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Nitric Oxide and Potassium Channels but Not Opioid and Cannabinoid Receptors Mediate Tramadol-Induced Peripheral Antinociception in Rat Model of Paw Pressure Withdrawal

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Abstract : Tramadol, an analgesic classified as an 'atypical opioid,' exhibits both opioid and non-opioid mechanisms of action. This study aimed to explore these mechanisms, specifically the opioid-, cannabinoid-, nitric oxide-, and potassium channel-based mechanisms, which contribute to the peripheral antinociception effect of tramadol, in an experimental rat model. The nociceptive threshold was determined using paw pressure withdrawal. To examine the mechanisms of action, several substances were administered intraplantarly: naloxone, a non-selective opioid antagonist (50 µg/paw); AM251 (80 µg/paw) and AM630 (100 µg/paw) as the selective antagonists for type 1 and type 2 cannabinoid receptors, respectively; nitric oxide synthase inhibitors L-NOArg, L-NIO, L-NPA, and L-NIL (24 µg/paw); and the enzyme inhibitors of guanylatocyclase and phosphodiesterase of cGMP, ODQ and zaprinast. Additionally, potassium channel blockers glibenclamide, tetraethylammonium, dequalinium, and paxillin were used. The results showed that opioid and cannabinoid receptor antagonists did not reverse tramadol's effects. L-NOarg, L-NIO, and L-NPA partially reversed antinociception, while ODQ completely reversed, and zaprinast enhanced tramadol's antinociception effect. Notably, glibenclamide blocked tramadol's antinociception in a dose-dependent manner. These findings suggest that tramadol's peripheral antinociception effect is likely mediated by the nitrergic pathway and sensitive ATP potassium channels, rather than the opioid and cannabinoid pathways.

Keywords : tramadol, nitric oxide, potassium channels, peripheral analgesia, opioid
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