Niacin-induced “Flush” Involves Release of Prostaglandin D<sub>2</sub> from Mast Cells and Serotonin from Platelets: Evidence from Human Cells in Vitro and an Animal Model

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Received May 20, 2008; accepted September 9, 2008

ABSTRACT

Niacin lowers serum cholesterol, low-density lipoprotein, and triglycerides, and it raises high-density lipoprotein. However, most patients experience cutaneous warmth and vasodilation (flush). Acetylsalicylic acid (ASA) can reduce this flush, presumably by decreasing prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) release from macrophages. Here, we show that methyl nicotinate induces significant PGD<sub>2</sub> release from human mast cells and serotonin from human platelets. Intradermal injection of methyl nicotinate induces rat skin vasodilation and vascular permeability. Niacin increases plasma PGD<sub>2</sub> and serotonin in a rat model of flush. The phenothiazine prochlorperazine, the H<sub>1</sub> serotonin receptor antagonist cyproheptadine, and the specific serotonin receptor-2A antagonist ketanserin inhibit niacin-induced temperature increase by 90% (n = 5, p < 0.05), 90 and 50% (n = 3, p < 0.05), and 85% (n = 6, p = 0.0008), respectively, in this animal model. These results indicate that niacin-induced flush involves both PGD<sub>2</sub> and serotonin, suggesting that drugs other than ASA are required to effectively inhibit niacin-induced flush.

Despite increased efforts to identify risk factors and availability of better drugs for cardiovascular disease, deaths from cardiovascular disease continue to increase (Libby, 2005).

This study was supported in part by Kos Pharmaceuticals, Inc. (Cranbury, NJ) and by Theta Biomedical Consulting and Development Co., Inc. (Brookline, MA).


ABBREVIATIONS: HDL, high-density lipoprotein; LDL, low-density lipoprotein; PGD<sub>2</sub>, prostaglandin D<sub>2</sub>; ASA, acetylsalicylic acid; hCBMC, human cord blood mononuclear cell; EIA, enzyme immunoassay; MK-0524, [(3R)-4-(4-chlorobenzyl)-7-fluoro-5-(methylsulfonyl)-1,2,3,4-tetrahydrocyclopentainol-3-yl]acetic acid.

Niacin is thought to induce flush by stimulating the release of prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) from the skin (Morrow et al., 1989, 1992). The actual cell type responsible for PGD<sub>2</sub> release in response to niacin is unknown, but dermal macrophages (Urade et al., 1989) and Langerhans cells (Benyo et al., 2006) have been implicated. However, coadministration of acetylsalicylic acid (ASA) to reduce PGD<sub>2</sub> levels has not been particularly effective (only 30% inhibition) in blocking niacin flush (Dunn et al., 1995; Jungnickel et al., 1997), implying...
that molecules other than PGD₂ may be involved. These may include histamine and serotonin, which could be released from mast cells (Kushnir-Sukhov et al., 2007). Serotonin is also released from platelets (D’Souza et al., 2006) and from enterochromaffin cells, especially in carcinoid syndrome, which commonly presents with facial flush (Loong et al., 1968).

Here, we investigated whether niacin could induce histamine and PGD₂ release from human mast cells, and serotonin release from human platelets. We also investigated whether niacin could induce skin vasodilatation and vascular permeability in rat skin. Finally, we investigated whether niacin could increase plasma PGD₂ and serotonin in a rat model of niacin-induced flush (Turenne et al., 2001) and whether serotonin receptor antagonists could inhibit this effect. Our results show that niacin-induced flush involves both PGD₂ from mast cells and serotonin from platelets. Serotonin-receptor antagonists block niacin-induced flush and could be helpful clinically.

