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Identification of benzomorphan-κ opiate receptors in cerebral arteries which subserve relaxation

Bella T. Altura, Burton M. Altura & Remi Quirion[1]*

Department of Physiology, State University of New York, Downstate Medical Center, Brooklyn, New York 11203 and Biological Psychiatry Branch*, National Institute of Mental Health, Bethesda, Maryland 20205, U.S.A.

1 Several 'so-called' κ-opiate receptor agonists e.g., ketocyclazocine (Kc), ethylketocyclazocine (Ekc), bremazocine, MR-2034 and U-50488H, were tested on basilar and middle cerebral arteries of the dog *in vitro* for relaxant or contractile activities.

2 Ekc, Kc and bremazocine were found to produce concentration-dependent reductions in basal tone and to relax cerebral arteries contracted with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). All three agonists appear to act on benzomorphan-κ opiate receptors which subserve relaxation in cerebral blood vessels.

3 MR-2034 and U-50488H were found to induce contraction in the cerebral arteries. These opiate agonists appear to act on phencyclidine (PCP) or σ-opiate receptors which subserve contraction.

4 A variety of pharmacological antagonists (phentolamine, propranolol, methysergide, atropine, diphenhydramine, cimetidine, naloxone) did not modify any of the cerebral vascular effects produced by the opiates.

5 These results suggest: (1) specific benzomorphan-κ opiate receptors which subserve relaxation exist in cerebral blood vessels; (2) some κ agonists appear to produce, primarily, contraction in cerebral vessels via PCP or σ-opiate receptors: and (3) cerebral vascular muscle may provide a useful tool to analyse the molecular constitution of these two distinct and opposite-acting opiate receptors.

Introduction

In a series of papers, we have provided evidence for the existence of σ-opiate receptors in rat and canine cerebral blood vessels which subserve contraction (Altura & Altura, 1981; 1983; 1984; Altura *et al.*, 1983). Phencyclidine (PCP; 'Angel dust'), its analogues and a variety of benzomorphans were found to produce cerebrovasospasm of arterioles, arteries and venules via specific σ-opiate receptors. No evidence for μ- and δ-opiate receptors which subserve relaxation could be found on these cerebral blood vessels, in these *in vivo* and *in vitro* studies, despite the fact that such μ- and δ-opiate receptors have been observed on certain peripheral blood vessels (Altura *et al.*, 1980 a, b; Altura & Altura, 1984).

In preliminary studies (Altura *et al.*, 1983), we noted that a typical κ-opiate receptor ligand (Kosterlitz *et al.*, 1981; Wood & Charleson, 1982), namely ethylketocyclazocine (Ekc), appeared to produce dose-dependent relaxation of cerebral vessels. The present *in vitro* studies were, therefore, undertaken to determine whether a specific κ-opiate receptor does, indeed, exist in cerebral blood vessels and to make an attempt to characterize the latter.

[1]Present address: Douglas Hospital, Research Center, Verdun, Quebec, Canada H4H1R3.

Methods

Animals and cerebral artery preparations

Mongrel dogs of either sex weighing 15–20 kg were anaesthetized with pentobarbitone sodium (30 mg kg^{-1}, i.v.). After craniotomy the brain was rapidly removed and the basilar and middle cerebral arteries were excised (Altura & Altura, 1980). Helical strips were cut from segments of these cerebral arteries; the strips were 15 mm long by 1.5–2.0 mm wide (Altura & Altura, 1980). The strips were suspended isometrically under 1.0 g tension and incubated in 10 ml muscle chambers containing normal Krebs-Ringer bicarbonate solution (composition mM: NaCl 118, KCl 4.7, $CaCl_2$ 2.5, KH_2PO_4 1.2,

$MgSO_4$ 1.2, glucose 10 and $NaHCO_3$ 25) at 37°C, through which O_2 (95%) and CO_2 (5%) was bubbled. The loading tension was periodically adjusted and maintained throughout the equilibration time. The incubation media were routinely changed every 10 to 15 min as a precaution against interfering metabolites (Altura & Altura, 1970). The force of contraction was measured with Grass FT-03 force-displacement transducers and recorded on a Grass Model 7 polygraph. Two hours after incubation under tension, the preparations were tested with 30 mM KCl, then after an approximate 0.5 h washout, followed by relaxation to baseline tension, the experiments were carried out.

