

INTRAVESICAL DOXORUBICIN ENHANCES NEUROGENIC RESPONSES OF DETRUSOR SMOOTH MUSCLE.

Hypothesis / aims of study

Intravesical doxorubicin is used in the treatment of superficial bladder cancer, but can cause urological adverse effects including urgency and frequency in a significant number of patients [1]. This study investigates the effects of luminal doxorubicin administration on the subsequent responsiveness of detrusor smooth muscle to muscarinic receptor stimulation and also neurogenic responses of the detrusor via electrical field stimulation.

Study design, materials and methods

Isolated full thickness sheets of bladder wall from the dome of the porcine bladder were set up in gassed Krebs-bicarbonate solution and incubated at 37°C for 1 hour with a therapeutic concentration (1mg/mL) of doxorubicin applied to the inner urothelial surface. Following this luminal treatment, strips of detrusor muscle (with urothelium removed) were isolated, and contractions were obtained to the muscarinic agonist carbachol and neurogenic contractions to electrical field stimulation (20V, 0.5ms pulse-width, applied for 5s every 100s) were also investigated. Responses of doxorubicin pretreated tissues were compared with tissues receiving a control incubation without addition of doxorubicin.

Results

The maximum responses of detrusor muscle strips to carbachol were similar in tissues taken from treated (18.88 ± 2.93 g, n=5) and control bladders (18.91 ± 3.38 g, n=5). The sensitivity of muscle strips to carbachol were also similar in control ($pEC_{50} = 5.07 \pm 0.30$) and doxorubicin treated ($pEC_{50} = 5.14 \pm 0.26$) muscle strips (Figure 1).

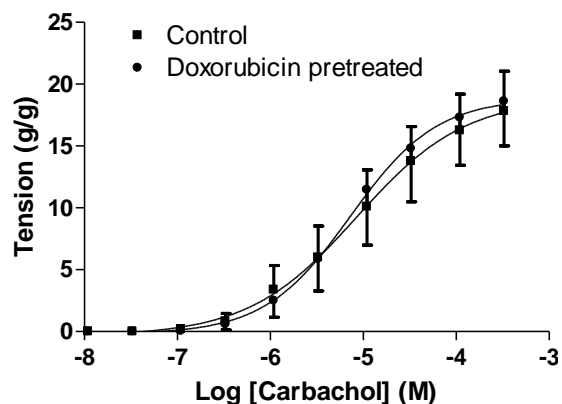
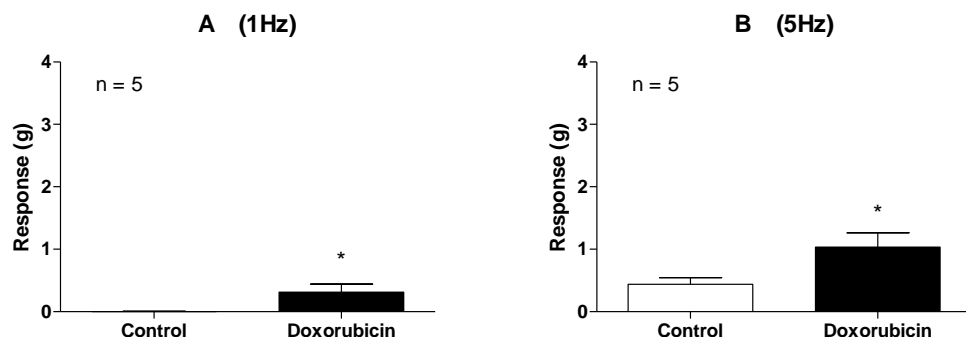


Figure 1: Effect of luminal pre-incubation with doxorubicin (1mg/mL, 1hr) on subsequent responses of intact and urothelium denuded bladder strips to carbachol.

When nerve mediated contractile responses of isolated detrusor muscle strips were examined, the responses to electrical field stimulation were significantly enhanced in the doxorubicin treated tissues (Figure 2). At the lowest stimulation frequency of 1Hz, control tissues failed to respond (n=5), but after doxorubicin treatment tissues contracted by 0.31 ± 0.13 g, ($P < 0.05$ compared with control responses, n=5). With increasing stimulation frequency, response increased, but at every frequency examined (1, 5, 10 & 20Hz) responses were significantly greater ($P < 0.05$) in tissues that had received the doxorubicin pretreatment (Figure 2).



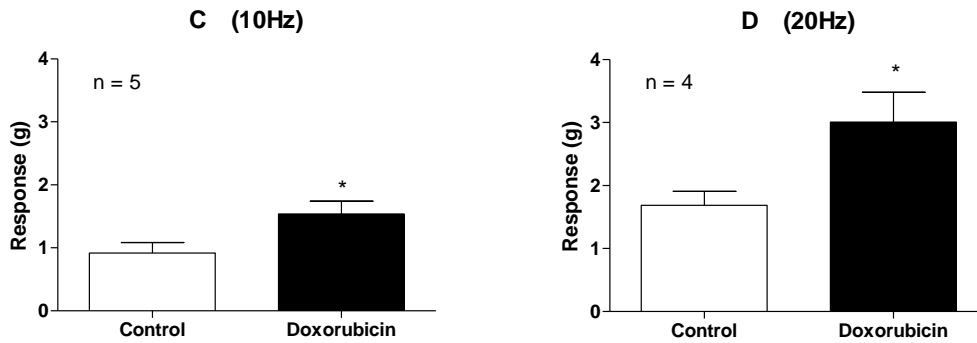


Figure 2: Effect of doxorubicin treatment on mean (\pm sem) detrusor responses to electrical field stimulation at (A) 1Hz, (B) 5Hz, (C) 10Hz and (D) 20Hz. * $P < 0.05$ compared to control incubated tissues.

Interpretation of results

Detrusor muscle responses mediated via transmitter release following electrical stimulation of nerves were enhanced following pretreatment with doxorubicin. However the responsiveness of the muscle itself was not altered since the responses to direct stimulation with a muscarinic receptor agonist were not altered by doxorubicin pretreatment. These results suggest that luminal application of doxorubicin at therapeutic concentrations and duration, enhances the release of neurotransmitters that mediate contraction within the detrusor muscle of the bladder wall

Concluding message

The results suggest that doxorubicin when administered intravesically for bladder cancer may increase neurotransmitter release within the detrusor smooth muscle layers. This may be one mechanism by which this drug elicits adverse effects such as urgency and frequency in patients who have received this drug intravesically.

References

1. Thrasher JB & Crawford ED (1992) Complications of intravesical chemotherapy. *Urol. Clin. North Am*, 19(3): 529-539.

Disclosures

Funding: This study was supported by the Faculty of Health Sciences and Medicine, Bond University and Cancer Council Queensland. **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Porcine (Pig) bladder tissue was used for this study. **Ethics not Req'd:** Porcine bladder tissue was collected from a local abattoir, therefore ethical approval was not needed.