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Role of Central opiate System in Control of Cardiovascular Function of Experimental Hypertensive Rats

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ABSTRACT

The possible inolvement of central opiate system in the control of cardiovascular function and in the antihypertensive action of clonidine has been examined in unanesthetized rats with sham-operated or 2-kidney, 1-clip (2K1C) renal hypertension. In both groups of rats, intraventricular clonidine (3-30 μg/kg) produced hypotension and bradycardia.

Hypotensive action of clonidine was more potent in the hypertensive rats than in the normotensive sham-operated rats. Yohimbine (30 μg/kg, i.v.t.) inhibited the hypotension and bradycardia produced by clonidine. Naloxone (50 μg/kg, i.v.t) inhibited the action of clonidine in 2K1C hypertensive rats but not influenced in the sham-operated rats. Intraventricular morphine (10-100 μg/kg) also reduced rats. Intraventricular morphine (10-100 μg/kg) also reduced blood pressure and heart rate in both groups of rats. But these effects were not affected by yohimbine, but antagonized by naloxone (50 μg/kg, i.v.t.). Chronic treatment of 2K1C rats with clonidine (3×20 μg/kg, p.o., for 14 days from 1 day after 2K1C operation) suppressed the development of hypertension and maintained the blood pressure in normal level and this errect of clonidine was abolished by naloxone (2 mg/kg, i. p.).

In the 2K1C hypertensive rats, immunoreactive β-endorphin content was significantly decreased, but maximum binding (Bmax) of (^{3}H)-naloxone was significantly increased in brain of 2K1C hypertensive rats. However, Kd value was not changed.

These results suggest that the opioidergic component might be involved in the antihypertensive action of clonidine only in hypertensive and that central opiate system might play important roles in pathophysiology of development and maintenance of hypertension.

Key Words: 2K1C, Hypertension, Clonidine, Opiate system.

INTRODUCTION

It is well established that the central sympathetic nervous system plays an important role in the control of blood pressure and heart rate. Antihypertensive action of clonidine is believed to be mediated by activation of α-adrenoceptors in the medulla oblongata (van Zwieten and Timmermans, 1971a; 1983b). Morphine and some opioid peptides can also cause similar cardiovas cular effects that can be antagonized by naloxone (Laubie *et al.*, 1974; Bolmen *et al.*, 1978).

There are much evidence that indicate an interaction between the central adrenergic and opiate receptor system. Naloxone has been to antagonize clonidine-induced depression of blood pressure in spontaneously hypertensive rats (SHR) (Farsang *et al.*, 1980). Clonidine has been shown to have antinociceptive effects (Chance, 1983; Hirst *et al.*, 1983). Furthermore, clonidine increase the release of immunoreactive β-endorphin from superfused slices of brainstem of SHR and clonidine administration to the SHR can increase the plasma concentration of β-endorphin (Kunos and Farsang, 1981). Central blood pressure and pain regulatory mechanisms might be closely associated. Considerable evidence to support this contention has accumulated over the past

several years. Both in genetic (Sisten and de Jong, 1984) and various forms of experimentally-induced hypertensive rats (Zamir and Segal, 1979a; 1980b; Naranzo *et al.,* 1986; Fuentes *et al.,* 1984), a decreased sensitivity to noxious stimuli has been reported. The concentration of met-enkephalin in the adrenal glands, sympathetic ganglia, and salivary glands of SHR is reduced (Di Giullio and yang, 1979). In addition, opiate receptor numbers in particulate fractions from the brains of young hypertensive SHR has been reported (Martucci and Hahn, 1979). These facts support the involvement of endogenous opioids in the development of hypertension.

The objective of the present study was to investigate whether development of effects of clonidine and morphine, in the content of immunoreactive β-endorphin, and in the characteristics of specific opiate receptor binding.

MATERIAL AND METHOD

Animals: Experiments were performed in conscious male Sprague-Dawley rats weighing about 200 g. The animals were housed in plastic cages with water and food supplied ad libitum.

Operation: Renal hypertension was induced by applying a silver clip with an internal diameter of 0.20 mm on the left renal artery, leaving the right kidney untouched. Control animals were subjected to the same procedure without a clip on the artery.

Drug administration: For cannulation of the lateral ventricle, rats were anesthetized with pentobarbital (30 mg/kg), and the head was fixed in a stereotaxic apparatus (DKI). A 10 mm-long stainless steel guide cannula (0.65 mm in dia.) was implanted into the lateral ventricle of rat using following coordinates: AP 0.0, L 1.7, H 3.5 mm according to the atlas of Pellegrino *et al.,* (1979). The cannula was to the skull with dental cement. ivt Injections were done by briefly restraining the conscious rat and using a injection cannula (0.25 mm in dia). Adequate placement of the cannula was verified by gross morphological inspection of the brain, when animals were killed 1 hr aftr the injection of 1% methylene blue.

In the experiment for the chronic effects of clonidine, clonidine (20 μg/kg/day, tid, p.o.) was administered for 14 days from the day after the 2K1C operation.

