2

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Institution: Department of Clinical Pharmacology
Title: EFFECTS OF TIAGABINE, A GABA REUPTAKE INHIBITOR, ON RAT BLADDER FUNCTION

Purpose:

Flaccidity commonly occurs after spinal cord injury, but this phenomenon is transient and the gradual return of reflex activity can be anticipated. Several mechanisms of nervous plasticity after spinal cord injury have been suggested, but the actual process is unclear. In the central nervous system, glutamate is considered to be the major excitatory neurotransmitter, and glycine is a postsynaptic inhibitory neurotransmitter (1-3). Since amino acid neurotransmitters play a major role in the maintenance of muscle tone, abnormal neurotransmitter concentrations are associated with hypertonic or hypotonic states. In this study, we examined how amino acid neurotransmitter (glutamate and glycine) levels in the central nervous system were concerned to bladder activity after spinal cord injury and whether changes of these neurotransmitters in the central nervous system were reflected by the serum concentrations.

Materials and Methods:

Spinal cord injury rats : Fifty-three female Sprague-Dawley rats weighting between 250-300 g were used in the study. The rats were divided into the following three groups: 1) intact control group (n = 7), 2) spinal cord injury group (n = 42), and 3) sham-operated group (n = 14). Rats were anesthetized with halothane, and the spinal cord was completely transected between the 9th and 10th thoracic vertebrae under direct vision. Rats from the sham- operated group only underwent laminectomy by the same procedure. In spinal cord injury rats, the central nervous system and blood sample were harvested at 1 and 3 days, and at 1, 2, 4, and 8 weeks (n = 7 each) after surgery. The glutamate and glycine levels in the cerebrum, cerebellum, brain stem, cervicothoracic cord, lumbosacral cord, and serum were measured by a capillary electrophoresis system.
Patients with spinal cord injury : We collected serum samples from patients with chronic spinal cord injury (n = 54) and healthy controls (n = 153). Their serum glutamate and glycine levels were also measured by a capillary electrophoresis system.
Results are reported as the mean±standard deviation. Student's *t*-test for paired data was used for statistical analysis, and $P < 0.05$ was considered to be statistically significant.

Results:

Spinal cord injury rats : Three days after spinal cord injury, pinching of the tail induced body movement as a spinal reflex. Urinary retention was observed acutely, but bladder contractions occurred after 2 weeks. The glutamate and glycine levels in intact control rats and sham-operated rats at 1 day (n = 7) or 8 weeks (n = 7) after surgery were not significantly different in each central nervous system region and the serum. In spinal cord injury rats, however, the glycine level was significantly increased in the lumbosacral cord at 1 day after spinal cord injury (1.53±0.30 mM) compared with that in the sham-operated rats (0.86±0.20 mM)(P = 0.002), although it stabilized at the baseline level after 1 week (0.91±0.20 mM). The glycine level subsequently showed a significant decrease below baseline at 2 weeks (0.49±0.08 mM)(P = 0.004). The serum glycine level was also significantly increased after 1 week (0.23±0.03 mM) compared with that in sham-operated rats

(0.19±0.03 mM) (P = 0.044). It returned to baseline after 2 weeks (0.19±0.02 mM), and was significantly decreased at 4 weeks (0.14±0.02 mg/L)(P = 0.002) and 8 weeks (0.12±0.04 mg/L)(P = 0.006). After spinal cord injury, the glutamate levels in the central nervous system and serum were not different from those in the sham-operated group.

Patients with spinal cord injury: The serum glutamate level was higher in the patients with spinal cord injury (13.76±10.58 mg/L) than in the controls (10.13±7.28 mg/L) (P = 0.023), while the glycine level was lower in the patients (12.83±6.21 mg/L) than controls (17.58±6.19 mg/L) (P < 0.001).

Conclusion

The glycine level in the lumbosacral cord may influence bladder activity after spinal cord injury, and this change may be reflected in the serum level after a few weeks later. Therefore, it may be possible to use the serum glycine level as an index of spinal inhibitory glycinergic neuronal activity.

References

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Aims of study:

Previous reports have demonstrated an inhibitory effect of exogenous GABA on micturition. We wanted to investigate if increased endogenous GABA would affect normal micturition in rats. We therefore evaluated the effects of tiagabine, a GABA reuptake inhibitor, on normal micturition and also studied in vitro effects on rat isolated detrusor tissue.

Methods:

Female Sprague-Dawley rats were used. 1) For in vivo studies, a catheter was placed in the bladder. Catheters were also placed in the femoral vein and intrathecally for administration of drug. Three days after the operation, the rats underwent a cystometric investigation. Micturition was stimulated by infusing saline intravesically. Micturition parameters were recorded and compared before and after drug administration. 2) In vitro, the effects of tiagabine on electrically- as well as carbachol-induced contractions in rat bladder strips were investigated. Furthermore, we studied if tiagabine may interfere with electrically induced release of acetylcholine.

Results:

The i.v. administration of tiagabine [5 mg/kg:n=7 or 20 mg/kg:n=8] decreased micturition pressure [21±11%:$p<0.05$;41±10%:$p<0.01$, respectively] and also decreased micturition volume [31±9%:$p<0.05$;36±9%:$p<0.01$, respectively]. Bladder capacity was slightly decreased [10±9%:n.s.;14±4%:$p<0.05$, respectively]. Tiagabine 20 mg/kg i.v. increased residual volume [$p<0.01$]. Intrathecal tiagabine 100 μg [n=7] reduced micturition pressure [35±10%:$p<0.05$] and increased bladder capacity [35±9%:$p<0.01$] and residual volume [$p<0.01$]. However, micturition volume was not changed. In vitro studies demonstrated, that tiagabine [10-100 μM] concentration-dependently attenuated bladder contractions induced by electrical field stimulation [n=6] [30.6±5.6%:$p<0.001$ at 100 μM]. However, tiagabine 100 μM did not affect contractions induced by carbachol [10^{-8} to 10^{-4} M] [n=6]. Release studies showed that tiagabine 30 and 100 μM inhibited electrically induced release of ^{3}H-choline [6±3%:n.s.;18±4%:$p<0.05$, respectively] [n=6].

Conclusion:

The present results suggest that tiagabine may influence normal rat micturition through spinal and peripheral effects. Supraspinal effects are also likely [1]. The spinal effects may be related to GABAergic influence on the motorneurones modulating the urethral sphincter, thereby reducing urethral resistance. Another spinal effect may be attenuation of afferent transmission. The inhibitory effect of tiagabine on electrically induced contractions in the bladder, may contribute to the effects of the drug on micturition. This effect seems to be exerted presynaptically, attenuating neurogenic release of acetylcholine.

Enhancement of endogenous GABA levels by tiagabine has inhibitory effects on micturition in rats. The principle of GABA reuptake inhibition as a treatment for detrusor overactivity may be further explored.

References:

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