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In the present phase of our study, we have investigated the relationship between the nerve growth factor protein (NGF) and the hypothalamus-pituitary-adrenocortical axis (HPAA), a neuroendocrine system active in the response to stress and the immune system. We found that NGF is not able to stimulate the release of corticosterone from the adrenal glands in rats bearing a pharmacological block of the hypothalamus. Also, this activation of the HPAA can be reduced with anti-NGF. Thus, the stimulatory action of NGF on HPAA requires adrenocorticotropic hormone secretagogues release from the hypothalamus and that NGF modulates HPAA function.

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Overview of Purpose

This report will focus on work performed on this project during the last year as other aspects have been discussed in previous reports.

NGF Effects on Hypothalamo-Pituitary-Adrenocortical Axis During Stress

The hypothalamus-pituitary-adrenocortical axis (HPAA) is the best characterized neuroendocrine system that is activated by stress stimuli. In response to stress, corticotropin-releasing factor (CRF) is released from the hypothalamus into the portal circulation of the hypophysial stalk where it stimulates the release of adrenocorticotrophic hormone (ACTH) from the anterior lobes of the pituitary. Once in the general circulation, ACTH stimulates the release of corticosteroid hormones from the adrenal glands. Circulating corticosteroids, in turn, negatively modulate HPAA activity via specific receptors in the pituitary, hypothalamus and hippocampus. In addition, the binding of glucocorticoid hormones to the hippocampus is essential for the acquisition and retention of behavioral tasks in rodents. In summary, HPAA activation is more complex than a linear cascade of hormonal events that occur in response to stress.

The nerve growth factor protein (NGF) is known to be essential for the development and maintenance of sympathetic and sensory neurons of the peripheral nervous system (PNS). The presence of NGF and NGF receptors (NGFR) has been demonstrated in the CNS where NGF supports cholinergic neurons of the basal forebrain and septum under certain conditions.

In addition to its neuronotrophic action in the nervous system, NGF can act as a cytokine factor in immune responses.

NGF and glucocorticoids appear to be functionally related. During development, ambient levels of NGF or of glucocorticoids determine adrenal medullary chromaffin cells and sympathetic neuron phenotype. Both these cell types are derived from the neural crest. While 17β-estradiol induces NGF synthesis and secretion of NGF by the glia-derived C-6 cell line, the synthetic glucocorticoid dexamethasone decreases NGF binding and NGFR mRNA in the PC12, a rat pheochromocytoma cell line. Adrenalectomy decreases NGF levels in the hippocampus while it increases NGFR in the septum. Exposure to cold stress reduces NGF binding in the hippocampus and basal forebrain of young adult rats. Aggressive behavior, a form of social stress, stimulates the release of NGF from the submaxillary glands into the circulation and elevates NGF mRNA and protein in the hypothalamus of mice. The first evidence for a direct action of NGF on the HPAA activity was the demonstration by Otten and coworkers in 1979 that intravenous injections of NGF stimulate

release of ACTH and corticosterone in the rat. However, this study did not address the question as to the site of NGF action in the CNS or its physiological significance.

Treatment with CPZ-MS-Nb completely abolishes the capability of the hypothalamus to secrete those humoral factors that stimulate the release of ACTH from the adenohypophysis. CPZ-MS-Nb treated rats do not respond to a variety of stressors, as measured by the absence of any elevation of serum corticosteroid levels. However, CPZ-MS-Nb treatment does not abolish the release of ACTH from the pituitary, or of corticosteroids from the adrenals, in response to an intravenous injection of CRF. Therefore, this pharmacological strategy allows functional inactivation of the HPAA at the hypothalamic level, while leaving the remaining components of the HPAA (pituitary and adrenals) active. Since we did not observe any rise in plasma corticosterone levels following NGF injection in rats that were pretreated with CPZ-MS-Nb, but we did observe an NGF-elicited increase in plasma corticosterone in untreated rats, we conclude that the site of action of NGF in the stimulation of the HPAA activity should be the hypothalamus or some suprahypothalamic structure involved in the regulation of the HPAA, such as the hippocampus. Because the treatment with CPZ-MS-Nb did not affect the responsiveness of the pituitary to CRF, a direct effect of NGF on ACTH release from the corticotrophs seems unlikely. This is in agreement with the reported absence of NGFR on the ACTH-secreting anterior lobe of the pituitary.

Our finding that treatment of rats with antibodies directed against NGF significantly attenuates their response to a cold environment in terms of corticosterone release into the circulation would suggest that circulating NGF is essential for the proper activation of the HPAA during stress.

There are several possible mechanism(s) of action for the NGF modulation of the HPAA after stress or following the administration of NGF. One possibility is that NGF-immunodeprived animals are not able, during stress, to disengage those inhibitory mechanisms that normally are responsible for the maintenance of baseline HPAA activity. In this instance, the hippocampus would be a probable candidate as the site for the NGF action. The hippocampus is known to exert an inhibitory control on the hypothalamic activity during basal and stress-related condition. It has been postulated that, during the early phases of the stress response, the binding of corticosteroids with their receptors in the hippocampus releases the inhibition on the hypothalamus, and allows the activation of the HPAA. As the stress response progresses and the down-regulation of the corticosteroid receptors in the hippocampus takes place, the action of the hippocampus on the hypothalamus would reverse to an inhibitory one. The NGF released during stress might act at the hippocampus to participate in this early disinhibition of the HPAA activity, as suggested by the incomplete activation of the HPAA that we observed in the anti-NGF-treated rats.

Immediately after the injection of either NGF or cytochrome C

there is a non-specific activation of the HPAA due to the stress of the injection. After 60-90 min, however, the levels of plasma corticosterone in sham-injected rats returns to basal values while that in NGF-injected animals remains elevated for up to six hours. This would suggest that in the NGF-injected rats the inhibitory mechanisms that modulate the return of the HPAA to basal levels after a stress stimulation are affected by the treatment. The possibility that both the hippocampus and hypothalamus participate in the NGF stimulation of the HPAA cannot be ruled out.

In conclusion, peripherally injected NGF stimulates the activation of the HPAA by acting centrally, possibly at the hippocampus. Also, the NGF released into the circulation in response to stress may be essential for the proper activation of the HPAA. This would imply that NGF is critical to neuroendocrine function.