Measurement of blood pressure and heart rate: Systolic blood pressure and heart rate of unanesthetized rats were measured by the tail cuff method. The rat was placed in a restrainer maintained at 37℃ and were allowed to settle down. Pulsations of the tail artery, detected by pneumatic sensor (narcol1058) were monitored by a physiograph (Narco, MK-IV).

Specific opiate receptor binding assay: The maximum binding (Bmax) and affinity constant (Kd) of the opiate receptor were determined by the method of Bardo *et al.,* (1982). For determining the specific (^{3}H)-naloxone binding, tissue was homogenized (Polytron, setting 7, 10s) in 200 vols. of ice-cold 50 mM Tris-HCl buffer (pH 7.4) containing 100 mM NaCl. Portions (0.95 ml) of the tissue homogenate was incubated at 0℃ for 180 min with 1nM (3H)-naloxone in the presence of various concentrations of naloxone (0-10 nM, 10 μM). Incubation was terminated by filtration under vacuum pressure over glass fiber filter (GF/B) and washed with 5 ml of ice-cold Tris buffer. The specific binding of (3H)-naloxone bindings was calcurated by the method of Akera and Cheng (1977).

β-endorphin radioimmunoassay: β-Endorphin immunoreactivity was quantitated by radioimmunoassay. Brain tissue was placed in an inverted petri dish on salted ice at -5 to -10℃. The preparation was homogenized in 9 ml of 1N acetic acid for 1 g of wet tissue. The homogenate was centrifuged at 10,000$\times$g for 30 minutes. The supernate was resuspended with equal volume of 1 N acetone. The final suspension was evaporated at 20℃ and submitted to radioimmunoassay procedure by using NEN kit (NEK-0.03).

Protein was assayed by the method of Lowry *et al.,* (1951).

Data were analyzed by paired or unpaired student's t-test.

Drugs used were clonidine HCl (Sigma), yohimbine HCl (Sigma), morphine HCl (Samsung Pharm.) and naloxone HCl (Sigma).

RESULTS

The average systolic blood pressure for the control and 2K1C-operated groups is shown in Figure 1. The blood pressure of the control group showed little change throughout the 4 week after sham-operation. In 2K1C-operated animals, there was a significant increase in blood pressure as early as 1 week after the operation ($p<0.05$); the

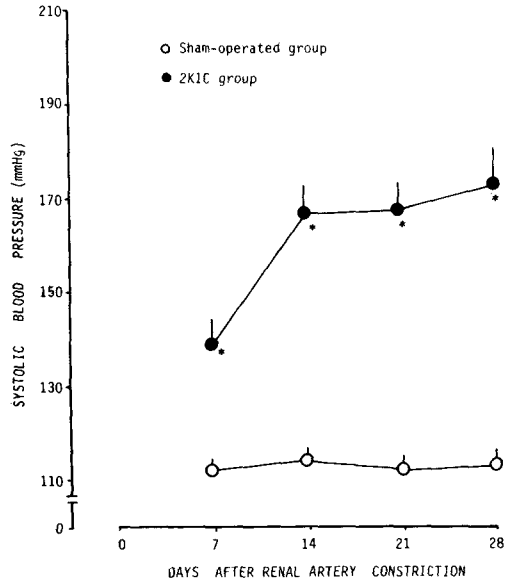

Fig. 1. Changes in blood pressure of 2-kidney, 1-clipped hypertensive rats. Each point with vertical bar denotes the mean with SEM from 8 experiments.
* Significantly different from corresponding sham-operated group ($p < 0.05$).

blood pressure continued to rise progressively during the following weeks, to reach a mean level of 169.4 mmHg at the end of 4 weeks.

Effects of intracerebroventricular clonidine

The icv clonidine caused initial transient (approximately 10 min) rise (+4−9 mmHg), followed by longer-lasting fall (−5−12 mmHg) of blood pressure in the unanesthetized normotensive rats in dose dependent manner. The peak effect was shown at about 30 min after the icv injection. This hypotensive effect of icv clonidine was more prominent (−16-33 mmHg) in the 2K1C hypertensive rats (Fig. 2 and 3).

Influence of yohimbine: Icv yohimbine (30 μg/kg) caused transient mild elevation (+10±3.4 mmHg) of blood pressure and increase (+26±3.2 bpm) of heart rate, and then normalized after about 10 min of drug administration. Cardiovascular effect of icv clonidine were significantly attenuated by yohimbine pretreatment in the normotensive and the 2K1C hypertensive rats (Fig. 4).

