ELSEVIER

European Journal of Pharmacology 430 (2001) 79–85

ejp

www.elsevier.com/locate/ejphar

Dexamethasone modulates hypotension induced by opioids in anaesthetised rats

Raffaella Sorrentino [a], Anna Capasso [b,*], Roberta d'Emmanuele di Villa Bianca [a], Aldo Pinto [b]

[a] *Department of Experimental Pharmacology, University of Naples "Federico II" via Domenico Montesano 49, 80131 Naples, Italy*
[b] *Department of Pharmaceutical Sciences, University of Salerno, via Ponte Don Melillo, 84084 Fisciano, Salerno, Italy*

Received 25 April 2001; received in revised form 6 August 2001; accepted 7 August 2001

Abstract

The effect of dexamethasone on hypotension induced by μ-, κ- and δ-opioid receptor agonists was investigated in pentobarbital-anaesthetised rats. Morphine (nonselective opioid receptor agonist), DAGO (D-Ala^2-*N*-methyl-[Phe^4-Gly^5-ol]enkephalin; μ-opioid receptor-selective agonist), U50-488H (*trans*(±)-3,4-dichloro-*N*-methyl-*N*-(2[1pyrrolidynyl]cyclohexyl)-benzeneacetamide; κ-opioid receptor-selective agonist) and deltorphin II (δ-opioid receptor-selective agonist), given intravenously, 5 μmol/kg, induced hypotension in rats. This hypotension was characterised by a fall in mean arterial blood pressure in 1–2 min that recovered in 30 min for morphine and U50-488H and in 5 or 20 min for DAGO and deltorphin II, respectively. Dexamethasone per se at a dose of 7.5 μmol/kg, i.v. did not significantly modify the mean arterial blood pressure of animals. Dexamethasone administration 90 min, but not 30 or 60 min, before the opioid agonists injection, prevented the hypotension induced by morphine or U50-488H, but not that induced by DAGO or deltorphin II. Pretreatment with RU-38486 (mifepristone; 7.5 μmol/kg, i.v.), a glucocorticoid receptor antagonist, 15 min before the steroid, prevented dexamethasone inhibition of hypotension induced by morphine and U50-488H. Furthermore, pretreatment with cycloheximide, a protein synthesis inhibitor (3.5 μmol/kg, i.v.), was also able to abolish the effects of dexamethasone on morphine- and U50-488H-induced hypotension. Results of the present study indicate that dexamethasone inhibited κ-opioid receptor-mediated hypotension in rats, indicating a further important functional interaction between corticosteroids and the opioid system at κ receptors. The ability of cycloheximide and RU-38486 to block dexamethasone effects indicates that steroid interference with κ-opioid receptor-mediated hypotension involves a protein synthesis-dependent mechanism via glucocorticoid receptors.

Keywords: Blood pressure; Glucocorticoid; Opioid; Hypotension

1. Introduction

Cardiovascular control by opioid peptides is a well-known phenomenon (Feuerstein and Siren, 1987) and, besides their presence in the central nervous system, opioid peptides are present in the heart, blood vessels, sympathetic nerves and adrenal glands (Hahnbauer et al., 1982; Starke et al., 1985). In vivo experimental evidence indicates that opioid administration induces bradycardia, hypotension, with an impairment of baroreceptor and chemoreceptor reflex activity (Holaday, 1983; Kastin et al., 1984; Feuerstein and Siren, 1987). It has been reported that opioids could act as modulators of arterial blood pressure under stress conditions (McCubbin, 1993; Bruehl et al., 1994) or during hypertension (Widera et al., 1992) and arrhythmia (Rabkin, 1993). Indeed, hypotension induced by septic or haemorragic shock has been shown to augment the plasma concentration of endogenous opioids (Mei et al., 1992), suggesting that opioids may play an important physiological role in the cardiovascular system. These have been significant advances in the understanding of opioid receptor involvement in cardiovascular control (Douglas and Kitchen, 1992) and now it is generally agreed that μ-, κ- and δ-opioid receptors are involved in the cardiovascular system control.

In our previous work, we have demonstrated that dexamethasone is able to modify the effects of opioids in analgesia, constipation, hypermotility, epilepsy and dependence (Pieretti et al., 1991, 1992, 1994; Capasso et al., 1992, 1996), indicating an important interaction between glucocorticoids and the opioid system. However, although the corticosteroid–opioid interaction has been widely studied, the effects of corticosteroids on the hypotension induced by selective opioid receptor agonists are unknown.

* Corresponding author. Tel./fax: +39-89-964357.
E-mail address: annacap@unisa.it (A. Capasso).

0014-2999/01/$ - see front matter
PII: S0014-2999(01)01279-1

This report concerns the effects of dexamethasone on opiate-induced hypotension and, if so, for possible effects, through the involvement of which specific opiate receptor subpopulation and its probable mechanism of action. The effect of dexamethasone on the hypotension induced by morphine (nonselective opioid receptor agonist), DAGO (D-Ala^2-*N*-methyl-[Phe^4-Gly^5-ol]enkephalin; μ-opioid receptor-selective agonist), U50-488H (*trans*(±)-3,4-dichloro-*N*-methyl-*N*-(2[1pyrrolidynyl]cyclohexyl)-benzeneacetamide; κ-opioid receptor-selective agonist) and deltorphin II (δ-opioid receptor-selective agonist) in pentobarbital-anaesthetised rats is evaluated.

