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Effects of Intracerebroventricular Calcium Antagonists on Changes of Blood Pressure and Heart Rate by Methoxamine and Clonidine in Rabbits

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ABSTRACT

To delineate the relationship between subtypes of central alpha-adrenoceptor and central calcium channel, influences of intracerebroventricular (icv) diltiazem and nifedipine on the changes of blood pressure and heart rate by icv methoxamine and clonidine were investigated in urethane-anesthetized rabbits.

1) Methoxamine (1mg, icv) produced pressor and bradycardiac effect and clonidine (30μg, icv) produced hypotension and bradycardia.

2) Icv diltiazem and nifedipine elicited dose-dependent depressor and bradycardiac responses. The depressor response to nifedipine was more prominent than that to diltiazem but the bradycardiac effect of nifedipine was smaller than that of diltiazem. The depressor responses to icv nifedipine (35μg) and icv diltiazem (400μg) were persistent but those to intravenous (iv) nifedipine (20μg/kg) and diltiazem (200 μg/kg) were transient.

3) The pressor response to methoxamine was little affected by pretreatment with icv diltiazem (400μg) or icv nifedipine (35, 350μg) but the bradycardiac response to methoxamine was significantly attenuated by the same pretreatment.

4) The depressor response to clonidine was markedly attenuated by pretreatment with icv diltiazem (400μg) or icv nifedipine (35, 350μg) but not affected by pretreatment with iv diltiazem (200μg/kg) or iv nifedipine (20μg/kg). Pretreatment with icv and iv diltiazem or nifedipine reduced the bradycardiac effect of clonidine.

5) Pretreatment with icv clonidine had no effect on the depressor and bradycardiac responses to icv diltiazem or icv nifedipine.

These results indicate that diltiazem and nifedipine have no effect on icv methoxamine-induced pressor response elicited by the activation of central alpha-1 adrenoceptors whereas the icv clonidine-induced depressor and bradycardiac effects which result from the activation of central alpha-2 adrenoceptors are inhibited by the calcium antagonists.

Key Words: nifedipine, diltiazem, central alpha-1 and alpha-2 adrenoceptors, blood pressure, heart rate

Abbreviations: ME; methoxamine, CLO; clonidine, NIF; nifedipine, DIL; diltiazem, icv; intracerebroventricular, iv; intravenous

INTRODUCTION

The observation by Fleckenstein (1964) that verapamil and prenylamine diminished cardiac contractile force by inhibiting cardiac excitation-contraction coupling and that this effect was reversed by increased extracellular calcium concentration led to the discovery of "calcium antagonism". And these agents were referred to as "calcium antagonists" (Fleckenstein *et al.*, 1969). Since then a multitude of papers related to calcium antagonists have been presented. Recently, calcium antagonists have been introduced as new therapeutic agents of cardiovascular disease, and the inhibition of extracellular calcium influx has been assumed to their

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mechanism of action (Triggle, 1981; Cauvin *et al.*, 1983; Goodman and Gilman, 1985).

The existence of both alpha-1 and alpha-2 adrenoceptors in brain has been proven by using radioligand binding method (Summers *et al.*, 1980, 1981; Jarrott *et al.*, 1982, 1983). It has been known that methoxamine (ME), a selective alpha-1 adrenoceptor agonist (Drew, 1977; Starke, 1981), when administered intracerebroventricularly (icv), produces pressor response via central alpha-1 adrenoceptor (Kim *et al.*, 1982; Chung, 1986), whereas a selective alpha-2 adrenoceptor agonist, clonidine (CLO), icv induces hypotension and bradycardia through central alpha-2 adrenoceptors (Kobinger, 1978; Timmermans *et al.*, 1981; Kim *et al.*, 1982; van Zwieten and Timmermans, 1983; Yoo, 1985).

