relaxation response (2). The vascular endothelial growth factor (VEGF), which is an angiogenic growth factor and an endothelial cell-specific mitogen, and whose actions are coupled to nitric oxide, is probably involved in this kind of injury, because it was found that intracavernosal injections of VEGF appear to protect corporal endothelium from hypercholesterolemia induced injury, preserving endothelial dependent corporal smooth muscle relaxation in hypercholesterolaemic rabbit (3). Recently, it was found a significantly lower in vivo and in vitro erectile response to phosphodiesterase-5 inhibition in hypercholesterolaemic rabbits than in controls (4).

The effect of experimental hypercholesterolemia on the ultrastructure of cavernosal smooth muscle cells, endothelial cells, elastic fibers, and collagen, which are the key structures for erection, were morphologically analyzed in hypercholesterolaemic rabbits, 5 years ago, by the same research group of the present paper (5). The findings shown that hypercholesterolemia in this animal model affect the percentage of staining for smooth muscle actin, endothelial cells, elastin, and collagen III and IV. However, the authors stated that this effect is temporary depending on the blood cholesterol levels, and, therefore, might not alter the erectile function.

The present study, by Karaboga et al., is very much important because demonstrates by the first time, in our knowledge, that the long-term chronic effects of experimental hypercholesterolemia on cavernosal smooth muscles might be irreversible and therefore might alter erectile function.

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RECONSTRUCTIVE UROLOGY

The Anatomy and Embryology of Posterior Urethral Valves

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Purpose: We reviewed the literature to better elucidate the history behind our understanding of the anatomy, classification and embryology of posterior urethral valves.
Materials and Methods: A directed MEDLINE literature review of the anatomy, classification and embryology of posterior urethral valves was performed. An effort was made to focus on the most frequently cited historical articles as well as those including detailed anatomical analyses of fetal specimens. Also included was the analysis of a specimen obtained at our institution in a novel manner that to our knowledge has not been previously described in the literature with respect to the anatomy of posterior urethral valves.
Results: The precise origins regarding the anatomy and embryology of posterior urethral valves remain undefined. However, the literature is abundant in theories regarding the origin of posterior urethral valves, based primarily on small uncontrolled series or case reports. There are a limited number of reports of the anatomy of posterior urethral valves in methodical fashion using reproducible scientific techniques such as histopathology. These reports are invaluable for providing a foundation of how to properly study and define the origins of posterior urethral valves.
Conclusions: Elucidating this most fundamental feature of a congenital condition central to the practice of pediatric urology is essential. More well designed studies specifically with this goal in mind are necessary. Incorporating new reconstructive imaging modalities may assist us in pinpointing the elusive origins of the embryology and anatomy of posterior urethral valves.

Editorial Comment

Although posterior urethral valves have a recognized incidence of 1/5000 to 8000 in male newborns, it is not known how common it might cause fetal demise (1).

Almost 2 centuries after its first description, the posterior urethral valves is newly investigated by Krishnan et al. with modern computer imaging in combination with histopathology in one of the few virgin cases of an untreated malformation known as a posterior urethral valve which helped to clarify its origin.

Until week 9, male and female urethral development is identical; whereas by week 14, the male urethra completes its development (2). Many of the former anatomical descriptions were misleading because of prior manipulations to the histological investigations with the result of several different described types first recognized by Dewan & Goh (3).

Krishnan et al. investigated the rare case of an untreated posterior urethral valve histologically by cross sectioning and reconstructed by three-dimensionally using computer imaging from the histology of the infant's urethra. With this investigation they revealed, as several times prior (4,5), the results of anatomical development in normal and malformed urethras. They demonstrated, with their outstanding work after an all-around literature analysis that the theory of Dewan et al. (6), seems to be the most likely with the single congenital obstructing posterior urethral membrane (COPUM).

Works similar to Krishnan et al. need our recognition/attention because they complete the understanding of the embryological development. This combination of histology and three-dimensional reconstruction helps to recognize and understand the embryonic development and will help to improve early treatment.

