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Studies on Involvement of Central GABAergic Mechanism and Central α_2-Adrenoceptors in Pressor Responses to Raised Intracranial Pressure

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ABSTRACT

Recent studies have shown that a GABAergic mechanism in the brain modulates arterial blood pressure (BP) through alterations of sympathetic activity in the brain. The purpose of the present study was to determine if this modulation is involved in the pressor response to raised intracranial pressure (ICP).

The pressor response to raised ICP was abolished by pretreatment of anesthetized rabbits with intracerebroventricular (icv) muscimol (a GABA agonist) as well as with icv clonidine (an α_2-agonist). Raising ICP in the hypertensive state after icv yohimbine (an α_2-antagonist) did not cause an additional increase in the BP, whereas raising ICP in the hypertensive state following icv bicuculline (a GABA antagonist) produced a further increase. Bicuculline produced an increase of the BP which had been lowered by muscimol or by clonidine, whereas it failed to increase the hypertensive state induced by either previous yohimbine or raised ICP. Yohimbine reversed the BP which had been made low by clonidine but was incapable of raising the hypotensive state after muscimol. Yohimbine failed to increase the heightened BP due to raised ICP, whereas bicuculline-induced pressor state was further elevated by yohimbine. Muscimol, besides the bicuculline-antagonizing property, inhibited the pressor response to yohimbine, suggesting participation of a GABAergic mechanism in the pressor action of yohimbine. From these results it was inferred that there were three ways in which BP could be increased via raised ICP: inactivation of the inhibitory sympathetic activity through ① α_2-adrenoceptors, ② bicuculline-sensitive GABA receptors, ③ yohimbine-sensitive, clonidine-acting GABAergic sites.

Key Words: Rabbit blood pressure, Intracranial pressure, Muscimol, Clonidine, Yohimbine, Bicuculline, Intracerebroventricular injection, GABAergic sites, α_2-adrenoceptors.

INTRODUCTION

Acute increase of intracranial pressure (ICP) leads to increase of arterial blood pressure (BP). It has been shown by many authors that this systemic pressor response is mediated by an increase in sympathetic activity of both central and peripheral origin (Kang and Woo 1973, Freeman and Jeffers 1940, Brown 1956, Tanaka *et al.*, 1976, Sadoshima *et al.*, 1981, Matsuura *et al.*, 1984,

Pasztor *et al.*, 1986, Kocsis *et al.*, 1989). From the fact that intracerebroventricular (icv) clonidine inhibited the pressor response to raised ICP in rabbits (Kim *et al.*, 1980), preferential suppression by increased cranial pressure of inhibitory α_2-adrenoceptors in the brain, as a mechanism of the pressor response, has been suggested.

Recently involvement of γ-aminobutyric acid (GABA) in the central regulation of cardiovascular functions has been documented (for review, see Defeudis 1983, Antonaccio 1984, Bousquet *et al.*, 1985). In addition it has been shown that the decrease of BP and heart rate by GABA-agonists is mediated by decreases of sympathetic outflow from the brain (Bousquet *et al.*, 1981a, Loscher 1982, Henry *et al.*, 1989) and that the increase of BP and heart rate by GABA-antagonists is accompanied by concomitant increases in sympathetic discharge (DiMicco and Abshire 1987, DiMicco *et al.*, 1986, Wible *et al.*, 1988, Waldrop and Bauer 1989).

The purpose of present experiments was to determine if a GABAergic mechanism in the brain modulated the pressor response to raised ICP.

METHODS

Urethane-anesthetized rabbits weighing 2 to 2.5 kg were used. The rabbits' trachea was cannulated, and ventilation was controlled with a respirator to minimize the effect of respiration on blood pressure. The animal was fastened prone with its head extended.

Blood pressure was taken from the left femoral artery and recorded on a physiograph by using a pressure transducer. Blood pressure (BP) was expressed as mean arterial blood pressure (mean± SE, mmHg).

Intracerebroventricular (icv) administrations of drugs were performed through a thin polyethylene tube (3 cm long and 1 mm diameter) inserted into the lateral cerebral ventricle. Drugs were given in a volume of 0.1 ml per animal. The drug solutions were kept at 36~38℃. At the end of each experiment the position of the tube was confirmed by removing the parietal bone and dissecting the brain. Intravenous (iv) injections were made into the left ear vein in a volume of 0.5 ml/kg.

