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GRC 6211, A NEW ORAL TRPV1 ANTAGONIST, DECREASES NEUROGENIC DETRUSOR OVERACTIVITY IN A RAT MODEL OF SPINAL CORD TRANSECTION.

Hypothesis / aims of study

Neurogenic detrusor overactivity (NDO) of spinal origin is mediated by a sacral micturition reflex triggered by sensory input conveyed in C-fibre bladder afferents. TRPV1, a calcium channel normally present in those fibers, is overexpressed in the bladder of NDO patients. TRPV1 desensitization by intravesical vanilloids have been used to block TRPV1 overactivity and to decrease its bladder expression in NDO patients. A decrease in the frequency of detrusor contractions for periods of time exceeding 6 months has been achieved in several clinical trials. Recently, TRPV1 competitive antagonists have been synthesized by several groups, offering another possibility to counteract the excess of the receptor. In this study we hypothesised that the blockade of TRPV1 by the novel competitive antagonist, GRC 6211, decreases the frequency of detrusor contractions seen during a cystometry in rats with NDO of spinal origin

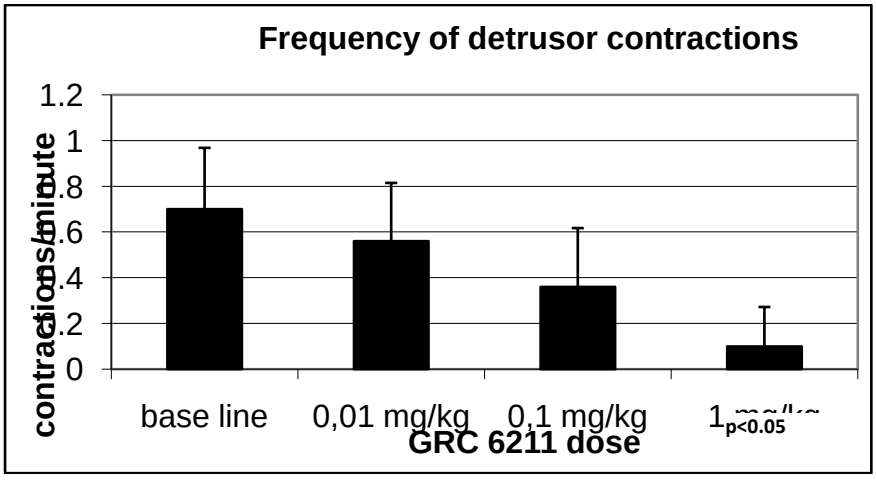
Study design, materials and methods

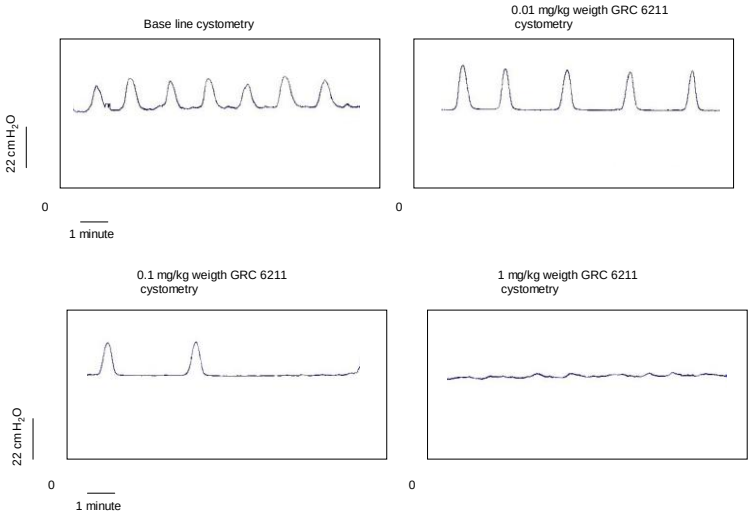
Wistar female rats were submitted to spinal cord transection at T 13 level under general anesthesia, induced by ketamin and metamedion. A small piece of gelfoam was placed between the two ends of the spinal medulla in order to decrease the chance of axonal re-growth. During the spinal shock period, the rats voided with the aid of the Credé manoeuvre. The end of the spinal shock period was noticed by a fall in the voided volume during Credé manoeuvre and by the appearance of reflex voiding and spoting.

After development of reflex voiding, the rats were anaesthetised with urethane subcutaneously. An abdominal mid-line incision was performed, and a 25 G catheter was placed in the first portion of the duodenum to administer 0.5 ml of a solution of 0.5 % of dimethylcellulose containing different concentrations of GRC 6211 (0.01, 0.1 and 1.0 mg/kg weight). Doses were given in a cumulative way with intervals of 1 hour between each dose. A 20 G supra-pubic needle was placed in the urinary bladder dome and cystometric recordings were obtained while infusing saline at 6 ml/h. Frequency, maximal detrusor pressure and duration of the detrusor contractions were recorded. Results are presented as mean ± Standard Deviation. Means were compared using a paired two-tailled students' t test. Statistical significance was considered when $p<0.05$.

Results

Five rats with a mean weight of 320 ± 11.6 gr were used. The recovery time from the spinal shock was 28 days and experiments were carried out 28-32 days after spinalization. At baseline mean frequency, maximal detrusor pressure and duration of detrusor contractions in the baseline cystometries were 0.7 ± 0.27 contractions/minute, 50.68 ± 4.57 cm H2O/ contraction and 91.30 ± 31.64 sec/contraction, respectively. After administration of 0.01 mg/Kg of GRC 6211, the results were 0.56 ± 0.26 contractions/minute (p=0.03), 49.04 ± 5.04 cm H2O/contraction (p=0.38) and 78.75 ± 16.97 sec/contraction (p=0.51), respectively, (p values when compared to baseline data); after administration of 0.1 mg/Kg of GRC 6211, the results were 0.36 ± 0.26 contractions/minute (p=0.04), 47.89 ± 7.12 cm H2O/contraction (p=0.32), and 72.14 ± 5.71 sec/contraction (p=0.24), respectively, (p values when compared to the baseline data); after administration of 1 mg/Kg of GRC 6211, mean frequency was reduced to 0.1 ± 0.17 contractions/minute (p=0.00047) and most of the urine was expelled by overflow. Table below summarizes data. Representative cystometries are also shown.





Interpretation of results

The TRPV1 antagonist GRC 6211 in doses ranging from 0.01-0.1 mg/kg is very effective in reducing bladder reflex activity in models of NDO of spinal origin. At doses of 1mg/kg weight GRC 6211 completely blocked detrusor activity.

Concluding message

GRC 6211 is a potent TRPV1 antagonist with very promising perspectives in the treatment of NDO in patients.

Specify source of funding or grant	**GRC 6211 was kindly offered by Glenmark Pharmaceuticals and Eli-Lilly Pharmaceuticals; Female Wistar rats were obtained from Charles River Laboratories.**
Is this a clinical trial?	**No**
What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**Ethics Committee of the Faculty of Medicine of Porto University**