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Centrally Administered Opioid Antagonists, Nor-Binaltorphimine, 16-Methyl Cyprenorphine and MR2266, Suppress Intake of a Sweet Solution

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CALCAGNETTI, D. J., R. L. CALCAGNETTI AND M. S. FANSELOW. *Centrally administered opioid antagonists, nor-binaltorphimine, 16-methyl cyprenorphine and MR2266, suppress intake of a sweet solution.* PHARMACOL BIOCHEM BEHAV **35**(1) 69–73, 1990.—Three opioid antagonists (MR2266, 16-methyl cyprenorphine and nor-binaltorphimine) were tested independently for their ability to suppress the intake of a highly palatable saccharin and glucose (S/G) solution after central administration. MR2266 is an equally potent antagonist at kappa (κ) and mu (μ) opioid receptors. Nor-binaltorphimine (N-BNI) and 16-methyl cyprenorphine (M80) are two recently developed opioid antagonists that were chosen based upon their ability to act more selectively than naloxone at κ and delta (δ) opioid receptor types, respectively. Prior research has demonstrated that when dissolved in acid and administered centrally, MR2266 (20 μg) fails to suppress S/G intake. Because all three antagonists are rather insoluble in water, they were dissolved in dimethyl sulfoxide (DMSO). Rats with chronic ventricular cannula were allowed to consume S/G for a 0.5 hr bout. They received a single intracerebroventricular (ICV) injection of antagonist (MR2266: 0, 10, 20 and 40 μg; M80: 0, 5, 10, 20 and 40 μg or N-BNI: 0, 1, 3, and 10 μg) 10 min prior to the start of the drinking bout. Administration of DMSO alone failed to alter drinking relative to saline, whereas each antagonist significantly attenuated S/G intake. We conclude that, when dissolved in DMSO, these antagonists suppress drinking by blockade of opioid receptors.

Opioid antagonists Intracerebroventricular Saccharin/glucose Drinking Endogenous opioids
Delta, kappa and mu opioid receptors Nor-binaltorphimine 16-Methyl cyprenorphine MR2266

STEMMING from the 1975 findings of Holtzman (15) that naloxone acts as a potent antidipsogenic agent, a large literature has developed characterizing in detail the suppressant effects of opioid antagonists on drinking. Several recent publications address and summarize the body of findings in this area (4, 8, 22, 24, 29). There is some evidence that the site of action for opioid antagonists on fluid intake is central (3, 9, 27). Two brain site specific studies, one using naloxone (26) and one using a quaternary form of naltrexone (34), naltrexone methobromide (QNTX), have revealed that several deep brain structures are involved in drinking and are sensitive to opioid receptor blockade. The sensitive sites include the paraventricular and supraoptic hypothalamic nuclei (34) and the ventral tegmental area (26).

The ability of the relatively mu (μ) receptor type preferring antagonists, naloxone and naltrexone, to suppress drinking has been well documented (16, 25, 28, 30) and summarized (22,24). However, the existence of at least three distinct types of centrally located opiate receptors has been established by several independent lines of evidence [for review see (6)]. Studies have identified and mapped μ, delta (δ) and kappa (κ) binding sites in rat brain by autoradiographic (19), ontogenic (18), pharmacological and anatomical (20,21) methods. Several opioid agonists have been determined to be relatively selective for their respective opiate receptor types (14). However, the role of κ and δ receptors in the control of drinking remains unclear mainly due to the lack of antagonists selective for these receptor types.

Recently, two opioid antagonists have been developed that display selectivity for κ and δ/μ receptors. The naltrexone-derived bivalent ligand, nor-binaltorphimine (N-BNI), has undergone in vitro and in vivo characterization (23). Reports of in vitro testing of N-BNI have agreed that it is a potent and highly selective κ antagonist (1, 2, 23, 32). Indeed, the κ versus μ selectivity of N-BNI in vitro is about 100 times greater than NTX when tested against ethylketazocine in the GPI preparation (23). Others have reported N-BNI to be 400-fold selective for κ versus μ receptors in the mouse vas deferens (2).

