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CATECHOLAMINES INHIBIT LEUKOTRIENE FORMATION AND DECREASE LEUKOTRIENE/PROSTAGLANDIN RATIO

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Abstract—Adrenaline, noradrenaline, isoprenaline, and to a lesser extent dopamine inhibit the release of leukotriene (LT) B_4 from calcium ionophore-stimulated human polymorphonuclear leukocytes, while the release of prostaglandin (PG) E_2 is proportionally elevated. The inactivity of salbutamol, a non-catechol adrenergic β_2-receptor agonist, and the inability of propranolol to antagonize the effects of adrenaline, suggest the mediation through β-receptor independent mechanisms. Neither are α-1-receptors involved, as prazosin, a specific antagonist, fails to inhibit the reaction. As the principles for biochemical regulation of LT- and PG-production are met by catecholamines in several tissues, the mechanism is considered to be of general physiological importance. Catecholamines may function as coenzymes/antioxidants which, by altering the redox state of the enzyme iron or heme, decrease the LT/PG ratio thus protecting the organism against tissue anaphylaxis and other LT-related pathophysiology.

Adrenaline, noradrenaline and dopamine stimulate biosynthesis of prostaglandins (PGs) acting as possible "natural coenzymes" [1]. Caffeic acid, structurally related to catecholamines, is as active as adrenaline [2], and several other phenolic compounds have the same effect [3, 4]. On the other hand, some compounds with catechol structure are known as potent inhibitors of leukotriene (LT) formation. These include 6,7-dihydroxycoumarin [5], some bioflavonoids [6], nordihydroguaiaretic acid [7, 8], derivatives of caffeic acid [9] and indirectly also isoprenaline [10]. Compounds with catechol structure thus seem to regulate the formation of LTs and PGs in diametrically opposite directions. This has not been studied previously in the same test system, however, and the effect of endogenous catecholamines on LT formation has not been established. We present evidence that catecholamines modify the formation of LTs and the LT/PG ratio, and thus possibly some pathophysiological reactions as reported preliminarily by us [11].

MATERIALS AND METHODS

Isolation of polymorphonuclear leukocytes (PMNs). Blood samples for PMNs were collected by venipuncture from healthy volunteers having abstained for at least 1 week from any drugs. PMNs were isolated with density gradient centrifugation. After isolation, 5×10^6 PMNs (>98% purity and >98% viability) were preincubated in 465 μL of Dulbecco's phosphate-buffered saline (components in g/L: $CaCl_2$ 0.1, KCl_2 0.2, KH_2PO_4 0.2, $MgCl \cdot 6H_2O$ 0.1, NaCl 8.0, $Na_2HPO_4 \cdot 7H_2O$ 2.16) for 15 min at 37°, and further 15 min with the test compound. The compounds were added in 25 μL of 0.9% NaCl solution. The final concentration range was 0.18 nM to 1800 μM for adrenaline, dopamine, isoprenaline, noradrenaline and salbutamol; for caffeic acid 0.37 nM – 370 μM.

Eicosanoid synthesis. Eicosanoid synthesis was triggered by Ca ionophore A23187 added in 10 μL of DMSO. The final concentrations of A23187 was 1 μM, incubation time was 10 min at 37°.

HPLC apparatus. The HPLC system consisted of a dual piston LKB Model 2150 HPLC pump (LKB, Bromma, Sweden), a Rheodyne Model 7125 injector (Rheodyne, Cotati, CA, U.S.A.) equipped with a 200 μL sample loop, a C_{18} column (particle size 5 μM, length 20 cm, i.d. 3 mm; Chrompack, Middelburg, Netherlands), a Waters model Lambda-Max 480 LC Spectrophotometer (Waters Associates, Milford, MA, U.S.A) and a Hewlett-Packard Model 3390A integrator (Hewlett-Packard, Avondale, PA, U.S.A.). In the assay of catecholamines a C_{18} column (particle size 5 μm, length 10 cm, i.d. 3 mm; Chrompack), a Bioanalytical Systems model LC-4 amperometric detector with glassy carbon electrode (Bioanalytical systems Inc., West Lafayette, IN, U.S.A.), and a LKB 2210 amplifier were used. For catecholamines the mobile phase was (per 1000 mL): 11.3 g Na-Ac·H_2O, 6.8 g $NaH_2PO_4 \cdot H_2O$, 1.2 g C_7SNa, 0.15 g EDTA, 10 mL 2M HCl, approx. 1 mL H_2PO_4 for adjustment of pH to 4.85, and finally 27.5 mL acetonitrile.

