J. Pharm. Pharmacol. 1999, 51: 1251–1256
Received March 24, 1999
Accepted June 17, 1999

κ-Opioid Receptors Behind the Blood–brain Barrier are Involved in the Anti-hypertensive Effects of Systemically Administered κ-Agonists in the Conscious Spontaneously Hypertensive Rat

S. SHEN AND A. J. INGENITO

Department of Pharmacology, School of Medicine, East Carolina University, Greenville, NC 27858-4353, USA

Abstract

We have shown previously that chronic intrahippocampal, intraperitoneal and subcutaneous administrations of non-peptide opioid receptor agonists induced depressor responses in the spontaneously hypertensive rat (SHR). However, it is not clear whether the hypotensive effect of systemic administration involves κ receptors behind the blood–brain barrier. In this study, the relative roles of central vs peripheral κ-opioid receptors in the hypotensive effect of κ-agonists was examined in conscious SHRs following chronic subcutaneous administration of two selective κ-agonists, BRL 52656 which freely penetrates the blood–brain barrier, and BRL 52974 which has only limited ability to do so.

Initial studies determined the dose–response relationship for each of the two drugs given intraperitoneally twice a day, while monitoring systolic arterial pressure (SAP), mean arterial pressure (MAP) and heart rate (HR) measured by the tail-cuff method. Both drugs caused biphasic arterial pressure responses, with lower doses of BRL 52656 causing depressor effects and higher doses resulting in pressor effects. By contrast, lower doses of BRL 52974 caused pressor effects and higher doses depressor effects. The biphasic effects occurred with BRL 52656 from 0·01 to 3·0 mg kg^{-1} and that for BRL 52974 from 0·1 to 30 mg kg^{-1}. In subsequent studies the drugs were infused chronically, subcutaneously via osmotic minipumps over a 14-day period, BRL 52656 at 0·2 or 0·5 mg kg^{-1}/day and BRL 52974 at 0·2 mg kg^{-1}/day. At lower doses, BRL 52656 decreased SAP, MAP and HR but at higher doses only bradycardia was observed. BRL 52974 given chronically subcutaneously over 14 days had no significant effects on arterial pressure and decreased heart rate only after seven days of treatment.

Collectively, the results established that only the κ-agonist, which gained access to the central nervous system, lowered arterial pressure and heart rate, whereas the compound with limited ability to cross the blood–brain barrier was ineffective at equivalent doses. The complex dose–response pattern found with both drugs suggests that κ-agonists have central hypotensive and bradycardic actions at low doses but at higher doses a mixture of both central and peripheral actions leads to hypertension and tachycardia.

Among central neuropeptides, κ-opioids have a remarkably broad distribution in brain regions (Holaday 1985). Activation of κ receptors that lay in neuron populations whose locations are related to cardiovascular regulation, lead to reductions of mean arterial pressure (MAP) and heart rate (HR) (Feuerstein & Faden 1982; Carter & Lightman 1985; Hassen & Broudy 1988; Verberne & Louis 1989; Keay et al 1997). However, peripheral administration of κ-opioid agonists has led to complex and variable cardiovascular effects (Randich et al 1993; Szeto et al 1996; Ur et al 1997). When non-peptide κ-agonists are injected as single intravenous doses into rats, they elicit hypotension and bradycardia (Gulati & Bhargava 1988; Wu & Martin 1989), the mechanisms of which may represent both central and peripheral effects. In the dog, when U-62,066E, a non-peptide κ-opioid agonist, was injected in single intravenous doses, it caused hypotension and bradycardia, which was said to be of peripheral κ-receptor origin (Hall et al 1988). The exact central and/or peripheral effects

Correspondence: A. J. Ingenito, Department of Pharmacology, School of Medicine, East Carolina University, Greenville, NC 27858-4353, USA.
E-Mail: ingenito@brody.med.ecu.edu

depend on the site of administration and other physiological factors in the animals (Feuerstein & Faden 1982; Holaday 1983). Our own studies have established that when non-peptide κ-agonists are given chronically subcutaneously and intraperitoneally to conscious rats they lower arterial pressure in the spontaneously hypertensive rat (SHR) (Zhai & Ingenito 1997; Shen & Ingenito 1999). The sites and mechanisms involved in the depressor response, however, are unclear.

