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PRELIMINARY COMMUNICATION

HALOPERIDOL BINDING TO AN OPIATE RECEPTOR SITE

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Several investigators (1-5) have recently provided evidence for receptors that bind opiate agonists and antagonists with stereospecific selectivity. Pert and Snyder (2,6) have used radiolabeled naloxone of very high specific activity to demonstrate a population of opiate receptors in rat neural tissue. They have shown that a number of opiate agonists and antagonists bind to this receptor population in vitro with a diverse range of affinities, and have demonstrated a very good correlation between binding affinity in vitro and pharmacologic efficacy in vivo with both agonists and antagonists.

Haloperidol is a non-narcotic neuroleptic drug that has been shown to suppress opiate withdrawal symptoms in animals (7) and to reduce morphine self-administration in addicted rats (8). More recently, haloperidol has been reported to effectively reduce narcotic withdrawal symptoms in humans receiving treatment for heroin addiction (9,10). The purpose of the present study was to determine whether haloperidol could also interact with opiate receptor sites.

METHODS AND MATERIALS

Male Sprague-Dawley rats (Charles River Laboratories, 180-200 g) were killed by cervical dislocation and the brains were quickly removed. The cerebellum was discarded and the remainder of the brains was homogenized in 0.05 M Tris buffer, pH 7.4. Receptor-binding activity of the homogenates was determined by the method of Pert and Snyder (6). [^{3}H]-(-)-naloxone, 23.6 Ci/m-mole, was purchased from the New England Nuclear Corp. Naloxone was supplied by Endo Laboratories, Garden City, N.Y., and levorphanol and dextrorphan by Hoffmann-LaRoche, Inc., Nutley, N.J.

RESULTS

The effect of varying concentrations of unlabeled morphine and haloperidol on the stereospecific binding of 8nM [^{3}H]-naloxone to rat brain homogenate is shown in Fig. 1. Morphine and haloperidol bind to the opiate receptor and inhibit binding of

labeled naloxone, but their affinities for the receptor differ markedly. The concentrations of morphine and haloperidol required to reduce the stereospecific binding of 8nM [^{3}H]-naloxone by 50 per cent (ED_{50}) were 12 and 880 nM respectively.

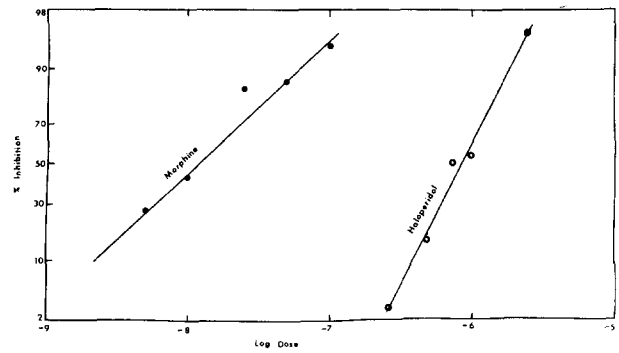

Fig. 1. Effect of morphine and haloperidol on [^{3}H]-naloxone binding. After a 5-min preincubation with five concentrations of each drug, rat brain homogenates were incubated for 20 min at 35° with 8 nM [^{3}H]-naloxone. Per cent inhibition of control [^{3}H]-naloxone specific binding was determined and plotted as a function of drug concentration on log-probit paper. Points are the mean value of six triplicate determinations.

The log-probit plots for the binding affinity of morphine and haloperidol to the [^{3}H]-naloxone receptor differ markedly. Morphine has a profile that parallels that of a large number of opiate agonists and antagonists (6, and G. Clay, unpublished data). Haloperidol, on the other hand, has a binding profile differing from that reported for morphine or other opiate agonists and antagonists.

In order to determine the nature of the haloperidol binding, saturation curves for the specific binding of [^{3}H]-naloxone to rat brain homogenates were determined in the presence and absence of 12 nM morphine and 880 nM haloperidol. Double reciprocal plots of these results, which are shown in Fig. 2, indicate that morphine and haloperidol were bound in a competitive manner to the opiate receptor. Other neuroleptics do not appear to alter [^{3}H]-naloxone binding. Pimozide (11) had no effect on opiate binding, and chlorpromazine and clozapine do not affect opiate binding at concentrations up to 10^{-3} M (G. Clay, unpublished data).

