Delta-Opioid Ligands Reverse Alfentanil-Induced Respiratory Depression but Not Antinociception

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ABSTRACT

Evidence suggests both opioid mu and delta receptors may participate in the regulation of respiration at different central nervous system sites. In the past, the overlapping receptor specificity of various opioid drugs has made it difficult to dissect the receptor subtype-specific activities involved in respiratory regulation. The new family of delta receptor selective agents such as cyclic[β-Pen^2,⁶][Leu⁵]enkephalin, deltorphin II and H-Tyr-Tic(ϕ)[CH2-NH]Phe-Phe-OH have now made it feasible to more clearly define the role of delta receptors in respiratory control. In a series of experiments we observed that systemic infusion of rats with the highly mu receptor-specific opioid alfentanil induced antinociception and hypercapnia, and both of these effects were antagonized by the mu antagonist β-Fmoc-Tyr-Orn-Thr-Pen-Thr-NH₂. However, peripheral administration of the delta receptor antagonist naltrindole reverses the hypercapnia but not the antinociceptive activity of alfentanil. This differential effect of naltrindole on antinociception and hypercapnia could also be produced with the delta agonist (+)-4-((α-R)-(2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide. We propose that in this experimental respiratory control model, the delta agonists naltrindole and H-Tyr-Tic(ϕ)[CH₂-NH]Phe-Phe-OH behave like delta agonists with low but sufficient intrinsic activities to reverse alfentanil-induced hypercapnia in rats. The results suggest that a function of the delta receptor is to modulate or counteract the respiratory depression induced by the mu receptor.

Respiratory depression is the most serious side effect associated with the use of opioid analgesics (Reisine and Pasternak, 1996). All opioids in clinical use today produce respiratory depression at therapeutic doses. The antinociceptive effect of depression is generally thought to be mediated by the mu receptor subtype. Early experimental evidence from animals seems to point to the possibility that both mu and delta receptors are linked to the respiratory action of opioids (McGilliard and Takemori, 1978; Ward and Takemori, 1983; Pazos and Florez, 1984; Yeadon and Kitchen, 1990). A direct approach by micro-application of mu or delta drugs into sensitive areas of the central nervous system confirmed the respiratory depressant effect of the opioids. The i.c.v. administration of beta-endorphin, met-enkephalin, [β-Ala^2, MePhe^4, Met(O)³-o]-enkephalin, [β-Ala^2, β-Leu^³]-enkephalin and dermorphin produced respiratory depression (Holaday, 1982; Haddad et al., 1982; Pazos and Florez, 1984; Feuerstein and Faden, 1983). Respiratory depression was believed to be associated with the inhibition of spontaneous discharge activity of neurons in the rostroventral surface of the pons, which was proposed to regulate basic rhythmicity that controls respiratory frequency. Such inhibition was demonstrated for morphine, met-enkephalin and [β-Ser², Leu²]-enkephalin-Thr suggesting that both mu and delta receptors might be involved in the respiratory depression (Hurle et al., 1985; Morin-Surun et al., 1984). The nucleus tractus solitarius and the nucleus ambiguus are also known to mediate opioid-induced respiratory depression (Hassen et al., 1982, 1984). However, the neural interactions among these nuclei and other brain-stem bulbo-pontine respiratory centers and the complex respiratory regulation involving opioid recep-
tors are still not fully understood (see reviews Mueller et al., 1982; Shook et al., 1990).

In addition, opioids might have a stimulatory effect on respiration. Microinjection of low doses of [d-Ala², d-Leu⁵]enkephalin, [d-Ala², MePhe⁴, Met(O)⁵]-enkephalin or morphine into selective areas of the brain stem of anesthetized rats increased respiratory frequency but reduced tidal volume (Hassen et al., 1982; Hurle et al., 1985). Morphine induced an increase of instantaneous minute ventilation when injected intracisternally into dogs (Haddad et al., 1984; Schaeffer and Haddad, 1985). At lower doses mu 1 agonists demorphin and analog Tyr-d-Arg²-Phe-sarcosine stimulate respiration (Paakkar et al., 1990, 1993). Szeto and colleagues also found stimulatory effects of opioids on respiration; the fetal breathing movement of lamb was stimulated by lower doses of DPDPE and deltorphin I (Cheng et al., 1992, 1993a, b). The involvement of the kappa receptor in respiratory control seems to be minimal (Pfeiffer et al., 1983; Butelman et al., 1993).

