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Title: KETAMINE ANESTHESIA AND ANALGESIA: NEUROCHEMICAL DIFFERENTIATION

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Introduction. Ketamine is a unique anesthetic agent, in that it induces a dissociative state between pain perception and cortical associational areas, ketamine has minimal actions on the respiratory and cardiovascular systems. The major drawback to the use of ketamine is its potential for producing hallucinosis in individuals. The exact neurochemical mechanisms underlying the anesthetic, analgesic, and psychotomimetic properties of ketamine are only poorly understood. To gain further insight into these mechanisms, we have investigated the actions of physostigmine on ketamine-induced anesthesia and analgesia as well as the behavioral actions of ketamine administration into discrete brain areas.

Methods. To test the direct action of ketamine in brain, we stereotactically placed, bilaterally, indwelling 0.8 mm diameter stainless steel cannulae into the nucleus accumbens and caudate-putamen nuclei of male albino Sprague-Dawley rats. In analgesia testing, indwelling cannulae were placed into the periaqueductal gray area of animals. Intracerebral injections were made in a total volume of 1 µl, administered at the rate of 0.5 µl/minute. To test analgesia, animals were either placed upon a hot plate maintained at 55°C, and latency of time to the initiation of paw licking used as an index of analgesia, or animals were restrained with their tails immersed in water maintained at 55°C, and the latency to tail flick used to measure analgesia. The latency to narcosis induced by ketamine was measured as beginning at the time of injection to the time of loss of righting reflex, whereas duration of narcosis was calculated as the total time during which animals lost the righting reflex. All injections were by an intraperitoneal route unless otherwise specified.

Results. The administration of ketamine (10 µg) bilaterally into two dopamine-rich areas of the brain either the nucleus accumbens, or caudate-putamen nucleus, produced intense stereotyped behavior consistent with the hypothesis that ketamine releases brain dopamine. When animals were pretreated with the catecholamine depleting agents, α-methyl-para-tyrosine (250 mg/kg) and reserpine (5 mg/kg) all ketamine-induced behavior was abolished. By comparison when ketamine (10 µg) was administered directly into the periaqueductal grey area of the brain it produced an analgesic response as measured by the hot plate test (increase in latency from 3.8 to 8.6 sec), whereas this effect was blocked by the intraperitoneal injection of nalaxone (20 mg/kg).

In testing the anesthetic properties of ketamine (75 mg/kg), we found that it produced a loss of righting reflex at 3 min after administration, this action lasting for a duration of 23 min 45 sec. Treatment with physostigmine (0.2 mg/kg) significantly lengthened the time to loss of righting reflex after ketamine administration, whereas the duration of action was shortened. In contrast, the anticholinergic agent benztropine significantly shortened the time to loss of righting reflex and prolonged this action. In testing analgesia produced by ketamine (75 mg/kg) as measured by the tail flick test, physostigmine failed to significantly affect analgesia, whereas benztropine markedly antagonized analgesia.

Discussion. The action of ketamine in producing hallucinosis in patients is only now being clearly delineated. Psychopharmacological research has led to the theory that dopamine overactivity in the brain is responsible for hallucinations in schizophrenic subjects. So too, it would appear that ketamines ability to release brain dopamine may account for its ability to be hallucinogenic. Our experiments demonstrate that ketamine not only produces dopamine-related behaviors (stereotyped behaviors), but that this effect is antagonized when brain dopamine is depleted.

It has previously been reported that physostigmine reversed the sedative, but not analgesic properties of ketamine in man (1). We observed in animals that physostigmine did in fact antagonize ketamine-induced narcosis in animals as measured by loss of righting reflex, whereas the anticholinergic agent benztropine produced opposite actions. By comparison, physostigmine failed to significantly affect analgesia, whereas benztropine was antagonistic. These results have important practical applications. With the current popular use of balanced anesthesia, the goal during postoperative recovery is to acheive wakefulness with effective anesthesia. At present, with patients in whom anesthesia is induced by narcotic agents, reversal of anesthesia by the use of naloxone is impractical, as the analgesic activity of the narcotic will also be antagonized. Our results would suggest that physostigmine may be used as an analeptic agent in terminating anesthesia, without also terminating analgesia.

Reference.

1) H.G.R. Balmer and S.R. Wyte, British Journal of Anaesthesia 49:510, 1977.