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HYPERTHERMIA THERAPY CAUSES DEPRESSED DETRUSOR AND UROTHELIAL RESPONSES WITH MUSCARINIC, ADRENERGIC AND NEUROGENIC STIMULATION.

Hypothesis / aims of study

Local hyperthermia has therapeutic benefits on cancer cells. Hyperthermia in combination with intravesical chemotherapy is currently undergoing Phase III trials as a treatment for bladder cancer. While there is no intrinsic difference in thermal sensitivity between normal and tumour cells, in vivo models using localised hyperthermia in bladder models have found that temperatures between 40-44°C exhibit a tumour killing effect [1]. This study investigates the effects of intravesical hyperthermia pre-treatment on the subsequent contractile responses of detrusor smooth muscle strips and urothelium/lamina propria strips to the muscarinic receptor agonist carbachol and the β-adrenoceptor agonist isoprenaline. Neurogenic responses of the detrusor smooth muscle to electrical field stimulation was also studied

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 either 37°C (control) or 42°C for 1 hour with a saline solution applied to the inner urothelial surface. Following this treatment, strips of detrusor smooth muscle with urothelium and lamina propria removed, and also strips of urothelium with lamina propria, were isolated and set up in organ baths containing gassed Krebs solution at 37°C. Contractile responses were obtained to carbachol, and after washout back to resting tension, tissues were then pre-contracted with carbachol (1μM) and relaxation responses to isoprenaline obtained. Neurogenic contractions of detrusor muscle strips to electrical field stimulation (20V, 0.5ms pulse width, applied for 5s every 100s) was also examined and the effects of the muscarinic antagonist atropine investigated.

Results

Both detrusor and urothelium/lamina propria tissues responded to carbachol. The responses of the detrusor from bladders pre-incubated at the higher temperature (42°C, n=8) were statistically smaller (P>0.05) than those of control tissues pre-incubated at 37°C (n=9). The lamina propria/urothelium pre-incubated at 42°C showed depressed responses to carbachol compared to the control at but these changes were not statistically significant (P=0.33) (Figure 1). Similarly, the potency of carbachol was not different between tissues pre-incubated at different temperatures (detrusor pEC50 values of -5.94±0.27 for 37°C and -5.88 ±0.33 at 42°C pre-incubations; urothelium/lamina propria pEC50 values of -5.92±0.24 for 37°C and -5.80±0.18 for 42°C pre-incubations).

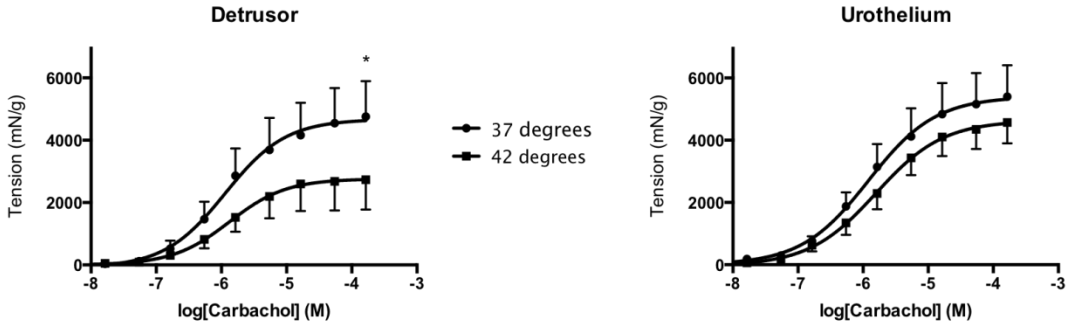

Figure 1: Effect of pre-incubation at 42°C on subsequent contractile responses of denuded detrusor and urothelium/lamina propria strips to carbachol

Isoprenaline induced relaxation of pre-contracted detrusor strips and urothelium/lamina propria strips (Figure 2). In detrusor strips, the potency (pEC50) of isoprenaline was similar in tissues pre-incubatged at 37°C (-6.66±0.31) and 42°C (-7.45±0.37), but the maximum responses of detrusor strips was significantly (P<0.001) reduced following incubation at 42 (486.70±59.11mN/g, n=8) compared to control (37°C) incubated tissues (1518±212.1, n=11). Similarly, the potency of urothelium/lamina propria strips was similar following incubation at the two temperatures (37°C=-6.34, 42=-6.77, but maximum responses were significantly (P<0.05) depressed following incubation at the higher temperature (1224mN/g, n=8) compared to controls (37°C, 2968mN/g, n=9).

