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STUDIES ON THE CARDIOVASCULAR ACTIONS OF HYDRALAZINE *

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SUMMARY

In conscious normotensive rabbits, the intravenous administration of hydralazine (0.3 mg/Kg) induced a significant decrease of mean arterial blood pressure (MBP) ($p<0.001$) and a significant increase of heart rate (HR) ($p<0.01$). Pretreatment of the animals with two prostaglandins (PGS) synthesis inhibitors, indomethacin (1 mg/Kg) and acetylsalicylic acid (10 mg/Kg) abolished the hypotensive effect ($p>0.05$) and did not modify the tachycardia. In the same model, the continuous infusion of a PGS precursor, arachidonic acid (7.5—10μg/Kg/min), modified the blood pressure lowering effect of hydralazine which began sooner and was considerably prolonged. In spontaneously beating guinea-pig isolated atria, hydralazine ($\times 10^{-5}$M) had no direct chronotropic effect and did not modify the responses to noradrenaline (2 to 8×10^{-7}M) and isoprenaline (1 to 4×10^{-8}M), but markedly enhanced the tachycardia provoked by tyramine (1.5 and 3.0×10^{-5}M). These results suggest that the hypotensive effect of hydralazine in normotensive conscious rabbits are related to the endogenous PGS system and that hydralazine has a stimulating effect on the heart probably mediated by a modification of the adrenergic neurotransmission to the heart.

INTRODUCTION

Hydralazine is an effective anti-hypertensive agent which produces a vasodilation of the precapillary resistance vessels and a reduction of peripheral vascular resistance (Ablad 1963; Mellander and Johansson 1968). Pharmacological data available today points to a direct effect on the arteriolar smooth muscle but, so far, the mechanism of this direct action is not completely understood (Ablad 1963; Gross 1977). Kirpekar and Lewis (1958) suggested a nonspecific depression of tissue metabolism, Ablad (1963) proposed an interaction with two different types of receptors, Schroeder (1959) supposed an interference with metal-containing enzymes and Anderson (1973) suggested that cyclic AMP mediates the relaxing activity of hydralazine. However, none of these mechanisms has been fully confirmed, namely in the whole animal or in humans (Gross 1977).

In the last years, the role of the renal hypotensive system in the pathogenesis of hypertension has been emphasized by Lee et al (1974, 1976). According to these authors,

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the renal PGS, which are powerful hypotensive acting substances, would have an effect opposed to the pressor system in the regulation of blood pressure. On the other hand, the importance of endogenous PGS in the hypotensive effect and in the anti-hypertensive activity of β-adrenoceptor blocking agents has been demonstrated by ourselves in conscious animals and in hypertensive patients (Durão and Rico 1977; Durão et al 1977). Based on these hypotheses, we investigated the action of two prostaglandin synthesis inhibitors, indomethacin and acetylsalicylic acid, and of a precursor of those substances, arachidonic acid, on the blood pressure lowering effect of hydralazine in the unanesthetized rabbit.

Simultaneously with the fall in blood pressure provoked by hydralazine, an increase in heart rate occurs (Ablad 1963; Brunner et al 1967; Koch-Weser 1974 a). Since no information is available about a direct chronotropic effect on the heart (Bein et al 1953; Koch-Weser 1974 b) hydralazine tachycardia is believed to be a consequence of enhanced peripheral sympathetic activity resulting from activation of the baroreceptors by the decrease in arterial pressure (Koch-Weser 1976; Gross 1977). In contrast, the results obtained in conscious rabbits reported in this paper, suggest that the heart rate responses are brought about by a mechanism other than that involving baroreceptors. In view of these observations it was considered pertinent to examine the effects of hydralazine upon the chronotropic responses of spontaneously beatings guinea-pig isolated atria.

MATERIALS AND METHODS

Conscious normotensive rabbits

Hyla normal male rabbits all of the same strain and of approximately similar age and weight (3.0-3.5 Kg) were given a standard diet of pellets and water ad libitum. The experiments were performed in the unanesthetized animals. Under local (procaine) anesthesia, polyethylene catheters were inserted into the central artery and vein of one ear. MBP and HR were continuously recorded from the arterial line on a Hewlett-Packard (HP) 7702 B recorder via a HP 8805 carrier pre-amplifier and an HP 8812 A rate-computer. The experiments were done in a quiet room at constant temperature ($23 \pm 1°C$). The animals were left to recover for a 90 min period which was long enough to stabilize MBP and HR. Both these parameters were measured every 15 min and the mean of 6 measurements at 10 sec intervals was recorded each time for 1 min. All the preparations were followed for 180 min after the injection of the drugs via the venous catheter in a constant volume of 1 ml/Kg body weight. Arachidonic acid was infused in the venous catheter with an automatic slow injection apparatus Palmer F 130 at a constant rate of 7.5 to 10 μg/Kg/min until the 150 min.

