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Relationship between vascular adrenergic receptors and prostaglandin biosyntheses in canine diabetic coronary arteries

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Summary. Before the onset of histologically detectable alterations of diabetic arteries, a considerable decrease of vasodilation ability develops. The role of an altered prostaglandin biosynthesis in this phenomenon was investigated in connection to the altered vascular adrenergic mechanisms. The effect of phenylephrine on prostacyclin production of isolated coronary arterial rings (100 μmol/l) as well as on conductivity of the coronary arterial bed (7.5-15-30-60 pmol · $kg^{-1} \cdot min^{-1}$) were compared in 12 metabolically healthy and 12 alloxan-diabetic (560 μmol/kg) dogs. Furthermore, the effect of phentolamine (5 μmol/l) on the prostacyclin and thromboxane productions of the isolated vessels (coronary, femoral and basilar arteries) was investigated by radioimmunoassay. Although the basal prostacyclin amounts synthesized by healthy and diabetic coronary vessels were not different (5.1 ± 1.6 and 4.9 ± 1.4 pg/mg vessel/30 min), similarly to femoral and basilar arteries, the diabetic arterial rings produced significantly ($p < 0.05$) more thromboxane than the control rings. The α-adrenergic blockade by phentolamine did not influence the prostacyclin production in the healthy arteries, but considerably ($p < 0.05$) increased it in the diabetic coronary arteries. Phentolamine normalised the thromboxane synthesis in the diabetic group ($p < 0.01$) and enhanced ($p < 0.05$) it in the metabolically healthy group. Phenylephrine was ineffective ($98 \pm 6\%$) on the prostacyclin production in vitro versus the stimulated ($150 \pm 22\%$) prostacyclin synthesis detected in the metabolically healthy group; and in vivo induced a more significant ($p < 0.05$) decrease in the coronary conductivity in diabetic than in control groups. These results refer to the supposition that altered adrenergic mechanisms are involved in the imbalance of the vasoactive prostaglandins contributing to the high incidence of ischaemic heart disease in diabetes mellitus.

Key words: Alloxan-diabetes, coronary artery, α-adrenergic receptors, prostacyclin, thromboxane, phenylephrine, phentolamine.

It is known that both the adrenergic receptor agonists [1] and the prostaglandins synthesized by the vascular tissue [2] may be involved in the regulation of coronary circulation. It has also been established that the reactivity of the diabetic vasculature to anoxia, hypercapnia, neurotransmitters and adrenergic stimuli is significantly modified [3-5]. Having been normalised under the influence of insulin, these pathological reactions are supposed to be the consequences of the metabolic disorder [6]. Disregarding a few exceptions [7, 8] most of the data demonstrate a vascular hypersensitivity against catecholamines in isolated diabetic mesenteric [9] and carotid [10] arteries as well as in rat [11, 12] and rabbit [13] aortae. On the other hand, a hyper-reactivity of the diabetic vascular tissue to vasoconstrictor eicosanoids [14, 15] has also been demonstrated. In isolated coronary strips of alloxan-diabetic dogs prostaglandin (PG) $F_{2\alpha}$ exerted a significantly higher tone-enhancing effect compared with metabolically healthy reactions [16] in the presence of cyclooxygenase inhibitor. A diminished synthesis of prostacyclin (PGI_2) in the isolated diabetic vessels and heart [17-20] on one hand, and an increased synthesis of thromboxane $(TX)A_2$ [21] on the other indicate a pathological imbalance among the products of arachidonate cascade; especially that of PGI_2/TXA_2 ratio, which has been attributed as an important factor in the generation of vascular diseases [22].

It has been reported that under physiological circumstances catecholamines stimulate the release and synthesis of PGI_2 in the myocardium [23]. However, it remains to be answered whether the altered adrenergic

mechanisms and the altered prostaglandin biosynthesis in the diabetic vascular wall occur independently, or if these changes are causally related.

In order to clarify this potential relationship the following problems have been studied: (1) the influence of α-adrenergic blockade on the production of PGI_2 and TXA_2 by coronary arteries; (2) the action of phenylephrine on PGI_2 production by coronary artery rings from metabolically healthy and alloxan-diabetic dogs; (3) the effect of the α_1-adrenergic receptor agonist phenylephrine on coronary conductivity in anaesthetised normal and alloxan-diabetic dogs.