In this study we have therefore determined the involvement of the CNS as a site of action of κ-receptor agonists by comparing the cardiovascular effects of two κ-agonists, BRL 52656 and BRL 52974, the latter of which, has difficulty crossing the blood–brain barrier (Brooks et al 1993). The data indicated that the κ-agonist that gained access to the CNS caused centrally-mediated hypotension in SHR, while equivalent doses of the agent which did not cross the blood–brain barrier did not affect arterial pressure.

Materials and Methods

Animals

The experiments were performed using 10- to 11-week-old male SHRs. The animals were obtained from Harlan Sprague Dawley Co. (Indianapolis, IN), and were housed three to a cage in a colony room maintained on a 12-h light–dark cycle in a controlled environment (constant temperature 23°C; humidity $50 \pm 10\%$). The animals were allowed free access to food and water. The animals were kept in our animal facility for at least four days before being used.

Arterial pressure measurement

Basal cardiovascular response was measured by the tail-cuff method using an IITC Co. computerized Model 31 system. Analogue recordings of tail-cuff pressures were converted to digital readouts by a computer software program that gave systolic arterial pressure (SAP), MAP and HR for each animal. All rats whose tail-cuff pressures were to be determined were first trained to accept brief confinement to a cylindrical Plexiglas holder and tail insertion into the pressure cuff. This was done over a four-day period before any actual arterial pressure determinations. The rats were kept in a temperature-controlled chamber at 28·5°C for 15 min before these determinations. The cardiovascular parameter value for each rat was calculated as the average of three separate measurements at each session.

Protocol 1: intraperitoneal injection of BRL 52656 and BRL 52974

Rats were randomly divided into three groups. They were injected with either BRL 52656 ($3\,\mu g\,kg^{-1}$–$3\,mg\,kg^{-1}$, i.p.), BRL 52974 ($30\,\mu g\,kg^{-1}$–$30\,mg\,kg^{-1}$, i.p.) or an equivalent volume ($1\,mL\,kg^{-1}$, i.p.) of sterile saline vehicle twice a day, morning and afternoon, the two identical doses being separated by a 6-h interval. SAP, MAP and HR were then determined on each rat 1 h after drug or vehicle administration. The average of the two daily SAP, MAP and HR determinations were tabulated as the response to each different dose.

Protocol 2: chronic subcutaneous infusion of BRL 52656 and BRL 52974

Rats were randomly divided into four groups. They were subcutaneously infused with saline, BRL 52656 0·5 or $0{\cdot}2\,mg\,kg^{-1}$/day, or BRL 52974 $0{\cdot}2\,mg\,kg^{-1}$/day by use of a pre-filled osmotic minipump (Alzet model 2001, Alza). To implant the pre-filled osmotic minipump the animals were anaesthetized with methohexital sodium ($50\,mg\,kg^{-1}$, i.p.), and then a minipump was implanted subcutaneously under the skin on the back of the rats. Sterile technique was used, and the rats were given ketorolac ($2\,mg\,kg^{-1}$) to relieve pain and benzathine penicillin G (50 000 units kg^{-1}) to prevent infection after the surgical procedure.

SAP, MAP and HR were measured daily under conscious conditions, beginning three days before the placement of the minipumps, and continuing daily for the next 14 days, between 0800 and 1000 h.

Average daily water intake and weight gain were recorded following intraperitoneal injection and subcutaneous infusion of the two agents.

Drugs

BRL 52656 (*S*-(−)-2-(1-pyrrolidinylmethyl)-1-(4-trifluoromethylphenyl) acetyl piperidine hydrochloride) and BRL 52974 (4-(1-pyrrolidinylmethyl)-5-(3,4-dichlorophenyl acetyl-4,5,6,7-tetrahydroimidazo [4,5-c] pyridine) were gifts from SmithKline Beecham.

Statistics

The results are presented as mean ± s.e.m. Data were analysed by a two-way analysis of variance followed by an a posteriori Student–Newman–Keuls test in order to study the differences among means, or by Student's paired or unpaired *t*-tests, as appropriate. The criterion for statistical significance used was $P < 0{\cdot}05$.