Two cannulas with small balloons were inserted into the epidural space, one for monitoring intracranial pressure (ICP) and one for raising ICP. The ICP was raised gradually by infusion of saline (36~38℃) at a rate of 0.06 to 0.08 ml per min. The increased ICP was lowered by removing the infused saline. The ICP was simultaneously recorded with BP through another transducer. All burr holes were tightly sealed with dental acrylic.

All drugs were administered intracerebroventricularly except otherwise stated.

Drugs used: muscimol hydrobromide (RBI), bicuculline methiodide (Sigma), clonidine hydrochloride (Sigma), yohimbine hydrochloride (Merck), and oxymetazoline hydrochloride (Merck). The stock solution of yohimbine (10 mg/ml) was dissolved in distilled water and diluted with saline before use. The other drugs were dissolved in saline.

The doses (per animal) employed: muscimol 2 μg, bicuculline 2 μg, clonidne 30 μg, and yohimbine 250 μg.

The Student's t-test for paired or unpaired data was used to analyse the results statistically.

RESULTS

BP responses to raised intracranial pressure

Raising of ICP produced a gradual increase in BP in all rabbits tested. Generally BP began to rise when ICP reached 50~70 mmHg. In some animals prior to the appearance of the rise in BP transitory slight decline of the pressure was observed. Continuation of the infusion of saline into the balloon for raising ICP produced a further rise in BP as well as ICP. But when the ICP reached some extent (70~110 mmHg) the BP began to decline in spite of the steadily rising ICP. The BP levels just before the appearance of the fall of BP were expressed as maximum BP in this paper. The result from 22 animals is shown in Table 1.

Effect of muscimol. This drug caused a decline of BP, reaching the lowest point within about 5 min (a fall of 40±4 mmHg, n=15) following administration. This marked hypotensive state persisted for 10 to 15 min and then BP was gradu-

Table 1. Effects of pretreatment with muscimol, clonidine, bicuculline, and yohimbine on the pressor response to raised intracranial pressure in rabbits

Pretreatment (dose per capita)	n	BP before raising ICP	ICP before raising ICP	Level of raised ICP	Magnitude of increase of BP at raised ICP
Saline (0.1 ml)	22	85±3(1)	20~35(2)	70~110(2)	46±6(3)
Muscimol (2 μg)	9	55±5	20~30	60~ 90	3±5*
Clonidine (30 μg)	6	60±4	20~35	70~110	10±4*
Clonidine (iv, 60 μg)	4	63±7	20~30	80~110	40±6
Bicuculline (2 μg)	5	106±8	20~25	90~130	21±4@
Yohimbine (250 μg)	4	119±1	20~25	90~120	2±2*

Pretreatment: all the drugs except clonidine (iv) were administered by icv route. As to the time interval between pretreatment and raising of ICP refer to text.

(1): Mean±SE (mmHg) of BP

(2): Range of ICP (mmHg)

(3): Mean±SE (mmHg) of differences between BP before raising ICP and maximum BP achieved by raising ICP.

*: No significant increase of BP.

@: Statistically significant increase ($p<0.01$), although the increase was less when compared to saline-pretreatment group ($p<0.01$).

ally restored to initial levels in about 2 hr.

When muscimol was injected once again 2~3 hr later, the fall of BP by this second dose was markedly attenuated: in 5 rabbits the magnitude of fall by the first dose was 42±7 mmHg and that by the second was 11±3 mmHg.

Ten to 15 min following injection of muscimol, when lowered BP had become stabilized, the ICP was raised. In these rabbits, even when levels of ICP reached 70 to 110 mmHg, 7 out of 9 rabbits did not show an increase in BP and the remaining 2 animals showed slight increases (Fig. 1-a, Table 1).

Intravenous muscimol (2 μg/kg) was without effect on BP.

Effect of clonidine. This drug caused a fall of BP. The fall reached a maximum (lowered to 50± 6 mmHg in 14 rabbits) within 2 to 5 min following injection, and the lowered BP persisted almost unchanged for a period of 15 to 20 min, then the pressure gradually returned to initial resting levels.

