Pharmacology Biochemistry & Behavior, Vol. 34, pp. 405–411. © Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

Cardiovascular and Respiratory Effects of an Opioid Kappa Agonist Ethylketazocine and Sigma Agonist N-Allylnormetazocine in Acutely Decerebrated Dogs

KUEI-MENG WU AND WILLIAM R. MARTIN

Department of Pharmacology, University of Kentucky, Lexington, KY 40536

Received 27 June 1988

WU, K.-M. AND W. R. MARTIN. *Cardiovascular and respiratory effects of an opioid kappa agonist ethylketazocine and sigma agonist N-allylnormetazocine in acutely decerebrated dogs.* PHARMACOL BIOCHEM BEHAV **34**(2) 405–411, 1989.—Effects of opioid kappa agonist ethylketazocine (EKC), sigma agonist (±)-N-allylnormetazocine (NANM), and naloxone alone and in combination on mean blood pressure (MBP), heart rate (HR), respiratory rate (RR) and minute volume (MV) were studied in acutely decerebrated dogs. EKC (0.5 mg/kg) decreased HR, MBP, RR and MV. Post-EKC NLX increased RR and MV and reversed the bradycardia and hypotension produced by EKC. NANM (1 mg/kg) produced respiratory depression and tachycardia without changing MBP. Post-NANM NLX antagonized tachycardia, increased MBP, however did not significantly change RR and MV. When decerebrate dogs were spinalized at the C-1 level, EKC decreased MBP and HR. These effects were antagonized by NLX. NANM did not change HR but raised MBP in spinalized decerebrate dogs. Since EKC- and NANM-induced cardiovascular and respiratory depression were not observed in conscious intact or chronic spinal dog, it is suggested that: 1) kappaergic system rostral to mesencephalon may play a role in counteracting these depressant effects of EKC; 2) sigma receptor-mediated tachypnea and tachycardia are dissociable; the tachypneic effect may be mediated through higher center while the medulla oblongata is involved in producing tachycardia. These results also suggest that (±)-NANM probably has several mechanisms of action at several brain sites in producing its effects on respiration and cardiovascular function.

Cardiovasular effects Respiratory effects Ethylketazocine N-Allylnormetazocine Dogs, decerebrated

ETHYLKETAZOCINE (EKC) and (±)-N-allylnormetazocine (NANM) have been widely adopted as prototypic opioid kappa and sigma agonists for the analysis of the mode of action of opioid compounds. EKC was first studied by Archer, Pierson and Michne (17). They found it was 10 times more potent than morphine in the mouse writhing test and mouse hot plate test. In guinea pig ileum assay, EKC was about 200-fold more potent than morphine (17). EKC is an unusual analgesic since it did not suppress or precipitate abstinence in morphine-dependent monkeys (34). EKC produces analgesia in tail compression, tail flick and intracarotid bradykinin tests in rats and depressed the flexor reflex in the chronic spinal dog (9, 29, 32). However, EKC was found to be inactive using the hot plate and hot water immersion tests in rats (36) and skin twitch reflex in chronic spinal dogs (9). Further, EKC shortened the latency of the skin twitch reflex in decerebrate dogs (43).

NANM produced little analgesia and marked psychotomimetic effects in man (15). It was for this reason that NANM was used as a prototypic and selective dysphoriant (22). In the chronic spinal dog it caused modest analgesia as measured by depression of the flexor reflex (21). NANM was found to be inactive in producing analgesia in mice using phenylquinone writhing test and was 2 to 3 times more potent than nalorphine in preventing meperidine analgesia using the rat tail flick procedure (30). NANM also antagonized morphine antinociception in the rat (14). NANM is about 0.13 times as potent as naloxone as an antagonist as estimated by its ability to precipitate abstinence in morphine-dependent dogs (20).

The effects of EKC and NANM on blood pressure, heart rate and respiration have not been thoroughly examined. In chronic spinal dogs, EKC and ketazocine, a kappa agonist, did not significantly change heart rate or respiratory rate in chronic spinal dogs (9). Ketazocine decreased diastolic blood pressure and heart rate without changing respiratory rate in pentobarbital anesthetized dogs (4). Pentazocine, a kappa agonist, increased blood pressure and heart rate in man, but depressed blood pressure and respiration in anesthetized dogs (11,35). In contrast, NANM produced a dose-related increase in heart and respiratory rate in chronic spinal dogs (20).

