Low-Dose Aspirin Inhibits Platelet-Induced Contraction of the Human Isolated Coronary Artery
A Role for Additional 5-Hydroxytryptamine Receptor Antagonism Against Coronary Vasospasm?

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Background The beneficial effect of low-dose aspirin in the prevention of coronary vasospasm is well documented. In this study, we investigated the contractile effect of human washed platelets on the human isolated coronary artery. We concentrated on the effect of low-dose aspirin (40 mg/d) taken by the platelet donor and on the efficacy of thromboxane A2 (TXA2) and 5-hydroxytryptamine (5-HT) receptor antagonists.

Methods and Results Human coronary artery segments were suspended in an organ bath set-up for isometric tension measurement. Platelets (10⁹ to 3 x 10¹⁰/L) elicited concentration-dependent contractile responses of the coronary artery segments, reaching 28.4±7.1% of contractions induced by 100 mmol/L K⁺. The contractile response tended to be decreased in vessel segments with histological signs of early atherosclerosis. Contraction was significantly attenuated after pretreatment of the vessel segments with ketanserin (5-HT1 receptor antagonist, 1 μmol/L) or SQ30741 (TXA2 receptor antagonist, 0.01 μmol/L), reaching 8.8±2.3% and 3.2±2.2% of contraction to 100 mmol/L K⁺, respectively. Platelets obtained from the same platelet donors after they had taken aspirin (40 mg/d for 7 to 13 days) caused significantly lower contractile responses (7.6±2.7% of 100 mmol/L K⁺) associated with an almost selective inhibition of the synthesis of thromboxane measured in the organ bath solution (untreated platelets, 2.19±0.43 nmol/L; aspirin-treated platelets, 0.66±0.05 nmol/L). The amount of 5-HT secreted in the organ bath remained unaltered (65.17±9.94 and 64.03±8.98 nmol/L, respectively). This explains why ketanserin significantly attenuated the residual contractile responses caused by platelets obtained from aspirin-treated subjects, whereas SQ30741 caused minor, nonsignificant additional attenuation.

Conclusions The results of the present study therefore suggest that additional antagonism of the contractile 5-HT receptors in the coronary artery may increase the efficacy of low-dose aspirin in vivo. (Circulation. 1994;89:623-629.)

Key Words • 5-hydroxytryptamine • thromboxane • aspirin

Aspirin has been shown extensively to be effective in the prevention of a number of cardiovascular diseases. A daily dose of 325 mg reduced the risk of myocardial infarction by 44%. Even a much lower dose, 20 to 40 mg, caused complete inhibition of the synthesis of thromboxane A2 (TXA2), which, together with 5-hydroxytryptamine (5-HT, serotonin), forms the major vasoconstrictor products involved in platelet-induced vasoconstriction. This same dose of aspirin (20 to 40 mg daily) hardly affected the endothelial production of prostacyclin (PGI₂), which has antiaggregatory and vasorelaxant effects. Guided by the latter observations, clinical investigators have focused their attention on low doses of aspirin. Thus, 75 mg aspirin daily resulted in a significant (60%) reduction of the risk of myocardial infarction and subsequent death in silent as well as in symptomatic ischemia. An even lower dose of aspirin, 30 mg, was found to be equally effective in the prevention of vascular events and had fewer adverse effects than a 283-mg dose in patients with a transient ischemic attack or minor stroke. Damage of the endothelial lining of the vascular wall is thought to incite platelet adhesion to the exposed subendothelial collagen, with the subsequent release of platelet products. Experimentally induced atherosclerosis in monkeys was found to alter the response to important platelet products like 5-HT, ADP, and TXA2 in a direction that would favor vasoconstriction when these products are released from aggregating platelets. Indeed, elevated levels of both 5-HT and thromboxane B2 (TXB2), the stable metabolite of TXA2, have been observed in patients with coronary artery lesions and angiina.

In the present experiments, we investigated the effect of low-dose aspirin, taken by the platelet donors, on platelet-induced contractions of the human isolated coronary artery. We concentrated on the relative importance of cyclooxygenase products and 5-HT, before and after aspirin treatment. We attempted to relate the

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contractile responses to the organ bath concentration of various vasoactive compounds that are believed to be involved in the generation and prevention of coronary vasospasm. Last, we microscopically examined sections of the vessel segments and tried to correlate early signs of atherosclerosis to functional responses.

