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Twenty-four hour growth hormone secretion in patients with panic disorder

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Summary *Background*. Patients with panic disorder have blunted growth hormone (GH) responses to clonidine, suggesting subsensitivity of post-synaptic alpha$_2$-adrenoreceptors, presumably in response to excessive central noradrenergic outflow. However, basal levels of GH release over a full circadian cycle have not been examined in panic. Reduced basal GH release would suggest an overall hypoactive GH system rather than a specific alpha-adrenergic abnormality.

Methods. To determine whether panic patients show reduced basal GH secretion, 20 patients and 12 healthy controls were studied. Blood samples were drawn every 15 min for 24 h and plasma was assayed for GH. Patients were restudied during successful treatment with alprazolam. Groups were compared on overnight and daytime GH secretion and circadian patterns of release.

Results. Patients showed normal levels on all measures of GH release. Treatment may have reduced nocturnal GH release slightly, but treated patients still did not differ from controls. The normal predominance of sleep over waking GH secretion was seen in both groups.

Conclusions. Panic patients, in contrast to depressed patients, have normal somatotrophic axis activity when measured in a resting state over a full circadian cycle. GH dysregulation may only be evident in these patients in activation paradigms and has been most consistently demonstrated by challenges with the alpha$_2$-noradrenergic agonist, clonidine.

1. Introduction

Patients with panic disorder have fairly consistently demonstrated blunted growth hormone (GH) responses to the alpha$_2$-adrenoreceptor partial agonist clonidine. Although there have been some

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discrepant reports (Schittecatte et al., 1988), multiple replications make this one of the best documented neurobiologic abnormalities identified in panic disorder (Abelson et al., 1992; Brambilla et al., 1995; Charney and Heninger, 1986; Coplan, 1995; Nutt, 1989; Uhde et al., 1986). The finding has generally been interpreted as suggesting reduced sensitivity of post-synaptic alpha$_2$-receptors that modulate GH release (Siever et al., 1982; Siever and Uhde, 1984). Such reduced sensitivity could occur in panic patients due to receptor down regulation in response to chronic, excessive noradrenergic outflow from the locus coeruleus (Coplan et al., 1997). This finding provides probably the most compelling evidence to date that dysregulation within the noradrenergic neurotransmitter system may play a critical role in the pathophysiology of this common and important anxiety disorder.

However, patients with panic disorder also have blunted GH responses to growth hormone-releasing hormone (GHRH) (Brambilla et al., 1995; Rapaport et al., 1989; Tancer et al., 1993), and possibly to caffeine and yohimbine (Uhde et al., 1992). These patients may have a generally hypo-active hypothalamic–pituitary somatotrophic (HPS) axis rather than a specific subsensitivity of alpha$_2$-receptors (Uhde et al., 1992). Release of GH is primarily controlled by the balance of activation via GHRH and inhibition via somatostatin, which are in turn modulated by cholinergic and dopaminergic, as well as adrenergic inputs (Devesa et al., 1992). Blunted responses to various HPS activating agents could reflect reduced sensitivity of alpha$_2$-receptors, but could also reflect defects in other neurotransmitter systems, via reduced input to GH release mechanisms or increased activity in the inhibitory component of the system. If there is a defect in overall secretory capacity or inhibitory activity, this should be evident in the resting state, and not only in response to receptor-specific activating agents. This appears to be the case in depression, where blunted responses to clonidine have been reported (Amsterdam et al., 1989; Siever et al., 1982), but abnormalities in HPS activity are also seen when it is monitored in its basal state over the circadian cycle (Jarrett et al., 1990; Mendlewicz et al., 1985). Because GH is released in discrete bursts, predominantly at night, basal activity is best assessed through monitoring over a full 24-h cycle. Such examinations of GH secretion have not yet been reported in panic disorder. To determine whether panic patients have a defect in basal GH secretory activity, we examined GH in patients and control subjects over a full circadian cycle, using frequent blood sampling to fully characterize resting activity in the HPS axis.

2. Methods

Twenty panic patients (mean age 30.6$\pm$6.1 years, 12 female) and 12 healthy control subjects (mean age 28.1$\pm$4.4 years, 9 female) were studied, after evaluation using a Structured Clinical Interview for DSM-III-R (Spitzer and Williams, 1986). Hypothalamic–pituitary–adrenal (HPA) axis data from these subjects have been previously reported, and additional methodological details are available in the prior reports (Abelson and Curtis, 1996a,b; Abelson et al., 1996). Subjects between 18 and 42 years of age were medically healthy, reported no exposure to psychoactive medication for at least 2 weeks and passed a urine drug screen and plasma benzodiazepine screen at time of entry, and were on no medication that might affect neuroendocrine activity. Female subjects were not taking birth control pills, had regular menstrual cycles for the prior 6 months, had a negative urine pregnancy screen, and were studied within 7 days of onset of menses.

Patients were recruited from routine referrals to our Anxiety Disorders Program and utilizing advertisements in community newspapers. They met DSM-III-R criteria for panic disorder and had experienced at least one panic attack per week for the prior 3 weeks. Fourteen had mild or moderate agoraphobia, while six had panic disorder alone (i.e. no agoraphobia). Two patients had histories of Major Depressive Disorder (MDD) and two had histories of substance abuse (all in remission for $>$6 months). In both cases with past depression, panic symptoms were identified as primary (occurring first and dominating the clinical picture). Exclusion of these two patients did not alter results, so they are included in the data presented. Four patients had current or past-generalized anxiety disorder. One patient had social phobia and one had a simple phobia (heights). No other current or past Axis I disorders were detected. Control subjects were recruited by advertisements in community newspapers. They had no current or past history of Axis I disorder and reported no Axis I disorder in first degree relatives.

The study was designed to provide detailed assessment of neuroendocrine activity in a resting state over a full circadian cycle and to assess the impact of 10 weeks of treatment with alprazolam on patients' neuroendocrine functioning. Subjects who met entry criteria and passed all screening tests provided written informed consent and were admitted to a General Clinical Research Center (GCRC) for study. Patients received free clinical care during the 10-week treatment protocol.