Effects of repeated administration of amitriptyline on modulation of noradrenergic descending inhibitory system in a rat model of neuropathic pain

Hiroki Tadanao.¹, Suto Takashi.¹, Saito Shigeru.¹, Obata Hideaki.²

1) Gunma University, Dept of Anesthesiology, Maebashi, Japan

2) Fukushima Medical University Hospital, Center of Pain Management, Fukushima, Japan

Background and Goal of Study

The tricyclic antidepressant amitriptyline, the serotonin and noradrenaline reuptake inhibitor duloxetine, and gabapentinoids are first-line drug for treatment of neuropathic pain. The analgesic effect of these drugs relates to brainstem-spinal descending noradrenergic (NA) systems. In the present study, we investigated the difference in NA dependency of each drug. We also examined whether amitriptyline modifies the descending NA systems.

Materials and methods

Seven days after L5 spinal nerve ligation (SNL), rats received N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP-4, 50 mg/kg) to degenerate NA fibers. The rats then received five daily intraperitoneal injections of amitriptyline (10 mg/kg), duloxetine (10 mg/kg), pregabalin (10 mg/kg), or gabapentin (50 mg/kg) from 21 days after SNL surgery. Paw withdrawal thresholds were determined to assess the analgesic effect of the drugs by paw pressure test. To determine whether five daily injections of amitriptyline activated NA neurons in the locus coeruleus (LC) and spinal cord, we performed immunohistochemistry using antibodies for c-Fos and dopamine beta-hydroxylase (DβH).

Fig. 2. Effect of idazoxan on the antihyperalgesic effect of AMI with DSP-4

Fig. 3. Effects of AMI/DSP-4 on neuronal activity and DβH-IR fibers in LC

Results and Discussion

Fig.1. The antihyperalgesic effects of drugs in SNL rats with DSP-4

AMI: amitriptyline, DLX: duloxetine, PGB: pregabalin, GBP: gabapentin.

N=6

*P < 0.01 vs the control (saline + vehicle) group

#P < 0.01 vs the saline + drug group

Fig. 4. Effects of AMI/DSP-4 on DβH-IR fibers in spinal dorsal horn

Conclusions

- Five daily injections of amitriptyline produced antihyperalgesic effects against neuropathic pain despite the condition that NA descending inhibitory systems are suppressed.
- Amitriptyline could still produce analgesia under pathological dysfunction of the descending NA system.
- In patients with neuropathic pain, amitriptyline may enhance the analgesic effects of drugs that require descending NA inhibitory systems, such as duloxetine and gabapentinoids.