Inferior Petrosal Sinus Sampling in Healthy Human Subjects Reveals a Unilateral Corticotropin-releasing Hormone–induced Arginine Vasopressin Release Associated with Ipsilateral Adrenocorticotropin Secretion

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Abstract

Arginine vasopressin (AVP) acts synergistically with corticotropin-releasing hormone (CRH) to stimulate ACTH release from the anterior pituitary. In a previous study of bilateral simultaneous inferior petrosal sinus (IPS) sampling in healthy human subjects, we observed lateralized ACTH secretion, suggesting lateralized secretion of an ACTH-regulating hypothalamic factor. To investigate this possibility, we measured ACTH, CRH, AVP, and oxytocin (OT) levels in the IPS and the peripheral circulation in nine normal volunteers, before and after 1 μg/kg i.v. bolus ovine CRH (oCRH). At baseline, ACTH, AVP, and OT exhibited a significant ($P < 0.05$) two to threefold intersinus gradient (ISG), indicating the existence of a dominant petrosal sinus. Endogenous CRH was undetectable in all samples. Despite similar exogenous oCRH levels in both petrosal sinuses, oCRH caused a significant increase ($P < 0.001$) in the ACTH ISG (15.8 ± 5.6, mean±SEM), suggesting increased responsiveness of one dominant side of the anterior pituitary. This was associated with an ipsilateral CRH-induced AVP release and a significant increase ($P < 0.01$) in the AVP ISG (8.6 ± 2.3), suggesting lateralized AVP secretion by the hypothalamus. Furthermore, the increased AVP ISG after oCRH correlated strongly with the ACTH ISG ($r = 0.92$, $P < 0.01$). oCRH administration did not affect OT. These findings suggest that there is a dominant petrosal sinus in healthy volunteers that appears to reflect a dominant side of the adenohypophysis, characterized by increased functional activity and/or responsiveness of the pituitary corticotrophs. This may reflect lateralized hypothalamic and/or suprahypothalamic function resulting in CRH-responsive lateralized secretion of AVP from parvocellular and/or magnocellular axons in the median eminence and the posterior pituitary. Although the functional and teleologic signif-

icance of these findings remains to be investigated, our data suggest a novel mechanism for CRH-mediated ACTH release, namely CRH-induced release of AVP which then enhances CRH action on the corticotrophs. Furthermore, our data represent the first direct evidence for the concept of brain lateralization with respect to neuroendocrine secretion. (*J. Clin. Invest.* 1996. 97:2045–2050.) Key words: hypothalamus • median eminence • adenohypophysis • neurohypophysis • oxytocin

Introduction

The capacity for assessment of human anterior pituitary secretory activity has been enhanced by the development of inferior petrosal sinus (IPS)[1] sampling. Blood from the venous plexus that drains the anterior and posterior pituitary empties into the right and left cavernous sinuses, which connect to the jugular veins via the inferior petrosal sinuses. Sampling of IPS blood thus provides a unique opportunity for assessment of pituitary secretion, before dilution by the systemic circulation. Simultaneous bilateral IPS sampling has been applied extensively for the differential diagnosis of patients with Cushing syndrome (1–3). In a recent report, Yanovski et al. found ACTH to be secreted in a lateralized fashion in the IPS of six healthy human subjects, resulting in the inability of IPS sampling to distinguish Cushing disease from normal physiology (4). Lateralized ACTH secretion in the IPS of patients with Cushing disease is a common finding, with increased ACTH secretion into the IPS ipsilateral to the tumor in ∼ 70% of the patients. However, lateralized ACTH secretion in normal subjects was an unexpected finding that suggested differences in the functional activity of the corticotrophs in the two sides of the anterior pituitary gland. Such differences could possibly be due to differential stimulation by lateralized secretion of ACTH-regulating hypothalamic factor(s).

