Vasopressin pressor receptor-mediated activation of HPA axis by acute ethanol stress in rats

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A high dose of orally administered ethanol generates gastric erosions in rats (61), and such lesions are often used to evaluate the gastric action of various drugs. Similar lesions can be observed in the gastric mucosa in animals exposed to different stress situations such as cold restraint, endotoxin injection, or hemorrhagic stress (28). Adrenal medullectomy (66), endogenous vasopressin [arginine vasopressin (AVP)] deficiency (29), administration of a pressor (V1) AVP antagonist (29), and orchidectomy (27) all protect the gastric mucosa against ethanol-induced damage. In contrast, adrenalectomy attenuates gastric mucosal protection against ethanol injury (66). These data demonstrate that various hormones participate as facilitatory or inhibitory mediators in the ethanol-induced generation of acute gastric mucosal stress erosions.

Among the stress hormones, ACTH is one of those responding most sensitively to various stimuli, and it is therefore a useful indicator for the monitoring of stress situations. The major physiological regulator of ACTH secretion following stress is corticotropin-releasing hormone (CRH), originating from the hypothalamus (21).

The aims of the present study were to learn more about hormonal changes following orally administered high-dose ethanol (known to cause gastric erosions) and the involvement, if any, of AVP in the changes observed following acute ethanol challenge.

MATERIALS AND METHODS

Animals. Male Wistar rats (from our breeding farm originating from different litters) weighing 180–220 g were fasted for 24 h, but they received water ad libitum. The animal care and research protocols were in accordance with the guidelines of our university. The animal house had artificial lighting (from 6 AM to 6 PM). Five rats were kept per cage. The rats had been handled and treated orally three times daily (8 AM, 2 PM, and 8 PM) with 1 ml of tap water via a gastric tube for 6 consecutive days before the experiment. This procedure was designed to accustom the rats to the presence of humans and to the insertion of the gastric tube to minimize the effects of nonspecific stress.

Measurements of plasma AVP, ACTH, and corticosterone levels in response to ethanol administration in the absence or presence of a V1 antagonist. Each experimental group consisted of 10 rats. In 10 groups, 1 ml of 75% ethanol or 1 ml of tap water (as control) was administered orally to the animals via a gastric tube. Zero, 5, 15, 30, or 60 min after ethanol or water administration, the rats were killed by decapitation between 8 and 9 AM, and trunk blood was collected in polystyrene tubes containing 180 μl of 1.6 M EDTA. Blood samples were kept on ice and centrifuged (3,000 rpm) at 4°C.
to obtain plasma for AVP, ACTH, and corticosterone determinations. A further 10 groups were treated with a highly selective V1b AVP receptor antagonist 5 min before ethanol or water administration. The V1b receptor antagonist [1-β-mercapto-β,β-cyclo pentamethylenepropionic acid-2-(O-methyl)-Tyr, Arg8]VP, called Manning peptide and abbreviated as d(CH3)2Tyr(Me)AVP, was used at a dose of 1.0 μg/kg body wt ip (41). The receptor-antagonist dose was determined according to published data (28, 31). The animals were killed at the above different times after ethanol or water administration, and their plasma was collected similarly.

**Plasma AVP level.** Plasma AVP level was determined with a specific RIA system (25). The extraction was performed on RPN 1902-C8 minicolumns (Amresco, Amersham, UK), with a recovery of >95%. Synthetic AVP (Arg2-vasopressin; Organon, Oss, The Netherlands) was used for antibody production, for the preparation of the tracer, and as a standard. The cross-reactivities of the AVP antibody used in the RIA were 0.03% with vasotocin, <0.01% with oxytocin, and 0.03% with ACTH1–24. The sensitivity of the RIA was 1 pg/ml. The intra- and interassay coefficients of variation proved to be 13.3 and 16.3%, respectively.

**Plasma ACTH level.** A direct RIA method was used (24). Rabbits were immunized with ACTH1–39 to obtain an antibody. The sensitivity of the method was 1 pg/ml, and the intra- and interassay coefficients were 4.7 and 7%, respectively. The cross-reaction with α-melanotrophic hormone was <0.2%.