Types of experiment

The following experiments were carried out:
(1) Single or cumulative doses of PCP, Ekc, ketocyclazocine (Kc), bremazocine, (−) - α - (1R, 5R, 9R)-5, 9-dimethyl-2-(L-tetrahydrofurfuryl)-2'-hydroxy-6,7-benzomorphan (MR-2034), and *trans*-3, 4, dichloro - N - methyl - N - (2 - (1-pyrrolidinyl) cyclohexyl)-benzeneacetamine (U-50488H) (Piercy *et al.*, 1982; Szmuskovicz & Von Voigtlander, 1982) were added to the incubated arteries to determine what influence these agents had on baseline resting tension.

(2) Some preparations were exposed to single or cumulative doses of PCP, Ekc, Kc, bremazocine, MR-2034 and U-50488H after induction of sustained contractile responses by $\cong EC_{50}$ doses of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) in order to determine whether any of these agents would induce relaxation of the $PGF_{2\alpha}$-induced contraction. These cumulative dose-responses were expressed as a percentage of control where the EC_{50} $PGF_{2\alpha}$ contractile tension response was set at 100%.

(3) In some additonal experiments, cerebral arteries were exposed to certain specific pharmacological antagonists 10–20 min before the addition of PCP, Ekc, Kc, bremazocine, MR-2034 and U-50488H to determine whether these agents are affected by α-adrenoceptor blockade (phentolamine, 0.5 μg ml^{-1}), β-adrenoceptor blockade (propranolol, 0.5 μg ml^{-1}), 5-hydroxytryptamine (5-HT) receptor blockade (methysergide maleate 0.5 μg ml^{-1}), cholinoceptor blockade (atropine sulphate, 0.5 μg ml^{-1}), histamine receptor blockade (diphenhydramine HCl and cimetidine, 0.5 μg ml^{-1}) or opiate receptor blockade (naloxone, 0.5–1.0 μg ml^{-1}). All of the pharmacological antagonists were used in concentrations that inhibit responses elicited to EC_{50}–EC_{70} concentrations of their respective agonists (Altura & Altura, 1981; Altura *et al.*, 1983).

Contractile and relaxant responses were evaluated by threshold concentration (concentration necessary to produce the first sign of contraction or relaxation). EC_{50} (concentration of agonist necessary to produce half-maximal tension), IC_{50} (concentration of agonist necessary to produce half-maximal relaxation), maximal contractile tension, and maximal relaxation.

Drugs

The following drugs and chemicals were used: phencyclidine HCl (National Institute on Drug Abuse), ethylketocyclazocine (Sterling-Winthrop Research Labs), ketocyclazocine (Sterling-Winthrop Research Labs), bremazocine (Sandoz Ltd.), MR-2034 (Boehringer Ingelheim), U-50488H (Dr VonVoigtlander, The UpJohn Company), phentolamine HCl (Regitine, Ciba Pharmaceutical Co.) (±)-propranolol HCl (Sigma Chemical Co.), methysergide maleate (Sandoz Ltd.), atropine sulphate (Mann Research Labs), diphenhydramine HCl (Benadryl, Parke Davis and Company), cimetidine HCl (Smith, Kline and French Labs), naloxone HCl (Endo Labs). $PGF_{2\alpha}$ (The UpJohn Company), 5-hydroxytryptamine (serotonin) creatinine sulphate (Sigma Chemical Co.) and potassium chloride (Fisher Scientific Company). The concentration of each drug or chemical is expressed as final bath concentration.

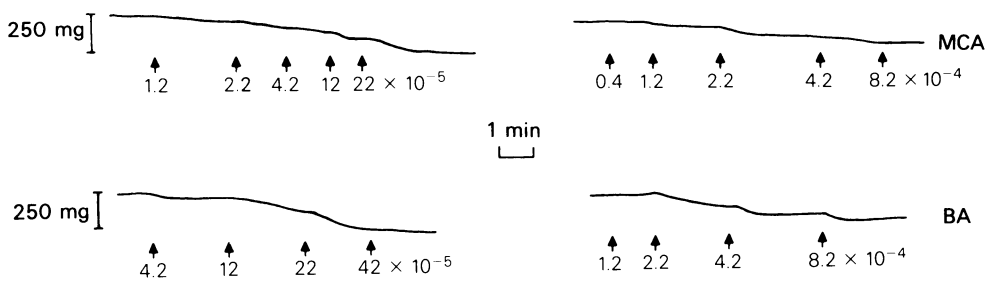

Figure 1 Influence of ethylketocyclazocine (left panels) and bremazocine (right panels) on resting tone of canine isolated middle cerebral (MCA) and basilar arteries (BA). Arrows indicate points at which cumulative concentrations (M) of the agonists were added.