Results

Dose–response relationships of intraperitoneal administration of BRL 52656 and BRL 52974

Doses in the range $3\,\mu g\,kg^{-1}$–$3\,mg\,kg^{-1}$ BRL 52656 and $30\,\mu g\,kg^{-1}$–$30\,mg\,kg^{-1}$ BRL 52974 were administered intraperitoneally to SHRs twice a day, one day for each increasing dose, and cardiovascular responses were measured 1 h after each injection using the tail-cuff method (Figure 1). The lowest doses, $3\,\mu g\,kg^{-1}$ BRL 52656 and $30\,\mu g\,kg^{-1}$ BRL 52974, did not produce significant changes in SAP, MAP and HR. The relationship between dose and cardiovascular response was complex, displaying biphasic responses. An S-shaped dose–response relationship in the BRL 52656 group was obtained with lower doses of the drug, causing depressor responses from $3\,\mu g\,kg^{-1}$ to $100\,\mu g\,kg^{-1}$ and pressor responses at higher doses. However, only the $1\text{-}mg\,kg^{-1}$ dose produced a statistically significant increase in SAP with BRL 52656. By contrast, the lower doses of BRL 52974 caused pressor responses while the higher doses elicited depressor responses. Doses of BRL 52656 greater than $3\,mg\,kg^{-1}$ and BRL 52974 greater than $30\,mg\,kg^{-1}$ were not used.

Changes in HR with each drug seemed to follow the arterial pressure patterns, with the lower doses of BRL 52656 tending to produce bradycardia but only the high doses of BRL 52974 causing a similar effect.

Effects of chronic subcutaneous infusion of BRL 52656 and BRL 52974 on SAP, MAP and HR

After determining the dose–response relationships, four groups of SHRs received chronic subcutaneous infusion of either BRL 52656 0·2 (n = 6) or $0{\cdot}5\,mg\,kg^{-1}$/day (n = 5), BRL 52974 $0{\cdot}2\,mg\,kg^{-1}$/day (n = 6) or saline (n = 5) for 14 days via osmotic minipumps. The doses were selected on the basis of the outcome of the dose–response relationships for the single doses. SAP (Figure 2), MAP (Figure 3) and HR (Figure 4) were monitored each day three days before and 14 days after the infusions. There were no differences in SAP and MAP of the SHRs treated with BRL 52656 ($0{\cdot}5\,mg\,kg^{-1}$/day) compared with the saline-treated groups. However, at the lower dose of $0{\cdot}2\,mg\,kg^{-1}$/day BRL 52656, SHRs had significantly lower SAP and MAP values throughout the 14-day treatment period, all times considered ($P < 0{\cdot}001$, analysis of variance). In contrast, SAP and MAP responses to BRL 52974 ($0{\cdot}2\,mg\,kg^{-1}$/day) were no different from the saline-treated groups. The patterns with SAP (Figure 2) and MAP (Figure 3) were very similar. Both doses of BRL 52656 caused a significant bradycardia throughout the infusion period whereas BRL 52974 did so only after seven days of drug infusion (Figure 4). Analysis of variance results indicated statistically significant bradycardia for both doses of BRL 52656 from days 1 through 14 compared with saline controls, but with BRL 52974 the analysis indicated significant bradycardia only from days 7–14.