In the rat, behavioral evidence supporting the in vivo selectivity of N-BNI comes from the research of Czlonkowski, Millian and Herz (10). They reported that in the tail-pressure test using rats, analgesia produced by trans-3,4-dichloro-N-methyl-N-12 [2(1-pyrrolidinyl) cyclohexyl] benzeneacetamide, methanesulfonate, hydrate (U50488H, 50 μg, ICV), was blocked by subcutaneous injection of N-BNI (5 mg/kg), but not naltrexone (0.1 mg/kg). In addition, when dissolved in acid vehicle, N-BNI (10 μg/rat, ICV)

has been shown to readily reverse the analgesia produced by U50488H (28 μg, ICV) in the formalin test (13).

The behavioral role of δ receptors types can be examined with the cyprenorphine analog 16-methyl cyprenorphine [N-cyclopropylmethyl-6, 14-endoetheno-7 alpha (1-hydroxy-1-methyl-16 alpha-methyl-6,7,8,14-tetrahydro nororipavine hydrochloride) (M80)]. M80 has high affinity for μ and δ receptors and displays limited selectivity for δ over μ receptors (3:1 in issolated tissue preparations) and very low affinity for κ receptors in vitro (31). When dissolved in acid and centrally administered, M80 dose-dependently reversed conditional fear-induced analgesia (12). Additionally, M80 was found to selectively block the analgesia produced by the δ selective agonist, (D-Pen^2, D-Pen^5) enkephalin (DPDPE, 3.5 μg, ICV), but not the analgesia produced by the μ selective agonist (D-Ala^2, N-Me-Phe^4, Gly^5-ol) enkephalin (DAGO, 0.25 μg, ICV) or the κ selective agonist, U50488H (28 μg, ICV) (12). Central administration of each agonist has been reported to serve as effective analgesic agents in the formalin test (5) and the doses tested against M80 were selected to produce an equivalent level of analgesia (12). Collectively, the results with M80 and N-BNI suggest that they are receptor type selective antagonists in vivo and may provide the tools necessary to examine the contribution of δ/μ and κ receptor types, respectively, in drinking.

A key role for the endogenous opioids seems to be in the modulation of motivated behavior (11). One way of motivating a nondeprived rat to drink is by presenting limited access to a solution of saccharin and glucose (S/G). Valenstein, Cox and Kakolewski reported that given 24 hr access to S/G, rats will consume an amount greater than their body weight daily, presumably due to its high palatability (35). Furthermore, intake of saccharin solutions is reduced by naloxone and naltrexone (7, 17, 30) indicating that opioid manipulations can alter this form of motivated behavior.

Fanselow, Calcagnetti and Helmstetter tested another opioid antagonist, (−)-(1R,5R,9R)-5,9-Diethyl-2-3(-furylmethyl)-2′-hydroxy-6,7-benzomorphan (MR2266), for its ability to dose-dependently reverse conditional analgesia and suppress drinking (11). MR2266 was selected to examine the contribution of μ and κ receptors, since MR2266 binds with nearly equal affinity to κ and μ opioid receptors and displays low affinity for δ receptors (31). When dissolved in acid (0.1 N hydrochloric acid) and administered centrally, MR2266 readily reversed conditional analgesia. Peripherally administered, MR2266 (1 mg/kg, pH = 5.8) significantly reduced water intake in 23.5-hr water-deprived rats. These results were consistent to the results obtained with peripherally administered naloxone and naltrexone. However, unlike the suppression of drinking produced by centrally administered naloxone and naltrexone, when administered ICV in a dose as high as 20 μg/rat, MR2266 failed to suppress drinking of S/G (11).