The secretion of ACTH by the anterior pituitary is regulated by two major hypothalamic secretagogues, corticotropin-releasing hormone (CRH) (5) and arginine vasopressin (AVP), which exerts a strong synergistic effect with CRH at the pituitary corticotroph (6–8). Both CRH and AVP are released into the long portal vessels by axons originating in the parvocellular

1. *Abbreviations used in this paper:* AVP, arginine vasopressin; CRH, corticotropin-releasing hormone; hCRH, human CRH; IPS, inferior petrosal sinus; ISG, intersinus gradient; ME, median eminence; oCRH, ovine CRH; OT, oxytocin.

division of the paraventricular nucleus of the hypothalamus and terminating in the external zone of the median eminence. In the nonstressed state, approximately half of parvocellular CRH-producing neurons coexpress AVP (9), while a small number coexpress oxytocin (OT) as well (10). The majority of peripherally circulating AVP originates, together with OT, from magnocellular neurons in the paraventricular nucleus and the supraoptic nucleus of the hypothalamus that terminate in the posterior pituitary. However, while passing through the median eminence and the hypophyseal stalk, magnocellular axons can also release AVP into the long portal system (11, 12). Furthermore, a number of neuroanatomical studies have shown the existence of short portal vessels that allow communication between the posterior and anterior pituitary (12–14). Thus, in addition to parvocellular AVP, magnocellular AVP may influence anterior pituitary ACTH secretion.

While the role of AVP in the regulation of ACTH secretion is well established, the role of OT is somewhat controversial. In the rat, OT, like AVP, exerts a strong synergistic effect with CRH to increase ACTH (7, 15). By contrast, in humans, endogenous OT induced by breast stimulation decreases plasma ACTH and cortisol (16, 17). Exogenously administered OT also appears to have a weak inhibitory effect as indicated by a number of human studies (18–21), however, such an effect has not always been found (22, 23).

In addition to the well established synergistic effects of CRH and AVP on the release of ACTH (6–8), CRH administration at a nonhypotensive dose has been shown to stimulate plasma AVP (24–26) and OT (27) in animals, but not in humans (28–30). Recently, Nussey et al. reported lateralized AVP and OT secretion into the IPS of patients with Cushing disease after administration of CRH, without a concomitant change in peripheral AVP or OT levels (31). However, this finding could have been caused by the presence of the pituitary adenoma and might not have represented normal physiology.

Therefore, we investigated the possibility of lateralized secretion of CRH, AVP, and OT, the three main hypothalamic regulators of ACTH, into the inferior petrosal sinuses of nine healthy human subjects. Since the observed lateralized ACTH secretion in healthy humans was even more prominent after CRH administration, and since CRH appears to stimulate AVP and OT, we also evaluated possible AVP and OT responses to exogenous ovine CRH (oCRH).

Methods

Subjects. Nine normal volunteers (one female and eight males; age 32.2±4.0 yr, mean±SD, range 26–37 yr) were enrolled in the study. Data from IPS sampling for ACTH from six of the nine subjects were included in our previous report (4). All subjects had normal urine free cortisol excretion (< 248 nmol/d); normal hepatic, renal, and thyroid function; and no history of affective disorder (normal Beck Depression Inventory scores) or other psychiatric illnesses. Subjects were medication free for at least 6 wk before the study. The protocol for IPS sampling with oCRH administration in normal volunteers was approved by the NICHD Investigational Review Board and the NIH Radiation Safety Committee. Informed consent was obtained from all subjects.

Inferior petrosal sinus sampling. Catheterization and sampling of the inferior petrosal sinuses was performed as previously described (32). Briefly, after sedation with intravenous diazepam (1–2 mg) and fentanyl (50–100 μg), and systemic anticoagulation with heparin

(3,000–4,000 IU), catheters were inserted into the femoral vein and advanced to the petrosal sinuses under fluoroscopic guidance. Blood samples (10 ml each) were obtained between 0900 and 1100, simultaneously from each petrosal sinus and a peripheral vein 5 and 1 min before and 3, 5, and 10 min after the intravenous injection of oCRH (1 μg/kg). All samples were collected in prechilled EDTA tubes and were kept on ice until centrifugation (within 2 h). The plasma was separated, aliquoted, and frozen at −20°C for ACTH, CRH, AVP, OT, and oCRH determinations. At the conclusion of the sampling, retrograde venography was performed to verify proper catheter placement.

