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Title: Modulation of the ACTH response to stress by IL-6, nitric oxide, diet and exercise

The release of ACTH from the anterior pituitary is one step in the activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis. The HPA axis is activated in response to stress and the secretion of ACTH is under the control of hypothalamic releasing factors. This thesis examined the role of several different factors in the modulation of the ACTH response to stress by testing the following hypotheses: 1) hypothalamic IL-6 is indirectly involved in stimulating the HPA response to stress by affecting the activity of corticotropin releasing hormone (CRH) neurons in the hypothalamus; 2) nitric oxide synthase (NOS) inhibition will result in an increase in ACTH response to stress and a decrease in blood flow to tissues of the HPA axis; and 3) high fat diet-induced changes in HPA activity could be attenuated with exercise training. The experimental design, results and discussion for each one of these hypotheses constitutes a single chapter in this thesis. The major findings include: 1) IL-6 is a novel hypothalamic factor found expressed in the external zone of the median eminence and released into the hypophyseal portal vessels in response to stress; 2) Compared to males, female pigs show a greater expression of IL-6 in the median eminence and a greater ACTH response to exercise and restraint stress; 3) Nitric oxide activates the HPA axis in response to restraint but limits the HPA response during maximal exercise; 4) Nitric oxide maintains basal cerebral blood flow; and 5) a high fat diet increases free fatty acids and attenuates the ACTH response to stress and exercise training reverses both of these high fat diet induced alterations. These data demonstrate that multiple factors influence the release of ACTH in response to stress. Thus, the ability of the body to respond to stress through the activation of the HPA axis can be affected by IL-6, nitric oxide, diet and exercise.