230

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REGIONAL PROFILE OF ADRENERGIC, CHOLINERGIC AND SEROTONERGIC RECEPTOR SUBTYPES IN THE HUMAN FEMALE URETHRA

Hypothesis / aims of study

The majority of human urethra neuroreceptor identification work has been performed on the male urethra. There is only a limited amount of data published on the receptor subtypes present in the human female urethra. The aim of our investigation is to determine the identity of monoamine and other receptor subtypes present in the human female urethra using a radioligand binding assay in tissue homogenates. The development of a profile of receptors present in human female urethra can provide a means for rational medication development.

Study design, materials and methods

Three full-length urethras from autopsy patients were obtained within 24 hours of death (ages 56-64). Information on patient's co-morbidities and estrogen status was collected. Specimens were harvested and skeletonized of periurethral fat. Specimens were measured, placed on dry ice, and then frozen at –80^{o}C. One small section of urethra was obtained in a live patient during anterior exenteration for bladder Ca. We separated the entire length of urethra (25 to 43mm) into five or six sections from bladder neck (BN) to distal tip of urethra and examined regional differences in receptor density. Five or six sections were taken from each urethra at equal distance from proximal to distal (e.g. 3.2cm urethra—1st specimen 5mm from BN, 2nd specimen 10mm BN….6th specimen 30mm from BN). Specimens were homogenized, filtered and pelleted by centrifugation. Radioligand receptor binding studies were used to determine the regional densities of ^{3}H-prazosin-labeled alpha-one adrenergic receptors (AR), ^{3}H-QNB-labeled muscarinic cholinergic receptors (CR) and ^{3}H-serotonin-labeled 5-HT$_1$ serotonergic receptors (SR) on consecutive sections of female urethra. Specific binding was defined as the difference between the total and non-specific binding of the respective radioliogands, defined by 10^{-6} M prazosin, 10^{-6} M atropine sulfate, and 10^{-6} M methiothepin, for alpha-one adrenergic, muscarinic cholinergic and serotonergic receptors, respectively.

Results

Preliminary results suggest a predominance of alpha-one adrenergic receptors in the proximal urethra versus distal urethra (figure 1). The total average femtamoles/mg tissue protein of all urethra specimens by section were (range): 1st-17.5 (12.3-21.1), 2nd-51.6 (9.7-74.4), 3rd-34.6 (10.6-73.0), 4th-20.7 (7.1-27.5), 5th-15.1 (5.5-22.3) and 6th-12.0 (12.0) fmol/mg protein, respectively. Preliminary data from a radioligand binding study of muscarinic CR in two urethras (5 sections examined in each urethra) showed negligible receptor density. Similarly, data from one urethra (4 sections) also showed negligible densities of 5-HT$_1$ serotonin receptors.

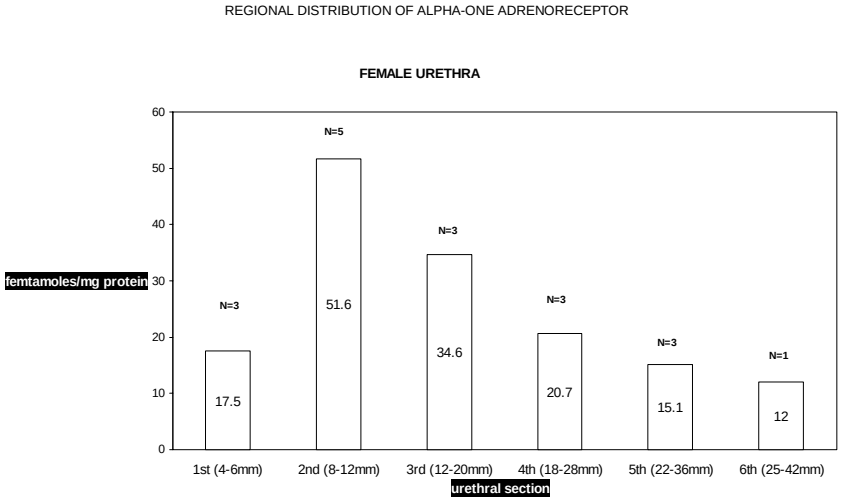

Fig 1. Mean of receptor density by urethral section.

Interpretation of results

Our preliminary results provide direct evidence of a predominance of alpha-one AR's in the proximal urethra which corresponds with the area of the smooth, lissosphincter. Our negative findings relating to CR and SR may reflect the absence of these receptors in this tissue or receptor densities below the level of detection using the homogenate binding assay. Subsequent studies (which we are currently performing) will employ more sensitive in-vitro autoradiography to identify urethral receptor subtypes (using the same urethras) in order to facilitate the pharmacologic treatment of stress-induced urinary incontinence. We are also staining the urethra cross sections for skeletal and smooth muscle to provide information as to which muscle group the neuroreceptor overlaps. The concentration of AR in our study is comparable to that found in studies done by *Kobayashi et al* on human male urethra [1] and in various animal studies. *Taki* [2] studied the functional response of human female urethra to noradrenaline and found a predominate effect in the proximal urethra. Similarly, *Nasu et al* [3] used RNase protection assays in human female urethra (only one was studied) and found a predominance of alpha-1a adrenoreceptor (versus 1b and 1d).

Concluding message

Our findings suggest direct evidence of a predominance of alpha-one adrenoreceptor in the proximal portion of the human female urethra. Further study with in-vitro autoradiography will allow more precise localization of this receptor population by urethral region and by cross-section and may provide information about alpha-one AR subtypes (1a, 1b and 1d). This information will aid in rational drug development to treat conditions such as urinary incontinence.

References

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