Radioimmunoassays. For measurement of plasma AVP and OT levels, frozen plasma samples (2.0 ml each) were thawed on ice and acidified with 10 ml of 0.1 N HCl. The acidified plasma samples were centrifuged and applied to Sep-Pak C_{18} cartridges (Waters Associates, Millipore Corp., Milford, MA), which had been activated with 10 ml of acetonitrile (CH_3CN) followed by 10 ml of 0.1 N HCl. The cartridges were then washed with 10 ml of 0.1% trifluoroacetic acid (TFA) and 3 ml of 10% CH_3CN in 0.1% TFA. The absorbed peptides were eluted with 4 ml of 80% CH_3CN in 0.1% TFA. The eluant was collected, and the solvent was removed by means of a speed vacuum concentrator (Savant Instruments, Inc., Farmingdale, NY).

The samples were reconstituted in 0.6 ml of assay buffer, consisting of 10 mM monobasic and 81 mM dibasic sodium phosphate, pH 7.4, 0.05 M NaCl, 0.01% NaN_3, 0.1% BSA, and 0.1% Triton X-100, and were allowed to dissolve overnight at 4°C. The RIA was performed in polystyrene tubes by mixing 100 μl of sample in duplicate (or standard in triplicate) and 100 μl of antiserum. (Arg^8)-vasopressin and OT standards were purchased from Peninsula Laboratories (Belmont, CA). Anti-AVP rabbit serum was obtained from Arnel Corp. (New York, NY), and OT antiserum (R-421) was kindly provided by Dr. Delbert A. Fisher (Torrance, CA). The antiserum titers were 1:90,000 and 1:27,000 for AVP and OT, respectively.

After incubation for 48 h at 4°C, 100 μl of ^{125}I-labeled AVP or OT (3,000 cpm) (both from Amersham Corp., Arlington Heights, IL) was added to each tube, and the incubation continued for another 48 h at 4°C. Bound and free fractions were then separated by adding 100 μl of goat anti–rabbit IgG serum and 100 μl of normal rabbit serum (Peninsula Laboratories). The precipitates were allowed to form overnight at 4°C, then 0.5 ml of assay buffer was added. The precipitate was collected by centrifugation at 1,700 *g* for 20 min, and the supernatant was removed by aspiration. The tubes were counted for ^{125}I in a scintillation well gamma counter.

Extraction recovery of AVP and OT added to silica-stripped plasma was > 85%. The standard curve concentration range was 0.36–92.2 pmol/liter for AVP and 1.0–248.2 pmol/liter for OT. The lower limit of detection for the AVP and OT assays was 0.53 and 1.2 pmol/liter, respectively. The half-maximal displacement of the tracer was 6.8 pmol/liter (AVP) and 16.2 pmol/liter (OT). The intra- and interassay coefficients of variation of the AVP assay were 5.3 and 7.9% at 2.9 pmol/liter, 4.8 and 10.7% at 5.8 pmol/liter, and 6.1 and 9.6% at 11.5 pmol/liter, respectively. The intra- and interassay coefficients of variation of the OT assay were 4.8 and 4.4% at 7.8 pmol/liter, 2.6 and 8.4% at 15.5 pmol/liter, and 3.9 and 7.1% at 31.0 pmol/liter, respectively.