Recently, intracerebral administration of kappa and sigma agonists have demonstrated the involvement of both subtypes of

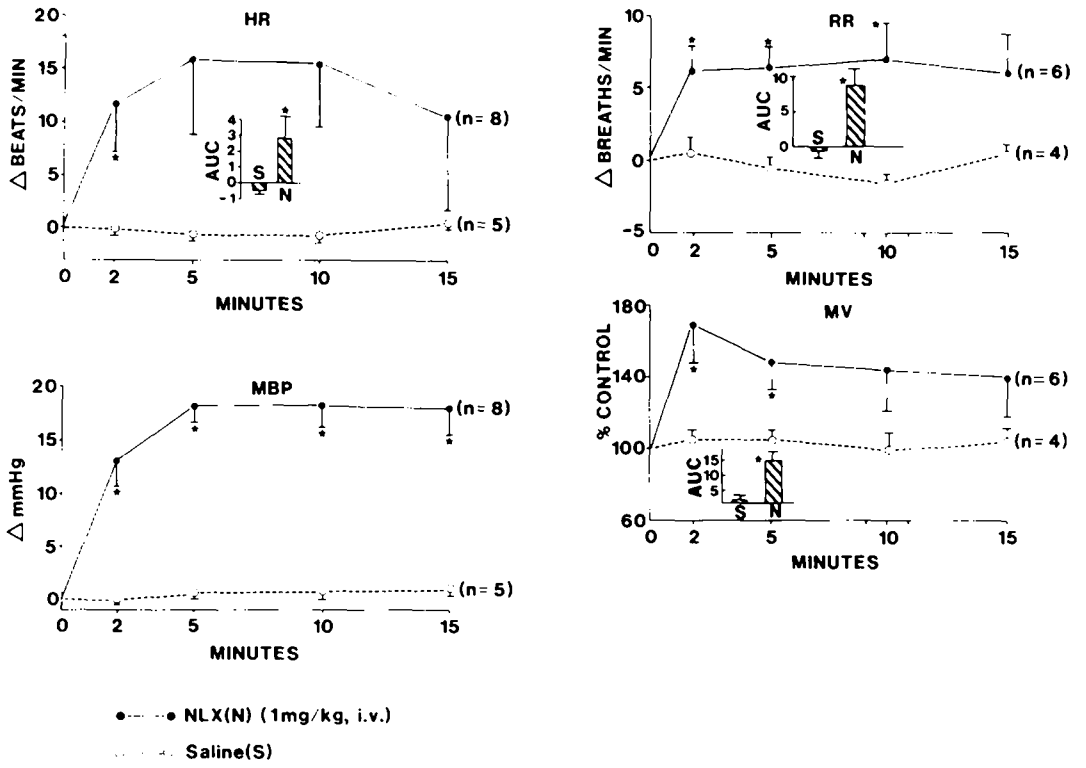

FIG. 1. Time course of effects of naloxone (NLX) on heart rate (HR), mean blood pressure (MBP), respiratory rate (RR), and minute volume (MV) in the acutely decerebrated dogs. AUC: area under the curve. *Indicates significant difference between NLX and saline control ($p<0.05$). Values are mean ± S.E.M.

opioid receptors in the regulation of cardiovascular and respiratory functions. Microinjections of kappa agonist MR 2034 into the anterior hypothalamic area of the awake rats depressed respiration but caused no cardiovascular changes (27). However, administration of a similar kappa agonist MRZ 2549 in the lateral ventricle caused tachycardia and a pressor response in conscious rats (28). Kappa agonists MRZ 2459 and bremazocine caused hypotension and respiratory depression when microinjected into the nucleus ambiguus of pentobarbital anesthetized rats (12). Both agents, when injected into the nucleus tractus solitarius, produced a similar profile of effects except that bremazocine did not depress respiration (12). In decerebrated dogs, EKC decreased blood pressure and heart rate when injected in the region of the nucleus ambiguus (41). Endogenous kappa agonist dynorphin injected into the nucleus tractus solitarius did not alter cardiovascular or respiratory variables in chloralose-urethane anesthetized cats (13), but produced hypotension and bradypnea when administered in the hypothalamic area of pentobarbital-anesthetized rats (5). In urethane-anesthetized rats, dynorphin injected in the ventrolateral pressor area decreased blood pressure and heart rate while in the ventrolateral depressor area it caused increases in these parameters (30). In the same study, NANM showed no effects in the depressor area, but decreased the blood pressure when applied in the pressor area. NANM did not cause any significant effects when injected in the area of nucleus ambiguus of the decerebrated dog (42). In summary, it is clear that central kappa receptors play an important role in opioid-induced cardiovascular and respiratory depression. However, the mode and site of action of sigma receptors on autonomic function is still not well-defined.

In the present study, we investigated the effects of EKC and NANM on blood pressure, heart rate, respiratory rate and minute volume in the acutely decerebrated dog.

METHOD

The decerebrate model was employed here for the following reasons: Decerebration 1) allows study of medullary vasomotor and respiratory systems without the confounding effects of anesthetics; 2) causes loss of consciousness without the use of anesthetics; and 3) eliminates the influence of opioid receptor-rich higher centers, such as the hypothalamus, limbic system and periaqueductal gray on the lower brainstem function.