It is possible that this difference between MR2266 and naloxone lies in the pharmacokinetics of these drugs. Naloxone and naltrexone are very soluble in water and lipophyllic. MR2266, in contrast to naloxone and naltrexone, displays a low solubility in water (personal communication with Dr. H. Merz). Perhaps MR2266 did not penetrate to brain sites involved in drinking when administered ICV in the acid vehicle (12). Similar results were obtained in a pilot experiment using M80 (0, 0.5, 2, 8 μg/rat, pH = 5.5). When M80 was dissolved in acid and injected ICV 15 min prior to the start of the drinking bout, it failed to reduce S/G intake in nondeprived rats (n = 22) (unpublished observations). Since MR2266, M80 and N-BNI are rather insoluble in water, we therefore employed dimethyl sulfoxide (DMSO) as a vehicle in order to enhance solubility and penetration of these antagonists into the brain. The present experiments were designed to assess the ability of centrally administered MR2266, M80 and N-BNI to suppress S/G drinking using DMSO as vehicle.

METHOD

Subjects

Adult female rats (220–345 g) of Long-Evans descent served as subjects. All rats were maintained and tested in an isolated room (12:12 hr light:dark cycle with dark onset at 2300 hr) and individually housed in hanging stainless steel cages equipped with ad lib access to food (Prolab 3000) and tap water. All testing took place in the middle of the light cycle with the 0.5 hr drinking bout beginning at 1600 hr. Subjects used in experiments involving MR2266 (n = 4–9 per group) and M80 (n = 6–10 per group) had been used previously in the formalin test (50 μl of 15% formalin was injected in to the right rear paw) where they had received two ICV injections (an agonist and antagonist combination) (11,12). The ICV injections consisted of one of the following agonists [DPDPE, (3.5 μg), DAGO (0.25 μg) or U50488H (28 μg)] in combination with a second ICV injection of one of the following antagonists [(D-Phe)-Cys-Try-(D-Trp)-Orn-Thr-(L-Pen)-Thr (CTOP), 0, 40 or 80 μg; or QNTX, 0, 5 or 10 μg]. A minimum of four days separated the present studies from previous testing. Subjects were counterbalanced for prior drug exposure and were naive to the present manipulations. Only naive female rats (n = 7 per group) were used in the experiment involving N-BNI.

Surgery

Rats were anesthetized with 100 mg/kg ketamine hydrochloride plus supplemental 0.04 ml as needed. A stainless steel outer cannula guide (22 gauge, Plastic Products, Roanoke, VA) was stereotaxically implanted into the right lateral ventricle (coordinates used were 0.5 mm posterior to bregma, 1.5 mm lateral to midline, and 3.2 mm ventral to the surface of the cortex, the skull was level between lambda and bregma landmarks).

Drugs and Injection

MR2266, and M80 were gifts of Drs. H. Merz and C. F. C. Smith respectively. N-BNI [17, 17′-Bis (cyclopropylmethyl)-6,6′,7,7′-tetradehydro 4,5:4′,5′-diepoxy-6,6′-(imino) (7,7′-bimorphian)-3,3′-14,14′-tetrol)] was purchased from Research Biochemicals Inc. (Natick, MA). Each antagonist was dissolved in 100% DMSO (Fisher Scientific) and briefly subjected to ultrasound sonification just prior to injection. DMSO served as the control injection. A 0.9% saline (SA) control group was included in the experiments involving MR2266 and M80 for comparison with the DMSO (vehicle alone) group. Doses used were selected based upon prior research or pilot studies (M2266, SA, 0, 10, 20 and 40; M80 SA, 5, 10, 20, and 40 and N-BNI, 0, 1, 3, and 10 μg/rat).

Intraventricular injections were accomplished by backloading the drug up a 28-gauge internal cannula (Plastic Products) into a 18 cm length of PE-50 tubing (Intramedic No. 7411). The tip of the internal cannula was ground to a point and cut to extend 0.5 mm beyond the guide cannula. A 10 μl injection volume was delivered at a rate of 10 μl/20 sec with a 100 μl Hamilton syringe mounted in a hand-held repeating dispenser. The inner cannula was held in place for at least 15 sec after the drug injection. At the end of each injection, the injection system was checked for possible occlusion. Visual inspection of positive flow assured drug delivery throughout the injection procedures.