Materials and Methods

Animals. Male Sprague-Dawley rats (300–350 g) were housed three per cage and were provided with food and water ad libitum. The room temperature was constant at 21 ± 1°C, with a 14/10-h light/dark schedule, with lights out at 7:00 PM. Animals were allowed to habituate to housing conditions and were handled daily for 3 days before they were used in any experiment. Niacin, methyl nicotinate, methyl nicotinamide, nicotinamide-N-oxide, nicotinuric acid, brompheniramine, chlorpheniramine, cyproheptadine, diphenhydramine, disodium cromoglycate (cromolyn), diprydiamole, hydroxyzine, ketotifen, ketotifen, and prochlorperazine were purchased from Sigma-Aldrich (St. Louis, MO), whereas azatadine was from Schering Plough (Kenilworth, NJ). All drugs were dissolved in 0.9% NaCl and were prepared fresh each day.

Assessment of Niacin-Induced Skin Temperature Changes. Temperature measurements were recorded using a hand-held infrared pyrometer (model OS613A; Omega Engineering, Inc., Stamford, CT) connected to a millivoltmeter. The probe was held at a distance of 1 to 2 mm from the animal’s skin, and temperature readings were taken from a circular area approximately 3 mm in diameter. Skin temperature was initially recorded from the abdominal area, the tail, and the ear, but it was determined that ear temperatures gave the most reliable results. Animals were habituated to handling and to the infrared probe for 3 days before use. On the day of the experiment, the animals were brought into the lab (9:00–10:00 AM), and temperature readings were recorded from the abdominal area, the tail, and the ear, but it was determined that ear temperatures gave the most reliable results. Animals were habituated to handling and to the infrared probe for 3 days before use. On the day of the experiment, the animals were brought into the lab (9:00–10:00 AM), and the ear temperature was measured. Three readings from the top half of each ear were recorded routinely for each time point, and they varied less than 15%. Baseline ear temperature was recorded immediately before animals were injected intraperitoneally with either niacin or the test drug. None of the experiments had a significant difference between baseline temperatures of each of the treatment groups. In some of the preliminary experiments, the animals were first anesthetized with a single intraperitoneal injection of 0.5 ml of solution containing ketamine (66 mg/kg) and xylazine (16.5 mg/kg). Ear temperature was then recorded at various intervals, and another baseline value was taken immediately before administration of niacin, after which the ear temperature was then measured every 10 min for a period of 60 min. The amount of niacin used varied between 8.25 and 33 mg/kg. The dose of 24.75 mg/kg chosen for most experiments was roughly equivalent to 1750 mg/80 kg, the average effective dose used in humans to induce significant reductions in triglycerides and LDL. The animals were returned to their cages between measurements. Animals were “rested” for 1 week and were used again; the effect of niacin was not changed in rats that were used more than once. This protocol was approved by the Tufts Medical Center Animal Use Committee (protocol no. 41-05).

Pretreatment with Various Drugs. Rats were randomly administered either vehicle followed by niacin (A) or test drug followed by niacin (B). The length of pretreatment before niacin injection varied, and it was recorded up to 8 h in some cases.

Isolation of CD34⁺ Cells and Mast Cell Culture. Human umbilical cord blood was collected as approved by the Tufts Medical Center’s Human Investigation Review Board (protocol no. 7305). Nonphagocytic mononuclear cells were separated by density-gradient centrifugation using Lymphocyte Separation Medium from OrganonTeknika (Durham, NC). The isolation of hematopoietic stem cells (CD34⁺) was performed by positive selection of CD34⁺/AC133⁺ cells by magnetic-associative cell sorting using an AC133⁺ cell isolation kit (Miltenyi Biotec Inc., Auburn, CA). Human umbilical cord blood-derived cultured mast cell (hCBMCs) were cultured as previously reported (Kempuraj et al., 1999). In brief, CD34⁺ cells were suspended in Iscove’s modified Dulbecco’s medium (Iscvtrigen, Carlsbad, CA), supplemented with 200 ng/ml recombinant stem cell factor, 50 ng/ml interleukin-6, 5% fetal bovine serum (Lonza Walkersville, Walkersville, MD), 5 × 10⁻⁵ M 2-mercaptoethanol, and 1% penicillin-streptomycin (Invivorten) for 12 to 16 weeks. The purity of hCBMCs was evaluated by immunocytochemical staining for tryptase as previously described (Kempuraj et al., 1999), and mast cell viability was determined by trypan blue (0.3%) exclusion.