2. Material and methods

2.1. Animals

Adult male Wistar rats (200–250 g; Charles River, Italy) were used. Animal care and use followed the directions of the Council of the European Communities for animal experimentation. The animals were housed in colony cages (five rats each) with free access to food and water. They were maintained in a climate- and light-controlled room (22 ± 1 °C, 12/12-h dark/light cycle) for at least 7 days before using.

2.2. Surgical technique

Rats were anaesthetised with pentobarbital (60 mg/kg, i.p.) and supplemental doses (1/10 dilution) were given i.v. when respiratory and blood pressure distress was observed so as to ensure an adequate level of anaesthesia. A thermal blanket kept to 37 °C was used to control the body temperature. The trachea was cannulated and all animals were artificially ventilated with a stroke volume of 10 ml/kg at a rate of 60 strokes/min, a regimen which keeps blood gases at normal levels in the rat (MacLean and Hiley, 1988). The left carotid artery was cannulated with a polyethylene cannula (PE 50) for blood pressure measurement, by connection with a Bentley 800 Trantec pressure transducer (Basile Comerio, Italy) and recorded by a Thermal Arraycorder WR 7400 (Graphtec Tokyo). The lines were filled with heparinised saline (5 units/ml). A PE 50 catheter was inserted in the internal jugular vein for drug administration.

The electrocardiogram (ECG) and the heart rate were recorded by insertion of needles to the upper and lower limbs and to the chest area connected to the electrocardiograph (Cardiette; Italy).

2.3. Experimental protocol

After the surgical procedure the rats were allowed 30 min to stabilise before opioid administration. Each animal received only one opioid once. After administration of morphine (5 μmol/kg), DAGO (5 μmol/kg), U50-488H (5 μmol/kg) or deltorphin II (5 μmol/kg) blood pressure was monitored up to 30 min; this time was experimentally chosen since a complete reversion of vascular opioid-induced hypotension was observed in 30 min.

In preliminary experiments, naloxone (1–10 μmol/kg, i.v.; depending on opioid agonist used), a nonspecific opioid receptor antagonist, was administered 5 min before opioid agonist injection to confirm an involvement of opioid receptors.

Dexamethasone was administered intravenously at different time intervals (30, 60 or 90 min before each opioid agonist) at a dose of 7.5 μmol/kg that was previously reported to prevent the neuronal effect of morphine (Pieretti et al., 1992).

Finally, RU-38486 (mefipristone; 7.5 μmol/kg), the specific competitive antagonist of glucocorticoid receptor,

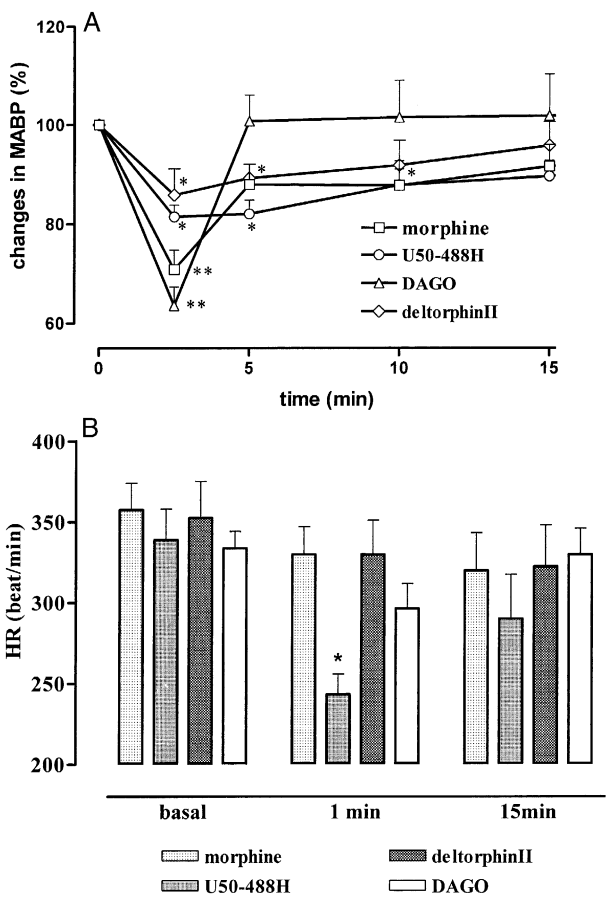

Fig. 1. The effect of morphine ($n = 12$), DAGO ($n = 6$), U50-488H ($n = 8$) or deltorphin II ($n = 6$), 5 μmol/kg (i.v.), on the mean arterial blood pressure (MABP; A) and heart rate (HR; B) in pentobarbital-anaesthetised rats. In A, results are expressed as means ± S.E.M. of percentage changes of basal mean arterial blood pressure and here they are shown for up to 15 min whereas observation was for 30 min. This time was experimentally chosen since a complete reversion of hypotension was observed. In B, results are expressed as means ± S.E.M. of beats/min. All curves for hypotension yielded statistically significant ($P < 0.01$) effective values (mmHg) as compared to basal mean arterial blood pressure by one-way analysis of variance (ANOVA) and Bonferroni's post-test for multiple comparison; $^{*}P < 0.05$ and $^{**}P < 0.01$.

or cycloheximide (3.5 μmol/kg), an inhibitor of protein synthesis, was administered 15 min before dexamethasone.

