

Neuronal inhibitory effects of methadone are predominately opioid receptor mediated in the rat spinal cord in vivo.

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Abstract:

This study aims to assess whether the antinociceptive actions of methadone are mediated solely through opioid mechanisms, or whether its reported affinity for NMDA receptors has physiological relevance in vivo. Methadone is a μ -opioid receptor agonist reported to relieve pain unresponsive to other opioids. It is a racemic mixture comprising d- and l-optical isomers; the d-isomer has a lower affinity for opioid receptors, and both also exhibit NMDA receptor binding, likely to indicate antagonist activity. d-Methadone is antinociceptive in behavioural studies via non-opioid mechanisms, which could include functional NMDA receptor-blocking activity. Here we investigate the ability of d- and dl-methadone to inhibit noxious and innocuous electrically-evoked responses of dorsal horn neurones in the anaesthetized rat.

Racemic methadone (5, 25, 50, 250 μ g) applied spinally, dose-relatedly inhibited the C-fibre evoked response, input and wind-up of the neurones, with a profile resembling that of morphine. d-Methadone (5, 25, 50, 250, 500 μ g) was also inhibitory, although less potent by a factor of between 13 and 48 depending on the neuronal measure; its profile of inhibition resembled that of the racemic mixture rather than an NMDA receptor antagonist. Both compounds had minimal effects on A β -fibre-evoked activity. The inhibitory effects of both d- and dl-methadone on noxious-evoked activity were naloxone reversible. The naloxone reversibility of d-methadone inhibitions is best interpreted as indicative of a purely opioid mechanism of action. However, the ability of naloxone to reverse the effects of d-methadone may also reflect a degree of synergy between weak NMDA antagonist and opioid agonist activity.

Comments:

Strengths/uniqueness: This study involved the standardized, laboratory-based experimental model designed to compare the in vivo actions of d- and dl-methadone.

Weakness: No specific weaknesses identified.

Relevance to Palliative Care: Methadone has acquired special status relative to other opioids in the treatment of chronic malignant pain, especially in the case of neuropathic pain and also in situations where opioid tolerance appears to have developed. This status has largely evolved as a result of case reports or case series. There is a great need, therefore, for controlled and comparative studies to assess the putative superior status of methadone. This animal-base study sends a cautionary message to those of us in chronic pain management who tend to ascribe much of methadone's success to NMDA receptor antagonist activity.