

## INCREASED PHASIC ACTIVITY OF BLADDER STRIPS IN AN OBESE MODEL OF PRE-DIABETES

### Hypothesis / aims of study

Diabetic patients suffer a range of complications which can severely affect their quality of life. Over 50% of diabetic patients develop some form of bladder dysfunction, ranging from poor sensation and inability to empty the bladder to bladder overactivity. We have recently shown altered bladder contractility in a model of type I diabetes (1), which has been used as a model of diabetic bladder dysfunction. Recently, although less clear, bladder dysfunction has also been linked with obesity and the metabolic syndrome (2) and a number of experimental studies have shown increased urinary frequency and non-voiding contractions in obese models (3). The aim of the present study was to investigate bladder function in bladder strips isolated from an obese model of pre-diabetes.

### Study design, materials and methods

8 week old male Wistar rats (~200g) were fed a control (control) or high fat/high carbohydrate diet (rat chow supplemented with sweetened condensed milk, solidified animal fat and raw sugar) (obese) ad libitum for 32 weeks. Bladder strips were isolated and mounted in tissue baths in Krebs solution (1.5g tension, 37°C, 95%O<sub>2</sub>/5%CO<sub>2</sub>). Amplitude and frequency of phasic activity (PA) were recorded and the effects of carbachol (0.05-0.5µM) and neostigmine (1µM) examined. Contractile responses to KCl (60mM), carbachol (0.01-10µM) and electrical field stimulation (nerve-evoked) were recorded (1-40Hz, 0.01ms duration, 40V for 5s every 100s), and relaxation responses to isoprenaline (1nM-30µM) were also obtained. All data are expressed as mean ± SEM. Amplitude and tension are expressed as g/mg tissue weight, whilst frequency is expressed as the number of contraction events per 5 minute period. Data was compared via Student's t test and P<0.05 considered significant.

### Results

Obese animals had significantly greater visceral fat compared to controls (44.2±3.7g vs 79.0±11.1g, P<0.01, n=8). Body weight and bladder weights were also greater in obese animals, though non-significantly (720.0±24.8g vs 845.3±58.6g and 119.9±12.8mg vs 140.3±12.7mg respectively).

Contractile responses to KCl were similar in bladder strips from control and obese animals (0.141±0.048g/mg vs 0.102±0.025g/mg) and concentration-response curves to carbachol and isoprenaline were also not altered in bladder strips from obese animals.

Electrical field stimulation (EFS) evoked contractile responses in bladder strips, and these were similar in obese and control animals. Atropine (1µM) reduced EFS-evoked contractions by 46.5±4.6% in strips from controls and 46.1±3.9% in strips from obese animals, and in combination with α,β-methylene-ATP (10µM) by 83.2±5.2% and 86.9±0.6% respectively. The remaining response was unaffected by L-NNA (100µM) and 1µM tetrodotoxin was able to completely abolish the EFS-evoked contractions.

Phasic activity was observed in all bladder strips. Frequency of PA, but not amplitude, was significantly greater in bladder strips from obese animals (events/5mins: 62.6±8.85 vs 36.4±23.96, P<0.05) (Fig. 1). Low concentrations of carbachol increased the amplitude and decreased the frequency of PA in a similar fashion in all tissues. Neostigmine (1µM) also increased amplitude and decreased frequency of PA, significantly so in obese bladder strips (events/5mins: 71.4±10.6 vs 26.1±1.4, P<0.001) (Fig. 2).

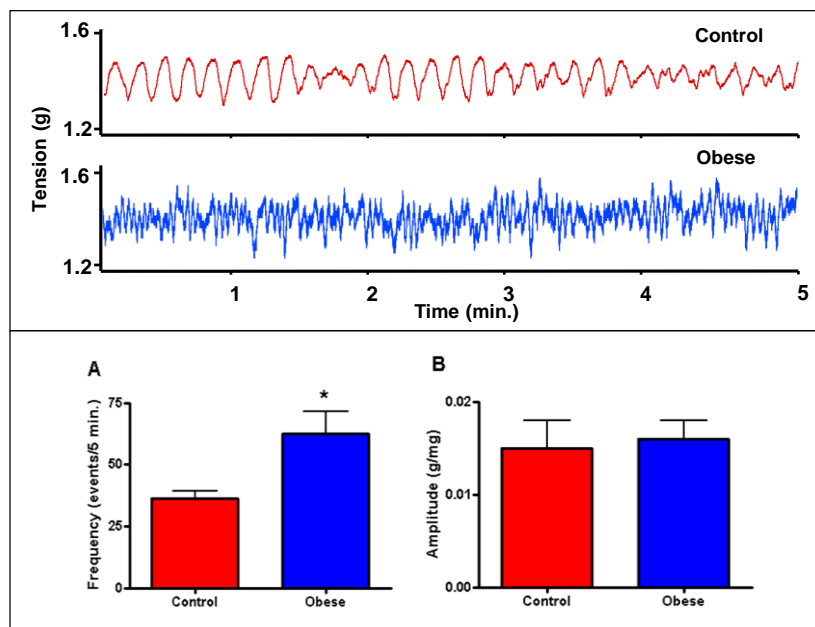


Figure 1. Typical phasic contractions in bladder strips. Mean frequency (A) and mean amplitude (B) of phasic contractions in control (n=10) and obese (n=15) \*P<0.05 vs control.

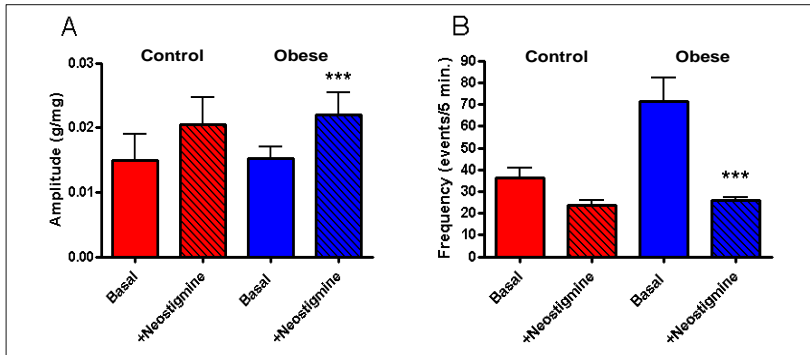


Figure 2. Effect of neostigmine on phasic contractions in bladder strips from control (n=6) and obese (n=10) \*\*\*P<0.05 vs basal (0µM)

#### Interpretation of results

In isolated bladder strips from an obese model of pre-diabetes agonist and nerve-mediated contractions of the detrusor are not altered in comparison to control animals. However basal phasic activity is altered in bladder strips from obese animals, with increased frequency of contractions. These contractions can be modulated by low concentrations of carbachol and the presence of the cholinesterase inhibitor neostigmine, suggesting a possible role for Ach release in phasic activity, which requires further investigation.

#### Concluding message

Phasic activity is increased in isolated bladder strips from an obese model of pre-diabetes. This phasic activity can be modulated cholinergically, suggesting a possible role for endogenous Ach release in this model.

#### References

1. Vahabi et al. (2011) Eur. Pharmacol. 660:431-437
2. Kirby et al. (2010) Neurourol. Urodynam. 29: 1360-1364
3. Tong & Cheng (2007) J Urol. 178(4 Pt 1):1537-42

#### Disclosures

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