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Opiate Receptor Mediated Hyperthermic Responses in Rat Following Ca^{++} Channel Antagonists

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PILLAI, N. P. AND D. H. ROSS. *Opiate receptor mediated hyperthermic responses in rat following Ca^{++} channel antagonists*. PHARMACOL BIOCHEM BEHAV **25**(3) 555–560, 1986.—The effects of morphine sulfate on rectal temperature and on Ca^{++}-stimulated Mg^{++}ATPase activity in crude synaptosomal fraction (P_2) of cortex, hypothalamus and cerebellum were investigated in rat. Morphine (3–15 mg/kg, SC) produced hyperthermia at 30–120 min after the drug administration. The Ca^{++}/Mg^{++} ATPase activity in hypothalamus and cortex was decreased while there was no change in Mg^{++}ATPase activity. The enzyme activity in cerebellum was not affected. The opiate antagonist naloxone hydrochloride (5 mg/kg, SC) antagonized the effect of morphine on rectal temperature and Ca^{++}/Mg^{++}ATPase activity. The effects of different calcium channel antagonists (nimodipine 1 mg/kg, verapamil 2.5 mg/kg and diltiazem 10 mg/kg, SC) on the changes induced by morphine were also investigated. These antagonists not only antagonized morphine hyperthermia, but also the inhibitory effect of morphine on Ca^{++}/Mg^{++}ATPase activity in hypothalamus. The calcium channel agonist BAY K8644 (3 mg/kg, SC) produced hypothermia and also stimulation of Ca^{++}/Mg^{++}ATPase activity in hypothalamus. Naloxone failed to alter these effects of BAY K8644. These studies demonstrate that Ca^{++} transport in hypothalamus, as indicated by Ca^{++}/Mg^{++}ATPase activity, plays an important role in thermoregulation and thermoregulatory changes induced by opiates.

Ca^{++} channel antagonists Hyperthermia Morphine

PREVIOUS studies have implicated a role for Ca^{++} in the mechanism of actions of opiates. (For review, see [7,27]). Ca^{++} can inhibit morphine-induced analgesia [12] while Ca^{++} antagonists such as La^{+++} and the Ca^{++} chelator EGTA, can inhibit the effect of Ca^{++} on opiate analgesia. In parallel with development of analgesia, opiates have been shown to reduce Ca^{++} content and binding in synaptosomal membrane fractions, and to inhibit voltage-dependent $^{45}Ca^{++}$ influx in intact synaptosomes [10,26]. These effects are stereospecific and blocked by naloxone. Tolerance develops to the biochemical changes with increased Ca^{++} content and binding in brain synaptosomal fractions [27].

Opiates and opiate peptides are known to produce profound changes in thermoregulation. (For review, see [1,8]). In unrestrained rats, morphine produces changes in body temperature dependent on dosage and route of administration [19–21]. Evidence suggests that this change in temperature may relate to Ca^{++} movements in the hypothalamus. Myers [23] has proposed that alterations in Ca^{++} movement in the hypothalamus can alter the set point for thermoregulation. The effect of opiates on Ca^{++} transport suggests that opiates may act as Ca^{++} antagonists in producing analgesia.

The use of specific organic Ca^{++} antagonists may be helpful in understanding the opiate mechanism of actions on temperature and to investigate the possible role for Ca^{++} in this pharmacological response. In the present study, we have used three classes of Ca^{++} antagonists represented by verapamil, diltiazem and nimodipine to investigate the role of Ca^{++} in opiate effects on thermoregulation. Although earlier studies have reported the relative ineffectiveness of Ca^{++} channel blocking drugs on voltage-dependent Ca^{++} influx in synaptosomes [9], recent studies [22,31] have demonstrated that BAY K8644 can induce Ca^{++} influx in a manner which is specifically blocked by dihydropyridine Ca^{++} antagonists. Thus, two types of channels, voltage sensitive and DHP sensitive may exist in many preparations. Additionally, recent studies have shown that chronic opiate treatment can increase dihydropyridine receptor binding, while *in vitro* treatment with opiates was ineffective [5,25]. This paradox may relate to the different mechanisms for opiate and dihydropyridine receptor coupling to the Ca^{++} channel by analogy to verapamil and deltiazem.