Since the original report by van Meel *et al.* (1981a) that both organic and inorganic calcium antagonists preferentially antagonized the alpha-2 adrenoceptor-mediated pressor responses in pithed rats, a considerable body of *in vivo* evidence either supporting or repudiating the conclusion have been presented (van Meel *et al.*, 1981b, 1982; Vanhoutte and Rimele, 1982; Cavero *et al.*, 1983; van Zwieten *et al.*, 1982; Wilffert *et al.*, 1984; Lew and Angus, 1985; Pedrinell and Tarazi, 1985).

Thus, the relationship between calcium antagonists and subtypes of alpha-adrenoceptor has been extensively investigated on vascular smooth muscle, but no report so far has been presented on central nervous system. Therefore, this study was undertaken to delineate the subtypes of central alpha-adrenoceptors affected by calcium antagonists, by observing the effects of typical calcium antagonists, diltiazem (DIL) and nifedipine (NIF), on the changes of blood pressure and heart rate elicited by icv ME and CLO in rabbits.

MATERIALS AND METHODS

Urethane-anesthetized rabbits weighing 1.8-2.2kg were used. The animal was fastened on the table in prone position with the head extended, and the trachea cannulated. Blood pressure taken from the left femoral artery was recorded on physiograph through pressure transducer. Heart rate was counted from the blood pressure curve and expressed as beats/min. Changes of blood pressure and heart rate by drug were expressed as percentage of maximal change from the value before drug administration. For the administration of the agents into a cerebral ventricle, a polyethylene tube (3cm long and 1mm O.D.) was introduced into a lateral ventricle. On terminating each experiment the position of the tip was confirmed by dissecting the brain. Icv administration was done through this tube in a volume less than 0.1 ml and iv administration through a marginal ear vein in a volume of 0.5 ml/kg.

Drugs used are methoxamine HCl (Vasoxyl, Burroughs Wellcome), clonidine HCl (Sigma), diltiazem HCl (Sigma), nifedipine HCl (Sigma). The stock solution of nifedipine (15mg/ml) was prepared in 95% ethanol, and diluted with distilled water immediately before use. In the experiments using

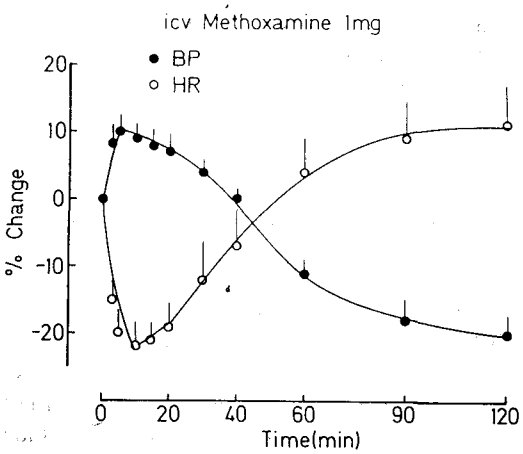

Fig. 1. Time course of intracerebroventricular (icv) 1 mg methoxamine-induced pressor and bradycardiac responses in rabbits. Each point represents the mean of % changes from 6 animals. Vertical bars are SEM.

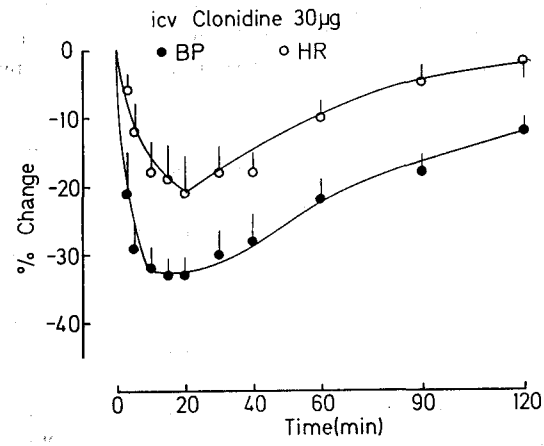

Fig. 2. Time-course of intracerebroventricular (icv) 30μg clonidine-induced hypotensive and bradycardiac effects in rabbits. Legends are the same as in Fig. 1.

nifedipine, appropriate control experiments were carried out with 95% and 47.5% ethanol. Other drugs are dissolved in or diluted with saline. Statistical significance was tested with Student's *t*-test.