Determination. After pelleting the cells (10,000 *g* for 60 sec), the samples were assayed for PGE_2 with RIA, having negligible cross reactivity with other arachidonic acid metabolites [12, 13]. LTB_4, 20-OH-LTB_4 and 20-COOH-LTB_4 were assayed with HPLC [14, 15]. For quantitation of LTB_4 tetrahydrofuran: methanol: 0.1% aqueous EDTA:acetic acid: ammonia (25:20:55: 0.1:0.1), pH adjusted to 5.5, and for 20-OH-LTB_4 and 20-COOH-LTB_4 methanol:water:acetic acid:ammonia (55:45:0.1:0.1) pH

adjusted to 4.0, were used as mobile phases. LTB_4, 20-OH-LTB_4, 20-COOH-LTB_4 and PGB_1 (internal standard) were detected at 280 nm. The intracellular catecholamine concentrations in PMNs, incubated with adrenaline or noradrenaline, were measured by HPLC with electrochemical detection after washing the cell pellets, precipitating protein with trichloroacetic acid (5%), and using aluminium oxide for extraction [16].

Drugs and chemicals. Adrenaline, caffeic acid, and isoprenaline came from Sigma Chemical Co. (St Louis, MO, U.S.A.), and noradrenaline as well as dopamine from Fluka AG (Buchs, Switzerland). Ca ionophore A23187 was obtained from Calbiochem (San Diego, CA, U.S.A.). Propranolol and salbutamol were kindly provided by Huhtamäki Pharmaceuticals (Turku, Finland) and prazosin by Orion Pharmaceutica (Espoo, Finland). LTB_4 for standards was kindly provided by Dr J. Rokach, Merck Frosst Laboratories, Pointe Claire, Dorval, Canada, and PGB_1 from Dr J. E. Pike, Upjohn Co., Kalamazoo, MI, U.S.A. The LT-metabolite standards, 20-COOH-LTB_4 and 20-OH-LTB_4, came from Cayman Chemical, (Ann Arbor, MI, U.S.A.). The antiserum was purchased from the Pasteur Institute (Paris, France) and [^{125}I]PGE_2 from New England Nuclear (Boston, MA, U.S.A.).

RESULTS

The main findings are summarized in Figs 1 and 2 and Table 1. Resting PMNs did not produce detectable amounts of LTB_4 or PGE_2. After exposure of the cells to A23187 (1 μM, 10 min, 37°) the LTB_4 concentration measured in the incubate was 8.1 ± 0.3 ng/10^6 cells (mean ± SE), and that of PGE_2 58 ± 5 pg/10^6 cells. All tested compounds with catechol structure enhanced the A23187-stimulated formation of PGE_2 and inhibited the release of LTB_4. Salbutamol, a non-catechol β_2-agonist, had neither of the effects. In stimulating PG-formation noradrenaline was the least effective amine, while adrenaline, isoprenaline and dopamine were active in a wide concentration scale. Also as inhibitors of LT synthesis, adrenaline and isoprenaline were the most potent compounds, while dopamine was effective only at relatively high concentrations.

The synthesis of PGE_2 was augmented dose-dependently by adrenaline and isoprenaline (a maximally two-fold increase), and considerably more by dopamine (a 4.5-fold increase). Noradrenaline, even at relatively high concentrations, was able to cause only a 40% increase in PGE_2. Caffeic acid was moderately active while salbutamol had no effect at all. The synthesis of LTB_4 was markedly inhibited by 18–180 μM of adrenaline and isoprenaline. Noradrenaline and caffeic acid were less effective. Dopamine was active only at millimolar concentration, and salbutamol was inactive (Fig. 1). The concentrations of adrenaline and noradrenaline in washed cell pellets after incubation are given in Table 1.