The literature summarized above seems to suggest that both mu and delta receptors are involved in the respiratory depressant effect of opioids, but the mechanism has yet to be delineated. One of the difficulties was the fact that opioid compounds used in the past have relatively poor receptor selectivity. [d-Ala², d-Leu⁵]enkephalin exhibits almost equal affinity for mu and delta receptors in both receptor binding and isolated tissue studies (Mosberg et al., 1983). The newer delta-specific agent DPDPE has a delta-selectivity of about 1000-fold. The antagonist NTI has a delta receptor selectivity of about 100-fold (Portoghese, 1991). TIPP(ψ) is the most selective delta antagonist; its selectivity for delta receptors is 10,000-fold over other receptors (Schiller et al., 1993). The poor receptor selectivity of delta drugs used in the past studies may have contributed to the disparate results concerning the delta receptor’s role in respiration. Other factors such as route of administration, animal species used and the pharmacodynamics of the drugs studied are also important variables in animal studies. The lack of delta-specific drugs that can penetrate the blood-brain barrier also hinders the research in this regard.

The first nonpeptide delta selective agonist, BW373U86 (Chang et al., 1993) is a potent analgesic that produces antinociceptive effect in mouse tail-flick and writhing tests when administered intrathecally (Wild et al., 1993). This action is clearly mediated through the delta receptor, because the effect is abolished by delta antagonists NTI and ICI174,864. BW373U86 makes it possible to delineate analgesia and respiratory depression mediated by peripherally administered delta-specific drugs. This compound could be the prototype of potentially useful nonpeptide delta agonists. The highly selective delta agonist Del II (Erspermer et al., 1989) is also a useful tool for studies of delta receptor-specific effects. Del II was reported to possess ≥10⁵ selectivity at delta sites over mu sites (mouse vas deferens compared to guinea pig ileum; Erspermer et al., 1989). The synthesis of the delta receptor selective antagonists NTI and TIPP(ψ) (Portoghese et al., 1988, 1991; Schiller et al., 1993) have now made the study of in vivo delta receptor activities feasible.

We report the effects of highly selective delta receptor ligands on systemic alfentanil-induced respiratory depression in conscious rats. The pharmacological characteristics of delta ligands suggest that delta receptors play a significant role in respiratory regulation.

**Materials and Methods**

**Materials.** DPDPE and Del II were purchased from Peninsula Laboratories, Inc. (Belmont, CA). NTI, NTB, 7-benzylidenenaltrexone were synthesized according to the published method of Portoghese et al. (1991). TIPP(ψ) was a gift from Dr. P.W. Schiller (Clinical Research Institute of Montreal, Quebec, Canada). Alfentanil was purchased from Janssen Pharmaceuticals (Titusville, NJ). The active isomer (+)-BW373U86 was synthesized by Bishop and McNutt (1995). All other chemicals were reagent grade and purchased from Sigma Chemical Co. (St. Louis, MO). Buffers and solutions were prepared with deionized-distilled water.

**Experimental procedures.** Male Sprague Dawley rats (275–325 g) were used. Rats were anesthetized with 3% halothane in a mixture of 30% O₂ and 70% N₂O. After the rat was anesthetized, halothane was reduced to 0.5%. The femoral artery and vein were cannulated with PE 50 tubing for drug injection and blood sampling. After surgery, the anesthetic gases were removed and the rat was allowed to rest in a plastic restrainer for 60 min to establish the baseline value of blood gas. Alfentanil or saline vehicle was infused via the venous line and blood samples were collected via the arterial line. A second venous line was also cannulated for bolus drug injection if needed.

For i.c.v. administration, rats were anesthetized with Nembutal (5 mg/kg, i.p.). A stainless steel guide cannula was stereotaxically inserted into the right lateral ventricle and fixed with instant glue (Eastman 910 adhesive, Eastman Kodak, Rochester, NY). Coordinates for the lateral ventricle are AP = −0.8 mm and L = 1.2 mm. The operation the rat was allowed to rest for 3 days with food and water ad libitum. On the day of experiment, the rat was anesthetized with anesthetic gas mixture as described above and an arterial catheter placed as described. After catheterization, the rat was placed in a plastic restrainer with a 30-g cannula (7.5 mm) inserted through the guide i.c.v. cannula. The injection cannula was connected by a polyethylene tubing to a Hamilton micro-syringe (Hamilton Company, Reno, NV). The rat was rested for 1 hr to recover from the anesthetic gases. The experiment was started with alfentanil or saline i.v. infusion. Drugs were then injected i.e.c.v. over a 30-sec period in a volume of 10 to 20 μl. Blood samples were taken and the tail-flick test performed at the indicated times.

