Title : CHRONIC NALTREXONE ENHANCEMENT OF MORPHINE ACTION

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Introduction. The discovery of the central nervous system's endogenous morphine-like compounds, the endorphins, has opened up new vistas in our understanding of both pain and analgesia. The endorphins are peptides, with putative neurotransmitter roles, which along with their receptors, are highly localized to brain areas which subserve functions of pain sensation and emotion. The endorphins produce morphine-like actions on both pain and emotional systems, and these actions are blocked by the specific narcotic antagonists naloxone and naltrexone. Although the endorphin systems are well characterized, few practical attempts have been made to manipulate this system so as to produce analgesia. We were particularly intrigued by the potential analogy between endorphin and other neurotransmitter systems, where the chronic administration of the antagonist results in a paradoxical potentiation of the agonist's actions. To test whether this phenomenon is obtained in the endorphin system, we have now tested the effects of chronic naltrexone on morphine-induced analgesia.

Methods. Animals used in studies were either white male Swiss mice (25-30g) or white male Sprague-Dawley rats (200-250g). Analgesia was measured by either the hot plate test or the tail-flick test. In the hot plate test, a plate is maintained at 55°C, and after an individual animal is placed on the plate, the time to jump is recorded. The maximum testing period is 45 sec, and animals are primed with a previous trial on the hot plate prior to pharmacological testing. In the tail-flick test, animals are restrained with their tails placed in a groove on which is focused a high intensity heat lamp. If the animal moves its tail within the 14 sec testing period, a photoelectrical cell immediately shuts off the timer. All drugs are dissolved in saline and injected intraperitoneally as their respective salts.

Results. We found with daily saline treatment of mice, and every-other-day analgesia testing, that there was a gradual increase in their latency to demonstrate pain, going from a baseline of 4 sec to an average of 17 sec prior to withdrawal from treatment. In contrast, animals receiving chronic naltrexone (20 mg/kg) failed to show any increase in latency to demonstrate pain, and actually showed a trend towards hyperalgesia. On the tenth day after withdrawal, animals were challenged with morphine sulfate (5 mg/kg), which produces an analgesic response corresponding to 13 sec in naive animals. In animals pretreated with saline, latency to response was 14 sec, however, in animals previously treated with naltrexone, the latency to response was 20 sec, and at 13 days after withdrawal the time was further increased to 27 sec. Similarly, in the tail-flick test, we found that one week after withdrawal of chronic pretreatment, the median latency to response to morphine (10 mg/kg) in salinepretreated animals was increased almost two-fold over baseline, whereas the response of animals pretreated with naltrexone was almost four-fold greater than baseline. This apparent hypersensitive response was reversed by two weeks after withdrawal.

Discussion. Our data shows that animals chronically treated with saline and tested for analgesia develop an apparent analgesia over time. This effect is most likely related to a stress-induced analgesia in response to the thermal stimulus used in testing. In contrast, animals receiving naltrexone under similar conditions failed to develop analgesia. This data would suggest that the stress-induced analgesia is most likely mediated via endorphin systems as would be consistent with its reversability by the specific narcotic antagonist naltrexone. There could be two potential mechanisms for this action of naltrexone. One mechanism would be naltrexone's blockade of the receptor actions of endorphins after their supposed stress-induced release, or that in light of the high endorphin content of the limbic system, naltrexone may exert an anxiolytic effect, and thus block the trigger for endorphin release.

The data also demonstrate that chronic naltrexone produces a marked potentiation of morphine-induced analgesia. This phenomenon may be explained by supposing either that naltrexone has produced a sensitization of opiate receptors, either by increasing their numbers or affinity, or by altering morphine's pharmacokinetics. The potential clinical significance of this work would be that either in the treatment of post-operative pain, or with the expected use of neuroleptanesthesia, prior treatment of patients with specific narcotic antagonists may lead to an increase efficacy, and thus a decreased dosage of the opiate used.