Influence of naloxone: icv Naloxone (50 ug/kg) did not caused any changes in blood pressure

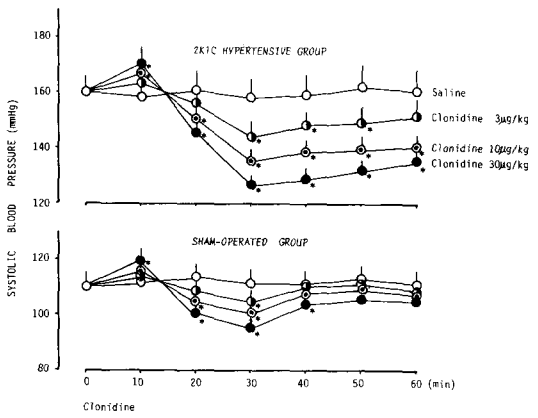

Fig. 2. Time course of the effect of intraventricular administered clonidine in 2K1C hypertensive rats (upper panel) and sham-operated rats (lower panel). Each point with vertical bar represents the mean with SEM from 6 experiments.
* Significantly different from the value of saline-treated group ($p < 0.05$).

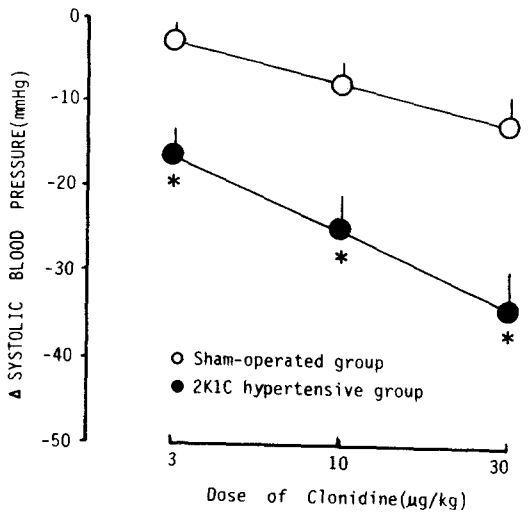

Fig. 3. Maximum changes in hypotensive effect of intraventricular clonidine in 2K1C hypertensive rats and sham-operated rats at 30 min after the administration of clonidine. Each point with vertical bar represents the mean with SEM from 6 experiments.
* Significantly different from sham-operated group ($p < 0.05$).

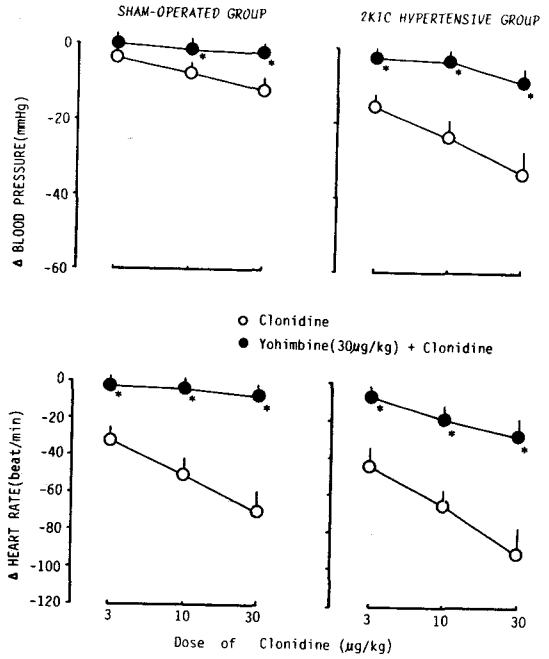

Fig. 4. The influence of yohimbine (30 μg/kg, i.v.t) on the hypotensive and bradycardiac effect of intraventricular clonidine in 2K1C hypertensive (right panel) and sham-operated (left panel) rats. Each point with vertical bar represents the mean with SEM from 6 experiments.
* Significantly different from corresponding saline-pretreated control value ($p < 0.05$).

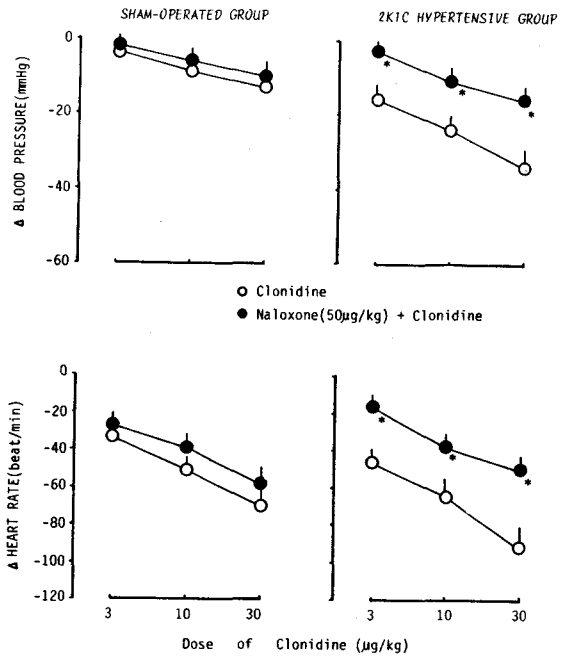

Fig. 5. The influence of naloxone (50 μg/kg, i.v.t.) on the hypotensive and bradycardiac effect of intraventricular clonidine in 2K1C hypertensive (right panel) and sham-operated (left panel) rats. Other legends are same as in Fig. 4.

or heart rate. The hypotensive and the bradycardiac effect of clonidine were almost not changed in the normotensive rats, but significantly inhibited in the 2K1C hypertensive rats (Fig. 5).

