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REVERSAL OF μ-OPIOID-MEDIATED RESPIRATORY DEPRESSION BY α_2-ADRENOCEPTOR ANTAGONISM

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Summary

The present study was performed in order to evaluate the effects of the selective α_2-adrenoceptor antagonist 6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine (SK&F 86466) on dermorphin-induced analgesia, respiratory depression and inhibition of locomotor activity in the conscious rat. Intracerebroventricular (icv) administration of dermorphin (3 nmol/rat) decreased respiration rate and relative ventilatory minute volume maximally by 38 % and 50 % of baseline respectively. SK&F 86466 dose-dependently reversed the dermorphin-induced depression of ventilatory parameters, while SK&F 86466 exerted no effect on dermorphin-induced analgesia or depression of locomotor activity due to catalepsia. It appears, therefore, that α_2-adrenoceptors selectively interact with μ_2-opioid-receptor mediated effects, such as respiratory depression, but are not involved in the modulation of μ_1-opioid-related effects, such as supraspinal analgesia and depression of locomotor activity.

The depression of vital cardiorespiratory functions poses the major limitation for the therapeutic use of opiates and represents the primary underlying cause of fatalities due to overdosage among habitual drug abusers (1). The biological actions of morphine and enkephalins are mediated through multiple opioid receptors, termed μ-, δ-, epsilon-, σ-, and κ-opioid receptors. Additionally, two subtypes of μ-receptors, μ_1- and μ_2- binding sites, were identified based on their relative selectivity for morphine and enkephalins (2). The μ-receptor subtypes were further suggested to mediate different functions: While μ_1-opioid binding sites seem to be involved in morphine-induced supraspinal analgesia, the opiate-related respiratory depression and spinal analgesia, at least in part, appear to be mediated through μ_2-binding sites (3,4,5). In addition to opioids, other neurotransmitters are known to induce analgesia. Thus, systemic administration of α_2-adrenoceptor agonists produces analgesia in various species (6,7,8). Moreover, central α_2-adrenoceptor activation with clonidine results in cardiorespiratory depression, which is attenuated by the α_2-adrenoceptor antagonist yohimbine (9,10,11). It appears, therefore, that the biological effects of opioids, especially those mediated by the μ_2-subclass, and those related to α_2 adrenergic receptors are similar in a qualitative sense, suggesting the involvement of a common mechanism.

The heptapeptide Tyr-D-Ala-Phe-Gly-Tyr-Pro-Ser-NH_2, dermorphin, a specific μ-opioid agonist, elicits analgesia and respiratory depression in pico- to nanomolar doses with an increased potency compared to morphine (5). In order to investigate, whether α_2-adrenoceptor antagonism would interact with dermorphin-induced analgesia and respiratory depression, we conducted a series of experiments in conscious, unrestrained rats, using a pretreatment schedule with 6-chloro-2,3,4,5-tetrahydro-3-methyl-

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1H-3-benzazepine (SK&F 86466), a specific α_2-adrenoceptor antagonist which was shown, in contrast to other functionally related agents, such as idazoxan, to be devoid of a notable affinity to central imidazole binding sites (12,13).

Methods

Surgical Procedures. Male Spraque-Dawley rats (270-358 g; Taconic Farms, Germantown, NY) were anesthetized with an intramuscular injection of ketamine (130 mg/kg) and acepromazine (1.3 mg/kg). A stainless steel guide cannula for icv injections was glued over the right cerebral hemisphere (Eastman 910 Adhesive) at the following coordinates: -0.8 mm AP, 1.2 mm LA from bregma. The right external jugular vein was then cannulated using PE-50 tubing filled with heparinized saline for intravenous (iv) drug administrations. The tubing was exteriorized at the neck of the animal and sealed by means of an electrical cauter iron. The animals were allowed to recover for at least 36 hours before the onset of the experiment.

On the experimental day, different groups of animals received a single iv injection of SK&F 86466 (1 or 5 mg/kg) or 0.9% saline solution 20 minutes before an icv injection of 10 μl of the μ-opioid agonist dermorphin or artificial cerebrospinal fluid (CSF) respectively. The icv injections were performed manually over 10 to 15 seconds using a 30 gauge cannula of 7.5 mm length which was inserted into the right cerebral ventricle via the previously implanted guide cannula and a 50 μl Hamilton syringe. At the end of the experiment the location of the icv administration was visualized by injection of methylene blue.