Arterial blood was withdrawn into a syringe prewetted with heparin. The syringes were capped immediately and were kept on ice and analyzed within 10 min with a blood gas analyzer (model 1306 PH/Gas Analyzer, Inst. Lab). The blood exposed to air at the tip of syringe was expelled and the blood was mixed by gentle inversion and an aliquot of 0.1 ml was injected into the blood gas analyzer. The volume of blood taken each time was 0.3 ml which allowed multiple determinations. The pH and partial pressure of O₂ and CO₂ (pO₂ and pCO₂, mm Hg) are measured.

The antinociceptive assay was the standard tail-flick test and antinociception was expressed as MPE as described previously (Wong et al., 1992). Briefly, the tail flick test was performed with rats in a restrainer and the tail was subjected to radiant heat from a high intensity light source. The intensity of the lamp was adjusted so that all control rats have a mean latency response of approximately 4 sec. This value was used as the baseline response time. An automatic cut-off setting at 10 sec prevents unnecessary tissue damage. After drug treatment, the latency response time, in seconds, was converted and expressed as MPE (MPE = response time − baseline time/cut-off time − baseline time, expressed in percent). Responses that fell below the baseline or above the cut-off time were assigned values of 0 and 100%, respectively.

In all figures presented, each data point is the average of values from six rats. The S.E.s are indicated by error bars.

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In all figures presented, each data point is the average of values from six rats. The S.E.s are indicated by error bars.
Results

Alfentanil infusion and respiratory depression in rats. In animals, administration of alfentanil by various routes produces respiratory depression in addition to antinociception. In conscious rats under systemic i.v. infusion of alfentanil, antinociception was quickly induced. Infusion rates of 3, 6 or 9 µg/kg/min induced antinociception, as measured in MPE, that reached a steady state in 10 min (fig. 1). Infusion rates of 6 or 9 µg/kg/min achieved maximal antinociception; infusion at 3 µg/kg/min produced about 70% MPE. Termination of infusion brought the MPE down to basal level within 15 to 30 min, indicating rapid pharmacological metabolism of the drug. Arterial blood samples taken at various time points of alfentanil infusion were analyzed for pCO2, pO2 and pH. The data show that alfentanil induces a rapid rise in arterial pCO2 and concomitant drop in pO2 and pH. Infusion at 3 µg/kg/min affected pCO2 only slightly, and the MPE never reached 100%. At infusion rates of 6 or 9 µg/kg/min the MPE for antinociception reached 100% at 10 min and was sustained at a maximal level throughout the infusion period; in contrast, the pCO2 takes 30 min to reach a steady level. Because the effects of alfentanil on MPE and blood gas parameters reach a peak at 6 µg/kg/min, this infusion rate was chosen for the rest of the studies. At this dose, the maximum increase of pCO2 is about 60%, increasing from a resting value of approximately 35 to 56 mmHg. Infusion with saline vehicle showed no significant change in the blood gas parameters tested (data not shown).

Antagonism by opioid mu antagonist CTOP on alfentanil effects. It is generally accepted that both antinociception and respiratory depression induced by opioids are mediated through mu receptors. Therefore, mu antagonists should readily block the alfentanil-induced antinociception and respiratory depression effects described above (increases in pCO2 and decreases in pO2 and pH). This was tested by using the highly specific mu receptor antagonist, CTOP. CTOP reversed the alfentanil induced antinociceptive effect as well as the elevated pCO2 level in a dose-dependent manner (fig. 2). In this experiment, CTOP was delivered by i.c.v. because it is a peptide drug. Over the dose range tested, CTOP produced a similar extent of reversal of both the antinociceptive and the respiratory effects induced by alfentanil. Given the high selectivity of CTOP for mu receptors, this result suggests that alfentanil-induced respiratory depression is mediated by mu receptors. CTOP injection also reversed pO2 and pH with time courses similar to that of pCO2 (data not shown). Bolus injection of CTOP by itself did not produce antinociception nor affect blood gas parameters (data not shown).