Effects of intracerebroventricular morphine

The icv morphine caused initial transient (approximatery 1-2 min) rise (+5-10 mmHg) of blood presure and increase (+14-36 bpm) of heart rate, and then followed by decrease of blood pressure and heart rate from 20 min after the icv injection in the unanesthetized normotensive and 2K1C hypertensive rats in dose dependent manner. The peak effect was shown at about 50 min after the icv injection. This hypotensive effect of icv morphine was more prominent in the 2K1C hypertensive (−8.4−49.2 mmHg) than in the normotensive (−9.5−27.3 mmHg) rats (Fig. 7.).

Influence of yohimbine: The cardiovascular

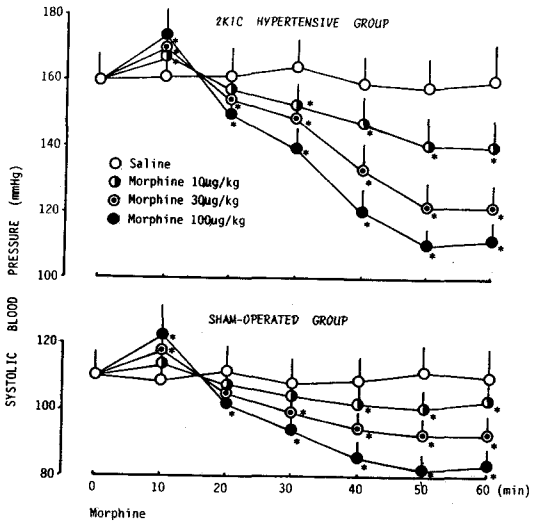

Fig. 6. Time course of the effect of intraventricular morphine in 2K1C hypertensive (upper panel) and sham-operated (lower panel) rats. Each point with vertical bar represents the mean with SEM from 6 experiments.
* Significantly different from the value of saline-treated group ($p < 0.05$).

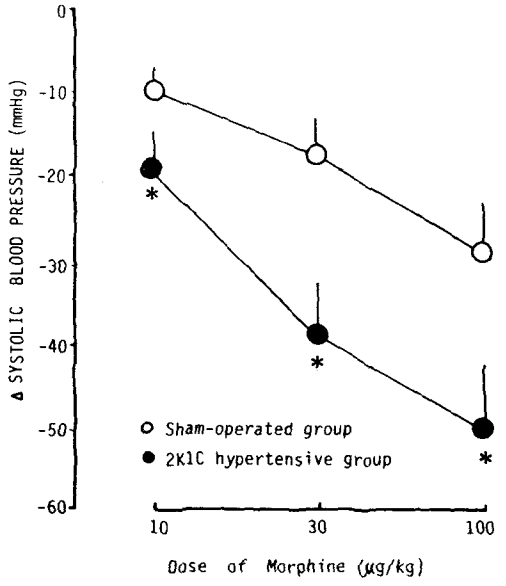

Fig. 7. Changes in hypotensive effect of intraventricular morphine in 2K1C hypertensive rats and sham-operated rats at 50 min after the administration of morphine. Each point with vertical bar represents the mean with SEM from 6 experiments.
* Significantly different from sham-operated group ($p < 0.05$).

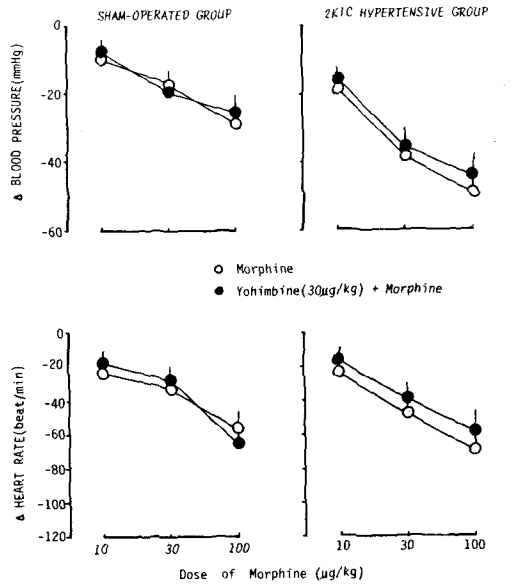

Fig. 8. The influence of yohimbine (30 μg/kg, i.v.t.) on the hypotensive and bradycardiac effect of intraventricular morphine in 2K1C hypertensive (right panel) and sham-operated (left panel) rats. Other legends are same as in Fig. 4.

effects of icv morphine were not influenced by icv yohimbine (30 μg/kg) pretreatment in both control and the 2K1C hypertensive rats (Fig. 8.).

Influence of naloxone: The above cardiovascular effects were severely inhibited by icv naloxone (50 ug/kg) pretreatment in the normotensive and the 2K1C hypertensive rats (Fig. 9).

