Experimental Investigations

Anaphylaxis of small arteries: putative role of nitric oxide and prostanoids

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Key words: anaphylaxis; guinea pig; endothelial relaxing factors; nitric oxide; indomethacin.

Summary. This study investigated possible implication of nitric oxide and prostanoids in anaphylactic reaction in small mesenteric and coronary arteries.

Material and methods. Isolated arteries from guinea pigs, sensitized with 0.5 mL of horse serum or sham-sensitized, were challenged with 1% of horse serum in vitro. Contractile responses of arteries (normalized diameter, 350–450 µm) were recorded by a small blood vessel wire myograph. For inhibition of the release of NO or prostanoids, vessels were pretreated with N(G)-nitro-L-arginine methyl ester (30 µM) or indomethacin (10 µM), respectively.

Results. Antigen challenge was followed by contraction of both coronary and mesenteric vessels. Two patterns of contraction were observed: 1) peak contraction – an immediate transient contraction of relatively high amplitude; this was the most common pattern; 2) biphasic: the initial peak contraction was followed by a slow growing contraction with low amplitude. Biphasic pattern was observed in 60% of the mesenteric vessels and 40% of the coronary vessels. Inhibition of NO synthase significantly increased the peak contraction in the coronary vessels and the second-phase contraction in the mesenteric vessels. Inhibition of cyclooxygenase caused a decrease in the peak and second-phase contraction of both the coronary and mesenteric vessels.

Conclusions. Despite anaphylactic contraction, nitric oxide seems to be released from the endothelium following antigen challenge in the small coronary and mesenteric arteries. This may contribute to the development of hypotension during anaphylaxis. Prostanoids are playing a different role – the contracting products of cyclooxygenase pathway are important for the development of anaphylactic contraction of the small isolated arteries.

Introduction

Anaphylactic shock is a generalized form of IgE hypersensitivity and is characterized by complex cardiovascular disorders including severe arterial hypotension. Although severe cardiovascular changes are not limited to the arterial hypotension, this state is one of the main conditions predisposing possible lethal outcome. The main possible cause of hypotension is the release of mediators of anaphylaxis, following the IgE hypersensitivity reaction. Vasoactive substances such as histamine (1–4), serotonin (5–7), and bradykinin (5, 8) are well-recognized mediators of cardiac anaphylaxis. The antigenic stimulation of sensitized tissues is associated also with the release of slow-reacting substance of anaphylaxis (SRS-A), which mainly consists of systemic vasoconstrictors leukotrienes – LTD, LTC, and LTE (9, 10) – as well as thromboxane and endothelin (11). The list of mediators is far from being completed.

Since the function of vascular endothelium was described, it became evident that vasoactive substances express their effects through the vascular endothelium. The endothelium regulates vascular tone via synthesis and release of vasodilatory substances including nitric oxide (NO) and prostacyclin (PGI₂) following the stimulation by various chemical substances or physical factors (12–15). Well-described agonists of endothelial relaxing factors are acetylcholine (12, 14), histamine in rat mesenteric arteries (16) or bradykinin in guinea pig aorta (17). Following stimulation of the receptors, endothelial NO synthase (NOS) converts L-arginine into NO (18-20); NO may produce relaxation by decreasing Ca²⁺ levels in smooth muscle cells through a cGMP-dependent pathway or through hyperpolarization due to increased conductance of K⁺ channels (21). Another relaxing
factor PGI$_2$ is produced by the action of prostacyclin synthase on endoperoxides, by the cyclooxygenase pathway (10, 22).

Since the same substances (like histamine and bradykinin) are recognized mediators of anaphylaxis on the one hand and endothelial agonists on the other hand, we hypothesize that hypotension during anaphylaxis is also related to the function of endothelium. However, the importance of endothelial factors for the responses of blood vessels during vascular anaphylaxis has not been extensively studied.

The present study was designed to examine the roles of two different endothelial relaxing factors, NO and prostacyclin, using their inhibitors in isolated small arteries from the guinea pig, the animal highly sensitive to anaphylaxis. Small arteries are attractive because of their great contribution to the regulation of blood pressure. Arteries from different vascular beds show heterogeneous mechanisms of vascular relaxation (23-25), and for this reason, we investigated arteries from different organs – coronary and mesenteric.

**Material and methods**

Male guinea pigs weighing 250–450 g were sensitized with a suspension of 0.5 mL of inactivated horse serum (HS) and 0.5 mL of complete Freund’s adjuvant or were sham-sensitized. Twenty days after sensitization animals were anesthetized with halothane inhalation and were killed by cervical dislocation followed by exsanguination, in accordance with ethical guidelines edited by the European Community (EC directive 86/609), the Council of Europe (Convention ETS 123) and approved by the Lithuanian State Food and Veterinary Service (License No. 0083).

