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ROLE OF PROSTAGLANDIN E2 AND EP-1 RECEPTOR ON DETRUSOR OVERACTIVITY IN SPINAL CORD INJURY

Hypothesis / aims of study

Injury to the spinal cord can lead to hyperreflexic bladder because of the emergence of a spinal micturition reflex pathway. Although it has been well known that neurogenic detrusor overactivity is the primary cause of the hyperreflexic bladder in spinal cord injury (SCI), the mechanism has not been clearly elucidated. Recent studies have shown that prostaglandins (PGs) act as local modulators of reflex micturition in the pathophysiological condition. In the present study, we have measured the release of PGE_2 from bladder urothelium, and have performed immunohistochemical staining of S-100 protein, calcitonin gene-related peptide (CGRP), cyclooxygenase-2 (COX-2), EP-1 receptor in the bladder of chronic spinal rats.

Study design, materials and methods

Spinal cord was transected at the level of Th8-9 in adult female Sprague-Dawley rats, and the amount of PGE_2 in the urine of SCI rats was measured after expressing the bladders of SCI rats manually two or three times daily. After cystometric study, the effects of EP-1 receptor antagonist on some rat bladders were investigated, and the bladders of the other rats were removed and the bladder strips were prepared. Using a microdialysis procedure, the dialysate was collected. Then the amount of PGE_2 in the dialysate was measured. And, the effects of resting tension and bladder urotherium on PGE_2 release were investigated. In addition, histological examination by S-100 protein, CGRP, COX-2, and EP-1 receptor immunohistochemical staing in bladder preparations of SCI and control rats were also performed. The amount of PGE_2 in the urine and from bladder strip was measured by radioimmunoassay (RIA).

Results

The excretion was significantly higher in SCI rats (137.7 ± 20.3 ng/day) than in control rats (21.4 ± 3.8 ng/day) ($P < 0.01$). The cystometric parameters were markedly different between spinal and control rats. Micturition volume, residual urine and volume threshold to micturition were significantly higher in SCI rats than in control rats. The amount of PGE_2 release from bladder strips in control rats with urothelium (3.23 ± 0.52 pg/mg tissue, n = 12) was significantly higher than that without urothelium (2.07 ± 0.38 pg/mg tissue, n = 12, $p < 0.05$). In SCI rats, the amount of PGE_2 release was significantly higher in strips with urothelium (9.36 ± 0.94 pg/mg tissue, n = 10) than that without urothelium (3.94 ± 0.71 pg/mg tissue, n = 10, $p < 0.02$). In both strips with or without urothelium, the amount of PGE_2 release was significantly higher in SCI rats than in control rats ($p < 0.05$). PGE_2 release from bladder strips in SCI rats was significantly higher than that in the control rats (Fig. 1). In the bladder strips with urothelium, there were significant ($p < 0.05$) resting tension-dependent increases in PGE_2 release in both control and SCI rats. The % increase in PGE_2 release was significantly higher ($p < 0.05$) in SCI rats than in control rats (Fig. 2). In the bladder strips without urothelium, stretches of the bladder strips of both control and SCI rats caused increases in PGE_2 release. However, there were not significant differences in PGE_2 release between control and SCI rats. When resting tension is 40mN, the % increase of PGE_2 release was significantly higher in SCI rats with urothelium (214.2 ± 14.3 %, n = 10) than in control rats with urothelium (51.8 ± 7.2 %, n = 12; $p = 0.01$), while the % increase in both control and SCI rats without urothelium showed similar values (22.4 ± 4.3 % and 25.0 ± 10.7 %, n = 12 and 10 for control and SCI rats, respectively). In the immuohistological examination, the number of CGRP positive neurons significantly increase, but the number of S-100 protein positive neurons decreased. Immunoreactivity of COX-2 and EP-1 receptors increased in SCI rats as compared to control.

Interpretation of results

The present data suggest that bladder urothelium releases PGE_2, and bladder distension increases the release. Activation of afferent neuron and EP-1 receptor by PGE_2 may be related to detrusor overactivity in spinal cord injury.

Concluding message

It is also possible that agents inhibiting of PGE_2 synthesis or antagonizing PGE_2 receptor may have useful effects for suppression of detrusor overactivity caused by an increase in PGE_2 release from the bladder.

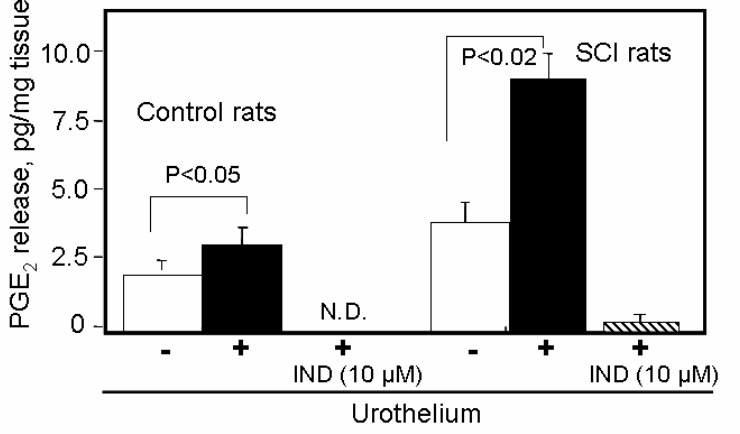

Fig.1 PGE_2 releases from bladder strips in the control and SCI rats. Each bar shows mean±S.E.M.. The effects of urothelium and treatments with indomethacin (IND: 10 μM) on PGE_2 release were evaluated in control (n=12) and SCI (n=10) rats. N.D=not detection; (+) = values of strips with urothelium; (-) = values of strips without urothelium

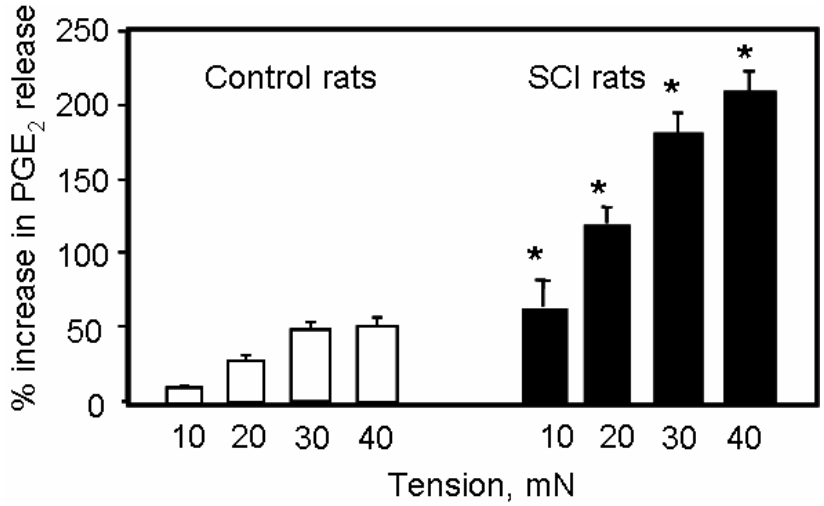

Fig.2 The effects of stretch of bladder strips with urothelium on PGE_2 release in control and SCI rats. Each bar shows mean±S.E.M.. At the various resting tensions, the % increase rates to the amount of PGE_2 release under 0 mN resting tension were calculated in control (n=12) and SCI (n=10) rats. Resting tension was changed from 0 to 40 mN.
* Significantly different from the values of comparable tensions in the control rats ($P < 0.05$)

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