The Role of Orexins in Hypothalamic-mediated Analgesia in Neuropathic Pain

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Introduction

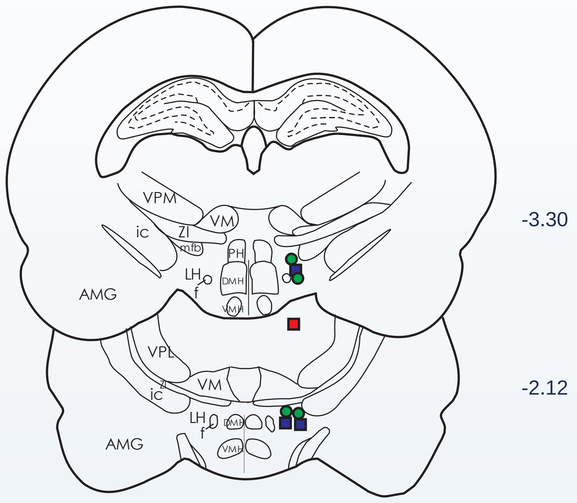
Chronic neuropathic pain is a major health problem in the US and current first-line therapies such as the selective noradrenergic reuptake inhibitors are only moderately effective. Deep brain stimulation of the lateral hypothalamus (LH) is being done clinically for rare, intractable headaches with minimal side effects, but has not been used for other types of untreatable pain. Stimulating the LH with the cholinergic agonist, carbachol, has effectively produced analgesia in an acute, nociceptive pain model in rats. However, its role in neuropathic pain is not well understood. One way the LH may produce analgesia is through release of the neurotransmitter orexins. Anatomical studies have demonstrated that orexin-containing neurons in the LH project to the spinal cord dorsal horn,[2] and orexins injected in the dorsal horn produce analgesia,[3,4] indicating a potential analgesic pathway. The purpose of this study was to investigate the role of orexins in LH-mediated analgesia in a model of neuropathic pain, the chronic constriction injury (CCI). We hypothesized that analgesia produced by stimulating the LH with cholinergic agonist carbachol would be blocked by intrathecal (IT) administration of the orexin-1 receptor antagonist SB334867.

Methods

- A pretest-posttest experimental design with control groups was used.
- Female Sprague-Dawley rats (250-325 g; n = 6-11 per group) received left sciatic nerve ligation (CCI).
- Following a two-week recovery, lightly anesthetized rats (pentobarbital; 35 mg/kg) were placed in a stereotaxic frame and received either carbachol (500 nmol), atropine sulfate (5 µg), or normal saline for control into the left LH.
- Separate groups of CCI rats received carbachol in the LH, followed by IT SB334867 (60 nmol) in DMSO, or DMSO or normal saline for control.
- Another group of rats received only intrathecal SB334867 (60 nmol) in DMSO, or DMSO or normal saline for control.
- A thermal stimulus was applied to the left hind paw using an analgesimeter.
- The time taken to withdraw the paw constituted the paw withdrawal latency (PWL).
- The longer the PWL, the greater the analgesic effect.
- Two-way repeated measures ANOVA with Holm-Sidak post-hoc comparisons was used for statistical analysis.