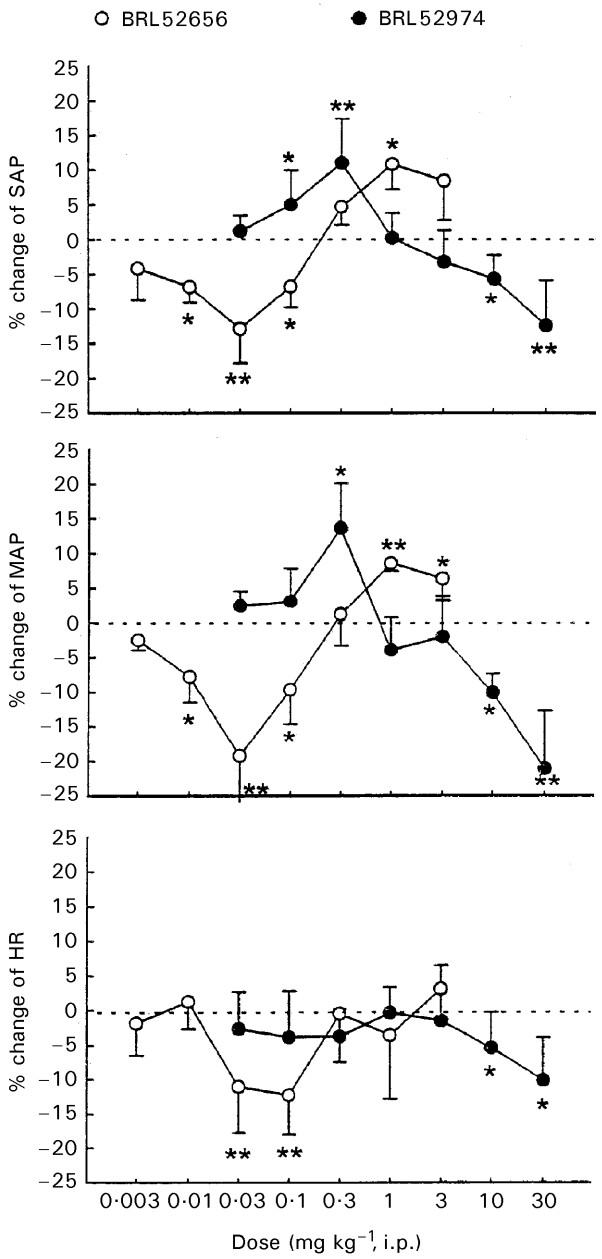

Figure 1. Dose–response relationships in SHRs during intraperitoneal administration of BRL 52656 and BRL 52974 twice a day for each dose (n = 4). $*P < 0{\cdot}05$ and $**P < 0{\cdot}01$ compared with the pre-drug value (Student's *t*-test).

Effects of intraperitoneal injection and subcutaneous infusion of BRL 52656 and BRL 52974 on body weight gain and water intake

After the intraperitoneal injections of different doses of either BRL 52656 or BRL 52974, no

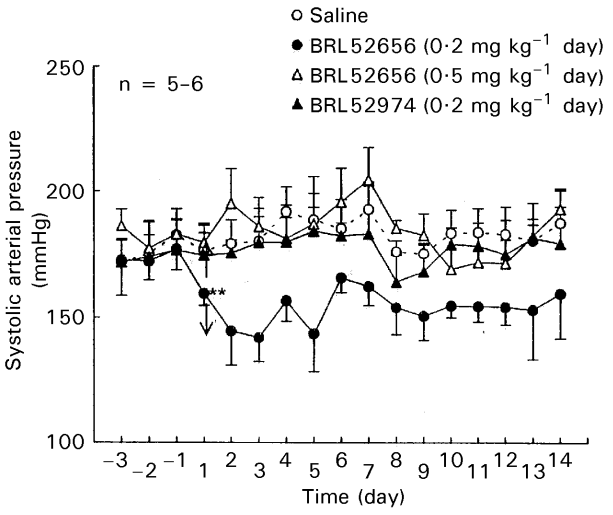

Figure 2. Systolic arterial pressure in SHRs during chronic subcutaneous administration of BRL 52656 and BRL 52974 for 14 days by osmotic minipump. n = number of animals. $^{**}P < 0.01$ for all values beginning on day 1 of drug infusions compared with the values of the saline group (analysis of variance), all days (1 through 14) considered.