Plasma ACTH (33), human CRH (hCRH) (34), and oCRH (33) levels were measured by RIA after extraction as previously described. The lower limit of detection for the ACTH, hCRH, and oCRH assays was 0.7, 1.8, and 2.1 pmol/liter, respectively. The mean intra- and interassay coefficients of variation for the ACTH assay were 3.8 and 7.2%, for the hCRH assay 7.0 and 9.7%, and for the oCRH assay 6.2 and 8.2%, respectively. None of the antibodies used for the above determinations exhibited any significant cross-reactivity with related peptide hormones (all < 1%, data not shown), except the hCRH-antibody, which showed significant cross-reactivity with oCRH (10%). For this reason, hCRH concentrations were only determined in the −5 and 0 min baseline samples. All samples from the same subject were analyzed in one assay.

Statistical analysis. All results were expressed as the mean±SEM. One and two factor repeated measures ANOVA was performed using Superanova and Statview 4.02 (Abacus Concepts, Berkeley, CA). Due to heteroscedasticity of variance, all values were subjected to logarithmic transformation before the analysis of variance. In some samples, the OT levels and more rarely the AVP levels in the nondominant IPS and the peripheral vein were below the detection limit of the assay. In such case the value of the detection limit was used for all statistical analyses. Fisher paired least significant difference tests were used for multiple comparisons. The dominant inferior petrosal sinus was defined as the sinus with the highest ACTH concentration at 3 min after oCRH. The intersinus gradient (ISG) was determined at the different time points for each subject, as the ratio of the dominant to nondominant IPS hormone concentrations. The relation between the AVP and ACTH ISG was determined using linear regression.

Results

Plasma ACTH. As previously reported (4), each subject consistently exhibited a much greater ACTH response to oCRH in one petrosal sinus, which was, therefore, termed the dominant petrosal sinus. Two-way ANOVA with repeated measures demonstrated a significant interaction of time before and after oCRH administration (-5, 0, 3, 5, or 10 min) and source of blood (dominant, nondominant petrosal sinus or peripheral vein) for ACTH (F = 31.2, df = 8, $P < 0.001$). Baseline plasma ACTH was significantly higher in the dominant petrosal sinus ($P < 0.05$) as compared to the periphery. After the administration of oCRH, plasma ACTH was significantly higher at all time points in the dominant IPS ($P < 0.001$) as compared to the nondominant IPS and the peripheral vein (Fig. 1 *A*).

The ACTH intersinus gradient (ISG) also increased significantly after oCRH administration (F = 5.4, df = 4, $P < 0.001$), at all time points (Fig. 2). The ACTH ISG increased from 2.2±0.7 at 0 min to a peak value of 15.8±5.6 at 5 min after oCRH. In seven of the nine subjects studied (all of whom were right-handed), the right petrosal sinus was dominant. The probability that the observed predominance of lateralization to the right petrosal sinus was due to chance was calculated from the binomial distribution to be 0.070.

Plasma AVP. Two-way ANOVA demonstrated a significant interaction of time before and after oCRH and source of blood for AVP (F = 3.5, df = 8, $P < 0.003$). Baseline plasma AVP was significantly higher in the dominant IPS as compared either to the nondominant IPS ($P < 0.05$) or the periphery ($P < 0.01$). Plasma AVP increased significantly after oCRH only in the dominant IPS (F = 3.7, df = 4, $P < 0.02$), but not in the nondominant IPS or the periphery (Fig. 1 *B*). CRH-induced AVP in the dominant IPS was significantly higher ($P < 0.01$) as compared to the nondominant IPS and the periphery at all time points. The unilateral increase in AVP resulted in a significant increase of the AVP ISG (F = 4.0, df = 4, $P < 0.01$), from a baseline value of 3.0±0.6 at 0 min to a peak value of 8.6±2.3 at 10 min after oCRH (Fig. 2).