Antagonism of alfentanil-induced hypercapnia by NTI. We found that the delta receptor antagonist NTI also reversed the alfentanil-induced pCO2 increase in rats. The effective dose by bolus i.v. route is in the range of 0.1 to 0.5 mg/kg (fig. 3). In contrast to mu antagonist CTOP, the antinociceptive effect of alfentanil was not affected by NTI even at the highest dose tested of 0.5 mg/kg (fig. 3), which was sufficient to reverse the hypercapnia almost to control level. In fact, the lowest dose of NTI that affected MPE was 4 mg/kg, eight times the dose that effectively antagonized the respiratory depression effect (data not shown). In addition, delta antagonists NTB and BNTX also produced similar results on blood gas parameters at doses of 0.2 and 0.5 mg/kg,

Fig. 1. Time course of changes in MPE, pCO2, pO2 and pH induced by alfentanil. Rats with indwelling catheter were infused with alfentanil at 3, 6 or 9 µg/kg/min via femoral artery as described in "Materials and Methods." The doses of each compound are indicated. At the time points indicated, the tail-flick test was performed, and a blood sample was taken and analyzed by blood gas analyzer.
respectively (fig. 4). At these doses no effect on antinociception was observed with these drugs (data not shown). These antagonists alone did not produce antinociception or changes in blood gas parameters.

**Delta agonist (+)BW373U86** also reversed the hypercapnia effect of alfentanil. (+)BW373U86 is a new synthetic nonpeptide delta agonist with unique antinociceptive properties (Chang et al., 1993). In vitro tissue studies showed that the drug has a good selectivity for delta receptors (700x). We discovered that (+)BW373U86, as with the antagonist NTI described above, also has a potent effect in reversing the respiratory depressant activity of alfentanil. At doses of 0.1, 0.2 and 0.5 mg/kg, bolus i.v. injection of (+)BW373U86 rapidly reversed the alfentanil-induced pCO₂ increase without affecting the antinociceptive activity of alfentanil (fig. 5). (+)BW373U86 also abrogates the changes of pO₂ and pH produced by alfentanil infusion. The reversal of respiratory depression was nearly complete at the dose of 0.5 mg/kg. At a higher alfentanil infusion rate of 9 μg/min/kg, the pCO₂ increase can also be reversed by increasing (+)BW373U86 to 1 mg/kg (data not shown). The reversal effect of (+)BW373U86 can also be demonstrated in morphine-induced respiratory depression (data not shown), suggesting that the effect of (+)BW373U86 is likely to be general against respiratory depression induced by all mu opiate drugs.

It has been previously reported that BW373U86 administered systemically or peripherally has no significant antinociceptive effect by itself in rats (Chang et al., 1993). We also found that in the absence of alfentanil infusion, i.v. injection of (+)BW373U86 alone did not produce any significant change in the antinociceptive response or pCO₂ values during a 60-min time course after bolus injection of 1 mg/kg of the drug (fig. 6).

**Opioid delta ligands produce the same effects by i.c.v. route.** To further explore the effects of other delta ligands, drugs were injected in small volumes into the lateral ventricle of rats under constant alfentanil infusion. Similar to results obtained by peripheral injection, the i.c.v. administration of microgram quantities of either delta agonists Del

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**Fig. 2.** Effects of mu antagonist CTOP on MPE and pCO₂ responses in alfentanil-infused rats. After 30 min of alfentanil infusion (6 μg/kg/min), CTOP was injected via catheter into the lateral ventricle as described in "Materials and Methods." At the time points indicated, the tail-flick test was performed, and a blood sample was taken and analyzed by blood gas analyzer.

**Fig. 3.** Effects of delta antagonist NTI on MPE and pCO₂ responses in alfentanil-infused rats. Different doses of NTI were injected via femoral artery. NTI injection was carried out 30 min after initiating alfentanil infusion (6 μg/kg/min). At the time points indicated, the tail-flick test was performed, and a blood sample was taken and analyzed by blood gas analyzer.

**Fig. 4.** Effects of delta agonists NTI, NTB and BNTX on pCO₂ response in alfentanil-infused rats. NTI, NTB or BNTX was injected via femoral artery. Injection was carried out 30 min after initiating alfentanil infusion (6 μg/kg/min). The doses of each compound are indicated. At the time points indicated, the tail-flick test was performed, and a blood sample was taken and analyzed by blood gas analyzer.
II, DPDPE, (+)BW373U86 or delta antagonists NTI and TIPP(ψ) rapidly reversed the respiratory depression induced by systemic alfentanil. At a dose of 10 μg, (+)BW373U86 decreased pCO₂ to near basal level in 15 min. Del II, DPDPE and TIPP(ψ) also produced similar effects at 5 to 20 μg (fig. 7). In all cases the MPE was not affected by i.c.v. injection of these drugs (data not shown). In separate experiments, i.c.v. injection of microgram amounts of these drugs into saline-infused rats (controls) did not produce any significant changes in the blood gas levels or in antinociception, under the same experimental conditions. The effective dose of (+)BW373U86 is 10 to 30 μg/kg or 0.1 to 0.5 mg/kg, for i.c.v. or i.v. administration, respectively.