As a biochemical index of thermoregulation, we have chosen to measure Ca^{++} ATPase activity to illustrate possible drug induced changes in parallel with hyperthermia.

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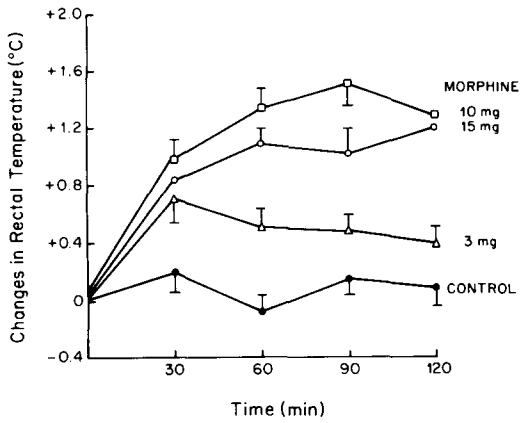

FIG. 1. Effect of different doses of morphine sulfate (3, 10 and 15 mg/kg, SC) on rectal temperature in rats. Each point denotes the mean±SEM of 4 experiments.

Opiates have been reported to alter Ca^{++} content, $^{45}Ca^{++}$ binding and voltage sensitive Ca^{++} influx (for review, see [27]). If Ca^{++} content and transport are reduced by opiates, then other intracellular mechanisms for regulation of Ca^{++} transport may also be altered. Ca^{++} ATPase activity was chosen for study since this enzyme is responsible for a major buffering activity to regulate free cytosolic Ca^{++} [28]. If opiates are altering free intracellular Ca^{++}, this index of Ca^{++} transport may be responsive and highly sensitive to rapid changes in cytosolic Ca^{++}. Myers [23] has reviewed the data suggesting that Ca^{++} in the hypothalamus may be important for regulating temperature set point. Therefore, we have studied Ca^{++} ATPase activity following morphine induced hyperthermia.

METHOD

Measurement of Body Temperature

All experiments were performed at ambient temperature of 24±1°C. Male Sprague-Dawley rats weighing between 150–200 g were used throughout all experiments. Rectal temperature was monitored using a telethermometer (Yellow Springs Instrument, Co.) and insertion of the probe to the depth of 6.5 cm. Temperature readings were taken following a stabilization period of 1 minute. During temperature measurement, rats were unrestrained and maximum care was taken to avoid stress due to handling. Basal temperature prior to beginning experiments was taken as the average of two initial readings. Drug administration was initiated between 7:30–8:30 a.m. with readings taken at 30 min intervals for two hours following drug administration. Following the last temperture reading, animals were sacrificed by decapitation and brains removed for biochemical studies. Nimodipine was dissolved in polyethylene glycol-400. Morphine sulphate was diluted from a stock concentration of 15 mg/ml (Eli Lilly Co.) into 0.9% saline. Diltiazem and verapamil were weighed out and dissolved into 0.9% saline.

Preparation of Brain Region Synaptosomal Fractions

Following removal of rat brains, the cortex, hypothalamus and cerebellum were dissected, immediately placed in ice cold saline and rinsed free of adhering blood vessels. A 10% homogenate of each brain region in 0.32 M sucrose was prepared with a teflon-glass homogenizer. The homogenate was centrifuged at 1500×g for 10 min and the supernatant collected. This supernatant was then centrifuged at 9000×g for 20 minutes to yield the crude synaptosomal pellet. This P_2 pellet was lysed with a buffer containing 20 mM Tris and DTE (0.5 mM) pH 8.5 for 60 min. This final suspension was then washed and resuspended following a 40,000×g spin to yield a protein concentration of approximately 1 mg/ml.