Plasma OT. Two-way repeated measures ANOVA demonstrated a significant interaction of the source of blood for OT (F = 7.6, df = 2, $P < 0.005$), but no interaction of time before and after oCRH. Plasma OT concentrations were significantly higher in the dominant IPS ($P < 0.05$) as compared to the nondominant IPS and the periphery at all time points (Fig. 1 *C*). OT levels were clearly detectable in all samples obtained from the dominant IPS, while they were below the detection
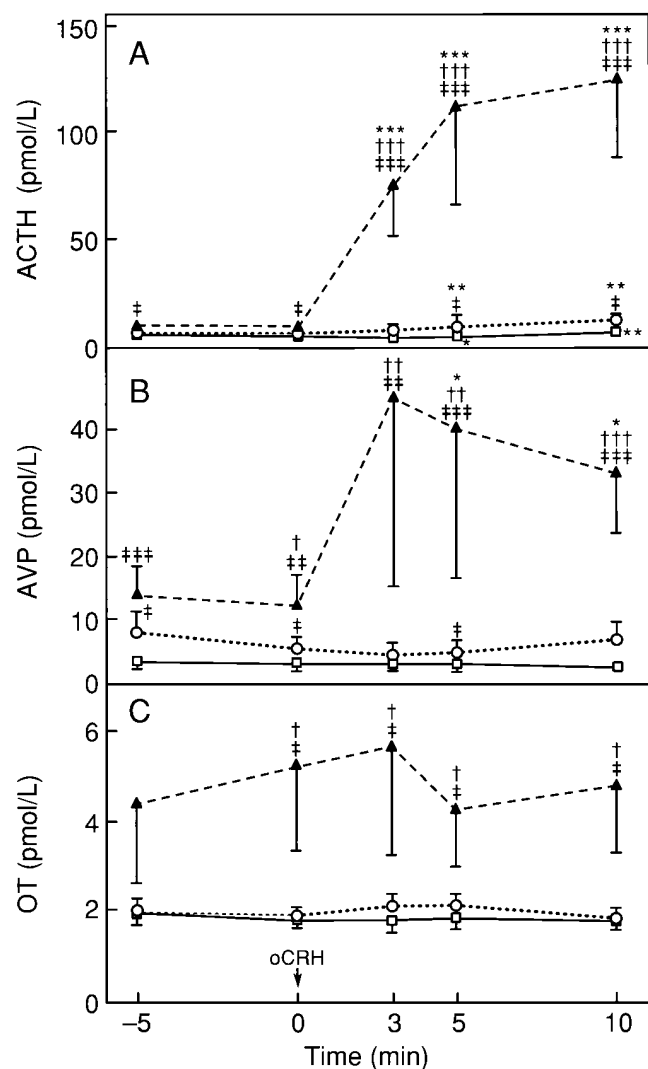

Figure 1. Concurrent plasma concentrations (mean±SEM) of ACTH (*A*), AVP (*B*), and OT (*C*) in the dominant petrosal sinus (▲) (defined as the petrosal sinus with the highest ACTH level 3 min after oCRH administration), the nondominant petrosal sinus (○), and a peripheral vein (□) in nine healthy human subjects. Concentrations at the basal state (-5 and 0 min) and in response to intravenous administration of 1 μg/kg oCRH (3, 5, and 10 min) are depicted. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$; compared to baseline concentrations. †$P < 0.05$, ††$P < 0.01$, †††$P < 0.001$; compared to the nondominant petrosal sinus. ‡$P < 0.05$, ‡‡$P < 0.01$, ‡‡‡$P < 0.001$; compared to the peripheral vein.

limit of the assay in some samples from the nondominant IPS and the peripheral vein. Neither plasma OT nor OT ISG changed after oCRH administration (Fig. 2).

Plasma hCRH. Endogenous plasma CRH concentrations in the IPS and the periphery were below the detection limit of the assay (< 1.8 pmol/liter) in all subjects (data not shown).