A section of the small intestine about 10 cm below the stomach was clamped and removed with the intact mesentery for isolation of a second-order branch of the mesenteric artery. The heart was removed for dissection of a second-order branch of the left main coronary artery. All tissues were placed in chilled, preoxygenated (95% O$_2$, 5% CO$_2$) Krebs-Ringer bicarbonate solution (composition, in mM: NaCl, 139.3; KCl, 3.5; CaCl$_2$, 2.3; MgCl$_2$, 1.2; NaH$_2$PO$_4$, 2.1; NaHCO$_3$, 25; glucose, 11.1).

Coronary and mesenteric small arteries (normalized diameter, 350–450 μm) were dissected under the dissection scope (Olympus, Japan). Segments about 2 mm in length were isolated and mounted on an organ bath of a small vessel wire myograph (JP Trading, Aarhus, Denmark) between two wires for isometric force measurements. One coronary and one mesenteric vessel from a single animal were used for the experiment.

**Protocol.** After equilibration at 37°C in the oxygenated Krebs buffer solution for at least 30 min, the internal lumen diameter of the small arteries was normalized using the procedure developed previously (26, 27). Vessels were set to a normalized internal circumference $L_1=0.9L_{100}$ (where $L_{100}$ is the internal circumference of the vessel, corresponding to a transmural pressure of 100 mm Hg). The contractile capacity of each vessel segment was examined by exposure to a K$^+$-rich (80 mM) solution, which had the same composition as the Krebs-Ringer solution except that some of NaCl was exchanged for an equimolar concentration of KCl. When two reproducible contractions to high potassium solution had been achieved (variation less than 10%), the vessels were used for further studies. The endothelium-dependent relaxation of mesenteric vessels was assessed by performing a dose-response curve to acetylcholine (10$^{-9}$ to 10$^{-5}$ M) in the mesenteric arteries, precontracted with phenylephrine (30 μM). The endothelium-dependent relaxation was investigated in the mesenteric arteries only, because coronary vessels are insensitive to the precontractor phenylephrine, which was used in the present study. Anaphylactic reaction was induced in vitro by challenging the vessels with 1% of HS. Coronary arteries were challenged at the basic tension and mesenteric arteries at the basic tension and under the supramaximal precontraction, induced by phenylephrine, in order to reveal possible relaxation after antigen challenge. Only one challenge per vessel was used. To determine the role of vasoactive prostanoids in the anaphylactic response, vessels were pretreated with indomethacin (10 μM), an inhibitor of cyclooxygenase, for 20 min before the antigen challenge. To determine the role of NO in the anaphylactic response, vessels were preincubated with the nitric oxide synthase (NOS) inhibitor, N(G)-nitro-L-arginine methyl ester (L-NAME; 30 μM), for 20 min before performing the challenge.

**Chemicals.** All chemicals used in this study were obtained from Sigma Chemical Company (St. Louis, USA). Indomethacin was dissolved in distilled water in the presence of 94 mM Na$_2$CO$_3$. L-NAME and all other agents were dissolved in distilled water and diluted in Krebs-Ringer solution to the final concentration in the organ bath.

**Data analysis.** The mechanical responses of the vessels are expressed as mean ± SEM. In all groups, $n$ refers to the number of animals from which the
arteries were taken. Statistical analysis was carried out using GraphPad Prism 3.0 for PC (San Diego, California, USA). Responses of vessels in different experimental groups were compared using one-way analysis of variance (ANOVA). Statistical significance was set at \( P<0.05 \).

Results

Reaction of small arteries to antigen challenge

Antigen challenge was followed by contraction of small arteries, both mesenteric and coronary, when compared to the arteries from sham-sensitized animals (Fig. 1). The most common pattern was an immediate transient contraction (peak contraction) of relatively high amplitude (3.69±1.72 mN in the mesenteric and 3.45±1.02 mN in the coronary arteries). Another characteristic pattern of contraction was biphasic; in some arteries (60% of mesenteric, \( n=7 \), and 40% of coronary, \( n=10 \)), initial peak contraction was followed by the slow growing contraction with low amplitude of 0.05–0.2 mN (second-phase contraction).

HS challenge in the mesenteric arteries precontracted with phenylephrine was followed by contraction as well. No significant relaxations were revealed; only insignificant fall in contraction force (\( P>0.05 \)) was noticed in the precontracted mesenteric arteries before the peak contraction.