2.4. Statistical analysis

The hypotension was calculated as percent of mean arterial blood pressure values and results are expressed as means ± S.E.M. Statistical comparisons were carried out by using one-way analysis of variance (one-way ANOVA) and Bonferroni's post-test for multiple comparison calculated by GraphPad Instat program (GraphPad Software). Results were considered significant at $P < 0.05$.

2.5. Drugs

All drugs used in the experimental sessions were purchased from Sigma Aldrich (Milan, Italy) with the exception of morphine HCl purchased from Carlo Erba (Milan, Italy).

3. Results

3.1. Effect of opioids on mean arterial blood pressure and heart rate in rats

The basal value of mean arterial blood pressure of rats was 98.8 ± 5.1 mmHg ($n = 32$). Intravenous administration of morphine ($n = 12$), DAGO ($n = 6$), U50-488H ($n = 8$) or deltorphin II ($n = 6$) at a dose of 5 μmol/kg, induced a significant ($P < 0.01$) hypotension in pentobarbital-anaesthetised rats (Fig. 1A). Morphine produced a rapid fall in mean arterial blood pressure that reached a maximum in 1 or 2 min and partially recovered in 5 min, followed by a lasting phase which completely recovered in 30 min (Fig. 1A). DAGO-induced hypotension was similar in onset to that with morphine, but had completely recovered in 5 min (Fig. 1A). Conversely, the hypotension induced by U50-488H or deltorphin II was slow in onset and recovery, and of smaller peak magnitude than that elicited by morphine and DAGO (Fig. 1A). The above

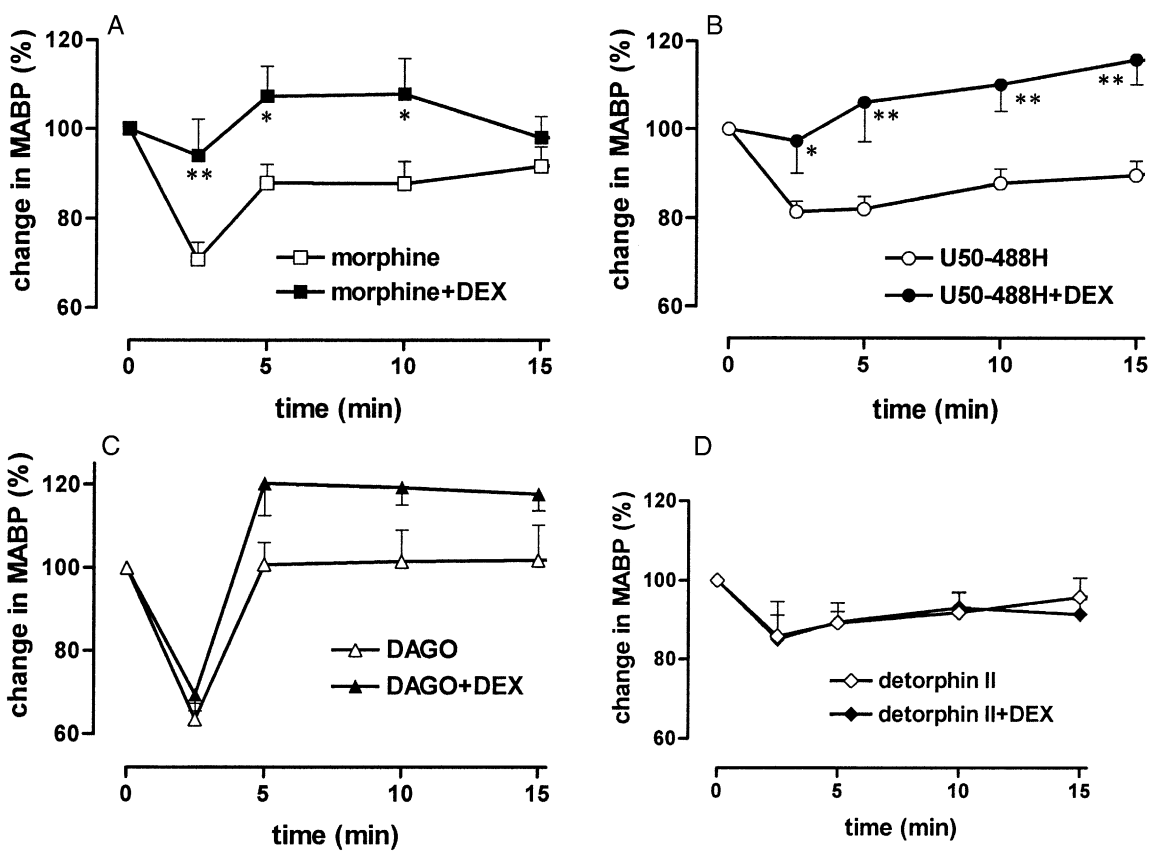

Fig. 2. The effect of dexamethasone (DEX; 7.5 μmol/kg, i.v.) on the hypotension induced by morphine (A; $n = 4$), U50-488H (B; $n = 4$), DAGO (C; $n = 4$) and deltorphin II (D; $n = 4$) in pentobarbital-anaesthetised rats. Dexamethasone was administrated 90 min before opioid agonist injection (5 μmol/kg, i.v.). Results are expressed as means ± S.E.M. of percentage changes of basal mean arterial blood pressure (MABP) and here they are shown for 15 min whereas the observation was for 30 min. The dexamethasone curve for morphine and U50-488H, but not for DAGO and deltorphin II, showed statistical significance ($P < 0.01$) as compared to the opioid alone, using one-way analysis of variance (one-way ANOVA) and Bonferroni's post-test for multiple comparison; $^{*}P < 0.05$ and $^{**}P < 0.01$. Data of control curves are the same reported in Fig. 1.