Plasma oCRH levels. Plasma oCRH levels were similar in the two petrosal sinuses at all time points. oCRH levels in the dominant versus nondominant petrosal sinuses reached a peak of 2.3±0.3 vs. 2.6±0.3 nmol/liter at 3 min, and gradually declined to 1.3±0.1 vs. 1.3±0.2 nmol/liter 10 min after the administration of oCRH (data not shown).
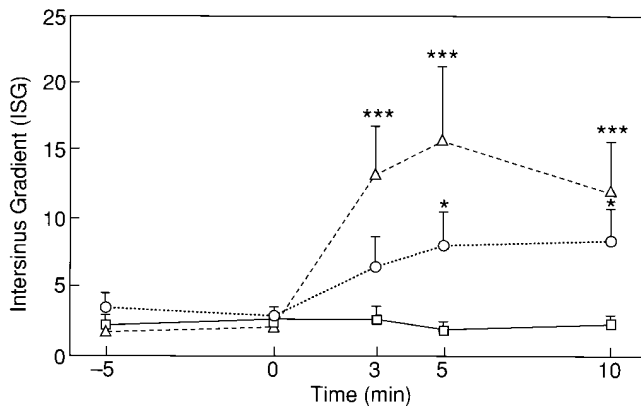
Figure 2. Intersinus Gradient (ISG) (mean±SEM) of plasma ACTH (△), AVP (○), and OT (□) concentrations before (−5 and 0 min) and after (3, 5, and 10 min) intravenous administration of 1 μg/kg oCRH. *$P < 0.05$, ***$P < 0.001$ - compared to baseline ISG.

Correlation between AVP and ACTH intersinus gradients. No statistically significant correlations were found between the AVP and ACTH ISG at −5 or 0 min (Fig. 3 *A*). However, after the administration of oCRH, highly significant positive correlations were found between the AVP and ACTH ISG (Fig. 3 *B*). The correlation coefficient (*r*) was 0.08 and −0.11 at −5 and 0 min before, and 0.67 ($P < 0.05$), 0.63 ($P < 0.05$) and 0.92 ($P < 0.01$) at 3, 5, and 10 min after the administration of oCRH, respectively.

Discussion

Our data from simultaneous bilateral inferior petrosal sinus sampling demonstrate a single dominant petrosal sinus in healthy human subjects with respect to basal and oCRH-stim-
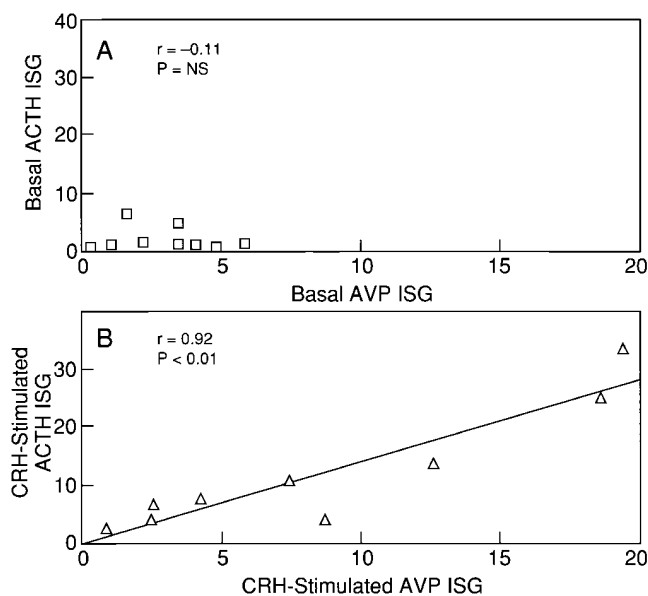

Figure 3. Correlation between basal AVP and ACTH intersinus gradients (ISG) at 0 min (*A*) and between CRH-stimulated AVP and ACTH ISG at 10 min (*B*).

ulated ACTH and AVP concentrations. AVP did not change after oCRH in the nondominant IPS or the periphery. Basal OT also showed an intersinus gradient, from the same dominant IPS. In contrast to its effects on ACTH and AVP, CRH did not change petrosal sinus OT. Basal endogenous CRH in the petrosal sinuses and the periphery was found to be below the detection limit of the assay. After oCRH administration, exogenous oCRH levels were similar in the two petrosal sinuses.