The inhibitory effect of adrenaline on TL release was not reduced by the adrenergic α_1-receptor antagonist prazosin (Fig. 2A), nor β-receptor antagonist propranolol (Fig. 2B). Salbutamol, a non-catechol β_2-agonist, did not inhibit LT release, whereas caffeic acid, a non-adrenegic catechol compound, was effective.

To test the importance of metabolism, the effect of adrenaline on the formation of 20-OH-LTB_4 and 20-COOH-LTB_4, metabolites of LTB_4, was measured in A23187-stimulated PMNs. The basal levels of 20-COOH-LTB_4 was 21 ng/10^6 cells and of 20-COOH-LTB_4 4 ng/10^6 cells. The formation of both metabolites declined during adrenaline stimulation in a dose-dependent manner thus excluding the possibility that the decline in LTB_4 had been caused by increased metabolism.

DISCUSSION

Our major finding was a marked and diametrically opposite effect of catecholamines on the synthesis of PGs and LTs. Although it is known that adrenaline, noradrenaline and dopamine stimulated PG-biosynthesis [1, 4, 17], and that various compounds with catechol structure inhibit formation of LTs [5–10], the effect of endogenous catecholamines on LT production has not been substantiated. Particularly the studies have not been conducted in the same test system. Therefore a change in the LT/PG ratio with its possible physiological implications has not been revealed. On the other hand, the existing abundant preliminary evidence with catechol compounds, both in PG and LT synthesis, gives our findings in PMNs wider biological importance as a kind of model.

In inhibition of LT synthesis, the potency of adrenaline and isoprenaline was comparable to that of timegadine [12] and BW 755C [7], which inhibit both cyclo-oxygenase and lipoxygenase, but much less than the potency of specific inhibitors of lipoxygenase [18]. The biological effects of PGs and LTs are very different, and any major change in the LT/PG ratio could be related to some specific properties of catecholamines. On the other hand, from our data it is quite evident that the changes in the LT/PG ratio do not represent a mere shift in the metabolism of arachidonic acid. PGE_2 comprises only a fraction (about 1%) of the amount of LTB_4, and the same enzymes may not produce both PGs and LTs. PGE_2 is a factor that may reduce LT release [10], but even this explanation is not likely as the effects of catecholamines were not blocked by indomethacin (data not shown).

Neither α- nor β-adrenergic blockade could reverse the inhibition of LT formation, and rather a *chemical interaction with the enzymes* is suggested. The distinction is important, as non-receptor-mediated mechanisms open the possibility that endogenous catecholamines, i.e. those inside the cell, could regulate intracellular eicosanoid metabolism. The activity of caffeic acid further supports chemical interaction, as also the inactivity of salbutamol, a non-catechol β-receptor agonist. A catechol or related phenolic structure is apparently required. The somewhat differing activity of dopamine suggests the importance of side-chain hydroxyl as is the case in PG biosynthesis [17], in which catecholamine may have roles as coenzymes or cosubstrates [1].