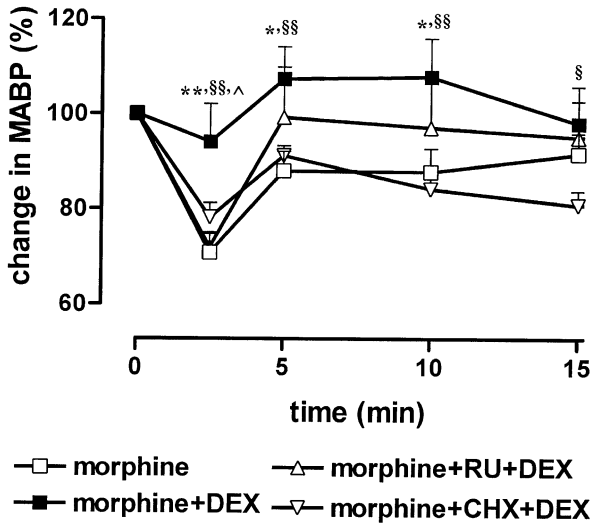

Fig. 3. The effect of RU-38486 (RU; 7.5 μmol/kg, i.v.; $n = 4$) and cycloheximide (CHX; 3.5 μmol/kg, i.v.; $n = 4$), on dexamethasone (DEX; 7.5 μmol/kg, i.v.) prevention of the effect on the hypotension induced by morphine (5 μmol/kg, i.v.) in pentobarbital-anaesthetised rats. RU and CHX were given 15 and 30 min before dexamethasone, respectively. Dexamethasone was given 90 min before morphine. Results are expressed as means ± S.E.M. of percentage changes of basal mean arterial blood pressure. The morphine curve with RU-38486 or cycloheximide resulted in statistically significant values ($P < 0.01$) compared to dexamethasone alone but not to opioid alone, by one-way analysis of variance (one-way ANOVA) and Bonferroni's post-test for multiple comparison; $^{*}P < 0.05$ and $^{**}P < 0.01$ for morphine + DEX vs. morphine; §$P < 0.05$ and §§$P < 0.01$ for morphine + DEX vs. morphine + CHX + DEX; $^{\wedge}P < 0.01$ for morphine + DEX vs. morphine + RU + DEX. Data for control or DEX curves are the same as reported in Figs. 1 and 2, respectively.

opioid hypotension was totally prevented by naloxone (1–10 μmol/kg, i.v.; $n = 3$ for each opioid agonist) pretreatment (data not shown).

The administration of morphine, DAGO and deltorphin II (5 μmol/kg, i.v.) did not significantly affect heart rate (Fig. 1B). In contrast, U50-488H (5 μmol/kg, i.v.) induced a significant ($P < 0.01$) reduction of heart rate (Fig. 1B) and this effect was prevented by naloxone (5 μmol/kg, i.v.).

3.2. Effect of dexamethasone on the hypotension induced by opioids in rats

Dexamethasone per se at a dose of 7.5 μmol/kg, i.v. did not significantly modify mean arterial blood pressure or heart rate of the animals when administered 30, 60 or 90 min before the opioid.

The administration of dexamethasone 30 min ($n = 3$) and 60 min ($n = 3$) before each opioid agonist did not significantly modify opioid hypotension. Dexamethasone, administered 90 min before opioid injection ($n = 6$ for each opioid agonist used), was able to prevent only the hypotension induced by morphine and U50-488H (Fig. 2A, B), whereas neither DAGO nor deltorphin II-induced hypotension was modified (Fig. 2C, D). Although dexamethasone seems to induce an increase in mean arterial blood pressure after DAGO hypotension (Fig. 2C), this increase was not statistically significant ($P > 0.05$). Furthermore, dexamethasone, 90 min before the opioid agonist, was also able to prevent the U50-488H induced reduction of heart rate (basal value was 350 ± 37 beats/min, after U50-488H was 279 ± 20 beats/min and after dexamethasone + U50-488H was 370 ± 10 beats/min).

3.3. The effect of RU-38486 and cycloheximide on dexamethasone prevention of morphine- and U50-488H-induced hypotension

The glucocorticoid receptor antagonist, RU-38486, administered to the rats 15 min before dexamethasone per se at an equimolar dose (7.5 μmol/kg, i.v.; $n = 4$ for each opioid receptor agonist used), did not significantly modify mean arterial blood pressure, heart rate or morphine-U50-488H-induced hypotension (data not shown). In contrast, RU-38486 was able totally to reverse the dexamethasone prevention of morphine- or U50-488H-induced hypotension in rats (Figs. 3 and 4).

