Aspirin modifies nitric oxide synthase activity in platelets: effects of acute versus chronic aspirin treatment

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Abstract

Objective: We examined the effects of aspirin on basal and β-adrenoceptor (β-AR)-mediated nitric oxide synthase (NOS) activity in normal platelets. Methods: NOS activity was determined from the conversion of L-[¹H]arginine to L-[¹H]citrulline, both basally and following β-AR stimulation, in platelets from healthy human subjects following both short- and long-term aspirin administration. Results: Basal L-[¹H]citrulline increased following aspirin 800 mg administered intravenously in vivo, from 0.31±0.12 to 0.76±0.14 pmol/10⁸ platelets (P<0.01). Isoproterenol at 1 μmol/l increased platelet NOS activity before but not following intravenous aspirin. After short-term in vitro treatment with aspirin 10 μmol/l, 400 μmol/l or 4 mmol/l, basal platelet L-[¹H]citrulline increased similarly, an effect not seen with indomethacin 100 μmol/l or ibuprofen 10 μmol/l. Platelet NOS activity was not increased by albuterol 1 μmol/l, in the presence of indomethacin, ibuprofen or aspirin in vitro. By contrast, oral aspirin 75 mg daily for 14 days did not affect basal platelet NOS activity, but abolished β-adrenergic NOS activation. Conclusions: Aspirin activates basal platelet NOS acutely, but not chronically, through a mechanism independent of cyclooxygenase (COX) inhibition. By contrast, both short- and long-term aspirin treatment inhibit platelet β-adrenergic NOS activation by a COX-dependent mechanism. This indicates that aspirin exerts divergent effects on basal and β-AR-stimulated platelet NOS activity, which are likely to be of clinical relevance.

Keywords: Adrenergic; Anticoagulants; Nitric oxide; Platelets; Vasoactive agents

1. Introduction

Human platelets synthesise nitric oxide (NO) through the action of the enzyme nitric oxide synthase (NOS), which catalyses the oxidation of the terminal guanidino nitrogen atom of L-arginine to form L-citrulline [1]. Two of the three known isoforms of NOS are found in platelets: endothelial (eNOS, NOS3) and inducible (iNOS, NOS2) types [2,3], with NOS 3 being predominant. NO has important antithrombotic properties including inhibition of platelet aggregation [3] and of platelet adhesion to vascular endothelium [4] through activation of soluble guanylyl cyclase and consequent elevation in cGMP. Platelet-derived NO may also play an important role in regulation of both platelet recruitment and platelet aggregation after a pro-aggregatory stimulus [5].

β-Adrenoceptors (β-AR) are present on human platelets and have been characterised to be of the β₂-subtype as determined by radioligand binding [6,7]. They are coupled to adenylyl cyclase and, when activated, cause an increase in intracellular cAMP concentration leading to inhibition of platelet aggregation [8]. We have recently demonstrated a link between β-AR and NOS activity in human platelets [9]. β₂-AR stimulation activates NOS through cAMP
elevation, and this action is responsible for mediating inhibition of platelet adhesion to vascular endothelium in response to $\beta_2$-adrenergic activation.

In addition to NOS, platelets express cyclooxygenase type 1 (COX-1), which catalyses the conversion of arachidonic acid to thromboxane $A_2$ and other eicosanoids. Thromboxane $A_2$ is a potent stimulus for platelet aggregation and a potent vasoconstrictor, in contrast to prostacyclin (an endothelium-derived eicosanoid), which opposes these effects by inhibiting platelet aggregation and acting as a vasodilator.

In disease states, the equilibrium between the detrimental effects of thromboxane $A_2$ and the beneficial effects of prostacyclin on the cardiovascular system may be disturbed. Impaired endothelium-dependent inhibition of platelet aggregation occurs in patients with atherosclerotic disease [10], and reduced basal platelet NO production has been found in patients with acute coronary syndrome [11]. The anti-platelet agent aspirin has become widely used clinically in view of its demonstrated mortality and morbidity benefits in patients with acute myocardial infarction [12], acute coronary syndrome [13], acute cerebrovascular events [14] and following coronary artery bypass graft surgery [15]. These effects are largely ascribed to the ability of aspirin to acetylate irreversibly the serine 529 residue in COX-1 preventing the formation of thromboxane $A_2$ [16]. However, COX inhibition may decrease NO activity in healthy human platelets [17], and aspirin has been shown to inhibit NOS 2 expression in the infarcted rabbit heart [18]. By contrast, other workers have reported that aspirin can increase NO generation from leucocytes, and can increase nitrite/nitrate concentration (an index of whole body NO generation) in the plasma [19].