When clonidine was reinjected 2 hr later, the response to the second dose was much weaker. In 8 rabbits the first dose produced a fall of 31± 5 mmHg but the second 12±2 mmHg.

As reported from our labaratory (Kim *et al.*, 1980) clonidine inhibited the pressor response to raised ICP (Fig. 1-b, Table 1).

Intravenous clonidine (30 μg/kg), as did icv clonidine (30 μg), caused a fall of BP. ICP was raised at 2 to 5 min after iv clonidine injection when the BP had become comparatively stabilized. In these iv clonidine-administered rabbits, raising ICP elicited an increase of BP as in non-treated rabbits (Fig. 1-c, Table 1).

Effect of bicuculline. This drug elicited a distinct pressor response. The rise of BP reached a peak at 1~2 min after injection and the peak persisted for about 2~3 min and then began to decline, returning to preinjection levels in 5~10 min (Fig. 2-a, Table 2). The second and third injections given at 2 hr intervals produced almost the same responses. In 6 rabbits the first dose produced rise of 23±5 mmHg, the second 20±4 mmHg, and the third 21±4 mmHg.

About 5 min following injection of bicuculline, when BP showed a compartively steady state, ICP was raised. In these rabbits, when levels of ICP exceeded approximately 90 mmHg, a distinct pressor response appeared, though the magnitude was less than that in control animals (Fig. 1-d, Table 1).

Intravenous bicuculline (2 μg/kg) produced little effect on BP.

Effect of yohimbine. This drug caused an in-

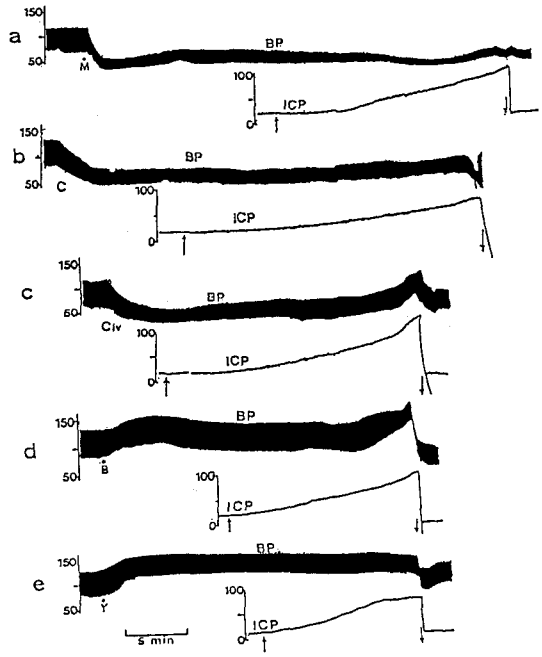

Fig. 1. Arterial blood pressure (BP) and intracranial pressure (ICP) of rabbits. ICP was raised by infusion of saline (0.06 ml/min) into a balloon placed in the epidural space. Left scale and numerals: mmHg. ↑: Starting of infusion. ↓: Removal of saline from the balloon. Before raising ICP, muscimol (M) in **a**, clonidine (C) in **b**, iv clonidine (30 μg, Civ) in **c**, bicuculline (B) in **d**, and yohimbine (Y) in **e**, was each given.

Muscimol and clonidine inhibited the pressor response to raised ICP but intravenous clonidine did not. Raising ICP produced pressor response in bicuculline-hypertensive state but did not in yohimbine-hypertensive state.

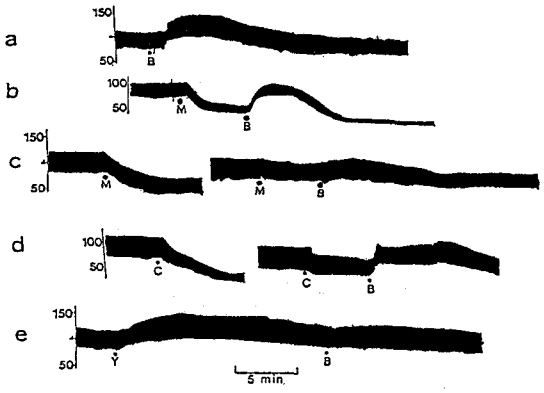

Fig. 2. Increase in BP by bicuculline (B) in rabbits. Left scale and numerals: mmHg.

