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NEUROTENSIN-INDUCED ACTIVATION OF HYPOTHALAMIC DOPAMINERGIC NEURONS IS ACCOMPANIED BY A DECREASE IN PITUITARY SECRETION OF PROLACTIN AND α-MELANOCYTE-STIMULATING HORMONE

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Summary

The effects of neurotensin on the activity of hypothalamic tuberoinfundibular and periventricular-hypophysial dopaminergic (DA) neurons, and on the secretion of pituitary hormones that are tonically regulated by these neurons (i.e. prolactin and α-melanocyte-stimulating hormone [αMSH], respectively) were examined in estrogen-primed ovariectomized rats. The activity of tuberoinfundibular and periventricular-hypophysial DA neurons was estimated by measuring concentrations of the dopamine metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) in the terminals of these neurons in the median eminence and intermediate lobe of the posterior pituitary, respectively. Intracerebroventricular administration of neurotensin caused a dose- and time-related increase in DOPAC concentrations in both the median eminence and intermediate lobe, and a concurrent decrease in plasma levels of prolactin and αMSH. These results suggest that neurotensin-induced inhibition of secretion of prolactin and αMSH from the pituitary may be due to the stimulatory action of this neuropeptide on the release of dopamine from tuberoinfundibular and periventricular-hypophysial neurons.

Neurotensin, a tridecapeptide first isolated from bovine hypothalamus (1), has a widespread distribution throughout the nervous system (2-4), with the highest concentrations found in the nucleus accumbens, preoptic area, and mediobasal hypothalamus (3,5). Immunoreactive neurotensin cell bodies have been localized in various regions of the hypothalamus, including the arcuate and periventricular nuclei (6); regions containing cell bodies of dopaminergic (DA) neurons comprising the periventricular-hypophysial (formerly referred to as tuberohypophysial DA neurons, 7) and tuberoinfundibular DA neurons, respectively. Neurotensin fulfills all the major criteria that classify a substance as a

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neurotransmitter or neuromodulator (8). Of particular interest is the growing body of pharmacological, anatomical, and neurochemical evidence that neurotensin interacts with central DA neurons (8,9). Most of these studies have involved nigrostriatal and mesolimbic neurons (8,9); only a few studies have focused on hypothalamic tuberoinfundibular DA neurons (10) that tonically inhibit the secretion of prolactin from the anterior pituitary, or periventricular-hypophysial DA neurons that inhibit the secretion of α-melanocyte stimulating hormone (αMSH) from the intermediate lobe of the pituitary (7,11).

The role of neurotensin in regulating the release of hormones from the anterior pituitary has been reviewed by Aronin et al. (12). Intracerebroventricular (icv) administration of neurotensin inhibits basal release of prolactin from the anterior pituitary, as well as stimulated release of prolactin induced by 5-hydroxytryptophan, thyrotropin-releasing hormone, prostaglandin E_2, enkephalin and stress (13-18). It has been suggested that the suppressive effect of neurotensin on prolactin release involves an enhanced release of dopamine from tuberoinfundibular neurons (16,17,19), but there has been little effort to test this proposal directly. Gudelsky et al. (10) reported that icv administration of neurotensin activates tuberoinfundibular DA neurons but did not attempt to correlate this effect with the secretion of prolactin. There have been no reports on the in vivo effects of neurotensin on periventricular-hypophysial DA neurons or the release of αMSH from the intermediate lobe of the pituitary.

In the present study, the time-course and dose-response effects of central neurotensin administration on the activity of tuberoinfundibular and periventricular-hypophysial DA neurons, and plasma prolactin and αMSH levels were examined concurrently in ovariectomized, estrogen-treated (OVX+E_2) rats. OVX+E_2 rats were used in these studies to avoid normal cyclic variations in ovarian E_2 secretion which occur during the estrous cycle. E_2 was administered to OVX rats at a dose which reinstates hormone concentrations at a level normally attained on the morning of proestrus to maximize the stimulatory effects of E_2 on prolactin secretion, and thereby increase the likelihood of detecting significant neurotensin-induced decreases in secretion of this hormone. The activity of tuberoinfundibular and periventricular-hypophysial DA neurons was estimated by measuring concentrations of the dopamine metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) in the terminals of these neurons in the median eminence and intermediate lobe of the posterior pituitary, respectively. The results reveal that neurotensin-induced inhibition of pituitary prolactin and αMSH secretion is accompanied by an increase in the activity of tuberoinfundibular and periventricular-hypophysial neurons.

Materials and Methods

Adult female Long-Evans rats weighing 200-225 g were purchased from Harlan Sprague-Dawley, Inc (Indianapolis, IN). Rats were ovariectomized 2 days after arrival (Day 0). On day 4, a 23-gauge stainless steel guide cannula was implanted in a lateral ventricle for icv injection and an estrogen capsule containing estradiol-17ß (E_2, 150 μg/ml corn oil, Sigma Chemical Co., St. Louis, MO) in 20 mm Silastic tube (#602-285, Dow Corning Corp., Midland, MI) was implanted sc. On the morning of day 7, rats were injected icv with either artificial cerebroventricular fluid (ACSF, 3 μl) or various doses of neurotensin (1.25, 5 and 20 μg/rat/3 μl ACSF, Sigma) and the animals were decapitated either 30, 60, 120 and 240 min later. Plasma samples were collected and stored at -20°C until assayed for their hormone levels. Brains and pituitaries were quickly removed and frozen on dry ice. Frontal brain sections (600 μm) were prepared using a cryostat beginning at approximately A 9.2