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Authors: P. A. Longhurst
Institution: Albany College of Pharmacy and Albany Medical College
Title: IN VITRO BLADDER FUNCTION AFTER NEONATAL ESTROGENIZATION IN MALE RATS

Aims of Study:

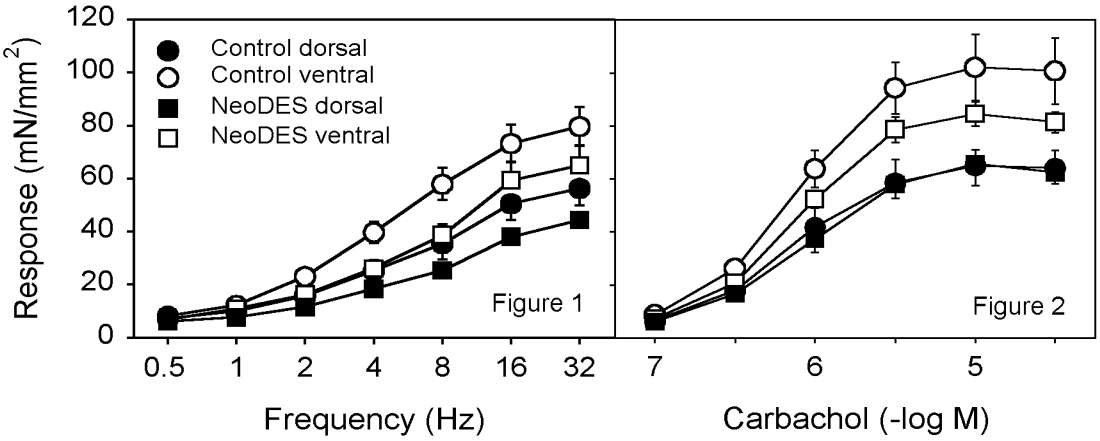
Previous studies have reported that neonatal estrogenization with diethylstilbestrol (neoDES) causes infravesical obstruction in rats and mice [1,2]. However, the observations have been largely subjective and the effects of neoDES on bladder strip contractility have not been reported. The aims of this study were to quantitate the effects of neoDES treatment on bladder mass and bladder strip contractility in rats.

Methods:

Male Noble rat pups were treated with daily subcutaneous injections of DES (10µg/day in 100µl peanut oil) on postnatal days 1 to 5 [2]. At 5 months of age, bladders were removed from 8 age-matched untreated controls and 8 neoDES rats and full thickness longitudinal ventral and dorsal 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.

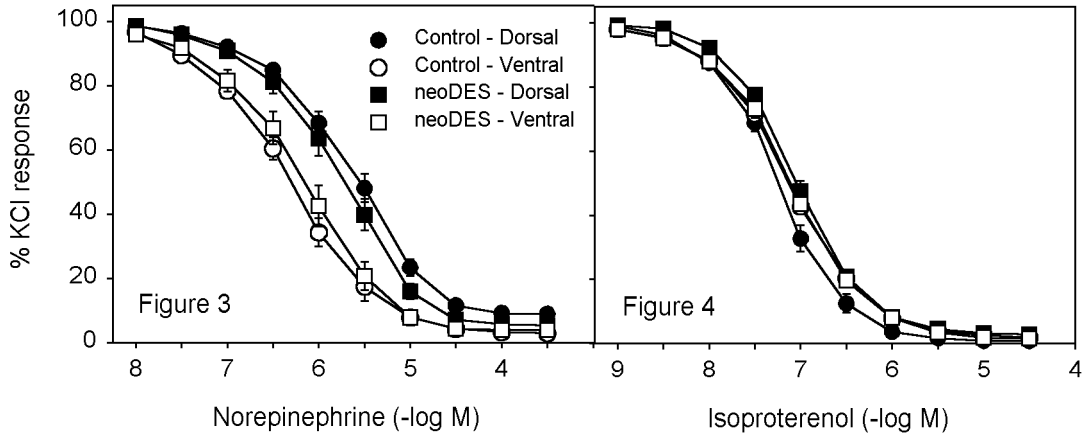
Results:

NeoDES treatment caused significant increases in bladder weight (Control: 159 ± 4mg; neoDES: 268 ± 11mg). There were no significant differences in sensitivity to electrical field stimulation (EFS) of any strips. Ventral strips from both control and neoDES rats responded to high frequencies of stimulation with significantly larger contractions than dorsal strips (figure 1). In addition, ventral strips from neoDES rats responded to 4 and 8Hz stimulation with significantly smaller contractions than ventral strips from controls. There were no differences in the magnitude of contractile responses or EC50 values for the muscarinic agonist, carbachol, when strips from control rats were compared to neoDES rats. However, ventral strips from both control and neoDES rats responded to carbachol with significantly larger contractions than dorsal strips (figure 2). There were no differences in contractile responses to the purinergic agonist, ATP (10mM).



Ventral strips from both control and neoDES rats were significantly more sensitive to the relaxant effects of the mixed adrenergic agonists, norepinephrine (figure 3) and epinephrine, than dorsal strips but there were no differences between strips from control and neoDES rats. In contrast, there were no differences between relaxant responses of ventral and dorsal strips to the ß-agonist, isoproterenol (figure 4). However control dorsal strips were significantly more sensitive to isoproterenol than neoDES dorsal strips. Although there was a

tendency for dorsal strips from both control and neoDES rats to respond to the α-agonist, phenylephrine, with greater sensitivity and efficacy than ventral strips, the differences were not significant.



Conclusions:

Neonatal DES treatment of male rats causes a mild but significant bladder hypertrophy. The modest (≈2-fold) increase in bladder mass associated with neoDES caused a small but significant decrease in responsiveness of ventral bladder strips to EFS, but no changes in direct muscarinic, adrenergic, or purinergic stimulation were noted. In both groups of rats, ventral strips were significantly more responsive to contractile stimuli than dorsal strips. Similarly, ventral strips were significantly more sensitive to ß-adrenergic stimulation. The increased sensitivity to ß-stimulation seemS to be modulated by the presence of α-adrenergic receptors, particularly in dorsal strips. Thus, neoDES treatment produces a mild outlet obstruction without causing significant alterations in in vitro bladder function.

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References:

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