Effects of inhibition of NOS on the vascular anaphylactic reaction

The preincubation with L-NAME did not change the baseline of vascular contraction, but resulted in an altered anaphylactic contraction of both types of small arteries investigated. The inhibition of NOS led to a significant increase in peak contraction evoked by the antigen in the coronary arteries, from 3.44±1.02 mN (\( n=7 \)) to 6.46±1.11 mN (\( n=7 \)) (\( P<0.05 \)). However, a different effect was observed in the mesenteric arteries: the peak contraction was insignificantly diminished from 5.72±2.43 mN (\( n=7 \)) to 3.67±1.19 mN (\( n=7 \)) (\( P>0.05 \)) (Fig. 2). The inhibition of NO release from the endothelium revealed some effects not only on the peak contraction, but on the second-phase contraction as well. This effect was especially clearly seen in the mesenteric vessels, where the second-phase contraction was potentiated by L-NAME, leading to a significant increase in amplitude 3-6 min after the peak contraction (Fig. 3).

Effects of cyclooxygenase inhibition on vascular anaphylactic reaction

An inhibition of cyclooxygenase by indomethacin did not change the baseline of contraction, but attenuated the peak contraction induced by antigen challenge in both types of small arteries investigated. In the coronary arteries, the peak contraction was diminished more than twice from 3.78±1.07 mN (\( n=7 \)) to 1.51±0.77 mN (\( n=7 \)) (\( P>0.05 \)) (Fig. 4). In mesenteric arteries, the peak contraction was almost totally abolished from 5.72±2.43 mN (\( n=7 \)) to 0.3±0.15 mN (\( n=7 \)) (\( P<0.05 \)) (Fig. 4). The second-phase contraction was inhibited by indomethacin in both types of arteries investigated. However, contraction to K+-rich solution was not changed.
Fig. 3. The effect of nitric oxide synthase inhibition by N(G)-nitro-L-arginine methyl ester (L-NAME; 30 \( \mu \)M) on the contractile responses of isolated mesenteric arteries from the sensitized guinea pig, induced by antigen challenge

*Significant difference in contraction force, \( P<0.05 \).

Fig. 4. The effect of cyclooxygenase inhibition by indomethacin (indo; 10 \( \mu \)M) on the peak contraction of isolated mesenteric (MES) and coronary (COR) arteries of the sensitized guinea pig, induced by antigen challenge

*Significant difference in contraction force, \( P<0.05 \).

Discussion

The isolated small coronary and mesenteric arteries of sensitized guinea pig in our experiments responded to the antigen challenge by the contraction, known as the Shultz-Dale reaction in conductance arteries or veins (28, 29). Some of the vessels showed the monophasic character of contraction, some of them biphasic. The contraction was observed even in precontracted small mesenteric arteries; the precontraction of intact blood vessels is the method, usually applied for revealing the relaxing effects. However, using this method, we failed to demonstrate any relaxing effect of the antigen challenge. Low doses of HS (0.01–1 \( \mu \)g/mL) had no relaxing effect too (data not presented).

The data about relaxing effects of antigen are scanty. As shown by Akar (29), ovalbumin at low doses (0.1 \( \mu \)g/mL) caused pronounced relaxations of the precontracted pulmonary arteries of sensitized guinea pigs. The difference in results may depend on the region of blood vessels used (pulmonary vs. mesenteric and coronary) and/or the nature of antigen (ovalbumin vs. horse serum). The relaxation of isolated blood vessels during anaphylaxis seems to be hardly demonstrated consistently (28–30). Although hypotension following hypersensitivity reaction could be attributed to the relaxation of arteries, the relaxing substances may be released from sources other than blood vessels themselves. Therefore, following the literature data and our own results, we concluded that the main reaction of small isolated mesenteric and coronary arteries to the antigen is the contraction.

Despite the lack of evidence of the direct relaxation in vitro, nevertheless endothelial factors may play a marked role in development of hypotension in vivo. Therefore, we intended to study the importance of endothelial factors NO and prostacyclin by inhibiting the synthesis of nitric oxide and prostaglandin with L-NAME and indomethacin, respectively.

Our results show that the inhibition of NO release leads to an increase of anaphylactic contraction in the mesenteric and coronary vessels, but in different phases: during the peak contraction in the coronary vessels and during the second-phase in the mesenteric vessels. The increase in contraction force during the anaphylactic reaction after NO inhibition suggests that the endogenous NO from the endothelium is stimulated by the antigen challenge. The release of NO acts against the contraction of arteries and could take part in the relaxation leading to hypotension in vivo. The immediate NO release, as it was observed in the coronary vessels, may contribute to the rapid development of hypotension. On the other hand, the prolonged release of NO in the mesenteric vessels could cause a dangerous redistribution of blood leading to a decreased perfusion of organs, extremely important for survival (e.g. brain and myocardium).

Our data are consistent with the data of other studies showing the release of endogenous NO during the anaphylaxis in the isolated pulmonary artery (29, 31), coronary arteries of the isolated heart (32–34), or veins of the isolated liver of the guinean pig (35). The long-lasting release of NO was shown in the
isolated heart of the guinea pig (34), the effect similar to our results in the isolated mesenteric vessels (see Fig. 3).