Statistical analyses

Where appropriate, the means ± s.e.means of the responses were compared for statistical significance by Student's t test and considered significant if $P < 0.05$.

Results

Influence of ketocyclazocine, ethylketocyclazocine and bremazocine on the baseline tension of canine middle cerebral and basilar arteries

Addition of either Ekc or bremazocine to canine isolated middle cerebral and basilar arteries produced a concentration-dependent reduction of baseline, resting tension (Figure 1). Threshold relaxations were usually elicited by concentrations of Ekc from 2.52 to 5.87×10^{-5} M and concentrations of bremazocine from 1.2 to 4.2×10^{-4} M. Although not shown, Kc was also found to elicit reductions of baseline tension at threshold concentrations of $6.2-8.5 \times 10^{-5}$ M. Maximum reductions in baseline tension for all three agonists ranged from 75 to 200 mg. In terms of a rank order of potency Ekc > Kc > bremazocine. In 70–80% of the experiments ($n = 12$), the middle cerebral arteries exhibited a lower threshold sensitivity than did the basilar arteries to the agonists, e.g., Ekc ($2.52 \pm 0.42 \times 10^{-5}$ M vs. $5.87 \pm 0.58 \times 10^{-5}$ M); bremazocine ($1.22 \pm 0.34 \times 10^{-4}$ M vs. $3.45 \pm 0.52 \times 10^{-4}$ M).

Influence of ethylketocyclazocine, ketocyclazocine and bremazocine on contractions induced by prostaglandin $F_{2\alpha}$

As shown in Figure 2, Ekc, Kc and bremazocine produced concentration-dependent relaxation of EC_{50} contractions induced by $PGF_{2\alpha}$ in middle cerebral and basilar arteries. Complete reversal of the induced spasms could be obtained with all opiate agonists (Figure 3). It is clear from the concentration-response curves (Figure 3) and the data in Table 1 that (1) there is a relative order of relaxant potency, where Ekc > Kc > bremazocine, (2) the concentration relaxant-response curves for all three opiates appear to be parallel, and (3) middle cerebral arteries appear to be more sensitive to the inhibitory actions of Ekc, Kc and bremazocine than are basilar arteries.

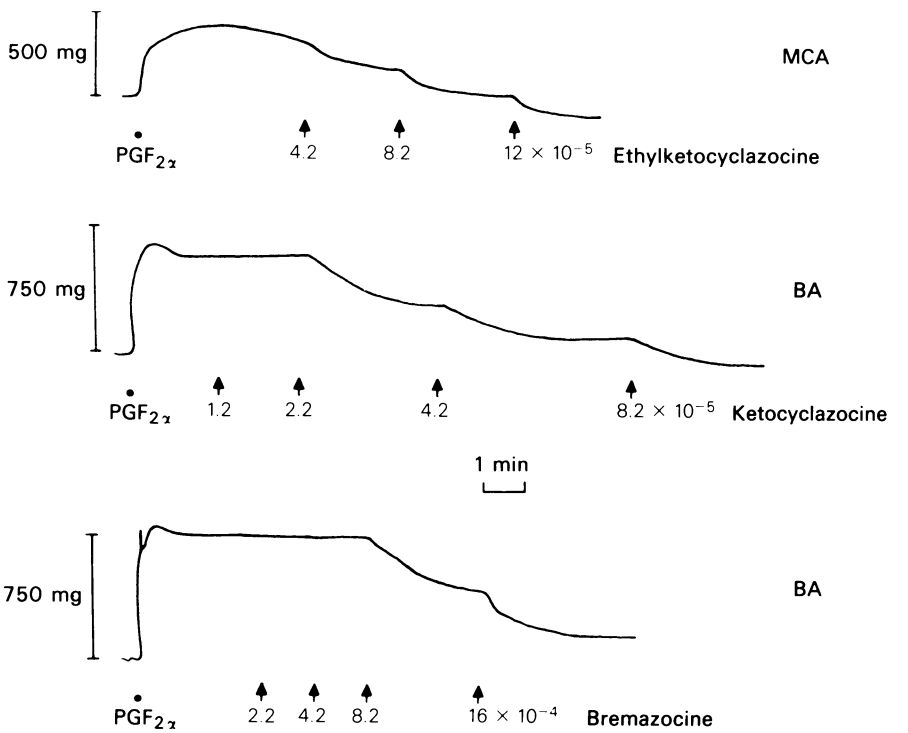

Figure 2 Ethylketocyclazocine, ketocyclazocine and bremazocine relax cerebral arterial spasms induced by prostaglandin $F_{2\alpha}$ ($1-2\ \mu g\ ml^{-1}$). $PGF_{2\alpha}$ was added at the dot prior to cumulative addition of increasing concentrations (M) of the various κ agonists.