TABLE 1

EFFECT OF MORPHINE ON Ca^{++} AND Mg^{++} ATPase ACTIVITY IN RAT BRAIN REGIONS

Brain Region	Enzyme Activity (nmoles/mg/min) Mean ± SEM (n) Ca^{++} ATPase	Mg^{++} ATPase
Hypothalamus		
Control	38.2 ± 0.6 (4)	267.3 ± 9.0 (4)
Morphine (15 mg/kg SC)	32.9 ± 1.5* (3)	256.5 ± 15.6 (4)
Cortex		
Control	91.8 ± 5.2 (4)	147.0 ± 9.0 (4)
Morphine (15 mg/kg SC)	77.6 ± 3.9* (3)	145.4 ± 3.7 (3)
Cerebellum		
Control	108.5 ± 4.1 (3)	152.0 ± 8.7 (3)
Morphine (15 mg/kg SC)	112.4 ± 4.8 (3)	162.6 ± 4.0 (3)

*$p<0.05$ vs. control (Student's t-test).

Assay of Enzyme Activity

Ca^{++}- and Mg^{++}ATPase activities were assayed according to methods previously outlined [28]. Aliquots of membrane protein (100 μg per tube) were incubated in buffer (pH 7.4) containing the following ingredients in final concentration: HEPES (20 mM), KCl (100 mM), $MgCl_2$ (150 μM), EGTA (100 μM), sodium azide (10 mM) and ouabain (0.5 mM) for 5 min at 37°C. Free Ca^{++} concentrations were determined using EGTA buffers according to the calculations of Bartfai [2]. The reaction was initiated by the addition of ATP 150 μM). Blanks contained no Ca^{++} or Mg^{++}. Reactions were run for two minutes and were terminated by the addition of 200 μl of 6 N HCl. Assay tubes were immediately removed to an ice bath and P_i release was estimated by the micromethod of Lanzetta *et al.* [16]. Two hundred μl of the assay mixture was added to 800 μl of malachite green reagent After 60 sec, the reaction was quenched by the addition of 100 μl of 34% sodium citrate. This reaction was allowed to stabilize at room temperture for 30 min following which the samples were read in a Beckman 35 spectrophotometer at 660 nm. Calcium or magnesium ATPase activities were expressed as P_i released/mg/min. Ca^{++}-stimulated ATPase is calculated as the difference between Ca^{++} + Mg^{++} (total) and Mg^{++} (basal) activity. Sodium azide was included to inhibit mitochondrial ATPase activity [17]. Protein concentrations were determined by the method of Lowry *et al.* [18] using bovine serum albumin as standard.

Materials and Chemicals

The following drugs were used and their sources are:

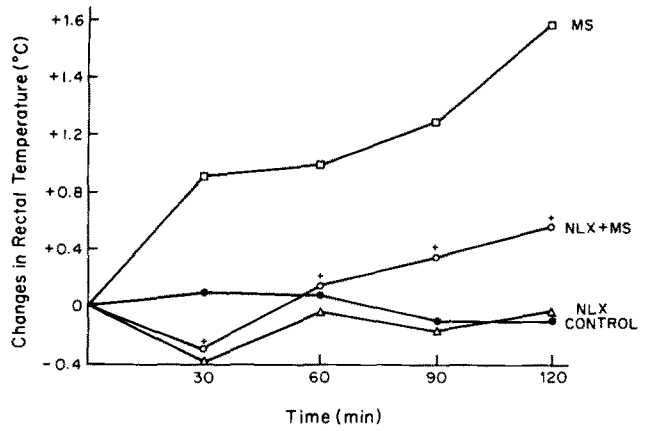

FIG. 2. Effect of naloxone HCl (NLX, 5 mg/kg, SC) on morphine (MS, 15 mg/kg, SC) induced hyperthermia. Naloxone was administered 15 min before morphine. $^{+}p<0.001$ vs. morphine (Student's t-test).

TABLE 2

EFFECT OF MORPHINE ON REGIONAL BRAIN Ca^{++} ATPase ACTIVITY

	Ca^{++} ATPase nmoles/mg/min Mean ± SEM		
	Hypothalamus	Cortex	Cerebellum
Control	39.0 ± 1.9	93.3 ± 5.4	118.2 ± 3.4
Morphine (15 mg/kg SC)	31.5 ± 2.3*	78.8 ± 5.6*	111.8 ± 5.0
Morphine + Naloxone	38.9 ± 1.6†	100.8 ± 9.7†	114.6 ± 1.6
Naloxone (5 mg/kg)	38.2 ± 2.9	92 ± 11.9	125.0 ± 5.9

*$p<0.05$ vs. control.
†$p<0.05$ vs. morphine.