a: control.

b: transitory reversal of muscimol (M)-hypotension by bicuculline.

c and **d**: the second dose of muscimol and clonidine (right panel) given 2 hr after the first (left panel) produced little hypotensive response, respectively. Bicuculline elicited little BP increase in **c** but a distinct increase in **d**.

e: failure of bicuculline to elicit pressor response in yohimbine (Y)-induced hypertensive state.

crease in BP. The increase began to appear in 1～2 min following injection, reaching a maximum in about 5 min, and the plateau persisted for a period of 5～10 min. Then BP began to decline and gradually returned to initial levels in about 10 min (Fig. 3-a, Table 2). The second dose given 2 hr later produced a smaller rise than the first: in 6 rabbits the rise by the first was 33±6 mmHg and the second 18±4 mmHg.

In the hypertensive state following yohimbine, raising ICP failed to produce a further increase in BP even when levels of ICP reached 90～120 mmHg (Fig. 1-e, Table 1).

Intravenous yohimbine (250 μg/kg) elicited only a very transient slight fall.

BP responses to bicuculline

Effect of muscimol. Bicuculline elicited a transitory reversal of the hypotensive state induced by muscimol (Fig. 2-b). As mentioned already, the second dose of muscimol given 2 hr after the first produced a much smaller fall of BP. In this almost normotensive state bicuculline caused little increase in BP (Fig. 2-c, Table 2).

Effect of clonidine. Bicuculline produced the pressor response not only in the hypotensive rabbits after clonidine, also in the almost normotensive ones after two successive doses given at a 2 hr interval (Fig. 2-d, Table 2).

Effect of yohimbine. The heightened BP level induced by yohimbine was not further elevated by an additional injection of bicuculline (Fig, 2-e,

Table 2. Effects of pretreatment with muscimol, clonidine, yohimbine, bicuculline, and of hypertensive state by raised intracranial pressure on the pressor response to bicuculline and yohimbine in rabbits

Pretreatment (dose per capita)	Magitude of increase of BP by					
	Bicuculline			Yohimbine		
	n	Initial BP	Increase	n	Initial BP	Increase
Saline (0.1 ml)	12	87±4(1)	23±6(2)	19	83±4(1)	36±5(2)
Muscimol (2×2 μg)	6	76±4	7±4*	4	73±5	−12±4*
Clonidine (2×30 μg)	4	71±3	17±2	4	77±5	5±5*
Yohimbine (250 μg)	5	117±6	4±3*			
Bicuculline (2 μg)				4	113±3	19±5@
Raising of ICP	4	108±6	4±4*	4	105±6	7±4*

Pretreatment : all the drugs were given by icv route. As to the method of pretreatment and the time interval between pretreatment and administration of yohimbine and bicuculline, refer to text.

(1): Mean±SE (mmHg) of BP.

(2): Mean±SE (mmHg) of differences between initial BP and maximum BP achieved by yohimbine and bicuculline. Minus sign means fall of BP.

*: No significant change in BP.

@: Statistically significant increase ($p<0.05$), although the increase was less when compared to saline-pretreatment group ($p<0.05$).

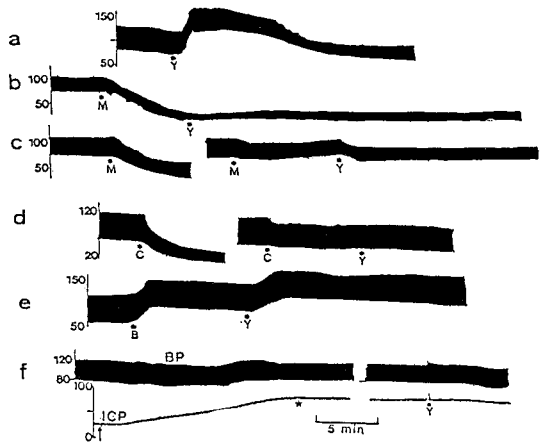

Fig. 3. Increase in BP by yohimbine (Y) in rabbits. Left scale and numerals: mmHg.

a: control.

b, c and **d:** ineffectiveness of yohimbine to elicit presor response after muscimol (**b** and **c**) and clonidine (**d**).

e: a further increase by yohimbine of bicuculline (B) effect.

f: ICP was initially raised by infusing saline (0.06 ml/min) (↑) into the balloon placed in the epidural space, and at ★ additional infusion was discontinued and 10 min later yohimbine was given. Yohimbine failed to produce an increase in BP.