The key to a chemical interaction could be in

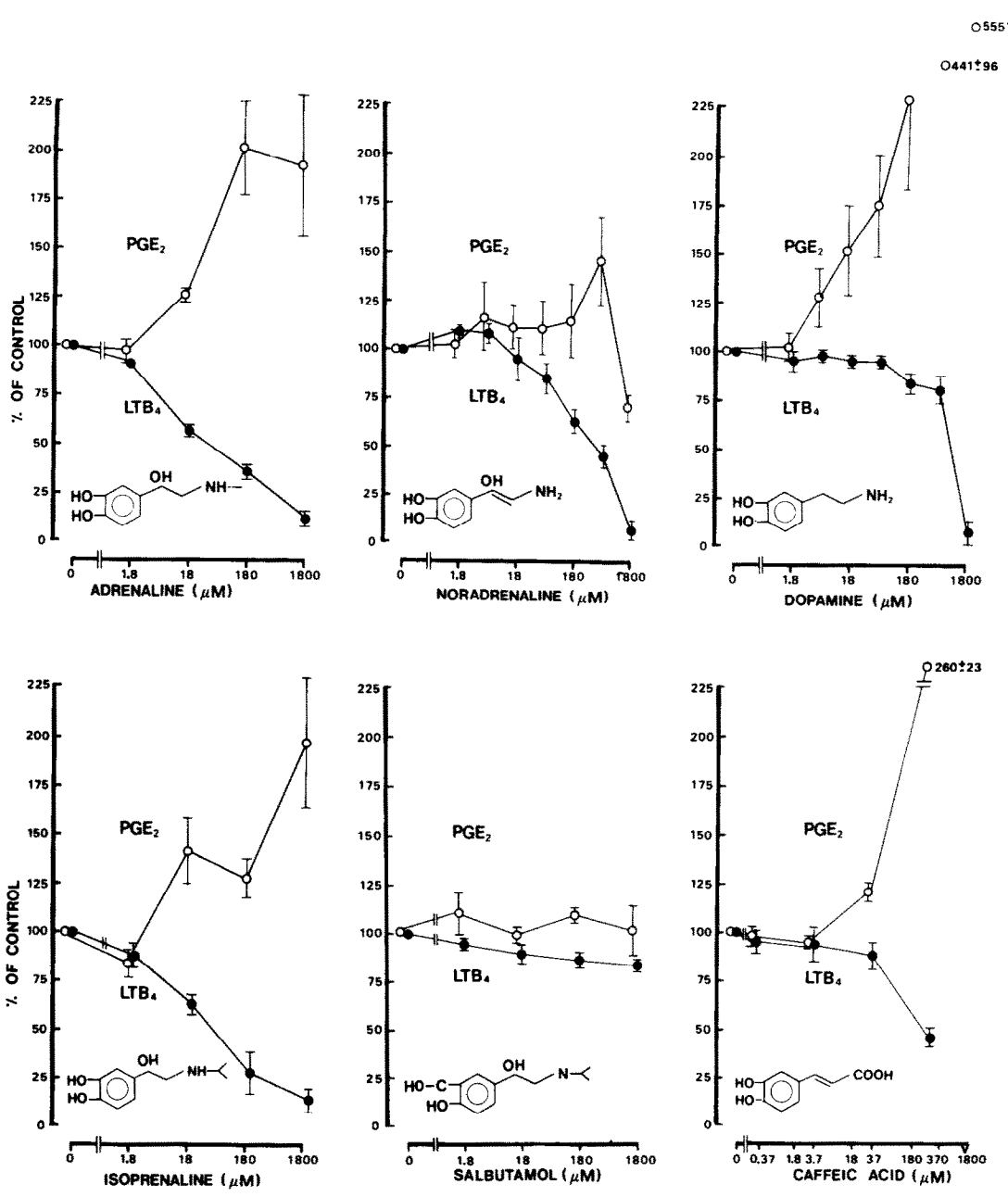

Fig. 1. Effects of catechol compounds on A23187-stimulated release of LTB_4 and PGE_2 from human PMNs (mean ± SE, N = 5–9). Baseline values for PGE_2 58 pg/10^6 cells, and for LTB_4 8.1 ng/10^6 cells. The IC_{50} values, calculated from semi-logarithmic dose–response curves, for LTB_4 release were as follows. Adrenaline 46 ± 10, isoprenaline 73 ± 73, caffeic acid 370 ± 100, noradrenaline 419 ± 105, and dopamine 990 ± 95 μM (mean ± SE, N = 5–9). Salbutamol had no effect.