Procedure and Apparatus

All subjects had at least seven days to recover following surgery prior to the administration of drugs. During this time they were handled daily and each cannula plug wire was removed and

swabbed with isopropyl alcohol. Tubes filled with S/G were presented daily for 4 days prior to drug injections on Day 5 of testing (the Drug Day), each rat received a single ICV injection of antagonist or control 10 min before the start of the drinking bout. At 1600 hr the drinking began when the tube was inserted along side of the water bottle at the front of the cage with the tip protruding into the cage. Due to the limited data on effects of N-BNI after ICV administration, a Postdrug Day of S/G intake was collected to test for nonspecific or toxic effects of N-BNI at the doses tested.

Saccharin and Glucose Solution Preparation and Presentation

S/G solution was prepared fresh daily and consisted of 1.25 g saccharin (Sigma Chemical) and 30 g of d-glucose anhydrous (Fisher Scientific) dissolved in 969 ml of tap water. Fifty ml volume polypropylene centrifuge vials fitted with stainless steel needle point sipping tubes were filled with about 35 g of S/G solution maintained at room temperature. The vials were weighed before and after the 0.5 hr drinking bout to the nearest 0.1 g.

Data Analysis and Histology

The antagonists were tested in experiments designed to generate dose-responsive curves using independent groups and employing similar procedures. Drinking data were analyzed by separate overall analysis of variance (ANOVA) and followed, where appropriate, by a priori planned comparisons.

At the conclusion of each experiment, the subjects were overdosed with sodium pentobarbital and injected ICV with 2 μl of ink. Approximately 5–15 min later they were perfused transcardially with SA followed by buffered formalin (10%). The brains were removed and coronal sections were made along the cannula tract. Positive cannula placement was verified by the presence of ink in the ventricles. Only those subjects for which positive placement was verified were included in the analyses. The inability to verify the cannula placement resulted in excluding one rat from Experiment 1 involving MR2266 and 3 rats from Experiment 2 involving M80.

RESULTS

Separate ANOVAs of the Predrug days for experiments involving MR2266 and M80 and N-BNI failed to reveal significant between group differences, $F(3,21)=0.08$, $F(4,39)=0.09$ and $F(3,24)=0.27$, respectively and none were expected because all groups were counterbalanced based upon Predrug Day intake. Since *t*-tests (two-tailed) for unpaired groups revealed that the SA and DMSO groups were not significantly different on the Drug Day (p's>0.6), these two groups were pooled for further statistical comparison.

Experiment 1: MR2266

On the Drug Day, ANOVA indicated a reliable between groups difference, $F(3,21)=3.33$, $p<0.04$. A planned comparison between groups revealed a significant linear component for dose, $F(1,21)=62.3$, $p<0.01$, indicating that reduction of intake took place in a dose-related manner. As Predrug Day intake served as control, all Drug Day intake data were transformed to a percentage of control for this and the two following experiments. Figure 1 (top panel) depicts the intake of S/G solution expressed as the mean percent of control. The two highest doses tested suppressed intake to about 50% of control. The mean weight of S/G consumed on the Drug Day was SA = 12.48 g (S.D. = 3.4, n = 4), DMSO = 11.38 g (S.D. = 6.9, n = 9), 10 = 11.12 g (S.D. = 3.7, n = 4), 20 = 4.55 g (S.D. = 2.8, n = 4) and 40 μg/rat = 5.8 g (S.D. = 3.26, n = 4).

Experiment 2: M80

ANOVA of Drug Day intake indicated significant between group differences, $F(4,39)=4.18$, $p<0.007$. Subsequent planned comparisons failed to reveal a significant linear component for dose. Figure 1 (middle panel) illustrates the effects of M80 on S/G intake presented as the mean percent of Predrug Day. The 5, 10, 20 and 40 μg/rat doses each reduced intake to about 50% of control. Collectively, these results indicate that ICV administration of M80 produced a significant attenuation of S/G intake. The mean weight of S/G consumed on the Drug Day was SA = 10.8 g (S.D. = 3.2, n = 7), DMSO = 11.25 g (S.D. = 6.5, n = 10), 5 = 5.98 g (S.D. = 3.59, n = 6), 10 = 5.57 g (S.D. = 3.78, n = 7), 20 = 7.07 g (S.D. = 4.2, n = 7) and 40 μg/rat = 3.77 g (S.D. = 1.72, n = 7).