Table 2).

Effect of hypertensive state by raised ICP. It was attempted to investigate if the hypertensive state by raised ICP caused alterations in pressor response to bicuculline.

When the increase in BP of approximately 20 mmHg was attained by infusion of saline, an additional infusion was discontinued. Then both the heightened BP and ICP remained almost unchanged for a peirod of about next 30 min. In this state bicuculline elicited no pressor response (Table 2).

BP responses to yohimbine

Effect of muscimol. Pretreatment of animals with a single dose of muscimol or with two successive doses given at an interval of 2~3 hr abolished the pressor response to yohimbine (Fig. 3-b, 3-c, Table 2).

Effect of clonidine. In the hypotensive state after clonidine yohimbine produced pressor response as in control animals (not shown in Fig. 3). However, yohimbine was ineffective to produce a marked pressor response in the normotensive state following two successive doses of clonidine given at 2 hr interval (Fig. 3-d, Table 2).

Effect of bicuculline. In the hypertensive state

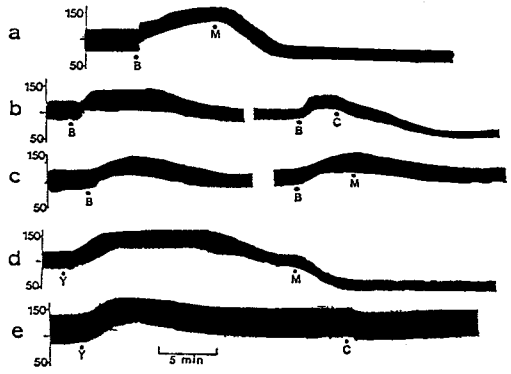

Fig. 4. Effect of bicuculline (B) and yohimbine (Y) on BP response to muscimol (M) and clonidine (C) in rabbits. Left scale and numerals: mmHg.
a: depression by muscimol of bicuculline-hypertension
b: effective depressor effect of clonidine on BP elevated by bicuculline
c: the second dose of bicuculline (right panel) given 2 hr after the first (left panel) produced a rise in BP as the first did. Muscimol, however, elicited little hypotensive effect in this occassion.
d: yohimbine did not affect the muscimol effect.
e: yohimbine inhibited the clonidine effect.

induced by bicuculline yohimbine elicited a further increase in BP (Fig. 3-e, Table 2).

Effect of hypertensive state by raised ICP. In the hypertensive state produced by raised ICP as described previously, yohimbine, as well as bicuculline, elicited no pressor response (Fig. 3-f, Table 2). These hypertensive rabbits, however, responded with a rise of BP (34±2 mmHg, n=4) to oxymetazoline (500 μg per animal) which has been shown to act on α_1-adrenoceptors in the rabbit brain (Park 1982).

BP responses to muscimol and clonidine

Effect of bicuculline. Elevated BP levels after bicuculline injection were downed by muscimol (in 4 rabbits a fall of 52±5 mmHg from preinjection level of 111±6 mmHg) (Fig. 4-a). However, muscimol's depressor action was much smaller (a fall of 10±4 mmHg in 6 rabbits) in the hypertensive and normotensive state after two successive injections of bicuculline with an interval of 2 hr (Fig. 4-c).

Clonidine, by contrast, elicited depressor responses as in control animals when given in the hypertensive state after a single dose (in 4 rabbits a fall of 46±6 mmHg from 106±7 mmHg) and after two successive doses of bicuculline (in 4 rabbits a fall of 38±4 mmHg from 102±6 mmHg) (Fig. 4-b).

Effect of yohimbine. At about 10~20 min after yohimbine administration, when BP was elevated, injection of muscimol produced a marked fall of BP (in 6 rabbits a fall of 63±5 mmHg from the preinjection level of 114±4 mmHg) (Fig. 4-d) but clonidine made little decrease (in 6 rabbits a fall of 6±4 mmHg from 106±3 mmHg) (Fig. 4-e).

