学 位 論 文 の 要 旨

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学 位 論 文 名　**Profound Reduction of Somatic and Visceral Pain in Mice by Intrathecal Administration of the Anti-migraine Drug, Sumatriptan**

発 表 雑 誌 名　**Pain**

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論 文 内 容 の 要 旨

Introduction

Sumatriptan and other triptan drugs target the serotonin receptor subtypes - 5-hydroxytryptamine receptor $(5\text{-HT})_{1B}$, 5-HT_{1D}, and 5-HT_{1F} - and are widely prescribed for migraine treatment. Triptans are postulated to have antimigraine action at multiple targets within the brain and at the central and peripheral terminals of trigeminal pain-sensory fibers. However, as triptan receptors are also located on "pain-sensory" afferents throughout the body, it is surprising that triptans only reduce migraine pain in humans. Here we tested the hypothesis that sumatriptan can indeed reduce non-cranial, somatic and visceral pain in behavioral models in mice.

Material and Methods

The study population included wild-type CD1 male mice (weight, 20–30 g). All the experiments were approved by our Institutional Animal Care and Use Committee and complied

with the recommendations of the International Association for the Study of Pain. Sumatriptan was administered systemically (subcutaneous injection, 300 or 600 μg/kg) or intrathecally (0.006, 0.02, 0.06, or 0.6 μg) because it has to cross the blood–brain barrier to reach the somatic afferent terminals in the spinal cord. The mice were habituated to the test room before initiating the tests. Mechanical thresholds were determined using "up and down" methods, with calibrated monofilaments. The thermal threshold was measured in terms of the withdrawal latency to focused radiant light by using a paw thermal stimulator. These nociceptive tests were performed immediately before as well as at 30, 60, 90, 120, and 240 min after drug administration. A persistent inflammation model (3% carrageenan lambda) and neuropathic pain model (spared nerve injury) were prepared to determine the antihyperalgesic effect of sumatriptan for thermal and mechanical stimulation. In the spared nerve injury model, we transected two of the three branches of the sciatic nerve, sparing the tibial branch. It is known that mice demonstrate a pronounced mechanical hypersensitivity of the partially denervated hindpaw. The licking behavior of the mice after hindpaw injection of 2% formalin was assessed for 1 hour to determine whether sumatriptan can inhibit spinal plasticity. Formalin induces biphasic pain behavioral responses, i.e., in phase 1 (0 – 10 min) and phase 2 (10 – 60 min). Phase 1 is thought to result from direct nociceptor activation. Phase 2 is a delayed inflammatory state, which depends not only upon prolonged activity of nociceptors, but also upon a phase 1-induced central sensitization of pain transmission circuits within the spinal cord. The acetic acid test was performed to study the effect of sumatriptan on inflammatory visceral pain. Furthermore, mice were tested on a rotarod to screen for sedative and other adverse sensorimotor effects.

Results and Discussion

Acute nociceptive thresholds for thermal and mechanical stimulation were not altered by sumatriptan pretreatment, regardless of the administration route. However, we observed profound anti thermal hyperalgesic and anti-allodynic action on intrathecal - but not systemic -

sumatriptan administration in the carrageenan pain model. In addition, intrathecally administered sumatriptan caused a dose-dependent decrease in pain behavior in phase 2, rather than in phase 1 in formalin test. In contrast, sumatriptan was ineffective for mechanical allodynia in the spared nerve injury model, regardless of the dose and route of delivery used. A significant antinociceptive effect was noted after intrathecally administered sumatriptan reduced the number of acetic acid-induced abdominal stretches in the visceral pain model. Intrathecally administered sumatriptan did not significantly interfere with motor function on a rotarod at any dosage.

The greater efficacy of intrathecally administered sumatriptan over systemically administered sumatriptan in reversing inflammation-induced pain emphasizes that the blood brain barrier may be a critical factor in triptan action against inflammation-associated somatic and visceral pain. The fact that sumatriptan only influenced pain behavior generated by nociceptors sensitized by prior tissue injury strongly suggests that the central terminal of the primary afferent nociceptor is a major target of sumatriptan for relief from inflammatory pain. One possibility for the lack of effect of sumatriptan in the neuropathic pain model is that the mechanical allodynia caused by nerve injury is mediated by myelinated afferents, which do not express the 5-HT_{1D} receptor. A contribution of increased spontaneous activity from injured unmyelinated afferents would also not be regulated by sumatriptan because nerve injury dramatically downregulates the 5-HT_{1D} receptor in the central terminals of these afferents. Sumatriptan works as a 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} agonist. Further studies are required to clarify the role of each receptor in pain modulation.

Conclusion

The pronounced activity of intrathecal sumatriptan against inflammatory pain in mice indicates that the spectrum of therapeutic indications for triptans may extend beyond headaches.