Experiment 3: N-BNI

ANOVA of Drug Day S/G consumption revealed significant between group differences, $F(3,24)=3.58$, $p<0.03$. Planned comparisons indicated a reliable linear component for dose, $F(1,24)=9.2$, $p<0.01$. The 3 and 10 μg doses reduced intake to about 50% of control, reduction of drinking was dose-related. The effects of N-BNI on S/G intake are presented in Fig. 1 (bottom panel) as the mean percent of control. The mean weight of S/G consumed on the Drug Day was 0 = 7.6 g (S.D. = 1.6), 1 = 5.8 g (S.D. = 1.5), 3 = 3.26 g (S.D. = 1.3), 10 μg/rat = 3.0 g (S.D. = 0.72).

ANOVA of Postdrug Day nontransformed intake failed to reveal statistically reliable between group differences, $F(3,24)=2.5$, $p=0.09$.

DISCUSSION

We found that three opioid receptor antagonists (MR2266, M80 and N-BNI) produced significant reductions in the consumption of S/G solution. The effects of MR2266 and N-BNI were found to be dose-dependent. Previous research from our laboratory indicated that M80 (unpublished observations) and MR2266 (11) failed to reduce S/G intake after central administration when dissolved in an acid vehicle. Perhaps upon ICV administration, these antagonists depend upon low and stable pH conditions to remain in solution. They might precipitate out of solution on contact with cerebrospinal fluid. It is possible that the use of DMSO as a vehicle allows these antagonists to penetrate to anatomical locations that influence drinking, whereas an acidified water vehicle does not. Importantly, in Experiments 1 and 2, the ICV administration of DMSO alone (vehicle) failed to suppress drinking in comparison to saline controls.

Evidence suggests that MR2266 potently antagonizes both κ and μ receptor ligands (32), but is relatively ineffective at δ receptors (31). It is possible that MR2266 suppressed drinking by blockade of both κ and μ receptors. However, given the selectivity of N-BNI for κ receptors, it is unlikely that the reduction in intake produced by this antagonist involved μ or δ receptors. However, some caution regarding the selectivity of N-BNI must be exercised as its selective κ antagonist profile was not apparent in antinociceptive tests using mice and rats [1–3 mg/kg, subcutaneously, (1)]. Also, in the acetylcholine-induced mouse abdominal constriction test, N-BNI (30 min pretreatment, 3 mg/kg, subcutaneously and 30 μg, ICV) failed to antagonize the analgesia produced by ICV U50488H (1). However, these negative findings might be due to N-BNI's unusually long latency to effect (e.g., 2 hr after

