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THE EFFECT OF A MUCOSA-DERIVED SUBSTANCE TO ACTIVATE SPONTANEOUS CONTRACTIONS IS MORE PRONOUNCED WITH INCREASING BLADDER WEIGHT IN A RAT MODEL OF BLADDER OUTLET OBSTRUCTION AND MAY BE ASSOCIATED WITH IN-VIVO NON-VOIDING CONTRACTIONS

Hypothesis / aims of study
Bladder dysfunction due to bladder outlet obstruction (BOO) has been studied in animal models using both in-vitro bladder strips and in-vivo cystometry. However, little is known about the relationship between in-vitro and in-vivo experimental data.
Although it is well known that non-voiding contractions (NVCs) are induced by BOO, the relationship between NVCs and the degree of BOO remains unknown. We have previously reported that cromakalim, an ATP-sensitive potassium channel opener, suppresses spontaneous contractions (SCs) in rat bladder and it is less potent when the mucosa is present; suggesting that the mucosa may release a substance to activate SCs and this effect of a mucosa-derived substance is pronounced by BOO. Regarding this effect it also remains unknown whether it is associated with the degree of BOO.
The aim of the present study was to correlate SCs of bladder strips with NVCs from cystometrograms, and to correlate SCs and NVCs with bladder weight in a rat model of BOO. Bladder weight is considered to be indicative of the degree of BOO in a rat model of BOO. The effect of a mucosa-derived substance to activate SCs was also correlated with NVCs and bladder weight.

Study design, materials and methods
Partial BOO was induced by incomplete urethral ligation (urethral outer diameter of 1.1 mm) in female Wistar rats (n=12). Cystometry was performed in the awakened condition 4 weeks following induction of BOO. The frequency and amplitude of NVCs were recorded. Bladders were removed and weighed within 48 hours of cystometry and three strips were taken form the bladder body of each bladder. The mucosa was removed from two of these strips (denuded strips). One intact strip and two denuded strips from each bladder were mounted in tissue baths and equilibrated at 1 g resting tension. One of the two denuded strips was co-incubated with a strip of mucosa, attached to the same tissue holder and loaded with 1 g tension. Spontaneous activity was allowed to develop and recorded, and then cumulative concentration-response curves to cromakalim were obtained. Since co-incubation with a mucosal strip decreases the potency of cromakalim in denuded strips, the effect of a mucosa-derived substance to activate SCs was estimated for each bladder by calculating the difference in potency (pEC50) of cromakalim in denuded strips between with and without co-incubation with a mucosal strip.

Results
1) The frequency and amplitude of NVCs did not correlate with the frequency and amplitude of SCs of mucosa-intact strips.
2) There was no significant relationship between the frequency or amplitude of SCs in intact strips and bladder weight. The frequency of NVCs was negatively correlated with bladder weight ($p<0.05$). There was a trend towards increasing amplitude of NVCs with bladder weight, but not significant.
3) The effect of the mucosa on the suppressive effect of cromakalim on the frequency of SCs significantly correlated with bladder weight ($p<0.05$). This effect was negatively related with the frequency of NVCs ($p<0.05$). The effect of the mucosa on the suppressive effect of cromakalim on the amplitude of SCs did not correlate with bladder weight ($p=0.24$), but seemed to be negatively related with the frequency of NVCs ($p=0.058$). No relationship was observed between the amplitude of NVCs and the effect of a mucosa-derived substance to inhibit the suppressive effect of cromakalim on SCs.
4) The frequency of SCs in mucosa-denuded strips was likely to be decreased by co-incubation with a mucosal strip; the frequency of SCs were 3.23 ± 0.25/minute (mean ± SEM) and 2.66 ± 0.22/mminute in the denuded strip without and with co-incubation with a mucosal strip, respectively ($p=0.053$). The amplitude of SCs in denuded strips was increased by co-incubation with a mucosal strip; the amplitude of SCs were 0.19 ± 0.04 g and 0.49 ± 0.13 g in the denuded-strip without and with co-incubation with a mucosal strip, respectively ($p<0.05$).

Interpretation of results
The nature of the in-vitro SCs does not appear to represent the nature of the NVCs in in-vivo cystometrogram in this rat model of BOO.
The frequency of the NVC was decreased with increasing bladder weight without the decrease in the amplitude of the NVC, suggesting that the higher degree of BOO induces the slower and bigger NVCs.
The effect of a mucosa-derived substance to inhibit the suppressive effect of cromakalim on SCs, i.e. the effect of the mucosa to activate SCs was more pronounced with increasing bladder weight and related to the decrease in the frequency of the NVCs. Co-incubation of the mucosa-denuded strip with a mucosal strip is likely to decrease the frequency of SCs in mucosa-denuded strips and increases the amplitude of SCs in those strips. These results suggest that the effect of a mucosa-derived substance is more pronounced with higher degree of BOO and may be involved in the generation of slow and big NVCs seen in BOO.

Concluding message
The nature of the in-vitro SCs does not appear to represent the nature of the NVCs in in-vivo cystometrogram in this rat model of BOO. However, the effect of a mucosa-derived substance to activate SCs is more pronounced with increasing bladder weight and may be involved in the generation of NVCs seen in BOO.

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Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
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