Influence of naloxone on the chronic effect of clonidine

Effective treatment of hypertension involves chronic administration of antihypertensive drugs. Under such conditions the mode of action of some drugs may be different from that after their acute administration. We therefore tested the effect of naloxone on blood pressure of 2K1C hypertensive rats chronically treated with clonidine.

Chronic clonidine treatment almost completely suppressed the development of hypertension in 2K1C-operated rats, but the antihypertensive effect of clonidine was reversed by single intraperitoneal injection of naloxone (2 mg/kg) (Fig. 10.).

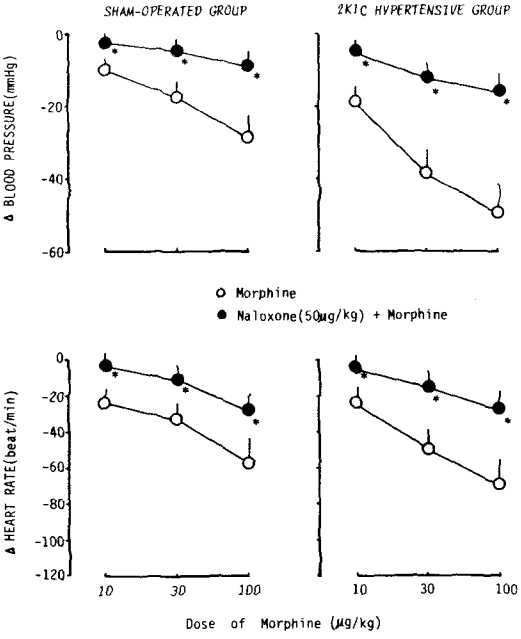

Fig. 9. The influence of naloxone (50 μg/kg, i.v.t.) on the hypotensive and bardycardiac effect of intraventricular morphine in 2K1C hypertensive (right panel) and sham-operated (left panel) rats. Other legends are same as in Fig. 4.

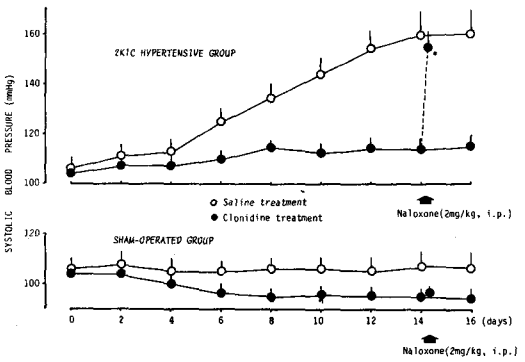

Fig. 10. The influence of naloxone (2 mg/kg, i.p.) on the chronic antihypertensive effect of clonidine (3 x 20 μg/kg/day, p.o., for 14 days) in 2K1C hypertensive (upper panel) and sham-operated (lower panel) rats. Each point with vertical bar represents the mean with SEM from 6 experiments.
* Significantly different from the value of corresponding sham-operated group ($p < 0.05$).

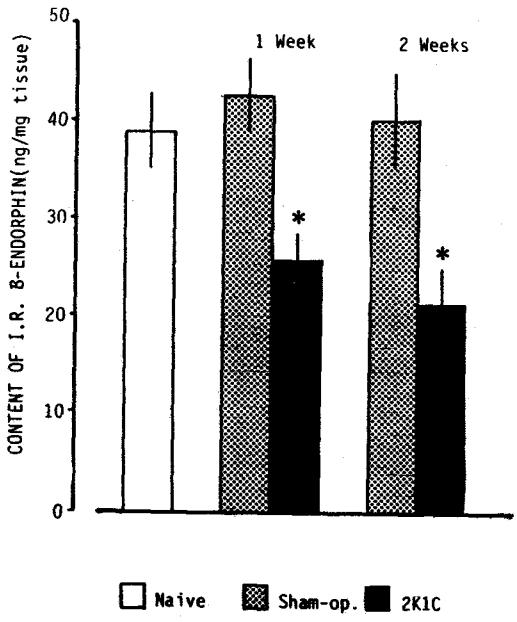

Fig. 11. Contents of immunoreactive β-endorphin in brain of 2K1C or sham-operated rats. Rats were sacrificed at 1 or 2 weeks (s) after operation. Values are mean ± SEM from 6 experiments.
* Significantly different from the value of corresponding sham-operated control ($p < 0.05$).

Table 1. Specific binding of [^{3}H] naloxone in two kidney one clip (2K1C) Goldblatt hypertensive rats and in sham-operated controls

Groups	Specific [^{3}H] naloxone binding	
	B_{max} (Pmol/mg protein)	K_d (nM)
Naive	68.8 ± 7.3	7.8 ± 0.9
1 wk after op.		
Sham	62.5 ± 7.6	7.2 ± 0.9
2K1C	97.2 ± 9.9[a, b]	7.6 ± 7.6
2 wks after op.		
Sham	64.3 ± 6.8	8.4 ± 0.8
2K1C	106.5 ± 11.3[a, b]	8.0 ± 0.9

Each value represents the mean with SEM from 6 midbrain preparations. a : Significantly different from the non-operated naive group ($p < 0.05$).
b ; Significantly different from the sham-operated control group ($p < 0.05$).

