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Kappa opioid receptor agonists, respiratory function, rats
The Kappa Opioid Agonist U-50,488H Antagonizes Respiratory Effects of Mu Opioid Receptor Agonists in Conscious Rats

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ABSTRACT

The interactive effects of mu and kappa opioid receptor agonists on respiratory function were investigated following their i.c.v. injection into conscious rats. The highly selective mu receptor agonist [δ-Ala², N-Methyl-Phe⁶, Gly-ol] enkephalin (DAMGO; 1.2-10 nmol) and the relatively selective mu agonist morphine (20 and 30 nmol) significantly decreased arterial pH and PO₄ and increased arterial PCO₂ and blood pressure. Morphine and a low dose of DAMGO (1.2 nmol) also significantly elevated respiratory rate. Heart rate was decreased by DAMGO and, depending upon dose, was either decreased (20 nmol) or increased (30 nmol) by morphine. The selective kappa opioid agonist U-50,488H (200 nmol i.c.v.), which by itself had no significant effect on either respiration or cardiovascular function, dose-dependently antagonized the acidic, hypoxicemic and hypercapnic effects of both DAMGO (2.5 nmol) and morphine (30 nmol). Furthermore, these mu antagonist properties of U-50,488H were blocked completely after pretreatment with 25 nmol of the highly selective kappa opioid antagonist nor-binaltorphimine. These results indicate that the antagonism of mu opioid respiratory depressant effects by U-50,488H is kappa opioid receptor mediated.

Narcotic opioid analgesics such as morphine are of tremendous therapeutic importance for the clinical management of pain. Unfortunately, these desired pharmacological effects are generally compromised by a number of associated liabilities, including potentially life-threatening cardiorespiratory depression (for review, see Yeadon and Kitchen, 1989; Shook et al., 1990). Consequently, novel opioid or nonopioid analgesics free of these complicating side-effects have been continuously sought.

Following the recognition of multiple types of opioid receptors (e.g., mu, delta and kappa) and the associated development of relatively selective opioid receptor ligands, a large number of investigations have been conducted to identify the relative involvement of each receptor class in the diverse pharmacology of opioids in vivo, and to potentially dissociate and/or correlate distinct opioid effects (such as analgesia and respiratory depression) through the use of ligands targeted at specific receptor types (for review, see Martin, 1983). Work with highly selective opioid ligands has also revealed distinct patterns of intriguing interactions among mu, delta and kappa opioid receptors, based upon the net in vivo responses recorded after administration of combinations of highly selective opioid agonists and antagonists. For example, delta opioid agonists appear to significantly potentiate or enhance antinociceptive (Vaught and Takemori, 1979; Porreca et al., 1987; Heyman et al., 1989; Jiang et al., 1990) and autonomic (Sheldon et al., 1989) effects of mu agonists. In addition, recent studies revealed that kappa receptor agonists can selectively antagonize the effects of mu agonists on bladder motility (Porreca and Tortella, 1987; Sheldon et al., 1987, 1989), seizure threshold (Tortella and Holaday, 1986; Porreca and Tortella, 1987) and nociceptive responsiveness (Ramarao et al., 1988) in rats. Moreover, characterizations of a variety of mu opioid ligands in several of these latter studies further revealed that mu opioid receptor agonists could be divided or grouped into two distinct subtypes based upon their manner of interactions with kappa receptor agonists.

Despite an intriguing preliminary report from Wood and coworkers (1982), interactive effects of selective mu and kappa opioid receptor agonists on central cardiorespiratory regulation have not yet been clearly and quantitatively established. Moreover, the impact of highly selective opioid ligands on respiratory status is somewhat ambiguous due to the limited selectivities of ligands used in earlier studies (Yeadon and Kitchen, 1989; Shook et al., 1990). Therefore, the objective of the present study was to characterize cardiorespiratory responses to i.c.v. injec-

ABBREVIATIONS: DAMGO, [δ-Ala², N-Methyl-Phe⁶, Gly-ol] enkephalin; nor-BNI, nor-binaltorphimine; EKC, ethylketocyclazocine.
tions of mu and kappa opioid ligands and to evaluate potential interactions between these two receptor systems on brain regulation of respiratory function in conscious unrestrained rats.