The respiratory effects of delta-ligands are reversed by DPI2505. It is a paradox that both delta agonists and antagonists, administered peripherally or centrally, produced a similar pattern of reversal of alfentanil-induced hypocapnia. Further screening of other novel delta compounds by this experimental method led to the discovery of an unique new synthetic compound DPI2505 that has a chemical structure of DPI2505 (fig. 8). This compound displayed antagonist activity against delta opioids in both receptor binding and in vitro tissue assays. The affinity of DPI2505 for delta receptors in the binding assay was estimated to be approximately 1.5 nM, and its selectivity for delta receptors over mu receptors was 400-fold. The detailed activities of this compound will be published separately (K-J Chang, unpublished data).

In our experimental respiration model, i.v. administration of DPI2505 produced no measurable effect on blood gas parameters or antinociception in rats infused with saline (data not shown). In alfentanil-infused rats it also did not produce significant effects on MPE or pCO₂, but it antagonized the respiratory depression-reversal effect produced by (+)BW373U86 (fig. 9). In this experiment, bolus i.v. doses of DPI2505 delivered 10 min after bolus i.v. administration of (+)BW373U86 effectively reversed the effect of (+)BW373U86 in a dose-dependent manner. Other blood gas parameters were similarly reversed (data not shown).

Furthermore, DPI2505 was able to antagonize the hypocapnia reversal effect of all delta ligands described above. Bolus i.v. injected DPI2505 antagonized the effect of peripherally administered NTI and i.c.v. administered Del II,
DPDPE and TIPP (fig. 10). The DPI2505 antagonism is rapid and long lasting, and in all cases there was no significant effect on antinociception. Thus, the new delta ligand DPI2505 exhibited an activity completely opposite to other known delta drugs, and it antagonized the respiratory effects of other delta agonist and antagonist ligands in this experimental protocol.

Discussion

The nature of the respiratory depressant effect of opioids is yet to be fully understood. Although the literature is replete with observations on the respiratory depressant effect of various mu opioids the precise mechanism remains elusive.

The role of delta or kappa receptors in respiratory control is even less well understood. This study showed that mu receptors in the central nervous system mediate the respiratory response of opioid stimulation. This is demonstrated by the respiratory effect of alfentanil infusion and the antagonistic action of CTOP on alfentanil-induced antinociception and hypercapnia (figs. 1 and 2). CTOP is a high affinity mu ligand with mu to delta selectivity of 2000x (Pelton et al., 1986; Hawkins et al., 1989). It is clear that both antinociception and hypercapnia are antagonized in parallel by CTOP with
no significant difference in the dosage requirement. This suggests that both the antinociception and the respiratory depression are brought about by stimulation of mu receptors. The fact that delta agonist (+)BW373U86 and other delta agonists tested have no direct effect on respiration (fig. 6) further supports the notion that mu receptors play a significant role in mediating opioid-induced respiratory depression. It has been suggested by Pasternak (1986) that respiratory depression is mediated by the mu 2 receptor subtype. Because CTOP is not able to differentiate between mu 1 and mu 2 activities, it is not clear which subtype is more important in the respiratory actions of opioids. Whether opioids affect respiration by directly interacting with mu receptors in the central respiration centers or indirectly through other neurotransmitter interactions is still not known (Bonham, 1995).

The effect of delta antagonists is quite different. When administered peripherally, all three nonpeptide delta antagonists NTI, NTB and BNTX produced reversal of alfentanil-induced hypercapnia at doses that do not affect antinociception (figs. 3 and 4). Moreover, by i.c.v. administration, the highly selective peptide antagonist TIPP(\(\psi\)) also produced the same effect (fig. 7). It should be noted that these delta antagonists reverse the already depressed respiratory effects of alfentanil; however, by themselves they showed no direct effect on respiration, either stimulatory or inhibitory (data not shown). NTI has a delta receptor selectivity of about 100-fold (Portoghese, 1991), and TIPP(\(\psi\)) is the most selective delta antagonist with a selectivity for delta receptors of 10,000-fold over other opioid receptors (Schiller et al., 1993). With these degrees of receptor selectivity it is thus argued that the observed hypercapnia-reversal effect is mediated through delta receptor antagonism. Freye et al. (1991, 1992) observed that NTI and NTB reversed sufentanil-induced respiratory depression in conscious mongrel dogs. Based on the potent effect of these antagonists they proposed that the delta receptor plays an important role in respiratory regulation and the respiratory depression induced by mu ligands is mediated by interaction with delta receptors. This is the simplest model to explain the delta antagonists' effect we observe in this report. However, this model is insufficient to explain the data on delta agonists.

