

ESTROGEN RECEPTORS IN CENTRAL NERVOUS SYSTEM MICTURITION PATHWAYS IN A RAT MODEL

Hypothesis / aims of study

Estrogen affects continence by modulating central nervous system micturition pathways. Urinary incontinence affects approximately 1/3 of post-menopausal women. Circulating estrogen levels fall at menopause, but there is conflicting evidence whether voiding symptoms in these women are related to hypoestrogenism or aging itself. Although the innervation of the lower urinary tract and the spinal pathways to the pontine micturition center (PMC) in the brainstem are fairly well understood, the exact mechanisms by which higher brain centers modulate voluntary control of the micturition reflex have yet to be elucidated. Interconnections do exist between the PMC and the periaqueductal gray (PAG) and between the PMC and the medial preoptic area (MPO) (1,2) . In addition, a PET scan study by Blok et al (3) revealed increased blood flow to the PAG and the preoptic area during micturition. The aim of this neuroanatomical study was to determine whether specific central nervous system (CNS) pathways that project to the PMC are estrogen sensitive in a rat model.

Study design, materials and methods

Using adult female Sprague-Dawley rats, stereotaxic procedures were used to accurately localize the PMC, using coordinates based on landmarks on the skull. A fluorescent retrograde neuroanatomical tracer was injected into the PMC to identify neurons in the MPO and PAG that project to the PMC. In addition, bilateral ovariectomy was performed one week before sacrifice to reduce estrogen-dependent negative feedback, and thus maximize ER expression. Immunohistochemistry was performed using antibodies directed against estrogen receptor (ER)-alpha and ER-beta to identify estrogen-sensitive neurons. The brain sections were examined using fluorescence microscopy to identify cells that project to the PMC (contain fluorescent tracer) and also express ER (are immunoreactive for ER).

Results

The distribution of neurons in the PAG and MPO that project to the PMC was similar to that reported in previous studies. The pattern of ER-positive cell bodies in the brain sections was also consistent with known locations of ERs in the CNS. Finally, some neurons in the PAG and MPO were double labeled, showing that subsets of neurons projecting from the PAG and MPO to the PMC are estrogen-sensitive.

Interpretation of results

These results demonstrate that there are estrogen-sensitive neurons projecting from the MPO and the PAG to the PMC in a rat model, raising the possibility that estrogenic regulation of forebrain and midbrain neuronal function may modulate the micturition reflex.

Concluding message

Although it has been shown that estrogen-sensitive neurons are present in CNS micturition pathways, additional studies are needed to investigate the exact role of these receptors in the micturition reflex. These results support the idea that development of drugs that alter the function of these estrogen-sensitive CNS pathways may provide future therapeutic strategies to treat post-menopausal incontinence.

References

1. Direct projections from the periaqueductal gray to pontine micturition center neurons projecting to the lumbosacral cord segments: an electron microscopic study in the rat. *Neurosci Lett* 1998;242:97-100.
2. Preoptic projections to Barrington's nucleus and the pericoerulear region: architecture and terminal organization. *J Comp Neurol* 1994;347:1-24.
3. A PET study on brain control of micturition in humans. *Brain* 1997;120 (Pt 1):111-21.