Materials and methods

Twenty-four young mongrel dogs (15-34 kg) of both sexes, kept on the same diet consisting of 25% protein, 60% carbohydrate, 15% fat, vitamins and mineral salts ad libitum, were examined. Twelve dogs were made diabetic by alloxan (560 μmol/kg i.v. Alloxan-tetrahydrate, Merck, Darmstadt, FRG), while the remaining twelve animals served as controls. Plasma disappearance rate of glucose [24], blood glucose [25] and urea nitrogen [26] levels were determined at the beginning of the study and subsequently once a month, while daily acetone [27] and glucose excretions [25] as well as body weight were measured at least once a week. Three months after the induction of diabetes, on the day before the examination, all the variables were redetermined.

Six metabolically healthy and six alloxan-diabetic dogs were anaesthetised (133 μmol/kg, Nembutal, Ceva, Paris, France), the heart was excised, the left anterior descending and circumflex coronary arteries removed, very cautiously freed from fat and adventitia were cut into 1-2 mm rings. To compare the basal values of arteries from different vascular regions basilar and femoral arteries were also cut out and similarly prepared. The arterial rings were placed into a bath of 3 ml volume containing Krebs-Henseleit solution that was aerated with a mixture of 95% O_2 and 5% CO_2. The bathing fluid was replaced with fresh Krebs-Henseleit solution every 30 min. In order to avoid an artificial increase of prostaglandin formation described after mechanical irritation [28] and to reach a stable minimal output of same, [29], the samples collected were used for assaying prostanoid production after a 2 h equilibrium period.

The vessel rings were divided into two groups. The first was placed into normal Krebs-Henseleit solution, while the second one into a bath containing 5 μmol/l phentolamine (Regitin, Ciba-Geigy, Basle, Switzerland). In this way all interventions were also carried out in α-adrenergic blockade.

Adrenergic stimulus was produced by 100 μmol/l phenylephrine (phenylephrine hydrochloride, Serva, Heidelberg, FRG). 6-oxo-PGF_α and TXB_2 were determined by selective radioimmunoassay [19]. The diluted samples were incubated overnight with antiserum (°C4; Pasteur Institute, Paris, France). Free tracer was separated from antibody-bound tracer by precipitation using the polyethylene glycol method. Radioactivity was determined after addition of 0.5 ml of 1% sodium dodecyl sulphate (Pierce Chem. Comp., Rockford, Ill., USA) and 3 ml liquid scintillation cocktail (Quickszint, Zinsser, Frankfurt, FRG) by a β-counter (Kontron, Münchenstein, Switzerland). All samples were assayed in triplicate in a single assay. The sensitivity of the method was 10 pg/ml, interassay variation 10% and intra-assay variation <3%.

In the remaining six metabolically healthy and six alloxan-diabetic dogs under pentobarbital anaesthesia the chest was opened, the left anterior descending coronary artery exposed and its blood flow measured by an electromagnetic flowmeter (Godard Statham, SP 2202). Arterial blood pressure was determined in the thoracic aorta through the femoral artery with a Statham gauge (P23Db). A polyaethylene cannula was inserted through a collateral branch into the coronary artery for drug infusion. After recording of the basal values on a multiscriptor (Medicor, R-61) 7.5-15-30-60 pmol·kg^{-1}·min^{-1} phenylephrine was infused until the steady state was reached. The conductivity of the coronary arterial bed was calculated by the flow/pressure ratio.

Statistical analysis

The synthesized prostaglandin amounts were expressed in pg/mg vascular tissue/30 min. The alteration of the conductivity of the coronary arterial bed in the presence of phenylephrine was expressed in a percentage of the basal value. The results given as means ± SEM were evaluated by using Student's paired or unpaired t-tests as well as regression analysis.

