351

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THERAPEUTIC EFFECTS OF GLYCINE TRANSPORTER TYPE 2 (GLYT-2) INHIBITOR ON NEUROGENIC DETRUSOR OVERACTIVITY IN RATS WITH SPINAL CORD INJURY

Hypothesis / aims of study

Glycine is a major inhibitory neurotransmitter in the central nervous system including the spinal cord. The concentration of glycine at synaptic nerve terminals is regulated by two types of glycine transporters (GlyTs): GlyT-1 and GlyT-2. GlyT-1 is mainly located at glial cells and/or glutamatergic nerve terminals to modulate glycine concentration at NMDA receptor expressing synapses. On the other hand, GlyT-2 is located on glycinergic nerve terminals with high degree overlap with the expression pattern with strychnine sensitive glycine receptor (GlyR). A recent study demonstrated that a GlyT-2 inhibitor suppresses bladder overactivity induced by chemical bladder irritation in rats [1] although it is not known whether GlyT inhibitors have therapeutic effects on bladder overactivity in chronic disease conditions. Therefore, we investigate the effects of glycine transporter (GlyT) inhibitors on neurogenic detrusor overactivity as shown by non-voiding contractions (NVCs) during the storage phase in rats with spinal cord injury (SCI).

Study design, materials and methods

Adult Sprague-Dawley female rats were used. SCI was produced by complete transection of the Th8 to Th9 spinal cord. After 4 weeks, cystometry under an awake condition was performed by continuously infusing saline (0.08 ml/min) into the bladder. Selective GlyT-1 or GlyT-2 inhibitors (sacrosine or ALX-1397, respectively) were administered intrathecally via a PE-10 catheter connected with a 30G needle and placed at the L6 spinal cord level. Cystometric parameters evaluated in this study included the amplitude of NVCs (cmH_2O), the number of NVCs (N) and the frequency of NVCs (N/min). All data are shown as the mean plus or minus standard error of the mean. Statistical significance was evaluated using the paired *t* test. *P* values <0.05 were considered significant.

Results

Intrathecal application of sarcosine (250μg), a selective GlyT-1 inhibitor, did not elicit significant changes in any cystometric parameters. In contrast, intrathecal application of ALX-1393 (30μg), a selective GlyT-2 inhibitor, significantly reduced the amplitude (37% reduction) and frequency (76% reduction) of NVCs ($p<0.05$ and $p<0.01$, respectively) (n=6) (Fig. 1).

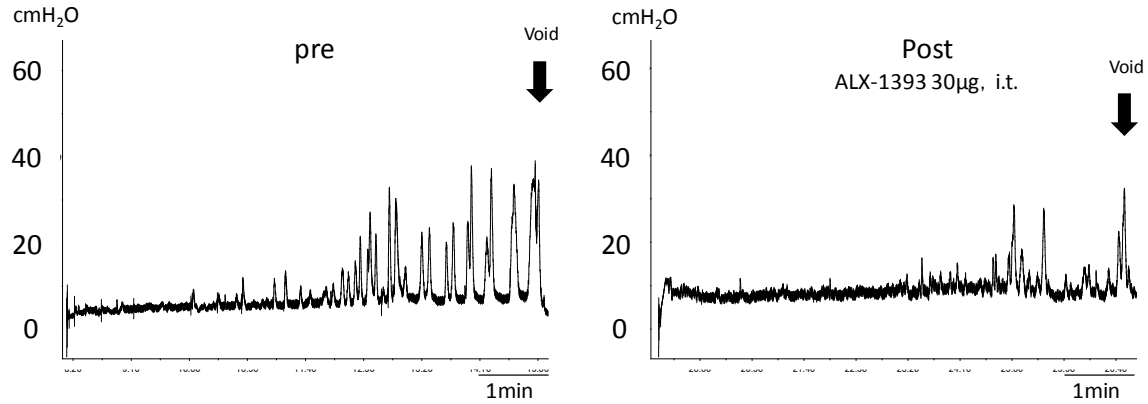

Fig. 1. Representative traces of cystometrograms before (Pre) and after (Post) intrathecal (i.t.) application of ALX-1393 (30μg) GlyT-2 inhibitor in a SCI rat

Interpretation of results

The findings in this study indicate that the GlyT2 inhibitor-mediated enhancement of spinal glycinergic pathways by inhibiting the uptake of glycine at the nerve terminals can suppress neurogenic detrusor overactivity as evidenced by the inhibition of NVCs in chronic SCI rats. Because sensitization bladder afferent pathways and increased signal transduction in the spinal cord have been proposed as important mechanisms inducing neurogenic detrusor overactivity [2], GlyT-2 inhibitors might be effective for reducing neurogenic detrusor overactivity by suppressing sensory inputs from the bladder to the spinal cord.

Concluding message

GlyT-2 inhibitor, not GlyT-1 inhibitor, reduced neurogenic detrusor overactivity in rats with chronic spinal cord injury. GlyT-2 could be a novel therapeutic target for the treatment of overactive bladder induced by neurogenic detrusor overactivity.

References

1. Eur Urology 2012; 62:704-712.
2. Experimental Neurology 2012; 235: 123–132.

Disclosures

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