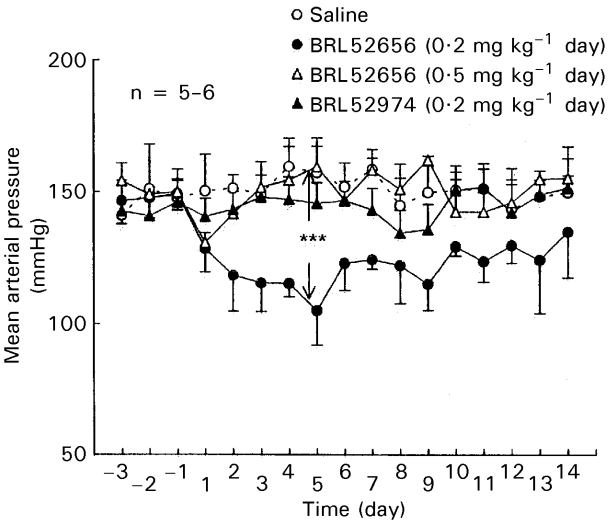

Figure 3. Mean arterial pressure in SHRs during chronic subcutaneous administration of BRL 52656 and BRL 52974 for 14 days by osmotic minipump. n = number of animals. $^{***}P < 0.001$ for all values beginning on day 1 of drug infusions compared with the values of the saline group (analysis of variance), all days (1 through 14) considered.

significant differences in daily weight gain were noted compared with those of saline-treated controls (data not shown). Higher doses of both BRL 52656 (0·3–3 mg kg^{-1}) and BRL 52974 (1–30 mg kg^{-1}) resulted in dose-dependent increases in water intake (Figure 5). However, BRL 52974 was approximately 30-times less potent than BRL 52656.

With the chronic subcutaneous infusion of BRL 52656 (0·2 and 0·5 mg kg^{-1}/day) and BRL 52974 (0·2 mg kg^{-1}/day) for 14 days, none of the κ-agonists resulted in significant weight gain change differences compared with those of saline-treated controls. Average daily weights gained were $15 \pm 1{\cdot}6$, $17 \pm 0{\cdot}9$, $18 \pm 0{\cdot}6$ and $16 \pm 1{\cdot}3$ g respectively for saline, BRL 52656 (0·2 and 0·5 mg kg^{-1}/day), and BRL 52974 (0·2 mg kg^{-1}/day)-treated SHRs. Daily water intake measured throughout the 14-day observation period was slightly increased in the κ-agonist-treated groups. However, none of the group differences were significant compared with saline-treated control at the doses used, averaging 119 ± 9, 118 ± 15, 128 ± 21 and 125 ± 12 mL kg^{-1}/day for saline, BRL 52656 (0·2 and 0·5 mg kg^{-1}/day), and BRL 52974 (0·2 mg kg^{-1}/day)-treated SHRs, respectively.

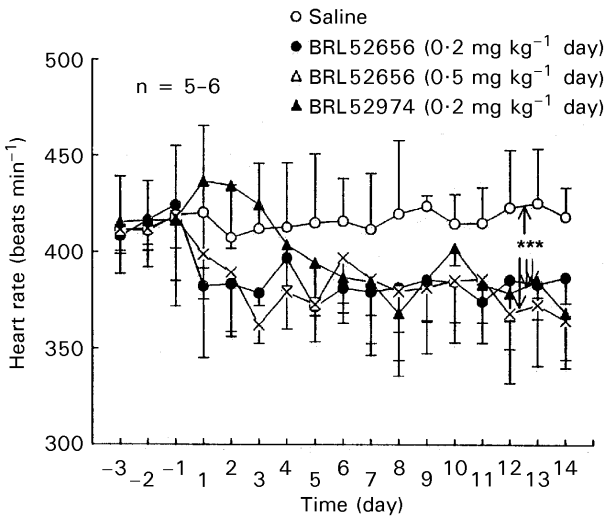

Figure 4. Heart rate in SHRs during chronic subcutaneous administration of BRL 52656 and BRL 52974 for 14 days by minipump. n = number of animals. $^{***}P < 0.001$ for all values beginning on day 1 of drug infusions compared with the values of the saline group (analysis of variance). For both doses of BRL 52656 all values from day 1 through day 14 were considered but for BRL 52974 only days 7 through 14 were considered.

