Co-Release of ACTH and β-Endorphin Immunoreactivity in Human Subjects in Response to Central Cholinergic Stimulation

We have reported that phystostigmine, an acetylcholinesterase inhibitor with both nicotinic and muscarinic cholinomimetic properties, increases plasma levels of cortisol and β-endorphin immunoreactivity in human subjects (1). In our manuscript we commented that we were surprised that there was no significant correlation between increases in plasma concentrations of cortisol and β-endorphin immunoreactivity, since co-release of adrenocorticotropic hormone (ACTH) and β-endorphin from the anterior pituitary was observed in animal stress paradigms (2). However, we have recently measured plasma ACTH immunoreactivity concentrations in our original plasma samples using a newly developed assay (3), and we have found significant and highly correlated elevations in β-endorphin and ACTH immunoreactivity in plasma (Fig. 1). These results with phystostigmine are now consistent with recent reports of apparent concomitant release of ACTH and β-endorphin in man in response to other stimuli including hypoglycemia, Pitressin administration and other conditions (4). Changes in plasma concentrations of ACTH and cortisol immunoreactivity were only weakly and nonsignificantly correlated.

In fact, more than 10 years ago Krieger and associates reported that while there was a close temporal correlation between plasma ACTH and corticosteroid peaks, there was no apparent proportionality between spontaneously released plasma ACTH and corticosterone levels either within or among individuals (5). This lack of proportionality may be reflective of differing adrenal receptor sensitivities to ACTH, or differences in metabolic clearance rates of plasma ACTH and cortisol. Krieger has also suggested that the magnitude of corticosteroid response to ACTH is in part dependent on the recent history of prior adrenal exposure to ACTH. In addition, Holaday and associates (6) have reported a synchronized ultradian cortisol rhythm in monkeys which persists during supramaximal infusions of ACTH and suggested that bursts of cortisol secretion are not entirely dependent upon an immediately preceding release of ACTH.

Our new data suggests that central cholinergic stimulation may in part modulate the co-release of ACTH and β-endorphin immunoreactivity, and that in this paradigm, and possibly in others, plasma cortisol values may not be a good reflection of concomitant ACTH changes.

S. C. Risch
Department of Psychiatry
School of Medicine
University of California, San Diego
La Jolla, California 9203

Ned H. Kalin
Department of Psychiatry, School of Medicine, University of Wisconsin, Madison, Wisconsin 53141

David S. Janowsky
Department of Psychiatry
School of Medicine
University of California, San Diego

Robert M. Cohen
Clinical Neuropharmacology Branch
National Institute of Mental Health
Bethesda, Maryland 20205

David Pickar
Biological Psychiatry Branch
National Institute of Mental Health

Dennis L. Murphy
Clinical Neuropharmacology Branch
National Institute of Mental Health

References and Notes
3. Samples were collected as previously described (1). All samples were assayed in duplicate within the same assay using an equilibration radioimmunoassay utilizing a rabbit antiporcine ACTH antibody from Immunonuclear Corporation. The antibody has less than 0.1 percent cross-reactivity with α-MSH, β-endorphin, β-lipotro-
phin, leucine and methionine enkephalin, β-lactam, parathyroid hormone, prolactin, somato-
statin, neuropeptide Y, enkephalin, calcitonin, calcitonin gene-related protein, or calcitonin gene-related peptide.
5. H. Yoshimi, Y. Matsukura, S. Sueoka, M. Yokota, Y. Hirato, T. Fujita, Endo-
7. J. W. Holaday, H. M. Martinez, B. H. Niatel-

Fig. 1. Scatter diagram of maximal changes in plasma β-endorphin and ACTH immunoreactivity following phystostigmine administration in nine subjects. Preinfusion values of plasma β-endorphin and ACTH immunoreactivity were compared with twenty minute postinfusion values. This postinfusion time point re-
flects peak increases in the individual hor-
mones. Linear regression analysis was per-
formed to determine the relationship and sig-
nificance of phystostigmine induced changes over time in plasma β-endorphin and ACTH immunoreactivity within individual subjects. (r = 0.85, P < 0.01)
Co-release of ACTH and beta-endorphin immunoreactivity in human subjects in response to central cholinergic stimulation
SC Risch, NH Kalin, DS Janowsky, RM Cohen, D Pickar and DL Murphy

Science 222 (4619), 77.
DOI: 10.1126/science.6312560