There were 8 groups of experiments. Time of injection and test agents used in each group are shown in table 1.

Guinea-pig isolated atria

Guinea-pigs of either sex and weight range 350-500 g were killed by a blow on the head. The thorax was rapidly opened and the heart removed. The isolated atria were suspended in a 50 ml organ bath containing Krebs-Henseleit solution of the following composition (mM): NaCl 112.91, KCl 4.69, $CaCl_2$ 2.55, $MgCl_2$ 2.44, KH_2PO_4 1.19, $NaHCO_3$ 24.76, glucose 11.56. The solution was gassed by a mixture of 95 % O_2 + 5 %

CO_2 and maintained at a temperature of 37 ± 0.5°C. In these conditions the pH was approximately 7.4. The atria were attached to an isometric HP FTA 10-1 transducer and the resting tension was adjusted to give approximately 0.5 g. The atria were allowed to beat spontaneously and the rate of contraction was recorded by means of a HP 8812 A rate-computer triggered by the tension signal of a HP 8805 carrier pre-amplifier on a HP 7702 B recorder. A 60-90 min equilibration period with several changes of bathing medium was allowed in each experiment before addition of any drug. Non-cumulative dose-response curves for various amines were obtained by adding gradually increasing concentrations to the organ bath and washing the preparation after each concentration until the pre-drug control value was obtained. Responses were calculated as increase in the HR above the initial rate of the atria in each experiment. The contact time necessary to obtain the maximal response to each agonist was determined in previous experiments and was 60 sec with a dose cycle of approximately 8 min for noradrenaline and 120-150 sec with a dose cycle of 12 min for isoprenaline and tyramine. Since changes in sensitivity of isolated atria to sympathomimetic amines have been reported (Clark and Poyser 1977; Nicholson and Broadley 1978) three dose-response curves were determined in each preparation with an interval of about 15 min. When noradrenaline and isoprenaline were used as agonists, three concentrations were employed for each curve. In the experiments with tyramine only two doses were used to minimize tachyphylaxis.

There were two groups of experiments with each agonist. In group A the three curves were determined only in presence of the agonist. This group served as control to group B, in which hydralazine (4×10^{-5}M) was added to the bath 5 min before each dose of the agonist for determination of the second curve. Only three dose-response curves with the same agonist were determined in each preparation.

In some experiments with atria, acetylsalisylic acid (1×10^{-3}M) was added to the bathing solution 60 min prior to the determination of the first dose-response curve and maintained until the end of the third curve.

Drugs

Drugs used were: hydralazine (Ciba-Geigy), indomethacin (Merck, Sharp & Dohme), acetylsalicylic acid (Bayer), arachidonic acid (grade I — 99 % pure, Sigma), (−)-norepinephrine bitartrate (Sigma), (±)-isoproterenol hydrochloride (Sigma) and tyramine hydrochloride (British Drug Houses). In the experiments with conscious rabbits test agents were dissolved in 0.9 % saline except indomethacin which was dissolved in 0.1 M potassium phosphate buffer pH 8 (Larsson et al 1974). Arachidonic acid was dissolved in 0.1 ml of 95 % ethanol, converted to the sodium salt with 0.08 ml of 0.5 M sodium carbonate and diluted to the final concentration with 0.9 % saline (Ryan et al 1977). In the experiments with atria all drugs were dissolved in distilled water. The maximum volume added to the bath was 0.6 ml. Ascorbic acid, in the final concentration of 1 μg/ml, was added to the isoprenaline and noradrenaline solutions. Drug concentrations were expressed as the final molar bath concentration. All these solutions were freshly prepared in the day of the experiment and used only once.

Statistical analysis

Results are expressed as mean ± standard error of the mean (SEM). Significance of the data were calculated according to Student's t-test. A p value of less than 0.05 was considered statistically significant.