The inhibition of prostaglandin production, according to our results, leads to a decrease of the anaphylactic contraction in the coronary vessels and to almost complete disappearance of the contraction in the mesenteric vessels. An inhibitor of cyclooxygenase, indomethacin, has an obvious influence on the reaction of isolated small arteries to the antigen challenge. However, this effect of indomethacin could not be attributed to the inhibition of relaxing effect of PGI2, the main relaxing prostaglandin produced by the endothelium. An inhibition of the prostaglandin release would lead to an increased contraction of blood vessels. The suppressed contraction to the antigen could be explained in different ways. One possibility is that indomethacin may inhibit the degranulation of mast cells, but a substantial decrease of the histamine and serotonin release from rat peritoneal mast cells was observed only using the drug at a concentration of 1 mM, and it was not affected by lower concentrations (36). The concentration used in our experiments (10 µM) seems to be ineffective for suppression of the mast cell degranulation. Another possible explanation could be the direct effect of indomethacin on the contractility of arteries, but this should be excluded because the drug did not affect the contraction to K+-rich solution. The most probable explanation of our results may be that indomethacin inhibits not only the release of prostacyclin from the endothelium, but also the release of other contracting cyclooxygenase products induced by the antigen challenge.

The inhibition of prostacyclin release from the endothelium by indomethacin is of limited use for the studies of anaphylaxis, because relaxing effects of prostacyclin are covered by the action of the contracting cyclooxygenase products. This hypothesis is supported by the demonstration of the release of contracting prostaglandins PGF1 and TXB2 from the isolated heart (37) and PGF2α from the lung (38) of the guinea pig during anaphylaxis. Similar effects of indomethacin were obtained in dogs in vivo, where the anaphylactic coronary contraction was considerably diminished (39). These results may supplement the classical point of view that the main mediators of anaphylaxis eliciting the peak contraction to the antigen are histamine or/and serotonin (4, 8). The interactions between their effects and the effects of cyclooxygenase products may be complicated, and unfortunately, there is almost no clear evidence of these interactions. Release of histamine is hardly affected by indomethacin (40). Thus, the mechanism by which indomethacin inhibits anaphylactic contraction in the small mesenteric and coronary arteries remains unclear and requires further investigations.

Conclusions

According to our results, antigen challenge in the small isolated mesenteric and coronary arteries from the sensitized guinea pig is followed by anaphylactic contraction but not relaxation. However, the relaxing factor NO is released from the endothelium of small arteries during the antigen challenge, and it may contribute to the development of hypotension or redistribution of blood during anaphylaxis. Prostanoids play a different role: the contracting products of cyclooxygenase pathway are very important for the development of the small artery constriction in anaphylaxis and counteract the development of the relaxation and hypotension. In conclusion, arterial contraction induced by anaphylaxis could be partially attenuated by the endothelium-derived NO and enhanced by the cyclooxygenase products in the small coronary and mesenteric arteries.

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Smulkijų arterijų anafilaksija: galima azoto monoksido ir prostanoidų įtaka

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Raktažodžiai: anafilaksija, jūrų kiaulytės, endotelio išskiriami atpalaiduojantys veiksniai, azoto monoksidas, indometacinas.

Santrauka. Tirta azoto monoksido ir prostanoidų galima įtaka smulkijų pasaito bei vainikinių arterijų anafilaksinei reakcijai.

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Tyrimo meto. Tyrimams naudotos sensibilizuotųjų ir kontroliniųjų kraują abų in vitro reakcijai, yra nustatytas smulkiosios pasiunų ir vainikių arterijų atsiverimas. Smulkiosios pasiunų arterijų atsiverimui išsiskyrė tik šių dujų: arba vienfazė esąs baisas, arba dvifazė, kai po šios fazės atsiranda lėtai augantis žemos amplitudės (0.5–1.5 mN) susitraukimai. Dvifazė susitraukimo būdas registruodavosi 60 proc. pasiunų ir 40 proc. vainikių arterijų. NO sintezės Slopinimas reiškė geriausias atsaką (p<0.05) vainikių arterijų maksimalų susitraukimų bei pasiunų arterijų antrosios faze susitraukimai (p>0.05). Cikloksigenazės Slopinimas sumažino maksimalų bei antrosios faze susitraukimų abiejų tipų kaują kaują ir darė didesnį ir didesnį susitraukimą.

Išvados. Nepaisant smulkiių vainikių ir pasiunų arterijų susitraukimo anafilaksijos metu, jų endotelis išskiria azoto monoksidą, kuris gali turėti įtakos hipotenzijai. Prostanoidų vaidmuo kitoks – jie daugiausia nulemia anafilaksijų izoliotų smulkiių arterijų susitraukimą.

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