β-Endorphin immunoreactivity in brain of 2K1C hypertensive rats.

In this tudy we observed the changes of content of β-endorphin immunoreactivity in the control and the 2K1C hypertensive rats. There was no difference in the contents of β-endorphin immunoreactivity between the non-operated (38.4+ 4.1 ng/mg tissue) and sham-operated group. But the content of β-endorphin was significantly decreased after 2K1C operation compared with the non-operated or the sham-operated group ($p<0.05$) (Figure 11).

Specific [^{3}H]-naloxone binding in brain of the 2K1C hypertensive rats.

Table 1 represents the change of the specific (^{3}H)-naloxone binding in the non-operated, sham-operated and 2K1C-operated groups. At 1 and 2 weeks after 2K1C operation, maximum binding of specific opiate receptor were significantly increased compared with non-operated normal or sham-operated groups ($p<0.05$). But Kd values were not changed in all preparations.

DISCUSSION

In the present study icv clonidine produced

transient hypertension followed by long-lasting hypertension in dose dependent manner in the unanesthetized 2K1C and the normotensive rats. The hypertensive effect of icv clonidine was significantly attenuated by icv yohimbine pretreatment. This well-known cardiovascular effect of clonidine have been observed in several species of unanesthetized (Beckett and Finch, 1982) and anesthetized (Kellar *et al.*, 1984; Anden *et al.*, 1976) animals by numerous workers. It is widely recognized that the hypotensive effect of clonidine is the result of activation of central α-adrenoceptors in the medulla oblongata that lead to decrease of sympathetic tone. And also, the hypertensive effect of clonidine was more prominent in the 2K1C hypertensive rats than in the normotensive one. Similar findings observed in SHR (Lokhandwala and Eikenberg, 1983; Yarbrough *et al.*, 1982), renal hypertensive dog and cat (Zeigler *et al.*, 1984), and these reports together with our present observation, indicate an increment of cardiovascular responsiveness in hypertensive states to clonidine.

In our results icv naloxone pretreatment significantly inhibited the hypertensive effect of clonidine in the 2K1C hypertensive rats but not in the normotensive rats. Naloxone-reversible hypotension induced by clonidine was also observed in SHR (Ramirez-Gonzales *et al.*, 1983), but there has not been reported in arbitrarily-induced hypertensive animals.

And we observed that chronic treatment of 2K1C hypertensive rat with clonidine reduced blood pressure and this effect was acutely reversed by a single injection of naloxone. Clonidine was shown to have antinociceptive effects (Chance, 1983; Hirst *et al.*, 1983) and to reverse opiate withdrawal symptoms (Thoolen *et al.*, 1981). Moreover, the symptoms of withdrawal of opiate and clonidine are remarkably similar (Engberg and Svenson, 1981).

These similarities suggest some interactions between central opiate system and the α-adrenoceptors. Clonidine and naloxone did not cross-react with each other's binding sites in the brain (Glombiowska-Nikitin *et al.*, 1980) and clonidine was shown to increase the release of β-endorphin immunoreactivity in brain slice preparations obtained from SHR (Kunos and Farsang, 1981). Our results, with above metioned obserbations, strongly suggest that the release of an endogenous opiate from the area that participate in the central control of blood pressure contributes to the antihypertensive action of central α-adrenoceptor stimulants not only in the SHR but also in the 2K1C hypertensive rat. And it is possible that a similar mechanism is either not stimulated or inactive in the normotensive rats.

Opiate receptors have been indentified in the brain (Pert, and snyder 1973), and later, in the pituitary sympathetic ganglia, kidney, liver, gastrointestinal tract, and heart (Kuhar and Pert 1973). Subsequently a series of compounds that exhibited specific binding to these receptors were isolated from various tissues, including the brain, and were named enkephalins and endorphins (Hughes, 1975). These opiate receptors are distributed in corresponding area that major sites of action of the opiates in the processing of pain stimuli, ie; the substantia gelatinosa, the periventricular grey matter, and the medial thalamus. On the other hand, opiate receptors are also found at sites that are not primarily concerned with pain sensation, including infundibulum of the hypothalamus, the area postrema of the medulla, the locus coeruleus, and the caudate nucleus (Pert and Kuhar, 1976). It has been proposed that these receptors are important in respiration and cardiovascular control. Recently, considerable evidences are cumulated that suggest the important roles in the control of cardiovascular function. ICV narcotic analgesics, including morphine and β-endorphin, decreased blood pressure and antagonized by naloxone in the cat and the rat (Feldberg and Wei, 1977; Laubie *et al.*, 1974; Bolme *et al.*, 1978)

In our study the Bmax of specific opiate receptor binding was increased in brain of 2K1C hypertensive rats.