Table 1

Time of injection and test agents used in each group of experiments in conscious normotensive rabbits

Groups	I (N = 7)	II (N = 5)	III (N = 6)	IV (N = 5)	V (N = 6)	VI (N = 6)	VII (N = 7)	VIII (N = 5)
— 15 min	Saline (1 ml/Kg)	Indomethacin (1 mg/Kg)	Acetylsalicylic acid (10 mg/Kg)	Arachidonic acid (7,5-10 µg/Kg/min)	Saline (1 ml/Kg)	Indomethacin (1 mg/Kg)	Acetylsalicylic acid (10 mg/Kg)	Arachidonic acid (o,3 mg/Kg)
0 min	Saline (1 ml/Kg)	Saline (1 ml/Kg)	Saline (1 ml/Kg)	Saline (1 ml/Kg)	Hydralazine (o,3 mg/Kg)	Hydralazine (o,3 mg/Kg)	Hydralazine (o,3 mg/Kg)	Hydralazine (7,5-10 µg/Kg/min)

Test agents were administered in the venous catheter by single IV injection, except arachidonic acid in groups IV and VIII, which was administered by continuous infusion from minus 15 min until 150 min. All agents were administered in a constant volume of 1 ml/Kg body weight.

RESULTS

Conscious normotensive rabbits

Controls (Groups I, II, III and IV)

The single injection of saline, indomethacin and acetylsalicylic acid (Fig. 1) did not affect MBP ($p>0.05$) or HR ($p>0.05$). The continuous infusion of arachidonic acid induced a transient significant increase of MBP and a slight non significant increase in HR (Fig. 1). There was no difference between MBP and HR control values of the 4 groups ($p>0.05$).

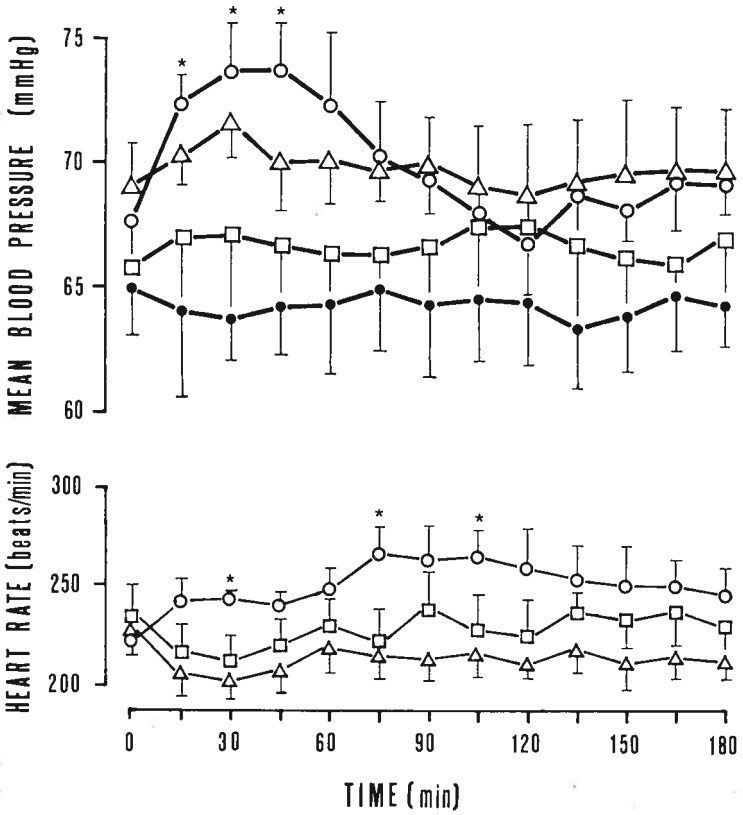

Fig. 1 — *Effects of single intravenous injections of saline, 1 ml/Kg (●——● Group I; n=7), indomethacin, mg/Kg (□——□ Group II; n=5), acetylsalicylic acid, 10 mg/Kg (△——△ Group III, n=6) and continuous infusion of arachidonic acid, 7.5 to 10 µg/Kg/min (O——O Group IV; n=5) on MBP (upper panel) and HR (lower panel) of conscious normotensive rabbits. Each point represents the mean ± SEM and statistical analysis were calculated according to Student's t-test in relation to the initial control values of each group.* ★ $p<0.05$

Hydralazine (Group V)

The blood pressure lowering effect of hydralazine was significant ($p<0.05$) only at 30 min and attained its lowest value between 45 and 75 min (Fig. 2). All values obtained from 30 until 150 min were significantly different from control values ($p<0.05$ to $p<0.001$). HR increased significantly at 15 min ($p<0.01$) and remained elevated until 105 min (Fig. 2).