Human Platelets. Freshly isolated human platelets were purchased from AllCells, LLC (Emeryville, CA) and sent to us overnight. Platelets were used the day of arrival after washing as indicated below.

The hCBMCs or human platelets were washed once in Dulbecco’s phosphate-buffered saline and human Tyrod’s buffer. Cells were stimulated in Tyrode’s buffer in a 37°C shaking water bath. Then the tubes were centrifuged, and the supernatant fluid was collected and stored at −80°C until assays. Histamine level was assayed from the supernatant and pellet, and the percentage histamine release was calculated as reported previously (Kempuraj et al., 2005). PGD₂ levels in the hCBMCs supernatant fluid was assayed by enzyme immunoassay (EIA) using a commercial kit (Cayman Chemical, Ann Arbor, MI) as per the kit procedure (Papaliodis et al., 2008).

Blood Mediator Measurements. In certain cases, plasma levels of PGD₂ and serotonin (Beckman Coulter, Fullerton, CA) were assayed by EIA as per the kit’s procedure.

Intradermal Injection and Measurement of Vascular Permeability. Rats were anesthetized with a single intraperitoneal injection of 0.3 ml of ketamine (66 mg/kg) and xylazine (16.5 mg/kg). While under anesthesia, an amount of 0.3 ml of Evans blue (1%) was injected in the tail vein. Thirty minutes later, the test drugs (niacin, niacin metabolites, neureotensin, as a positive control) and normal saline (as a negative control) were injected (0.05 ml) intradermally at different adjacent spots on the back of the rat using tuberculin syringes at the concentrations noted in the appropriate legend (Fig. 4). At the end of the injections, the animal was kept under anesthesia for another 15 min, after which it was killed by asphyxiation over CO₂ vapor and decapitated. The skin was then removed, turned over, and photographed. Any vascular permeability is noted as dye extravasation (Theoharides et al., 1998).

Statistical Analysis. The six ear temperature measurements (three from each ear) were averaged for each time point. All data from multiple rats were from separate experiments and were presented as mean ± S.D. or percentage change from that recorded after niacin administration and varied less than 15%. Any temperature change was calculated by subtracting from the mean value for each experimental time point the baseline temperature obtained immediately before the drug/vehicle was injected, or the baseline was measured immediately before niacin administration, which ever was appropriate. The human platelet serotonin values presented as a scattergram, with the mean group value shown by a horizontal bar to show the variability from different donors. Paired comparisons be...
tween niacin and control or niacin and drug pretreatment followed by niacin were analyzed with either the paired Student’s t test or the nonparametric Mann-Whitney U test; the latter was used because it was not known whether the effect of niacin followed a normal distribution. Multivariate analysis of variance analysis was performed on all other comparisons. Significance is denoted by \( p < 0.05 \).

Results

Effect of Niacin and Niacin Metabolites on Human Mast Cell and Platelet Secretion. Methylnicotinate had a small dose-response effect on human mast cell secretion of histamine (Fig. 1A) and an impressive dose-dependent effect on mast cell secretion of \( \text{PGD}_2 \) (Fig. 1B). Niacin, nicotinamide, and nicotinuric acid had negligible effects (results not shown).

Niacin and its derivatives, nicotinamide and nicotinuric acid, and the niacin derivative (synthetic niacin ester) methylnicotinate (at approximately 0.1 mM) all induced serotonin release from human platelets (Fig. 2). These results are shown as a scattergram, including group means, to point out the different reactivity of platelets from individual platelet donors; this variability may explain the well known differences in flush severity experienced by different patients.

