**Effects of 5-HT<sub>7</sub> receptor ligands in rats suffering from chronic neuropathic pain**

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### Introduction

- **Neuropathic pain**, characterized by long-lasting exaggerated pain behaviors such as hyperalgesia/allodynia (generally resistant to classical analgesic drugs [10]), presents a high degree of comorbidity with depression [1], notably in complex disorders such as fibromyalgia.

- The 5-HT<sub>7</sub>-type serotonin receptors (5-HT<sub>7</sub>-R) is involved in pain control at peripheral, spinal and supraspinal levels [5], but its role in the modulation of nociceptive transmission is still unclear. In fact, conflicting data have been reported to date using selective agonists and antagonists [3, 4, 7, 9].

- 5-HT<sub>7</sub>-R blockade is also known to exert antidepressant- and anxiolytic-like effects in validated animal models [6].

- Thus 5-HT<sub>7</sub>-R might be potential targets for concomitant alleviation of pain and depression. In the present studies, attention was particularly devoted to the possible implication of 5-HT<sub>7</sub>-R in the modulation of chronic pain in neuropathic rats.

### Materials and Methods

- 5-HT<sub>7</sub>-R blockade by the antagonist SB-269970 increased pressure threshold to trigger vocalization but not paw withdrawal (Fig. 1A).

- 5-HT<sub>7</sub>-R receptor activation by the agonists E-55888 and AS-19 markedly increased thresholds to evoke noxious responses to hindpaw pressure. SB-269970 prevented the effects of both agonists (Fig. 1B).

- Blockade of GABA<sub>5</sub>-R, GABA<sub>B</sub>-R and opioid-R by systemic administration of bicuculline, phaclofen and naloxone, respectively, did not affect E-55888-induced anti-alloodynia/anti-hyperalgesia (Fig. 2 A, B, C).

- In contrast, GABA<sub>5</sub>-R receptor blockade at spinal level (by intrathecal administration of bicuculline) completely prevented the effects of E-55888 (Fig. 3).

### Results

**Effects of 5-HT<sub>7</sub>-R blockade**

- 5-HT<sub>7</sub>-R receptor blockade by the antagonist SB-269970 increased pressure threshold to trigger vocalization but not paw withdrawal (Fig. 1A).

- 5-HT<sub>7</sub>-R receptor activation by the agonists E-55888 and AS-19 markedly increased thresholds to evoke noxious responses to hindpaw pressure. SB-269970 prevented the effects of both agonists (Fig. 1B).

**Effects of 5-HT<sub>7</sub>-R activation**

- Blockade of GABA<sub>5</sub>-R, GABA<sub>B</sub>-R and opioid-R by systemic administration of bicuculline, phaclofen and naloxone, respectively, did not affect E-55888-induced anti-alloodynia/anti-hyperalgesia (Fig. 2 A, B, C).

- In contrast, GABA<sub>5</sub>-R receptor blockade at spinal level (by intrathecal administration of bicuculline) completely prevented the effects of E-55888 (Fig. 3).

### Conclusion

- In rats suffering from neuropathic pain, the anti-hyperalgesic effect of 5-HT<sub>7</sub>-R blockade by SB-269970 suggests that tonic activation of excitatory 5-HT<sub>7</sub>-R (on primary afferent fibers ?) by endogenous 5-HT contributes (but to a limited extent) to hyperalgesia.

- The marked anti-hyperalgesic effects of 5-HT<sub>7</sub>-R stimulation by E-55888 suggests that non-tonically activated - 5-HT<sub>7</sub>-R are those expressed by spinal GABAergic interneurons [5]. At this level, 5-HT<sub>7</sub>-R-mediated excitation probably promotes GABA release and subsequent GABA<sub>B</sub>-R activation.

- These data suggest that spinal 5-HT<sub>7</sub>-R are promising targets for alleviating neuropathic pain.

### References