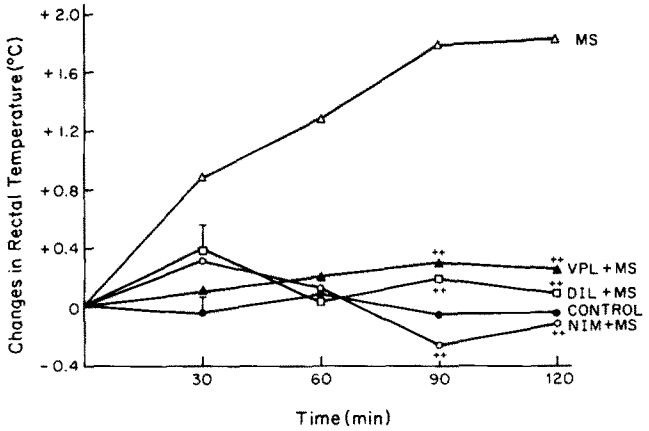

FIG. 3. Effect of calcium channel antagonists on morphine (15 mg/kg, SC) hyperthermia. The calcium channel antagonists were administered (SC) 15 min before morphine. VPL-Verapamil (2.5 mg/kg), DIL-Diltiazem (10 mg/kg) and NIM-Nimodipine (1 mg/kg). $^{++}p<0.01$ vs. morphine (Student's t-test).

TABLE 3

EFFECTS OF Ca^{++} ANTAGONISTS ON MORPHINE INHIBITION OF Ca^{++} ATPase IN HYPOTHALAMUS

	Ca^{++} ATPase nmoles/mg/min Mean ± SEM
Control	34.0 ± 1.8
Morphine (15 mg/kg SC)	24.0 ± 1.3*
Morphine + Verapamil (2.5 mg/kg)	35.8 ± 3.7†
Morphine + Diltiazem (10 mg/kg)	36.6 ± 5.2†
Morphine + Nimodipine (1 mg/kg)	41.2 ± 4.3‡
Verapamil (2.5 mg/kg)	35.3 ± 1.6
Diltiazem (10 mg/kg)	34.4 ± 4.6
Nimodipine (1 mg/kg)	34.3 ± 4.2

*$p<0.01$ vs. control.
†$p<0.05$ and ‡$p<0.01$ vs. morphine, n=4.

BAY K8644 and nimodipine (Miles Laboratories), verapamil HCl (Knoll, AG), diltiazem (Sigma), morphine sulfate (Eli Lilly), naloxone HCl (Endo), ATP (Boehringer Mannheim), ammonium molybdate tetrahydrate (Aldrich), calcium chloride (Fisher), EGTA (Sigma Chemical, Co.), dithioerythritol (DTE) (Sigma), bovine serum albumin (Sigma), KCl, KH_2PO_4, $MgCl_2$ (Fisher), malachite green HCl (Aldrich), ouabain (Sigma), Na_2CO_3, sodium citrate, sodium azide, sucrose (Sigma) and Trisma (Fisher).

RESULTS

Effects of Morphine Sulfate on Temperature Response

In order to accurately establish conditions for freely moving unrestrained rats, we performed dose response curves at various times to determine the magnitude of opiate responses. Figure 1 outlines the effects of morphine (3–15 mg/kg SC) on body temperature at time intervals ranging from 30–120 minutes. As seen from this experiment, each of the three doses used produced a significant elevation of body temperature at 30 min. Morphine (3 mg/kg)-induced hyperthermia remained constant throughout the remainder of the time period from 60–120 min. At higher doses (10 and 15 mg/kg), morphine continued to produce elevations in body temperature at 60–120 minutes. At 120 minutes, both doses produced hyperthermia which was significantly greater than control.

Morphine-Induced Changes in Enzyme Activity

Cortex and hypothalamus have high densities of μ opiate receptors, while cerebellum has a relatively low density of such receptors [6]. In addition, the hypothalamus is the accepted focus for thermoregulation set point [23]. This ap-

proach allows us to study both opiate receptor mediated responses and biochemical changes which may be coupled to the thermoregulation process. As seen in Table 1, administration of morphine sulfate produced a significant decrease (20%) in Ca^{++}ATPase activity in the hypothalamus. Ca^{++}ATPase activity in the cortex was also inhibited at 15 mg/kg while cerebellar enzyme activity was not altered. Mg^{++}ATPase activity was also measured in each brain region following morphine. No changes in Mg^{++}ATPase activity were seen in any brain region tested.