Results

Plasma disappearance rate of glucose and body weight decreased after alloxan-treatment ($p<0.001$), whereas fasting blood glucose level and urinary glucose excretion increased ($p<0.001$). Acetone excretion was never detected. Animals with enhanced blood urea nitrogen level were excluded from the study. These changes strongly suggest the presence of a manifest form of diabetes mellitus (Table 1).

In the basal state there were no significant differences between the amounts of PGI_2 produced by metabolically healthy and alloxan-diabetic isolated vessel rings from the basilar, coronary or femoral arteries (Table 2). However, it was remarkable that the PGI_2-synthesizing capacity of the basilar artery was much higher than those of the coronary and femoral arteries.

In relation to TXA_2 production, a significantly higher rate of synthesis ($p<0.05$; $p<0.01$) could be

Table 1. Metabolic state of control and alloxan-diabetic dogs

	Plasma disappearance rate of glucose (μmol/min)	Plasma glucose (mmol/1)	Glucose excretion (mmol/day)	Body weight (kg)
Control ($n=12$)	16±1	5.4±0.4	0	23.0±3.9
Diabetic ($n=12$)				
before alloxan	15±1	5.2±0.3	0	23.2±1.7
after alloxan	5±1[a]	13.8±4.2[a]	68±74[a]	20.3±1.7

Data are expressed as mean ± SEM. significance referred to values obtained before alloxan treatment is indicated by: [a] $p<0.001$

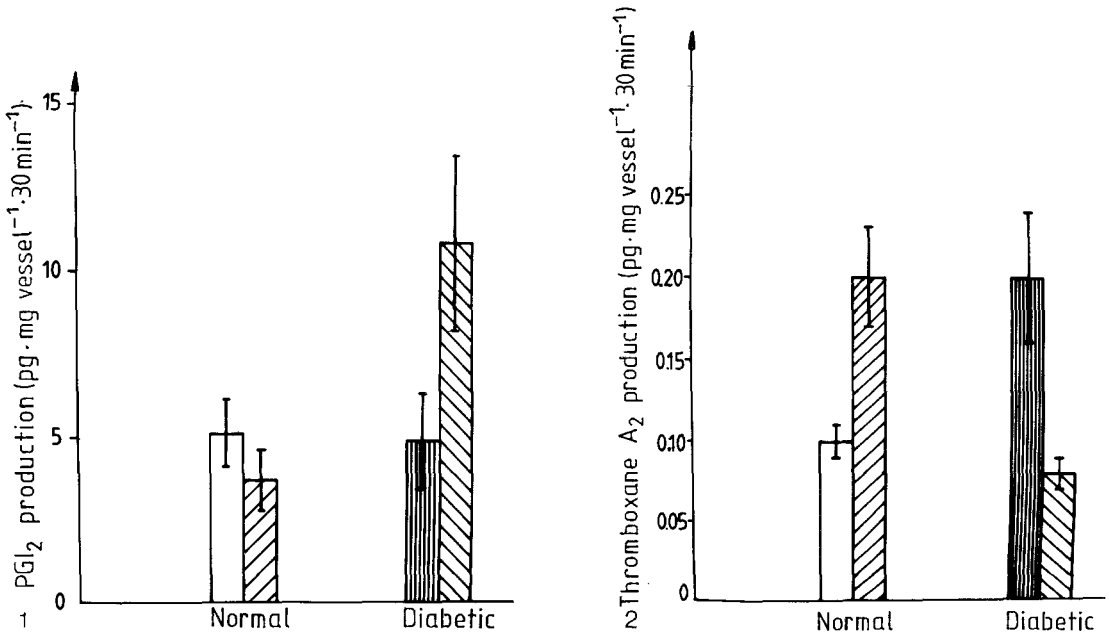

Fig. 1. Effect of phentolamine (5 μmol/l) on PGI_2 synthesis by isolated healthy and diabetic canine coronary arteries. Groups: metabolically healthy vessel rings without □ and with ▨ phentolamine treatment; alloxan-diabetic vessel rings without ▥ and with ▧ phentolamine treatment. Each bar is the mean ± SEM of 6-6 individual experiments. Significant differences refer to a comparison between the healthy phentolamine-treated and diabetic phentolamine-treated groups at a level of $p < 0.01$, while between the non-treated and phentolamine-treated diabetic groups at a level of $p < 0.05$