Discussion

BRL 52656, a compound with established selective κ-agonist activity and the ability to cross the blood–brain barrier, produced a clear-cut hypotensive response when given systemically at an equivalent dose to BRL 52974, which has only limited ability to cross the blood–brain barrier (Brooks et al 1993), and which did not cause hypotension. This finding suggests that low doses of selective κ-agonists which gain access to the brain when given systemically produce their hypotensive effects by CNS mechanisms. Accordingly, a central mechanism of action would appear to account for the hypotensive and bradycardic

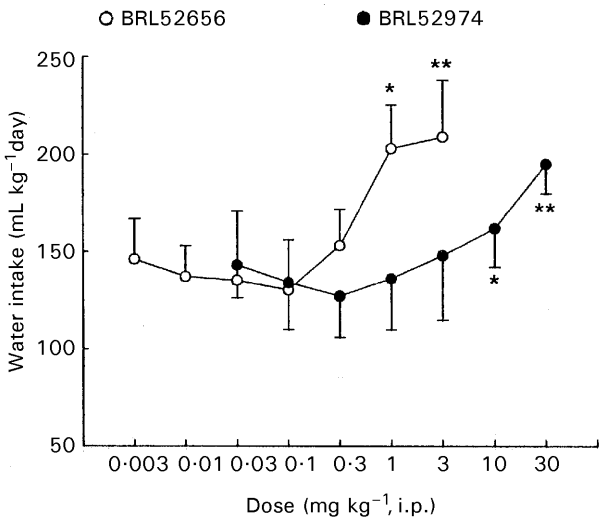

Figure 5. Water intake in SHRs during intraperitoneal administration of BRL 52656 and BRL 52974 twice a day for each dose (n = 4). *$P < 0.05$ and **$P > 0.01$ compared with the pre-drug value (Student's t-test).

effects of the non-peptide κ-agonists U-62,066E and U-50,488H which we observed previously in conscious rats with chronic systemic administration of these drugs given subcutaneously by minipump (Zhai & Ingenito 1997). Both U-50,488H and U-62,066E are known to gain access to the brain and to produce centrally-mediated analgesic effects (Vonvoightlander et al 1983; Vonvoightlander & Lewis 1988).

The establishment of dose thresholds for this central depressor mechanism is important for several reasons if, as we have previously proposed, non-peptide κ-agonists may have potential for use as anti-hypertensive drugs. Firstly, it is always prudent to use only the lowest doses consistent with the desired effect (hypotension). Higher doses are likely to induce other undesirable CNS effects such as observed with single acute doses of κ-agonists in man, i.e. sedation, dysphoria and psychotomimesis (Pfeiffer et al 1986; Reece et al 1994). Secondly, the use of higher doses is likely to result in opposite effects, i.e. hypertension and tachycardia. These latter responses have, in fact, been observed in this study with the higher doses of BRL 52656 and the lower doses of BRL 52974, which we assume were unable to enter the CNS but were above threshold for producing peripherally-mediated hypertension and tachycardia. A number of published studies in rats have demonstrated peripherally-mediated actions of κ-agonists which result in hypertension (Thornhill et al 1990; Szeto et al 1996). We have recently discovered that subthreshold doses of κ-agonists, administered to the hippocampus, will produce a synergistic hypotensive effect with a subthreshold dose of an α_2-adrenergic agonist, similarly administered (unpublished observations).

A mixture of both central and peripheral mechanisms of action is likely to account for the biphasic cardiovascular effects observed after intraperitoneal injections of both drugs (Figure 1). It is likely that low doses of BRL 52656, which has good penetration into the CNS, might account for a centrally-mediated hypotension and bradycardia. Higher intraperitoneal doses of this compound, above that necessary for the hypotensive effect, i.e. above $300\,\mu g\,kg^{-1}$, might produce hypertension because competing peripheral pressor actions may compete with the centrally-mediated hypotensive action. Similarly, we might assume that the low doses of BRL 52974 were unable to gain access to the CNS but were able to activate the peripherally-mediated pressor mechanisms (top panel, Figure 1), while the larger doses, above $3\,mg\,kg^{-1}$, were able to penetrate the CNS to a sufficient degree to cause centrally-mediated hypotension and bradycardia (Figure 3). However, without having established actual drug levels of either compound in brain, the above explanations of the biphasic effects of the drugs are only conjectural. The most likely explanation to account for the surprising lack of a hypotensive effect of $0.5\,mg\,kg^{-1}$/day BRL 52656 is that we had somehow managed to select a dose in which central hypotensive and peripheral hypertensive effects cancelled each other out. To establish whether this idea has merit would require an additional study with nor-binaltorphimine, a selective κ-opioid antagonist, administered peripherally, in an attempt to block the peripheral κ-agonist hypertensive effects of BRL 52974. This would determine whether the centrally-mediated hypotensive effect remained.