Effect of Niacin on Rat Plasma \( \text{PGD}_2 \) and Serotonin Levels. We then investigated the effect of niacin and the effect of certain test drugs on rat, serum \( \text{PGD}_2 \), and plasma serotonin. Niacin (24.75 mg/kg) increased plasma \( \text{PGD}_2 \) from 933 ± 94 to 1750 ± 352 pg/ml at 45 min (\( n = 3 \), \( p = 0.018 \); Fig. 3A) and plasma serotonin from 137 ± 37 (\( n = 4 \), \( p = 0.70 \)). There was no effect on serotonin. Niacin (24.75 mg/kg) increased plasma \( \text{PGD}_2 \) from 933 ± 94 to 1750 ± 352 pg/ml at 45 min (\( n = 3 \), \( p = 0.018 \); Fig. 3A) and plasma serotonin from 137 ± 37 (\( n = 4 \), \( p = 0.01 \); Fig. 3B).
serum histamine or PGE$_2$ (results not shown). Pretreatment for 2 h with ASA (4.02 mg/kg) reduced plasma PGD$_2$ by 85% to 1050 ± 212 pg/ml (n = 3, p = 0.018, Fig. 3A) but had no statistically significant inhibitory effect on plasma serotonin levels (Fig. 3B). Cyproheptadine (56.4 µg/kg) did not affect either plasma PGD$_2$ or serotonin (n = 4, p = 0.7023; Fig. 3B).

**Effect of Niacin and Metabolites on Rat Skin Vasodilation and Vascular Permeability.** We then investigated whether intradermal injection of niacin or its key metabolites could induce skin vascular permeability that could explain human flush. Methylnicotinate induced significant Evans blue extravasation in rat skin (Fig. 4A) that was comparable with intradermal injection of either histamine (0.01 mM) or serotonin (0.1 mM); the most potent drug was neurotensin (Fig. 4A). The niacin metabolites nicotinamide, methyl nicotinamide, nicotinamide-N-oxide, and nicotinuric acid had no appreciable effect (Fig. 4B).

**Effect of Niacin on Rat Skin Temperature.** We also investigated the ability of niacin to induce vasodilation as determined by an increase in ear skin temperature. The normal mean ear temperature was 26.5 to 28.5°C (n = 27), recorded at 9:00 to 11:00 AM. Niacin (10 mg/rat) was first administered either i.v. or intradermally in anesthetized rats; however, niacin failed to increase the skin temperature, most likely because of interference by the anesthetics (ketamine/xylazine). Niacin (24.75 mg/kg, equivalent to 1750 mg/80 kg human) administered intraperitoneally in conscious rats induced a time-dependent temperature increase, with a maximum 1.9 ± 0.2°C (n = 5, p = 0.0002) that occurred at slightly different times in four groups of animals (30, 40, 50, and 60 min), with a mean increase at 45 min (Fig. 5A). A dose-response of niacin (8.25–33 mg/kg, n = 5) showed a maximal temperature increase of 2.0 ± 0.1°C (p = 0.001) achieved with 24.75 mg/kg rat at 45 min (Fig. 5B).

**Effect of H$_1$-Receptor Antagonists on Niacin-Induced Skin Temperature Increase.** As histamine is a key vasodilatory molecule, we investigated whether the H$_1$-receptor antagonist (10-min pretreatment) could prevent intraperitoneal niacin (16.5 mg/kg)-induced temperature increase 45 min later. Brompheniramine, chlorpheniramine, diphenhydramine, and ketotifen used at their approximate maximal human equivalent doses had no effect on niacin-induced temperature increase (n = 5, Fig. 6A). The heterocyclic H$_1$-receptor antagonist hydroxyzine, which also partially inhibits mast cell activation, inhibited the temperature increase by −20% (n = 5, p < 0.05) and so did (p < 0.05) the “mast cell stabilizer” cromolyn (n = 5, Fig. 6A). This experiment was repeated using 5 and 10 times higher concentrations of these drugs (n = 3, Fig. 6B). There was no apparent dose-response curve, and the strongest inhibition was 94%, again with prochlorperazine (Fig. 6B).

