Chronic codeine - More pain than gain?

The first evidence of codeine induced hyperalgesia

Background

• Chronic opioid therapy is associated with increased sensitivity to pain or noxious stimuli, known as opioid-induced hyperalgesia.1

• Codeine is a weak opioid analgesic easily accessed & used widely across Australia to manage pain.2

• In humans around 10% of the oral codeine dose is metabolised via CYP2D6 to morphine, which has been implicated in opioid induced hyperalgesia in pre-clinical & clinical studies.1

• Recent pre-clinical evidence indicates chronic morphine administration may exacerbate pain in the long-term by non-specifically activating the innate immune system pattern-recognition receptor, toll-like receptor-4, on glial cells, as illustrated in Figure 1.3

• Binding simulations suggest codeine also binds to toll-like receptor-4 causing the release of proinflammatory cytokines such as IL-1β & TNFα, which has been implicated in opioid induced hyperalgesia.4

Aims

• Experiment 1: To determine if chronic codeine administration is capable of inducing opioid induced hyperalgesia to the same degree as morphine.

• Experiment 2: To determine if prior partial nerve injury primes for opioid induced hyperalgesia.

Methods

• Hyperalgesia & allodynia were assessed in male BALB/c mice using the hot plate & the von Frey tests respectively (Figure 2).5

• In Experiment 2 a modified chronic constriction injury surgery6 was used to assess the impact of partial nerve injury, & subsequent glial activation, on opioid induced hyperalgesia.

• During this surgery a single chronic gut suture was loosely tied around the left sciatic nerve & 3 pieces of chronic gut were placed subcutaneously, under isoflurane anaesthesia.

• Repeated measures two-way ANOVA tests corrected for multiple comparisons were used to analyse results.

Results

• Codeine & morphine reduced hot plate latency compared to saline at day 5 in Experiment 1 & days 3 & 5 in Experiment 2, indicating opioid induced hyperalgesia exacerbated by prior partial nerve injury (Figure 3).7

• Despite the low comparative analgesic efficacy of codeine vs morphine, there were no significant differences between hyperalgesia induced by equimolar doses of these two drugs.

• Only morphine induced allodynia, as demonstrated by a reduction in the number of paw non-withdrawals during the von Frey test in Experiment 1. Following partial nerve injury no opioid induced allodynia could be distinguished.

Conclusions

Codeine can induce hyperalgesia, equivalent to that induced my morphine at an equimolar dose, suggesting codeine does not solely rely upon conversion to morphine to increase sensitivity to noxious stimuli. No evidence of codeine induced allodynia was found.

Prior partial nerve injury induces both hyperalgesia & allodynia at baseline. This priming leads to earlier development of hyperalgesia following codeine & morphine administration.