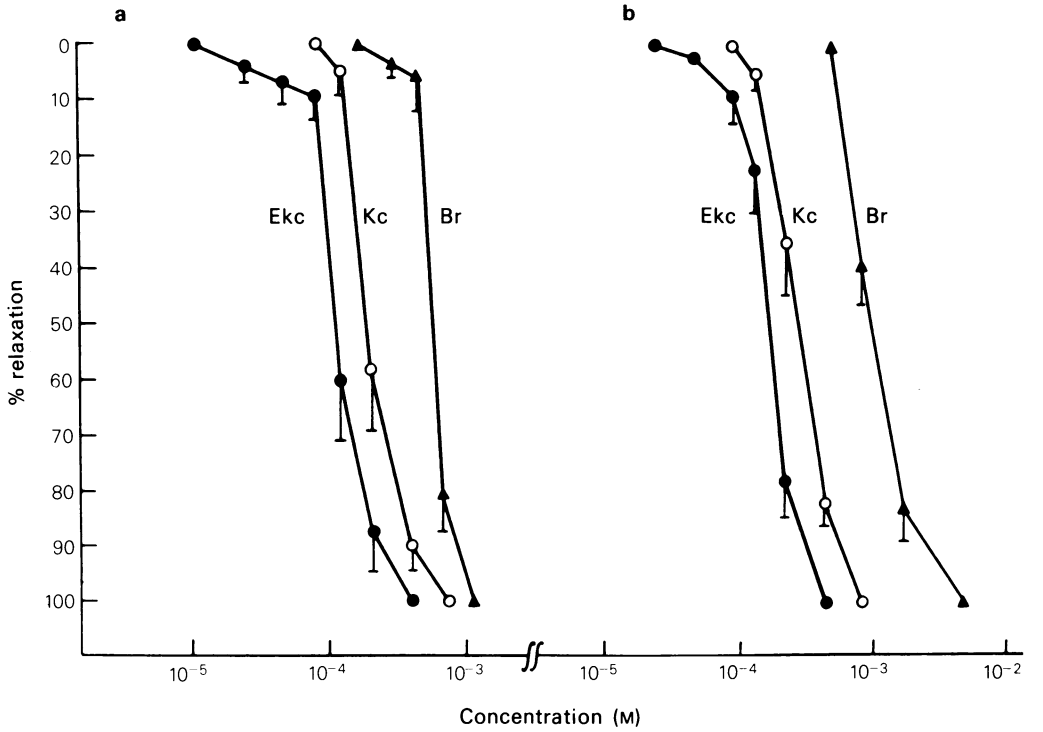

Figure 3 Comparative inhibitory potency of ethylketocyclazocine (●, Ekc), ketocyclazocine (○, Kc) and bremazocine (▲, Br) on EC_{50} prostaglandin $F_{2\alpha}$-induced contractions in canine isolated middle cerebral (a) and basilar (b) artery. $n = 5$. Values are means, with s.e.means shown by vertical lines.

Table 1 Comparison of the concentrations of ethylketocyclazocine (Ekc), ketocyclazocine (Kc) and bremazocine required to cause threshold inhibition and to reduce to one-half contractions induced by prostaglandin $F_{2\alpha}$ in canine isolated middle cerebral and basilar arteries

Agonist	*Threshold inhibitory concentration* ($\times 10^{-4}$ M)	IC_{50} ($\times 10^{-4}$ M)
Middle cerebral artery		
Ekc	0.34 ± 0.07	1.18 ± 0.22
Kc	1.26 ± 0.22	2.13 ± 0.31
Bremazocine	3.68 ± 0.47	6.06 ± 0.58
Basilar artery		
Ekc	0.58 ± 0.08	1.92 ± 0.36
Kc	1.42 ± 0.24	2.92 ± 0.47
Bremazocine	7.12 ± 0.61	9.83 ± 0.87

The values in the table are the mean(± s.e.mean) from 5 different dogs for each agonist.