Surgical Procedures

Dogs of either sex weighing 8–18 kg were anesthetized with ether. The trachea was cannulated and polyethylene cannuli were placed in the femoral vein and artery. The decerebration procedures have been previously described (40). In brief, the dog was mounted in a David Kopf stereotaxic instrument. Electrolytic decerebration was performed at the coordinates of anterior-posterior +4 to +5 mm using a pair of insulated 22-gauge electrodes (90 mm long) spaced 3–4 mm apart and bared for 17.5 mm from the tip. The electrodes were oriented straddling the sagittal sinus for the first lesion. The second and third lesions were placed bilaterally with the tip of the medial electrode 3–4 mm away from the central lesion. Vertically, the lesions were located from −1 mm to +16.5 mm. Two 5–10 seconds burns were made with polarity reversed for each lesion. This procedure produced a complete transection zone of about +1 mm in thickness and 8 mm

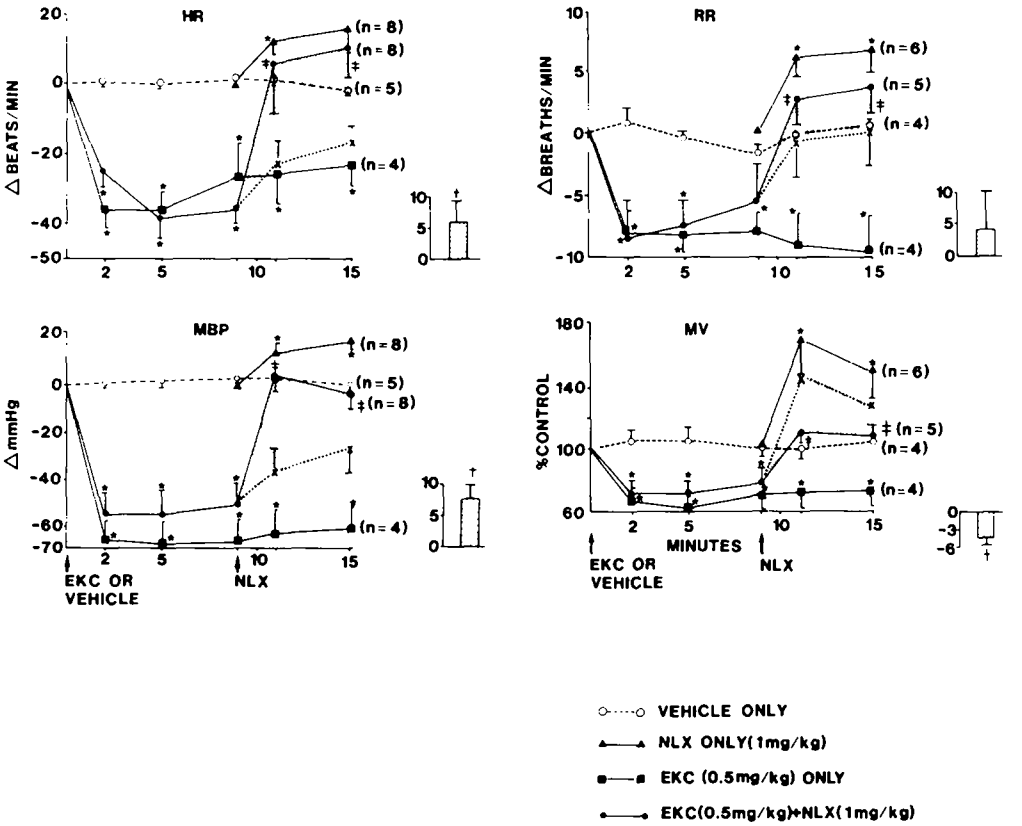

FIG. 2. Time action course of EKC and naloxone (NLX) alone and in combination on heart rate (HR), mean blood pressure (MBP), respiratory rate (RR) and minute volume (MV) in decerebrate dogs. *Indicates significant difference between vehicle and treatments ($p<0.05$). †Indicates significant difference between EKC (■) and post-EKC NLX (●) ($p<0.05$). The hypothetical curve (x) was constructed by adding the NLX values (▲) to the EKC values (■) at corresponding times (i.e., 9–15 minutes). The resulting curve represents algebraic sum of NLX's and EKC's independent action and is the best estimate of what NLX would do had it not antagonized the effects of EKC. The stippled area indicates the effects of NLX attributable to its antagonizing EKC's action. The bar diagram represents the area of stippled region (AUC). The ordinated units of the bar diagrams for each of the following parameters studied are: HR: beats; MBP: mmHg × min; RR: breaths; MV: % × min. The significance of the bar diagram ($p<0.05$) was expressed by †.

in width at the midcollicular level. Ether was discontinued immediately before decerebration and 2.5 to 3 hours elapsed before the study was begun.

A total of 35 dogs was used for decerebrate studies. Of these, 8 were used for naloxone study, 12 for EKC study, 10 for NANM and 5 for controls. Additionally, one group of 13 decerebrate dogs was spinalized by blunt transection and suction at the C-1 level (6 animals were used for the EKC study and 7 for the NANM study). Gelfoam and thrombin were wedged between the cut ends of the spinal cord to control bleeding.