Analgesia. Analgesia was monitored using a tail-flick apparatus (Socrel Inc., Milano, Italy). A 12 second cut-off time was chosen in order to limit temperature-derived tissue damage. Tail-flick response times as a measure of analgetic activity are represented as percentage of the maximal possible effect (% of MPE) following the equation:

$$\% \text{ of MPE} = \frac{\text{post drug latency - predrug response latency}}{\text{cut-off time - predrug response latency}} \times 100$$

At the start of the experiment, 0.9% saline solution (100 μl/100 g body weight) or SK&F 86466 (5 mg/kg) were administered iv, followed by an icv injection of 30 (n=6) or 100 (n=6) pmol/rat dermorphin or artificial CSF (n=3) after 20 minutes. The analgesia induced by dermorphin was assessed at 15, 30, 60, 90, 120, and 150 minutes after icv injection.

Respiration. Respiration rate (f), relative tidal volume (rV_T), O_2 consumption, and CO_2 production were measured in conscious, unrestrained animals using the OXYMAX '85 system (Columbus Instr., Columbus, OH). The system consists of three transparent plexiglass chambers of 6.55 liters volume each with a constant flow of 2 liters of room air per minute. Two of the chambers are used for the actual recording of ventilatory parameters, while the third serves as a reference. Alternate measurements are performed every 2 minutes. The respiration rate is determined based on the frequency (respirations/minute, rpm) of pressure changes due to the ventilatory movements of the animal's thorax. The tidal volume (V_T) is recorded as an integral of pulses, which is proportional to the amplitude of the pressure changes and compared to the pulse count in the first sample measure of the experiment. Tidal volume is therefore expressed as relative tidal volume (rV_T) in arbitrary units. The relative ventilatory minute volume ($r\dot{V}_E$) is calculated as the arithmetical product of f and rV_T. The O_2 and CO_2 contents of the animal chambers are measured against the reference chamber. The arithmetical differences are then expressed as O_2 consumption and CO_2 production respectively.

The animals were placed into the chambers at the onset of the experiment. After 75 minutes, a period which is sufficient for the animals to get accustomed to the new environment, SK&F 86466 (1 mg/kg, n=6; 5 mg/kg, n=6) or 0.9 % saline solution (100 μl/100 g body weight, n=7) was injected iv over a period of 30 seconds. Respiratory parameters were monitored for an additional 20 minutes, before both groups received a single icv injection of dermorphin (3 nmol/rat) or artificial CSF. The

measurement of respiratory effects was thereafter continued for 115 minutes; the overall recording time per experiment was 3.5 hours. The results are expressed as changes in percent of baseline values which were obtained as averages of the parameter values during the last 30 minutes preceding the iv drug injection, when the animals were in resting conditions. The effects of the pretreatments with SK&F 86466 or vehicle were assessed as areas under the curves depicting the parameter changes over time (20 min), using a trapezoidal method. This approximative procedure consists of the summation of the areas of various trapezoids fitted to the curve segment representing the pretreatment period.

Locomotor activity. Simultaneously to the measurement of respiratory parameters, locomotor activity (LA) of the animals was monitored, using two Digiscan Optical Sensor Activity Monitors (Columbus Instr., Columbus, OH). The estimation of locomotor activity is based on the interruption of infrared light beams, which are located 2.5 cm above ground, caused by the locomotion of the animals in the OXYMAX'85 system chambers. The data were collected as counts per 2 minutes. The effects of pretreatment with SK&F 86466 (5 mg/kg) or saline iv and treatment with dermorphin or CSF icv were calculated as sums of counts during the respective observation periods.

Statistics. Data reduction for statistical evaluation and graphing purposes was performed by averaging three consecutive samples. One way analysis of variance (ANOVA) followed by Tukey's test was used to analyze the effects of dermorphin vs. artificial CSF icv. The effects of the respective pretreatment-treatment combination over time within each group was assessed, using the ANOVA test for repeated measures (MANOVA). Differences of the curve areas during the period of iv pretreatment and maximal parameter changes due to different pretreatment-treatment combinations were compared using the Kruskal-Wallis procedure, followed by the Mann-Whitney-U test. Data are presented as means $\pm$ S.E.M.