Methods

Preparation of Tissue

Right epicardial coronary arteries were obtained from 10 organ donors with beating hearts who had died of noncardiac disorders less than 24 hours before the tissue was taken to the laboratory (3 cerebrovascular accident, 3 polytrauma, 4 cerebral hypoxia; 8 male, 2 female; age, 7 to 48 years). The hearts were provided by the Rotterdam Heart Valve Bank (Bio Implant Services/Eurotransplant Foundation) after removal of the aortic and pulmonary valves for valve transplantation. The study was approved by the Ethical Committee of the University Hospital Rotterdam “Dijkzigt.” The hearts were stored at 0°C to 4°C in a sterile organ-protecting solution immediately after circulatory arrest. After arrival in the laboratory, the right coronary artery was removed and placed in a cold, oxygenated Krebs bicarbonate solution of the following composition (in mmol/L): NaCl 118, KCl 4.7, CaCl2 2.5, MgSO4 1.2, KHP04 1.2, NaHCO3 25, and glucose 8.3; pH 7.4. Vessels were cut into rings approximately 4 mm long, suspended on stainless steel hooks in 8-mL organ baths containing the Krebs bicarbonate solution, aerated with 95% O2/5% CO2, and maintained at 37°C. Vessel segments containing distinct, macroscopically visible atherosclerotic lesions were not used.

Experimental Protocol

The segments were allowed to equilibrate for at least 30 minutes and were washed every 15 minutes. Changes in tension were recorded with a Harvard isometric transducer. Preparations were stretched to a pre-tension of 2 g. The tissue was exposed to potassium (30 mmol/L) twice. Subsequently, the functional integrity of the endothelium was verified as relaxation to substance P (1 nmol/L) after preconstriction to prostaglandin F2α (PGF2α, 1 µmol/L). One segment did not relax to substance P and was discarded from the experiments. After washout, the tissue was exposed to 100 mmol/L potassium to determine the maximal contractile response. The tissue was then allowed to equilibrate for 30 minutes. A cumulative concentration-response curve was obtained after another 30-minute period. During this period, some segments remained untreated (controls), whereas others were incubated in parallel with a receptor antagonist. In some cases, control curves were obtained in duplicate or triplicate, which were averaged and regarded as one curve in further analysis. The contractile response was expressed as a percentage of contraction induced by 100 mmol/L potassium.

Isolation of Platelets

Approximately 23 mL of blood was obtained from each of six healthy male donors (age, 26 to 52 years) who had not taken antiplatelet drugs for at least 14 days before the experiment. Platelets were isolated essentially according to Yang et al.1 In brief, blood was centrifuged for 40 minutes at 55g and 20°C, after which the platelet-rich plasma was pipetted off and an equal volume of citrate anticoagulant solution (in mmol/L: KCl 3, glucose 105, sodium citrate 93, citric acid 7; pH 6.5) was added. Centrifugation for 20 minutes at 570g and 20°C resulted in a platelet pellet, which was resuspended in 2.5 mL of the citrate solution. The platelet concentration in the suspension obtained was determined with a platelet analyzer (Hematology Series 810, Baker Instruments, Allentown, Pa). The suspension was added in a cumulative manner to the organ baths in appropriate volumes to result in bath concentrations of 10/ to 3×10/6 platelets/L. Since the platelets were readily activated after they were added to the organ bath, resulting in platelet product release and consequential functional responses, we did not further regulate or induce the state of platelet activation. Care was taken to minimize the time during which the platelets had to be kept before they were added (<35 minutes). After the first experiment, the platelet donors were treated with aspirin (acetylsalicylic acid, Pharmachemie bv, Haarlem, The Netherlands) 40 mg/d, once daily, at regular intervals until human coronary tissue was again available for experimentation. This period varied between 7 and 13 days. Then, another 23 mL of blood was drawn from the platelet donor, and the experiment was repeated as described above.