In view of the close relationship between the NOS and COX systems, the conflicting evidence regarding the effects of aspirin on the NO system, the widespread use of aspirin in the treatment of cardiovascular disease and the importance of platelet NO production in the regulation of platelet function, the aim of the present study was to explore further the effects of aspirin on the L-arginine/NO pathway in healthy human platelets both under basal and stimulated conditions. In the treatment of patients with cardiovascular disease, low doses of aspirin (up to 325 mg daily) are used; at such doses, the systemic vascular endothelium undergoes minimal exposure to aspirin due to its extensive pre-systemic hepatic metabolism, whereas platelets in the portal circulation undergo much greater exposure. We investigated the effects both of high-dose intravenous aspirin in vivo and of low- and high-concentration aspirin in vitro, in platelets. We also examined the effects of chronic oral low-dose aspirin on platelet NOS activity. In our studies, we used $\beta$-AR agonists as stimulators of the L-arginine/NO system, since we have previously demonstrated that $\beta_2$-AR activate NOS to an important degree in platelets, an effect which gives rise to inhibition of platelet adhesion to vascular endothelial cells [9].

2. Methods

2.1. Subjects

Studies were performed on healthy normotensive subjects who gave written informed consent. All subjects took no medications (and, in particular, had taken no anti-platelet agents for at least 14 days prior to study), were aged 24–60 years, and underwent a complete history and laboratory tests to exclude diabetes, renal, hepatic and hematological disease. Blood samplings for all experiments were performed after breakfast, between 09:00 and 11:00 h. The investigation conformed with the principles outlined in the Declaration of Helsinki (Cardiovasc Res 1997;35:2–3), and all experiments were approved by the St. Thomas’ Hospital Local Research Ethics Committee.

2.2. Study 1: effect of acute high-dose aspirin administration on basal and $\beta$-AR-stimulated NOS activity in platelets

Eight healthy male subjects took part in this study. Subject characteristics are detailed in Table 1. Platelets were isolated from 60 ml of venous blood, counted and used for measurement of both basal and $\beta$-AR stimulated NOS activity. Platelet aliquots (1 ml) were incubated with 1.0 $\mu$Ci $l$-[3H]arginine in the absence or presence of 100 $\mu$mol/l $\text{N}^\text{G}$-monomethyl-$l$-arginine (L-NMMA, a NOS

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<td>Number and sex</td>
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inhibitor) for 15 min at 37 °C. Isoproterenol 1 μmol/l (a non-selective β-AR agonist) or vehicle was then added for a further 25 min at 37 °C. After terminating the reaction, 1-[^3]H]citrulline was measured as detailed below. Aspirin (800 mg) dissolved in 20 ml of sterile saline was then administered at a rate of 1.5 ml/min via an intravenous cannula, which had been inserted at the start of the study. A further venous blood sample (60 ml) was drawn 1 h after aspirin administration, platelets were isolated and the platelet NOS activity experiments repeated as before.

2.3. Study 2: effect of aspirin on basal and β-AR-stimulated NOS activity in platelets in vitro

Eleven healthy male and 10 healthy female subjects participated in this study (Table 1). Platelets were isolated from 100 ml of venous blood, counted and used for measurement of both basal and β-AR stimulated NOS activity. Platelet aliquots (1 ml) were first incubated with either aspirin 10 μmol/l, aspirin 400 μmol/l, aspirin 4 mmol/l, indomethacin 100 μmol/l (stock solution made up at 10 mmol/l in DMSO, and diluted 1:100 in platelet aliquots), ibuprofen 10 μmol/l or vehicle for 45 min at 37 °C prior to addition of 1.0 μCi 1-[^3]H]arginine in the absence or presence of L-NMMA 100 μmol/l for 15 further minutes. Albuterol 1 μmol/l (a selective β₂-AR agonist) or vehicle was then added for a final 25 min. After terminating the reaction, 1-[^3]H]citrulline was measured as detailed below. In preliminary experiments, DMSO alone, at the concentrations present here, had no effect on platelet NOS activity (data not shown).