Fig. 2. Effect of phentolamine (5 μmol/l) on TXA_2 synthesis by isolated healthy and diabetic canine coronary arteries. Groups: metabolically healthy vessel rings without □ and with ▨ phentolamine treatment; alloxan-diabetic vessel rings without ▥ and with ▧ phentolamine treatment. Each bar is the mean ± SEM of 6-6 individual experiments. Significant differences refer to a comparison between the non-treated healthy and diabetic groups at a level of $p < 0.05$; between the phentolamine-treated healthy and diabetic groups at a level of $p < 0.01$; between the healthy non-treated and phentolamine-treated animals at a level of $p < 0.005$; between the non-treated and phentolamine-treated diabetic animals at a level of $p < 0.01$

Table 2. Prostacyclin (PGI_2) and thromboxane (TXA_2) production (pg·mg vessel^{-1}·30 min^{-1}) by various canine arteries

		Metabolically healthy $n=6$	Alloxan-diabetic $n=6$
Basilar artery	PGI_2	28.0 ±3.8	39.0 ±6.0
	TXA_2	0.8 ±0.1	1.3 ±0.2[a]
Coronary artery	PGI_2	5.1 ±1.60	4.9 ±1.40
	TXA_2	0.1 ±0.01	0.2 ±0.04[a]
Femoral artery	PGI_2	11.10±1.70	10.70±3.10
	TXA_2	0.13±0.01	0.22±0.01[b]

Data expressed as mean ± SEM. Significance refers to values obtained in the controls.
[a] $p < 0.05$; [b] $p < 0.001$

detected in the diabetic arterial rings versus the controls (Table 2).

Whilst the basal synthesis of PGI_2 was similar in normal and diabetic coronary artery rings, it was changed by phentolamine in the two groups of vessels differently. The α-adrenoceptor antagonist failed to alter the basal PGI_2 production by normal coronary rings. By contrast, this drug markedly increased ($p < 0.01$) the resting synthesis of PGI_2 in diabetic vessels (Fig. 1).

Phentolamine also produced differential changes in the TXA_2 synthesis of normal and diabetic coronary arteries: the resting production of TXA_2 was doubled in the former group of vessels, whereas it was considerably reduced ($p < 0.01$) in the latter vascular rings in the presence of the α-adrenoceptor antagonist (Fig. 2).

In vitro phenylephrine increased the PGI_2 amount synthesized by metabolically healthy coronary arterial rings, while it did not affect the PGI_2 production of diabetic vessels (Fig. 3). In the metabolically healthy coronaries pretreatment with the α-adrenergic blocker phentolamine prevented the enhancement of PGI_2 release without altering the PGI_2 amount synthesized by diabetic arterial rings.

It was interesting to see whether or not these phenylephrine-induced changes in PGI_2 production resulted in alteration of the vasomotor responsiveness in vivo to the α-adrenoceptor agonist. We found that intracoronarily-administered phenylephrine exerted a dose-dependent decrease in the conductivity of the coronary arterial bed (Fig. 4). This effect of the α-adrenergic agonist was much more expressed in alloxan-diabetic dogs than in metabolically healthy ones.