opposite redox requirements of the enzymes lipoxygenase and cyclo-oxygenase. In active soybean lipoxygenase iron is in the ferric (Fe^{3+}) state, and the inhibitory action of a catechol compound (nordihydroguaiaretic acid) may be based on reduction of the iron to ferrous (Fe^{2+}) state [8]. Ferric iron is required also by human platelet 12-lipoxygenase [19]. On the other hand, in the formation of PGs the reductive capacity of catecholamines increases the synthetic activity [4]. During PG synthesis, higher oxidation states are created with transient radical intermediates [20]. Phenols, and related compounds are oxidized to preserve the enzyme from self-catalysed destruction by the resulting free radicals [21], which in PMNs may be hydroxyl radical [22]. In this sense, catecholamines may function as potent antioxidants that favour a low LT/PG ratio. Depletion, oxidation or other elimination of the phenolic protection could lead to increased levels of free radicals, activation lipoxygenases with a resulting

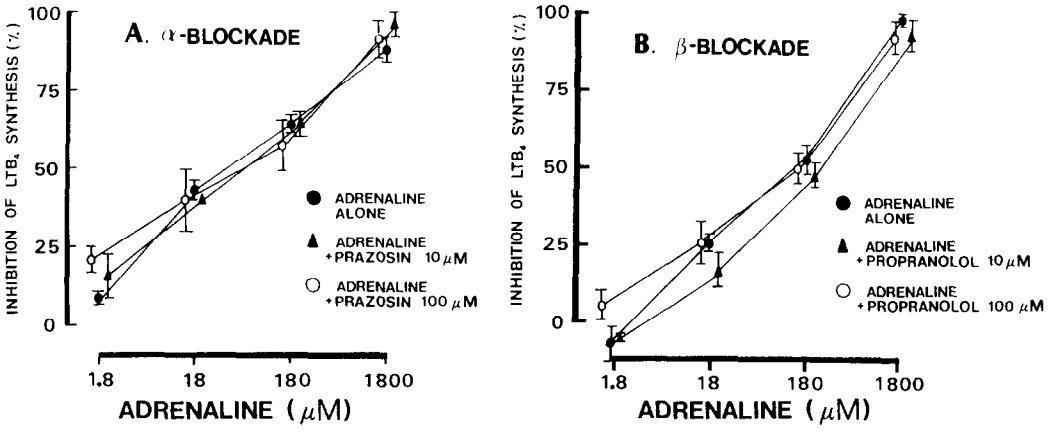

Fig. 2. The inability of adrenergic receptor blockade with prazosin (A) or propranolol (B) to alter the inhibitory action of adrenaline on LTB_4 release from A23187-stimulated human PMNs. Mean ± SE, N = 4.

Table 1.

Concentration of the added amine (μM, final)	Intracellular concentration in the washed PMN pellet (pmol/10^6 cells) Adrenaline	Noradrenaline
0	0.3 ± 0.2	1.2 ± 0.6
1.8	0.5 ± 0.3	16 ± 4
18	2.6 ± 1.3	77 ± 16
180	47 ± 18	325 ± 36
1800	654 ± 126	1082 ± 226

Adrenaline and noradrenaline concentrations in the washed PMN cell pellets after incubation (mean ± SE, N = 6).

overproduction of lipid peroxides with increased LT/PG ratio. Against a biochemical mechanism is the evidence that isoprenaline inhibits LTB_4 release from PMNs through a β-receptor mediated mechanism [10]. The coexistence of both receptor-dependent and intracellular mechanisms only emphasize the importance of catecholamines in LT synthesis.

When the *physiological importance* of the findings is evaluated, the critical question is the tissue concentrations of catecholamines. Their plasma levels in man, in rest about 1–2 nM [23], are far too low to be effective in the model described. Catecholamine levels are, however, markedly higher during stress reactions, as well as in some therapeutic uses of adrenaline, isoprenaline, dopamine or their precursors. Moreover, their concentrations in the tissues vary between 1 and 50 μM, and even millimolar concentrations are detected in specialized cells [24, 25], thus quite sufficient to affect eicosanoid metabolism.