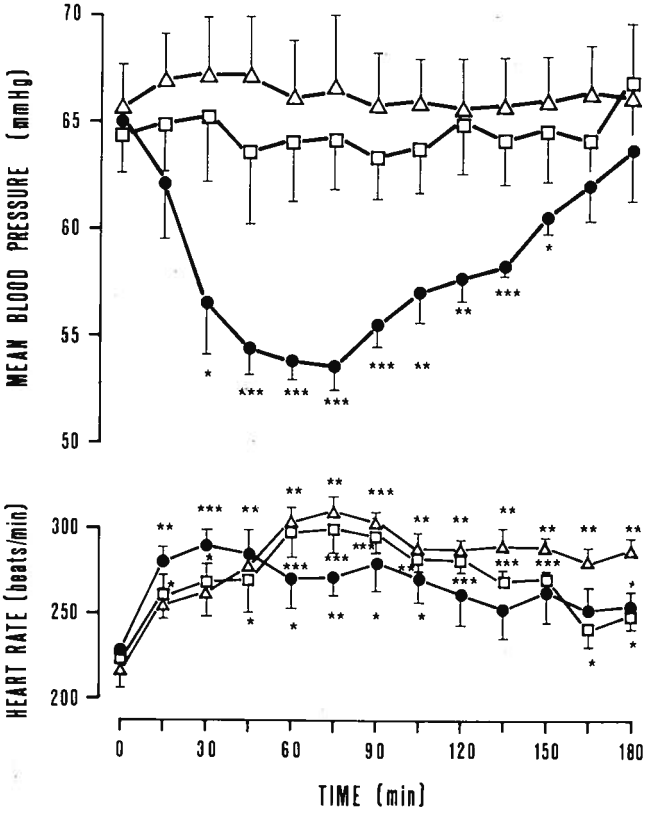

Fig. 2 — *Effects of single intravenous injections of hydralazine, 0.3 mg/Kg (●——● Group V, n=6), hydralazine, 0.3 mg/Kg, after pretreatment with indomethacin, 1 mg/Kg (□——□ Group VI; n=6) and hydralazine, 0.3 mg/Kg, after pretreatment with acetylsalicylic acid, 10 mg/Kg (△——△ Group VII, n=7) on MBP (upper panel) and HR (lower panel) of conscious normotensive rabbits. Each point represents the mean ± SEM and statistical analysis were calculated according to Student's t-test in relation to the initial control values of each group. * $p<0.05$; ** $p<0.01$; *** $p<0.001$*

Hydralazine after prostaglandin synthesis inhibitors (Groups VI and VII)

The hypotensive effect of hydralazine was markedly inhibited by the pretreatment of the animals with indomethacin and acetylsalisylic acid (Fig. 2). The MBP values were never different from control value ($p>0.05$), and were significantly different from the

values obtained in group V ($p<0.05$ to $p<0.01$) between 30 and 135 min (not represented). In both groups HR increased significantly ($p<0.05$ to $p<0.001$) and remained elevated until the end of the experiments, despite the absence of hypotensive effect (Fig. 2).

Hydralazine plus arachidonic acid (Group VIII)

The simultaneous infusion of arachidonic acid modified the blood pressure lowering effect of hydralazine (Fig. 3).

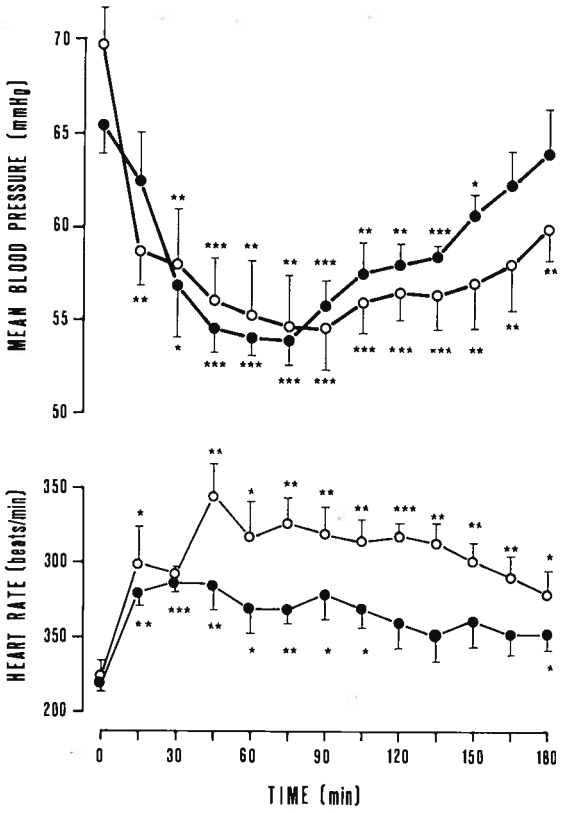

Fig. 3 — *Effects of single intravenous injections of hydralazine, 0.3 mg/Kg (●——● Group V; n=6) and hydralazine, 0.3 mg/Kg, plus continuous infusion of arachidonic acid, 7.5 to 10 μg/Kg/min (O——O Group VIII; n=5) on MBP (upper panel) and HR (lower panel) of conscious normotensive rabbits. Each point represents the mean ± SEM and statistical analysis were calculated according to Student's t-test in relation to the initial control values of each group. * $p<0.05$; ** $p<0.01$; *** $p<0.001$*