Physiological Parameter Measurements

The body temperature was measured by a rectal probe with YSI telethermometer and maintained at 38 ± 1°C by either heat lamps or cooling pads. Pulse pressure and mean arterial blood pressure were determined from the femoral artery using a Gould-Statham P23 Dc transducer. Heart rate was counted from the blood pressure or ECG tracings. A bipolar EEG was recorded from two bilateral electrodes placed on the dura of the frontal lobe. Respiratory volume was measured from the tracheal cannula connected by a Rudolph valve to a Fleish pneumotachograph and differential pressure transducer (Gould-Statham PM 15 ETC). The output was integrated and recorded using Grass 7D polygraph. The air flow was calibrated by a Lab-Crest Low Flow rotameter.

Drugs

The drugs and doses used in the experiments were: naloxone hydrochloride (1 mg/kg) (Endo Laboratories, Inc., Garden City, NY), ethylketazocine methanesulfonate (EKC) (0.5 mg/kg) and (±)-N-allylnormetazocine (NANM, SKF-10,047) (1 mg/kg) (gifts from Dr. William Michne of Sterling-Winthrop Research Institute, Rensselaer, NY). EKC was dissolved in an acid solvent (pH 3.75), which consisted of a 3:2 ratio of 4.25% lactic acid and 0.05 N NaOH. The vehicle solution for NANM was composed of one-fifth lactic acid (4.25%) and four-fifths of normal saline. Drugs were administered over 10 seconds in 2 ml through the femoral vein cannula. Normal saline or acid solvent was administered via the same route and served as vehicle controls.

Statistics

Results from mean blood pressure (MBP), heart rate (HR) and

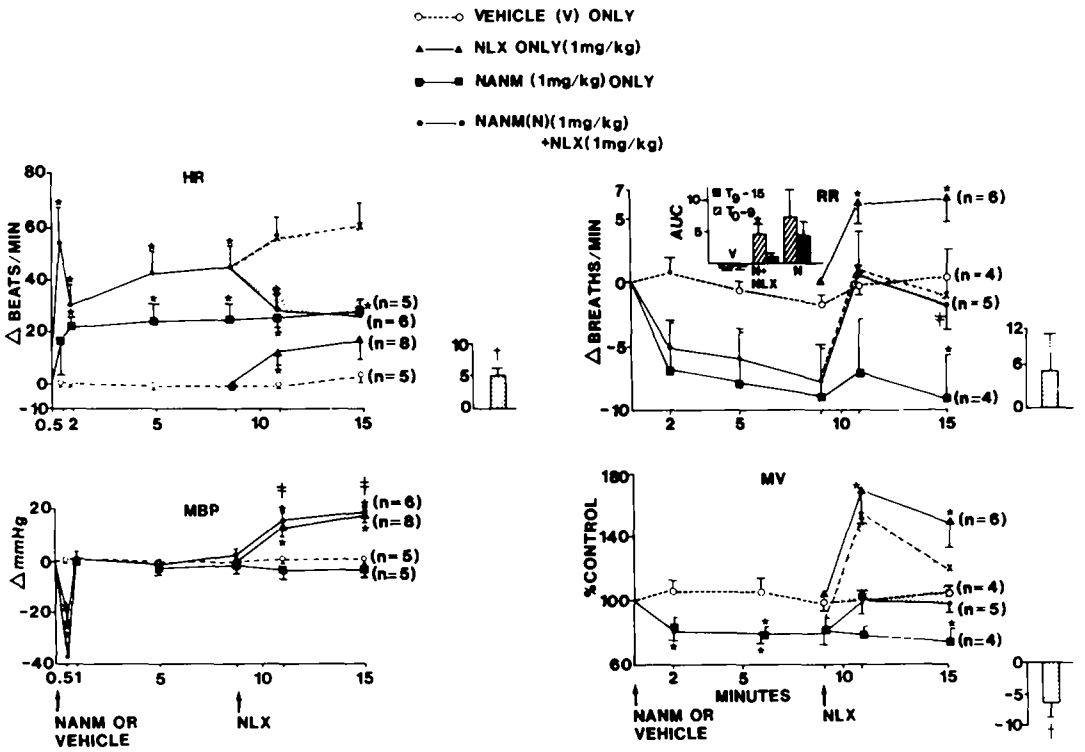

FIG. 3. Time action course of NANM and naloxone (NLX) alone and in combination on heart rate (HR), mean blood pressure (MBP), respiratory rate (RR) and minute volume (MV) in decerebrate dogs. *Indicates significant difference between vehicle and treatments ($p<0.05$). †Indicates significant difference between NANM (■) and post-NANM NLX (●) ($p<0.05$). The hypothetical curve (x) was constructed by adding the NLX values (▲) to the NANM values (■) at corresponding times (i.e., 9–15 minutes). The resulting curve, which represents algebraic sum of NLX's and NANM's independent action, is the best estimate of what NLX would do had it not antagonized the effects of NANM. The stippled area indicates the effect of NLX attributable to its antagonizing NANM's action. The bar diagrams and their units were explained in detail in Fig. 2. The inset on the top of RR graph shows the area (AUC) in each time period (minute).

respiratory rate (RR) were expressed as differences in MBP (mmHg), HR (beats/min) and RR (breaths/min) between predrug control and treatment values. Respiratory minute volume was expressed as a percent of predrug control value. Statistical analysis was done using a two-way analysis of variance and Dunnett's t-test for EKC and NANM studies. A Student's t-test was used for naloxone study.

