TITLE: NEUROCHEMICAL BASIS OF KETAMINE AND MORPHINE ANALGESIA

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Ketamine (KH) may produce its analgesic effect by altering neurotransmission in pain-transmitting neurons. KH interacts with opiate receptors (Smith et al., Life Sci. 26:789, 1980), as well as inhibiting the neuronal reuptake of norepinephrine (NE) and serotonin (5HT), two important transmitters in pain pathways (Azzaro & Smith, Neuropharm. 16:349, 1977). The opiate analgesic morphine (MS) interacts directly with opiate and indirectly with 5HT systems to produce its analgesia (Yaksh & Rudy, Pain 4:299, 1978). While MS analgesic mechanisms may be dissociated into supraspinal and spinal sites, the loci of KH's analgesic mechanisms have not been determined.

Central activation of the medullary nucleus raphe magnus (NRM) through MS-opiate receptor interaction in the midbrain periaqueductal gray (PAG) has been shown to inhibit pain transmission in laminae I & V of the dorsal horn through activation of descending 5HT fibers (Fields & Basbaum, Ann. Rev. Physiol. 40: 217, 1978). Destruction of the NRM attenuates MS analgesia (Proudfit & Anderson, Brain Res. 98:612, 1975). A spinal opiate receptor interaction also contributes to MS analgesia (Barton et al., Brain Res. 188:487, 1980). KH, as MS, may utilize the PAG-NRM-dorsal horn pathway as well as spinal opiate receptors to produce its analgesia. With this in mind, an evaluation of KH and MS was made in rats comparing the effects of biogenic amine depletion, spinal transection and receptor antagonism on analgesia in the tail-flick test, where exposure to the noxious heat stimulus was terminated at 15 sec. Doses of KH (160 mg/kg) and MS (4 mg/kg) producing 70% analgesia were administered i.p. Antagonists were given 10 minutes before KH and 5 minutes after MS. Control tail flick latencies were determined prior to drug administration. Statistical comparisons were made using a Tukey test after an analysis of variance.

50% inhibition (ID50, mg/kg) of the analgesic effect of MS and KH was determined from dose-response curves after several doses of either methysergide (5HT receptor antagonist), phentolamine (NE receptor antagonist) or naloxone (opiate receptor antagonist). Comparing KH to MS, 4 fold less methysergide (ID50 0.41 cf. 1.65), 47 times less phentolamine (ID50 0.18 cf. 8.5) and 20 times more naloxone (ID 50 0.46 cf. 0.02) were needed to inhibit KH analgesia. These data confirm the interaction of KH and MS with these systems, although there are differences between KH and MS as to the magnitude of each interaction.

Depletion of brain and spinal 5HT by pretreatment with p-chlorophenylalanine (300 mg/kg, 48h prior) attenuates both KH and MS analgesia. Depletion of brain and spinal NE with FLA-63 (25mg/kg, 6h prior) causes an increase in KH analgesia while not affecting MS analgesia. This increase in KH analgesia was reduced by naloxone (1 mg/kg) or methysergide (1 mg/kg) but not by phentolamine (.5 mg/kg) suggesting an analgesic interaction of KH with opiate and 5HT processes independent of NE.

Spinal transection at T4-6 produced an 8-fold decrease in the dose of KH needed to produce analgesia, while producing a 2-fold increase in the dose of MS required. Methysergide (1 mg/kg) was able to inhibit KH analgesia, while only dimimishing MS analgesia produced by a high dose (16 mg/kg), suggesting a spinal 5HT influence of KH analgesia which is not required for MS analgesia. Phentolamine (4 mg/kg) or naloxone (10 mg/kg) had no effect on KH analgesia while naloxone inhibited MS analgesia, indicating that KH may not interact with the spinal opiate receptors which contribute to MS analgesia, and that the opioid and NE components of KH analgesia require intact spinofugal connections.

These data demonstrate important neuroanatomical and neurochemical similarities and differences in the mechanisms underlying KH and MS analgesia. NE appears important only to KH analgesia, although its effects are paradoxical. This may be due to opposing actions of central and spinal NE neurons. Central NE depletion enhances analgesia while antagonism of NE spinally attenuates analgesia (Akil & Liebeskind, Brain Res. 94:279, 1975; Yaksh, Brain Res. 160:180, 1979). In NE-depleted rats, KH's analgesia is produced by opioid and 5HT mechanisms. The fact that naloxone inhibits KH analgesia in these animals but not in transected animals confirms a central site for KH-opiate interaction, which is likely to be the PAG. Complete inhibition of KH analgesia herein also suggests that the isolated spinal serotonergic component seen in transected animals is due to changes after transection and is not normally active. The 5HT-KH interaction reversible by methysergide in NE-depleted and intact animals must be dependent on the central KH-opiate interaction, and is probably spinofugal in nature. The most likely site is the NRM-dorsal horn pathway. KH may activate this system via central PAG opiate stimulation, and simultaneously directly enhance the effects of spinally released 5HT via neuronal reuptake blockade.

We feel that the major sites of KH analgesia are present in the PAG-NRM-dorsal horn pathway and that this interaction involves opiate and 5HT neurochemical mechanisms previously established for this system. A contribution may also be made by a spinofugal NE influence.