Determination of the Concentration of Eicosanoids and 5-HT

Thirty minutes after the highest concentration of platelets was added, a 1.8-mL sample was drawn from the organ bath in a polypropylene tube, and indomethacin (30 µmol/L) was added to stop cyclooxygenase activity. The samples were centrifuged at 570g for 20 minutes. The solution above the pellet was pipetted off and stored at −80°C until assay. The following eicosanoids were determined in this organ bath sample: TXB2, PGE2, and 6-keto-PGF1α (stable metabolite of PGI2). Twenty-microliter (TXB2) and 100-µL (PGE2 and 6-keto-PGF1α) portions of the organ bath solution were used for radiomunomassay.14 Tritiated compounds were purchased from Amersham (UK), standards from Sigma Chemical Co (St Louis, Mo), and antiseria from Advanced Magnetics Inc. The lower detection limits of the TXB2, PGE2, and 6-keto-PGF1α assays were 1.25, 2.5, and 5 pg per tube, respectively. Radioactivity was determined by counting scintillation with a Packard 1500 Tricarb. Calculations were performed with additional software using spline functions.

5-HT was determined by high-performance liquid chromatography (HPLC) with electrochemical detection. Organ bath solution (400 µL) was mixed with an equal amount of mobile phase, and 20-µL samples were injected onto a reversed-phase column (Bio-Sil C18 A/B, 5 µm, 150×4.6 mm, Bio-Rad Laboratories, Brussels, Belgium). The mobile phase consisted of 75 mmol/L sodium acetate, 0.27 mmol/L disodium EDTA, 2.13 mmol/L heptane sulfonic acid, and 20% methanol, pH 4.15 (flow rate, 0.8 mL/min; column temperature, 40°C). The detection system consisted of a model 5100A Coulomboc detector equipped with a 5021 conditioning cell and a 5011 high-sensitivity cell (ESA, Bedford, Mass). Potentials for the conditioning cell and detectors 1 and 2 were −0.20, +0.08, and +0.45 V, respectively (gain, 30×100). Quantification was done by measuring peak heights. The lower detection limit for 5-HT was estimated at 5 mmol/L. In samples in which the eicosanoids or 5-HT could not be detected, the concentration was assumed to equal the lower detection limit concentration.

Histological Examination

Thirteen coronary artery segments obtained from six hearts, which were used for a control concentration-response curve by untreated platelets, were analyzed histologically to correlate the functional results to signs of early atherosclerosis. After the organ bath experiment, the vessel segments were fixed in 10% formalin and stained with hematoxylin-eosin and elastic Van Gieson stains. Sections were examined microscopically, and signs of atherosclerosis were scored in two independent sessions in a semiquantitative fashion, modified from Ginsburg et al.15 In brief, three vessel characteristics were scored: degree of luminal occlusion, fragmentation of the internal elastic lamina, and intimal hyperproliferation. Each category was scored on a scale from 1 to 3, with 1 being completely healthy and 3 being severely diseased. Thus, the mean coronary artery disease scale (CADS) was calculated for each vessel segment and correlated to functional parameters.
Analysis of Data

All data are presented as mean±SEM. ANOVA for multiple comparisons (Duncan) followed by a Student’s t test, for paired data where appropriate, was used for comparison of mean contractile responses and organ bath concentrations. A correlation coefficient, r, was calculated according to Pearson. A value of P<.05 was assumed to denote a significant difference.

Compounds Used in the Study

The following compounds were used during the organ bath experiments: ketanserin tartrate (gift from Janssen Pharmaceutica, Beerse, Belgium); PGF$_{2\alpha}$ (Tris salt) and substance P acetate (Sigma); and SQ30741 (1S-[1>2,2<Z,3<,4<]-7-[4-[4]-[1-oxoheptyl]amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid) (gift from Bristol-Myers Squibb, Princeton, NJ). All compounds were dissolved in distilled water except SQ30741, which was dissolved in ethanol.

Results

Responses of Coronary Artery Segments

Mean relaxation to substance P was 74±8% of pre-contracture to PGF$_{2\alpha}$ (1 μmol/L), which is in accordance with previous studies on human coronary arteries obtained from heart transplant recipients.8 Potassium (100 mmol/L) caused a mean contractile response of 55.5±7.6 mN. No difference in the mean contractile response to potassium (100 mmol/L) was observed in any of the groups compared.