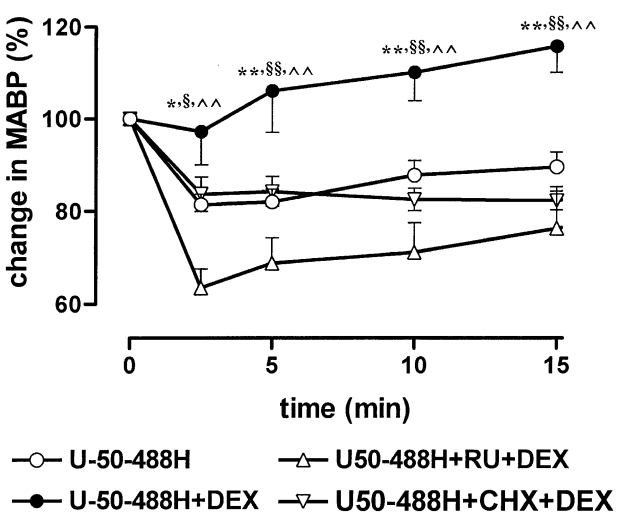

Fig. 4. The effect of RU-38486 (RU; 7.5 μmol/kg, i.v.; $n = 4$) and cycloheximide (CHX; 3.5 μmol/kg, i.v.; $n = 4$), on dexamethasone (DEX; 7.5 μmol/kg, i.v.) prevention of the hypotension induced by U50-488H (5 μmol/kg, i.v.) in pentobarbital-anaesthetised rats. RU and CHX were given 15 and 30 min before dexamethasone, respectively. Dexamethasone was given 90 min before U50-488H. Results are expressed as means ± S.E.M. of percentage changes of basal mean arterial blood pressure. The U50-488H curve with RU-38486 or cycloheximide yielded statistically significant values ($P < 0.01$) compared to dexamethasone alone and to opioid alone, by one-way analysis of variance (one-way ANOVA) and Bonferroni's post-test for multiple comparison; $^{*}P < 0.05$ and $^{**}P < 0.01$ for RU-38486 + DEX vs. RU-38486; §$P <$ 0.05 and §§$P < 0.01$ for RU-38486 + DEX vs. RU-38486 + CHX + DEX; $^{\wedge\wedge}P < 0.01$ for RU-38486 + DEX vs. RU-38486 + RU + DEX. Data for control or DEX curves are the same as reported in Figs. 1 and 2, respectively.

Also, cycloheximide (3.5 μmol/kg, i.v.; $n = 4$), the protein synthesis inhibitor, given 15 min before dexamethasone, completely and significantly abolished the corticosteroid prevention of morphine- and U50-488H-induced hypotension (Figs. 3 and 4).

The administration of cycloheximide per se did not affect mean arterial blood pressure, the heart rate or morphine- or U50-488H-induced hypotension (data not shown).

4. Discussion

The present results indicated that dexamethasone reduces opiate hypotension in rats and that the steroid was effective to prevent hypotension when it was administered 90 min before opioid agonists. Dexamethasone is able to reduce the hypotension induced by morphine and U50-488H, whereas it is ineffective on DAGO and deltorphin II-induced hypotension. These results indicate an important functional interaction between glucocorticoids and opioid hypotension, primarily at the κ receptor, because the steroid was able to block only κ-mediated hypotension without altering μ- and δ-induced hypotension.

Since corticosteroids mediate their effects by involving specific glucocorticoid receptors and protein synthesis, we also investigated the effects of the glucocorticoid receptor antagonist, RU-38486 (Gaillard et al., 1984, 1985; Moguilewski and Philbet, 1984; Peers et al., 1988; Ratka et al., 1988a,b), and the protein synthesis inhibitor, cycloheximide (Blackwell et al., 1980), on the effects induced by dexamethasone on opiate-induced hypotension. Both RU-38486 and cycloheximide are capable of blocking the dexamethasone prevention of morphine and U50-488H hypotension. These results confirm and extend our previous findings (Pieretti et al., 1991, 1992, 1994; Capasso et al., 1992, 1996), indicating that corticosteroid-opioid interaction might involve, at vascular levels, κ opiate receptors.

Corticosteroids exert many of their effects on target cells through intracellular receptor mechanisms (O'Malley and Means, 1974; Thompson and Lippman, 1974; Barnes and Adcock, 1993). Two types of receptors for corticosteroids are known, type 1 and type 2 (De Kloet and Reul, 1987). Type 2 receptors display a higher affinity for synthetic glucocorticoids, such as dexamethasone, than does corticosterone (Reul and De Kloet, 1986), and RU-38486 antagonises dexamethasone effects at the type 2 receptor binding sites (Gaillard et al., 1984, 1985; Moguilewski and Philbet, 1984; Peers et al., 1988). In the present study, the possible involvement of glucocorticoid receptors was confirmed by experiments performed with RU-38486, which blocks the dexamethasone reduction of opiate hypotension. Dexamethasone also displays a time-related inhibitory effect on opiate hypotension. Various reports in the literature support the view that effects mediated by corticosteroids are time-related and involve intracellular mechanisms or protein synthesis (O'Malley and Means, 1974; Thompson and Lippman, 1974; Church and Miller, 1978; Blackwell et al., 1980). Our results indicate that the inhibitory effects of dexamethasone on opiate hypotension are prevented by cycloheximide, a protein synthesis inhibitor, which suggests that dexamethasone may exert inhibitory effects on opiate hypotension through a protein synthesis-dependent mechanism. The dexamethasone lag time, 90 min, required for the appearance of corticosteroid action further support this hypothesis. Therefore, considering that steroid action depends on receptor occupation and protein synthesis (Blackwell et al., 1980), the results obtained with RU-38486 and cycloheximide suggest that, in our experiments, dexamethasone reduces opioid hypotension through a synthesis-dependent mechanism via glucocorticoid receptors.