Receptor Mediated Antagonism of Morphine Induced Hyperthermia

In order to evaluate the degree of specificity of morphine in producing hyperthermia in freely moving rats, we administered naloxone to study opiate receptor sensitivity. McDougal *et al.* [21] have previously reported that doses of morphine from 3.8–45 mg/kg significantly increased temperature in the unrestrained rat. However, they did not report naloxone antagonism.

In the present study, naloxone (5 mg/kg) was administered to rats receiving saline 120 min prior to sacrifice, or 15 min prior to morphine treatment. The saline treatment served as the vehicle control for morphine-treated rats. Rats were then evaluated 30 min after morphine for temperature changes over periods of 0–120 min. These results are expressed in Fig. 2. Naloxone (5 mg/kg) significantly reduced morphine-induced hyperthermia at each of the four times tested ($p<0.001$). Naloxone alone produced no significant change in temperature at the dose used. Higher doses of naloxone were not tested since they have been reported to alter temperature [8]. Naloxone antagonism of the morphine-induced decrease in Ca^{++}ATPase activity was also evaluated. Table 2 illustrates the effects of naloxone alone and in combination with morphine on enzyme activity in the hypothalamus, cortex and cerebellum. Significant decreases in enzyme activity ($p<0.05$) seen in the hypothalamus and cortex were prevented when naloxone (5 mg/kg) was used as a pretreatment. No changes in enzyme activity were seen for any drug treatment in the cerebellum. Mg^{++}ATPase activity was measured (data not shown) with no changes in enzyme activity following naloxone or morphine plus naloxone.

Effects of Ca^{++} Channel Antagonists on Morphine Induced Hyperthermia

Previous studies [26] have demonstrated an effect of opiates on voltage sensitive Ca^{++} influx following acute, chronic and *in vitro* treatment. These studies have recently been confirmed by other laboratories [10, 14, 15]. The inhibition of Ca^{++} influx by opiates suggests that opiates may function as Ca^{++} antagonists. In view of this idea, and since Ca^{++} movement in the hypothalamus may signal events in thermoregulation, we have studied the effects of other well known Ca^{++} channel antagonists on the morphine-induced hyperthermic response. We have chosen three classes of Ca^{++} channel antagonists including verapamil (phenylalkylamine), diltiazem (benzothiazepine) and nimodipine (1,4 dihydropyridine). These studies are presented in Fig. 3. Morphine administration produced a pronounced hyperthermia which was significantly different from control at 30–120 min. Each of the Ca^{++} channel antagonists was evaluated at a dose which by itself produced no effect on temperature. The Ca^{++} channel antagonists were used 15 min prior to administration of morphine (15 mg/kg SC). Animals were sacrificed after the 120 min reading for measurement of enzyme activities. As seen in Fig. 3, verapamil (2.5 mg/kg), diltiazem (10 mg/kg) or nimodipine (1 mg/kg) significantly blocked the rise in temperature seen after morphine at each time tested (30–120 min).

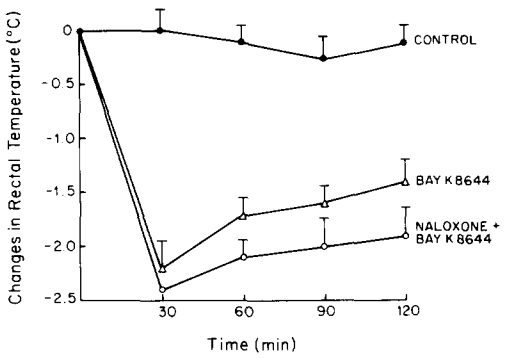

FIG. 4. Effect of naloxone (5 mg/kg, SC) on BAY K8644 (3 mg/kg, SC) induced hypothermia. Naloxone was administered 15 min before BAY K8644. The values after BAY K8644 were significantly different from control, $p<0.001$.