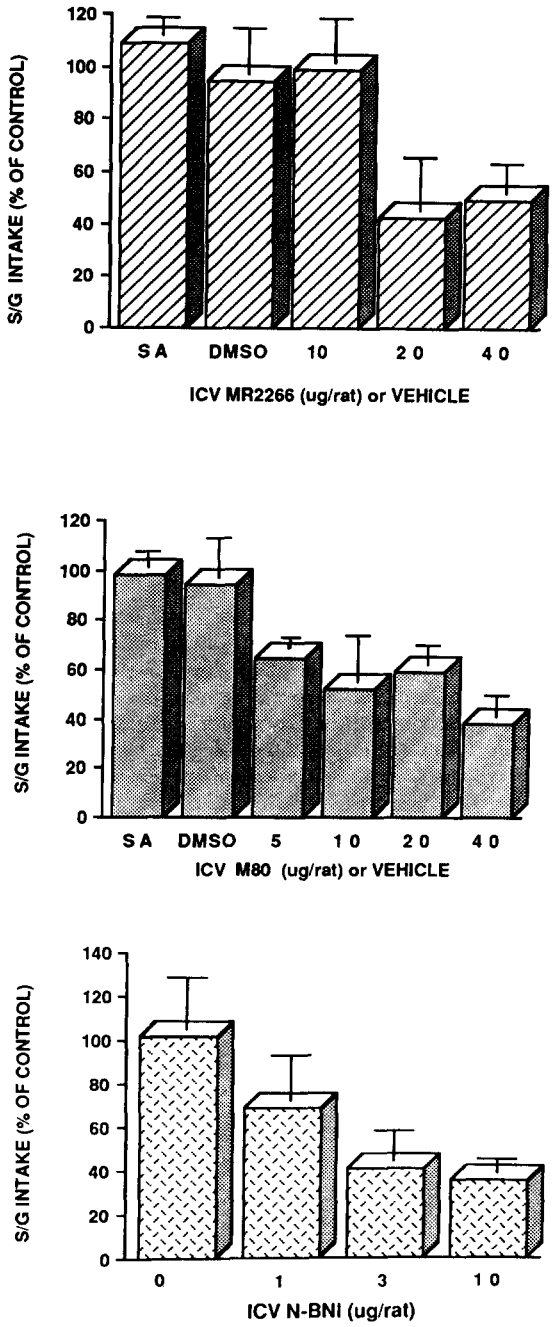

FIG. 1. (Top panel) depicts the effect of four ICV administered doses of MR2266 (0, 10, 20, 40 μg/rat, n=4–9 per group) and of five ICV administered doses of 16-methyl cyprenorphine [(M80); 0, 5, 10, 20 and 40 μg/rat, n=6–10 per group] (middle panel), and an independent saline control during a session wherein rats were allowed to consume S/G for 0.5 hr. Also depicted (bottom panel) is the effect of four ICV administered doses of nor-binaltorphimine (N-BNI, 0, 1, 3 and 10 μg/rat, n=7 per group) for rats allowed to consume S/G for 0.5 hr drinking bout. Each opioid antagonist was dissolved in DMSO which also served as vehicle. All drinking data are presented as intake of S/G transformed to percent of control (Predrug Day intake).

subcutaneous administration). For ICV administration in mice, the onset time of action for N-BNI has been reported to be about 20 min with a peak effect at 60 min (32). We found that using DMSO as vehicle, a 10-min pretreatment time was all that was necessary for N-BNI to suppress drinking in rats.

Behavioral evidence for the in vivo selectivity of M80 in the rat is suggested by the findings of Fanselow, Calcagnetti and Helmstetter (12). When dissolved in an acid vehicle, M80 (5 μg, ICV) selectively reversed DPDPE, but not DAGO-induced analgesia. Since M80 in the present study was dissolved in DMSO instead of acidified water, direct comparison is inappropriate since potency may vary depending upon the vehicle selected. Although possible, we have no evidence to suggest that δ receptors were selectively blocked by M80 at the doses tested. Since we found an equivalent reduction of S/G intake using an 8 times higher dose of M80, it is likely that blockade of μ receptors contributed to the suppression of drinking. However, given the pharmacological profile of M80, it is very unlikely that blockade of κ receptors contributed to the suppression of drinking.

Since there is little parametric data in rats using these compounds in vivo, the issue of nonspecific suppression of behavior remains. It has been reported that a high dose of N-BNI (40 μg, ICV) can result in nonspecific behavioral effects in rats (33). However, at no time during the drinking bouts did we observe sedation or locomotor dysfunction in our subjects with any antagonist at the doses tested. With N-BNI-treated subjects, a Postdrug Day drinking measure was taken to ascertain if some aversive conditioning had occurred that would be manifest as a reduction of S/G intake. Analysis of Postdrug Day intake revealed no differences between groups and the overall mean intake of S/G was slightly higher than Predrug Day. Immediately after ICV injection of the highest dose of M80 tested, we notice that our subjects appeared to be hyperactive. These observations remain to be quantified.

In conclusion, when dissolved in DMSO as vehicle and centrally administered, MR2266, N-BNI and M80 suppressed S/G drinking. Given the pharmacological profiles of these antagonists, our results suggest that blockade of κ and/or δ/μ receptors results in suppression of S/G drinking.

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