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THE NATURE OF NON-VOIDING CONTRACTIONS IN THE RAT: A PHARMACOLOGICAL INVESTIGATION USING A NOVEL VIDEO URODYNAMICS TECHNIQUE

Hypothesis / aims of study

Non-voiding contractions (NVC) during filling are often utilized as surrogates for urgency in preclinical studies. Last year we reported results from our laboratory which suggested that some NVC may be a normal part of the filling mechanism, directing urine from the base to the dome in a peristaltic wave. These filling contractions often appear shortly after a the alternating paired injection of fluid via the ureters, and we have hypothesized that they may arise as a continuation of the electrical activity propagated down the ureters, to be coordinated and redirected by the trigone.

Another source of NVCs is the dome of the bladder, and this type of NVC characteristically appears toward the end of the filling cycle, if they are to appear at all, as a response to the inflation of the dome by the base-to-dome filling contraction. These visually evident dome muscular contractions have been referred to by others when referring to cystometric traces as prodromal contractions, and in our hands they had the appearance of a strongly coordinated detrusor contraction, resulting in both bladder neck and proximal urethral dilation. Thus, we hypothesized that it is these latter NVCs which are the true surrogates for urgency, due to their reciprocal inflation of the bladder neck and proximal urethra. We further hypothesized that these contractions arose from a spinal reflex, which gave the appearance of a micturition reflex but without the relaxation of the external urethral sphincter. We sought to test this hypothesis and further discriminate between base-to-dome contractions and dome-to-base NVCs using pharmacological manipulation of autonomic function.

Study design, materials and methods

The lower urinary tracts of 6 urethane anesthetized (1.2 g/kg) female SD rats were exposed by midline laparotomy and pubic symphysis reduction or removal (Figure 2). The animals were mounted on a frame and their abdomens filled with mineral oil. Cystometric investigation utilized transureteral filling at a physiological flow rate (0.02-0.04 ml/min) and a static transurethral catheter for pressure recording. Video capture of bladder motility was performed using a high speed video camera with a LabView frame grabber program. Pressure recordings were made using LabChart. Under these conditions, numerous non−voiding pressure waves during each filling cycle and their associated bladder contractile activity are readily evident along with subsequent micturition events (Figure 1). Two animals received hexamethonium only following a control period. In four other animals, we sequentially administered atropine (0.4-0.8 mg/kg), hexamethonium (25-50 mg/kg), a beta 3 adrenergic agonist (CL−316,243; 100 ug/kg) and/or isoproterenol (100 ug/kg).

Results

Atropine had little effect on either filling contractions (a.k.a. “Initial NVCs”) or apparent prodromal contractions (Figure 1), even though it increased compliance. Continued bladder activity was verified both by cystometric trace and video. Ganglionic blockade by hexamethonium resulted in a dramatic increase in amplitude and area of NVCs. CL−316,243 and isoproterenol resulted in an initial almost total abolition of contractile activity, and thus NVCs. It should be noted that only one of the animals demonstrated an apparent full coordinated contraction of the dome during prodromal contraction. Of note, when prodromal activity became apparent, it appeared to result in a decrease in baseline bladder pressures.

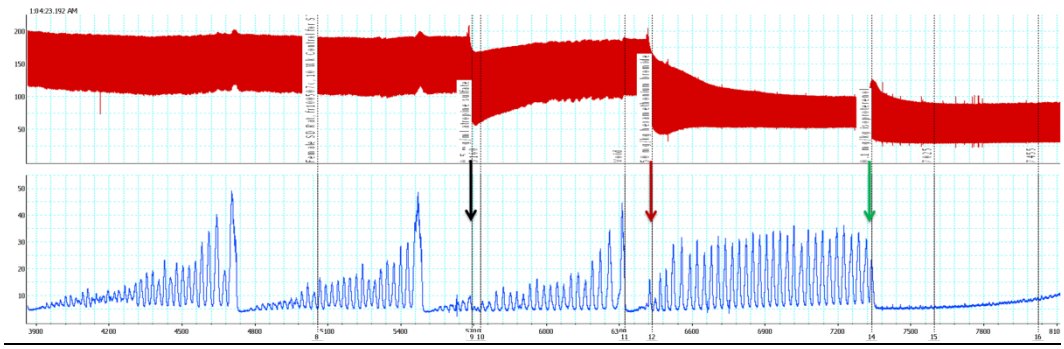

Figure 1. Cystometric trace during video urodynamic study of normal female rats before and after drug treatment – The top trace is carotid artery pressure, bottom trace is transurethral bladder pressure. Following control micturition cycles, atropine was administered (black arrow), followed by hexamethonium (red arrow) and finally isoproterenol (green arrow). Only beta adrenergic agonists were capable of quieting the bladder NVCs in this preparation.

Interpretation of results

The results of the current study suggest that autonomic efferent pathways are not responsible for producing filling NVCs in this preparation, and in fact the sympathetic nervous system appears to keep this activity in check, as evidenced by hexamethonium enhancement and beta agonist quieting of NVCs. That muscarinic blockade was ineffective in eliminating filling NVCs and that atropine and hexamethonium seemed to have no effect on prodromal NVCs of this series suggests the prodromal contractions seen here were not neurogenic in origin. However, it must be stated that these prodromal contractions were not precisely similar to those which preceded the micturition-like, fully coordinated dome contractions in previous

experiments. It may be the case that these differences in coordination represent two different mechanisms for NVC production. Thus, we are unable to state conclusively that we have shown all prodromal dome-to-base contractile activity to be non-neural. Future studies will attempt to elicit the putatively neurally-mediated reflex contractions with bladder irritation in order to test whether atropine and hexamethonium have any effect on these more coordinated, micturition-like dome contractions.

Concluding message

Thus, we now believe that the bladder is a rather noisy storage unit, with myogenic contractile activity directing urine from the base to the dome, along with "reflex" dome activity as the dome is expanded, some of which gives the appearance of regional coordination but overall "mixing" and by these results appear to be myogenic in origin, while in other cases there appears to be coordination which mimics a true micturition event, but without relaxation of the external urethral sphincter. This type of NVC was not present in the current study, and therefore has not yet been tested pharmacologically. As such they may be neutrally mediated in origin. Nonetheless, the finding of high amplitude NVCs of non-neural origin may explain why some OAB patients do not respond well to antimuscarinic therapy.

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