**Plasma corticosterone level.** This method was described by Mihály et al. (45). Twenty-one-corticosterone-albumin conjugate was used for immunization in rabbits. Endogenous corticosteroid-binding globulin was inactivated with methanol. A direct RIA was used. The sensitivity of the method was 3 μg/dl, and the intra- and interassay coefficients were 9 and 13.7%, respectively. The cross-reactions with progesterone and estrone were 7.3 and 0.1%, respectively.

**Measurements of CRH content of hypothalamus.** After the rats' decapitation, brains were quickly removed, and the hypothalamus was isolated on ice. The hypothalamus was defined as the tissue within 3 mm of the ventral surface of the brain, within the following borders: optic chiasm, mammillary bodies, and lateral hypothalamic sulci. The whole stalk median eminence was included in the hypothalamic preparations. CRH concentration was determined by a RIA technique (64). The hypothalamus was homogenized with ultrason (Soniprep 150 MSE) in 100 mM HCl containing 1 mM ascorbic acid, and an aliquot was taken for protein measurements (38). The residual homogenate was centrifuged at 6,000 g for 20 min at 4°C, and aliquots were taken and lyophilized for RIA. The CRH antisem (P. Vecsei, Heidelberg, Germany) was obtained from a rabbit immunized with human CRH. The CRH antibody (43) was specific for the C-terminal region of the CRH1–41 molecule because it did not cross-react with the fragments CRH1–20 and CRH21–41. The CRH tracer was prepared with the use of a modified iodogen method to minimize damage to the iodinated peptide (35). The labeled material was purified via two steps of reverse-phase chromatography (17), a gradient HPLC system being applied in the second step. The specific radioactivity of the purified tracer was 1,700–1,900 Ci/mmol. The freeze-dried residues were redissolved in 1 ml of assay buffer [50 mM phosphate (Sigma), pH 7.4, containing 0.25% human serum albumin (Izinta) and 0.1% Triton X-100 (Reanal)], and 200-μl aliquots were subjected to RIA. The RIA standard was a synthetic human/rat (h/r) CRH preparation (Bachem, Bubendorf, Switzerland).

The procedure involved a nonequilibrium system; a 16-h preincubation of the samples or standards with antisem (100 μl, working dilution 1:10,000) was followed by a 24-h incubation with corticotropin-releasing factor tracer (100 μl, 10,000 cpm). The immunologically bound and free fractions were separated with a second antibody (raised in our laboratory in sheep against whole rabbit IgG) and subsequently by polyethylene glycol (PEG) 6,000 precipitation (Ferak Laboratory, Berlin, Germany) by the double-antibody/PEG method. The lower limit of assay detection was 7–8 pg/tube. The intra- and interassay coefficients of variation were 4.0 and 13.8%, respectively. CRH immunoreactivity in hypothalamic extracts subjected to HPLC has been shown to cochromatograph with synthetic h/rCRH1–41 (64). The CRH content of the hypothalamus is expressed in picograms per milligrams protein. Each group consisted of 10 rats.

To determine whether the hypothalamic CRH response to ethanol stress can be ascribed to the increased protein synthesis, rats were treated with the protein synthesis-blocking compound cycloheximide before oral ethanol administration. The rats were killed 30 or 60 min after ethanol administration, and the CRH content of the hypothalamus was measured.