Drugs. Dermorphin (Peninsula) for icv injections was dissolved in artificial CSF containing 127 mM NaCl, 2.5 mM KCl, 1.3 mM $CaCl_2$, and 0.9 $MgCl_2$ in deionized water. SK&F 86466 was a generous gift from Dr. G. Z. Feuerstein, SmithKline Beecham Research and Development, King of Prussia, PA. For iv administration, SK&F 86466 was dissolved in 0.9% saline solution.

Results

Analgesia. Dermorphin doses of 30 and 100 pmol/rat induced a potent, dose-related analgesia (Fig. 1). The maximum analgetic effects were reached approximately 30 to 60 minutes after icv injection. Although treatment with the α_2-adrenoceptor antagonist SK&F 86466 (5 mg/kg) appeared to potentiate the analgetic effect of the low dose dermorphin treatment somewhat, no statistical significance could be detected between the SK&F 86466 and the saline pretreated groups of animals. Additionally, SK&F 86466 iv, followed by artificial CSF icv did not exhibit analgetic properties (Fig. 1).

Respiration. Baseline values for all respiratory parameters are shown in table 1. Pretreatment with SK&F 86466 produced a dose-related decrease of the curve areas for f (Fig. 2, $p < 0.001$, Kruskal-Wallis) as compared to the stimulation of f seen after saline administration. This stimulation is most likely based on the environmental stress due to the handling of the animals during the iv injection procedure. The effect on f subsided about 20 minutes after injection and was accompanied by a counterbalancing increase of rV_T in animals receiving 5 mg/kg SK&F 86466 (Fig. 2, $p < 0.01$, Kruskal-Wallis). Thus no change of $r\dot{V}_E$ could be detected in this group (Fig. 2). A similar change of rV_T was not apparent after 1 mg/kg SK&F 86466 iv, leading to a reduction of $r\dot{V}_E$ ($p < 0.05$, Kruskal-Wallis). Additionally, O_2 consumption but not CO_2 production after SK&F 86466 iv differed significantly from saline controls ($p < 0.05$, Kruskal-Wallis).

Icv injection of dermorphin (3 nmol/rat) caused significant decreases of f (Fig. 3), $r\dot{V}_E$ (Fig. 3), O_2 consumption, and CO_2 production ($p < 0.05$ vs. CSF icv, Tukey's test), which became maximal at 60 minutes after the administration. The rV_T on the other hand was significantly elevated after dermorphin icv ($p < 0.05$ vs. CSF icv, Tukey's test). Maximum effects were assessed and compared by averaging 6 sample values derived from the region of maximal change of each parameter (between 65

and 75 minutes after the icv injection of dermorphin, Fig. 3). Dermorphin icv significantly reduced $r\dot{V}_E$ and f by 38 % and 50 % respectively, when compared to CSF icv controls ($p<0.05$, Kruskal-Wallis, Fig. 4). Moreover, O_2 consumption and CO_2 production were reduced by 26 % and 22 % (n.s. vs. CSF icv).

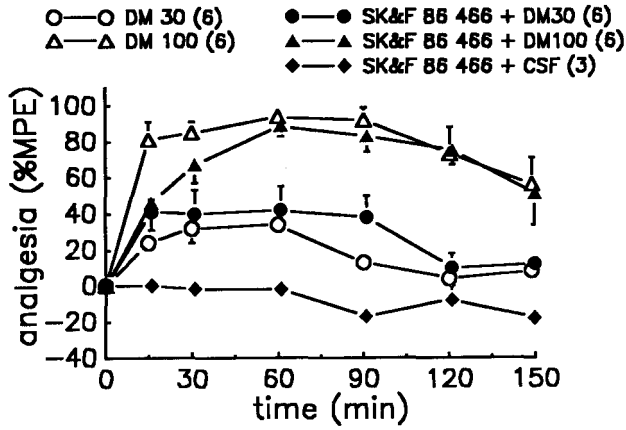

FIG. 1

Effect of SK&F 86466 on dermorphin (DM)-induced analgesia. An iv injection of SK&F 86466 (5 mg/kg, n=6) or vehicle (saline, n=6) was administered 20 minutes before an icv injection of 30 or 100 pmol/rat of dermorphin or 10 μl artificial CSF (n=3). The 0 time point on the abscissa denotes the icv injection.