Methods

Chemicals. Morphine sulfate and U-50,488H were kindly donated by Dr. John D. Minna (National Cancer Institute, Bethesda, MD) and the Upjohn Company (Kalamazoo, MI), respectively. DAMGO (Peninsula Laboratories, Inc., Belmont, CA) and nor-BNI (Research Biochemicals Inc., Natick, MA) were purchased. Drugs were dissolved in saline in a fixed volume such that each rat received 5 μl of drug solution per injection. Saline alone in the same volume was injected as a vehicle.

Animal preparation. Male Sprague-Dawley rats (350-400 g; Zivic Miller, Pittsburgh, PA) were housed in a room with controlled temperature (24 °C, humidity 55%) and light-dark cycles (lights on from 6:00 A.M.-6:00 P.M.) for at least 2 weeks before experiments. Food and water were provided ad libitum.

On the day preceding experiments, rats were anesthetized with ketamine hydrochloride (70 mg/kg i.m.) and xylazine (6 mg/kg i.m.) for cannulation of the right lateral cerebral ventricle, the tail artery, and the external jugular vein. For i.c.v. drug injections, a 27-gauge needle attached to 5 cm of polyethylene tubing (PE-20) was implanted into the right lateral cerebral ventricle and fixed to the skull with dental cement. Coordinates for implantation into the lateral ventricle were 2 mm caudal to the bregma, 2 mm lateral to the mid sagittal suture and 4 mm deep from the skull surface. After exposure by blunt dissection, both the tail artery and the external jugular vein were cannulated with PE-50 catheters. The tail artery catheter was used to monitor heart rate and mean arterial blood pressure and to withdraw arterial blood samples for arterial blood gas analysis. The jugular cannula was advanced into the superior vena cava to monitor respiratory rate and changes in intrathoracic pressure. These cannulae were directed s.e.c. to emerge at the back of the neck and extend from the cage through a protective wire spring. Arterial and venous cannulae were kept patent with twice daily 0.5-ml injections of a solution of heparin sodium (100 U/ml).

Assessment of cardiorespiratory function. The jugular catheter was connected to a microtransducer (Physiological Pressure Transducer, Narco Bio-systems, Houston, TX) for the monitoring of intrathoracic pressure which is synchronized with ventilatory movement of the chest. Intrathoracic pressure changes were recorded on a multichannel recorder (Linear recorder Mark VIII/B/101, Western Graphic Inc., Irvine, CA) and were manually counted in order to obtain respiratory rates. The tail artery catheter was connected to another microtransducer which interfaced with a Cardiorespiratory Analyzer (Burco Electronics, Sharon, CT) and a personal computer for measurement of heart rates and mean arterial pressures.

Arterial blood samples (300 μl) were collected from the tail artery catheter into heparinized syringes. The pH, PO2, (PaO2) and PCO2, (PaCO2) of arterial blood samples were analyzed by a blood gas analyzer (System 1306, pH/?O2/PCO2 gas analyzer, Instrumentation Laboratory, Lexington, MA). To minimize possible cardiovascular changes induced by the repeated blood withdrawal, immediately after their collection blood samples were replaced with an equal volume of a 5% dextran solution injected through the jugular catheter.

Experimental protocol. Rats remained individually housed in their home cages throughout experiments. After 2 hr of acclimation to surroundings and stable breathing, baseline respiratory rates, heart rates and mean arterial pressures were measured and 300 μl of arterial blood were collected for arterial blood gas analysis. Immediately after these measurements, drugs were administered. All compounds were dissolved in saline and were injected i.c.v. in a 5-μl volume followed by a 3-μl cannula flush. Saline in the same volume was injected in control rats. The time-course characteristics of the responses to each drug dose or drug combination were monitored and established in individual rats.

Results

Cardiorespiratory effects of DAMGO agonists. The effects of DAMGO on cardiovascular and respiratory function are shown in figure 1, A-F. The i.c.v. injection of 0.6-10 nmol of DAMGO produced the dose-dependent development of acidosis (fig. 1A), hypoxemia (fig. 1B) and hypercapnia (fig. 1C). In addition, the 1.2-nmol dose of DAMGO induced a transient elevation in respiratory rate through a 20-min postinjection (interval). DAMGO significantly increased mean arterial pressure (fig. 1E; 1.2, 2.5 and 10 nmol) and decreased heart rate (fig. 1F; 2.5 and 10 nmol). All responses occurred within 10 min of DAMGO injection and persisted through at least a 30-min postinjection.