**Anterior pituitary tissue culture.** Monolayer pituitary cell cultures of Wistar rats weighing 180–230 g were prepared (19). Ten pituitaries were used in every tissue culture experiment. The hypothalamus was sterilized and immediately after decapitation of the rats. The anterior lobe of the pituitary gland was isolated under a preparative microscope, and the tissue was digested in the presence of trypsin, collagenase, deoxyribonuclease I and II, and dispase (GIBCO). The dispersed cells were placed in plastic collagen-coated Petri dishes and suspended in Dulbecco’s modified Eagle’s medium supplemented with 20% fetal bovine serum (GIBCO). The cultures were maintained at 37°C in a humidified atmosphere of 10% CO2 in air and washed every 3 days. Experiments were performed on 14-day cultures. We performed the standardization of the cell cultures by immunoreactivity of ACTH at the start and at the end of experiments, determining the relative frequency of immunoreactive ACTH containing cells per unit area. If the relative frequency proved to be no more than 5 to 7%, the cell cultures were used. The standardized monolayer cell cultures were functionally controlled with potassium (30 mM, 30 min) as a nonspecific releasing agent. Viability was 97–100%. In our experimental conditions, the stable equilibrium in ACTH release developed after ~90 min. This was the reason for the use of the longer incubation period. The viability did not change during incubation. During pilot experiments, we tried several doses of AVP, CRH, and V1 receptor antagonist, and we used the maximal effective dose (10–6 M) later. The cells were incubated for 3 h with 10–6 M AVP or 10–6 M CRH (Bachem) alone or 10–6 M AVP + 10–6 M CRH together, for 3 h with 10–6 M V1 receptor antagonist alone, and for 2 h with 10–6 M V1 receptor antagonist followed by 1 h with 10–6 M AVP or 10–6 M CRH together. During the control period, the incubation was performed without any additions. The ACTH concentrations from 100-μl supernatant media samples were measured by direct RIA (24). The method of ACTH determination was the same as in the case of plasma. The data were calculated on the basis of the 12 measurements in each group.

**Statistics.** All data are presented as means ± SE. The Mann-Whitney’s U test was used for comparisons involving...
tong groups. The curves were analyzed via the Kruskal-Wallis test. A probability level of <0.05 was accepted as indicating a statistically significant difference.

RESULTS

Plasma AVP level. The oral administration of water led to slightly increased plasma AVP levels at 5 and 15 min, but the AVP level later returned to the normal range. Elevated AVP levels were detected at 5, 15, 30, and 60 min after ethanol administration. The maximum AVP concentration was measured at 15 min after ethanol (Fig. 1).

Plasma ACTH level. The baseline plasma ACTH and corticosterone levels are relatively high and probably reflect the cumulative effects of fasting and the response to the control procedure. Water similarly led to increased plasma ACTH levels at 5 and 15 min, but normalization had occurred by 30 min. V₁ receptor antagonist injection before water administration prevented the transient increase in ACTH concentration. Ethanol administration resulted in increased ACTH levels between 5 and 60 min. The ACTH levels decreased 15 min after every treatment, possibly because of the feedback action of the increased corticosterone level. Treatment with the V₁ receptor antagonist before ethanol administration significantly inhibited the ACTH rise normally seen between 15 and 60 min after ethanol administration (Fig. 2).

Plasma corticosterone level. The plasma corticosterone levels were also higher between 5 and 15 min after water administration. V₁ receptor antagonist injection significantly decreased the plasma corticosterone level between 5 and 10 min after water administration. Ethanol yielded an elevated plasma corticosterone level at 5 min, and the level remained high up to 60 min. V₁ receptor antagonist injection reduced the plasma corticosterone concentrations between 15 and 60 min after ethanol administration (Fig. 3).

Hypothalamic CRH content. As Fig. 4 shows, water administration through the gastric tube did not induce any change in the CRH content of the hypothalamus. Similar results were observed after V₁ receptor antagonist and water administration. Higher contents of hypothalamic CRH were measured at 30 and 60 min after ethanol administration. The V₁ receptor antagonist injected 5 min before ethanol administration blocked the rise in hypothalamic CRH content, which then remained within the control range after ethanol stress.

Actions of cycloheximide on CRH. After cycloheximide and oral water administration, there was no change in the hypothalamic CRH content (Fig. 5).
Higher CRH levels were detected after ethanol administration. Smaller doses of cycloheximide treatment before ethanol administration significantly inhibited the hypothalamic CRH enhancement; however, the CRH concentration remained above the control level at both 30 and 60 min after ethanol administration. However, higher doses (30 mg/kg body wt) of cycloheximide prevented the increase in the hypothalamic CRH content after ethanol administration. Inhibition of protein synthesis with cycloheximide dose dependently reduced the stress-induced increase in CRH in the hypothalamus, as shown in Fig. 5.