Phencyclidine, MR-2034 and U-50488H produce concentration-dependent contraction of canine middle cerebral and basilar arteries

Since MR-2034 and U-50488H have been reported to act as κ-opiate agonists on some mammalian test systems (Wood *et al.*, 1981; Piercey *et al.*, 1982; Szmuskovicz & VonVoigtlander, 1982; Wood & Charleson, 1982; VonVoigtlander *et al.*, 1983), it was of interest to determine whether these agonists can also produce relaxation of cerebral arteries, as does Ekc, Kc and bremazocine. However, as can be seen in Figure 4, both MR-2034 and U-50488H produced contractile responses, similar to those elicited by PCP. In view of the latter unexpected finding, we examined a complete, wide range of concentrations of MR-2034 and U-50488H (e.g. 10^{-8} to 5×10^{-2} M) and compared these contractile concentration-response curves to those elicited by PCP. The data shown in Figure 5 and Table 2 indicate that (1) the concentration-effect curves for both MR-2034 and U-50488H are either parallel to those for

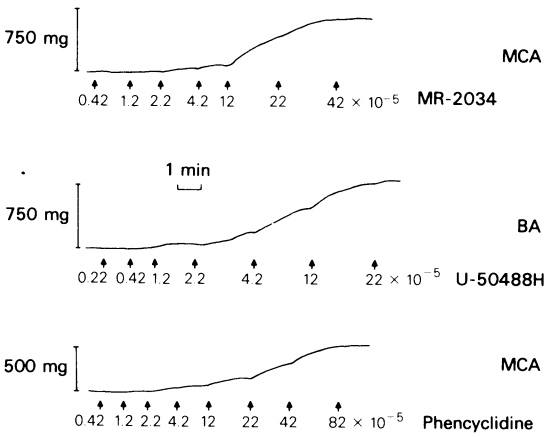

Figure 4 MR-2034, U-50488H and phencyclidine produce concentration-dependent contractions of canine isolated cerebral arteries.

PCP or occupy approximately the same positions; (2) the contractile concentration-effect curves for U-50488H are displaced to the left of those for PCP on both types of cerebral arteries; and (3) the maximal contractile responses (i.e., intrinsic activities) for both MR-2034 and U-50488H are significantly smaller than those for PCP.

It should be stated that addition of either PCP, MR-2034 or U-50488H to EC_{50} $PGF_{2\alpha}$-induced contractions only elicited further increments in contractile tension, quite unlike the relaxations noted for Ekc, Kc and bremazocine.

Influence of receptor occupation by phencyclidine on subsequent responses to MR-2034 and U-50488H

If MR-2034 and U-50488H are partial agonists which act on the PCP receptor, which subserves contraction, then PCP at a concentration above that needed to produce a maximum contraction should interfere or prevent contractions induced by MR-2034 and U-50488H; other contractile agonists acting on other receptors, however, should not interfere with either of the latter drugs.

The representative experiments ($n = 10$) shown in Figure 6 indicate that incubation of cerebral arteries with maximal concentrations of PCP prevents subsequent contractile responses to MR-2034 and U-50488H and *vice-versa*, despite the fact that the tissues are capable of developing greater tensions to KCl and 5-HT. In addition, these tracings demonstrate that neither MR-2034 nor U-50488H prevent subsequent contractile responses to other agonists such as 5-HT and $PGF_{2\alpha}$ (above).