TABLE 1

	$r\dot{V}_E$	rV_T	f	O_2 cons.	CO_2 prod.
saline iv CSF icv	112±15	149±18	76± 3	1035±82	889±30[a]
saline iv dermorphin icv	265±94	270±86	94± 4	1189±49	1119±29
SK&F 86466 iv (5 mg/kg) CSF icv	68± 9	93±13	74± 5	970±22[b]	909±21[b]
SK&F 86466 iv (1 mg/kg) dermorphin icv	164±21	183±20	89± 3	1092±26	986±19[a]
SK&F 86466 iv (5 mg/kg) dermorphin icv	201±62	225±66	88± 3	1167±26	1052±24

Table 1: Synopsis of Parameter Baseline Values (n=5-7). The dimensions for the respiratory rate (f) and O_2 consumption (O_2 cons.) or CO_2 production (CO_2 prod.) are respirations/minute (rpm) and ml/kg/min respectively. The relative tidal volume (rV_T) is expressed in arbitrary units in percent of the first sample initially recorded at the onset of the experiment. Therefore the $r\dot{V}_E$ is expressed in rpm. [a]) denotes a significant difference between the groups receiving dermorphin icv ($p<0.01$, Kruskal-Wallis); [b]) compares the groups receiving SK&F 86466 (5 mg/kg iv) as pretreatment ($p<0.01$, Kruskal-Wallis).

Pretreatment with SK&F 86466 potently and dose-dependently abolished or even reversed the effects of dermorphin on ventilation (Fig. 3&4). While values for f after dermorphin icv in SK&F 86466 (5 mg/kg) pretreated animals did not differ from baseline values taken at 60 minutes after the onset of the experiment, $r\dot{V}_E$ ($p < 0.05$, MANOVA), O_2 consumption ($p < 0.05$, MANOVA), and CO_2 production ($p < 0.001$, MANOVA) were significantly elevated.

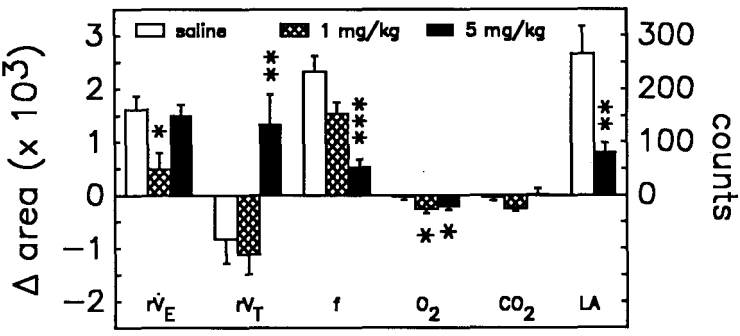

FIG. 2

Effects of SK&F 86466 (1 mg/kg, n=6; 5 mg/kg, n=11) or vehicle (n=12) treatment on respiratory parameters and locomotor activity. Areas of the curves (left ordinate) representing the ventilatory changes from baseline during a 20 minute observation period after the iv injection of SK&F 86466 or saline were calculated using a trapezoidal method. Locomotor activity (LA) was assessed as sum of counts over the same 20 minute period (right ordinate). *) = $p < 0.05$, **) = $p < 0.01$, and ***) = $p < 0.001$ (vs. saline, Kruskal-Wallis).

