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Review

Role of hypothalamic corticotropin-releasing factor in mediating alcohol-induced activation of the rat hypothalamic–pituitary–adrenal axis

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ABSTRACT

Alcohol stimulates the hypothalamic–pituitary–adrenal (HPA) axis through brain-based mechanisms in which endogenous corticotropin-releasing factor (CRF) plays a major role. This review first discusses the evidence for this role, as well as the possible importance of intermediates such as vasopressin, nitric oxide and catecholamines. We then illustrate the long-term influence exerted by alcohol on the HPA axis, such as the ability of a first exposure to this drug during adolescence, to permanently blunt neuroendocrine responses to subsequent exposure of the drug. In view of the role played by CRF in addiction, it is likely that a better understanding of the mechanisms through which this drug stimulates the HPA axis may lead to the development of new therapies used in the treatment of alcohol abuse, including clinically relevant CRF antagonists.

Introduction

The ability of alcohol to activate the hypothalamic–pituitary–adrenal (HPA) axis in rodents is well documented (see Rivier (1996) for review). Most reported work has been done following investigator-controlled administration of the drug (whether by systemic injection, gavage or vapors), which may involve brain regions different from those acted upon by self-administration (Moolten and Kornetsky, 1990). Nevertheless, there is evidence that rodents that drink alcohol also have an activated HPA axis (Richardson et al., 2008), and it is well known that humans who chronically abuse this drug can develop pseudo-Cushing's syndrome (see Veldman and Meinders (1996)), a disease characterized by pathologically elevated cortisol levels. Also, while for technical reasons (insertion of cannulae, multiple bleedings, etc.), most of the work has been done in rats rather than mice, to our knowledge, the ability of alcohol to stimulate the HPA axis, and the role played by endogenous CRF in this response, appear comparable in both species. Finally, while the amount of alcohol that people need to drink to stimulate their HPA axis, as well as the potential requirement for gastric discomfort in eliciting this response, remain an issue of debate, there is strong evidence that human alcoholics display significant perturbations of the activity of this axis (Gianoulakis et al., 2003; Inder et al., 1995a; Waltman et al., 1993; Wand and Dobs, 1991). Consequently, it is likely that a better understanding of the mechanisms through which this drug stimulates the HPA axis may lead to the development of new therapies used in the treatment of alcohol abuse.

Overview

The mechanisms responsible for the HPA axis' response to alcohol have been the topic of much investigation. In the adult rat, we reported that intraperitoneal (ip), intragastric (ig) and intracerebroventricular (icv) (see Lee et al. (2004), Ogilvie et al. (1997b,a) and Rivier (1996)) all significantly elevated plasma ACTH levels. In rats exposed to alcohol vapors, this response is already significant in 22 d-old animals (Lee and Rivier, 2003). Basically, alcohol could act at one of three levels: the brain, the anterior pituitary and/or the adrenals. While there had been some reports of a direct action of this drug on the corticotrophs (Keith et al., 1986; Redei et al., 1986), it currently seems unlikely that this mechanism plays an important role, as we will discuss at the end of this article. Indeed, at present, most, if not all, valid evidence supports a role of the hypothalamic peptide corticotropin-releasing factor (CRF) in mediating alcohol-induced ACTH release (Rivier et al., 1984a). This will therefore represent the main thrust of what follows. We would also like to point out that this is not intended as an exhaustive review of the literature pertaining to alcohol and the HPA axis, but rather will focus on the role of CRF, to which the late Dr. W. Vale made significant contributions.

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Most of the work done in our laboratory used two approaches in order to avoid the confounding effect of handling the animals. First, rats were implanted with permanent indwelling jugular cannulae which allowed blood sampling in freely-moving subjects; second, we administered alcohol via permanent ip, ig or icv catheters, which permitted delivery of the drug in a remote, stress-free manner. For studies that relied on alcohol vapors, no special precautions were required to avoid a non-specific (i.e., not due to alcohol) activation of the HPA axis, as we had shown that being in the chambers by itself did not alter neuroendocrine functions (Lee et al., 2000). While most of our research was done in male rats, it is of interest to mention that as is the case of the HPA axis response to other stressors (Rhodes and Rubin, 1999; Seeman et al., 2001), females release more ACTH and corticosterone than males when administered alcohol (Ogilvie and Rivier, 1996, 1997; Rivier, 1993a), a difference that is abolished by gonadectomy (Rivier, 1999a). Even though there are functional sex differences in the brain control of the HPA axis (Seeman et al., 2001), we also observed that pituitary activation by exogenous CRF showed a similar sex-specific specificity (Rivier, 1999a). Finally, in the first phase of our research, systemic alcohol administration was usually done via ip cannulae. However, the subsequent discovery of the stimulatory influence of cytokines on the HPA axis (ref. in Turnbull and Rivier (1999)) suggested that despite the fact that we routinely injected lidocaine together with alcohol to alleviate potential abdominal discomfort, the presence of this drug was likely to induce the release of pro-inflammatory immune-derived proteins in the peritoneal cavity. Our subsequent studies therefore relied more on the systemic administration of alcohol through permanent ig cannulae, which activates the HPA axis by mechanisms qualitatively comparable to those present during ip injections (Ogilvie et al., 1997b,a). For long-term delivery, we used an intermittent vapor delivery system (Lee et al., 2000).