Platelets contracted the vessel segments in a concentration-dependent manner. No contractile or relaxant response was elicited by the citrate buffer itself in which the platelets were suspended (data not shown). At the highest platelet concentration tested, the concentration-response curve had not reached the maximum response (Fig 1). Since one is restricted by the amount of blood that can be drawn from platelet donors, higher platelet concentrations were not used. The maximal response at 3×10$^9$ platelets/L reached 28.4±7.1% of the response to potassium (100 mmol/L). Both ketanserin (1 μmol/L, a 5-HT$_2$ receptor antagonist) and SQ30741 (0.01 μmol/L, a TXA$_2$ receptor antagonist) reduced (P<.05) the maximal response to platelets, to 8.8±2.3% and 3.2±2.2% of potassium-induced responses, respectively. A combination of these two compounds practically abolished the contractile response and even caused platelets to evoke small relaxations in some vessel segments (relaxation, 0.9±1.9% of potassium-induced responses; Fig 1).

During the period in which the platelet donors took aspirin (range, 7 to 13 days), no adverse effects were observed. The contractile response to platelets obtained after aspirin treatment was significantly decreased, reaching a maximum of only 7.6±2.7% of potassium-induced contraction (Fig 2). Although SQ30741 (0.01 μmol/L) was more potent than ketanserin (1 μmol/L) against untreated platelets (Fig 1), ketanserin appeared to be more potent than SQ30741 against platelets from aspirin-treated platelet donors. As depicted in Fig 3, SQ30741 (0.01 μmol/L) no longer significantly reduced the residual contractile responses. Contractions to aspirin-treated platelets, however, were significantly attenuated by ketanserin (1 μmol/L) (contraction, 0.9±1.9% of potassium-induced contraction). Pretreatment with a combination of ketanserin and SQ30741 now caused a clear concentration-dependent platelet-induced relaxation of the coronary artery segments (−5.0±1.8% of the potassium-induced contractile effect; Fig 3).

Concentrations of Eicosanoids and 5-HT in the Organ Bath Solution

The concentrations of eicosanoids (TXB$_2$, PGE$_3$, 6-keto-PGF$_{1\alpha}$) and 5-HT in the organ bath solution are

![Graph showing contraction of the human isolated coronary artery to activated platelets. The symbol ○ indicates control concentration-response curve; △, curve in the presence of ketanserin (1 μmol/L); ○, curve in the presence of SQ30741 (0.01 μmol/L); and ◊, curve in the presence of the combination of ketanserin (1 μmol/L) and SQ30741 (0.01 μmol/L); n=6 each. Contractions are expressed as a percentage of contraction induced by 100 mmol/L potassium. *P<.05 vs control response; #P<.05 vs control response and also vs the response to platelets in the presence of ketanserin alone. At a concentration of 10$^{-9}$ platelets/L, the response to platelets in the presence of SQ30741 alone was found to be significantly different (*P<.05) from the control curve, whereas the contractile response to platelets in the presence of the combination of ketanserin and SQ30741 was significantly different (#P<.05) both from the control response and from the response in the presence of ketanserin alone. When no error bar is visible, error falls within the limits of the symbol.](http://circ.ahajournals.org/doi/fig/10.1161/01.ATH.88.5.625/C电路/发/图1)
shown in the Table. When citrate buffer without platelets was added to the organ bath, no PGE₂, 6-keto-PGF₁α, or 5-HT could be measured at levels significantly different from the lower detection limits (Table, section A). The concentration of TXB₂ in these organ baths, however, was significantly higher than the lower detection limit. After addition of 3×10⁻⁷ non–aspirin-treated platelets/L (Table, section B), a significant increase of TXB₂, PGE₂, and 5-HT was measured. The concentration of 6-keto-PGF₁α increased from below the lower detection limit to 0.29±0.08 nmol/L. Ketanserin or SQ30741 did not influence the amount of TXB₂, PGE₂, 6-keto-PGF₁α, or 5-HT in the organ baths. Platelets obtained from aspirin-treated platelet donors (Table, section C) secreted significantly smaller amounts of TXA₂ in the organ baths, as measured by the concentration of TXB₂. The amount of PGE₂, 6-keto-PGF₁α, or 5-HT in the organ bath was not significantly affected by the treatment with aspirin.