RESULTS

Acutely decerebrated dogs exhibited the following signs: small pupil (1.6 ± 0.3 mm, $n = 7$), relaxation of the nictating membrane and a high amplitude slow wave EEG. Mean blood pressure ranged from 105 to 140 mmHg and heart rate from 120 to 160 beats/min. Naloxone (1 mg/kg) significantly increased mean blood pressure, heart rate, respiratory rate and minute volume (Fig. 1). Similar effects of naloxone have been reported previously (40).

Unlike the unchanged heart rate and respiratory rate observed in chronic spinal dogs (9) and intact dog (41), EKC (0.5 mg/kg) significantly decreased heart rate, respiratory rate, blood pressure and minute volume in the acutely decerebrated dog (Fig. 2). Naloxone injected at the ninth minute decreased the bradycardia, hypotension and respiratory depression produced by EKC. Since naloxone produced effects on these cardiovascular and respiratory parameters, the post-EKC naloxone data were corrected so that the effect of naloxone alone was subtracted as illustrated by the line connecting the X's. The stipple area represents naloxone's antagonism of EKC's effect and is presented as a bar graph and its standard error whose ordinate is the product of effect and time (min) (effect × min). This analysis showed that the effects of EKC on heart rate, blood pressure, and respiratory rate were significantly antagonized by naloxone and that minute volume was further depressed by naloxone.

NANM (1 mg/kg) produced tachycardia and a transient depressor response followed by a return of blood pressure to control level. The respiratory minute volume was decreased and respiratory rate was slightly depressed (Fig. 3). Naloxone (1 mg/kg) injected at the ninth minute after NANM increased blood pressure without significantly altering respiratory rate and minute volume. When post-NANM naloxone tachycardia data was corrected for the heart rate effect of naloxone (stippled area), it significantly antagonized NANM-induced tachycardia (stippled bar). Further, naloxone's stimulatory action on minute volume was significantly less in NANM-treated dogs than in vehicle-treated dogs (stippled area and bar).

To further understand the role of the lower brainstem and the spinal cord on the effects of EKC and NANM on blood pressure and heart rate, EKC and NANM were administered to artificially respired acutely spinalized decerebrated dogs (Table 1). EKC (0.5 mg/kg) lowered blood pressure and slowed heart rate in the C-1 spinalized decerebrated dog. Naloxone (1 mg/kg) injected at the ninth minute following administration of EKC antagonized these effects. NANM (1 mg/kg) did not change heart rate but slightly increased mean blood pressure in the spinalized decerebrated dog.

TABLE 1

EFFECT OF EKC AND NANM ON MEAN BLOOD PRESSURE AND HEART RATE IN THE SPINALIZED ACUTELY DECEREBRATED DOG

	Control	EKC (0.5 mg/kg)	Post-EKC NLX (1 mg/kg)
Heart rate (beats/minute)	131 ± 12	106 ± 7*	121 ± 8†
Mean blood pressure (mmHg)	64 ± 3	48 ± 3*	66 ± 4†
	Control	NANM (1 mg/kg)	
Heart rate (beats/minute)	127 ± 14	133 ± 13	
Mean blood pressure pressure (mmHg)	66 ± 3	70 ± 3*	

Values are mean ± S.E.M. (n=6 in EKC study; n=7 in NANM study).

*Significant difference between control and treatment ($p<0.05$) using a paired t-test comparison.

†Significant difference between EKC and post-EKC naloxone (NLX) ($p<0.05$).

DISCUSSION

These results speak to two issues, the multiple sites and mechanisms of action of EKC and NANM. EKC decreased heart rate, blood pressure and depressed respiration in acutely decerebrated dogs. Spinalization at C-1 level in the decerebrate dog reduced, but did not abolish hypotension and bradycardia produced by EKC suggesting that both a brainstem vasomotor center and a spinal cord or peripheral mechanism are involved in EKC-induced cardiovascular depression. This is in agreement with the observations that EKC microinjected into the region of nucleus ambiguus of the decerebrate dog produced bradycardia and hypotension (42). Similarly, MRZ 2459 and bremazocine, microinjected into the nucleus ambiguus produced hypotension, bradycardia and respiratory depression in anesthetized rats (12). It is interesting that EKC did not produce statistically significant changes in heart rate or respiratory rate in chronic spinal (9) and intact dogs (41). To explain these differences in effect of EKC between preparations, it is suggested that there may be kappaergic stimulant sites located above the level of the mesencephalon which counteract medullary kappa receptor-mediated vasomotor and respiratory depressant effects. It is well known that discrete areas of higher centers such as the hypothalamus, limbic systems and other cortical areas, when stimulated electrically, produced tachycardia, hypertension and facilitated respiration (16,39). The fact that MRZ 2549, when injected in the lateral ventricle of the conscious rats, produced tachycardia and hypertension (28) seems to be in line with the above reasoning on the stimulant kappaergic mechanism in higher centers. Further, kappa receptors have been found in the cortex, striatum, hippocampus, pyriform cortex and nucleus accumbens of other species (10).