**Fig. 4.** Representative photographs of rat skin showing vasodilation and vascular permeability as shown by extravasation in response to: A, niacin and methylnicotinate (0.01 mM) compared with neurotensin (0.1 µM), histamine, and serotonin (0.1 mM); and B, methylnicotinate, methyl nicotinamide, niacin, nicotinamide, nicotinamide-N-oxide, and nicotinuric acid (0.01 mM) neurotensin (0.1 µM), serotonin and histamine (0.1 mM), and saline.

**Fig. 5.** A, time course of the effect of a single intraperitoneal niacin (724.75 mg/kg) on net ear temperature increase (n = 5). All time points were significant (p = 0.0002). B, dose response of the effect of a single intraperitoneal niacin injection on net ear temperature increase recorded 45 min later (n = 5). Niacin rat doses were based on 80-kg human (h) doses as follows: 8.25 mg/kg = 583 mg/human, 16.5 mg/kg = 1167 mg/human, and 24.75 mg/kg = 1750 mg/human, 33 mg/kg = 2334 mg/human; the effect of all doses was significant (p = 0.0001).
Effect of Serotonin Receptor Antagonists on Niacin-Induced Skin Temperature Increase. The phenothiazine prochlorperazine, which also has serotonin receptor blocking activity, produced almost 90% inhibition of the skin temperature increase because of intraperitoneal niacin (16.5 mg/kg) (n = 5, p < 0.05, Fig. 6). The mixed H₁-receptor and serotonin receptor antagonist cyproheptadine (51.3 μg/kg, equivalent to 4 mg/80 kg), administered as one intraperitoneal injection 10 min before intraperitoneal niacin (16.5 mg/kg), completely inhibiting (n = 3, p = 0.0036) the niacin effect measured at 45 min postinjection (Fig. 7A), were quite effective; cyproheptadine alone actually decreased even the baseline temperature of 26.5°C by 0.7 ± 0.2°C (n = 3, p = 0.0011, Fig. 7A).

We then investigated the inhibitory effect of different concentrations of cyproheptadine administered 6 h before 16.5 mg/kg niacin administration. The inhibitory effect of cyproheptadine was evident, whether its dose was 28.05, 42.24, or 56.4 μg/kg (Fig. 7B). Cyproheptadine (51.3 μg/kg, equivalent to 4 mg/80 kg) reduced the effect of niacin by more than 50% (n = 3, p = 0.008), whether it was administered 30 min or 8 h before niacin (Fig. 7C). The structurally similar drug azatadine had similar effects (data not shown). These results suggested that serotonin receptor antagonism may be important. As a consequence, we used the specific serotonin 5-hydroxytryptamine₂A receptor antagonist ketanserin, which inhibited niacin-induced temperature increase by 85% (n = 6, p = 0.0008, Fig. 8).

Finally, we tested dipyriramole, which inhibits platelet aggregation; this drug inhibited niacin-induced temperature increase by 72% (n = 6, p = 0.0004, Fig. 8).

Effect of Nonsteroidal Anti-Inflammatory Drugs on Niacin-Induced Skin Temperature Increase. We also investigated whether pretreatment for 2 h with two common nonsteroidal anti-inflammatory drugs could inhibit vasodilatory effect of niacin in this animal model (Fig. 8). ASA (1.22 mg, equivalent to 325 mg/80 kg) and indomethacin (375 μg, equivalent to 100 mg/80 kg) had a weak (30%) inhibitory effect (n = 6, p < 0.0001) (Fig. 8A).

We also used 5 and 10 times higher concentrations of the serotonin receptor antagonists and the nonsteroidal anti-inflammatory drugs (Fig. 8B). It is apparent that there is no clear dose response, but the most potent drug were again cyproheptadine (77.8 and 94.4% inhibition) and indomethacin (44.4 and 83.3% inhibition), at their respective concentrations (Fig. 8B).