TABLE 4

EFFECTS OF BAY K8644 ON Ca^{++} ATPase IN HYPOTHALAMUS

	Ca^{++} ATPase nmoles/mg/min MEAN ± SEM
Control	33.2 ± 1.3
BAY K8644 (3 mg/kg)	43.9 ± 2.4*
Naloxone (5 mg/kg)	35.1 ± 2.8
Naloxone + BAY K8644	40.6 ± 2.4*

*($p<0.01$) vs. control.

Examination of corresponding changes in enzyme activity reveals that Ca^{++} channel antagonists also effectively reversed the inhibition of Ca^{++}ATPase seen following morphine treatment (Table 3). No changes in Mg^{++}ATPase activity were seen when morphine was given in combination with Ca^{++} channel antagonists. Ca^{++}ATPase activity in the cortex was inhibited by morphine to a similar extent as that seen in hypothalamus. However, Ca^{++} channel antagonists reversed this enzyme inhibition without producing any effects on enzyme activity when used alone. No enzyme changes in the cerebellar Ca^{++} or Mg^{++}ATPase activities were seen when morphine was used in combination with Ca^{++} channel antagonists.

Effect of Naloxone on BAY K8644 Response to Temperature Regulation

Our studies demonstrate that Ca^{++} channel antagonists completely reverse the hyperthermia seen following the opiate agonist morphine. Additionally, the opiate agonist effect is blocked by the corresponding opiate antagonist naloxone. The possibility arises that a single agonist site which may reside on the channel may be modulated by both

morphine and Ca^{++} channel antagonists. To investigate this possibility, we have studied naloxone's efficacy in altering the effect of a Ca^{++} channel agonist BAY K8644. BAY K8644 promotes Ca^{++} entry and functional activity in a number of systems [29] and is a competitive inhibitor of ^{3}H-dihydropyridine (DHP) binding in brain tissue and cell cultures [4, 11, 13]. We have demonstrated this compound (BAY K8644) to be a very potent agent in reducing temperature in freely moving rats [24]. If opiates and Ca^{++} channel antagonists are acting through a common site, then naloxone may be expected to alter the response to the Ca^{++} agonist BAY K8644.

We have studied the effect of naloxone on BAY K8644 induced hypothermia and these results are shown in Fig. 4. BAY K8644 produces a significant reduction in body temperature at 30–120 min. Naloxone (5 mg/kg) was used to attempt blockade of this effect when administered as a 15 min pretreatment to BAY K8644. As seen in Fig. 4, naloxone was ineffective in blocking the hypothermic response seen following the Ca^{++} agonist. Corresponding changes in Ca^{++} agonist activity reflect findings in other systems with BAY K8644. This Ca^{++} entry promoter is known to bind to and compete with ^{3}H-DHP sites on brain membranes [13], and to increase Ca^{++} entry and Ca^{++}-dependent contractile activity in vascular and intestinal smooth muscle [27]. In the *in vivo* system, we find BAY K8644 stimulates Ca^{++}ATPase activity in hypothalamus (Table 4) but not in cortex or cerebellum (data not shown) possibly due to increased Ca^{++} entry into hypothalamus. Thus, we can use this biochemical measurement as an index of Ca^{++} entry into the cell as a correlate with thermoregulation. No changes in Mg^{++}ATPase activity were seen in cortex, hypothalamus or cerebellum (data not shown). Naloxone was unable to reverse the stimulation seen in Ca^{++}ATPase following BAY K8644.

DISCUSSION

Opiate Receptor Mediated Changes in Temperature and Enzyme Activity

Studies presented in this report demonstrate that morphine produces an increase in body temperature in freely moving rats. This response is significantly antagonized by the narcotic antagonist naloxone at a concentration which does not alter body temperature. These findings confirm the observations of others [21] who have reported hyperthermia following morphine administration to freely moving rats but hypothermia or biphasic responses in rats under partial or complete restraint [3]. These findings underscore the primary temperature effect under physiological conditions as being hyperthermia. In parallel with development of opiate induced hyperthermia, we observed a change in Ca^{++}ATPase activity in cortex and hypothalamus. Morphine produces naloxone sensitive inhibition of Ca^{++}ATPase in both cortex and hypothalamus but not cerebellum, while Mg^{++}ATPase was unaffected in any brain region.