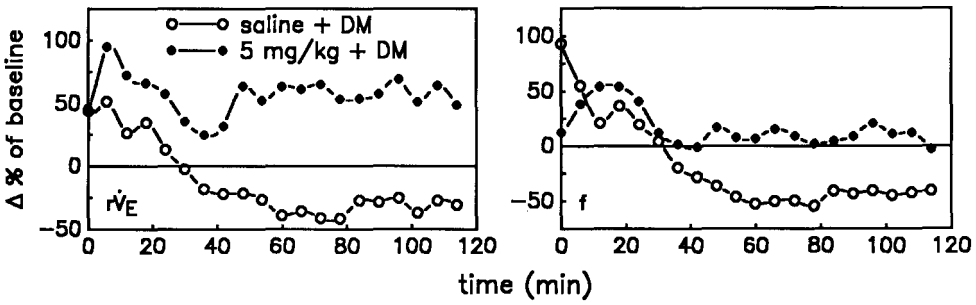

FIG. 3

Time course of the changes of relative ventilatory minute volume ($r\dot{V}_E$) and respiration rate (f) in percent of baseline after the icv injection of dermorphin (3 nmol/rat) in saline (n=7) or SK&F 86466 (5 mg/kg, n=6) treated rats. The time point 0 on the abscissa denotes the icv injection. Data points represent mean values of three consecutive samples.

Locomotor activity. Injection of 5 mg/kg of SK&F 86466 caused a significant decrease of LA counts when compared to saline controls ($p < 0.01$, Mann-Whitney-U, Fig. 2). No significant differences

between the groups were found after the injection of artificial CSF or dermorphin icv when the LA was calculated over the entire observation period following the icv injections. This result apparently was due to an initial activation of LA after the injection of both, artificial CSF or dermorphin, which lasted about 30 minutes. After this time the animals receiving dermorphin icv appeared clearly cataleptic, while the control animals (CSF icv) still exhibited periodic bursts of LA. Thus, the LA after dermorphin was almost entirely suppressed between 30 and 115 minutes after icv administration of dermorphin ($p < 0.01$ vs. CSF icv, Kruskal-Wallis, Fig. 4). Pretreatment with SK&F 86466 did not modify the effect on either, CSF or dermorphin treated animals.

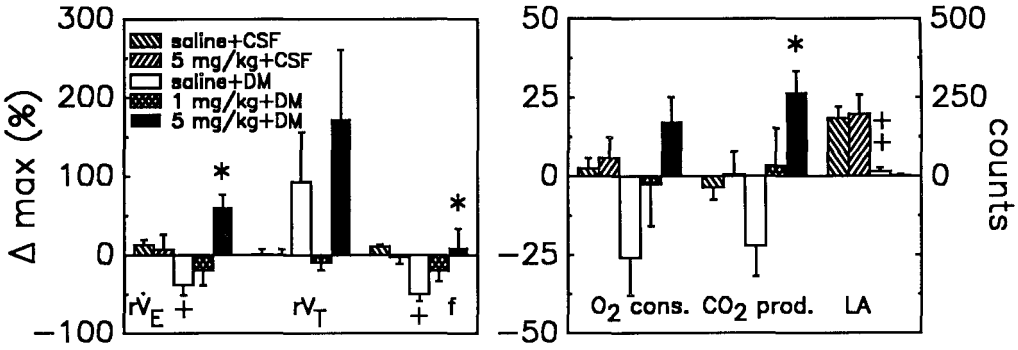

FIG. 4

Maximum changes of ventilatory parameters and locomotor activity. Ventilatory data represent means ± S.E.M. of six successive samples taken from the region of the maximum effect of dermorphin (DM) icv. The groups consist of n=5 (saline iv, CSF icv), n=5 (5 mg/kg SK&F 86466 iv, CSF icv), n=7 (saline iv, DM icv), and n=6 (1 and 5 mg/kg SK&F 86466 iv, DM icv) rats. Locomotor activity (LA, right ordinate) was calculated as sum of LA counts over a 85 minute period following 30 minutes after the icv injection of dermorphin. *) = $p < 0.05$ (Kruskal-Wallis) denotes significant differences between the saline or SK&F 86466 pretreated animals, while $^{+}$) = $p < 0.05$ and $^{++}$) = $p < 0.01$ (Kruskal-Wallis) represent statistical significance between the groups receiving dermorphin (3 nmol/rat) or artificial CSF after an iv pretreatment with 0.9 % saline solution.