**ACTH levels in pituitary tissue culture.** Increased ACTH levels were demonstrated in the anterior pituitary tissue culture media after the addition of 30 mM K+ to the incubation medium, due to a depolarization-induced ACTH release (Fig. 6). The ACTH concentration was significantly enhanced after the administration of 10^{-6} M AVP or 10^{-6} M CRH alone. A higher ACTH level was found after the administration of AVP and CRH together. A slightly decreased ACTH release was observed after V1 receptor antagonist administration alone. The AVP- or CRH-induced, increased release of ACTH was prevented by the administration of V1 receptor antagonist. A moderate enhancement of ACTH level was detected when AVP+CRH was administered after the V1 receptor antagonist treatment. The data were calculated on the basis of 12 measurements in each group.

**DISCUSSION**

The series of studies presented here shows that the plasma AVP, ACTH, and corticosterone levels and the hypothalamic CRH content are elevated after acute stress induced by a high concentration of orally administered ethanol, and these responses can be reversed by an AVP V1 receptor antagonist. These findings are in agreement with previous observations that a high dose of orally administered ethanol causes AVP release in humans and in rats (27, 34). These results, however, are in apparent conflict with the established finding that ethanol in low concentration inhibits the release of AVP (54, 63). The paradoxical action of orally administered ethanol on AVP release might possibly reflect the high dose of ethanol used. It is known that after stress, CRH and AVP are coreleased into the primary capillaries of the portal circulation in the stalk-median eminence region from where the blood carries the neuropeptides to the anterior lobe. This AVP is unlikely to reach the systemic circulation in quantities high enough to elevate the plasma AVP level. Instead, the plasma AVP changes probably reflect the activity of the
magnocellular neurons with terminals in the neural lobe, and this AVP may reach the anterior lobe only after dilution in the general circulation (21). We have observed that the AVP elevation is sufficiently high to influence the hypothalamic CRH cells after administration of a high dose of ethanol into the stomach, as shown by the preventive effect of the V1 receptor antagonist. We consider it likely that stimulation of the CRH/AVP containing parvocellular neurons will be involved in the release of ACTH and corticosterone after ethanol administration.

Our experiments revealed increased plasma AVP and hypothalamic CRH contents after ethanol administration. There was no elevation of the CRH content in the hypothalamus after ethanol administration when the V1 receptor antagonist was injected before ethanol administration. This suggests that systemic AVP sends signals via the V1 receptors to the hypothalamus to stimulate either directly or indirectly the CRH-producing hypothalamic neurons. We suggest that AVP may act in a dual manner: 1) in the pituitary portal blood, AVP and CRH are cosecreted, and AVP potentiates the actions of CRH; and 2) in the systemic circulation, AVP may signal the presence of stress to the hypothalamus (21). Many data in the literature provide evidence of a physiological synergistic interaction between CRH and AVP at the level of the pituitary. Exogenously administered AVP significantly potentiates CRH-stimulated ACTH release in rats (12, 67) and humans (26, 37). Endogenous AVP can also potentiate CRH-stimulated ACTH secretion in humans; synthetic human CRH resulted in higher ACTH and cortisol responses after a water restriction than after a water load (69). The role of endogenous AVP in the ACTH response to stress is suggested by the results of Guillaume et al. (13), who found significantly reduced ACTH and cortisol responses to insulin stress and restraint stress and CRH injection in anti-AVP-immunized rams compared with controls. In accordance with our finding, Rivier et al. (58) reported that ACTH secretion induced by ether stress, which stimulates CRH secretion, is significantly moderated by pretreatment with an AVP antagonist analog. All of these data are compatible with a dual role of AVP in the regulation of the hypothalamic-pituitary-adrenocortical (HPA) axis.

