TITLE: ANALGESIC DOSES OF KETAMINE INTERACT WITH OPIATE RECEPTORS IN VIVO

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INTRODUCTION: It has been reported previously that ketamine interacts with opiate receptors in vitro[1,2] as an agonist.[3] However, in comparison to the classical opiate drugs like morphine, rather high concentrations (μM) of ketamine are required to produce its effects. Consequently, the present study was done to determine if analgesic doses of ketamine would result in concentrations sufficient to interact with opiate receptors in selected regions of the central nervous system of intact animals.

METHODS: An in vivo opiate receptor binding assay using ^{3}H-naloxone was performed by a modification of the method of Pert & Snyder[4]. Briefly, ^{3}H-naloxone (1 μg/kg; 33 μCi/kg) was injected into the tail vein of male, Sprague-Dawley rats and the animals were decapitated 15 min. later (preliminary experiments demonstrated that ^{3}H-naloxone accumulation was maximal 15 min. after injection). When ketamine was administered to compete for radioligand binding, it was administered (i.p.) simultaneously with the ^{3}H-naloxone. (It has been shown[5] that the maximal analgesic effect of ketamine, and thus, it is assumed highest concentration of the drug, occurs at 15 min. after i.p. administration). After the animals were sacrificed, the brain (or brain regions) and spinal cord were rapidly dissected on ice and homogenized in 1.0N HCl using a Polytron (setting 6; 20 sec.). The homogenate was centrifuged and aliquots of the supernatant were assayed in duplicate using liquid scintillation spectrophotometry. The extraction procedure recovers 90-95% of the ^{3}H-naloxone.

Specific opiate receptor binding (fmoles/gm tissue) was determined by subtracting the value for the cerebellum (a region devoid of opiate receptors; confirmed in preliminary experiments) from that obtained in other CNS regions. Binding in tissues from ketamine-treated rats was compared to that in saline-treated animals and differences were tested for significance using the Student's t-test.

RESULTS: It was observed that ketamine caused a dose-dependent reduction in ^{3}H-naloxone binding in the brain (minus cerebellum) and spinal cord tissues which was significant at 120 mg/kg of the drug (Table 1). Only doses of the drug (i.p.) that have previously[5] been shown to produce analgesia (80, 120 & 160 mg/kg) were effective while a dose without analgesic action (40 mg/kg) was ineffective.

The 120 mg/kg dose of ketamine which appeared to produce maximal displacement of ^{3}H-naloxone was also studied for its effect in various regions of the rat CNS. The drug caused a reduction in all areas studied but the reduction was significant in only those regions denoted with an asterisk in Table 2.

DISCUSSION: These results demonstrate that the concentration of ketamine achieved in the rat CNS after administration of analgesic doses of the drug effectively interacts with opiate receptors. Since it has been shown that ketamine acts as an agonist of opiate receptors in vitro,[3] it seems likely that the analgesic action of the drug may be partially mediated[5] through opiate-activated neuronal processes.

TABLE 1

	Ketamine (mg/kg)				
	Saline	40	80	120	160
Cerebellum	628±52	635±30	556±40	562±39	613±74
Brain+	673±96	703±81	530±74	459±71*	528±104
Spinal Cord+	308±70	294±44	244±48	172±38*	181±39*

Values are fmoles 3H naloxone/gm tissue ± S.E.
+ values are minus cerebellum and represent specific binding. *Significantly different from control, $P \leq 0.05$. $N \geq 9$/group.

TABLE 2

	Ketamine (120 mg/kg)	Saline
Cerebellum	593±23	638±17
Medulla	367±44	495±59
Hippocampus*	571±93	810±99
Midbrain	1013±126	1103±64
Thalamus*	1040±104	1270±38
Hypothalamus	877±215	1062±320
Striatum*	703±186	1031±24
Cortex*	620±55	1004±60
Spinal Cord*	298±21	441±69

Values are expressed as in Table 1 and, with the exception of the cerebellum value, represent specific binding. *Significantly reduced by ketamine $P \leq 0.05$. n=9

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