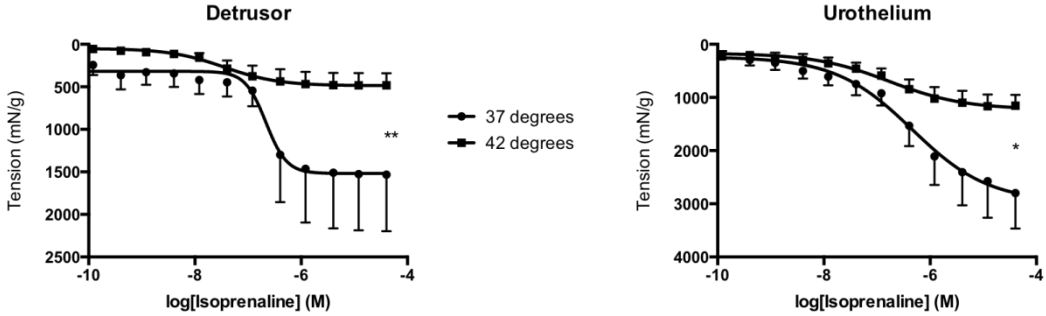

Figure 2: Effect of pre-incubation at 42℃ on subsequent responses of denuded detrusor and urothelium bladder strips to isoprenaline

Contraction due to nuerogenic stimulation was depressed at all in frequencies basally and in the presence of atropine and α,β-methylene ATP. The only significant difference was observed in atropine (P<0.05, n=12 [37°C], n=8 [42°C])

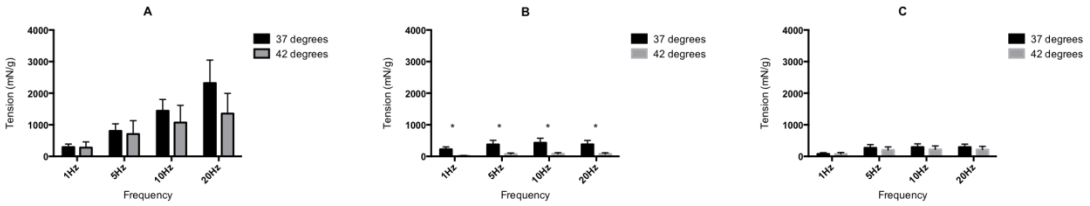

Figure 3: Effect of pre-incubation at 42℃ on mean (±SEM) detrusor responses to electrical field stimulation at 1, 5, 10 and 20Hz basally (A), in the presence of 1μM atropine (B) and 10μM α,β-methylene ATP (C).

Interpretation of results

Detrusor muscle responses to carbachol, isoprenaline and neurogenic stimulation were depressed after incubation at hyperthermia temperatures. Comparing the 42°C to the 37°C pre-incubation, the urothelium showed depressed reponses to isoprenaline but little change with addition of the muscarinic agonist carbachol. It could be suggested from these results that hyperthermia treatment depresses the release of neurotransmitters that mediate contraction within the detrusor muscle of the bladder wall. Similarily, it appears that the urothelium is desensitized by hyperthermia therapy, showing depressed responses to isoprenaline.

Concluding message

The results suggest that hyperthermia therapy used for bladder cancer therapy may depress the release of neurotransmitters that cause contraction of the detrusor muscle.

References

1. RAMPERSAUD, E. N., VUJASKOVIC, Z. & INMAN, B. A. 2010. Hyperthermia as a treatment for bladder cancer. Oncology (Williston Park), 24, 1149-55.

Disclosures

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