2.4. Study 3: effect of chronic oral low-dose aspirin administration on basal and β-AR-stimulated NOS activity in platelets

Eight healthy male and four healthy female subjects were enrolled in this study (Table 1). Platelet NOS activity was measured before and after each subject had taken 75 mg of aspirin orally for each of 14 consecutive days. Platelets were isolated from 60 ml of venous blood, counted and used for measurement of both basal and β-AR stimulated NOS activity. Platelet aliquots (1 ml) were incubated with 1.0 μCi 1-[^3]H]arginine in the absence or presence of L-NMMA 100 μmol/l for 15 min at 37 °C. Isoproterenol 1 μmol/l, albuterol 1 μmol/l or vehicle were added for a further 25 min. After terminating the reaction, 1-[^3]H]citrulline was measured as outlined below.

2.5. Isolation of platelets

Venous blood (60–100 ml) was collected into trisodium citrate (0.38% w/v final concentration). Platelet-rich plasma (PRP), prepared by centrifugation (800×g for 8 min), was passed through a Sepharose™ CL-2B Gel column. Platelets were eluted with, and collected in, calcium-free Tyrodes buffer (composition in mmol/l: NaCl 137, KCl 2.7, MgCl₂ 1.0, NaH₂PO₄ 0.35, NaHCO₃ 11.9 and glucose 5.5; pH 7.4) containing 0.38% trisodium citrate, to prevent platelet aggregation. The platelet count in the eluate was measured using a Coulter counter. Eluates were used for NOS activity assay if platelet concentration was greater than 10¹¹/l.

2.6. Determination of platelet NOS activity

NOS activity in platelets was assessed by measuring the conversion of 1-[^3]H]arginine to 1-[^3]H]citrulline as previously described [9]. Platelet suspensions (volume 1 ml) were incubated with 1.0 μCi 1-[^3]H]arginine in the absence or presence of appropriate agonists and/or antagonists, as described for each study. The reaction was terminated by addition of ice-cold Tyrodes buffer containing N⁶-nitro-L-arginine methyl ester (L-NAME) 100 μmol/l. Platelets were pelleted at 2000×g for 20 min, following which they were lysed by addition of 1 ml perchloric acid (0.3 mol/l) and sonication for 30 min. The acid was neutralised by addition of 65 μl of K₂CO₃, 3 mol/l. 1-[^3]H]arginine and 1-[^3]H]citrulline in platelet lysates were separated using Dowex-resin (Na⁺ form) cation exchange chromatography, and [³H] counts in the L-citrulline fraction were measured by liquid scintillation counting. 1-Citrulline formation was calculated from the following equation:

\[
\text{pmol L-citrulline} = (\text{cpm}_s - \text{cpm}_a)/\text{cpm}_s \times 14
\]

where cpmₐ and cpmₐ are the cpm in the sample in the absence and presence, respectively, of L-NMMA, and cpmₐ is the cpm in the standard (all standards contained 1 μCi 1-[^3]H]arginine, corresponding to 14 pmol). Results were corrected for number of platelets in each reaction.

2.7. Materials and drugs

Sepharose™ CL-2B Gel was obtained from Amersham Pharmacia Biotech (UK). 1-[^3]H]arginine monohydrochloride solution was from Amersham Life Science (UK). Intravenous aspirin (aspirin lysine) was obtained from Synthelabo Groupe (France) and saline from Baxter Healthcare (UK). All other chemicals were from Sigma-Aldrich Company Ltd (UK).

2.8. Statistical analysis

All platelet NOS activity experiments were performed in triplicate and the mean of each triplicate was used for further statistical analysis. Data were analysed using paired t-test or repeated measures ANOVA as appropriate (Graph Pad Prism version 3 software), and statistical significance was taken as \( P<0.05 \) (two-tailed). All data are expressed as mean±S.E.M.
3. Results

3.1. Study 1: effect of acute high-dose aspirin administration on basal and β-AR-stimulated NOS activity in platelets

Platelet NOS activity was measured from the conversion of radiolabelled L-arginine to L-citrulline, in platelets from eight healthy subjects before and after acute systemic aspirin exposure (800 mg intravenously). Basal NOS activity was significantly increased following aspirin administration, from 0.31±0.12 to 0.76±0.14 pmol L-citrulline/10^6 platelets (P<0.01, Fig. 1A). We have previously demonstrated that β-AR stimulation increases platelet NOS activity [9]. In accordance with these findings, isoproterenol 1 μmol/l increased platelet L-citrulline production significantly above basal, before aspirin treatment; however, following aspirin exposure, isoproterenol elicited no further increase in platelet NOS activity above basal (Fig. 1B).