These results indicate the possibility that the opioidergic component can be altered by hypertension itself. These results were partialy agrees with the findings that decreased sensitivity to noxious stimuli in the spontaneously (Zamir *et al.*, 1980; Sisten and de Jong, 1984) or experimentally induced hypertensive animals (Zamir and Segal, 1979; Naranzo *et al.*, 1986; Fuentes *et al.*, 1984).

REFERENCES

Akera T, Cheng VJK: *A simple method for the determination of affinity and binding site concentration in receptor binding studies. Biochim. et Biophy. Acta 470:412-423, 1977*

Anden NE, Grabowska M, Strombom U: *Different α-adrenoceptors in the central nervous system mediating biochemical and functional effects of clonidine and receptor blocking agents. Naunyn-Schmiedeberg's ARch Pharmacol 292:43-52, 1976*

Bardo MT, Bhatnager RK, Gebhart GF: *An improved filtration procedure for measuring opiate receptors in small regions of rat brain. J of Neurochem 39 (6):1751-1754, 1982*

Beckett PJ, Finch L: *The α_1-and α_2-adrenoceptor involvement in the central cardiovascular action of clonidine in the conscious renal hypertensive cat. Eur J Pharmacol 82:155-160, 1982*

Bolme P, Fuxe K, Agnati LF: *Cardiovascular effects of morphine and opioid peptides following intracisternal administration in chloralose-anesthetized rats. Eur J Pharmacol 48:319-324, 1978*

Chance WT: *Clonidine analgesia: Tolerance and cross-tolerance to autoanalgesia. Life Sci 33:2241-2246, 1983*

Di Giulio AM, Yang HYT, Fratta W, Costa E: *Decreased content of immunoreactive enkephalin-like peptide in peripheral tissues of spontaneously hypertensive rats. Nature 278:646-647, 1979*

Engber G, Elam M, Svensson TH: *Clonidnie withdrawal: Activation of brain noradrenergic neurons with specifically reduced α_2-adrenoceptor sensitivity. Life Sci 30:235-243, 1981*

Farsang C, Ramirez-Gonzalez MD, Mucci L, kunos G: *Possible role of an endogenous opiate in the stimulation in spontaneously hypertensive rats. J Pharmacol Exp Ther 214 1:203-208, 1980*

Feldberg W, Wei E: *Central sites at which morphine acts when producing cardiovascular effects. J Physol 275, 57p, 1977*

Fuentes JA, Borrell J, Naranzo JR: *Opioid involvement in hypertension induced by short-term isolation. Clin Exper Hypertension A6 (10 & 11): 2041-2044, 1984*

Golombiowska-Nikitin K, Pilc A, Vetulani J: *Opiates and specific receptor binding of (3H)-clonidine. J Pharm Pharmacol 32:70-71, 1980*

Hirst M, Kavaliers M, Teskey GC: *Age and day-night changes in clonidine-induced analgesia in mice. Can J Physiol Pharmacol 62: 1102-1105, 1983*

Hughes J: *Isolation of an endogenous compounds from the brain with pharmacological properties similar to morphine. Brain Res 88:295-308, 1975*

Kuhar MJ, Pert CB: *Regional distribution of opiate receptor binding in kidney and human brain. Nature (London) 245:447-450, 1973*

Kunos G, Farsang C: *Beta-endorphin: Possible involvement in the antihypertensive effect of central alpha-recetpor activation, Scinence (Washington) 211:82-84, 1981*

Kunos G, Robertson B, Kan WH, Preiksaitis H, Mucci L: *Adrenergic reactivity of the myocardium in hypertension. Life Sci 22:847-854, 1978*

Laubie M, Schmitt H, Cannellas J, Roquebert J, Demichel P: *Central mediated bradycardia and hypertension induced by narcotic analgesics: Dextromoramide and fentanyl. Eur J Pharmacol 28: 66-75, 1974*

Lokhandwala MF, Eikenberg DC: *Presynaptic receptors and alterations in norepinephrine release in spontaneously hypertensive rats. Life Sic 33:1527-1542, 1983*

Lowry OH, Rosebrough NJ, Farr AL, Randall RJ: *Protein measurement with the Folin phenol reagent. J Biol Chem 193:265-275, 1951*

Martucci CP, Hahn EF: *Brain opiate receptor concentrations are increased in adult spontaneously hypertensive rats. Endocrinol Res Commun 6:291-297, 1979*

Naranjo JR, Urdin MC, Borrell J, Fuentes JA: *Evidence for a central but not adrenal opioid mediation in hypertension induced by brief isolation in the rat. Life Sci 38:1923-1930, 1986*

Pellegrino LJ, Pellegrino AS, Cushman AJ: *A stereotaxic atlas of the rat brain. Plenum Press, 1979*

Pert CB, Snyder SH: *Opiate receptor: Demonstration in nervous tissue. Science 179:1011-1014, 1973*