The hypotensive effect began sooner, with MBP values already significantly different from control value at 15 min ($p<0.01$) and was prolonged until the end of the

experiments. MBP values were significantly different from 0 time value ($p<0.01$ to $p<0.001$). The difference between the MBP values obtained at 15 min in this group was also significantly different ($p<0.05$) from the control value of group V. HR was significantly increased ($p<0.05$ to $p<0.001$) during all the observation period (Fig. 3).

Guinea-pig isolated atria

Hydralazine

Hydralazine, in concentrations from 10^{-8}M to 5×10^{-2}M induced a modest inotropic action, statistically non-significant, and did not modify the rate of concentration of spontaneously beating atria (not represented).

Hydralazine and direct sympathomimetic amines

The dose-response curves for the chronotropic effect of noradrenaline (2 to 8×10^{-7}M) and isoprenaline (1 to 4×10^{-8}M) are represented in fig. 4 and 5.

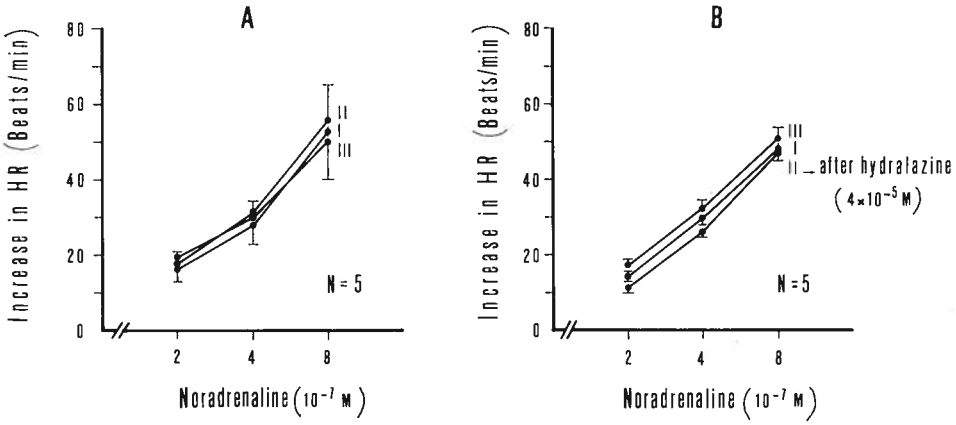

Fig. 4 — *Effect of moradrenaline on heart rate of spontaneously beating isolated guinea-pig atria. (A) Non-cumulative dose-response curves obtained with the agonist alone. (B) Non-cumulative dose-response curves to the same agonist after addition of hydralazine to the organ bath prior to the determination of the second curve. The responses were calculated as increase in the HR above the initial rate of the atria in each experiment. Each point represents the mean ± SEM (see text, Methods)*

The three curves obtained with the agonists alone were similar and quantitatively superposable (group A). The addition of hydralazine (4×10^{-5}M) to the organ bath prior to the determination of the second curve did not modify the responses to the agonists (group B). A slight decrease of the responses to isoprenaline at the third curve was observed, but there were no significant differences between the curves (group B-Fig. 5).

