The overactive bladder and the role of P2Y agonists

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**Introduction.** Spinal cord injury (SCI) generates an overactive bladder phenotype, but the pathophysiology is unknown. In a rat SCI model overactive behaviour is associated with an increase of suburothelial interstitial cell (IC) number [1]. P2Y-receptor agonists such as ADP and UTP generate excitatory responses in ICs, whereas they generally suppress directly smooth muscle contractility. We hypothesised that the action of P2Y agonists is more efficacious on ICs and thus should augment bladder overactivity and thereby demonstrate a crucial role for the mucosa in regulating the contractile function of the bladder.

**Methods.** We used a rat model of SCI (T8/T9 trans-section). Spontaneous contractile activity and simultaneous optical imaging of electrical and Ca$^{2+}$-waves were measured, in the presence of P2Y agonists. Optical signals were recorded as propagating either across the bladder wall surface, in the presence or absence of mucosa, or across transverse sections of the bladder between mucosa and detrusor. Data are recorded as mean±SD, the null hypothesis rejected at $p<0.05$.

**Results Contractile Function.** Fig 1 shows ADP increased spontaneous contractile activity of bladder sheets with an intact mucosa (left). UTP, UDP and ATP had similar actions. With isolated detrusor strips ADP caused muscle relaxation (right). With mucosa-intact preparations ADP increased the amplitude (163±25% control) but not the frequency 119±24% control) of contractions.

**Discussion.** We have shown that P2Y-receptor agonists, ADP, UTP, UDP, augment significantly spontaneous contractile activity in bladder preparations from spinal cord injured rats that have an overactive bladder phenotype. Augmented contractile activity was accompanied by an increased conduction velocity of intracellular Ca$^{2+}$ and membrane potential (Em) waves that propagated across the bladder wall and could in principle coordinate the larger contractions. The signals always originated from regions with an intact mucosa. Imaging transverse sections showed that spontaneous Ca$^{2+}$ and Em waves originated in the suburothelium and subsequently propagated to the detrusor and urothelium. Analysis of these waves showed that P2Y agonists altered their characteristics to suggest that the increased conduction velocity was due to larger excitatory currents in the contributing cells.

**Conclusions.** P2Y agonists augment spontaneous contractile activity in detrusor animals with an overactive bladder phenotype and enhance propagating Ca$^{2+}$ and Em waves. The requirement for an intact mucosa for these propagating waves and their origin in the suburothelium, indicate that this region is crucial for such overactive behaviour and offers an attractive therapeutic target to suppress such activity.

**Reference:** Ikeda et al Am J Physiol 2007; 293: F1018-1025. **Supported by:** NIH and EU FP7 (INComb)