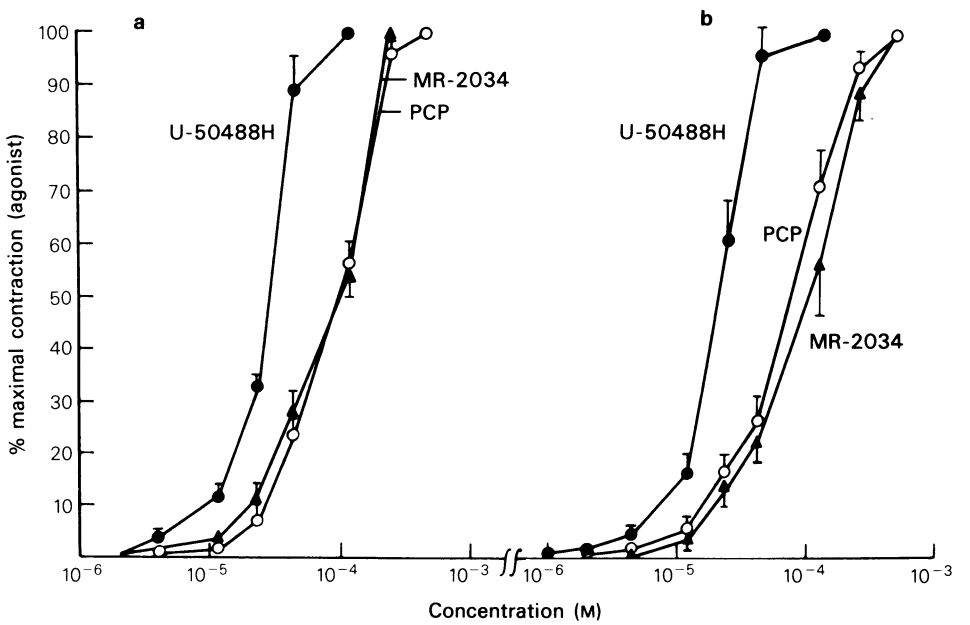

Figure 5 Contractile concentration-effect curves for U-50488H (●), MR-2034 (▲) and phencyclidine (○, PCP) on canine isolated middle cerebral (a) and basilar (b) arteries. Values are means with s.e.means shown by vertical lines, $n = 20$ and 19, respectively.

Table 2 Relative contractile sensitivity of canine isolated middle cerebral and basilar arteries to U-50488H, MR-2034 and phencyclidine HCl (PCP)

Agonist	*Minimal effective concentration* ($\times 10^{-6}$ M)	EC_{50} ($\times 10^{-5}$ M)	*Maximal tension* (mg)
Middle cerebral artery			
U-50488H	3.84 ± 0.34*	2.74 ± 0.32*	202 ± 15.4*
MR-2034	4.86 ± 0.28*	8.89 ± 0.68	226 ± 16.8*
PCP	15.4 ± 1.18	8.84 ± 0.66	303 ± 18.6
Basilar artery			
U-50488H	2.42 ± 0.28*	1.82 ± 0.18*	320 ± 28.6*
MR-2034	3.88 ± 0.36*	9.74 ± 0.88*	382 ± 36.5*
PCP	12.4 ± 1.06	6.88 ± 0.58	542 ± 42.4

Values are means (± s.e.means) of 20 and 18 dogs respectively.
*Significantly different from mean value for PCP ($P < 0.05$)

Influence of pharmacological antagonists on ethylketocyclazocine, bremazocine, phencyclidine, MR-2034 and U-50488H responses of cerebral arteries

Adrenoceptor (phentolamine, propranolol), 5-HT receptor (methysergide), cholinoceptor (atropine), histamine receptor (diphenhydramine, cimetidine), and opiate receptor (naloxone) antagonists could not modify either the Ekc, Kc and bremazocine-relaxations or the PCP, MR-2034 and U-50488H-induced contractions observed in the canine middle cerebral and basilar arteries.

Discussion

According to the pioneering studies of Martin and co-workers (Martin *et al.*, 1976; Iwamoto & Martin, 1981; as well as Lord *et al.*, 1977), there are multiple types of opiate receptors: μ, κ, σ and δ. This concept has resulted in the design of drugs that are thought to be specific for several of these opiate receptors in a number of mammalian test systems, for example, MR-2034 and U-50488H for the κ receptor (Charleson *et al.*, 1981; Iwamoto & Martin, 1981; Piercey *et al.*, 1982; Szmuskovicz & Von Voigtlander, 1982). With reference to the actions of, and types of receptors for, opiates on the cerebral and peripheral circulation, it is not clear whether κ opiate receptors subserve relaxation or constriction (Altura *et al.*, 1980a; Holaday, 1983). In addition, no definitive information is available as to whether there are multiple opiate receptor types on cerebral vascular smooth muscle.