3.2. Study 2: effect of aspirin on basal and β-AR-stimulated NOS activity in platelets in vitro

Platelet NOS activity was again assessed from the conversion of radiolabelled L-arginine to L-citrulline, in platelets from healthy subjects. In response to incubation of platelets with three different concentrations of aspirin (10 μmol/l, typical of the plasma concentrations found in patients taking 75–80 mg aspirin per day orally, and 400 μmol/l and 4 mmol/l, both well above plasma concentrations found in patients treated with aspirin orally at a dosage of 325 mg daily or less), basal L-citrulline production was significantly increased as compared with that in the absence of aspirin (Fig. 2A–C). By contrast, no such effect was observed following incubation with two other COX inhibitors, indomethacin 100 μmol/l (Fig. 2D) and ibuprofen 10 μmol/l (Fig. 2E). The increase in basal NOS activity with aspirin ranged from approximately 30 to 60% (depending on the concentration of aspirin used). For comparison, we also examined the effect of collagen 8 μg/ml on platelet NOS in six subjects. Collagen increased platelet NOS activity by 96.32±5.82% above basal (P<0.05 as compared with all concentrations of aspirin). Therefore, the stimulation of NOS activity by aspirin was submaximal.

As predicted from our previous work [9], stimulation of β₂-AR with albuterol 1 μmol/l increased platelet L-citrulline production significantly above basal (P<0.002 for each), in the absence of aspirin or indomethacin. In the presence of 10 μmol/l or 400 μmol/l aspirin, albuterol produced no further rise in NOS activity above basal (Fig. 2A,B). In the presence of 4 mmol/l aspirin, albuterol-mediated NOS activity actually decreased from basal (Fig. 2C). The rise in albuterol-mediated L-citrulline production was similarly abolished by incubation with indomethacin 100 μmol/l (Fig. 2D) or ibuprofen 10 μmol/l (Fig. 2E).

In a subset of our subjects (n=5), we determined the effect of aspirin 10 μmol/l, 400 μmol/l and 4 mmol/l, and of albuterol 1 μmol/l, on platelet cGMP using a proprietary radioimmunoassay kit (Amersham Biosciences, UK). Basal cGMP was 2.44±0.26 pmol/10^8 platelets; this increased significantly in response to each concentration of aspirin (3.42±0.22, 3.10±0.34 and 3.26±0.44 pmol/10^8 platelets for 10 μmol/l, 400 μmol/l and 4 mmol/l aspirin, respectively, P<0.05 for each) and to albuterol (3.61±0.48 pmol/10^8 platelets, P<0.05), thus confirming that the increase in NOS activity in response to these agents was mirrored by an increase in cGMP (an index of bioavailable NO, which stimulates intracellular soluble guanylyl cyclase).

We also determined whether inhibition of cAMP synthesis blocked the increase in platelet NOS activity in
Fig. 2. Basal and albuterol-mediated nitric oxide synthase (NOS) activity in platelets, incubated in vitro with: (A) aspirin 10 μmol/l, n = 6; (B) aspirin 400 μmol/l, n = 14; (C) aspirin 4 mmol/l, n = 14; (D) indomethacin 100 μmol/l, n = 13; (E) ibuprofen 10 μmol/l, n = 6. Responses are shown in the absence and presence of the relevant cyclooxygenase (COX) inhibitor. *P<0.05 as compared with basal response in the absence of the COX inhibitor. #P<0.05 as compared with basal response in the presence of the COX inhibitor.
response to aspirin 10 \( \mu \text{mol/l} \), 400 \( \mu \text{mol/l} \) and 4 \( \text{mmol/l} \), and to albuterol 1 \( \mu \text{mol/l} \). For this purpose, the effect of SQ22536 50 \( \mu \text{mol/l} \) (a specific membrane-permeable adenylyl cyclase inhibitor) on platelet NOS activity in response to these agents was determined in a subset of our subjects \((n=5)\). Basal L-citrulline formation was 0.30\(\pm\)0.08 pmol/10\(^8\) platelets; this increased in response to each concentration of aspirin \((0.40\pm0.07, 0.42\pm0.05\) and \(0.42\pm0.07\) pmol/10\(^8\) platelets for 10 \( \mu \text{mol/l} \), 400 \( \mu \text{mol/l} \) and 4 \( \text{mmol/l} \) aspirin, respectively, \(P<0.05\) for each) and to albuterol \((0.45\pm0.05\) pmol/10\(^8\) platelets, \(P<0.05\)). SQ22536 significantly suppressed the increase in L-citrulline in response to albuterol \((0.32\pm0.07\) pmol/10\(^8\) platelets, \(P<0.05\) as compared with the absence of SQ22536), but did not suppress L-citrulline formation in response to any concentration of aspirin \((0.39\pm0.06, 0.40\pm0.06\) and \(0.39\pm0.05\) pmol/10\(^8\) platelets for 10 \( \mu \text{mol/l} \), 400 \( \mu \text{mol/l} \) and 4 \( \text{mmol/l} \) aspirin, respectively), demonstrating that the stimulant effect of aspirin on NOS activity, unlike that of \( \beta \)-adrenergic stimulation, was not dependent on adenylyl cyclase stimulation.