The respiratory and cardiovascular responses to morphine were qualitatively quite similar to those seen with DAMGO (fig. 2, A-F). In addition to significantly lowering blood pH (fig. 2A) and PaO2 (fig. 2B) and increasing blood PaCO2 (fig. 2C), 20- and 30-nmol doses of morphine significantly elevated respiratory rate (fig. 2D). Mean arterial pressure was increased

![Fig. 1. A-F. effects of i.c.v. DAMGO on cardiorespiratory parameters in conscious rats. Data are presented as means ± S.E.M. for dose-treatment groups of six to nine rats. O, vehicle; □, DAMGO (0.6 nmol); ■, DAMGO (1.2 nmol); ○, DAMGO (2.5 nmol); □, DAMGO (10 nmol). *P < .05; **P < .01 when compared to vehicle-injected rats.](image-url)
and heart rate was decreased by 30 nmol of morphine, whereas paradoxically rats treated with 20 nmol of morphine instead had pressor responses that were accompanied by a delayed tachycardia (fig. 2F). All responses to i.c.v. morphine were slower in onset and were more persistent than were seen with i.c.v. DAMGO and generally lasted through at least a 120-min postinjection interval.

**Kappa ligand interactions with mu agonist effects on respiration.** As seen in table 1, respiratory and cardiovascular parameters were unaffected by either the kappa opioid agonist U-50,488H (20 and 200 nmol i.c.v.) or the kappa opioid antagonist nor-BNI (25 nmol i.c.v.). Although without measurable effects themselves, pretreatment with these ligands did significantly influence subsequent responses to both DAMGO and morphine. The interaction of U-50,488H with the effects of DAMGO on respiratory function is shown in figure 3. In the central rats pretreated with saline vehicle, as was seen in the initial experiments (figs. 1A and 2), the 2.5-nmol i.c.v. dose of DAMGO induced acidosis (fig. 1A), hypoxemia (fig. 1B) and hypercapniaemia (fig. 1C), without significantly altering respiratory rate (results not shown). In contrast, in rats pretreated with U-50,488H (200 nmol i.c.v.) the subsequent effects of DAMGO on arterial pH, PaO₂, and PaCO₂ were substantially eliminated (fig. 3). Although occurring over a more prolonged time course, the effect of U-50,488H on morphine-induced respiratory depression was quite similar to that seen with DAMGO. Specifically, as shown in figures 4A through 4C, 200 nmol of U-50,488H significantly antagonized morphine-induced acidosis, hypercapniaemia and hypoxemia. As was seen in the initial dose-response experiments, i.c.v. morphine also significantly increased respiratory rate; however, in contrast to the other respiratory parameters, U-50,488H did not inhibit this response to morphine (results not shown). These modulatory effects of U-50,488H appeared to be dose-dependent in that i.c.v. pretreatment with 20 or 63 nmol of U-50,488H did not consistently alter subsequent responses to either DAMGO or morphine (results not shown).

The kappa opioid antagonist nor-BNI (25 nmol i.c.v.) did not by itself alter subsequent respiratory responses to DAMGO, but it did substantially eliminate the modulatory effects of U-50,488H on DAMGO-induced respiratory depression (fig. 5). Specifically, relative to the rats injected initially with saline vehicle, rats administered nor-BNI (25 nmol i.c.v.) 15 min before injection of U-50,488H (200 nmol i.c.v.) had restored responses to a subsequent injection of DAMGO (2.5 nmol i.c.v.). Thus, the kappa opioid antagonist nor-BNI blocked the inhibitory influence of the kappa opioid agonist U-50,488H on the respiratory depressant actions of the mu agonist DAMGO.