RESULTS

Effects of ME, CLO, DIL, NIF

ME: Icv injection of 1 mg increased blood pressure and decreased heart rate. The increase in blood pressure reached a maximum ($+10 \pm 2.3\%$, mean $\pm$ SE from 6 experiments) within 5 to 10 min. The pressure gradually returned to initial resting level in about 40 min., and slightly decreased further below the initial level. The decrease in heart rate reached a maximum ($-22 \pm 3.8\%$, in 6 experiments) in 10 to 20 min, and then gradually returned to initial level (Fig. 1).

CLO: Icv CLO 30μg produced hypotensive and bradycardiac responses. These effects were apparent

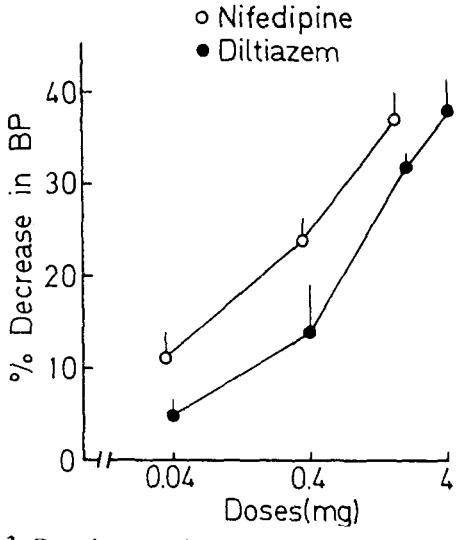

Fig. 3. Dose-hypotensive response curves to intracerebroventricular nifedipine and diltiazem in rabbits. Each point represents the mean % decrease from 4-6 animals. Other legends are the same as in Fig. 1.

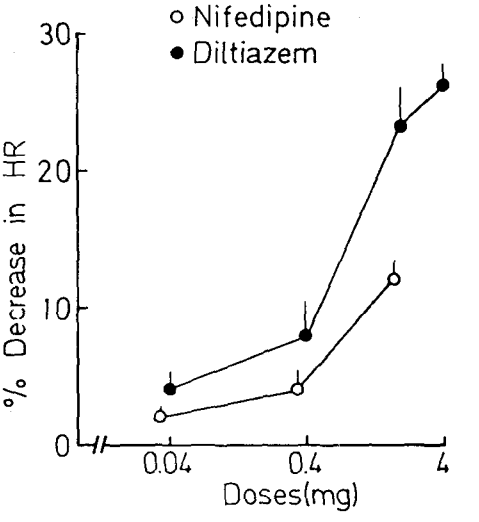

Fig. 4. Dose-bradycardiac response curves to icv nifedipine and diltiazem in rabbits. Other legends are the same as in Fig. 3.

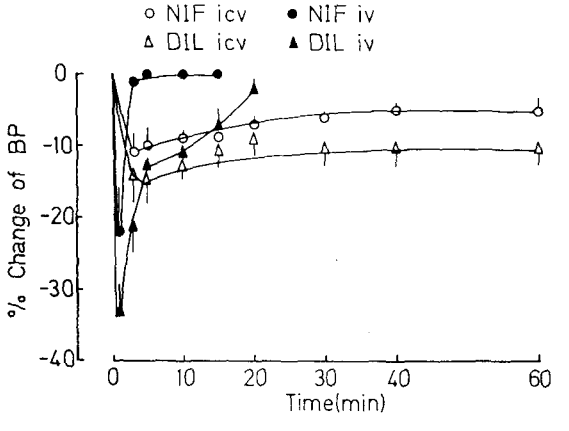

Fig. 5. Time-course of intracerebroventricular (icv) and intravenous (iv) nifedipine (NIF, 35μg and 40μg) and diltiazem (DIL, 400μg)-induced hypotensive effects in rabbits.

