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## SUPRASPINAL DOPAMINE UPTAKE INHIBITION INFLUENCES THE MICTURITION REFLEX IN URETHANE-ANESTHETIZED RATS

### Hypothesis / aims of study

Dopamine is an important neurotransmitter in the central nervous system, including neural pathways controlling the lower urinary tract [1,2]. However, it is unknown whether dopamine uptake inhibitor has a role in the regulation of neural mechanisms controlling the micturition reflex. The aim of this study is to investigate the effects of GBR12935, a selective dopamine uptake inhibitor that increases endogenous dopamine concentration, on the micturition reflex in urethane anesthetized rats.

### Study design, materials and methods

A total of 48 adult female Sprague-Dawley rats weighing 242-267 g were used in this study. Rats were anesthetized with isoflurane followed by urethane (1.2 g/kg, administered subcutaneously). Thereafter the abdomen was opened by a midline incision and a PE-60 polyethylene catheter was implanted into the bladder through the bladder dome. The catheter was connected via a three-way stopcock to a pressure transducer and a pump for continuous saline infusion. Continuous cystometrograms (CMG, 0.04ml/min) were performed in two groups of urethane-anesthetized rats. 24 rats were administered intrathecal GBR12935 via PE-10 intrathecal catheters, which were implanted at Th11 via an incision in the dura under isoflurane anesthesia 3 days before the experiments. For the experiment, firstly saline was continuously infused for 2 hours to evaluate bladder activity during a control period. Then, GBR12935 (1, 3 and 10 µg, n=6 per dose) was administered intrathecally to evaluate changes in bladder activity. The catheter was directed caudally into the spinal subarachnoid space and positioned at the level of the L6-S1 spinal cord. The volume of fluid in the catheter was kept constant at 6 µl. Single doses of drugs were then administered in a volume of 2 µl, followed by a 6 µl flush with saline. In the other group of 24 rats, GBR12935 (1, 3 and 10 µg, n=6 per dose) was administered intracerebroventricularly. Using a stereotaxic micro-injector, a 30 gauge needle attached to a 10 µl Hamilton syringe was inserted into the lateral ventricle, and single doses of drugs were administered in a volume of 2 µl during 2 minutes. Cystometric parameters were recorded and compared before and after drug administration. All data values are expressed as the mean ± standard deviation. A one-way ANOVA followed by Dunnett's multiple comparison test was used for the statistical analysis between the vehicle and drug-treated groups. Wilcoxon signed rank test was used to compare cystometric variables before and after treatment. For all statistical tests, p<0.05 was considered significant.

### Results

Intracerebroventricular administration of GBR12935 at 1, 3 and 10 µg (n=8 per dose) increased intercontraction intervals in dose dependent fashion to 127.1 ± 10.6%, 137.5 ± 9.7% and 162.1 ± 12.2% of the control value, respectively (p <0.01), but did not affect maximum pressure, basal pressure or post void residual at any doses tested. These inhibitory effects were observed immediately after administration. Intracerebroventricular administration of GBR12935 at 1, 3 and 10 µg also increased threshold pressure in a dose-dependent fashion to 10.48 ± 1.02 cmH<sub>2</sub>O, 14.17 ± 0.95 cmH<sub>2</sub>O and 17.41 ± 1.95 cmH<sub>2</sub>O, respectively (p <0.01). However, when GBR12935 (1, 3 and 10 µg, n=8 per dose) were administered intrathecally, there were no significant changes in intercontraction intervals, threshold pressure, maximum pressure, basal pressure or post void residual at any doses tested.

### Interpretation of results

In urethane-anesthetized rats, suppression of dopamine uptake by intracerebroventricularly administered GBR12935 has an inhibitory effect on the micturition reflex, as shown by the observed increases in intercontraction intervals and threshold pressure. The main function of GBR12935 seems to be mediated by modulation of afferent activity, rather than efferent or smooth muscle activity, because GBR12935 induced increases in intercontraction intervals and threshold pressure without affecting maximum pressure or basal pressure. Moreover, GBR12935 administered intrathecally in the present study failed to affect the micturition reflex. We postulate that the site of action may be the supraspinal site.

### Concluding message

The results of our study indicate that in urethane-anesthetized rats suppression of dopamine uptake by GBR12935 has an inhibitory effect on the micturition reflex at supraspinal site. Thus dopamine uptake inhibitor could be a effective for the treatment of bladder dysfunction such as overactive bladder.

### References

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### Disclosures

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