

THE ROLE OF THE UROTHELIUM IN POTASSIUM SENSITIVITY TESTING IN THE CLINIC.Hypothesis / aims of study

Potassium sensitivity testing (high K⁺) for diagnosis in patients with bladder disorders is controversial, although it is considered predictive of increased urothelial permeability. As such high K⁺, as it diffuses across a leaky urothelium, is considered to directly depolarise sensory nerve endings. However, we hypothesised that high K⁺ may act at the level of the urothelium to release mediators that modulate afferent sensitivity indirectly.

Study design, materials and methods

Mouse bladder afferents were recorded electrophysiologically, in vitro, during perfusion with isotonic NaCl or a high K⁺ solution (50mMKCl/100mMNaCl). The role of the urothelium was assessed after intravesicular administration of 10mg/ml protamine sulphate (PS) for 1 hour which resulted in histologically verified urothelial denudation. The response to high K⁺ was also examined in the presence of a cocktail of pharmacological mediators designed to block the actions of nitric oxide (L-name, 1mM), prostanoids (indomethacin, 50uM), acetylcholine (atropine, 10uM), ATP (suramin, 500uM), and endocannabinoids (SR141716A, 10uM + SR144528, 10uM). Afferent firing (mean± SEM) was quantified (in spikes/s), at baseline and during distension. Statistical analysis was conducted using 1- and 2-way ANOVA.

Results

Bladder distension evoked an afferent response profile indicative of both low and high threshold afferent firing quantified at 10 and 40 mmHg respectively. Following 30 minutes intraluminal application of high K⁺, firing was reduced at 10mmHg (from 127.14± 24.2 to 73.6 ± 20.75 spikes/s, P<0.0001, n=6), and 40mmHg distension (from 204.77 ± 39.3 to 106.78 ± 21.81 spikes/s, P<0.0001, n=6). Baseline firing was unaffected. Baseline firing and distension responses were increased by PS. After PS the inhibitory effect of high K⁺ solution was reversed causing augmented firing at both 10mmHg (from 39.0 ±13.7 to 87.90±21.7 spikes/s, P=0.003, n=6) and 40mmHg, (from 190.0 ±33.12 to 252.1± 57.1 spikes/s, P=0.003, n=6). Treatment with the pharmacological cocktail attenuated the inhibitory response to high K⁺ (P=0.007, n=6) an effect that was fully reversed following washout.

Interpretation of results

These data demonstrate that high K⁺ stimulates the release of urothelial factor(s) that down regulated bladder afferent sensitivity. Urothelial damage with PS abolishes this inhibitory response and unmasks an excitatory effect. The nature of the inhibitory mediator remains to be determined.

Concluding message

This data suggests that the potassium sensitivity test in patients may reveal information on the ability of the urothelium to modulate afferent sensitivity rather than a simple test of permeability.

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<i>Is this a clinical trial?</i>	No
<i>What were the subjects in the study?</i>	ANIMAL
<i>Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?</i>	Yes
<i>Name of ethics committee</i>	Sheffield University ethics committee