The increased plasma ACTH and corticosterone levels in response to a high dose of orally administered ethanol relate to a stress situation (55–57). During stress, AVP plays an important role in ACTH stimulation. The involvement of AVP in the ACTH response to restraint stress is supported by the observation that the ACTH response is impaired in genetically AVP-deficient Brattleboro rats (5, 11, 22, 44, 70, 71). Furthermore, the ACTH responses to ether stress and adrenalectomy are blunted in Brattleboro homozygous rats (11). As Brattleboro rats do not differ from the normal controls with respect to the hypothalamic CRH content (22), the impaired ACTH response in these rats is most probably explained by their AVP deficiency. The role of endogenous AVP in stress-induced ACTH release has previously been demonstrated in several studies involving the use of the passive immunization technique with an AVP antiserum or the administration of synthetic AVP antagonists. In the rat, intraperitoneal administration of anti-AVP immunoglobulins reduces the ACTH responses to restraint stress and formalin stress (36). The intracerebroventricular administration of AVP antiserum leads to a moderate but significant reduction in plasma ACTH level after ether stress (50). V1 receptor antagonists attenuate the AVP-induced increase in plasma ACTH when administered before AVP injection in the rat (4, 18). Besides the animal observations, we have some human experiences (32), i.e., the incidence of human gastroduodenal ulceration is significantly higher in the normal population (in whom the release of AVP is presumed to be intact) than in the AVP-deficient population (central diabetes insipidus patients). These findings indicate that endogenous AVP plays an aggressive role in the development of gastrointestinal mucosal injury.

The question arises of how ACTH secretion is influenced by AVP after stress. We refer here to the mini-review by Kjaer (21); the action of AVP on ACTH release is exerted in direct and indirect ways. The direct effect influences the ACTH production of the anterior pituitary gland. The principal effect of systemic AVP on ACTH secretion in conscious rats is produced indirectly via the stimulation of hypothalamic CRH. The indirect effect of AVP is probably more significant when AVP is administered in vivo (47), because it is known to have marked cardiovascular effects even in low concentrations. Moreover, the pituitary AVP receptor differs from the classical V1 receptor, and the designation V1b (as opposed to V1a for the classical receptor) has been proposed (4, 6, 22, 23). Under in vivo conditions, however, V1a receptors appear to be involved, because V1a receptor antagonists were effective in inhibiting the release of ACTH or corticosterone (2, 9, 40, 42, 47, 59, 60, 65) and because the pressor activity of V1 receptor agonists correlated with their ability to release ACTH and corticosterone (2, 47). Our in vivo results fit with the above explanation; the ACTH and corticosterone secretions after ethanol stress were considerably inhibited if the rats were treated with the V1 receptor antagonist d(CH2)5Tyr(Me)AVP immediately before ethanol administration. Our in vitro experiments, however, indicate that the ACTH-blocking effect of the V1 receptor antagonist does not develop only through the decrease of the hypothalamic CRH content; in high concentrations, the compound can also directly block the ACTH-increasing effect of AVP in the anterior tissue culture. The observation with AVP demonstrates that d(CH2)5Tyr(Me)AVP is a mixed antagonist with direct V1b receptor antagonist character, which is in accordance with the findings of Jard et al. (18), Antoni et al. (4), and Bernardini et al. (8). The latter finding with CRH is rather surprising, and it might possibly relate to a still unidentified interaction of V1 receptor antagonists with CRH receptors on the pituitary ACTH-producing cell;
however, this phenomenon needs further experimental validation.