We also tested all the drugs at their highest concentration used for any effect on niacin-induced serotonin release. It appears that prochlorperazine and ketanserin may also have some inhibitory effect on serotonin release (Fig. 9), in addition to their well known serotonin receptor antagonistic effect.
was equivalent to that previously used in the same rat model (Turenne et al., 2001) and within the range of doses (1.5–2 g/day) given orally to patients with hyperlipidemia (Gupta and Ito, 2002). Drug doses 5 and 10 times higher did not produce any stronger inhibition, except in the case of cyproheptadine and indomethacin. Methylnicotinate had a weak effect on inducing histamine release from human mast cells, whereas niacin did not increase rat plasma histamine levels. Moreover, the H1-receptor antagonists brompheniramine, chlorpheniramine, diphenhydramine, and ketotifen did not block niacin-induced skin temperature increases. Combined, these results suggest that histamine is not involved in niacin-induced flush.

In contrast, the phenothiazine, prochlorperazine, the serotonin-receptor antagonists cyproheptadine and azatadine, and the specific serotonin receptor-2A antagonist, ketanserin, were potent inhibitors of niacin-induced skin temperature increase in rats. The tricyclic H1-receptor antagonist hydroxyzine, which has some inhibitory effect on mast cell activation, and the “mast cell stabilizer” cromolyn also weakly inhibited the effect of niacin.

So far, only PGD2 has been implicated in niacin “flush” (Morrow et al., 1989, 1992). In one of these studies, topical superpharmacological administration of methylnicotinate (10^{-3}–10^{-1} M) on forearms of normal volunteers dramatically increased serum PGD2 (Morrow et al., 1992). Niacin was shown to stimulate PGD2 synthase in macrophages (Knowles et al., 2006) through activation of a unique G-protein-coupled receptor (Lorenzen et al., 2002) and, after 30 min of stimulation, resulted in a 3-fold PGD2 release from cultured macrophages but not from monocytes or endothelial cells (Meyers et al., 2007). As the authors admitted, these in vitro findings did not reflect the amount of PGD2 release in vivo or the fact that the niacin flush occurs within a few minutes in humans (Meyers et al., 2007). In contrast, PGD2 was reported to decrease macrophage production of the potent vasodilator nitric oxide (Belly et al., 2006). Other reports indicated that nicotinic acid increased expression of prostanoid synthase in epidermal Langerhans cells; depletion of these cells, but not macrophages, eliminated nicotinic acid-induced flushing (Benyó et al., 2006). Nicotinic acid receptors have been identified (Soudijin et al., 2007). Skin was shown to express the nicotinic acid receptor (GPR109A) and its activation resulted in PGD2 release; the responsible cells were again shown to be Langerhans cells (Maciejewski-Lenoir et al., 2006). Mice lacking GPR109A did not show niacin-induced flush; nevertheless, blocking PGD2 and PGD2 receptors was associated with reduced but still substantial flushing (Benyó et al., 2005). An oral PGD2 receptor-1 antagonist (MK-0524) could block nicotinic acid- and PGD2-induced vasodilation in female mice but strangely only partially in male mice (Cheng et al., 2006). Moreover, coadministration of a PGD2 receptor antagonist with extended release niacin in humans reduced flush only by 50% (Lai et al., 2007). These results clearly indicate that PGD2 accounts only for part of niacin’s induced flush.