**Discussion**

The present results confirm that, through actions within the central nervous system, the highly mu-selective opioid agonist DAMGO depresses respiration and increases mean arterial pressure in a fashion similar to morphine, albeit with slightly different time courses. In contrast, by themselves the kappa-selective ligands U-50,488H and nor-BNI failed to significantly alter any of the cardiorespiratory parameters monitored after i.c.v. drug injection. These results support the conclusions drawn from a number of earlier studies in which mu (but not kappa) opioid receptors were consistently identified as being primarily responsible for the central mediation of the respiratory depressant effects of morphine and other opioid analgesics (Yeadon and Kitchen, 1989; Shook et al., 1989). Although there are also some indications that delta opioid receptors might contribute to a lesser degree to the respiratory depressant effects of opioid analgesics, these results have been less clear-cut due in part to variable outcomes, incomplete respiratory assessments and limited receptor ligand selectivities in a number of these studies (Holaday, 1982; Pazos and Florez, 1983, 1984). Regardless of these previous arguments concerning relatively greater or lesser roles of mu, delta and kappa receptors in the depression of respiration, it appears from the present and other collective results that a prominent (if not exclusive) role for mu opioid receptors can be postulated and, that along with their well-described antinociceptive effects, mu opioid agonists also clearly appear to be efficacious respiratory depressants in rats. Furthermore, the occasional disparities seen between drug effects on blood gases and respiratory rates underscore previously stated concerns regarding the accuracy and utility of the latter endpoint as a measure of respiratory status (Yeadon and Kitchen, 1989).

Several laboratories have provided evidence to suggest that the respiratory depressant effects of morphine and related narcotic analgesics are not mediated by the same class of receptors that is responsible for the antinociceptive actions of these drugs (McGilliard and Takemori, 1978; Ward and Takemori, 1983; Ling et al., 1983; Wood et al., 1982). For example, naloxonazine has been shown to selectively block the analgesic but not the respiratory depressant actions of morphine, prompt-
TABLE 1
Effect of U-50,488H and nor-BNI on cardiorespiratory function after i.c.v. injection in conscious rats
Values are expressed as means ± S.E.M. for each treatment group. NR, not recorded

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Time</th>
<th>Treatment</th>
<th>U-50,488H</th>
<th>nor-BNI</th>
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<tr>
<td></td>
<td></td>
<td>Treatment</td>
<td>Vehicle</td>
<td>20 nmol</td>
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<td></td>
<td></td>
<td></td>
<td>(n = 8)</td>
<td>(n = 8)</td>
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<tr>
<td>Arterial pH</td>
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<td>Pretreatment</td>
<td>7.475 ± 0.015</td>
<td>7.470 ± 0.010</td>
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<tr>
<td></td>
<td></td>
<td>30 min</td>
<td>7.477 ± 0.018</td>
<td>7.481 ± 0.014</td>
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<tr>
<td></td>
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<td>60 min</td>
<td>7.490 ± 0.014</td>
<td>7.466 ± 0.019</td>
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<tr>
<td>PaO₂</td>
<td></td>
<td>Pretreatment</td>
<td>94 ± 4</td>
<td>88 ± 1</td>
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<td>30 min</td>
<td>95 ± 6</td>
<td>92 ± 3</td>
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<td></td>
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<td>60 min</td>
<td>97 ± 7</td>
<td>89 ± 3</td>
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<tr>
<td>PaCO₂</td>
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<td>Pretreatment</td>
<td>32 ± 2</td>
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<tr>
<td></td>
<td></td>
<td>30 min</td>
<td>34 ± 2</td>
<td>31 ± 1</td>
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<td></td>
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<td>60 min</td>
<td>31 ± 1</td>
<td>31 ± 1</td>
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<tr>
<td>Respiratory rate (breaths)</td>
<td></td>
<td>Pretreatment</td>
<td>112 ± 14</td>
<td>104 ± 7</td>
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<tr>
<td></td>
<td></td>
<td>30 min</td>
<td>107 ± 10</td>
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<td></td>
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<td>60 min</td>
<td>109 ± 9</td>
<td>111 ± 8</td>
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<td>Heart rate (beats)</td>
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<td>Pretreatment</td>
<td>377 ± 19</td>
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<td>30 min</td>
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<td></td>
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<td>60 min</td>
<td>404 ± 19</td>
<td>379 ± 15</td>
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<tr>
<td>Mean arterial pressure</td>
<td></td>
<td>Pretreatment</td>
<td>103 ± 4</td>
<td>104 ± 3</td>
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<tr>
<td></td>
<td></td>
<td>30 min</td>
<td>107 ± 4</td>
<td>104 ± 3</td>
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<tr>
<td></td>
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<td>60 min</td>
<td>99 ± 4</td>
<td>102 ± 3</td>
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<tr>
<td>a) Mm of mercury</td>
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<tr>
<td>b) Breaths per minute</td>
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<tr>
<td>c) Beats per minute</td>
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The interpretation that naloxonazine-insensitive mu-2 receptors mediate respiratory depression whereas naloxonazine-sensitive mu-1 receptors mediate antinociceptive responses to morphine and related opioid analogues (Lang et al., 1983, 1985). In a closely related study, Wood et al. (1982) used lethality as a measure of respiratory depression and showed conversely that the kappa agonists EKC and MR 2034 selectively antagonized morphine-induced respiratory depression (as well as several other putatively mu-2-mediated neurochemical effects), without disrupting analgesia. These results preliminarily suggested that kappa opioid agonists might pharmacologically discriminate among putative mu isoreceptors and might thereby provide an approach to therapeutically dissociate mu receptor-mediated analgesia from respiratory depression side effects.

