dependent parents often develop alcohol use disorders themselves, and more than half of their increased risk can be attributed to genetic factors (Heath et al., 1997; Prescott and Kendler, 1999). In order to find underlying mechanisms, many researchers turned to experimental studies comparing offspring of alcohol-dependent parents with control subjects without alcoholic relatives. In order to distinguish pre-existing alterations from alcohol-induced harm, such studies are preferably performed in young adults who have not yet developed alcohol use disorders themselves. This research strategy revealed anatomical (Hill et al., 2001), electrophysiological (Hada et al., 2001) and endocrine abnormalities (Wand et al., 1998), but the most important findings come from alcohol challenge experiments with these high-risk subjects. For example, the sons of alcoholics were found to show less subjective (Schuckit and Gold, 1988), cognitive (Erblich and Earleywine, 1999), and hypothalamic-pituitary-adrenal (HPA) system alteration (Schuckit et al., 1988, 1987b) in response to an acute alcohol dose, and this turned out to be a risk factor for later development of alcoholism independent from family history for alcoholism (Schuckit and Smith, 1996). Other authors specifically investigated acute tolerance to alcohol, which was found to be more pronounced in the sons and daughters of alcoholics (Blekher et al., 2002; Morzorati et al., 2002). More of this literature was reviewed earlier by Newlin and Thomson (1990).

While these results imply that developing less of the intoxicating alcohol effects can promote alcoholism, research on the stress-dampening properties of alcohol suggests that those may actually be more pronounced in offspring of alcoholics. In the context of hypotheses referring to alcohol-induced tension-reduction (Conger, 1956) or appraisal disruption (Sayette, 1993), this might comprise another mechanism of risk. The autonomic and physiological responses to stressors such as electrical shocks are dampened by prior alcohol administration and this effect is stronger in offspring of alcoholics or even limited to this population (Sinha et al., 1998; Conrod et al., 1998; Finn et al., 1992, 1990; Finn and Pihl, 1987; Sher and Levenson, 1982). Some more recent studies looked at the core parameter defining a stress response, i.e., activation of the hypothalamic-pituitary-adrenal (HPA) system and found somewhat conflicting results: both Uhart et al. (2006) and Zimmermann et al. (2004a,b) found that the HPA response to public speaking stress was higher in offspring of alcoholics than in family history negative controls, but was brought down to the controls' level by prior administration of a moderate alcohol dose. Using a different stressor, Dai et al. observed less adrenocorticotropin (ACTH) response in high-risk than low-risk subjects, which was equally dampened in both risk groups (Dai et al., 2002). Possible explanations for this inconsistency were discussed earlier (Zimmermann et al., 2004a). They include that, in contrast to our study, Dai et al. used a mere cognitive stressor without psychosocial component, which resulted in considerably lower endocrine stress response. Also, their definition of genetic risk required alcoholism in the father and grandfather, and part of the risk group differences observed by them was due to baseline differences in ACTH secretion.

In addition to the HPA system, several other hormones are activated in response to acute stress, including prolactin (Van de Kar and Blair, 1999). While the functional role of prolactin in the stress response remains unclear, this hormone might be particularly interesting for addiction research for two reasons: (i) its unique regulation by dopamine (Ben Jonathan and Hnasko, 2001); (ii) a prior report of less prolactin stimulation in response to a high-dose alcohol challenge in sons of alcoholics (Schuckit et al., 1987a). Prolactin secretion is controlled by the dopaminergic tuberoinfundibular system, consisting of neurons located in the hypothalamic arcuate and paraventricular nuclei that project to the median eminence. Dopamine secreted by these neurons reaches the anterior pituitary via the long portal vessels where it binds to dopamine D2 receptors on lactotroph cells, resulting in robust suppression of prolactin release (Ben Jonathan and Hnasko, 2001). Therefore, medial basal hypothalamic ablation (Sato et al., 1996) or treatment with dopamine receptor antagonists results in tonically increased prolactin levels.

Stimulatory control of prolactin is more complex and involves heterogeneous factors, some of which act at least partly via inhibition of hypothalamic dopaminergic neurons. This applies to endogenous opiates and to a lesser extent to serotonin and GABA, while vasoactive intestinal peptide and thyrotropin-releasing hormone stimulate prolactin directly at the level of the pituitary. In general, the stimulant effect of prolactin-releasing factors is considerably less potent than dopaminergic inhibition; therefore, most researchers agree that inhibition by dopamine represents the main mechanism controlling prolactin release (Ben Jonathan and Hnasko, 2001).

Several researchers found that alcohol administration stimulated prolactin secretion in rats (Sato et al., 1996) and in humans. After doses ranging up to 0.8 g/kg, this effect was equal between groups with vs. without a paternal history for alcoholism (PHA) (Schuckit et al., 1987a; Moss et al., 1989). However, after administration of 0.9 g/kg, Schuckit et al. (1987a) observed less prolactin stimulation in the PHA group. The recent family history study by Uhart et al. (2006) found no risk group differences in prolactin response to public speaking stress, but did not include an alcohol challenge.

For these reasons we investigated whether the prolactin response to alcohol challenge, public speaking stress, and their combination differs between sons of alcoholics compared to family history negative controls.

Prolactin was measured in samples obtained during a study that was described earlier and consisted of four experimental sessions (Zimmermann et al., 2004a,c). The first part (first 2 days) involved psychosocial stress exposure. During the second part (days 3 and 4), acoustic startle response was studied which did neither involve psychosocial stress nor activate the HPA system. Therefore the second part served as a no-stress comparison condition. Both paradigms involved prior randomized administration of alcohol (0.6 g/kg) or placebo. Together, these four experiments allowed us to control for all experimental factors, i.e., genetic risk, stress exposure, and alcohol administration. Based on our prior findings concerning stress-induced HPA stimulation we hypothesized that alcohol would dampen the prolactin stress response and that this effect would be more pronounced in sons of alcoholics than in family history negative (FHN) controls.