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ELECTRICAL STIMULATION OF THE L6 AND S1 SPINAL NERVES REDUCES THE BLADDER OVERACTIVITY INDUCED BY CYCLOPHOSPHAMIDE IN ANESTHETIZED RATS

Aims of Study

It has been hypothesized that the positive effects of sacral nerves neuromodulation on bladder overactivity was due to an inhibition of the activity of afferent C-fibers. To ascertain this hypothesis, we investigated to which extent electrical stimulation of either A-δ fibers alone or A-δ+C-fibers present in the L6 and S1 spinal nerves (corresponding to the sacral nerves in humans) could alleviate bladder overactivity induced by cyclophosphamide injection.

Methods

All experiments were carried in isoflurane-anesthetized Wistar rats. Chemical irritation of the bladder responsible for overactivity was induced by intraperitoneal delivery of cyclophosphamide (CYP) delivery (150 mg/kg, 48h before the experiment) and saline injection (VEH) was used as control. To determine threshold intensities for A-δ fibers or A-δ+C-fibers, neurograms were performed by placing a recording electrode on the pelvic nerve and a stimulating electrode on either the L6 or S1 ipsilateral spinal nerve in both CYP and VEH treated rats (4 groups of 3 rats). ES consisted of square wave pulses of 0.2 ms duration. Intensity tested ranged from 25 µA to 4 mA. The impact of continuous ES of both the left L6 and right S1 spinal nerves at intensities specifically recruiting either A-δ fibers or A-δ+C-fibers on transvesical cystometry was assessed in 4 other groups of 6 rats treated with CYP or VEH (named $VEH_{A-\delta}$, $VEH_{A-\delta+C}$, $CYP_{A-\delta}$ and $CYP_{A-\delta+C}$). Transvesical cystometry was performed with a perfusion rate of 50 µl/min warm saline through the bladder dome, and bladder pressure was continuously monitored through the same catheter. Cystometry was performed and recorded for 30 min (control recording) before the beginning of the L6/S1 spinal nerves electrical stimulation (ES).

Results

There was no noticeable difference in the neurograms generated from the S1 and L6 spinal nerves, and between CYP and VEH treated rats. According to the neurograms, intensities of 200 µA and 2 mA were chosen to recruit the maximal amount of A-δ fibers without recruiting any C-fibers, and to recruit both A-δ and C-fibers respectively. Pooled results from the control recording ($VEH_{A-\delta}$+$VEH_{A-\delta+C}$ and $CYP_{A-\delta}$+$CYP_{A-\delta+C}$) showed that CYP treatment resulted in a significant increase in the frequency of voiding contractions (5.3±0.6 to 8.6±1.4 h^{-1}, p=0.04) and non-voiding contractions (1.0±0.4 to 3.9±1.1 h^{-1}, p=0.02). Two way ANOVA with repeated measures showed that continuous ES of the L6/S1 spinal nerves at 200 µA, 20 Hz, marginally reduced the frequency of voiding contractions in control rats ($VEH_{A-\delta}$, 4.0±0.8 h^{-1} during the ES versus 6.3±0.8 h^{-1} before the ES of the L6/S1 spinal nerves, p=0.23) whereas it significantly reduced the frequency of voiding contractions in CYP treated rats ($CYP_{A-\delta}$, 6.2±1.1 h^{-1} during the ES versus 10.9±2.2 h^{-1} before the ES of the L6/S1 spinal nerves, p=0.03). As a matter of consequence, whereas frequency of voiding contractions was significantly greater in the CYP treated group than in the VEH group before the ES of the L6/S1 spinal nerves at 200 µA (p=0.03), there was no significant difference in the frequency of voiding contractions after ES of the L6/S1 spinal nerves between these 2 groups (p=0.3). The frequency of non-voiding contractions in the VEH group, which was consistently low, was not affected by ES of the L6/S1 spinal nerves at 200 µA (0.5±0.3 h^{-1} after the ES versus 0.6±0.4 h^{-1} before the ES of the L6/S1 spinal nerves, p=0.9). In contrast, the frequency of non-voiding contractions was high in the CYP group, and significantly decreased by ES of the L6/S1 spinal nerves at 200 µA (0.2±0.2 h^{-1} after the ES versus 4.2±1.9 h^{-1} before the ES of the L6/S1 spinal nerves, p=0.009). Although there was a drastic difference in the basal frequency of non-voiding contractions in the CYP group (0.6 h^{-1} in the VEH group versus 4.2 h^{-1} in the CYP group), two-way ANOVA with repeated measures could not find a significant effect of the treatment. ES of the L6/S1 spinal nerves at 200 µA also favorably changed other parameters of cystometry in the CYP group (*i.e*. it increased pressure threshold for initiation

of contraction, decreased basal pressure after micturition and maximal pressure during micturition). Those changes were however marginal. ES of the L6/S1 spinal nerves at higher intensities (2 mA) resulted in the quasi suppression of the voiding contractions, and was accompanied by continuous leakage of urine at the urethral meatus.

Conclusions

ES of the L6 and S1 spinal nerves at an intensity allowing recruitment of A-δ fibers, but not C fibers, lowered the number of voiding contractions in CYP treated rats to a level non significantly different from the value observed in control rats. These results support the ability of ES of the L6 and S1 spinal nerves to reduce bladder overactivity in a pathophysiological model of chemical irritation of the bladder mimicking interstitial cystitis.