Our previous results (4) and those of the present study show that lateralization of CRH-induced ACTH release is not limited to Cushing disease, as previously reported (1–3) but is rather a generalized phenomenon exhibited by healthy individuals. Moreover, the present data show that in response to CRH, AVP is secreted into the same dominant petrosal sinus as is ACTH. To our knowledge, this is the first study to demonstrate a stimulatory effect of CRH on petrosal AVP concentrations in normal human subjects. Despite evidence that CRH stimulates plasma AVP and OT in animals (24–27), a number of studies measuring peripheral AVP have failed to demonstrate such an effect in humans (28–30). In the present study, however, CRH-induced AVP secretion was detectable only in the dominant IPS, before the dilution of pituitary effluent by the systemic circulation. Our findings support those of Oelkers and Ahmed who found high circulating AVP and hyponatremia in primary hypopituitarism (35) and Addison disease (36), respectively. This might be, to a certain extent, the result of chronic hypersecretion of CRH. It is also conceivable that other causes of inappropriate AVP secretion, such as stress, pain, malignant and nonmalignant lung disease, and central nervous system trauma and infections (37–39) may act, at least in part, through eutopic or ectopic CRH hypersecretion.

The cell body that secretes AVP in response to CRH is unknown. In rats, specific, high affinity CRH receptors have been identified by autoradiography in the median eminence (ME) and the intermediate lobe but not in the posterior lobe of the pituitary (40–44). Although CRH has been shown to stimulate magnocellular AVP and OT from the isolated rat neurointermediate pituitary (45, 46), this mechanism is not likely to pertain to humans in whom the intermediate lobe is rudimentary. However, it may explain the observed clear stimulatory effect of CRH on peripheral plasma AVP and OT in animals (24–27) and the absence of an effect in humans (28–30). AVP terminals in the ME are of parvocellular origin; however, we believe that the observed AVP elevation in the dominant petrosal sinus is predominantly of magnocellular origin, for the following reasons: The amount of parvocellular AVP is at least one order of magnitude lower than that released by magnocellular neurons (47). In agreement with this notion, endogenous CRH levels in the IPS of our subjects were below the detection limit of our assay (< 1.8 pmol/liter), indicating that the amount of parvocellular AVP measurable in the IPS should also be quite small. Finally, magnocellular axons as they pass through the ME can be stimulated to release AVP from distinct swellings, known as Herring bodies, in which AVP secretory vesicles are abundant (11). Therefore, we postulate that CRH may induce predominantly magnocellular and to a smaller extent parvocellular AVP secretion, through ME and possibly as yet unidentified posterior pituitary CRH receptors, that could in turn, gain access to the anterior pituitary through both long and short portal vessels and thus modulate ACTH release.

Our data lead us to speculate that even endogenous CRH,

released from parvocellular nerve terminals during stress, might act directly to release AVP from the ME, an effect that could enhance CRH-mediated ACTH secretion. This could represent a novel mechanism by which endogenous CRH promotes ACTH secretion. The existence of such a mechanism implies that CRH-induced ACTH secretion might involve factors other than basal plasma cortisol levels and anterior pituitary CRH receptor number but also CRH receptor number in the ME and the releasability of AVP in response to CRH.

The existence of a basal intersinus gradient of multiple anterior pituitary hormones previously noted in Cushing disease (48, 49), as well as the currently noted ISG for ACTH, AVP, and OT, might be explained as an artifact of the IPS sampling technique per se. Thus, variations in the location of the two catheters at the time of collection, in the anatomy of the two petrosal sinuses, in the extent of blood flow through the intercavernous sinuses, in the amount of nonpituitary blood mixing with cavernous sinus blood, or in the relative number of corticotrophs drained by each petrosal sinus could cause differences in the amount of pituitary hormones found in the two petrosal sinuses in the basal state. While these factors associated with the IPS sampling technique might account for the small intersinus ACTH gradient observed in normal subjects during baseline conditions (2.2 ± 0.7), it seems unlikely that they could explain the sevenfold increase in the intersinus ACTH gradient after the administration of CRH. For instance, if the higher baseline ACTH concentrations seen in one petrosal sinus were merely reflecting a dominant petrosal sinus draining a greater number of pituicytes, which were nevertheless exposed to similar concentrations of hypothalamic secretagogues, one would expect a comparable degree of ACTH stimulation in response to CRH in both petrosal sinuses and no net change in the ACTH ISG after the administration of CRH. Therefore, we suggest that the existence of a dominant petrosal sinus with respect to ACTH secretion in normal human subjects appears to reflect a dominant side of the anterior pituitary gland itself, characterized by increased functional activity and/or responsiveness of the pituitary corticotrophs, which may be a result of greater ipsilateral AVP secretion.