The nature of the apparent centrally-mediated hypotensive effect of the κ-agonists observed here deserves some comment. Microinjections of κ-agonists under acute conditions into a number of brain areas related to cardiovascular control have led to decreases in MAP and HR in several animal species. These areas include the ventrolateral periaqueductal gray, the anterior and periventricular hypothalamus, the nucleus ambiguus and the nucleus tractus solitarius (Feuerstein & Faden 1982; Carter & Lightman 1985; Hassen & Broudy 1988; Verberne & Louis 1989; Keay et al 1997). Our own studies have established that both dorsal and ventral hippocampus represent important sites for the hypotensive and bradycardic effects of these compounds and that the effects are κ-receptor mediated (Wang & Ingenito 1992, 1994). Since we found the effects to be more pronounced in SHRs than Wistar Kyoto rats and other non-hypertensive

rat strains (Wang & Ingenito 1992, 1994), we used SHRs in this study. κ-Receptors are present in the brain at a greater density than in normotensive rats (Bhargava & Gulati 1988), which might account for the stronger response to κ-agonists in SHRs. The rapidity with which the response occurs on intrahippocampal administration, within 10 min (Wang & Ingenito 1992, 1994), suggests a neural response rather than through endocrine mechanisms such as through the well-established diuretic effect of κ-agonists mediated possibly via inhibition of vasopressin release by κ-agonists (Yamada et al 1988; Brooks et al 1993). Previously, we suggested (Wang & Ingenito 1992) that the neural effect is due partly to central inhibition of sympathoadrenal discharge and partly to a vagotonic effect on the brain. There was no significant effect of the drugs on water consumption in this study, suggesting that a water diuresis did not account for the hypotensive effect of the drugs observed here. Our previous study with U-50,488H and U-62,066E administered chronically over a 14-day period arrived at a similar conclusion as to the lack of correlation between diuresis and hypotensive effect (Zhai & Ingenito 1997).

In conclusion, we believe that this study provides definitive evidence that the systemic administration of non-peptide κ-opioid agonist drugs lowers arterial pressure and heart rate by an action on κ receptors behind the blood–brain barrier.

Acknowledgements

The authors are grateful to Ms Sheila Taylor for her technical assistance and SmithKline Beecham Co. for the gift of BRL 52656 and BRL 52974.

References

Bhargava, H. N., Gulati, A. (1988) Kappa opioid receptor activity in spontaneously hypertensive rats. J. Pharmacol. Exp. Ther. 245: 460–465

Brooks, D. P., Giardina, G., Gellai, M., Dondio, G., Edwards, R. M., Petrone, G., DePalma, P. D., Sbacchi, M., Jugus, M., Misiano, P., Wang, Y. X., Clarke, G. D. (1993) Opiate receptors within the blood–brain barrier mediate kappa agonist-induced water diuresis. J. Pharmacol. Exp. Ther. 266: 164–171

Carter, D. A., Lightman, S. L. (1985) Selective cardiovascular and neuroendocrine effects of a kappa-opioid agonist in the nucleus tractus solitarii of rats. J. Physiol. 367: 363–375

Feuerstein, G., Faden, A. I. (1982) Differential cardiovascular effects of mu, delta and kappa opiate agonists at discrete hypothalamic sites in the anesthetized rat. Life Sci. 31: 2197–2200

Gulati, A., Bhargava, H. N. (1988) Cardiovascular responses to kappa opioid agonists in intact and adrenal demodulated rats. Eur. J. Pharmacol. 156: 247–257

Hall, E. D., Wolf, D. L., McCall, R. B. (1988) Cardiovascular depressant effects of the kappa opioid receptor agonists U50488H and spiradoline mesylate. Circ. Shock 26: 409–417

Hassen, A. H., Broudy, E. P. (1988) Selective autonomic modulation by mu- and kappa-opioid receptors in the hindbrain. Peptides 9 (Suppl. 1): 63–67