Previous studies have reported the effects of opiates on voltage-dependent Ca^{++} influx in rat brain [26]. Both *in vitro* and *in vivo* opiates are shown to inhibit Ca^{++} uptake into synaptosomes in a receptor specific, stereoselective fashion. These findings have been recently confirmed and extended in other laboratories [10, 14, 15]. Inhibition of Ca^{++}ATPase seen in cortex and hypothalamus may result from reduced Ca^{++} influx, necessary to maintain the sensitive high affinity Ca^{++} pump during depolarization conditions. This could occur as a result of morphine effects on voltage-dependent Ca^{++} channels.

When morphine was used in combination with Ca^{++} channel antagonists, verapamil, diltiazem or nimodipine, hyperthermia is prevented and Ca^{++}ATPase inhibition is reversed. This suggests that Ca^{++} channel antagonists may selectively block the opiate receptor mediated action possibly by interfering with opiate receptor coupling to the channel. Other reports support these findings. Benedek and Szikszay [3] have reported that morphine hyperthermia in freely moving rats is significantly antagonized by both verapamil (10 mg/kg SC) and diltiazem (20 mg/kg SC). The diversity of Ca^{++} channel antagonists used here suggests that the antagonism of morphine effect probably occurs at a step distal to the occupation of opiate receptors. To test this idea, we attempted to reverse the effects of BAY K8644 on temperature and enzyme activity (Fig. 4). Naloxone (5 mg/kg) was ineffective in reversing BAY K8644-induced hypothermia and activation of Ca^{++}ATPase. Nimodipine (1 mg/kg), but not verapamil (2.5 mg/kg) nor diltiazem (10 mg/kg), was, however, effective in preventing BAY K8644 hypothermia and enzyme changes [24]. Bolger *et al.* [4] have previously reported the behavioral actions of BAY K8644 in altering rotorod performance were also antagonized by nimodipine but not verapamil suggesting specific CNS actions of the Ca^{++} agonist.

Our studies suggest that opiate agonists do not interact with the dihydropyridine receptor to alter temperature and enzyme activity. More likely the opiate receptor is located at an allosteric site such that occupation of the site limits Ca^{++} influx. The Ca^{++} channel antagonists at the concentration used in the present study do not themselves alter temperature but may bind to the channel and alter opiate modulation. In this classical sense, the Ca^{++} antagonists bind but do not produce changes in temperature. Ca^{++} antagonists at higher doses have pharmacological properties as reported by Benedek and Szikszay [3].

Ca^{++} has been implicated in the setpoint control of temperature by the hypothalamus. Infusion of hypocalcemic solutions promotes hyperthermia in many species tested [23]. Thus, if a drug influences Ca^{++} translocation and/or localization, it may actively potentiate or antagonize morphine's primary effect on Ca^{++} influx.

In summary, the effect of morphine in producing hyperthermia is blocked by naloxone. Inhibition of Ca^{++}ATPase may be a direct effect of opiate receptor activation, or indirect, due to limiting Ca^{++} entry into the cell. BAY K8644-induced decreases in temperature and activation of Ca^{++}ATPase suggests morphine may be acting in a fashion to limit Ca^{++} entry. Failure of naloxone to block the BAY K8644 hypothermia and enzyme activation suggests that morphine-induced changes are mediated through changes at the level of opiate receptor, while the effects of BAY K8644 are mediated through dihydropyridine receptor with both linked to the channel. At concentrations of Ca^{++} channel antagonists which, given alone, do not influence temperature and enzyme activity, morphine effects on temperature and enzyme activity were inhibited. These findings suggest that two types of receptor interaction with the Ca^{++} channel may be present. One type of interaction results from activation of opiate receptors and is antagonized by naloxone. A second type of receptor interaction is seen with the dihydropyridine Ca^{++} agonist BAY K8644 to induce hypothermia. This interaction is not blocked by naloxone but is reversed by nimodipine (data not shown). Ca^{++} channel antagonists also

block opiate receptor mediated hyperthermia providing evidence that the opiate effect is at the level of the channel. These studies also demonstrate for the first time that an additional pharmacological action of morphine, i.e., hyperthermia, may involve changes in Ca^{++} transport.

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