Discussion

The present study demonstrates the interaction of an α_2-adrenoceptor antagonist, SK&F 86466, with the respiratory depressant, but not the analgetic and locomotor depressant properties of icv administered dermorphin, a μ-opioid receptor specific agonist, in conscious rats. Dermorphin produced a significant depression of f. A concomitant increase of V_T was insufficient to counteract the decrease of f, resulting in a significant depression of $\dot{V}_E$. Although decreases in both, O_2 consumption and CO_2 production were observed after dermorphin treatment, these effects did not statistically differ from controls receiving artificial CSF icv. In the case of CO_2 production, however, this lack of a significant depression may have been due to a lower baseline level in the CSF treated group. SK&F 86466 potently reversed the depression of $r\dot{V}_E$, f, and CO_2 production caused by dermorphin. No significant effects, however, were detectable on rV_T, O_2 consumption, the depression of locomotion, and, most importantly, on dermorphin-induced analgesia.

Studies using biochemical, anatomical, and pharmacological approaches suggest that multiple opioid receptors mediate the effects of morphine in the central nervous system (for review see 2). These

receptors may be separated, among other criteria, according to their differential affinities for morphine and enkephalin. While μ_2- and δ-opioid receptors exert a high affinity for either morphine or enkephalin respectively, the μ_1-sites bind both with equally high affinity (2). Functionally, μ_1- and μ_2-opioid binding sites appear to be involved in the mediation of different opiate-induced biological effects. Thus, μ_1-opioid binding sites seem to mediate supraspinal analgesia (2,5). This hypothesis is corroborated by evidence showing that μ_1-opioid binding sites are preferentially located in CNS structures, which may represent the anatomical correlates for opiate-induced supraspinal analgesia (14,15,16). Additionally, recent evidence (17) revealed a selective decrease of μ_1 binding sites in the aforementioned CNS locations in a mouse strain which appears insensitive to morphine analgesia. Further, μ_1-opioid binding sites may also mediate the stimulation of respiration and locomotor activity in rats after icv administration of low doses of the unselective μ-agonist dermorphin, since these effects were effectively abolished after pretreatment with the selective μ_1-antagonist naloxonazine (5). Similarly, opiate-induced catalepsy was drastically antagonized with another μ_1-selective antagonist, naloxazone, indicating that both, locomotor stimulation and catalepsy may be mediated through a μ_1-opioid receptor related mechanism (18).

In contrast, μ_2 sites in addition to δ- and κ-receptors appear to mediate the opiate-induced spinal analgesia, since naloxonazine has no effect on the antinociception produced by intrathecal (it) injections of the μ-selective agonist [D-Ala^2, N-methyl-Phe^4, Gly^5-ol]enkephalin (DAMGO), but effectively prevents the analgesia induced by DAMGO icv (4). Additionally, the respiratory depressant effect of opiates is attributed to the μ_2-opioid binding site (2,5). Thus, the unspecific μ-opioid antagonist naloxone blocked the hypoxemia and hypercapnia due to morphine-induced respiratory depression, while the μ_1-selective antagonist naloxonazine was ineffective (19).

An increasing amount of evidence emphasizes the opiate-like actions of α_2-adrenoceptor-related compounds such as clonidine. Thus, systemic administration of the α_2-adrenoceptor agonist clonidine has been shown to produce analgesia in various species (6,7,8). Interestingly, clonidine does not elicit any antinociceptive effects, when administered locally into the periaquaeductal grey, which is presumed to be crucially involved in the generation of supraspinal, μ_1-opioid-related analgesia (20). On the other hand, intrathecal injections of clonidine and norepinephrine exhibited potent antinociceptive actions, which were antagonized with the selective α_2-adrenoceptor antagonist yohimbine, suggesting that α_2-adrenoceptors may mediate the analgetic response to catecholamines on a spinal level (16). Indeed, descending, catecholaminergic projections from the locus coeruleus (LC) to various spinal segments appear to be involved in the generation of spinal analgesia (21). Thus, LC lesions were accompanied by a decrease of spinal norepinephrine content, leading to a compensatory upregulation of spinal α_2-adrenoceptors combined with an enhancement of the antinociceptive effect of an α_2-adrenoceptor agonist (21). Interestingly, administration of the α_2-adrenoceptor agonist ST-91 (it) was shown to potentiate the analgetic effect of morphine (it), suggesting a synergistic interaction of spinal μ-opioid and α_2-adrenoceptor mechanisms (22).