Our present results further indicate that ASA has only a weak inhibitory effect on niacin-induced flush in a rat model, as also shown in clinical trials, even though it blocks serum PGD2 levels. In one placebo-controlled study, 60% of subjects on placebo experienced “flush”-related symptoms after ingesting 500 mg of immediate-release niacin; there was a
decrease to 41% of subjects taking daily 325 mg of ASA for 4 days and to 29% subjects on 4 days of daily 650 mg of ASA before niacin, but there was no statistical difference between the two treatments (Jungnickel et al., 1997). In another double-blinded, crossover study, pretreatment with 325 mg but not 165 mg of ASA or 200 mg of ibuprofen partially reduced flush-related symptoms because of 500 mg of immediate-release niacin (Dunn et al., 1995). It should be pointed out that these modest (about 30%) reductions were for flush caused by 500 mg of niacin, whereas 1500 to 2000 mg is required for effective treatment, suggesting that these amounts of ASA are likely to be even less effective at the higher niacin doses used clinically. A recent paper reported that a new “optimized” extended release 1000-mg niacin tablet induced flush in 89% in 156 healthy male volunteers, with a 43% reduction in median flush duration (Cefali et al., 2006). Coadministration of ASA (650 mg) further reduced the subjects who experienced flush from 77% on placebo to 61%, whereas the duration of flush was reduced from 60 to 48 min (Cefali et al., 2007). It is obvious from the above that >60% of subjects still experience flush even on an “optimized” extended release niacin with together with ASA. Moreover, 650 mg of daily ASA could lead to gastritis.

The ability of niacin and methyl nicotinate to induce serotonin release from human platelets and the ability of niacin to increase rat plasma serotonin levels, and of serotonin-receptor antagonists to block niacin-induced flush in this rat model, is novel. These results could help explain the inhibitory effect of the phenothiazines haloperidol (Turenne et al., 2000) and prochlorperazine (shown here) because they also antagonize serotonin receptors but have no apparent effect on PGD2 (Cosi and Koek, 2001). The vasodilatory action of serotonin on superficial skin vasculature is apparently contrary to the brain vessel vasoconstrictive effects of serotonin best known from the pathophysiology of migraineurs. However, serotonin is the main vasodilatory amine in rodents (Askne et al., 1980). Moreover, serotonin is responsible for the facial flush associated with the carcinoid syndrome in humans. In fact, during flushing of carcinoid patients, plasma serotonin levels increase significantly (Matushansky and Launay, 1995). In addition, flushing in the carcinoid syndrome is induced by an antiserotonergic agent (Loong et al., 1968) and by cyproheptadine (Plank and Feldman, 1975). Interestingly, one paper reported that prostaglandins may control plasma serotonin levels (Utsunomiya et al., 1981), whereas another reported that subthreshold serotonin concentrations potentiated the effect of low arachidonic acid on human platelet aggregation (Saeed et al., 2003). The possibility still remains that serotonin may be inducing PGE2 release or vice versa. At present, it is not known whether PGD2 and serotonin operate individually, sequentially, together, or indirectly by promoting the release of yet another vasodilatory molecule, such as nitric oxide.

Increasing evidence indicates the superior ability of a niacin-statin combination to reduce triglycerides, LDL, very low-density lipoprotein, and apolipoprotein-a, while increasing HDL (Morgan et al., 1998; Gupta and Ito, 2002; Carlson, 2005). However, the rate of niacin discontinuation because of flushing has been reported to be considerable, even with extended release niacin (Guyton et al., 1998; McCormack and Keating, 2005), and it increases over the course of treatment (McKenney, 2004); this is also true for the combination of lovastatin and extended-release niacin (Gupta and Ito, 2002). As a consequence, inhibition of niacin-induced flush is of critical importance for compliance, a problem that was recently termed the “sixth vital sign” (Rosenow, 2005).

The present findings suggest that both PGD2 and serotonin may be involved in niacin-induced flush. Plasma PGD2 and serotonin, along with urine serotonin metabolites, should be measured in subjects receiving therapeutic amounts of niacin because no animal or in vitro model accurately reflects the human condition. The possibility of administering or formulating niacin together with cyproheptadine or the flavonoid luteolin, which was recently shown to inhibit niacin flush in rats (Papalios et al., 2008), certainly warrants further investigation.

Acknowledgments
We thank Jessica Christian for patience and word processing skills. We thank Amgen Biologicals (Thousand Oaks, CA) for the generous gift of human recombinant stem cell factor. We also thank the doctors and nurses of the department of Obstetrics and Gynecology, Tufts Medical Center (Boston, MA) for collecting and providing umbilical cord blood.

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