Our results on EKC-induced cardiovascular depression suggest that a peripheral mechanism may also be involved. Gautret and Schmitt (8) have shown that intravenous EKC-induced hypotension and bradycardia in pentobarbital-anesthetized rats could not be fully abolished by vagotomy and atropine. They also showed that EKC could still slow the heart rate in beta-blocker tertatolol-treated pithed rats. Therefore, kappa receptors in the myocardium may be involved in EKC's action. Diprenorphine binding in the atrium can be competitively displaced by EKC (19) indicating opioid receptors in this tissue. Further, EKC diminished stimulation-evoked norepinephrine release from sympathetic nerve terminals innervating the sinus node of the isolated atrium, suggesting the existence of presynaptic kappa receptors in the heart (33).

The fact that naloxone rapidly and effectively reversed the cardiovascular depression produced by EKC indicates that these effects are opioid-receptor mediated. However, the observation that respiration was further depressed by naloxone in the EKC-pretreated decerebrate dog is perplexing particularly in view of naloxone's respiratory stimulant effect and the respiratory depressant actions of endogenous opioid peptides (6,7).

NANM produces tachycardia in both chronic spinal (21) and decerebrated dogs, but not in spinalized decerebrated dogs suggesting that the sympathetic vasomotor centers in the lower brainstem are required for NANM-induced tachycardia. NANM produced tachypnea in chronic spinal dog, but depressed respiratory rate and minute volume in decerebrate dog indicating that NANM's site of action in evoking tachypnea is located in supramedullary higher centers. Tachypnea can also be elicited by electrical stimulation in many discrete regions of higher centers such as perifornical nucleus, cingulate gyrus and lateral hypothalamus (39). It is not clear whether the sigma-mediated psychotomimetic effects are related to tachypnea. However, it has been shown that nalorphine and cyclazocine produced psychotomimetic effects together with respiratory depression in man (23,24), indicating that tachypnea and psychotomimetic effect are dissociable.

The mechanisms of action of NANM are complex. Certain effects of NANM cannot be reversed by naloxone or naltrexone. They are discriminative stimulus properties (1,31), thermoregulatory effects (3) and autonomic and behavioral effects (at 3.75 mg/kg) (37,38). Other effects of NANM, such as locomotor activity (14), inhibition of mouse writhing (25) and depression of the flexor reflex of the chronic spinal dog (22,38) can be reversed by doses of naloxone which are larger than those required to reverse morphine's actions. In the present study, post-NANM naloxone effectively antagonized NANM's effect on heart rate but not on respiration. It has been suggested (38) that (−)-NANM's naloxone antagonizable depression of the flexor reflex is due to its kappaergic activity. This hypothesis is an unlikely explanation of the ability of naloxone to antagonize (±)-NANM-induced tachycardia in the acutely decerebrated dog since EKC produces bradycardia in this preparation. The subtype of sigma receptors mediating respiratory stimulation could be different from those producing tachycardia and as previously discussed are located at different central nervous system sites. There is both pharmacologic and binding data indicating that there are multiple PCP-δ-type receptors (2, 44, 45) which may be related. Binding data indicate that these receptors do not interact with the opioid antagonists naloxone and naltrexone. There are, however, effects of NANM which can be antagonized by naloxone and naltrexone which cannot be attributed to μ and κ agonistic actions (e.g., tachycardia).

In summary, the present study has shown that the kappa agonist EKC produced cardiovascular and respiratory depression, phenomenon not observed in chronic spinal dog or intact dog studies, suggesting that there are kappaergic stimulant actions rostral to the mesencephalon which counteract the medullary depressant effects of EKC. NANM-induced tachypnea and tachycardia are dissociable in the acutely decerebrated dog. NANM-induced tachypnea may be evoked from supramedullary sites and involve nonopioid receptors, while the medulla oblongata is involved in NANM's naloxone antagonizable evoked tachycardia. The multiple and frequently antagonistic sites of action of NANM and EKC are revealed in different preparations and species. The anesthetic used

in preparing animals and in the conduct of experiments may also influence which sites and modes of action become manifest.

ACKNOWLEDGEMENT

This research was supported by a grant from the Tobacco and Health Research Institute of the University of Kentucky.