There are several reasons why the basal AVP ISG did not correlate with the ACTH ISG. The stimulatory effect of increased AVP in the dominant petrosal sinus may have been neutralized by the inhibitory effect of elevated OT concentrations. Furthermore, AVP by itself is a weak ACTH secretagogue and requires CRH to exert a potent effect on the release of ACTH. Even though inferior petrosal sinus cannulation is regarded as a stressful procedure, endogenous CRH levels in both petrosal sinuses were found to be below the detection limit of our assay, probably due to the pretreatment of our subjects with fentanyl and diazepam, both of which are known to inhibit hypothalamic CRH secretion (50, 51). Therefore, low CRH secretion during baseline sampling and a diminished synergistic effect with AVP probably account for the absence of a correlation between the ACTH and the AVP ISG. However, the dynamics of ACTH secretion changed dramatically after administration of exogenous CRH, especially on the dominant side of the anterior pituitary. CRH induced AVP secretion in the dominant petrosal sinus only, resulting in a threefold increase in the AVP ISG. Furthermore, increased levels of exogenously administered oCRH were then available to synergize with the increased AVP concentrations on the pu-

tative dominant side. The result was secretion of ACTH predominantly into the dominant petrosal sinus, a sevenfold increase in the ACTH ISG and a highly statistically significant correlation between the AVP and the ACTH ISG.

We cannot definitively determine the etiology of lateralized AVP and OT secretion. It is conceivable that parvocellular and/or magnocellular nerve terminals are distributed in an asymmetric fashion in the ME and the posterior pituitary, and thus drain asymmetrically into the petrosal sinuses. However, while this may account for basal AVP and OT gradients, it can not explain the significant threefold increase in the AVP ISG observed after the administration of oCRH. A nonspecific effect on IPS hemodynamics caused by oCRH is also unlikely, since no change in the OT ISG was observed. Therefore, an intriguing hypothesis arises from our finding; the concept of a dominant side of the hypothalamus with respect to neurosecretory activity and responsiveness. Such a dominant side of the hypothalamus could result from increased stimulatory input from higher centers in the limbic system and/or the cortex. At present there is widespread evidence from neuroanatomical and functional studies that, in right-handed individuals, the left hemisphere is specialized for handedness, speech, and neuroimmunomodulation while the right hemisphere predominates in spatial abilities, expression of affect, and control of vital functions supporting survival (52). Recent data by Wittling et al. suggest that, in 80% of right-handed individuals, activation of the hypothalamic-pituitary-adrenal axis is controlled by the right hemisphere (53, 54). This is consonant with our results, since in 78% of our right-handed subjects, the right petrosal sinus was dominant, with respect to ACTH, AVP, and OT secretion.

The functional and teleologic significance of a normally occurring dominant side of the anterior pituitary gland with respect to ACTH secretion is not known. Whether it has physiological relevance during severe chronic stress and whether the nondominant half of the anterior pituitary might constitute a pool of ACTH that would be releasable under extreme conditions remains to be elucidated. Furthermore, the intriguing concept of brain lateralization with respect to neuroendocrine secretion and the possible implications on asymmetric involvement of the two hemispheres in the pathophysiology of somatic and mental illness deserve further investigation.

Acknowledgments

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