

TITLE: KETAMINE INTERACTS WITH OPIATE RECEPTORS AS AN AGONIST

AUTHORS: D.J. Smith, Ph.D., D.P. Westfall, Ph.D., and J.D. Adams, B.S.

AFFILIATION: Departments of Anesthesiology & Pharmacology  
West Virginia University Medical Center  
Morgantown, WV 26506

The analgesic effect of ketamine HCl is inhibited by the narcotic receptor antagonist naloxone, indicating that endogenous opiate neuronal processes are involved in the action of the drug (Ryder *et al.*, *Europ. J. Pharmacol.* 49:15, 1978, Smith *et al.*, *Life Science* 26:789, 1980). An effect involving endogenous opiates may be direct (i.e., alterations in the metabolism of enkephalins or an interaction with opiate receptors) and/or indirect through activation of other neurons involved in pain pathways that converge on endogenous opiate neurons.

Recently, we reported that ketamine does interact with opiate receptors (Smith *et al.*, *Life Science* 26:789, 1980). Ketamine displaced <sup>3</sup>H-naloxone from opiate receptors on rat brain membranes (IC 50, 68.3 μM) with the (+) HCl salt (levorotatory free base) being more effective than (-) salt. Since the displacement of <sup>3</sup>H-naloxone was sensitive to sodium ion (6 fold reduction in the potency of ketamine), it was suggested that the interaction of ketamine with the receptor was like that of an agonist. However, in order to demonstrate conclusively that the drug is an agonist, studies were done comparing the ability of morphine and ketamine to induce opiate receptor mediated effects in the guinea pig ileum.

The study was done in the coaxially stimulated longitudinal muscle-myenteric plexus preparation (Rang, *Brit. J. Pharmacol.* 22:356, 1964). The preparation was bathed in Krebs-Henseleit solution and was stimulated with 0.5 msec pulses delivered transmurally at a frequency of 0.1 Hz using supramaximal voltage (approximately 60V). Drugs were applied for 3 min. with a 20 min. wash and recovery period prior to the administration of the next dose. Dose-response curves were constructed and the ability of naloxone to antagonize the effect of the drugs was analyzed.

The dose-response curves for ketamine were obtained in the presence of 30 μM cocaine, since ketamine inhibits the high affinity transport systems for norepinephrine and serotonin (Azzaro & Smith, *Neuropharmacol* 16:349, 1977) and these transmitters modify the response of the ileum. Comparing cocaine-treated to control preparations revealed a slight involvement of these monoamines in the action of high doses (3-10X10<sup>-4</sup>M) of ketamine.

Ketamine and morphine both caused a concentration dependent inhibition of the twitch response of the guinea pig ileum and were antagonized by naloxone (Table 1). Therefore it may be concluded that ketamine interacts as an agonist of opiate receptors. It would appear, however, that the effect of ketamine on the ileum is not identical to that of morphine

since naloxone was considerably less effective in antagonizing ketamine.

Naloxone (moles/L)	Ketamine ID 50	Morphine
0	1.15±0.31 X10 <sup>-4</sup>	2.98±0.61 X10 <sup>-8</sup>
	SHIFT OF THE ID 50	
3.2X10 <sup>-9</sup>		2.45±0.41
1.0X10 <sup>-8</sup>	2.60±0.54	5.37±0.82
3.2X10 <sup>-8</sup>	3.93±0.47	17.32±3.7
1.0X10 <sup>-7</sup>	10.50±2.19	

An explanation for the reduced potency of naloxone as an antagonist of ketamine may be that ketamine interacts with a population of opiate receptors different from those preferentially acted upon by morphine (see heterogeneous opiate receptors, Chang & Cuatrecasas, *J. Biol. Chem.* 254:2610, 1979). This possibility was evaluated by a kinetic analysis comparing the potency of naloxone as an antagonist of morphine and ketamine. Schild plots (Brit. J. Pharmacol. 2:189, 1947) were constructed and mean pA<sub>2</sub> values\* determined as an index of affinity<sup>2</sup> in the naloxone-ketamine and naloxone - morphine interactions. The naloxone-ketamine pA<sub>2</sub> (8.24) was less than the value for naloxone-morphine (8.65). However, the mean slope of the Schild plot of naloxone versus ketamine varied significantly from -1.0 indicating that the interaction was not a simple equilibrium competitive antagonism. A possible reason for a slope different than -1.0 is that ketamine interacts with more than one receptor (opioid and/or non-opioid). This is being investigated using agonists and antagonists specific for various populations of opiate receptors.

Presently, it can be concluded that ketamine is an agonist of opiate receptors. Studies of its agonistic properties in the guinea pig ileum have suggested that it may interact with a sub-population of opiate receptors. However it is not yet possible to rule out effects on other neuronal systems that may contribute to the response of this preparation to ketamine.

\*pA<sub>2</sub> is the negative log 10 of the molar concentration of antagonist that shifts the dose response curve of the agonist two fold. If two agonist are being compared, equal antagonist pA<sub>2</sub> values demonstrate that both agonists interact at the same receptor, providing equilibrium competitive antagonism is demonstrated.