### Histology and Functional Parameters

Histological examination of the control vessel segments used for experiments with untreated platelets revealed early signs of atherosclerosis: modest intimal hyperplasia, internal elastic lamina fragmentation, and luminal occlusion. The mean CADS varied from 1.15 in a vessel segment obtained from a 7-year-old tissue donor to 2.00 in a segment obtained from a 47-year-old tissue donor. The CADS correlated positively with age (r=0.84, P=0.000) but negatively with the percentage of relaxation to substance P (1 nmol/L) after precontraction with PGE₂ (1 µmol/L) (r=−0.67, P=0.006). The CADS also correlated negatively with the contractile response to untreated platelets (3×10⁴/L), both when expressed as a percentage of potassium (100 mmol/L)–induced contractions (r=−0.60, P=0.01) and when expressed as contractions in mN (r=−0.63, P=0.01).

### Discussion

In the present study, we showed that both a TXA₂ receptor antagonist and a 5-HT₁ receptor antagonist or low-dose aspirin, taken by the platelet donors, can attenuate platelet-induced contractions of human isolated coronary arteries. A 5-HT₁ receptor antagonist caused a significant further reduction of the residual contractile response caused by aspirin-treated platelets. A TXA₂ receptor antagonist caused only minor, nonsig-
significant further attenuation of contractions induced by the aspirin-treated platelets.

**Effect of a TXA₂ Receptor Antagonist**

Platelets have been described to contract human isolated blood vessels by releasing 5-HT and TXA₂, whereas platelet-derived ADP caused both the human coronary artery and the internal mammary artery to relax via the induction of endothelium-derived relaxing factor (nitric oxide, NO). The thromboxane synthase inhibitor decymegrel, however, only slightly enhanced platelet-induced relaxations of the precontracted (PGF₂α) human coronary artery. The blockade of thromboxane synthase by decymegrel resulted in an increased synthesis by platelets of both PGF₂α and PGE₂, which were found to take over a part of the contractile effect of TXA₂. This seemed to be a major limitation to the clinical efficacy of thromboxane synthase inhibitors. More potent antagonism of platelet-induced contractions was achieved with the TXA₂ receptor antagonist SQ30741, which, in a concentration of 0.01 μmol/L, caused marked inhibition of platelet-induced contraction of the human internal mammary artery and the human saphenous vein. The present experiments show this to be valid also for the effect of untreated platelets on the human isolated coronary artery (Fig 1). Although another TXA₂ receptor antagonist (GR32191B) has been shown to be ineffective in the prevention of coronary restenosis after percutaneous transluminal coronary angioplasty, inhibition of the TXA₂ receptors may still have clinical utility in the prevention of coronary vasospasm, since they undoubtfully have potent receptor antagonist activity and do not affect the production of PG₁₂ and PGE₂. On the other hand, high concentrations of TXA₂, which may be present close to the vascular smooth muscle cell, could displace a competitive TXA₂ receptor antagonist, limiting the potential clinical efficacy of this new class of antiplatelet drugs.

**Effect of 5-HT Receptor Antagonism**

Ketanserin (1 μmol/L), a 5-HT₁ receptor antagonist, caused significant attenuation of platelet-induced contractions, indicating that the 5-HT₁ receptor plays an important role in the contractile response, as was found previously for both the human isolated internal mammary artery and the saphenous vein. The contractile response to exogenous 5-HT is mediated by a mixed population of 5-HT₁a-like and 5-HT₁c receptors, but predominant mediation by 5-HT₁c receptors has been reported. It is quite likely, however, that the 5-HT₁a-like receptor also plays a significant role. First, ketanserin alone was not found to be effective in the prevention of vasospastic angina. Second, one may expect that 5-HT in low concentrations (<1 μmol/L) activates especially 5-HT₁a-like receptors, since it has significantly higher affinity for the different 5-HT₁ receptor subtypes than for the 5-HT₁c receptor. Indeed, several authors have suggested that a mixed 5-HT₁a-like/5-HT₁c receptor antagonist may be more effective in the treatment of coronary vasospasm.

