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UROTHELIAL MAXIK ACTIVITY REGULATES BOTH UROTHELIAL AND DETRUSOR METABOLISM.

Hypothesis / aims of study

The importance of the MaxiK potassium channel (also known as BK, KCNMA1) in normal bladder function has been shown unequivocally in MaxiK ($slo^{-/-}$) knock-out mice, where the absence of MaxiK results in enhanced myogenic and nerve-mediated detrusor contractility and increased voiding frequency. However, these studies, as with the majority of studies on the role of MaxiK channel in bladder function, fail to distinguish between the role of MaxiK in urothelial and detrusor tissue. Because MaxiK has a well-documented role in regulating smooth muscle contractility, it is widely assumed that the role of MaxiK in bladder physiology is primarily mediated through the detrusor smooth muscle. However, recent studies have identified MaxiK activity in human urothelium, and in patients with overactive bladder (OAB) there is an association in the urothelium between polyamine metabolism and MaxiK activity. It is increasingly recognized that MaxiK plays several roles in addition to regulating smooth muscle tone, including an effect on metabolism. A direct role of the MaxiK channel in bladder metabolism has never been demonstrated; to address this we have used metabolomic analysis to compare and contrast the effects of an inhibitor of MaxiK (iberiotoxin, IBTX) on urothelial and detrusor metabolism.

Study design, materials and methods

All experimental protocols were approved by our Institutional Animal Care and Use Committee. Sixteen F344 rats were separated into two groups that received either IBTX or vehicle (phosphate buffered saline, PBS) for one hour via bladder lumen instillation. To determine the effect of IBTX on bladder physiology urodynamic parameters were determined through continuous flow cystometry in conscious rats for one hour before, and one hour after, installation of IBTX or vehicle. After euthanization, urothelial and detrusors layers were then separated. Metabolomic profiling was performed by Metabolon Corp. ANOVA was used to identify significant changes in the expression of metabolites.

Results

It is well established that IBTX does not cross the plasma membrane and therefore when instilled into the bladder lumen it will only effect MaxiK channels on the luminal membrane of the urothelium. Interestingly, despite the expected restriction of IBTX effects to the urothelium, IBTX treatment caused the levels of significantly more detrusor metabolites (17%) to be changed than urothelial metabolites (6%). In the urothelium the major effects on metabolites can be linked to mitochondrial mediated metabolism which impacts fatty acid catabolism and amino acid metabolism, as well as reducing levels of N-acetylation and glycine conjugation of several amino acids. Histidine metabolism and sulfonation of several substrates, which occurs in the cytosol, were also negatively impacted, although the activity of these pathways are highly dependent on mitochondrially generated co-factors. In the detrusor, similar mitochondrial metabolic pathways were effected by IBTX as in the urothelium, but in addition, there was significant effects on metabolites involved in the energy generating pathways of glycolysis and the TCA cycle. The changes in energy generating metabolic pathways could be a secondary effect of IBTX on bladder physiology (eg. changes in detrusor tone) although the only urodynamic parameter that was significantly affected within the one hour time course of these experiments was intermicturition pressure (IMP).

Interpretation of results

This is the first report documenting global changes in metabolism in response to inhibition of urothelial MaxiK channel activity. It definitively demonstrates a role for MaxiK in regulating bladder metabolism. In the urothelium the effect is primarily targeted to mitochondrial metabolism. It also demonstrates that changes in the metabolism of the urothelium effects detrusor metabolism. Potentially the effect on energy generating pathways in the detrusor would in turn effect smooth muscle contractility, supporting a role of urothelial MaxiK in regulating bladder physiology. Although the study was not designed to identify specific urothelial-detrusor signalling “metabolites” an effect on urothelial mitochondrial function would certainly effect several factors thought to be involved in this process, such as ATP and acetylcholine.

Concluding message

These studies support a role for urothelially expressed MaxiK in regulating both urothelial and detrusor metabolism; urothelial regulation of detrusor metabolism could thereby be a major determinant of overall bladder physiology.

Disclosures

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