Muscimol versus clonidine. Clonidine-lowered BP, 64±5 mmHg (n=7), was further reduced by muscimol to 50±5 mmHg; muscimol-lowered BP, 66±3 mmHg (n=4), was further declined by clonidine to 36±4 mmHg. The magnitude of fall in the latter (30±2 mmHg) was greater ($P<0.01$) than that in the former (14±2 mmHg).

DISCUSSION

Muscimol and bicuculline

Before analysing data about pressor response to raised ICP, it seems necessary to confirm the involvement of a GABAergic mechanism in the central modulation of the rabbit BP. It has been demonstrated that the GABA agonist muscimol causes depressor response through an inhibitory effect on sympathetic discharge (Lisa *et al.*, 1988, Waldrop and Bauer 1989, Bousquet *et al.*, 1981b) and that the GABA antagonist bicuculline causes pressor response and reverses the hypotension of muscimol by eliciting increases in sympthetic outflow (Bousquet *et al.*, 1985, Waldrop and Bauer 1989, Johnston *et al.*, 1972). In the present study icv muscimol lowered not only the elevated BP levels following icv bicuculline, it also reduced basal BP levels, suggesting the involvement of a central GABAergic mechanism in rabbit BP control.

Furthermore it was noted that bicuculline was almost incapable of eliciting the response in the normotensive state after pretreatment of rabbits

with two successive doses of muscimol (Fig. 2-c); similarly muscimol failed to produce the marked depressor response in the hypertensive and normotensive state after two successive doses of bicuculline (Fig. 4-c). These findings are clearly demonstrating mutual antagonism between muscimol and bicuculline, although the underlying mechanism of this antagonism could not be inferred from the results of the present experiments.

Clonidine and yohimbine

It is well established that clonidine acts on α_2-adrenoceptors and causes hypotension by reducing the outflow of sympathetic impulses originating in the brain (Bolme and Fuxe 1971, Schmitt *et al.*, 1973, Haeusler 1973, Schmitt and Schmitt 1970) and that icv yohimbine causes hypertension and it inhibits the clonidine effect by acting on the same receptors (Kim *et al.*, 1982, Timmermans *et al.*, 1981). Rabbit BP responses performed in this study correlated well with the above documentation.

In addition to inhibition by yohimbine of clonidine hypotension (Fig. 4-e), disappearance of yohimbine hypertension after two successive doses of clonidine (Fig. 3-d) was observed. This phenomenon is similar to the relation of hypertensive bicuculline to hypotensive muscimol (Fig. 2-c).

GABAergic system and α_2-adrenoceptor system

Clonidine hypotension was not affected by bicuculline (Fig. 4-b) but was abolished by yohimbine (Fig. 4-e), whereas muscimol hypotension was not affected by yohimbine (Fig. 4-d) but was markedly attenuated by bicuculline (Fig. 4-c). In additon bicuculline was an effective pressor agent after clonidine (Fig. 2-d) but was ineffective after two doses of muscimol (Fig. 2-c). These findings suggest the presence of two distinct, independent systems, GABAergic and α_2-adrenoceptors, controlling the rabbit BP.

In contrast to these findings muscimol too, as clonidine did, abolished yohimbine's effects (Fig. 3-b, 3-c). These suggested the action sites for pressor yohimbine and those for depressor muscimol were intimately related. Recently some reports of evidence have been provided for direct relations of clonidine's and yohimbine's actions with GABAergic system. In synaptsomal preparations of the rat brain (Pittaluga and Raiteri 1988, Maura *et al.*, 1988, Tingley and Arneric 1990) and in strips of guinea pig bladder (Shirakawa *et al.*, 1988), clonidine and norepinephrine enhanced the release of GABA and this effect was prevented by yohimbine; clonidine stimulated GABA release from the guinea pig brain (Moroni *et al.*, 1982, Moroni *et al.*, 1983). It was also shown that hypotensive action of clonidine was related to simulation of GABAergic system (Marmo *et al.*, 1987, Czyzewska-Szafran *et al.*, 1991) and that yohimbine-seizures of mice were mediated through the impairment of GABAergic transmission (Dun and Corbett 1992). These reports, together with the finding of abolishment by muscimol of yohimbine's effects in the present study, seemed to indicate that muscimol exerted the hypotensive effect by acting on not only bicuculline-sensitive GABA receptors, also on clonidine-acting, yohimbine-sensitive sites to enhane GABA release.