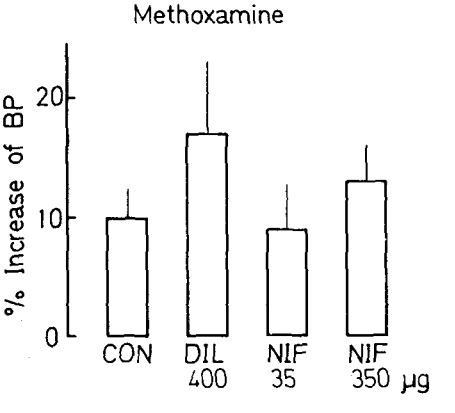

Fig. 6. Effects of icv diltiazem (DIL) and nifedipine (NIF) on icv 1 mg methoxamine-induced pressor response in rabbits. Each column is the mean of % increase from 4-6 animals and vertical bars are SEM. CON: control.

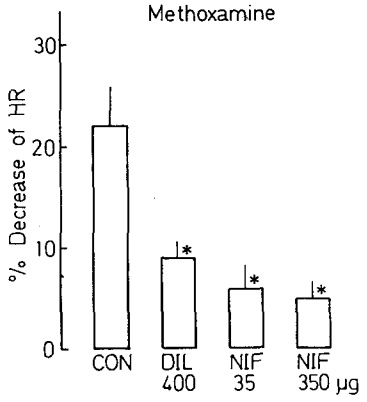

Fig. 7. Effects of icv diltiazem (DIL) and nifedipine (NIF) on icv 1 mg methoxamine-induced bradycardiac response in rabbits. Asterisks indicate significant difference from control value (*p<0.05). Other legends are the same as in Fig. 6.

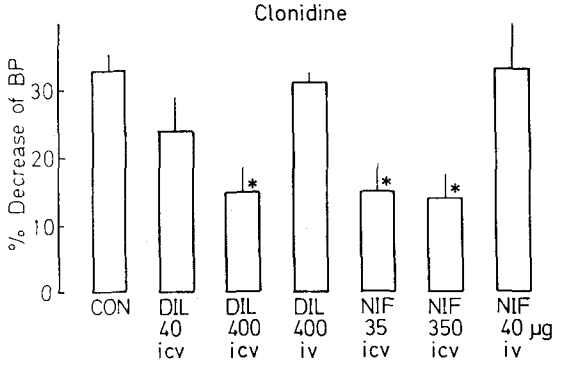

Fig. 8. Effects of iv and icv diltiazem (DIL) and nifedipine (NIF) on icv 30μg clonidine-induced hypotensive response in rabbits. Asterisks indicate significant difference from control value (*p<0.05). Other legends are the same as in Fig. 6.

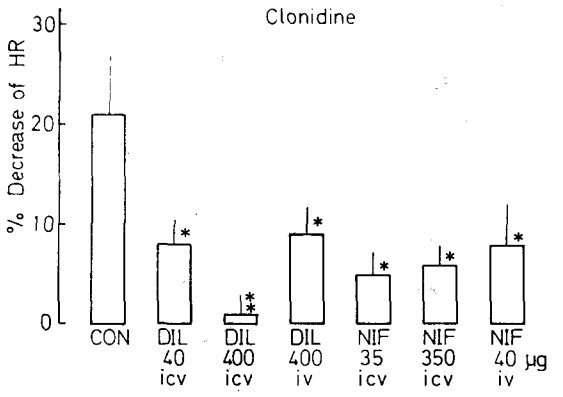

Fig. 9. Effects of iv and icv diltazem (DIL) and nifedipine (NIF) on icv 30μg clonidine-induced bradycardiac response in rabbits. Asterisks indicate significant difference from control value (*p<0.05, **p<0.01). Other legends are the same as in Fig. 6.