The ability of dexamethasone to reverse the hypotension mediated by κ-, rather than that mediated by μ- and δ-opioid receptor agonists, may be related to the different intracellular biochemical mechanisms mediating the actions of opioids, since μ- and δ-opioid receptor agonists increase K^+ conductance, whereas κ-opioid receptor agonists reduce Ca^{2+} conductance (North, 1986).

However, although it seems that the effect induced by κ-opioid receptor agonists is mainly due to the excitation of cholinergic neurones, as with μ- and δ-opioid receptor agonists, it is unknown whether these two opioid agonists activate the same neurones, and whether the sequence of biochemical and neuronal events leading to the development of hypotension and its symptoms is different for the three agonists (Valeri et al., 1990). Our data, however, may also indicate the existence of hypotension systems that are activated in different ways, depending on biochemical or neuronal mechanisms which are still unclear (personal communication).

The discussion about possible mechanisms by which dexamethasone causes a reducing effect on opiate hypotension is still open.

It has been reported that naloxone is able to reverse the hypotension of endotoxin shock, suggesting that endorphins might be involved in the pathophysiology of septic shock (Holaday and Faden, 1978; North, 1986). The effect of naloxone to reverse the hypotension of both endotoxin and hypovolemic shock suggests that endorphins might be critical hypotensive factors in other forms of shock (burn shock, neurogenic shock, etc.) (Holaday and Faden, 1978; Faden and Holaday, 1979). In this respect, it was also suggested that the established therapeutic efficacy of synthetic corticosteroids (Gilbert, 1960; Nies, 1972) in the treatment of shock may be a partial consequence of their inhibitory effects on pituitary β-endorphin release (Guillemin et al., 1977). The enhanced sensitivity of adrenalectomised animals to shock states (Zweifach and Thomas, 1957) as well as to intravenous β-endorphin injections (Holaday et al., 1977), the effects of both of which are attenuated by corticosteroid pretreatment, is also consistent with the hypothesis that endorphin release is important in the pathophysiology of shock.

Also, it has been demonstrated that phospholipase A_2 plays an important role in the pathogenesis of the hypotension of endotoxin shock (Vadas and Hay, 1983; Green et al., 1991; Pruzanski et al., 1992a,b) because high levels of circulating phospholipase A_2 were detected in volunteers following intravenous administration of endotoxin (Pruzanski et al., 1992a,b).

Therefore, given the above evidence, we cannot exclude the possibility that, under our experimental conditions, opioid hypotension may be mediated by the involvement of phospholipase A_2 and that the ability of dexamethasone to block opioid hypotension may be related to the inhibition of phospholipase A_2 activity through phospholipase A_2 inhibitory proteins (Blackwell et al., 1980). The ability of RU-38486 and cycloheximide to block the dexamethasone effect may further support this hypothesis.

On the other hand, we cannot exclude another possibility: dexamethasone may exert its action on opiate hypotension by a mechanism that probably alters the sensitivity to opioids. This hypothesis may be supported by results of several studies showing a link between glucocorticoids and the opiate system, most prominently regarding the glucocorticoid-induced changes of opioid receptors. In this regard, it has been suggested that glucocorticoids may act, directly or indirectly, upon the same neuronal pathways as do recognized opiates (La Bella et al., 1978). This latter work supports the possibility that glucocorticoids may interact with receptors having a lesser affinity for recognized opiates, but which are coupled to the activation of the same neuronal pathway. Also, glucocorticoids may produce their effects by controlling the rate of production, release or degradation of endogenous opioid ligands (La Bella et al., 1978). Furthermore, the steroid-dependent changes in opioid receptors and related to altered opioid-induced hypotension have been suggested as a possible mechanism underlying this interaction (Ratka et al., 1988b). This hypothesis was further supported by data showing that the number of opioid receptors and some morphine effects are reduced in stressed animals in which high corticosteroid levels are detected (Seeger et al., 1984).

Finally, the finding that dexamethasone is able to block the hypotension induced by opioids suggests that glucocorticoids play a important role in the control of the cardiovascular system. This finding may well provide an explanation for the clinical observation that patients with adrenal insufficiency are more susceptible to the development of severe circulatory failure in response to low-grade endotoxemia (Cullen et al., 1980). On the other hand, the physio-pathological significance of the effects exerted by dexamethasone in opioid-induced hypotension may be relevant, considering the several diseases related to drug abuse. For example, one of the most important life-threatening adverse effects occurring during opiate overdose is hypovolemic shock and the fact that dexamethasone is able to block opiate hypotension, makes it a particularly attractive potential therapeutic agent.

