TITLE: KETAMINE AND N-ALLYLNORMETAZOCINE INTERACT SIMILARLY WITH MULTIPLE OPIATE RECEPTORS

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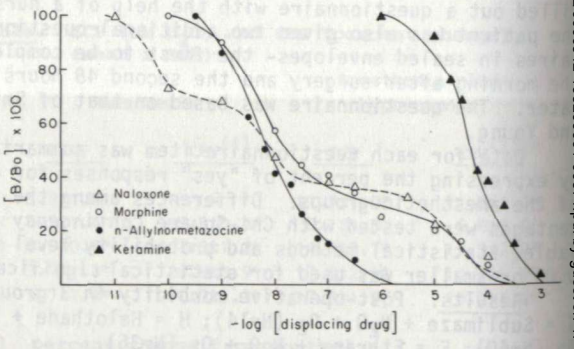
INTRODUCTION: The analgesic action of ketamine appears to be partially related to an interaction of the drug with opiate receptors.[1-3] However, several sub-types of opiate receptors exist and at least one of these, the sigma (σ) opiate receptor, seems to be responsible for mediating hallucinosis[4] like that observed with the use of ketamine. Therefore, the study reported here was done to determine if ketamine might preferably interact with a particular sub-type of opiate receptor, and perhaps show some similarities with hallucinogenic opiates like n-allylnormetazocine, a sigma opiate ligand.

METHODS: Opiate receptor binding assays[1] were established for radioligands presumed to be specific for μ receptors (^{3}H-dihydromorphine), K receptors (^{3}H-ethylketocyclazocine), δ receptors (^{3}H-leucine-enkephalin) and σ receptors (^{3}H-n-allylnormetazocine). Briefly, a rat brain membrane fraction was prepared and was incubated (18 mg original tissue in 0.05 M Tris-HCl buffer, pH 7.7, 25^{0}C) with 1 nM of each radioligand for times that were appropriate to allow binding to reach equilibrium. The incubation tubes also contained various concentrations of displacing ligands or an excess (μM) of unlabeled homologous ligand for the determination of non-specific binding. The incubation was terminated by the rapid filtration and washing of the membrane on Whatman GF/B filters. The filters were then extracted in Dimilume scintillation solution and radioactivity was determined by liquid scintillation analysis. Specific opiate receptor binding was calculated by subtracting non-specific binding (obtained in the presence of excess unlabeled ligand) from total binding in incubation tubes containing only radioligand or radioligand and displacing drugs. Competition for radioligand binding was then calculated as specific binding in the presence of displacing drugs (B) over specific binding in the absence of displacing drugs (Bo) X 100. Concentrations of drugs that caused 50% inhibition of binding (IC50) were determined by regression analysis. Modified Hill coefficients were calculated to evaluate binding site multiplicity with a single radioligand. Analysis of variance was used for statistical treatment of data. ($P<0.05$).

RESULTS: Ketamine displaced each of the radioligands studied but exhibited a low potency and IC50 values that fell within a narrow range (μM of ketamine for the displacement of ^{3}H-dihydromorphine, 27±7.6; ^{3}H-n-allylnormetazocine, 66±10; ^{3}H-ethylketocyclazocine, 85±26; ^{3}H-leucine enkephalin, 100±9.0). N-allylnormetazocine had characteristics that were qualitatively similar to ketamine in each binding assay, although the former drug was more potent (IC50 values of approximately 10 nM). Both drugs generated steep, monophasic displacement curves, regardless of the radioligand being studied, with Hill coefficients ranging from 0.8-1.0. Coefficients in this range suggests that the radioligand is being displaced from a single population of binding sites or that the displacing drug has a similar affinity at multiple radioligand binding sites. The latter explanation seems most likely for ketamine and n-allylnormetazocine, since other displacing drugs (morphine, ethylketocyclazocine and leucine enkephalin) distinguished multiple sites in at least two of the assays (^{3}H-leucine enkephalin and ^{3}H-n-allylnormetazocine). These drugs either generated biphasic displacement curves (see Figure for example of interactions with ^{3}H-n-allylnormetazocine) or Hill values of < 0.8 (multiple sites). In addition, naloxone was capable of distinguishing 3 binding sites (triphasic curve) for ^{3}H-n-allylnormetazocine. It is apparent from these data that although the radioligands used in this study may show preference for particular subtypes of opiate receptors, they do not label them selectively. However, ketamine and n-allynormetazocine are incapable of distinguishing among these multiple site interactions, presumably because the two drugs individually have similar affinities for all binding sites.

DISCUSSION: Ketamine has now been shown to interact with several sub-types of opiate receptors, but does not appear to demonstrate a striking preference for a particular class. The drug does however appear to interact qualitatively similarly to the sigma opiate receptor ligand n-allylnormetazocine. Thus, it may be that ketamine induces dysphoric reactions by behaving like a sigma ligand to produce opiate-linked psychosis.



LEGEND: Displacement of specifically bound ^{3}H-n-allylnormetazocine. Leucine enkephalin, ethylketocyclazocine and morphine had similar curves, only morphine's is shown.

REFERENCES:

1) Smith, D.J., et al: The interaction of ketamine with the opiate receptor. Life Sci. 26:789-795, 1980.

2) Pekoe, G.M. & Smith, D.J.: The involvement of opiate and monoaminergic neuronal systems in the analgesic effects of ketamine. Pain 12:57-73, 1982.

3) Finck, A.D. & Ngai, S.H.: A possible mechanism of ketamine-induced analgesia. Anesthesiology 51: S34, 1979.

4) Martin, W.R., et al: The effects of morphine- and nalorphine-like drugs in the non-dependent and morphine dependent chronic spinal dog J. Pharmacol Exp. Ther. 197:517-532, 1976.