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Title: ROLE OF SEX HORMONES IN THE FUNCTIONAL DEVELOPMENT OF THE RAT URINARY BLADDER

Aims of Study:

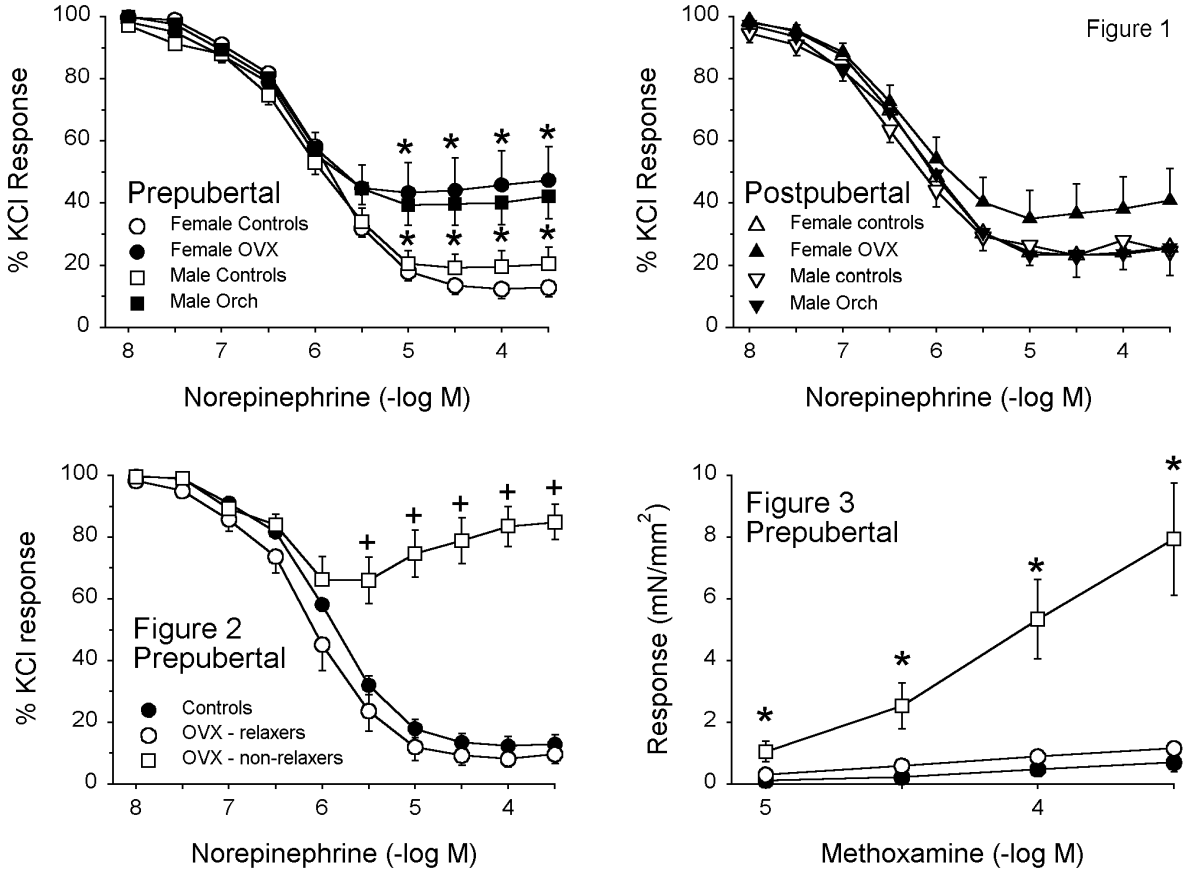
Although it is well established that sex hormones can modulate lower urinary tract function in adult animals, little is known of the role of sex hormones during maturation of the bladder. Thus, the aim of this study was to examine the effects of sex hormone depletion on the functional development of the rat bladder.

Methods:

Prepubertal and postpubertal male and female Sprague Dawley rats were castrated at 30 and 70 days of age, respectively. Their bladders were removed for organ bath studies, 30-40 days later. Bladders were also taken from immature (30 days old) rats. Full thickness longitudinal detrusor strips were prepared for contraction or relaxation studies. Data are presented as means ± SEM. Statistical analyses were done using t-test or Bonferroni analysis, as appropriate. $P<0.05$ was required for significance.

Results:

There were no differences between immature male and female rats in the contractile responsiveness of bladder strips to electrical field stimulation (EFS), the muscarinic agonist, carbachol, the purinergic agonist, ATP, or KCl. Compared to the age-matched controls, pre- and postpubertal castration had no effects on contractile responses to EFS, carbachol, ATP, or KCl. After precontraction with 40mM KCl, the ß-adrenergic agonist, isoproterenol, almost completely relaxed all bladder strips in a concentration-dependent manner; there were no significant differences among any of the groups studied in either responsiveness or sensitivity. Similarly, bladder strips from immature rats relaxed almost completely in response to the mixed α- and ß-agonist, norepinephrine. Bladder strips from pre- and postpubertally castrated rats relaxed fully in response to isoproterenol, but strips from prepubertally castrated rats relaxed significantly less in response to norepinephrine than those from age-matched controls (figure 1). Figure 2 shows that the female prepubertally castrated rats can be divided into two distinct groups; one with bladders that relax fully in response to norepinephrine (7 rats) that we have called “relaxers”, and another where the bladders failed to relax by at least 50% (5 rats) that we have called “non-relaxers”. A similar division may be made for the male prepubertally castrated rats, where 6/10 bladders were non-relaxers. In contrast, among the postpubertal rats, only one or two bladders in each group failed to relax almost completely in response to norepinephrine (figure 1). The large error bars seen for the response to norepinephrine of the postpubertally castrated females are due to one bladder (out of 11) that failed to relax. Bladders from prepubertal rats which relaxed completely in response to norepinephrine, were generally unresponsive to the selective α-agonist, methoxamine. However, bladder strips that were non-relaxers were significantly more responsive to α-adrenergic stimulation (figure 3).



*Indicates significantly different from controls and +significantly different from both controls and non-relaxers at P<0.05.

Conclusions:

Our data suggest that sex hormones modulate the relative distribution and/or density of α- and ß-adrenergic receptors in detrusor smooth muscle during development. If rats are castrated before puberty, there is an increased likelihood of an increase in detrusor α-adrenergic responsiveness, which prevents normal ß-receptor-mediated relaxation. Levin et al. previously described an increased responsiveness of rabbit detrusor strips to α-stimulation after estradiol treatment but no change in ß-responsiveness [1]. However, to our knowledge this is the first report of increases in detrusor α-adrenergic responsiveness after castration. We speculate that this results from a change in the relative numbers of α- and ß-receptors on the smooth muscle. The reason(s) why some bladders become “relaxers” and others are “non-relaxers” is unknown. We have excluded the possibility that portions of bladder base were included in the strips and contributed to an exaggerated α-adrenergic response. Other potential mechanisms, such as the development of urothelial defects after prepubertal castation, are currently being investigated.

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References:

1. Levin, R.M., Shofer, F.S., & Wein, A.J. (1980). Estrogen-induced alterations in the autonomic responses of the rabbit urinary bladder. J Pharmacol Exp Ther 215, 614-618.