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SUPRASPINAL PROJECTION OF SEROTONERGIC AND ADRENERGIC PATHWAYS MODULATES NOCICEPTIVE TRANSMISSION IN THE LOWER URINARY TRACT OF RATS

Hypothesis / aims of study

Since the etiology of bladder pain syndrome (BPS) / interstitial cystitis (IC), which cause persistent pelvic pain, pressure, or discomfort perceived to be related to the lower urinary tract (LUT), is unknown, BPS/IC management is currently focused on pain relief. Although 5-hydroxytryptamine (5-HT) and norepinephrine have been implicated as mediators of endogenous analgesic mechanisms in the descending pain pathways [1], the effect of these supraspinal projection has been still unknown in the LUT. In the present study, we therefore investigated the effect of descending serotonergic and adrenergic pathways on nociception in the LUT.

Study design, materials and methods

Female Sprague-Dawley rats were used. Regarding spinal cord injury (SCI) rats, the spinal cord was completely cut with scissors and experiment was performed at 8 weeks after SCI. Following intraperitoneal administration of Vehicle or Milnacipran (30mg/kg), which is a serotonin-norepinephrine reuptake inhibitor (SNRI) [2], 0.1% acetic acid was infused into the bladder in normal (n=4, each) and SCI (n=4, each) rats for 2 hours on consciousness and rats were dissected under deep anesthesia to remove the spinal cord. Coronal sections were made at the L6 level, and c-fos, 5-HT and adrenergic dopamine-beta-hydroxylase (DβH) were stained using immunohistochemistry at the L6 spinal cord.

Results

There were many 5-HT and DβH-positive fibers at the L6 spinal cord in normal rats, while 5-HT or DβH-positive fibers were not observed in SCI rats (Fig. 1). The total number of c-fos-positive cells was significantly increased in SCI rats compared to normal rats (209.4+/-7.1 in Normal, 336.4+/-28.9 in SCI, $p<0.05$) (Fig. 2). Regarding the effect of Milnacipran administration, the number of c-fos-positive cells was significantly decreased at all regions of the L6 spinal cord in normal rats with Milnacipran administration, while this reduction was not observed in SCI rats (Fig. 3, *: $p<0.05$).

Interpretation of results

The result of an increase of c-fos positive cells in SCI rats indicates that the interruption of supraspinal modulation enhances nocieptive transmission in the LUT. Meanwhile, administration of a SNRI attenuates nocieptive transmission in the LUT, which means that 5-HT and norepinephrine work as mediators of endogenous analgesic mechanisms in the descending modulatory pathways. However, this analgesic effect of a SNRI was disrupted after SCI, possibly by the interruption of serotonergic and adrenergic pathways into the lumbosacral spinal cord.

Concluding message

Supraspinal projections of descending serotonergic and adrenergic pathways into the lumbosacral spinal cord modulate nocieptive transmission in the LUT. Administration of a SNRI attenuates nocieptive transmission in the LUT, which could result from enhancement of descending serotonergic and adrenergic pathways.

Fig. 1: 5-HT- and DβH-positive fibers at the L6 spinal cord

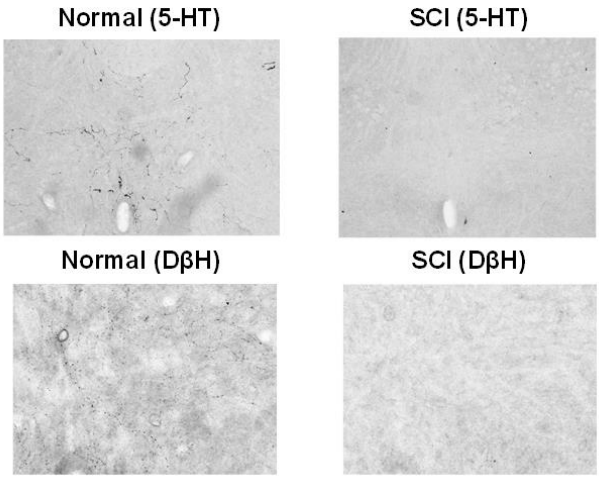


Fig. 2: c-fos positive cells at the L6 spinal cord in Normal and SCI rats

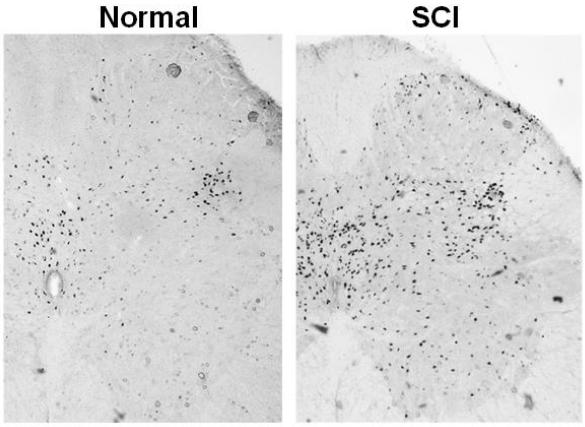
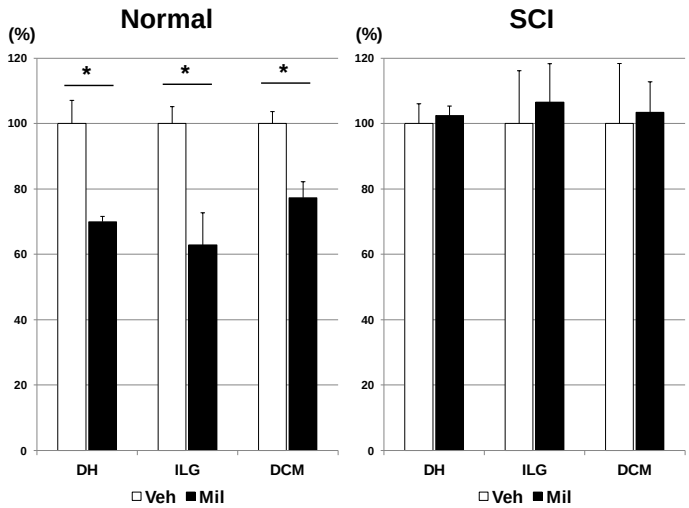


Fig. 3: Difference of Milnacipran's effects on c-fos expression between Normal and SCI rats at the L6 spinal cord



Veh: vehicle, Mil: Milnacipran, DH: dorsal horn, ILG: intermediolateral gray, DCM: dorsal commissure

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Disclosures

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