**Effect of Low-Dose Aspirin**

The mechanism by which aspirin decreases morbidity and mortality from cardiovascular disease is believed to be a generalized inhibition of production of contractile cyclooxygenase products, such as PGH₂, TXA₂, and PGE₂. This process can be counteracted by a concurrent aspirin-induced decrease of the production of vasorelaxant and antiaggregatory PG₁₂. The present experiments show that the systemic use of low-dose aspirin results in a relatively selective decrease of TXA₂ production. The production of PGE₂ was left almost unaltered (Table). Although the vessel segments in our study had not been exposed to aspirin, this same dose has previously been shown to preserve prostacyclin production in humans in vivo. 6-Keto-PGF₁α could only be detected after addition of platelets to the organ bath, indicating a presumably endothelial response to platelets or platelet products and the absence of a basal prostacyclin production in vitro. TXB₂ was detected in the organ bath even when no platelets had been added, indicating basal vascular production of TXA₂, although TXA₂ derived from leftover tissue-donor platelets cannot be entirely excluded. The concentration of 5-HT was left unchanged by the treatment with low-dose aspirin. Apart from HPLC measurements, this could also be reasoned from the fact that ketanserin was still significantly active as an antagonist after treatment of the platelets with aspirin (Fig 3), whereas SQ30741 caused only minor, nonsignificant additional attenuation of the residual contractile response. This was presumably a result of a decrease of the TXA₂-induced part of the platelet-induced contractile response caused by treatment with aspirin.

**Correlation of Histology and Functional Parameters**

Despite the fact that the coronary arteries were obtained from relatively young, apparently healthy organ donors, most vessel segments showed modest, age-related signs of atherosclerosis: intimal hyperplasia, internal elastic lamina fragmentation, and luminal occlusion. It must be kept in mind, however, that we avoided the use of vascular segments with distinct, macroscopically visible, atherosclerotic lesions. This analysis therefore refers only to early atherosclerotic development. The present CADS appears to be in line with Ginsburg et al., who found that CADS in coronary arteries ranged from 1.5 to 10 years of age up to 2.2 between 40 and 50 years of age. We observed that relaxation to substance P was inversely correlated with the development of early atherosclerosis, confirming earlier reports concluding that atherosclerosis reduces the endothelium-dependent, NO-mediated, relaxant response to substance P in the human isolated coronary artery.

In contrast to some animal models, we observed a tendency toward a decreased platelet-induced contractile response in mildly diseased vessel segments. In the present setup, both the luminal and serosal sides were exposed to the platelet products. Kaul and coworkers studied a perfusion model in which platelets were added on either the luminal or the serosal side. Indeed, only intraluminal, and not abluminal, activation of platelets resulted in different responses of atherosclerotic and normal perfused arteries. It would therefore be of great interest to develop a similar model for the human isolated coronary artery. Furthermore, it must be noted that different platelet-stimulating agonists may induce
the release of a somewhat different spectrum of platelet products. In this model, as well as in previously adopted models, platelets are apparently activated on exposure to tissue collagen and Ca\(^{2+}\) in the Krebs solution. Thus, despite the human nature of both platelets and coronary arteries and in vivo application of low-dose aspirin, care must be taken when extrapolating results obtained in vitro to the in vivo situation.

**Interactions Between Platelet Products**

5-HT and TXA\(_2\) are known to take part in an amplifying interaction at the vascular smooth muscle level. Therefore, it seems rational not only to counteract the contractile effects of both TXA\(_2\) and 5-HT per se but also to interfere with the amplifying interaction. Interestingly, the presence of the stable TXA\(_2\) mimetic U46619 increased the response mediated by 5-HT\(_1\)-like receptors but not by 5-HT\(_2\) receptors, emphasizing also in this respect the potentially beneficial effect of a mixed 5-HT\(_1\)-like/5-HT\(_2\) receptor antagonist compared with a selective 5-HT\(_2\) receptor antagonist like ketanserin.

Whether the effect of TXA\(_2\) in vivo could be counteracted more effectively by a thromboxane synthase inhibitor, TXA\(_2\) receptor antagonists, or a combined synthase inhibitor/receptor antagonist than by low-dose aspirin still remains to be shown, since low-dose aspirin is clinically very effective at low cost. In conclusion, the present study shows that additional antagonism of the coronary artery contractile 5-HT receptors may increase the efficacy of low-dose aspirin in vivo.

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