REFERENCES

1. Brady, K. T.; Balster, R. L.; May, E. L. Stereoisomers of N-allyl-normetazocine: Phencyclidine-like behavioral effects in squirrel monkeys and rats. Science 215:178–180; 1982.
2. Chang, K-J.; Cuatrecasas, P. Heterogeneity and properties of opiate receptors. Fed. Proc. 40:2729–2734; 1981.
3. Clark, W. G.; Bemardini, G. L.; Ponder, S. W. Central injection of a sigma opioid receptor agonist alters body temperature of cats. Brain Res. Bull. 7:279–281; 1981.
4. Cowan, A.; Doxey, J. C.; Metcalf, G. A comparison of pharmacological effects produced by leucine-enkephalin, methionine-enkephalin, morphine and ketacyclazocine. In: Kosterlitz, H. W., ed. Opiates and endogenous opioid peptides. Amsterdam: Elsevier/North Holland; 1976:29–102.
5. Feuerstein, G.; Faden, A. I. Differential cardiovascular effects of mu, delta and kappa opiate agonists at discrete hypothalamic sites in the anesthetized rat. Life Sci. 31:2197–2200; 1982.
6. Florez, J.; Mediavilla, A.; Pazos, A. Respiratory effects of β-endorpin, D-ala^2 Met-enkephalin-amide and met-enkephalin injected into the lateral ventricle and the ponomedullary subarachnoid space. Brain Res. 199:197–206; 1980.
7. Florez, J.; Pazos, A. Comparative effects of opioid peptides on respiration and analgesia in rats. Life Sci. 31:1275–1277; 1982.
8. Gautret, B.; Schmitt, H. Cardiac slowing induced by peripheral kappa opiate receptor stimulation in rats. Eur. J. Pharmacol. 102:159–163; 1983.
9. Gilbert, R. E.; Martin, W. R. The effects of morphine- and nalorphine-like drugs in the nondependent, morphine-dependent and cyclazocine-dependent chronic spinal dog. J. Pharmacol. Exp. Ther. 198:66–82; 1976.
10. Goodman, R. R.; Adler, B. A.; Pasternak, G. W. Regional distribution of opioid receptors. In: Pasternak, G. W., ed. The opioid receptors. Clifton, NJ: Humana Press; 1988:197–230.
11. Harris, L. S. Narcotic antagonists in the benzomorphan series: Respiratory, cardiovascular and behavioral effects in dogs. Naunyn Schmiedebergs Arch. Exp. Pathol. Pharmacol. 248:426–436; 1964.
12. Hassen, A. H.; Feuerstein, G.; Faden, A. I. Kappa opioid receptors modulate cardiorespiratory function in hindbrain nuclei of rat. J. Neurosci. 4:2213–2221; 1984.
13. Hassen, A. H.; Feuerstein, G.; Pfeiffer, A.; Faden, A. I. σ versus μ receptors: cardiovascular and respiratory effects of opiate agonists microinjected into nucleus tractus solitarius of cats. Regul. Pept. 4:299–309; 1982.
14. Iwamoto, E. T. Locomotor activity and antinociception after putative mu, kappa and sigma opioid receptor antagonists in the rat: Influence of dopaminergic agonist and antagonists. J. Pharmacol. Exp. Ther. 217:452–460; 1981.
15. Keats, A. S.; Telford, J. Narcotic antagonist as analgesics. In: Gould, R. F., ed. Molecular modification in drug design, advances in chemistry series No. 45. Washington: American Chemical Society; 1964:170–176.
16. Korner, P. I. Central nervous control of autonomic cardiovascular function. In: Berne, R. M., ed. Handbook of physiology, section 2, vol. I. The heart. Washington, DC: Am. Physiol. Soc.; 1980: 691–739.
17. Kosterlitz, H. W.; Waterfield, A. A.; Berthoud, V. Progress report on the assessment of the agonist and antagonist properties of narcotic analgesic drugs by their actions on the morphine receptor in the guinea-pig ileum. Presented to Committee on Problems of Drug Dependence, National Research Council; 1973:131–166.
18. Kosterlitz, H. W.; Paterson, S. J.; Robson, L. E. Characterization of the kappa-subtype to the opiate receptor in the guinea-pig brain. Br. J. Pharmacol. 73:939–949; 1981.
19. Krumins, S. A.; Faden, A. I.; Feuerstein, G. Opiate binding in rats hearts: modulation of binding after hemorrhagic shock. Biochem. Biophys. Res. Commun. 127:120–128; 1985.
20. Martin, W. R.; Eades, C. G.; Thompson, W. D.; Thompson, J. A.; Flanary, H. G. Morphine physical dependence in the dog. J. Pharmacol. Exp. Ther. 189:759–771; 1974.
21. Martin, W. R.; Eades, C. G.; Thompson, J. A.; Huppler, R. E.; Gilbert, P. E. The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. J. Pharmacol. Exp. Ther. 197:517–532; 1976.
22. Martin, W. R.; Eades, C. G.; Gilbert, P. E.; Thompson, J. A. Tolerance to and physical dependence on N-allylnormetazocine (NANM) in chronic spinal dogs. Subst. Alcohol Actions Misuse 1:269–279; 1980.