### 3.3. Study 3: effect of chronic oral low-dose aspirin administration on basal and \( \beta \)-AR-stimulated NOS activity in platelets

We determined whether chronic low-dose treatment with aspirin exerted similar functional effects, on both basal and \( \beta \)-AR-stimulated NOS activity in platelets, as acute exposure. To this end, we treated healthy subjects \((n=12)\) with aspirin 75 mg orally daily (a low dose which is commonly used clinically for cardiovascular protection) for 14 days. Platelet NOS activity was measured both before and after this period of treatment. In contrast to our findings with acute aspirin exposure, there was no significant effect of chronic low-dose aspirin therapy on basal NOS activity \((0.31\pm0.06\) before vs. \(0.38\pm0.08\) pmol L-citrulline/10\(^8\) platelets after aspirin therapy, Fig. 3A). In response to isoproterenol 1 \( \mu \text{mol/l} \) or albuterol 1 \( \mu \text{mol/l} \), platelet NOS activity increased as before, in subjects before aspirin treatment (Fig. 3B). However, following 14 days of aspirin therapy, the increase in response to either \( \beta \)-AR agonist was abolished.

### 4. Discussion

These studies have highlighted differences in the effects of acute and chronic aspirin exposure on platelet NOS activity. Acute high-dose exposure of platelets to aspirin in vivo following intravenous injection activates basal NOS activity. Similarly, in vitro incubation of platelets with aspirin at three different concentrations \((10 \mu \text{mol/l, representative of plasma levels found during aspirin treatment at the low doses used in cardiovascular disease prophylaxis [20]; 400 \mu \text{mol/l, which is representative of plasma levels obtained during aspirin treatment at anti-inflammatory doses or during intravenous infusion of aspirin at the dosage used in our study [21]; and 4 \text{mmol/l, which is within the range of plasma concentration found in patients with aspirin toxicity] increases NOS activity basally. This acute stimulatory effect of aspirin on NOS is not shared by indomethacin or ibuprofen. Although this study cannot exclude a small stimulatory effect of indomethacin or ibuprofen on NOS, such an effect—if present—would be considerably smaller than that observed with aspirin. These results suggest that acute in vivo or in vitro exposure to aspirin increases basal NOS activity in platelets through a mechanism independent of COX inhibition. We found no effect of aspirin, at any of the concentrations used in our
experiments, on NOS 3 expression or NOS 3 phosphorylation in platelets, as determined by immunoprecipitation of NOS 3 and Western blotting (data not shown).