The finding that bicuculline did not produce an additional BP increase in yohimbine hypertensive state but yohimbine further increased bicuculline hypertension (Fig. 2-e, Fig. 3-e) suggests pathways for bicuculline hypertension were involved in those for yohimbine hypertension. The fact that the doses of muscimol and clonidine employed in the present study produced almost the same degree of depressor response in normotensive state and that clonidine and muscimol elicited a further fall of BP in muscimol-lowered BP and clonidine-lowered BP, respectively, indicated distinct difference of action sites of both drugs. However, the magnitude of BP fall by muscimol in clonidine depressive state was significantly smaller than that by clonidine in muscimol depressive state. This seemed to show that part of muscimol-acting sites were already invaded by clonidine, causing to diminish the muscimol response.

Pressor response to raised ICP

Prevention by pretreatment with muscimol and clonidine of pressor response to raised ICP could be interpreted as the involvement of central GABAergic mechanism and central α_2-adrenoceptors in this pressor response. Raising ICP and yohimbine failed to elicit an additional increase of BP in the yohimbine-induced hypertensive state and the pressor state by raised ICP,

respectively, suggesting participation of the same mechanisms in the pressor responses to ICP increase and that to yohimbine. The finding that the bicuculline-induced elevated BP was further heightened by increasing ICP, whereas the pressor state by raised ICP was not altered by bicuculline suggested the involvement of pathways for bicuculline-hypertension in those for the hypertension via raised ICP. Oxymetazoline which has been shown to act on α_1-adrenoceptors to cause pressor response (Park 1982) made a further increase of elevated BP by ICP increase. This fact indicated that raising ICP affected the pathways for yohimbine and bicuculline hypertension but not those for oxymetazoline hypertension. Intravenous clonidine produced marked depressor response as icv clonidine did, but did not prevent the pressor response to raised ICP, indicating the low BP itself after icv clonidine and muscimol was not a contributing factor to inhibit pressor response to ICP elevation.

In conclusion it was inferred that there were three ways in which BP could be increased via raised ICP: inactivation of the inhibitory sympathetic activity through ① α_2-adrenoceptors, ② bicuculline-sensitive GABA receptors, ③ yohimbine-sensitive, clonidine-acting GABAergic sites.

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=국문초록=

두개내압상승에 의한 혈압상승작용과 중추 GABA계 및 중추 α_2-아드레날린 수용체와의 관계

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GABA계가 뇌내의 교감신경계기능에 영향을 주어서 혈압조절에 관여함이 알려져 있다. 본 연구에서는 마취가토에서 GABA계가 두개내압증가에 의한 혈압상승에 관여하는가를 조사하였다.

두개내압증가에 의한 승압은 측뇌실내 muscimol (GABA 작용약)이나 clonidine (α_2-작용약) 전처리후에는 볼 수 없었다. 측뇌실내 yohimbine (α_2-길항약)으로 일으킨 고혈압은 두개내압증가를 하여도 더 이상 상승하지 않았으나, 측뇌실내 bicuculline (GABA 길항약)으로 일으킨 고혈압은 두개내압증가로 더욱 상승하였다. Bicuculline은 muscimol이나 clonidine 저혈압에서는 승압을 일으켰으나 yohimbine이나 두개내압증가에 의한 고혈압에서는 무효였다. Yohimbine은 clonidine 저혈압은 상승시켰으나 muscimol 저혈압에 있어서는 무효였다. Yohimbine은 두개내압증가에 따른 승압상태는 더 올리지 못하였으나 bicuculline 승압상태는 더욱 상승시켰다. Muscimol은 bicuculline과의 길항성이외에 yohimbine 승압을 억제함을 알았으며 yohimbine 승압에 GABA계가 관여함을 추측할 수 있었다. 이러한 실험결과로 두개내압증가에 따른 승압상승은 ① α_2-수용체, ② bicuculline-감수성 GABA 수용체, ③ yohimbine-감수성인 clonidine이 작용하는 GABA계 부위의 세가지 방법으로 억제성인 교감신경기능을 불활성화하여 일어나는 것으로 추론하였다.