Table 1. Effect of intracerebroventricular (icv) 30μg clonidine on the hypotensive and bradycardiac responses to icv diltiazem (400μg) and nifedipine (350μg).

	Diltiazem % Change of			Nifedipine % Change of	
	n	BP	HR	n	BP	HR
Control	6	−14±5.1	−8±2.5	6	−24±2.5	−4±1.5
after clonidine	4	−19±3.5	−14±2.6	5	−25±3.8	−6±1.7

BP: Blood Pressure, HR: Heart Rate

immediately following injection, reaching maxima (blood pressure: 33±2.4% decrease, heart rate: 21±5.8% decrease, in 6 experiments) within 10 to 20 min. Both the pressure and heart rate recovered gradually (Fig. 2).

DIL: Icv administration of DIL induced dose-dependent depressor and bradycardiac effects (Fig. 3, 4). 40μg of icv DIL produced slight and transient decrease in blood pressure and heart rate. 400 μg of icv DIL decreased blood pressure with maximum (14% decrease in 6 experiments) within 3 to 5 min and this state was sustained for 60 min. But iv injection of DIL 200 μg/ kg, the equivalent dose to icv 400 μg, transiently decreased blood pressure with maximum (33% decrease in 6 experiments) within 1 min and then, the pressure returned to initial level in about 20 to 30 min (Fig. 5). 2mg and 4mg of icv DIL produced depressor response with maxima (2mg:32%, 4mg:38% decrease in 6 experiments respectively) within 5 to 10 min and sustained this hypotensive state for 30-40 min and the decrease in heart rate reached maxima (23% and 27% decrease in 6 experiments respectively) within 10 to 20 min, and heart rate gradually returned to initial level, thereafter.

NIF: Icv injection produced dose-dependent depressor response (Fig. 3). The patterns of depressor responses to icv 35μg, 350μg, 1.75mg NIF are similar to those to icv 400μg, 2mg, 4mg DIL respectively. The depressor response to the equivalent dose of icv NIF was more prominent than that to DIL (Fig. 3). Iv injection of NIF 20μg/kg, the equivalent dose to

icv 35μg, produced hypotension with maximum (22% decrease in 4 experiments) within 1 min, after that the pressure rapidly returned to initial level in 3 to 5 min (Fig. 5). Icv 35μg and 350μg of NIF slightly decreased heart rate. And the bradycardiac effect of icv NIF 1.75mg was very weak as compared with that of DIL and hypotensive effect of NIF.

Response to icv ME after the treatment with icv DIL or NIF

In this experiment, the maximal % changes of blood pressure and heart rate by ME were compared with those after pretreatment with DIL or NIF. In about 10 to 15 min after administration of DIL or NIF, when the blood pressure and heart rate levels were stabilized, the effects of ME were examined. Pretreatment with DIL 400μg or NIF 35, 350μg had little effect on the pressor response to ME but significantly inhibited the bradycardiac effect of ME (Fig. 6,7).

Response to icv CLO after the treatment with DIL or NIF

In the same manner as with ME, the effects of CLO were examined. The depressor response to CLO was markedly attenuated by pretreatment with icv DIL (400μg) or icv NIF (35, 350μg) but not affected by pretreatment with iv DIL 200μg/kg or iv nifedipine 20μg/kg, the equivalent doses of icv administration. Pretreatment with icv and iv DIL or NIF reduced the bradycardiac effect of CLO (Fig. 8,9).

Responses to icv DIL and NIF after the treatment with icv CLO

As it was shown the pretreatment with icv DIL or NIF antagonized the bradycardiac and depressor responses to icv CLO, the effects of pretreatment with CLO on the hypotensive and bradycardiac responses to DIL and NIF were examined. In about 20 min after administration of CLO, when the blood pressure and heart rate decreased maximally, DIL or NIF was injected. As shown in table 1, pretreatment with CLO had no effect on the depressor and bradycardiac responses to icv DIL or icv NIF.

