Thesis Abstract: Neuroendocrine Studies on the Function of the Normal and Abnormal Human Hypothalamic-Pituitary-Adrenal Axis

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This thesis reports several studies which assessed the function of the hypothalamic-pituitary-adrenal axis (HPAA) in healthy human subjects and in patients with (1) myotonic dystrophy (DM), an autosomal dominantly transmitted form of muscular dystrophy which involves multiple organ systems; and (2) post-traumatic stress disorder (PTSD), a psychiatric condition which results from exposure to a very stressful, dangerous situation. Plasma concentrations of adrenocorticotropic hormone (ACTH), cortisol, and arginine vasopressin (AVP) were measured in response to administration of the opioid antagonist naloxone, exogenous AVP and synthetic ACTH. All studies were placebo-controlled and singleblinded.

In healthy volunteers, administration of both naloxone and AVP resulted in a synergistic ACTH response compared to administration of each agent alone, similar to the synergism previously reported between corticotropin-releasing hormone (CRH) and AVP. This finding indicates that, in humans, naloxone stimulates the HPAA predominantly or exclusively via increased release of hypothalamic CRH, similar to its mechanism of action in animal studies.

In DM patients, the ACTH response to naloxone was markedly increased compared to control subjects. Pre-treatment with nifedipine (which blocks dihydropyridine (DHP)-sensitive Ca^{2+} transport via L-type voltage-dependent Ca^{2+} channels) delayed the ACTH and cortisol responses to naloxone in the DM group without altering the magnitude of these responses. In contrast, nifedipine reduced but did not delay the ACTH and cortisol responses to naloxone in the control group. These findings suggest the presence of an abnormality of DHP-insensitive Ca^{2+} transport in the corticotrophs of DM patients. Pre-treatment with aspirin (which inhibits the cyclooxygenase pathway of arachidonic acid metabolism) resulted in an increased ACTH response to naloxone in the control group, but a paradoxical decrease in the ACTH response of the DM patients. This finding implies that the interaction between arachidonic acid metabolites and ACTH secretion is abnormal in DM patients. The effects of nifedipine and aspirin on the
HPAA are probably occurring at the pituitary level of the axis. The abnormal findings in the DM patients are likely to be due to altered cAMP-dependent protein kinase function in this condition.

The PTSD patients were studied by sequential injections of naloxone and AVP in separate dose-response protocols. Half of the PTSD patients had greater ACTH responses to the lowest dose of naloxone than did any of the control subjects. Detailed statistical analysis confirmed that these PTSD patients constituted a distinct subgroup, with greater ACTH and cortisol responses to naloxone than the other PTSD patients or the control subjects. However, there were no differences in the responses to AVP between the PTSD patients and the control subjects. These findings suggest that there is an abnormality in PTSD which may cause hypersensitivity to naloxone-stimulated CRH secretion, and that it is probably located at a supra-pituitary, rather than pituitary, level of the HPAA.

In conclusion, this thesis reports several findings on HPAA function in healthy control subjects, including the effects of nifedipine and aspirin, dose-response data for naloxone and AVP, and synergism (with regard to ACTH release) between naloxone and AVP. It also reports new abnormalities of HPA axis function in DM and PTSD which are probably related to the underlying pathophysiology of these conditions.

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