This paper demonstrates a relaxant activity on cerebral blood vessels for several types of κ opiate agonists: Kc, Ekc and bremazocine. However, we

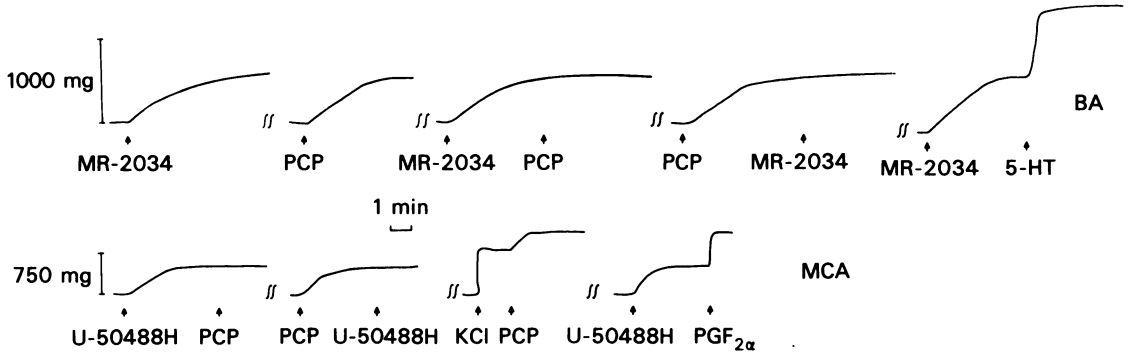

Figure 6 Influence of receptor, occupation by phencyclidine (PCP) on subsequent contractile responses to MR-2034 (2.2×10^{-4} M), U-50488H (8.2×10^{-5} M), 5-hydroxytryptamine (5-HT, 1 μg ml^{-1}) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$ 2 μg ml^{-1}). The various agonists were added at the arrows. The top panels represent results from a single basilar artery, whereas as the lower panels are the results from a single middle cerebral artery.

also show that other so-called κ opiate agonists, MR-2034 and U-50488H, produce contraction rather than relaxation on the same cerebral blood vessels.

Although Ekc and Kc and bremazocine are benzomorphan derivatives, we have recently found that other typical benzomorphans (e.g., pentazocine, cyclazocine, and N-allyinorcyclazocine) produce contractions, rather than relaxation of cerebral blood vessels, both *in vitro* and *in situ* (Altura *et al.*, 1983; Altura & Altura, 1984). The latter benzomorphan agonists appear to act on specific PCP σ-like receptors (Altura *et al.*, 1983), similar to the findings noted with MR-2034 and U-50488H in the present report. Since neither μ-opiate morphinans (e.g., morphine, codeine, levorphanol) nor δ-opiate enkephalins produce relaxation on either the cerebral arteries or intact rat cerebral (pial) arterioloes and venules (Altura *et al.*, 1983; Altura & Altura, 1984), it would appear that Ekc, Kc and bermazocine may act on specific benzomorphan-κ opiate receptors which subserve relaxation and vasodilatation in certain cerebral blood vessels. However, these benzomorphan-κ opiate receptors appear to be very different from κ-opiate binding sites characterized thus far. First, the order of potency of the agonists is different (e.g., Ekc > Kc > bremazocine *vs.* bremazocine > Ekc > Kc). Second, naloxone (an opiate receptor antagonist), in the concentrations used, did not block the relaxant effect of the benzomorphans in our bioassay. Thus, these observations suggest that these opiate receptors are different from those characterized, so far, in the CNS.

Although the other so-called κ agonists, MR-2034 and U-50488H, appear to act on PCP or σ-opiate receptors which subserve contraction, which is supported by the concentration-effect curves which are parallel to PCP and the cross-receptor occupation experiments (e.g., Figure 6), the possibility cannot be eliminated that MR-2034 and U-50488H might also possess some κ opiate relaxant activity which is masked by the strong σ-opiate receptor contractile actions. The reduced intrinsic contractile activity of MR-2034 and U-50488H could be used in support of the latter possibility. In other words, the decreased maximal contractile effects of MR-2034 and U-50488H could be a result of a strong, partial contraction and a weak, partial relaxation. It is also possible that these agonists could act on a type of κ receptor different from that for Ekc, Kc and bremazocine. The vasodilator-like actions of Ekc, Kc and bremazocine could be of potential clinical value in cases of cerebral vasospasm and cerebral resuscitation.

In view of the present findings and those reported elsewhere (Altura & Altura, 1981; 1983; 1984; Altura *et al.*, 1983), one must consider the possibility that cerebrovascular smooth muscle may provide a useful tool to analyse the molecular constitution of the benzomorphan-κ opiate receptor which subserves relaxation and the PCP receptor which subserves contraction. In addition, cerebral vascular muscle may provide specific bioassays for these two types of opposite acting receptors.

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