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Oger S[1], Behr-Roussel D[1], Gorny D[1], Bernabé J[1], Comperat E[2], Chartier-Kastler E[2], Denys P[3], Giuliano F[3]
1. Pelvipharm, 2. La Pitie Salpetriere Hospital, 3. Raymond Poincare Hospital

EFFECTS OF POTASSIUM CHANNEL MODULATORS ON MYOGENIC SPONTANEOUS PHASIC CONTRACTILE ACTIVITY IN HUMAN DETRUSOR SMOOTH MUSCLE FROM NEUROGENIC PATIENTS

Hypothesis / aims of study
We have previously demonstrated that adenosine triphosphate-sensitive potassium (K_{ATP}) and large conductance calcium-activated potassium (BK_{Ca}) channels play a role in the modulation of myogenic spontaneous phasic contracile activity developed by detrusor strips from patients without overactive bladder (control patients)[1]. In addition, we have recently identified an increase in this contractile activity in human detrusor smooth muscle from patients with neurogenic detrusor overactivity (NDO). The aim of this study was to evaluate the role of K_{ATP} and BK_{Ca} channels on myogenic spontaneous phasic contractions of detrusor strips form patients with NDO.

Study design, materials and methods
Human bladder samples were obtained from 6 different neurogenic patients who underwent partial or total cystectomy. Detrusor strips were mounted isometrically at a resting tension of 500 mg in a 5 ml organ bath filled with Krebs-HEPES buffer maintained at 37°C and bubbled with 95%O_2-5%CO_2. The strips were equilibrated for 90 minutes. Then, the strips were incubated with 10 □M pinacidil (K_{ATP} channel opener) or vehicle during 30 minutes and with 10 □M glibenclamide (K_{ATP} channel blocker) or vehicle for an additional 30 minute period. In another set of experiments, strips were incubated with 30 □M NS1619 (BK_{Ca} channel opener) or vehicle during 30 minutes and with 100 nM iberiotoxin (BK_{Ca} channel blocker) or vehicle for an additional 30 minute period. The effect of these K channel modulators was evaluated on amplitude, area under the curve (AUC), frequency and developed tension of spontaneous phasic contractile activity of detrusor strips from patients with NDO.

Results
Pinacidil markedly inhibited spontaneous phasic contractile activity of detrusor strips. It reduced amplitude to 17.1±7.6% of initial contractile activity versus 88.0±10.7% with vehicle ($p<0.001$); the AUC to 13.3±10.4% versus 112.4±26.1% with vehicle ($p<0.01$), frequency to 20.2±10.6% versus 92.4±5.9% with vehicle ($p<0.001$) and developed tension to 31.1±6.5% versus 97.1±7.9% for vehicle ($p< 0.0001$). This inhibitory effect was reversed by the addition of glibenclamide, more particularly on the amplitude (77.3±12.2%, $p<0.01$), the AUC (90.5±23.0%, $p<0.05$) and frequency (63.0±9.3%, $p<0.05$) of phasic contractile activity.
In contrast, the incubation of NS1619 followed by the incubation of iberiotoxin did not elicit any significant changes in phasic contractile activity.

Interpretation of results
K_{ATP} channels are involved in the regulation of myogenic phasic contractile activity of detrusor strips from patients with NDO. These results are in line with the results we previously obtained in control patients. In contrast, BK_{Ca} channels do not participate in the regulation of these phasic contractions of detrusor from NDO patients while we previously demonstrated that, they played a role in the regulation of phasic contractions in control patients.

Concluding message
K_{ATP} channels play a role in the modulation of myogenic phasic contractions of human detrusor from patients with NDO. In contrast, BK_{Ca} channels would not be involved in the regulation of these contractions in patients with NDO. These results are of great importance for the development of K channels openers for the treatment of NDO.

References
[1]Urology, (2006) 68; 442-448

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HUMAN SUBJECTS: This study did not need ethical approval because Human bladder samples are obtained from donors undergoing partial or total cystectomy for neurologic disorders. They are collected with patient informed consent. This procedure is sufficient to obtain such human bladder samples in France. but followed the Declaration of Helsinki Informed consent was obtained from the patients.