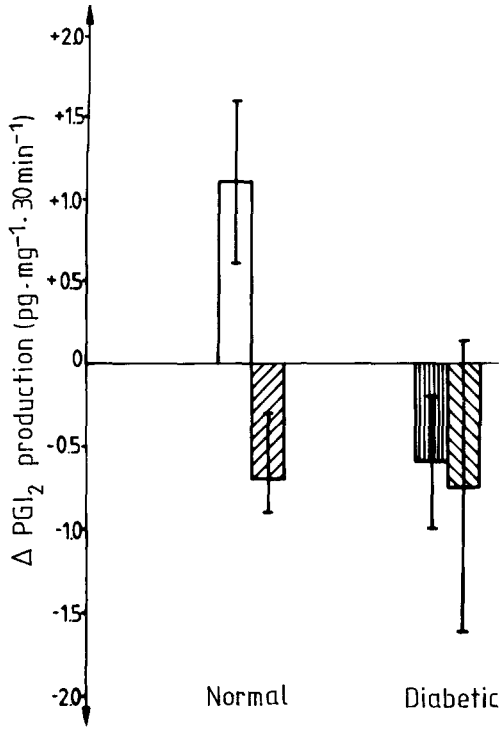

Fig. 3. Phenylephrine (100 μmol/l)-induced alteration in PGI_2 synthesis by isolated healthy and diabetic canine coronary arteries. Groups: metabolically healthy vessel rings without □ and with ▨ phentolamine (5 μmol/l) treatment; alloxan-diabetic vessel rings without ▥ and with ▧ phentolamine treatment. Each bar represents the mean alteration ± SEM of 5-5 individual experiments. Significant differences refer to a comparison between healthy and diabetic non-treated dogs at a level of $p < 0.05$; between the non-treated and phentolamine treated healthy groups at the level $p < 0.01$

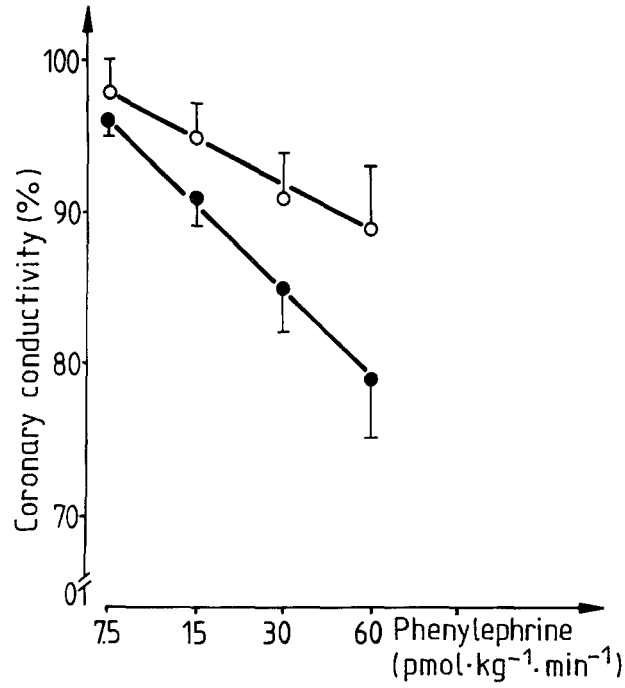

Fig. 4. Effect of phenylephrine on the conductivity in the coronary arterial bed expressed in percentage of initial values in metabolically healthy (○) and alloxan-diabetic (●) dogs. Each bar is the mean ± SEM of 6-6 individual experiments. Comparison was made between the slopes of the healthy and diabetic reactions representing a linear correlation. Significant difference was found at a level of $p < 0.01$

Discussion

Prostacyclin is known to be one of the most potent endogenous vasodilators in several vascular regions [2] including the coronary arterial bed. The majority of findings indicate that the synthesis of PGI_2 by various vessels [30, 31] decreases both in experimental and clinical diabetes [20, 32, 33]. This alteration might be dependent on the duration [34] and degree [35] of the diabetic metabolic disorder. Furthermore, according to Myers et al. [35] and Roth et al. [15] diabetic large arteries synthesize and release less amounts of PGI_2, while PGI_2 production by the small arteries was demonstrated to increase.

In addition to PGI_2, TXA_2 also has to be considered in the regulation of local coronary circulation [36]. This latter cyclo-oxygenase product synthesized by the vascular wall [37, 38] seems also to be involved in maintaining balance [39] among vasoactive prostaglandins. This balance might be disturbed in diabetes not only in the platelets [40] but also in the vasculature [17, 41, 42].

In our studies the basal PGI_2 synthesis was similar in each investigated vessel obtained either from healthy or alloxan-diabetic dogs. Jeremy et al. [43] observed that the rate of PGI_2 production by aortae of streptozotocin-diabetic rats was dependent on the duration and severity of the carbohydrate metabolic disorder. Thus our finding, i.e. the lack of effect of diabetes on basal PGI_2 synthesis, might be explained by the mild form of the alloxan-induced disorder without acetonuria.