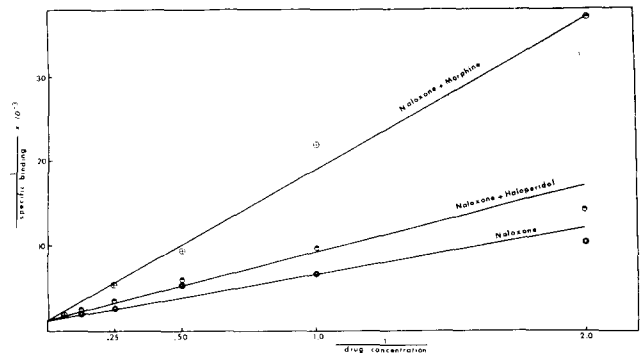

Fig. 2. Double reciprocal plots of [^{3}H]-naloxone binding to rat brain homogenates in the presence and absence of 12 nM morphine and 880 nM haloperidol. Points represent single determinations. Ordinate: reciprocal of specific binding X 10^{-3}; abscissa: reciprocal of [^{3}H]-naloxone concentration in nM.

Pert and Snyder (12) have differentiated opiate agonists from antagonists by their ability to bind to the opiate receptor in the presence or absence of Na^+. Opiate agonist binding is greatly reduced by 100 nM Na^+, while antagonist binding to the naloxone receptor site is unaffected by this Na^+ ion concentration. Haloperidol binding to the opiate receptor, at all concentrations, was abolished by 100 nM Na^+, but [^{3}H]-naloxone binding was not affected.

DISCUSSION

While haloperidol is normally considered to be a non-opiate, non-addicting neuroleptic, it has been used to suppress opiate withdrawal behavior in animals and humans (7-10). The exact mechanism by which haloperidol suppresses this behavior is not known.

One possible explanation would be for haloperidol to function as a weak agonist devoid of the normal opiate characteristics but capable of interacting with the same receptor population as the opiates. In this regard, our studies show that haloperidol, *in vitro*, can bind in a competitive manner to an opiate receptor population. In the presence of 100 nM Na^+, haloperidol binding is greatly reduced, and this finding is consistent with the data reported for known opiate agonists (5,12).

Binding affinity studies indicate, however, that haloperidol may be binding to the opiate receptor in a different manner than morphine. Pert and Snyder (6) have reported log-probit profiles of binding affinity for 15 opiates and their antagonists that are parallel, a finding that we have been able to confirm in our laboratory (G. Clay, unpublished data). The log-probit of the haloperidol-binding affinity has a much steeper slope than was obtained with morphine. Hill plots of the inhibition of binding of [^{3}H]-naloxone by unlabeled morphine and haloperidol (Fig. 3) suggest cooperativity in the binding of haloperidol to the opiate receptor (13).

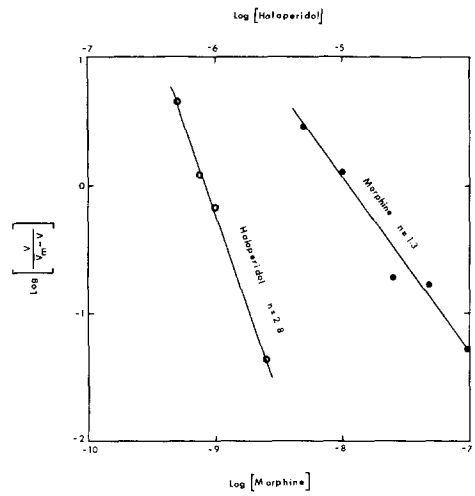

Fig. 3. Hill plot of the effect of morphine and haloperidol on [^{3}H]-naloxone specific binding. V = specific binding observed at the concentration of inhibiting drug under consideration. n = Hill coefficient value. Points are the mean value of six triplicate determinations. For experimental conditions, see text of Fig. 1.

In summary, our data suggest that haloperidol may suppress opiate withdrawal behavior directly by interacting with a population of opiate receptors in the central nervous system and may be acting as a weak agonist. However, the slope of the log-probit profile for the binding affinity of haloperidol in vitro indicates that haloperidol does not interact with the opiate receptor population in the same manner as standard opiate agonists. Further studies are continuing on the significance of this interaction of a non-opiate with an opiate receptor population.

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