Pert CB, Kuhar MJ, Snyder SH: *Opiate receptor: Autoradiographic localization of opiate receptors in rat brain. Proc Natl Acad Sci USA 73:3729-3733, 1976*

Ramirez-Gonzalez, MD, Tchakarov L, Garcia RM, Kunos G: *beta-Endorphin acting on the brainstem is involved in the antihypertensive action of clondine and α-methyldopa in rats. Circ Res 53:150-157, 1983*

Sisten JMA, de Jong W: *Observation on pain perception and hypertension in spontaneously hypertensive rats. Clin and Exper Hypertension A6 (7): 1345-1356, 1984*

Thoolen MJMC, Timmermans PBMWM, van Zwieten PA: *Morphine suppresses the blood pressure responses to clonidine withdrawal in the spontaneously hypertensive rat. Eur J Pharmacol 71:351-353, 1981*

Yarbrough GG, Taylor DA, Antolik EK, Robinson EL: *Spontaneously hypertensive rats exhibit an enhanced mydriatic response to clonidine. Evidence for enhanced sensitivity of central α_2-adrenoceptors: Can J Physiol Pharmacol 61, 7*

Zamir N, Segal M: *Hypertension-induced analgesia: Changes in pain sensitivity in experimental hypertensive rats. Brain Res 160, 170-173, 1979*

Zamir N, Simantov R, Segal M: *Pain sensitivity and opioid activity in genetically and experimental hypertensive rats. Brain Res 184:299-310, 1980*

Ziegler DW, Shebuski RJ, Zimmerman BG: *Central and peripheral cardiovascular actions of urapadil in normotensive and Golblat hypertensive animals. The Am J Med 77:81-86, 1984*

Van Zwieten PA, Timmermans PBMWM: *Pharmacology and characterization of effect of centrally acting antihypertensive drugs. Chest 83 (2):340-343, 1983b*

Van Zwieten PA, Timmermans PBMWM: *The role of central alpha-adrenoceptors in the mode of action of hypertensive drugs. Trends Pharmacol Sci 1:39-41, 1979a*

= 국문초록 =

실험적 고혈압 백서의 심맥관계 기능조절에 있어서 중추 Opiate System의 역할

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Morphine을 비롯한 opioid peptide가 말초 또는 중추에 투여시 혈압하강과 심박동수감소를 보이며 opiate 수용체 길항제인 naloxone에 의해 길항됨이 관찰되었던 바 근래 몇몇 보고들은 중추신경내에서 adrenergic 및 opioidergic system이 서로 관련되어 있음을 시사하고 있다. 이에 본 실험에서 고혈압 연구에 널리 사용되고 있는 2-kidney, 1-clip (2K1C) 방법으로 실험적 고혈압을 유발시킨 백서의 측뇌실내 clonidine 또는 morphine의 심맥관계에 대한 효과와 각각의 차단제에 의한 영향 그리고 정상 및 고혈압상태 백서의 뇌내 β-endorphin의 함량과 specific opiate receptor binding을 정량하여 고혈압 유발에 따른 뇌내 opiate system의 변동을 관찰하였다.

2K1C 고혈압 또는 sham-operated 대조백서에서 측뇌실내 clonidine (3-30 μg/kg)은 용량에 비례하여 혈압하강과 심박동수감소를 일으켰으며 clonidine의 혈압강하 효과는 2K1C 고혈압 백서에서 더욱 현저하였다. clonidine의 혈압강하효과는 고혈압 백서에서 측뇌실내 yohimbine 또는 naloxone 전처리에 의해 약화되었고 대조군에서는 yohimbine (30 μg/kg, i.v.t.)에 의해 억제되었으나 naloxone (50μg/kg, i.v. t.)에 의해서는 영향받지 않았다. clonidine과 마찬가지로 측뇌실내 morphine (10-100 μg/kg)은 2K1C 고혈압 또는 sham-operated 대조백서에서 용량에 비례하여 혈압하강과 심박동수감소를 일으켰으며, morphine의 혈압강하효과는 2K1C 고혈압백서에서 더욱 현저하였다. 대조군과 고혈압군에서 morphine의 혈압강하효과는 naloxone 전처리에 의해 현저히 약화되었으나 yohimbine에 의해서는 영향받지 않았다.

2K1C 시술 익일부터 투여한 clonidine은 2K1C 시술에 의한 혈압 상승을 억제하였으며 naloxone (2 mg/kg, i.p.)에 의해 반전되었다.

2K1C 시술에 의해 고혈압이 유발된 백서의 뇌내 β-endorphin 함량은 sham-operated 군에 비하여 유의하게 감소되어 있었고 (3H)-naloxone의 specific binding의 Bmax는 증가되었으나 Kd치는 변동되지 않았다.

이상의 실험 성적은 뇌내 opiate계가 혈압조절에 중요한 역할을 담당하고 있으며 2K1C 고혈압백서의 고혈압상태 유지에 뇌내 opiate계의 기능저하가 일부관여하고 있음을 강력히 시사한다.