In contrast to the unchanged basal formation of PGI_2, the synthesis of TXA_2 by the coronary, femoral and basilar arteries was markedly enhanced in alloxan-diabetes. This observation is in accordance with the results of Fujii et al. [41] who reported that streptozotocin treatment increased the formation of TXA_2 by the mesenteric vascular bed of rats. As shown in Table 2, the rate of TXA_2 was about 15 to 20-fold less than that of PGI_2. Although TXA_2 is known to be a vasoconstrictor [44], nevertheless the importance of this very small quantity of TXA_2 in the healthy local coronary circulation remains to be understood. On the other hand, the pathogenic role of elevated TXA_2 formation in diabetes mellitus has to be considered.

Whereas the inhibition of the α-adrenoceptors does not significantly affect the resting PGI_2 production of the metabolically healthy coronary vessels (Fig. 1), it enhances considerably that of the diabetic coronary arteries. The TXA_2 synthesis by the phentolamine-treated control and diabetic coronary arterial

rings is oppositely altered (Fig.2): in diabetes, TXA_2 formation was reduced by the α-adrenoceptor antagonist to the control level, whilst it was markedly increased by the drug in healthy vessels. These data support the hypothesis that the relationship between the vascular α-adrenergic receptors and basal prostaglandin production [45] may be altered in diabetes mellitus not only in vas deferens [46], but also in coronary arteries.

However, it is not only the vascular α-adrenergic receptor in diabetes which influences the basal prostaglandin biosynthesis pathologically. The balance among the cyclo-oxygenase products must have been changed and disturbed independently of the function of α-adrenoceptors, since (1) the basal TXA_2 production by diabetic coronary arteries proves to be higher versus that of healthy vessels and (2) phentolamine does not exert an opposite influence on PGI_2 production – as was seen in the case of TXA_2 formation – in the metabolically healthy and alloxan-diabetic vascular tissues.

Phenylephrine, as an exogenous adrenergic stimulus potentiated PGI_2 production in isolated coronary rings from metabolically healthy dogs (Fig.3). With this effect the vascular α-adrenergic receptors are supposed to be specifically involved, since it could be prevented by phentolamine pretreatment. Phenylephrine does not exert a similar effect on PGI_2 formation in the diabetic coronary vessels. This phenomenon might be due: (1) to a lack of available precursors for a stimulated PGI_2 synthesis [47]; or (2) to the depression of PGI_2 formation by activation of adrenergic vascular receptors. The latter supposition is supported by the considerable increase in PGI_2 release from diabetic arteries, if the α-adrenoceptors are blocked by phentolamine (Fig.1). This hypothesis is also confirmed by the finding that phentolamine is not able to enhance the PGI_2 synthesis in the presence of adrenoceptor agonist phenylephrine in diabetes mellitus (Fig.3).

In this study, the α-adrenoceptor agonist phenylephrine was more effective in constricting the coronary vasculature of diabetic dogs than that of healthy animals (Fig.4). This finding is in line with our earlier in vivo results indicating that the conductance of the normal coronary arterial bed is increased, whilst the conductivity of diabetic coronary vessels is decreased, by sympathetic cardiac nerve stimulation [48]. Our observation is in accordance with the data of others who demonstrated similar α-adrenergic hyper-responsiveness in other regions of the diabetic vasculature [11, 49, 50]. This could be explained by diminished adrenergic ennervation [50, 51] that may result in denervation supersensitivity [52]. Furthermore, an imbalance detected among the synthesized prostaglandins is supposed to contribute to the more expressed vasoconstriction provoked by phenylephrine in the coronary arterial bed.

That imbalance, which was confirmed by the increased basal TXA_2 synthesis from diabetic arteries, might be masked under circulatory circumstances at rest when PGI_2 production is not altered. However, during adrenergic stimulation – which has no effect on PGI_2 synthesis or even depresses it – the oxygen supply due to the diminished vasodilatory capacity would be reduced, rather than increased, serving as a reliable contribution to the high incidence and severity of ischaemic heart disease in diabetes mellitus.

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