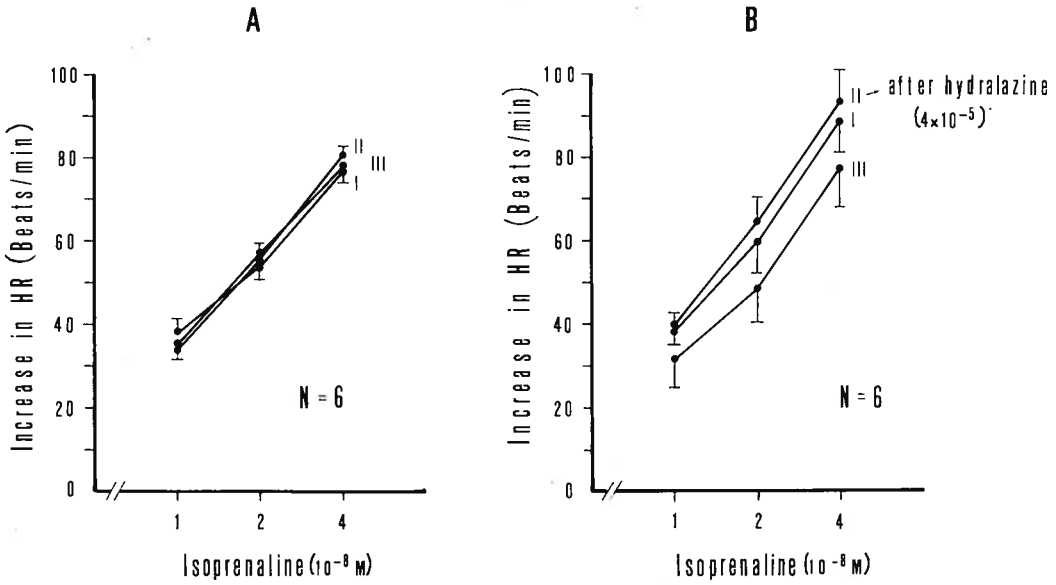

Fig. 5 — *Effect of isoprenaline on heart rate of spontaneously beating isolated guinea-pig atria. (A) Non-cumulative dose-response curves obtained with the agonist alone. (B) Non-cumulative dose-response curves to the same agonist after addition of hydralazine to the organ bath prior to the determination of the second curve. The responses were calculated as increase in the HR above the initial rate of the atria in each experiment. Each point represents the mean ± SEM. (see text, Methods)*

Hydralazine and indirect sympathomimetic amines

The responses obtained with tyramine, represented in fig. 6, have shown a slight tachyphylaxis, but the differences between the three curves were not significant (group A). The addition of hydralazine (4×10^{-5}M) to the organ bath induced a marked increase of the chronotropic effect of tyramine (group B). In this group, the heart rate responses obtained in the presence of hydralazine were highly significantly different ($p<0.001$) from the responses determined with tyramine alone. In a series of experiments performed with acetylsalicylic acid (1×10^{-3}M) added to the bathing solution, it was found that the effect of hydralazine upon the chronotropic responses of spontaneously beating atria to tyramine was further increased (Fig. 7). Acetylsalicylic acid also increased the responses to tyramine alone (curves I and III). These effects were more pronounced with the higher dose (3×10^{-5}M) of tyramine, and the differences between the heart rate responses to this concentration of the agonist in the presence and in the absence of acetylsalicylic acid were statistically significant ($p<0.05$ to $p<0.01$) (not represented).

DISCUSSION

The cardiovascular actions of hydralazine were studied in normotensive rabbits, because it is doubtful whether the effects observed with single artery strips or isolated vascular beds are of definitive significance for the whole hemodynamic response to hydralazine in vivo (Gross 1977). Furthermore, the experiments were performed in conscious animals because anaesthetic agents can affect the blood pressure control mechanisms by inhibition of cardiovascular reflexes as well as by direct central or peripheral actions

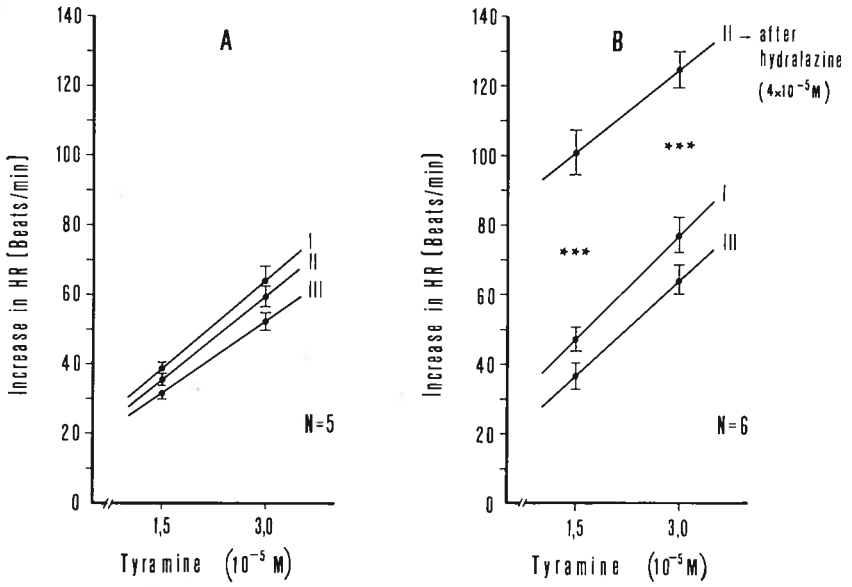

Fig. 6 — *Effect of tyramine on heart rate of spontaneously beating isolated guinea-pig atria. (A) Non-cumulative dose-response curves obtained with the agonist alone. (B) Non-cumulative dose-response curves to the same agonist after addition of hydralazine to the organ bath prior to the determination of the second curve. The responses were calculated as increase in the HR above the initial rate of the atria in each experiment. Each point represents the mean ± SEM. Statistical analysis were performed according to Student's t-test between curve II and curves I and III. *** $p<0.001$ (see text. Methods)*