The data presented in this study not only add to the already existing body of evidence concerning an opioid-catecholamine interaction, but further establish the basis for a putative mechanism thereof. Thus, pretreatment of the animals with SK&F 86466, a specific α_2-adrenoceptor antagonist (12), did not affect the presumably μ_1-opioid receptor mediated analgesia and catalepsy as shown by its lack of effect on the dermorphin-induced depression of LA. The μ_2-opioid receptor related respiratory depression, on the other hand, was effectively antagonized. The elevation of $r\dot{V}_E$, O_2 consumption, and CO_2 production above baseline levels after dermorphin icv in SK&F 86466 pretreated rats, may be due to the remaining action of dermorphin on μ_1-opioid receptors, which were shown to mediate dermorphin-induced respiratory stimulation (5). The fact that SK&F 86466 pretreatment did not affect dermorphin-induced analgesia, however, does not preclude an interaction of the α_2-adrenoceptor antagonist on this opioid effect under different experimental conditions. Thus, icv injection of dermorphin presumably induces a supraspinal, μ_1- receptor mediated analgesia, which may mask an effect on the spinal antinociception elicited by SK&F 86466. A μ_2-mediated, spinal component of the analgesia induced by an it injection of dermorphin may very well be subject to an antagonizing effect of SK&F 86466.

The mechanisms, involved in the interaction between μ_2-opioids and α_2-adrenoceptor agonists or antagonists can at this point only be speculative. Recent evidence suggests an involvement of central adrenergic pathways in the modulation of respiratory patterns. Thus, while β-adrenergic agents and α_2-adrenoceptor antagonists were shown to stimulate respiratory activity, α_2-adrenoceptor agonists exerted a depressing effect (9,11,23,24). Furthermore, the A5 noradrenergic cell group, located in the ventrolateral pons may represent an anatomic origin of noradrenergic fibers, modulating the medullary, respiratory rythm generator, predominantly in form of a tonic inhibition (24). Thus, electrical stimulation of the A5 region lead to a prominent inhibition of respiration, which was blocked by the α_2-adrenoceptor antagonists yohimbine and idazoxan (24). Therefore, it is conceivable that treatment with SK&F 86466 may antagonize norepinephrine action at postsynaptic α_2-adrenoceptors, located on medullary neurons, which are involved in the generation of respiratory rythms. The blockade of presynaptic α_2-adrenoceptors by SK&F 86466 would cause an increased norepinephrine release and would thus be expected to enhance the respiratory depression induced by dermorphin. Furthermore, it appears unlikely that the observed effects are due to a mere physiological antagonism, since no effects on $r\dot{V}_E$ were observed after iv administration of SK&F 86466 (Fig. 4). It is yet unclear, however, whether μ-opioids depress respiration through a direct, μ receptor-mediated action at medullary neurons, or indirectly through the modulation of noradrenergic input to these cells. The mechanism underlying the described antagonism may involve an interaction at the receptor level or at second messenger systems. A receptor based mechanism of interaction is supported by the colocalization of low affinity type α_2-adrenoceptors and μ_2-opioid binding sites (25,26). The mode of interaction at the μ_2-opioid receptor is probably not competitive, since azidomorphin and other opiates show only weak ability to displace [^{3}H]clonidine from its binding sites in rat cortex (27). However, a noncompetitive mode of action has to be considered as well, whereby α_2-adrenoceptors may modulate the affinity and/or density of μ_2-opioid receptors and vice versa in form of a (μ_2/α_2) receptor complex. Interaction on the second messenger level may also explain the antagonistic properties of SK&F 86466 on μ_2-mediated phenomena, since in both, brain membrane preparations and certain cell lines, opiate and α_2-adrenergic receptors are coupled to adenylate cyclase via G-proteins (28,29) emphasizing a possible mode of interaction through modulation of common, intracellular mechanisms. While the molecular mechanisms underlying the interaction of α_2-adrenoceptor agonists or antagonists and μ_2-opioid receptor-mediated responses are yet to be identified, the presented data indicate a potential, novel concept in the treatment and prophylaxis of opiate-induced respiratory depression at a maintained level of antinociception.

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