EXCESSIVE ADRENOCORTICAL RESPONSIVENESS TO SUBMAXIMAL DOSES OF COSYNTROPIN (ACTH α1-24) IN DEPRESSED PATIENTS

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Summary—Some studies have suggested that excessive cortisol secretion in depression might result from abnormalities at both central and peripheral sites within the hypothalamic–pituitary–adrenocortical (HPA) axis. In this regard, we have previously demonstrated a blunted ACTH and exaggerated cortisol response to CRH infusion, an increased cortisol secretion after cosyntropin administration, and subtle adrenal gland hypertrophy by computerized tomography.

To directly assess the phenomenon of heightened adrenocortical responsiveness to ACTH, we performed a series of studies using a 250 μg cosyntropin stimulation test and observed excessive cortisol secretion in patients with melancholic depression. These studies utilized a supramaximal dose of ACTH given at 09.00h when adrenocortical sensitivity to ACTH is at its maximum.

To test for differences in adrenocortical responsiveness at submaximal ACTH doses, we performed two separate cosyntropin tests using dose of 0.05 μg/kg and 0.2 μg/kg and compared differences in cumulative cortisol response (CCR) values over a 240 min period in 12 patients with major depression (7 melancholic and 5 nonmelancholic) and 6 healthy volunteers.

Results: when the CCR values were compared between ACTH doses, there was no difference in CCR values for melancholic patients ($P = 0.85$), whereas there were significant differences in the CCR values for controls ($P < 0.0001$) and nonmelancholic patients ($P < 0.05$). These data indicate the presence of a heightened adrenocortical responsiveness to very low doses of ACTH in melancholic patients, and support the hypothesis that excessive cortisol secretion in depression might result from abnormalities at several sites within the HPA axis.

SERIAL HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) STUDIES IN DEPRESSION: PROBLEMS AND PROMISES

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Summary—Research strategies used to study HPA functioning in depression have evolved through several phases. Initial studies emphasized cross-sectional, diagnostic adrenal assessments. These revealed that, in addition to diagnosis, there were important sources of variance that influenced the cortisol response to dexamethasone such as patient age, severity of depression, marked weight loss, medication or alcohol administration or withdrawal, dexamethasone bioavailability, and hospital stay. A second phase emphasized longitudinal assessments to examine the state relationship between HPA axis dysregulation and depression. This approach usually consisted of "before-and-after-treatment" assessments. Results strongly indicated that HPA dysregulation was state dependent, but this early longitudinal strategy could not address test/retest stability of laboratory measures in the absence of a change in state, or the temporal pattern of the changes. The second phase also assessed the ability of "before treatment" or "after treatment" HPA measures to predict response to specific treatments and/or risk of subsequent relapse. Pretreatment DST status does not appear to consistently aid in predicting response to antidepressant treatment, while there has been insufficient study of the relationship between an abnormal DST after clinical response and subsequent relapse. A third phase included the completion of repeated measures during the course of treatment, after remission and, in some patients, after relapse. A parallel development extended this strategy to include assessments of pituitary function using B-End/B-Lip responses to dexamethasone or CRH challenges.

Despite progress, many aspects of HPA dysregulation remain unclear. Key questions include: How closely associated in time are changes in neuroendocrine function and depressive state? Does neuroendocrine change consistently precede, coincide, or follow syndromal change? Does this relationship permit the utilization of test results in the ongoing clinical decision-making process? Does this aggregate of tests provide more information about the course of illness than single measures? Should the grouping criteria emphasize pretreatment or final test results? In an attempt to address these questions, we have combined the "serial-measure strategy" with simultaneous assessments of adrenal and pituitary function. Methodologically, this approach is complicated, but promising. We will present data obtained from 123 patients who have been followed with multiple assessments of HPA axis function during treatment of depression (7–75 weeks follow-up). All 123 Ss had serial DSTs with concurrent, blind clinical ratings and plasma dexamethasone levels. In 20 of 123 patients, we measured β-endorphin responses to dexamethasone, as well as the cortisol response. We will present findings from this study, and describe problems associated with this approach. The discussion should have relevance for serial assessments of other psychobiological measures such as sleep EEG, regional cerebral blood flow, etc.

RELIABILITY OF AUTOMATED EEG SLEEP MEASURES: A PARADIGM FOR ACROSS-CENTER ASSAY REPLICATIONS

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Summary—The past twenty years of research in psychiatry has seen the proliferation of laboratories devoted to polysomnography. Recent advances in computer technology have made possible more in-depth analysis of these measures. Despite editorial efforts to require sufficient detail to permit replication of results, it is not uncommon for new and intriguing findings to be difficult to reproduce in another laboratory. Differences in patient populations notwithstanding, the role of variations in techniques of data acquisition and analysis as an important contributor to this problem receives little systematic attention. As an example of a more rigorous approach to this problem, data will be presented for ongoing work concerning the development and demonstration of reliability across laboratories for computerized sleep analysis techniques.

The sleep laboratory at WPIC in Pittsburgh has developed and utilized a computerized sleep analysis system over the past decade. EEG sleep data are recorded on FM tape and later processed with a PDP11/44 minicomputer to determine counts of delta waves and rapid eye movements (REMs). The Pittsburgh laboratory has collaborated in recent attempts by the Sleep/Depression Unit of the University of Michigan to develop a similar capability. Rather than cloning the Pittsburgh FM tape recorder/minicomputer system, the Michigan laboratory has utilized a microcomputer system with on-line digitization and analysis using an adapted version of the Pittsburgh software.

Because of these changes in the hardware and acquistion system, it was necessary to conduct a reliability test of the Michigan vs Pittsburgh systems. An FM tape with analog recordings from several Pittsburgh patients was run through the Michigan system and resulting delta and REM counts were compared to counts obtained on the tape in Pittsburgh. Results showed that there was very high concordance between the two systems.

Advantages of the Pittsburgh system include its established utility. Advantages of the Michigan system include its lower capital costs and its potential utility in providing computer-timed interruptions for studies of sleep deprivation. As new proprietary sleep analysis systems become available, it will become important to continue efforts to establish the degree of reliability between apparently identical systems. Discussion will include a focus on the problems of across-laboratory replications in fields other than sleep, including the development of specific recommendations for undertaking attempts to address this issue.