Holaday, J. W. (1983) Cardiovascular effects of endogenous opiate systems. Ann. Rev. Pharmacol. Toxicol. 23: 541–594

Holaday, J. W. (1985) Endogenous Opioids and their Receptors. The Upjohn Co., Kalamazoo, MI

Keay, K. A., Crowfoot, L. J., Floyd, N. S., Henderson, L. A., Christie, M. J., Bandler, R. (1997) Cardiovascular effects of microinjections of opioid agonists into the 'depressor region' of the ventrolateral periaqueductal gray region. Brain Res. 762: 61–71

Pfeiffer, A., Brantl, V., Herz, A., Emrich, H. M. (1986) Psychotomimesis mediated by κ opiate receptors. Science 233: 774–776

Randich, A., Robertson, J. D., Willingham, T. (1993) The use of specific opioid agonists and antagonists to delineate the vagally mediated antinociceptive and cardiovascular effects of intravenous morphine. Brain Res. 603: 186–200

Reece, P. A., Sedman, A. J., Rose, S., Wright, D. S., Dawkins, R., Rajagopalan, R. (1994) Diuretic effects, pharmacokinetics and safety of a new centrally acting kappa-opioid agonist (CI-977) in humans. J. Clin. Pharmacol. 34: 1126–1132

Shen, S., Ingenito, A. J. (1999) Depressor effect of kappa opioid agonist on hypertension induced by isolation in the rat. Clin. Exp. Hypertens. 21: 275–297

Szeto, H. H., Wu, D., Yee, J. S., Soong, Y., Fukuda, S., Taylor, C. T. (1996) U50,488H-induced pressor effect in the ovine foetus is mediated by sympathetic activation and vasopressin. Eur. J. Pharmacol. 309: 183–187

Thornhill, J., Grogor, L., Pittman, Q. (1990) Pressor responses in rats following intravenous dynorphin A (1–13) administration are blocked by AVP-V1 receptor antagonism. Regul. Pept. 31: 1–10

Ur, E., Wright, D. M., Bouloux, P. M., Grossman, A. (1997) The effects of spiradoline (U-62066E), a kappa-opioid receptor agonist, on neuroendocrine function in man. Br. J. Pharmacol. 120: 781–784

Verberne, A. J., Louis, W. J. (1989) Interaction between the cardiovascular effects of clonidine and the kappa-opioid agonist U-50,488H in the anterior hypothalamic area of the rat brain. J. Pharm. Pharmacol. 41: 131–133

Vonvoightlander, P. F., Lahti, R. A., Ludens, J. H. (1983) U-50,488H: A selective and structurally novel non-mu (kappa) opioid agonist. J. Pharmacol. 224: 7–12

Vonvoightlander, P. F., Lewis, R. A. (1988) Analgesic and mechanistic evaluation of spiradoline, a potent kappa agonist. J. Pharmacol. Exp. Ther. 246: 259–262

Wang, J. Q., Ingenito, A. J. (1992) Centrally mediated cardiovascular actions of dynorphin A (1–8) on rat hippocampal formation. J. Pharmacol. Exp. Ther. 261: 678–685

Wang, J. Q., Ingenito, A. J. (1994) Cardiovascular responses to intra-hippocampal dynorphin A (1–8) in spontaneously hypertensive rats. Eur. J. Pharmacol. 256: 57–64

Wu, K. M., Martin, W. R. (1989) Cardiovascular and respiratory effects of an opioid kappa agonist ethylketazocine and sigma agonist N-allylnormetazocine in acutely decerebrated dogs. Pharmacol. Biochem. Behav. 34: 405–411

Yamada, T., Nakao, K., Itoh, H., Shirakami, G., Sugawara, A., Saito, Y., Mukoyama, M., Arai, H., Hosoda, K., Morii, N. (1988) Opioid modulation of vasopressin secretion in conscious rats. Clin. Exp. Hypertens. 10 (Suppl. 1): 361–367

Zhai, Q. Z., Ingenito, A. J. (1997) Sustained antihypertensive effects of chronic administration of two κ opioid agonists in spontaneously hypertensive rats. Am. J. Ther. 4: 173–180