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UROTHELIAL SPERMIDINE RELEASE ATTENUATES DETRUSOR MUSCLE CONTRACTION.

Hypothesis / aims of study

The urothelium releases a factor that inhibits detrusor contraction and has not been identified. We previously showed that darifenacin is less potent in inhibiting contraction of urinary bladder strips from certain organ donors and patients with neurogenic bladder. When co-incubated, the urothelium from bladders in which darifenacin is less potent inhibits rat bladder contraction, while urothelium from high potency bladders does not. HPLC analysis demonstrated that increased amounts of the polyamines spermidine and n-acetyl spermidine were released from human urothelium that inhibited rat bladder contraction compared to human mucosa that did not.

Study design, materials and methods

Cumulative carbachol concentration response curves were performed using rat bladder following 3 hour incubation with various concentrations of spermidine. In some experiments, the rat bladder was denuded of urothelium.

Results

As seen in figure 1, 30 and 100 µM spermidine significantly inhibit the maximal carbachol mediated bladder contraction. Spermidine also reduces the potency of darifenacin for inhibiting contraction (figure 2), while having no effect on the potency of methoctramine for inhibiting contraction. Spermidine has no inhibitory effect in urothelial denuded rat bladder strips, suggesting that the inhibitory effect of spermidine is mediated by the urothelium.

Interpretation of results

The urothelium from bladders in which darifenacin has low potency have an increase in M3 receptor density. Only urothelium with increased M3 receptors inhibits rat bladder contraction. The inhibitory effect of spermidine on the rat bladder requires an intact urothelium. Therefore, spermidine may activate an inhibitory pathway (negative feedback loop) mediated by urothelial M3 receptors.

Concluding message

This pathway may become altered in pathological conditions. The apparent low potency of darifenacin seen in some bladder specimens may be the result of inhibition of an augmented M3 mediated inhibitory pathway in these specimens. Bladder overactivity may result from dysregulation of this urothelial inhibitory mechanism.

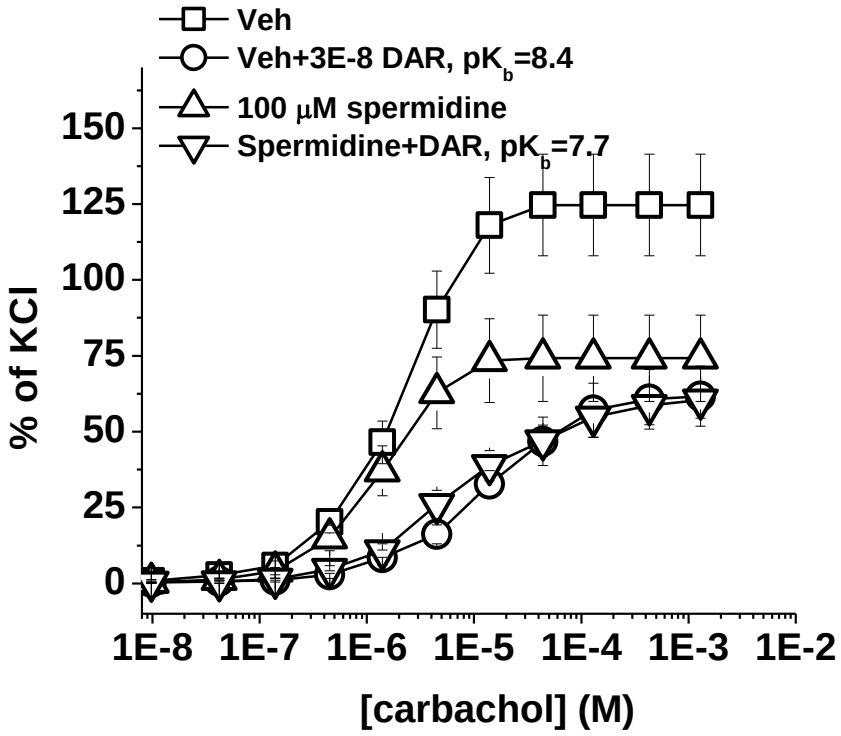

Figure 2

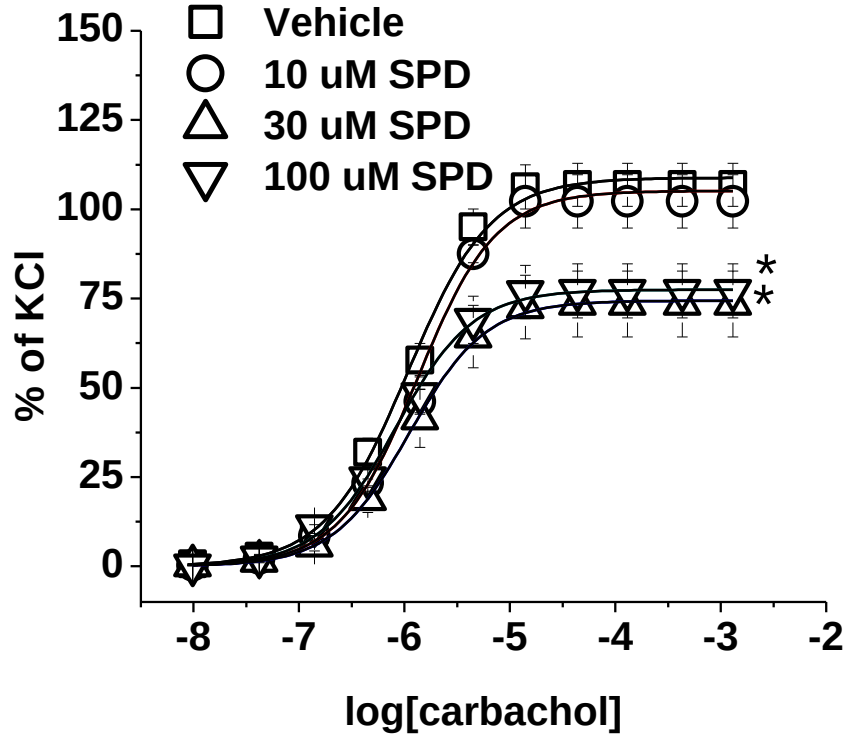

Figure 1

Specify source of funding or grant	**Pfizer Competitive Grants Award**
Is this a clinical trial?	**No**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**IRB**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**