For clarification of the role of CRH in the stress reaction after ethanol administration, the alterations in hypothalamic CRH content were also determined after high doses of orally administered ethanol. Many researchers have investigated the effects of different types of stress on the CRH content in the hypothalamus (51). Although determination of the CRH content in the hypothalamus alone is insufficient to establish whether the changes in release, storage, or synthesis are responsible, a difference between treated and control groups clearly reflects the involvement of CRH in the stress situation. Chappell et al. (10) reported that acute or chronic stress resulted in a 50% decrease in hypothalamic CRH content. Similar observations were published following acute (49, 52) or chronic stress (3). These reductions are thought to relate to the secretion of CRH from the hypothalamus in the acute situation, and to continued release in the chronic stress condition, when new CRH synthesis cannot keep pace with the demands for higher secretion. This hypothesis, however, has not yet been proved convincingly (51). Murakami et al. (48) reported a fast increase in the hypothalamic CRH content, already observed 2.5 min after ether stress. Moldow et al. (46) described a significant decrease in hypothalamic CRH content 15 min after the initiation of restraint stress. This was followed by an enhanced hypothalamic CRH concentration at 60 min, which could be blocked by cycloheximide administration before stress, indicating that new protein synthesis can explain the increased hypothalamic CRH level demonstrated at this time point. Analogous results were reported by Haas and George (14); a significant increase in hypothalamic CRH concentration was observed 24 h after a single 5-min foot shock, and when protein synthesis was eliminated by anisomycin pretreatment, it completely abolished the increase in hypothalamic CRH content. A number of recent investigations has directly studied CRH gene expression by measuring hypothalamic CRH mRNA concentrations. Different stressors, which activate the hypothalamic-adrenal axis, can also influence CRH gene expression. Swimming, hypertonic saline, or restraint stress led to an increased hypothalamic CRH mRNA expression within 4 h, and the level remained elevated for 24 h (15, 16, 33). Similar findings were observed after a 2-h immobilization stress (39) and a 1-h restraint stress (20). In our experiments, the increases in hypothalamic CRH content were blocked by cycloheximide pretreatment, which points to a role of enhanced protein synthesis in the increased hypothalamic CRH concentration after ethanol stress (1, 53). Whether the overall increase in hypothalamic CRH content, paralleling an enhanced release in our studies, reflects a rapid increase in translation and/or increased processing of the prohormone of CRH requires further studies.

In their review, Owens and Nemeroff (51) presented cumulative evidence that CRH integrates the overall physiological behavioral responses of an organism to stress. The neuroendocrine response to stress is primarily controlled by CRH neurons originating from the paraventricular nucleus of the hypothalamus, but the AVPergic magnocellular neurons presumably also participate in the development of a stress reaction. Our present results support the importance of the hypothalamo-neurohypophyseal or magnocellular AVP system in the development of physiological or pathological changes following various stress situations. It also suggests possible pharmacological strategies involving AVP antagonist agents to prevent such pathology.

Perspectives

Earlier we studied the development of gastrointestinal stress erosions in different rat experimental models, including mucosal injury provoked by ethanol, indomethacin, cold-restraint stress, and hemorrhagic and endotoxin shock (28, 68). We found that an increased AVP secretion during these stress situations has key importance in the initiation of damage (31). In the present work, the interaction between the HPA axis and AVP secretion was demonstrated following acute ethanol challenge. The lower incidence of gastrointestinal ulceration among AVP-deficient patients with central diabetes insipidus gives further support to the pathological importance of endogenous AVP release in the development of mucosal damage even under clinical circumstances (32).

Gastrointestinal mucosal stress erosions commonly appear among critically ill patients mostly in intensive care units after a number of acute conditions, such as severe trauma, burns, septic or hemorrhagic or cardiogenic shock, or injury of the central nervous system, etc. (62). Although it would be of high clinical significance, the problem of how to prevent the development of such mucosal erosions is not solved (7). The findings in earlier studies suggested that the use of vasopressin pressor receptor (V1a) antagonists in clinical practice might have potential therapeutic benefit (28, 29, 31, 32). The present results revealed that a vasopressin pressor receptor (V1a) antagonist could not only prevent the vasoconstrictive action of increased vasopressin secretion, but it could also block the elevation of the hypothalamic CRH response and ACTH-corticosterone secretion following acute ethanol challenge. These experimental and clinical observations lead us to conclude that vasopressin antagonists might have importance in the prevention of the generation of the life-threatening bleeding from gastrointestinal stress erosions.

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