The blood gas alterations measured in the present study obviously reinforce aspects of the earlier findings of Wood et al. (1982) by clearly revealing that the more highly selective kappa opioid agonist U-50,488H also significantly antagonizes the respiratory depression resulting from i.c.v. administration of either morphine or DAMGO. However, because this interactive effect has by now been shown to also extend to a number of other in vivo opioid responses (including antinociception), the potential therapeutic utility of kappa-mu opioid interactions, with regard to the selective elimination of respiratory depression, is less immediately obvious. Specifically, kappa agonists such as U-50,488H have been consistently recognized to act as mu antagonists in a variety of in vivo preparations, including rat bladder motility (Sheldon et al., 1987, 1989), antinociception (Ramarao et al., 1988; Bhargava et al., 1989) and seizure threshold models (Tortella and Holaday, 1986; Porreca and Tortella, 1987).

In these more recent studies, mu opioid agonists have been categorized on the basis of their sensitivity to this antagonism. For example, in the bladder motility preparation, the kappa opioid agonists U-50,488H, dynorphin A, EKC and tifluadom consistently antagonized responses to i.c.v. administration of the mu agonists morphine and normorphine, whereas responses to several other mu agonists such as DAMGO, PL017, phenazocine or meperidine were consistently unaffected by these kappa compounds (Sheldon et al., 1987, 1989). Similarly, Porreca and Tortella (1987) showed that U-50,488H, in doses lacking agonist effects, antagonized etorphine but not DAMGO in both bladder motility and flurothyl seizure threshold models.

The cellular mechanisms mediating this differential antagonism are presently unclear. As discussed by these investigators, variations in the relative receptor affinities (and potencies) of the different mu agonists used in these studies might conceivably render them differentially sensitive to antagonism by kappa agonists. Alternatively, subtypes of mu opioid receptors within the central nervous system might be proposed to explain these patterns. Because kappa agonists have been postulated to act as antagonists at mu-2 opioid receptors (Wood et al., 1982), one might suspect that morphine and normorphine predominantly exert their central effects on the bladder through actions at mu-2 receptors, whereas DAMGO, PL017 and phenazocine produce similar effects through actions at a different mu receptor site, such as the putative mu-1 receptor. However, as pointed out by Sheldon et al. (1987), inasmuch as bladder effects of i.c.v. morphine, DAMGO and D-Pen²-D-Pen⁵-ENK can all be antagonized by naloxonazine pretreatment, it is unlikely that the conventional mu-1 and mu-2 isoreceptor definition applies to the mu receptor distinctions made with kappa agonists in this particular in vivo preparation. Moreover, Pasternak and colleagues (Pasternak and Wood, 1986) have distinguished mu isoreceptors in vivo largely on the basis of differing naloxonazine-sensitive and-insensitive pharmacological responses, whereas these latter postulated isoreceptor distinctions are seen within groups of ligands producing identical shared responses. Regardless of the underlying mechanism, differential kappa sensitivity was not observed in the present study with respiratory depression as a pharmacological endpoint.