The effect of delta agonists is unexpected. In this experimental model, delta agonists also reverse the alfentanil-induced hypercapnia but not antinociception when administered by either i.v. or i.c.v. route. There is no apparent difference between the hypercapnia-reversal effects of the putative delta 1 agonist DPDPE and the delta 2 agonist Del II. At the dose of 10 \(\mu\)g i.c.v., these agonists did not produce measurable antinociception. This is possibly the first observation on the reversal effect of delta agonists on opioid-induced respiratory depression. The strikingly similar effect of delta agonists and antagonists is difficult to explain with a simple receptor model, and complex models invoking stimulatory or inhibitory feedback loops have to be constructed to accommodate the data. It is thus apparent that the involvement of opioid receptors in the physiological regulation of respiration is complex and multifaceted, involving complex

Fig. 10. Reversal of \(pCO_2\) effect of delta opioids by DPI2505 in alfentanil-infused rats. Conscious rats were continuously infused with alfentanil (6 \(\mu\)g/kg/min). Delta ligands were injected i.v. at 25 min, followed 5 min later by DPI2505 at doses indicated. At the time points indicated, the tail-flick test was performed, and a blood sample was taken and analyzed by blood gas analyzer.
pathways regulated by endogenous opioid systems and susceptible to pharmacologic modulations by both mu and delta ligands. This may explain the seemingly incongruous and sometime contradictory effects of opioid ligands on respiration often observed by laboratories with various experimental conditions. It is certain, however, that the effect of the delta ligands in reversing respiratory depression is centrally mediated.

Another important point is the lack of respiratory effects by delta agonists and antagonists in vivo and in vitro model. All delta agonists and antagonists when injected alone without alfentanil produced no changes in blood gas parameters in conscious rats. This suggests that central delta receptor systems blunt chemosensory-evoked respiratory depression, but have minimal direct role in regulating respiration under normal conditions. The data also exclude the possibility that alfentanil produces the respiratory depressant effect through its minor delta receptor activity.

The action of DPI2505 is unique in this system. Although it is inactive by itself on the alfentanil-induced antinociception and hypacapnia, it behaves like an “agonist” in blocking all other delta ligands’ effect on hypacapnia. One explanation is that there is a unique DPI2505-type receptor in the central nervous system specifically for respiratory stimulation that overrules other receptor systems. This is unlikely because DPI2505 completely and potently antagonizes the effect of delta agonists in mouse vas deferens, and competes with [3H]DPDPE, [3H]Deltorphin and [3H]Naltorphine for delta receptors in rat brain membrane (K-J Chang, unpublished data). Another explanation is that NTI, NTB and TIPPH(ψ) are, at least in this experimental respiration model, actually partial agonists with various degrees of intrinsic activities, and DPI2505 is the true delta antagonist that can block the effect of all other delta receptor-specific compounds.

If this conclusion is true, our results suggest that a function of the delta receptor in the central nervous system is to modulate or counteract the mu receptor mediated respiratory depression.

The control of ventilation is classically described as a system of feedback loops that keep arterial CO2 and O2 tensions constant. A number of neurotransmitter systems, including opioid, are involved (Bonham, 1995). Opioids can variably inhibit respiratory rate, tidal volume or hypoxic response depending on the agonist used, animal species studied, route of drug administration and the site of brain regions injected, if the drug is injected into central nervous system (see Berger et al., 1977; Mueller et al., 1982; Shook et al., 1990). Most previous studies examined changes in respiratory rate or ventilation. The measurements can vary significantly depending on the method and experimental condition (Ward and Takemori, 1983). Regardless of mechanisms involved, the end results are reflected in the changes in blood gas pCO2, pO2 and pH values. We examine the overall effects of the delta opioids on mu agonist-induced respiratory depression, rather than on the effect of individual ventilation parameters. The physiological mechanism(s) of the inhibitory effect of delta opioids on alfentanil-induced respiratory depression will be the subject of future studies.

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Respiration and Delta-Opioid Receptors

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