DISCUSSION

Central Effects of DIL and NIF

The present study shows that icv DIL and NIF produces dose-dependent hypotensive and bradycardiac responses. In contrast to the abrupt and transient effects of iv administration, the icv effects were gradual and sustained. Icv administration of these agents inhibited the hypotensive response to icv CLO but iv administration had no effect on the hypotension. These results indicate that the cardiovascular inhibitory effects of icv DIL and NIF are central in origin and do not result from leakage of the drugs into the systemic circulation.

It has been well known that both DIL and NIF, typical calcium antagonists, inhibit the activity of the cardiovascular system by blocking the influx of extracellular calcium into cardiac and vascular smooth muscle cells (Triggle, 1981; Fleckenstein, 1977, 1983; Millard *et al.*, 1983), but no report has been presented so far as to the central effects of these agents on the cardiovascular system, though there exist several lines of evidence suggesting the possibility. Recently, autoradiographic techniques have shown that specific binding of calcium antagonists takes place in brain and that the binding sites are mostly localized in certain brain areas, especially in the hippocampus (Murphy *et al.*, 1982; Ferry *et al.*, 1984). And calcium channels, which control the influx of extracellular calcium and hence neurotransmitter release, exist in the brain (Nelson *et al.*, 1984). In rat brain slices, Bay K 8644, a calcium agonist, can augment K^+-stimulated neurotransmitter release, and these effects of Bay K 8644 can be antagonized by NIF (Middlemiss and Spedding 1985; Spedding and Middlemiss 1985). All these reports may be considered to be supporting our observation that the cardiovascular inhibitory effects of icv DIL and NIF are central in origin.

Effects of DIL and NIF on ME- and CLO-induced Response

It has been reported that hypertension by icv ME is derived from activation of central alpha-1 adrenoceptors (Kim *et al.*, 1982) and that bradycardia is due to nonspecific actions on the center (Chung, 1986), and it has also been shown that icv CLO produces hypotension and bradycardia by activation of central alpha-2 adrenoceptors (Timmermans, *et al.*, 1981; Kim *et al.*, 1982; Yoo, 1985). In the present study, the pressor response to icv ME was not affected by pretreatment with icv DIL and NIF, but the hypotensive response to icv CLO was inhibited by the same pretreatment. And iv DIL and NIF had no influence on hypotensive response to icv CLO. It has been shown that the stimulation of both postsynaptic alpha-1 and alpha-2 adrenoceptors in

peripheral vascular smooth muscle induces pressor response, and that the alpha-1 mediated contractions are mostly effected by the release of intracellularly stored calcium whilst the alpha-2 mediated contractions are dependent on extracellular calcium influx (van Meel *et al.*, 1981 a, b, 1982; van Zwieten *et al.*, 1982; Godfraind *et al.*, 1982; Cavero *et al.*, 1983; Timmermans *et al.*, 1983; Hicks *et al.*, 1985). Even, it has been proposed that selective inhibition of alpha-2 mediated vasoconstriction should be taken as one of the prerequisite for classifying a compound as a calcium antagonist (Godfraind, 1982; Godfraind and Miller, 1982; Godfraind *et al.*, 1982). Therefore, our observations might be interpreted as suggesting that ME acts on central alpha-1 adrenoceptors, as in the periphery, to elicit the pressor response which is resistant to calcium antagonist, whereas the depressor response to CLO which is mediated by central alpha-2 adrenoceptors can be inhibited by calcium antagonist as in vascular smooth muscle.