The antagonistic effects of U-50,488H upon both morphine and DAMGO-induced respiratory depression apparently in-
Fig. 3. A-C. effects of U-50,488H on DAMGO-induced alterations in respiratory function. Six rats were pretreated i.c.v. with saline vehicle and nine rats received pretreatment (Pre) with 200 nmol of U-50,488H 15 min before i.c.v. injection of 2.5 nmol of DAMGO. U-50,488H attenuated the acidosis, hypoxemia and hypercapnia induced by DAMGO. Data are expressed as means ± S.E.M. *P < .05; **P < .01 in comparison with base-line values. #P < .05; ##P < .01 in comparison with DAMGO-injected rats pretreated with saline vehicle. Lower doses of U-50,488H (20 and 63 nmol) failed to alter subsequent responses to 2.5 nmol of DAMGO (results not shown).

Fig. 4. A-C. effects of U-50,488H on morphine-induced alterations in respiratory function. Eleven rats were pretreated (Pre) i.c.v. with saline vehicle and nine rats received i.c.v. Pre with 200 nmol of U-50,488H 15 min before i.c.v. injection of 30 nmol of morphine. U-50,488H attenuated the acidosis, hypoxemia and hypercapnia induced by morphine between 30- and 60-min postinjection. Data are expressed as means ± S.E.M. *P < .05 when compared to base-line data. #P < .05. ##P < .01 when compared to morphine-injected rats Pre with saline vehicle. Lower doses of U-50,488H (20 and 63 nmol) failed to alter subsequent responses to 30 nmol of morphine (results not shown).

Engulfed interactions with kappa opioid receptors, because in both cases they were blocked by pretreatment with the kappa antagonist nor-BNI. The antagonism of the respiratory depressant effects of DAMGO argues that the previously described distinctions of mu opioid agonists based upon their sensitivity to U-50,488H are relative and not absolute. It is possible that, if they lacked overt agonist activity in these other preparations, higher doses of U-50,488H and other kappa agonists might have antagonized the unresponsive mu effects of DAMGO and other ligands in earlier studies, particularly when one considers that, with a dose of U-50,488H comparable to that used in the earlier studies, we failed to see antagonism of either morphine- or DAMGO-induced respiratory depression. In fact, Porreca and co-workers have also noted that to some degree the interactive patterns they describe are not absolute in the sense that, whereas several kappa opioid agonists could block morphine and normorphine bladder motility effects, only U-50,488H could block the identical effects of etorphine and sufentanil (Sheldon et al., 1987).

Because the antagonism of the respiratory depressant effects of these mu opioid agonists by U-50,488H appears to be kappa.
receptor-mediated actions at these two receptor types seem to be somehow interactively coupled through an as yet unidentified convergence in opioid receptor effector mechanisms. The requirement for higher doses of U-50,488H for mu antagonism in the present study (200 nmol rather than the approximately 20-nmol dose of U-50,488H used in the aforementioned studies) was paralleled by similar requirements for greater doses of morphine and DAMGO to elicit respiratory depressant responses and might reflect an overall need for greater total receptor occupancy by morphine and other mu agonists to produce an appreciable depression of respiration. If so, it can be further reasoned that, through a kappa-mu receptor interactive coupling mechanism, a greater concentration of kappa agonist was required to antagonize the greater administered doses of morphine or DAMGO that were presumably occupying larger numbers of "kappa-sensitive" mu opioid receptors.

The utility of using antagonistic kappa-mu opioid interactions as a therapeutic approach to dissociate analgesic and respiratory depressant actions of opioid analgesics obviously hinges on the selective impact of these interactions on respiration and not analgesia. Kappa opioid agonists, in addition to having antinociceptive actions by themselves (Porreca et al., 1987), have also been shown to differentially influence mu opioid-induced antinociception in morphine-naive and morphine-tolerant rats (Tulunay et al., 1981; Ramarao et al., 1988; Bhargava et al., 1989), with antagonism seen in the former and potentiation seen in the latter. A similar loss of the antagonistic activity of kappa opioids after chronic morphine treatment has been described in a squirrel monkey shock titration procedure by Craft and Dykstra (1992). Whether kappa opioid antagonism of morphine’s respiratory depressive effects remains intact in morphine-tolerant rats, or is similarly differentially influenced, is presently uncertain. Clearly, future parallel assessments of the impact of kappa agonists on respiratory depressant actions of morphine-related analogues in tolerant animals will serve to distinguish the viability of this pharmacological strategy for patients receiving chronic opioid therapy.

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