COMMENTARY

The Mechanisms of Central Opioid and Serotonergic Receptors by using Tramadol and Tramadol with Caffeine Synergism

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DESCRIPTION

Caffeine has been able to enhance the analgesic impact of several analgesic combinations. Only combos with morphine and tramadol have been documented in relation to opioids, but several combinations with Non-Steroidal Anti Inflammatory Medications (NSAIDs) have been conducted. It is unclear that how these combos of anti-nociceptive synergism work. The present study was to ascertain how the opioidergic and serotonergic systems in the spinal and supra spinal regions of the brain contributed to the synergic impact of tramadol and caffeine in the rat formalin test. At the supra spinal level, the 5-HT_2 receptor antagonist ketanserin and the opioid antagonist naloxone both completely reversed the effects of the medication combination, but the 5-HT_3 receptor antagonist ondansetron had no impact.

All tramadol-caffeine combo effects were significantly diminished when the antagonists were given intrathecally. With regard to tramadol alone, the opioid system was significantly involved at the supra spinal level, whereas the serotonergic system was significantly involved at the spinal level *via* the two receptors tested. The opioid and serotonergic systems were synergistically engaged by the tramadol and caffeine combination to induce the anti-nociception both at the spinal level and at the supra spinal level.

Since a long time ago, analgesic combinations have been employed to achieve higher efficacy, allowing for the use of lower doses while yet increasing the therapeutic impact (synergism) and reducing side effects. Because it has been demonstrated that caffeine increases the effectiveness of many analgesics when provided together, it is regarded as an analgesic adjuvant. The mechanisms underlying this potentiation are less well understood, despite the fact that several studies indicate that co-administration of coffee with various NSAIDs and opioids might enhance the anti-nociceptive impact.

Caffeine is a methylated xanthine, at doses common to human ingestion, acts by antagonistically interacting with the adenosine, and receptors. High dosages of caffeine trigger mechanisms such the suppression of PDE or Ca^{2+} release. Adenosine receptors have been suggested as being involved in caffeine's claimed adjuvant and intrinsic analgesic activities in various experimental studies. Serotonergic and noradrenergic systems have been linked to anti-nociception in the formalin test, according to a different study. When caffeine and tramadol were provided together, it was able to have a synergistic impact. The combination is effective in treating human pain, and additional research must be done. It is generally known that serotonergic and opioidergic pathways both contribute to pain regulation. It has been noted that 5-HT_2 and 5-HT_3 receptors play a significant part in pain regulation at the spinal level during the formalin test.

Spinal serotonergic pathways are activated by morphine when it interacts with supra spinal receptors. The anti-nociceptive effect of morphine is found to be mediated by spinal 5-HT_7 receptors, whereas tactile allodynia and heat hyperalgesia are mediated by spinal 5-HT_3 receptors. Tramadol's anti-hyperalgesic and anti-nociceptive actions are partially mediated by spinal 5-HT_7 receptors. The medicines utilised in this investigation have mechanisms that function at the spinal or supra spinal level in the descending control pathway. These mechanisms may be a part of the synergism that is seen when they are used in conjunction. Therefore, the goal of this work was to show how the serotonergic and opioidergic systems, at both the supra spinal and spinal levels, are involved in the synergistic action of tramadol plus caffeine in the rat formalin test.

CONCLUSION

Opioid and 5-HT_2 receptors play a role in the anti-nociceptive synergism of tramadol plus caffeine at the supra spinal level, whereas opioid, 5-HT_2 and 5-HT_3 receptors play a role at the spinal level. Tramadol's anti-nociceptive effect is brought on by 5-HT_2 and 5-HT_3 receptors in the spinal level and opioid receptors in the supra spinal level.

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