Mechanisms mediating the stimulatory effect of alcohol on the HPA axis

Role of CRF

Most, if not all stressors (i.e., threats to homeostasis), activate the HPA axis (see Dallman et al. (1992), Herman et al. (2003), Rivier and Plotsky (1986), Sawchenko (2000) and Watts (1996)) and alcohol, which is considered a stressor, also does so (Rivier, 1996). This is illustrated, for example, by the ability of this drug to cause dose-related (Ogilvie et al., 1997b; Ogilvie and Rivier, 1996) increases in plasma ACTH levels regardless of the systemic route of administration (Fig. 1A). Hypothalamic CRF is a 41-amino acid peptide (Spiess et al., 1981; Vale et al., 1981) released into the portal vessels of the median eminence, that upon reaching the anterior pituitary promotes the dose-dependent secretion of ACTH (Rivier et al., 1982a). Stressors that stimulate the HPA axis do so through activation of neurons in the paraventricular nucleus (PVN) of the hypothalamus, specifically those that manufacture CRF and VP (Herman et al., 2003; Sawchenko, 2000; Watts, 1996). Alcohol acts similarly, as indicated by the ability of both its acute (Rivier and

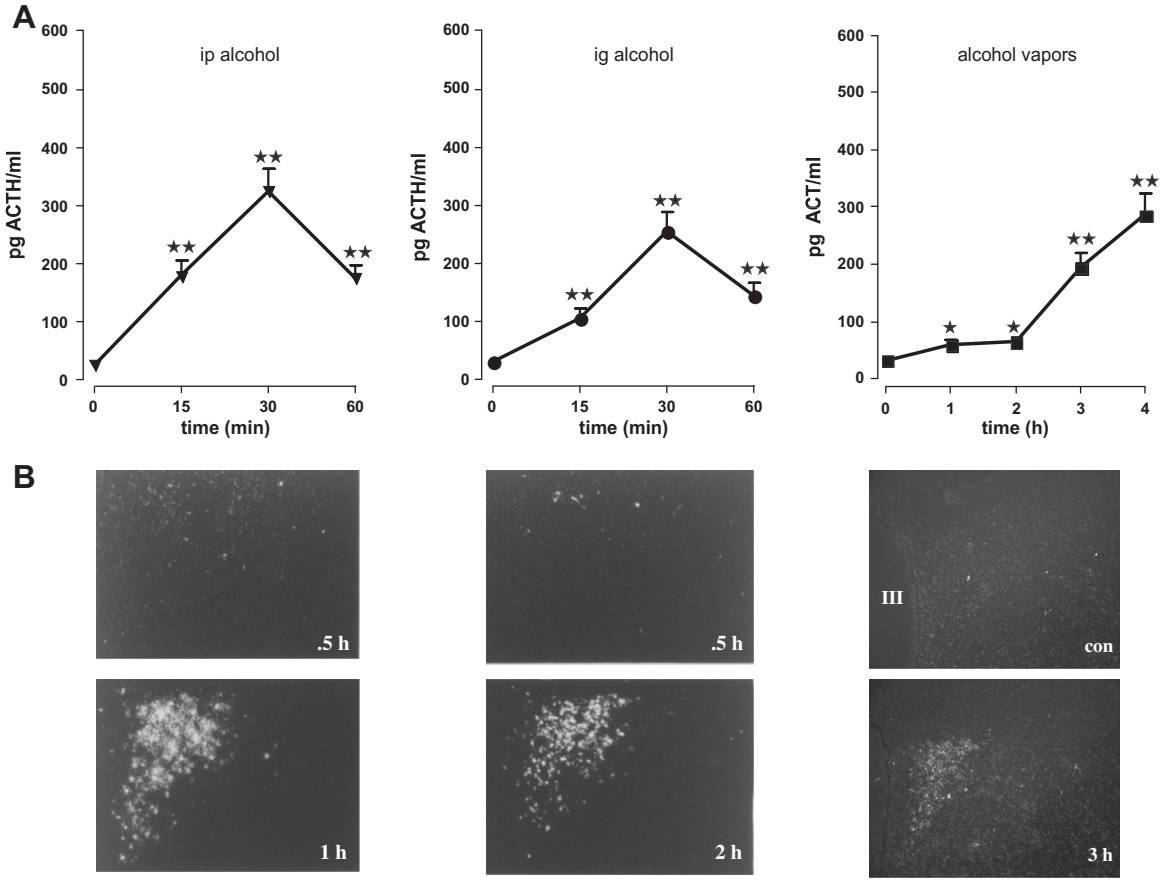

Fig. 1. The ip (3.0 g/kg) or ig (4.5 g/kg) injection of alcohol, or exposure to alcohol vapors (5 h/day for 5 days), increases plasma ACTH levels (A) or neuronal activity in PVN CRF cell bodies (B) in adult male rats. (A), each point represents the mean ± SEM of 5–6 rats. $^{*}P < 0.05$ and $^{**}P < 0.01$ from time 0. ACTH levels for control animals remained <50 pg/ml at all times and are not shown. (B), dark-field photomicrographs of coronal sections through the PVN brains following vehicle or alcohol injection. Methodology described in, and data modified or reproduced from Lee and Rivier (2003), Lee et al. (2004), Rivier (1999a) and Rivier et al. (2003) by permission.