Further on, the present study demonstrates that the depressor responses to icv DIL and NIF are not affected by pretreatment with icv CLO. This data indicates that both CLO and calcium antagonist used in this study, DIL and NIF, do not share the same site of action in producing hypotension. Kim (1983) reported that the hypotension of icv CLO was reversed by icv yohimbine. The fact that these NIF and DIL could not reverse the icv CLO effects might indicate that they do not act directly on central alpha-2 adrenoceptor. These premises are supported by the report of van Zwieten *et al.* (1982) which has shown that calcium antagonists do not possess sufficient affinity for alpha-2 adrenoceptor by observing that calcium antagonists are very weak competitors for specific binding of [^{3}H]-CLO to isolated rat brain membranes.

Chung (1986) described the bradycardiac response to icv ME as nonspecific on the ground that it could be partially blocked by pretreatments with either prazosin, atropine or yohimbine. In present study we observed that the bradycardiac response to icv ME was attenuated by pretreatment with DIL or NIF, and it was further observed that the bradycardia may be completely abolished by combined pretreatment with iv atropine and these agents (unpublished data). Timmermans *et al.* (1983) reported that the central receptor mediating vagal reflexive bradycardia is alpha-2 adrenoceptors, and that separate central regulatory centers are involved in the control of cardiac function and peripheral vascular tone (Ito and Shanberg, 1974; Cohen *et al.*, 1979). In view of all the evidence at hand, our observations may be considered as inferring that calcium influx may be participated in the process of central bradycardiac effect by icv ME.

Conclusively, it is suggested that calcium influx takes part in the process of the response mediated by central alpha-2 adrenoceptors, in the same manner as in the peripheral smooth muscles.

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=국문초록=

가토에서 뇌실내 Calcium Antagonists가 Methoxamine과 Clonidine의 혈압및 심박수 변동에 미치는 영향

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Urethane 마취 가토에서 뇌내 alpha-1 및 alpha-2 adrenoceptor의 작용에 미치는 calcium antagonist의 영향을 알아보고자 뇌실내 methoxamine과 clonidine의 혈압및 심박수 변동에 미치는 diltiazem, nifedipine의 영향을 조사한 결과,

1). 뇌실내 methoxamine(1mg)은 혈압상승및 심박수 감소를 일으켰고, 뇌실내 clonidine(30㎍)은 혈압하강및 심박수 감소를 일으켰다. 2). 뇌실내 diltiazem과 nifedipine은 dose-dependent한 혈압하강을 일으켰으며 심박수 감소를 일으켰다. Diltiazem에 비하여 nifedipine은 혈압하강 효과는 크고 심박수 감소효과는 작았다. 뇌실내 diltiazem(400㎍), nifedipine(35㎍)의 혈압하강 작용은 완만하고 지속적이었으나 같은 양의 정맥내 투여효과는 일과성이었다. 3). 뇌실내 diltiazem(400㎍)이나 nifedipine(35㎍, 350㎍) 처리후에 methoxamine(1mg)의 혈압상승 효과는 영향받지 않았으나 심박수감소 효과는 유의하게 감약되었다. 4). Clonidine의 혈압하강 작용은 뇌실내 diltiazem(400㎍)이나 nifedipine(35㎍, 350㎍) 처리후에 감약되었으나 정맥내 diltiazem(200㎍/kg)이나 nifedipine(30㎍/kg) 후에는 영향받지 않았다. Clonidine의 심박수 감소작용은 뇌실내및 정맥내 diltiazem이나 nifedipine 처리후에 감약되었다. 5). 뇌실내 clonidine(30㎍) 처리후 뇌실내 diltiazem(400㎍)과 nifedipine(350㎍)의 혈압하강및 심박수 감소효과는 영향받지 않고 그대로 나타났다.

이상의 결과로 diltiazem과 nifedipine은 가토뇌내에서 methoxamine에 의한 혈압상승의 작용점인 alpha-1 adrenoceptor의 흥분에는 영향을 미치지 못하나 clonidine의 작용점인 alpha-2 adrenoceptor의 흥분에 의한 혈압하강및 심박수 감소효과는 억제한다고 추론하였다.