Alpha-Adrenoceptor Function in Acute Paranoid Schizophrenia

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Introduction
Although the therapeutic effect of neuroleptic medication has been attributed largely to dopamine receptor blockade, noradrenergic transmission is also inhibited by administration of these drugs and should not be overlooked. In recent years extensive studies of the central noradrenergic metabolism led to the hypothesis of noradrenergic dysfunction in schizophrenia. Both norepinephrine and its metabolite MHPG have been found to be increased in the nucleus accumbens, mesencephalon, and limbic regions of the brain of paranoid schizophrenics (Farley et al. 1978).

In addition, investigations of noradrenergic receptor function have been conducted. Alpha-adrenergic receptors are found in hypothalamic, limbic, and cortical structures, whereas beta-receptors are found in cortical projections from the locus coeruleus. Although beta-adrenoceptor function has not yet been examined, alpha-adrenoceptor function on platelets, as a model for alpha-adrenergic function throughout the body, has been studied in schizophrenic patients. Elevated alpha-adrenoceptor numbers have been found in these patients associated with a deficiency of prostaglandine E₁-stimulated cyclic AMP production, a function known to be inhibited by alpha-receptor stimulation (Kafka and van Kammen 1983). It is not known, however, whether these peripheral findings parallel brain metabolism.

Pharmacological receptor manipulation has been another approach to investigate noradrenergic mechanisms, although neuroendocrine responses to pharmacological challenges have not been elucidated in detail (Matusek et al. 1980). Therefore, we compared endocrine responses of the hypothalamic-pituitary-adrenal and -somatotropic axes following clonidine (CLON), a predominantly centrally acting alpha₂-receptor agonist, in patients with acute paranoid schizophrenia and healthy subjects, in order to explore alpha-adrenoceptor function in schizophrenia.

Methods
Nine patients, five women and four men, with acute paranoid-type schizophrenia, were evaluated on the basis of a clinical interview using ICD-9 (295.3) and DSM-III criteria (295.33 and 295.34). Their mean age was 34.2 ± 3.7 years; two women were tested during the midproliferal phase and two during the midluteal phase of the menstrual cycle, one was postmenopausal. The study was performed after a drug-free period of at least 3 days. The Brief Psychiatric Rating Scale (BPRS) and the Clinical Global Impression (CGI) scale were completed for each patient one day prior to the CLON test. Mean BPRS score was 38.2 ± 3.6 and mean CGI scale score was 5.7 ± 0.3. Nine normal subjects triple-matched for age (37.9 ± 4.9 years), gender (5 women, 4 men) and ovarian status (2 women were in the midproliferal phase and 2 in the midluteal phase of the cycle, 1 was postmenopausal), also were studied.

The CLON stimulation test was conducted on all subjects at rest in bed at 8:00 a. m. after an overnight fast. One hour after the insertion of an intravenous line in an antecubital vein, 2 μg/kg CLON, diluted in 10 ml saline (0.9%), was injected slowly over 10 min. For measurement of plasma GH, ACTH, and cortisol, blood was collected at -15, 0, 15, 30, 45, 60, 90 and 120 min. Plasma GH and cortisol analyses employed standard RIA techniques. Plasma ACTH was measured by RIA after extraction using N-terminal specific antibodies.

The results are expressed as the mean ± SE. The GH, ACTH, and cortisol responses following CLON of patients and normal controls were calculated as the net and total area under the response curve (AUC), using trapezoidal integration. The data were analyzed using nonparametric statistical methods: group comparison by the Mann-Whitney U test; correlations by the Spearman's rank order correlation (rs). All significance levels are two-tailed.

Results
GH
Compared with healthy subjects, the schizophrenic patients exhibited a significantly attenuated GH response to CLON (436 ± 267 vs. 59 ± 44 ng·min/ml; U = 14, p < 0.05) associated with normal basal plasma GH concentrations (Figs. 1a and 2a).

ACTH
Although the total amount of ACTH secreted during CLON stimulation was significantly higher in schizophrenic patients (3313 ± 516 vs. 2013 ± 148 pg·min/ml; U = 15, p < 0.05), no difference in the CLON-induced inhibition of ACTH secretion was found between schizophrenic patients and controls (Figs. 1b and 2b). No relationship between CLON-induced GH and ACTH responses was found.

Cortisol
No difference in the CLON-induced inhibition of cortisol secretion and in the total cortisol secretion during CLON stimulation was found between schizophrenic patients and healthy subjects. When the relationship between ACTH and cortisol secretion during CLON stimulation was determined in all subjects, a positive correlation emerged which was significant at the trend level (rs = 0.40, p < 0.1). No correlation between GH and cortisol responses to CLON could be demonstrated.

Discussion
Although the role of alpha-adrenergic receptors in the neuroregulation of GH release is still a matter of controversy (Lesch et al. 1988), animal and human research suggests that the secretion of GH stimulated by the alpha₂-adrenoceptor agonist CLON may
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provide an indirect index of central alpha-adrenoceptor function. A blunted GH response to CLON has been consistently found in patients with major depression, but not in patients with secondary depression and dysthmic disorder (Matussek et al. 1980). In contrast to this previous study, our finding suggests that paranoid schizophrenic and depressed patients demonstrate a similar blunted GH response to CLON which is consistent with an emerging body of evidence suggesting a partial overlap in neurobiology of schizophrenia and depression. Although the two disorders are different in relation to hypothalamic-pituitary-adrenal axis dysregulation as indicated by increased ACTH but normal cortisol secretion in the schizophrenic patients (Lesch et al. 1988), recent attention has focused on the hypothesis that disturbances in noradrenergic function may be related to both disorders. In line with this perspective are the current findings of blunted GH responses to panic disorder, presumably reflecting distorted alpha-adrenergic neurotransmission as well (Uhde et al. 1986). Anxiety and situational stress present during the test procedure, particularly if they relate to the delusional system, may contribute to alpha-adrenoceptor-related neuroendocrine dysregulation. Moreover, both schizophrenic and panic disorder patients experience a transient reduction in symptoms with concurrent decrease of plasma norepinephrine and MHPG concentrations following CLON. Thus, although the pathophysiological significance of dysregulated noradrenergic function concerning state or trait dependency may vary between major depression and paranoid schizophrenia, some aspects of noradrenergic dysregulation, both in relation to receptor binding and neuroendocrine responses to alpha2-adrenergic agonists, seem to be common in both disorder. Therefore, we conclude that disturbances in noradrenergic function and, specifically, the attenuated GH response to CLON may simply represent a nonspecific change secondary to acute or chronic stress, rather than a marker of any psychiatric disorder.

References


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