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Facilitatory Neuromodulative Effect of Duloxetine on Pudendal Motor Neurons Controlling the Urethral Pressure: A Functional Urodynamic Study in Healthy Women

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Objective: The aim of this functional urodynamic experiment in healthy women was to study the effect of duloxetine, which is a combined serotonin and norepinephrine (5-HT/NE) reuptake inhibitor, on urethral resting pressure, excitability of pudendal motor neurons, and urethral sphincter contractility.
Methods: In 11 healthy female subjects three baseline urethral pressure profiles (UPPs) were obtained to study resting pressure. Afterward the individual motor threshold (MT) for external urethral sphincter (EUS) contraction in response to transcranial magnetic stimulation (TMS) was determined to study the excitability of pudendal motor neurons. Another three UPPs were recorded while sacral root magnetic stimulation (SMS) was performed to evoke reproducible urethral contractions to study urethral sphincter contractility. Then the women received 40 mg duloxetine and the protocol was repeated 4h after drug administration. The resting pressure values, MT values following TMS, and the EUS pressure amplitudes in response to SMS obtained at baseline were statistically compared to the corresponding values at follow-up after duloxetine.
Results: Oral administration of duloxetine significantly lowered MT for EUS contraction in response to TMS ($p = 0.013$). In addition, duloxetine significantly increased EUS pressure amplitudes in response to SMS ($p = 0.0007$, 5 of 11 subjects evaluated) but did not change urethral resting pressures.
Conclusions: This is the first functional, urodynamic controlled study to show that the combined 5-HT/NE reuptake inhibitor duloxetine has a significant effect on the excitability of pudendal motor neurons and on urethral sphincter contractility in healthy women in vivo but no significant effect on urethral resting tone. Our data confirm a facilitatory neuromodulative effect of duloxetine on sphincter motor neurons in humans.

Editorial Comment

The first investigation regarding the norepinephrine-serotonin (NE/5-HT) reuptake inhibitor duloxetine was performed in the cat model with induced cystitis causing the symptom of overactive bladder and stress urinary incontinence. The authors reported relaxing the bladder and increasing the outlet resistance (1). The paper presented here is the first dealing with the influence of the NE/5-HT reuptake inhibitor to the pelvic floor muscles in females. The authors recorded responses of transcranial and spinal cord magnetic stimulation thereby

demonstrating individual increases in the urethral sphincter pressure with duloxetine. Although it is an elegant way to demonstrate the effect of the NE/5-HT reuptake inhibitor, the magnetic stimulation field is not very selective and stimulates all (efferent as well as afferent) nerve fibers in the field of the coil. Efferent motor neurons stimulated by these methods supply the striated muscles of the pelvis but cannot be subdivided to the urethral sphincter only. Vodusek & Zidar suggested using a needle to record from the sphincter to identify specific urethral muscle functions from a general "mass contraction" (2).

The authors reported a decreased threshold for significant urethral pressure spikes in the mid urethra after sacral root magnetic stimulation through the influence of the NE/5-HT reuptake inhibitor in 45% of the subjects. This is in line with reports of decreased incontinence episode frequency of 50 – 100% in 51.4% of the trial group (n = 344) receiving duloxetine (3). An additional double-blind trial with a more representative sample of subjects should validate the drug effect on urethral pressure after magnetic stimulation.

In addition, the outcome of the single intake of the NE/5-HT reuptake inhibitor causes under normal physiological conditions does not lead to significant stimulation of postsynaptic 5-HT receptors.

After the administration of a NE/5-HT reuptake inhibitor all 5-HT transporters at the pre-synaptic membrane are blocked, leading to higher 5-HT levels in the synaptic cleft. At the same time, these increased 5-HT levels activate 5-HT1A and 5-HT1B auto-receptors, located at the pre-synaptic membrane. These pre-synaptic auto-receptors inhibit as negative feedback regulators the release of 5-HT (4-6). The simulated on-demand use causes only a mild or no increase of 5-HT neurotransmission, which might be an explanation of the experimental outcome.

Still this elegant approach might serve as a single dose-screening test to predict patients with beneficial treatment responses to the duloxetine effect in a potential patient avoiding possible side effects. The blood pressure rises induced by the magnetic coil stimulation might ask for other tests than the magnet coil stimulation to underline the outcome of this approach and demonstrate the effect to motor thresholds resulting in increased urethral pressure amplitude even in a higher proportion of subjects.

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