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Androgen modulation of neurotrophic factor action: A possible mechanism for sexually dimorphic neural development

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Abstract

Motoneurons of the spinal nucleus of the bulbocavernosus (SNB) reside in the lower lumbar spinal cord and innervate the bulbocavernosus (BC) and levator ani (LA) muscles. Adult males have larger BC and LA muscles and many more SNB motoneurons than do females. This sex difference comes about as a result of androgen-regulated cell death. ^ How is androgen stimulation of the BC/LA muscles translated into a live-or-die decision by the SNB motoneurons? Neurotrophic factors such as ciliary neurotrophic factor (CNTF) may play such a role. The experiments described in this dissertation are designed to (1) identify potential direct sites of CNTF action in the SNB neuromuscular system, (2) examine androgen regulation of CNTFRα gene expression in BC/LA muscle and lumbosacral spinal cord, and (3) to test whether endogenously produced neurotrophic factors normally influence SNB cell survival. ^ To determine whether CNTFRα is expressed in the developing SNB system, I first performed Northern blotting. The perineal muscles and motoneurons are potential sites of direct CNTF action. ^ Androgen regulation of CNTFRα expression was examined in prenatal animals by administering the androgen receptor blocker hydroxyflutamide from embryonic day 18 (E18) through E21. Expression of the CNTFRα, gene in BC/LA muscle is modulated by androgen. Transient up-regulation of CNTFRα following castration or androgen receptor blockade may represent a protective response designed to counteract the muscle atrophy normally induced by androgen withdrawal. ^ To detect CNTFRα, protein specifically in SNB motoneurons, two immunocytochemical experiments were performed. In the first experiment, CNTFRα immunoreactivity (CNTFRα-IR) was detected from E20 through postnatal day 14 (P14), which spans the cell death period for the SNB. There was no sex difference in CNTFRα-IR during this period. In the second experiment, CNTFRα-IR was compared in newborn (P3), prepubertal (P26) and adult rats (P54). CNTFRα-IR in the SNB remained relatively stable across the three ages examined in males, but declined significantly in females between P26 and P54. ^ To test whether endogenously produced trophic factors acting through CNTFRα, and/or trkB modulate SNB survival, I administered the antagonists, AADH-CNTF (blocking CNTFRα, trkB-IgG (blocking trkB) or PBS (as a control) to testosterone propionate (TP) treated neonatal female rats. SNB motoneuron numbers in females receiving TP plus AADH-CNTF or TP plus trkB-IgG were significantly lower than that of the TP plus PBS treated ones. This finding demonstrates an *in vivo* requirement for endogenous ligands of CNTFRα, and trkB in SNB motoneuron survival and sexual differentiation of the SNB system. ^ A working model is proposed for how androgens and neurotrophic factors may collaborate to cause a sex difference in the SNB. (Abstract shortened by UMI.)^

Subject Area

Neurosciences

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