In conclusion, the present results indicate an important interaction between corticosteroids and κ-opioid systems in mediating changes in arterial blood pressure.

References

Barnes, I.P., Adcock, I., 1993. Anti-inflammatory actions of steroids: molecular mechanisms. TIPS 14, 436–441.

Blackwell, G.J., Carniccio, R., Di Rosa, M., Flower, R.J., Parente, L., Persico, P., 1980. Macrocortin: a polyeptide causing the anti-phospholipase effect of glucocorticoids. Nature 287, 147–149.

Bruehl, S., McCubbin, J.A., Wilson, J.F., Ibarra, P., Carlson, C.R., 1994. Coping styles, opioid blockade and cardiovascular response to stress. J. Behav. Med. 17, 25–40.

Capasso, A., Di Giannuario, A., Loizzo, A., Pieretti, S., Sorrentino, L., 1992. Central interaction of dexamethasone and RU-38486 on morphine antinociception in mice. Life Sci. 51, PL139–PL143.

Capasso, A., Di Giannuario, A., Loizzo, A., Pieretti, S., Sagratella, S., Sorrentino, L., 1996. Dexamethasone selective inhibition of acute opioid physical dependence in isolated tissues. J. Pharmacol. Exp. Ther. 276, 743–751.

Church, M.K., Miller, P., 1978. Time course of the anti-anaphylactic and anti-inflammatory effects of dexamethasone in the rat and mouse. Br. J. Pharmacol. 62, 481–486.

Cullen, D.R., Reckless, J.P.D., McLaren, E.H., 1980. Clinical disorders involving adrenocortical insufficiency and overreactivity. In: Jones, I.C., Henderson, I.W. (Eds.), General Comparative and Clinical Endocrinology of the Adrenal Cortex. Academic Press, New York, pp. 57–77.

De Kloet, E.R., Reul, J.M.H.M., 1987. Feedback action and tonic influence of corticosteroids on brain function: a concept arising from the heterogeneity of brain receptor system. Psychoneuroendocrinology 12, 83–87.

Douglas, H., Kitchen, I., 1992. Mechanisms involved in the cardiovascular responses to opioid products of proenkephalin in the anaesthetised rat. Gen. Pharmacol. 23, 269–277.

Faden, A.I., Holaday, J.W., 1979. Opiate antagonists: a role in the treatment of hypovolemic shock. Science 205, 317–318.

Feuerstein, G., Siren, A.L., 1987. The opioid peptides. a role in hypertension? Hypertension 9, 561–565.

Gaillard, R.C., Riondel, A., Muller, A.F., Herrman, W., Bulieu, E.E., 1984. RU486 a steroid with antiglucocorticoid activity that only disinhibits the human pituitary-adrenal system at a specific time of day. Proc. Natl. Acad. Sci. U. S. A. 81, 3879–3882.

Gaillard, R.C., Poffet, D., Riondel, A.M., Saurat, J.H., 1985. RU 486 inhibits peripheral effects of glucocorticoids in humans. J. Clin. Endocrinol. Metab. 61, 1009–1015.

Gilbert, R.P., 1960. Mechanisms of emodinamic effect of endotoxin. Physiol. Rev. 40, 245–279.

Green, J.A., Smith, G.M., Buchta, R., Lee, R., Ho, K.Y., Rajkovic, I.A., Scott, K.F., 1991. Circulating pospholipase A_2 activity associated with sepsis and septic shock is indistinguishable from that associated with rheumatoid arthritis. Inflammation 15, 355–367.

Guillemin, R., Vargo, T., Rossier, J., Minick, S., Ling, N., Rivier, C., Vale, W., Bloom, F., 1977. β-endorphin and adrenocorticotrophin are secreted concomitantly by the pituitary gland. Science 197, 1367–1369.

Hahnbauer, I., Kelly, G.D., Saiani, L., Yang, Y.T., 1982. Met_5-enkephalin-like peptides of the adrenal medulla: release by nerve stimulation and functional implications. Peptides (Fayetteville) 3, 469–473.

Holaday, J.W., 1983. Cardiovascular effects of opiate systems. Annu. Rev. Pharmacol. Toxicol. 23, 541–594.

Holaday, J.W., Faden, A.I., 1978. Naloxone reversal of endotoxin hypotension suggests role of endorphins in shock. Nature 275, 450–451.

Holaday, J.W., Law, P.Y., Tseng, L.F., Loh, H.H., Li, C.H., 1977. β-endorphin: pituitary and adrenal glands modulation its action. Proc. Natl. Acad. Sci. U. S. A. 74, 4628–4632.

Kastin, A.J., Olson, G.A., Zadina, J.E., Olson, R.D., 1984. In: Muller, E.E., Gennazzani, A.R. (Eds.), Central and Peripheral Endorphins: Basic and Clinical Aspects. Raven Press, New York, pp. 99–108.

La Bella, F., Havlicek, V., Pinsky, C., Leybin, L., 1978. Opiate-like, naloxone-reversible effects of androsterone sulfate in rats. Can. J. Physiol. Pharmacol. 56, 940–944.

MacLean, M.R., Hiley, C.R., 1988. Effects of artificial respiratory volume on the cardiovascular responses to an α1 and α2 adrenoceptor agonist in the air-ventilated pithed rat. Br. J. Pharmacol. 78, 165–170.