Chen et al. have previously reported that aspirin and indomethacin both decrease NOS activity and nitrite/nitrate formation in platelets [17]. However, de la Cruz et al. found that aspirin increases NO production from neutrophils and elevates plasma nitrite/nitrate [19]. The reasons for discrepancies between results from different groups is unclear, but may relate to differences in the platelet preparation procedure; in particular, high-speed centrifugation of PRP may increase platelet activation basally, giving rise to an artificially high basal NOS activity, and such platelet activation will be reduced by COX inhibition. Our method of platelet isolation from PRP, namely Sepharose gel filtration, is much less likely to cause platelet activation basally. Our data suggest that, in fact, aspirin at both low and high concentration activates platelet NOS acutely. In contrast, we found that β-AR agonists failed to increase NOS activity in platelets exposed to aspirin, both in vivo and in vitro. It might be argued that, since aspirin stimulates NOS activity basally, no further increase in NOS activity could occur in response to β-adrenergic stimulation. However, this is unlikely to be the explanation, for two reasons. First, we found that NOS activity could be increased by almost 100% in response to collagen 8 μg/ml, whereas it was only increased by 30–60% by aspirin. Second, in vitro, we found that β-AR stimulation failed to activate NOS in platelets exposed to two other COX inhibitors, indomethacin and ibuprofen, despite no change in basal NOS activity in the presence of these drugs. Therefore, unlike its effect on basal NOS activity, the effect of aspirin on β-adrenergic NOS activation appears to be mediated through COX inhibition.

In contrast to the activating effect of acute aspirin on platelet NOS, we found that 2 weeks of low-dose (75 mg) oral aspirin therapy did not significantly affect basal platelet NOS activity. On the other hand, it did abolish β-AR-mediated NOS activation, as did acute aspirin (or other COX inhibitor) exposure. This indicates that platelets exposed to aspirin chronically at low dose in vivo behave differentially to those exposed to the drug acutely, with regard to basal NOS activity, although the mechanism underlying this effect is unclear at present. We used a dose of 75 mg aspirin once daily in this study, since this reflects the dosage typically used in patients long-term for cardiovascular prophylaxis, and therefore the results are readily applicable to the clinical situation. Such a dose gives rise to plasma levels in the micromolar range, which are much lower than those attained using 800 mg intravenously (as used in study 1). We performed our measurements of platelet NOS activity after 14 days treatment of subjects with low-dose oral aspirin, rather than after single dose treatment, since it is known that one single oral dose of 75 mg aspirin gives rise to extremely low plasma concentrations [20]. Although our study cannot exclude a small stimulatory effect of chronic low-dose aspirin therapy on basal platelet NOS activity, any such effect—if present—would be considerably smaller than that observed following acute aspirin exposure.

Our findings suggest that aspirin exerts two types of effect on platelet NOS, depending on the length of treatment. After both short- and long-term treatment, it inhibits β-AR-mediated NOS activation, and the fact that indomethacin and ibuprofen cause a similar effect suggests that this is secondary to COX inhibition, although the mechanism by which COX inhibition may affect stimulated NOS activity remains to be determined. After acute exposure, at both low and high concentration, aspirin can also stimulate basal platelet NOS activity, and this effect is COX-independent. β-AR-mediated inhibition of adhesion and aggregation in platelets may be important clinically as this may partially offset the pro-aggregatory effects of α-adrenoceptor stimulation in response to the endogenous catecholamines norepinephrine and epinephrine [22]. At rest, the circulating plasma concentrations of norepinephrine and epinephrine range between 0.3–3.0 and 0.1–0.5 nmol/l, respectively, which are lower than the reported affinity of these catecholamines for β-AR [7,8]. However, in times of stress, in particular during acute coronary syndrome and myocardial infarction, these levels may increase to more than 10 nmol/l [23], concentrations sufficient to induce significant activation of β-AR on platelets. Thus, effects of aspirin on β-AR-mediated platelet NOS activation may be of clinical relevance; this remains to be determined. Large clinical trials have repeatedly shown that long-term aspirin confers cardiovascular protection in those patients at risk of thromboembolic disease [24], implying that the effects on COX outweigh any adverse effect of inhibition of β-AR-mediated NOS activation. However, a substantial number of patients develop recurrent cardiovascular events despite aspirin therapy, suggesting that some patients may be at least partially aspirin resistant [25,26]. Our findings with regard to suppression of β-AR-mediated NOS activation following chronic low-dose aspirin therapy may be of relevance to this phenomenon, but this needs further investigation.

In conclusion, we have demonstrated that aspirin, in vivo and in vitro, can activate platelet NOS acutely by a mechanism that is independent of COX inhibition. In contrast, chronic aspirin treatment, at a low dose commonly used clinically for cardiovascular prophylaxis (75 mg), does not affect basal platelet NOS activity. Exposure of platelets to aspirin both at high and low concentration, and acutely as well as chronically, impairs β-AR-mediated NOS activation, and this effect is exerted through COX inhibition. Further studies are needed to determine the cellular mechanisms and clinical consequences of these effects.
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References