Results

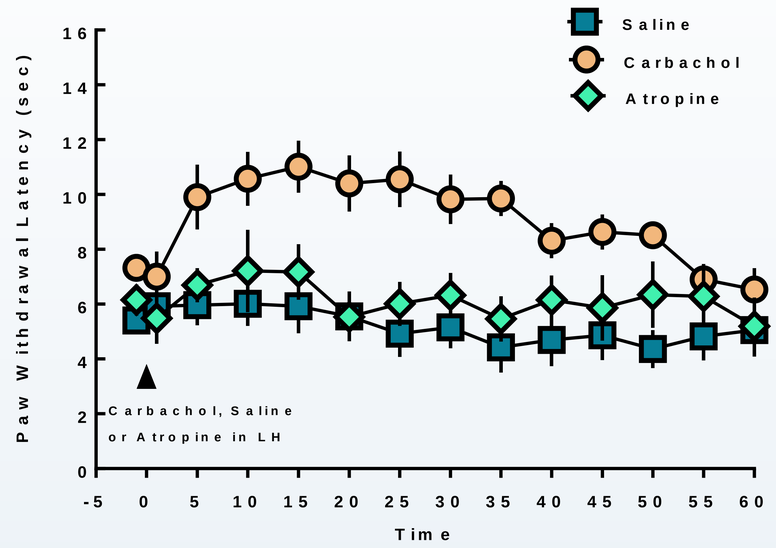
Microinjector Placement Sites



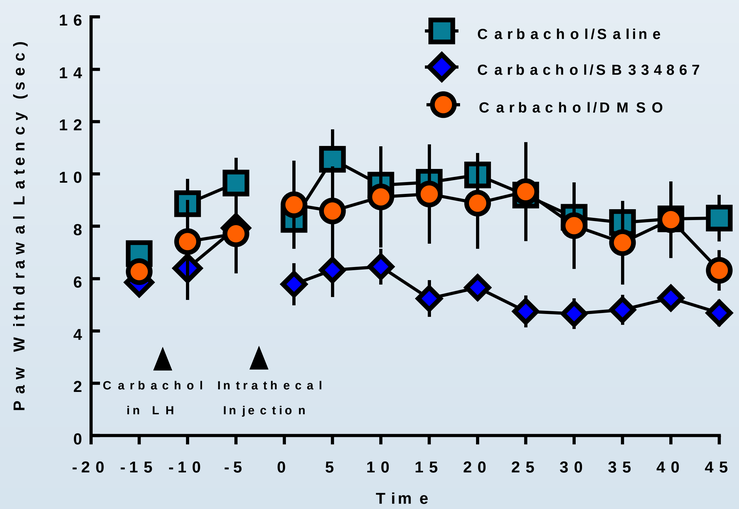
AMG, amygdala; DHM, dorsomedial nucleus. hypothalamus; f, fornix; ic, internal capsule; mfb, medial forebrain bundle; VM, ventromedial nucleus, thalamus; VMH, ventromedial nucleus, hypothalamus; VPL, ventral posterolateral nucleus, thalamus, ZI, zona incerta.

Paw withdrawal latencies at 15 min post carbachol:

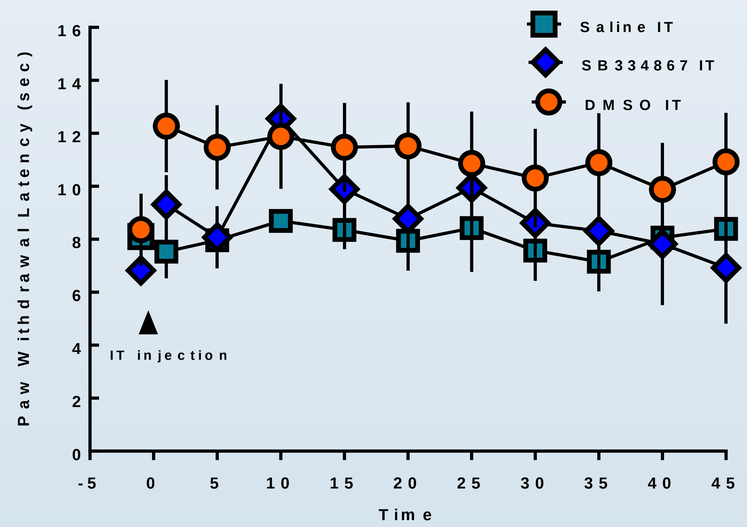
- 7-10 sec
- 11-15 sec
- 7-10 sec (outside of LH) omitted



- Rats given carbachol microinjection in the LH had significantly longer PWL (9.10 + 0.24 sec) than saline controls (5.20 + 0.23 sec, $p < 0.05$), an analgesic effect.
- Pretreatment of the LH with the cholinergic antagonist atropine sulfate blocked carbachol-induced analgesia (5.50 + 0.26, $p > 0.05$ compared to saline), indicating carbachol-induced analgesia was cholinergic receptor-mediated rather than from placing a microinjector in the LH.



- Following carbachol microinjection in the LH, rats given IT SB334867 withdrew their paws significantly faster than rats given saline or vehicle DMSO (5.37 + 0.33 sec, 8.99 + 0.28, 8.39 + 0.38 sec respectively, $p < 0.05$) indicating LH-induced analgesia was blocked by the orexins receptor antagonist compared to controls.



- IT DMSO alone produced a small but significant analgesic effect when compared to IT saline and SB334867 ($p < 0.05$). DMSO has analgesic properties itself, but note that when used as a vehicle for SB334867, analgesia from LH stimulation was blocked.

Summary

- Stimulating the LH with carbachol produced analgesia compared to controls in the female neuropathic pain model.
- IT application of the orexin1 receptor antagonist SB334867 blocked LH-mediated analgesia, indicating the orexins pathway contributes to LH-induced analgesia.

Conclusion

This is the first study to show that LH-induced analgesia, which is effective in decreasing chronic, neuropathic pain, may be mediated in part by the neurotransmitter orexins.

Further understanding of this pathway may lead to improvement in the clinical treatment of chronic pain.

Acknowledgement

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