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Title: A NON-OPIOID PEPTIDE IN SPINAL CORD AND BRAIN WITH ANALGESIC PROPERTIES

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Introduction. Within the past five years the discovery of endogenous opiate-like compounds, the endorphins, has revolutionized our understanding of the biochemical and neurophysiological basis of pain. The endorphins have been shown to have their own receptors in spinal cord and brain, and moreover, have been found to be highly concentrated in those brain regions and pathways believed to be associated with pain. The endorphins are all peptides, varying from five to over 30 amino acids in length. Given that peptide compounds may possess analgesic action, we have investigated this phenomenon using another peptide, namely substance P. This compound is an undecapeptide which has been proposed as a neurotransmitter for primary afferent information in the spinal cord, and is also found in the brain. The current use of intrathecal morphine and its potential for producing central depression makes attractive the possibility of spinal non-opioid analgesics such as substance P (1). We have now conducted studies to elucidate the potential role of substance P in analgesia.

Methods. To specifically test the possible role of substance P in the mediation of analgesia, we examined its actions on the responsiveness of albino male Swiss mice to thermal stimuli (hot plate test). Analgesia was measured as the latency to jumping during a 45 sec test period after placement of individual animals on a hot plate maintained at 55°C. Results are expressed as the median time to jump from the plate. We also assessed the analgesic actions of substance P by its intracerebral injection into the periaqueductal grey (PAG) region of the brain. This was achieved by stereotactically implanting a 0.80 mm stainless steel cannula into the PAG of white male Sprague-Dawley rats. Either morphine sulfate or substance P in 2µl volumes were infused at a rate of 1µl/min into the PAG. Animals were tested by either the hot plate test or the tail-flick test, in which restrained animal's tails were placed in the path of a high intensity light source. When the animals experienced pain, they moved their tails which then broke a photoelectric beam which stopped the timer.

Results. We found that saline pretreated control mice jumped at 7.24 sec, whereas substance P given intraperitoneally 45 min before testing, at a dose of 1 mg/kg significantly prolonged the time to jump (11.06 sec). When animals were pretreated with naloxone (40 mg/kg, 10 min), animals which had previously received saline jumped at 5.27 sec, and the analgesic actions of substance P (1 mg/kg) were completely reversed, with animals jumping at 3.11 sec. To test whether tolerance develops to the administration of substance P, mice were given daily injections of substance P over a four day period (dose on day one was 100 ng/kg and the dose was increased until at day four animals were receiving 100µg/kg). Animals were then treated with naloxone (40 mg/kg) and placed into a glass cylinder and the number of jumps made within 15 min recorded. There was no significant difference between saline control and substance P in the number of naloxone-induced withdrawal jumping in mice. In PAG cannulated animals, we found that intracerebral injection of 100µg substance P was euipotent to 10µg of intracerebral morphine in analgesic action in the tail flick test. In contrast, with similar doses of morphine and substance P as used above, morphine was four-fold more potent than substance P in eliciting analgesia in the hot plate test.

Discussion. The fact that substance P produces analgesia in mice which is equivalent to 5 mg/kg of systemic morphine, and that this effect is reversed by naloxone would be consistent with substance P acting upon endorphine receptors. Previous studies have however indicated that substance P has only a weak affinity for opiate receptors in the central nervous system. Moreover, administration of substance P did not produce tolerance, as would be expected if it worked through endorphine systems. This may suggest the alternative explanations that either endorphins in part mediate their effects via interactions with substance P receptors, or that substance P is a neuromodulator of endorphin neurons. In animals where intracerebral injections of substance P or morphine were made into the PAG, we found substance P to be a more potent analgetic agent as measured by the tail-flick test, and the reverse to be true when tested using the hot plate. The PAG is a brain area particularly rich in endorphins and opiate receptors, and electrical stimulation of this area results in profound analgesia. The fact that substance P is more analgetic in the test more specifically mediated by spinal mechanisms suggests that substance P may produce analgesia at the level of the spinal cord where it regulates afferent sensory information (2). Therefore, substance P may well be used intrathecally, with an analgesic potency rivalling that of morphine, but without producing central depression.

References.

1) G.K. Davies, C.L. Tolhurst-Cleave and T.L. James, Anesthesiology 52:280, 1980.
2) A.I. Basbaum and H.L. Fields, Annals of Neurology 4:451, 1978.