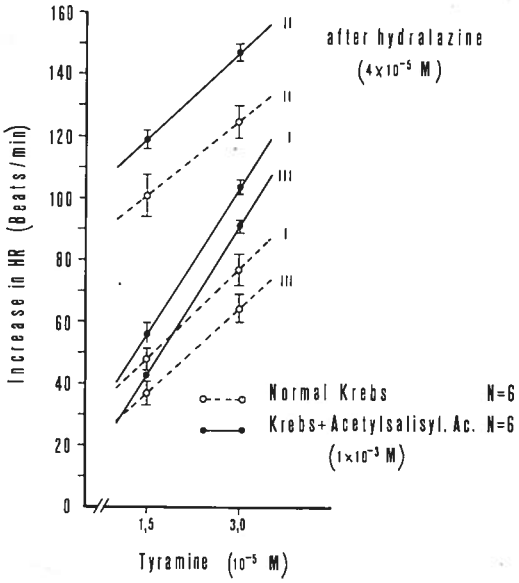

Fig. 7 — *Effect of hydralazine upon the chronotropic responses of spontaneously beating isolated guinea-pig atria to tyramine with and without acetylsalicylic acid in the Krebs-Henseleit bathing solution. The responses were calculated as increase in the HR above the initial rate of the atria in each experiment. Each point represents the mean ± SEM. (see text, Methods)*

(McGrath and Mackenzie 1977; Miller and Wiegman 1977). The utilization of nonanaesthetized normotensive rabbits with intact cardiovascular reflexes explain the moderate fall in MBP observed. However, the blood pressure lowering effect induced by hydralazine was highly statistically significant and was quantitatively similar to the effects obtained with other anti-hypertensive agents in this experimental model (Weber et al 1974; Durão and Rico 1977).

The inhibitors of PG synthesis used, indomethacin and acetylsalicylic acid, are effective both in vivo and in vitro (Vane 1971) and the doses administered were not hypertensive (groups II and III) agreeing with the results of Larsson et al (1974). The continuous infusion of arachidonic acid, the natural precursor of PGE_2, PGI_2 and $PGFA_\alpha$, was used in the present study in order to provide an increased amount of a physiological precursor of PG synthesis. It is generally believed that endogenous PG synthesis depends on the presence of essential fatty acid precursors, and the availability of these precursor acids in the free form has been suggested as a common rate-limiting step in enchanced biosynthesis that occurs in response to several influences (see Douglas 1975). The infusion rate utilized in our work was not hypotensive and no toxic effects were observed in the animals (group IV). These results are in accordance with the observations of Larsson and coworkers obtained in response to slightly higher infusion rates in the same experimental model (Larsson and Änggard 1974; Larsson et al 1974). A transient moderate rise in blood pressure similar to that observed in the beggining of the arachidonate infusion in group IV, has been reported by others, and is probably due to a vasoactive intermediate in the PG biosynthetic pathway (Fitzpatrick et al 1977). Also, the moderate increase in HR may be the result of a direct chronotropic effect induced by peroxides (Borbola et al 1977) or PGE_2 (Bhagat et al 1972) formed from arachidonic acid.

The effect of hydralazine on blood pressure develops gradually with a latency period of 15 to 20 min even after intravenous administration (Ablad 1963; Nickerson and Ruedy 1975). In our experiments the hypotensive effect was significant only after 30 min (group V). The infusion of the polyenoic precursor acid accelerated the beggining of the hypotensive action of hydralazine which was already significant at 15 min and was prolonged until the end of the experiments (group VIII). Simultaneously, a more marked tachycardia occurred. It is reasonable to think that no potentiation of the MBP decrease was observed, because the experiments were performed in conscious animals. Like all peripheral vasodilators, hydralazine in doses that lower blood pressure induces an increase in HR and cardiac output that counteracts to a certain degree the hypotensive effect in nonanaesthetized animals and man (Koch-Weser 1974a, 1976). The administration of higher doses does not induce a more marked fall in blood pressure, but a prolongation of the effect (Gross 1977). Furthermore, in our study, the inhibition of endogenous PG synthesis completely abolished the blood pressure lowering effect of hydralazine (groups VI and VII). In view of these observations it is suggested that endogenous PGS might therefore contribute to the hypotensive effect of hydralazine in conscious rabbits. PGS, particularly PGE_2 and PGI_2 which dilate peripheral arterioles and reduce total peripheral resistance (Lee et al 1976; Moncada et al 1976; Moncada et al 1977), could eventually mediate in part the characteristic changes in peripheral vascular resistance provoked by hidralazine, or they could, at least, be necessary to obtain the hypotensive action.