McCubbin, J.A., 1993. Stress and endogenous opioids: behavioral and circulatory interactions. Biol. Psychol. 35, 91–122.

Mei, L., Pu, S., Han, J., 1992. Effect of electroacupuncture tolerance by different frequencies on the cardiovascular inhibition of spinal opioid peptides of the rats. Chen. Tzu. Yen. Chiu 17, 179–182.

Moguilewski, M., Philbet, D., 1984. RU-38486: potent antiglucocorticoid activity correlates with strong binding to the cytosolic glucocorticoid receptor followed by an impaired activation. J. Steroid Biochem. 20, 271–277.

Nies, A.S., 1972. In: Melmon, K.L., Morelli, H.F. (Eds.), Clinical Pharmacology. Macmillan, New York.

North, R.A., 1986. Opioid receptor types and membrane ion channels. Trends Neurosci. 9, 114–117.

O'Malley, B.W., Means, A.R., 1974. Female steroid hormone and target cell nuclei: the effects of steroid hormones on target cell nuclei are the major importance in the induction of new cell function. Science 183, 610–613.

Peers, S.H., Moor, D., Flower, R.J., 1988. Reversal of anti-inflammatory effect of dexamethasone by the glucocorticoid antagonist RU-38486. Biochem. Pharmacol. 37, 556–557.

Pieretti, S., Capasso, A., Di Giannuario, A., Loizzo, A., Sorrentino, L., 1991. The interaction of peripherally and centrally administered dexamethasone and RU-38486 on morphine analgesia in mice. Gen. Pharmacol. 22, 929–933.

Pieretti, S., Di Giannuario, A., Loizzo, A., Sagratella, S., Scotti de Carolis, A., Capasso, A., Sorrentino, L., 1992. Dexamethasone prevents epileptiform activity induced by morphine in in vivo and in vitro experiments. J. Pharmacol. Exp. Ther. 263, 830–839.

Pieretti, S., Di Giannuario, A., Domenici, M.R., Sagratella, S., Capasso, A., Sorrentino, L., Loizzo, A., 1994. Dexamethasone-induced selective inhibition of the central μ opioid receptor: functional in vivo and in vitro evidence in rodents. Br. J. Pharmacol. 113, 1416–1422.

Pruzanski, W., Mackensen, A., Engelhardt, R., Stefanski, E., Vadas, P., 1992a. Induction of circulating phospholipase A2 activity by intravenous infusion of endotoxin in patients with neoplasia. J. Immunother. 12, 242–246.

Pruzanski, W., Wilmore, D.W., Suffredini, A., Matich, G.D., Hoffman, A.G.D., Browning, J.L., Stefanski, E., Sternby, B., Vadas, P., 1992b. Hyperphosphalipasemia A2 in human volunteers challenged with intravenous endotoxin. Inflammation 16, 561–570.

Rabkin, S.W., 1993. The opioid agonist ethylketocyclazocine accentuates epinephrine-induced cardiac arrhythmias in the rat through an action in the brain. Brain Res. Bull. 31, 427–432.

Ratka, A., Sutanto, W., De Kloet, E.R., 1988a. Long-lasting glucocorticoid suppression of opioid-induced antinociception. Neuroendocrinology 48, 439–444.

Ratka, A., Veldhuis, H.D., De Kloet, E.R., 1988b. Corticosteroid effect on morphine-induced antinociception as a function of two types of corticosteroid receptors in brain. Neuropharmacology 27, 15–21.

Reul, J.M.H.M., De Kloet, E.R., 1986. Anatomical resolution of two types of corticosterone receptor sites in rat brain with in vitro autoradiography and computerized image analysis. J. Steroid Biochem. 24, 269–273.

Seeger, T.F., Sforzo, G.A., Pert, C.B., Pert, A., 1984. In vivo autoradiography: visualization of stress-induced changes in opiate receptor occupancy in the rat brain. Brain Res. 305, 303–311.

Starke, K., Schoffel, E., Illes, P., 1985. The sympathetic axons innervating the sinus node of the rabbit possess presynaptic opioid κ- but not μ- or δ-receptors. Naunyn-Schmiedeberg's Arch. Pharmacol. 329, 206–209.

Thompson, E.B., Lippman, M.E., 1974. Mechanism of action of glucocorticoids. Metabolism 23, 159–202.

Vadas, P., Hay, J.B., 1983. Involvement of circulating phospholipase A_2 in the pathogenesis of the hemodynamic changes in endotoxin shock. Can. J. Physiol. Pharmacol. 61, 561–566.

Valeri, P., Morrone, L.A., Pimpinella, G., Romanelli, L., 1990. Some pharmacological characteristics of the guinea-pig ileum opioid system activated by cholecystokinin. Neuropharmacology 29, 231–236.

Widera, W., Kokot, F., Wiecek, A., 1992. Do opioid receptors participate in the regulation of atrial natriuretic peptide (anp) secretion in hypertensive patients? Clin. Nephrol. 38, 209–213.

Zweifach, B.W., Thomas, L., 1957. The relationship between the vascular manifestations of shock produced by endotoxin, trauma and hemorrhage: I. Certain similarities between reactions in normal and endotoxin-tolerant rats. J. Exp. Med. 106, 385–401.