23. Martin, W. R.; Fraser, H. F.; Gorodetzky, C. W.; Rosenberg, D. E. Studies of the dependence producing potential of the narcotic antagonists 2-cyclopropylmethyl-2-hydroxy-5,9-dimethyl-6,7-benzomorphan (Cyclazocin, Win 20,740,ARC MLT-C-3). J. Pharmacol. Exp. Ther. 150:426–436; 1965.
24. Martin, W. R.; Gorodetzky, C. W. Demonstration of tolerance and physical dependence on N-allylnormorphine (nalorphine). J. Pharmacol. Exp. Ther. 219:192–198; 1981.
25. Pasternak, G. W.; Carroll-Buatti, M.; Spiegel, K. The binding and analgesic properties of a sigma opiate SKF 100 47. J. Pharmacol. Exp. Ther. 219:192–198; 1981.
26. Pearl, J.; Harris, L. S. Inhibition of writhing by narcotic antagonists. J. Pharmacol. Exp. Ther. 154:319–323; 1966.
27. Pfeiffer, A.; Feuerstein, G.; Faden, A.; Kopin, I. J. Evidence for an involvement of mu-, but not delta- or kappa-opiate receptors in sympathetically and parasympathetically mediated cardiovascular responses to opiates upon anterior hypothalamic injection. Life Sci. 31:1279–1282; 1982.
28. Pfeiffer, A.; Feuerstein, G.; Zerbe, R. L.; Faden, A. I.; Kopin, I. J. Mu-receptors mediate opioid cardiovascular effects at anterior hypothalamic sites through sympatho-adrenomedullary and parasympathetic pathways. Endocrinology 113:929–938; 1983.
29. Pierson, A. K.; Rosenberg, F. J. Progress report on the WIN-35197-2: Another benzomorphan with a unique analgesic profile. Presented to Committee on Problems of Drug Dependence, National Research Council; 1976:949–965.
30. Punnen, S.; Sapru, H. N. Cardiovascular responses to medullary microinjections of opiate agonists in urethane-anesthetized rats. J. Cardiovasc. Pharmacol. 8:950–956; 1986.
31. Shannon, H. E. Pharmacological evaluation of N-allynormetazocine (SKF 10,047) on the basis of its discriminative stimulus properties in rat. J. Pharmacol. Exp. Ther. 225:144–152; 1983.
32. Skingle, M.; Tyers, M. B. Evaluation of antinociceptive activity using electrical stimulation of the tooth pulp in the conscious dog. J. Pharmacol. Methods 2:71–80; 1979.
33. Starke, K.; Schoffel, E.; Illes, P. The sympathetic axons innervating the sinus node of the rabbit possess presynaptic opioid kappa- but not mu- or delta-receptors. Arch. Pharmacol. 329:206–209; 1985.
34. Swain, H. H.; Seevers, M. H. Progress report on the evaluation of new compounds for morphine-like physical dependence in the rhesus monkey. Presented to Committee on Problems of Drug Dependence National Research Council; 1974:1168–1195.
35. Tammisto, T.; Takki, S.; Toikka, P. A comparison of the circulatory effects in man of the analgesics fentanyl, pentazocine and pethidine. Br. J. Anaesth. 42:317–324; 1970.
36. Tyers, M. B. A classification of opiate receptors that mediate antinociception in animals. Br. J. Pharmacol. 69:503–512; 1980.
37. Vaupel, D. B. Failure of naltrexone to antagonize phencyclidine and the opioid SKF 10,047 in the dog. Fed. Proc. 41:1333; 1982.
38. Vaupel, D. B.; Risner, M. E.; Shannon, H. E. Pharmacologic and reinforcing properties of phencyclidine and the enantiomers of n-allylnormetazocine in the dog. Drugs Alcohol Depend. 18:173–194; 1986.
39. Wang, S. C.; and Ngai, S. H. General organization of central respiratory mechanisms. In: Fenn, W. O.; Rahn, H., eds. Handbook of physiology, section 3, vol. 1, Respiration. Bethesda, MD: Am.

Physiol. Soc.; 1964:487–505.
40. Wu, K. M.; Martin, W. R. Effects of fentanyl and naloxone in acutely decerebrated dogs. Life Sci. 31:151–158; 1982.
41. Wu, K. M. Effects of fentanyl, ethylketazocine, N-allylnormetazocine and naloxone in acutely decerebrated dogs. Thesis, University of Kentucky; 1983.
42. Wu, K. M.; Martin, W. R. An analysis of nicotinic and opioid processes in the medulla oblongata and nucleus ambiguus of the dog. J. Pharmacol. Exp. Ther. 277:302–307; 1983.
43. Wu, K. M.; Martin, W. R.; Kamerling, S. G.; Wettstein, J. G. Possible medullary kappa hyperalgesic mechanisms. I. A new potential role for endogenous opioid peptides in pain perception. Life Sci. 33:1831–1838; 1983.
44. Zukin, R. S.; Zukin, S. R. Multiple opiate receptors: emerging concepts. Life Sci. 29:2681–2690; 1981.
45. Zukin, R. S.; Zukin, S. R. The σ receptor. In: Pasternak, G. W., ed. The opiate receptors. Clifton, NJ: Humana Press; 1988:143–163.