Our results obtained in nonanaesthetized animals also suggest that hydralazine tachycardia is brought about by a mechanism other than that involving baroreceptors. In groups VI and VII, the pretreatment of the rabbits with the PG synthesis inhibitors abolished the effect of hydralazine in MBP, but HR increased significantly, even slightly

more than in group V. In an attempt to elucidate the mechanism of this tachycardia, experiments were carried out with spontaneously beating guinea-pig isolated atria. The main finding of these experiments was that hydralazine markedly enhanced the chronotropic effect of tyramine. This action is not mediated by a direct effect on the myocardium or by an interaction with cardiac receptors because hydralazine failed to modify the spontaneous rate as well as the responses to noradrenaline and isoprenaline. Considering the above-mentioned facts, it seems reasonable to assume that the effect of hydralazine on the heart might be mediated by a modification of the release of the adrenergic neuro-transmitter or by interference with its inactivation (or of that of the releasing substance). These hypothesis are in agreement with the results obtained in conscious rabbits. The tachycardia observed in groups VI and VII, despite the absence of hypotensive effect, can thus be explained by a direct action of hydralazine on the adrenergic neuro-transmission to the heart.

Since a direct chronotropic action of PGE_2 has been reported (Bhagat et al 1972) a series of experiments with acetylsalicylic acid added to the bathing solution were performed in an attempt to investigate if endogenous PGS were related to the effect of hydralazine on the heart. The results have shown that the inhibition of PG synthesis enhanced the effect of hydralazine upon the chronotropic responses of the isolated atria to tyramine. This observation argues against the assuption that the endogenous PG could mediate the stimulating action of hydralazine on the heart. However, these findings are in good agreement with the hypothesis proposed by Hedqvist that PGS inhibit the transmitter release by a prejunctional action on adrenergic neuro-effector transmission (Frame and Hedqvist 1975; Hedqvist 1976). These results are also in good harmony with data obtained in the rabbits pretreated with PG synthesis inhibitors. In fact, the tachycardia induced in these animals by hydralazine, despite the absence of modifications of MBP (groups VI and VII), was slightly more marked than the increase in HR obtained in group V.

In conclusion, it seems reasonable to assume that the hypotensive effect of hydralazine in conscious normotensive rabbits may be somehow related to the endogenous PGS system. In addition, the results of the present study suggest that hydralazine has a stimulating effect on the heart probably mediated by a modification of the adrenergic neuro-transmission to the heart.

RESUMO

Em coelhos conscientes normais, a administração intravenosa de hidralazina (0.3 mg/Kg) provocou uma diminuição estatisticamente significativa da pressão arterial média ($p<0.001$) e um aumento significativo da frequência cardíaca ($p<0.01$). O tratamento prévio dos animais com dois inibidores da síntese das prostaglandinas (PGS), a indometacina (1 mg/Kg) e o ácido acetilsalicílico (10 mg/Kg), aboliu o efeito hipotensor e não modificou a taquicardia. No mesmo modelo experimental, a infusão contínua de um precursor das PGS, o ácido araquidónico (7,5-10 μg/Kg/ min), modificou o efeito hipotensor da hidralazina que começou mais cedo e foi consideravelmente prolongado. Em aurículas isoladas de cobaia pulsando expontaneamente, a hidralazina (4×10^{-5} M) não teve efeito cronotrópico directo e não modificou as respostas à noradrenalina (2 a 8×10^{-7} M) e à isoprenalina (1 a 4×10^{-8} M), mas aumentou marcadamente a taquicardia provocada pela tiramina (1,5 a 3.0×10^{-5} M). Estes resultados sugerem que o efeito hipotensor da hidralazina em coelhos normotensos conscientes está relacionado com o sistema das PGS endógenas e que a hidralazina tem um efeito estimulante sobre o coração, provavelmente mediado por uma modificação da neuro-transmissão adrenérgica.

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