The possible pathological importance of the catecholamine–eicosanoid interaction may best be evaluated in diseases in which both the LT/PG ratio and catecholamines are considered to be of significance. In *gastric mucosa* endogenous PGs, particularly PGE_2, have cytoprotective effects [26], while LTs may be involved in ulcer formation [27]. In the rat, intolerable stress depletes mucosal noradrenaline inducing the formation of gastric ulcers, and healing of ulcers occurs along with a spontaneous or augmented restoration of the noradrenaline stores [28]. For such a cytoprotective effect of catecholamines, maintenance of a low LT/PG ratio would be of particular importance. In *asthma*, LTs are considered as mediators of bronchial constriction [29] while PGEs have mainly bronchodilatory activity [30]. In asthmatic patients, about a threefold increase in the LT/PG ratio has been measured [31], and the enhanced LT release during attacks is markedly inhibited by adrenaline treatment [32]. Asthma has been characterized as a disease with adrenaline deficiency [33, 34], a factor which conveivably could explain the increased LT/PG ratio. In *psoriasis*, the skin lesions are often infiltrated with PMNs with a marked overproduction of LTB_4 (see Ref. 29). As also the PGE and PGF levels may be low [35], a lowered LT/PG balance can be inferred. Catecholamines may reduce mitotic activity in the skin [36], and psoriatic patients may improve from levodopa, a precursor of catecholamines [37].

High intracellular content of catecholamines may provide an antioxidant reserve which is lost when the amine stores are exhausted e.g. *ischemia and inflammation*. Hypoxia may initiate LTB_4-dependent neutrophil (PMN) sequestration [38], and depletion of catecholamines [39], both of which may occur in subarachnoidal hemorrhage [40, 41]. In intolerable pain-stress the noradrenaline contents in many tissues decrease to very low levels, in an inverse relation to vulnerability of the tissues [42]. *New therapeutic possibilities* may be opened, as catecholamines and their precursors could be used to reduce the LT/PG ratio in anaphylactic conditions and to restore lowered tissue level. Likewise, a simultaneous use of catecholamines and nonsteroidal anti-inflammatory drugs (NSAID) could provide means to block the formation of both PGs and LTs.

In *conclusion*, catecholamines have a marked regulatory effect on eicosanoid synthesis in PMNs,

particularly on the LT/PG ratio, through a receptor-independent chemical mechanism. As the principles that regulate biosynthesis of PGs and LTs are met, the mechanism could be physiologically valid in tissues with sufficient concentrations of the amines.

REFERENCES

1. Sih CJ, Takeguchi C and Foss P, Mechanism of prostaglandin biosynthesis. III. Catecholamines and serotonin as coenzymes. *J Am Chem Soc* **92**: 6670, 1970.
2. Baumann J, Wurm G and V Bruchhausen F, Hemmung der prostaglandinsynthetase durch Flavonoide und Phenolderivative im Vergleich mit deren O_2·⁻-radikalfängereigenschaften. *Arch Pharm* **313**: 330-337, 1980.
3. Collier HOJ, McDonald-Gibson J and Saeed SA, Inhibition by drugs of the stimulation of prostaglandin biosynthesis induced by apomorphine. In: *Advances in Prostaglandin and Thromboxane Research* (Eds. Samuelsson B and Paoletti R), Vol. 1, pp. 391–393. Raven Press, New York, 1976.
4. Yamamoto S, Ohki S, Ogino N, Shimizu T, Yoshimoto T, Watanabe K and Hayaishi O, Enzymes involved in the formation and further transformation of prostaglandin endoperoxides. In: *Advances in Prostaglandin and Thromboxane Research* (Eds. Samuelsson B, Ramwell P W and Paoletti R), Vol. 6, pp. 27–34. Raven Press, New York, 1980.
5. Panossian AG, Inhibition of arachidonic acid 5-lipoxygenase of human polymorphonuclear leukocytes by esculetin. *Biomed Biochim Acta* **43**: 1351–1355, 1984.
6. Landolfi R, Mower RL and Steiner M, Modification of platelet function and arachidonic acid metabolism by bioflavonoids. *Biochem Pharmacol* **33**: 1525–1530, 1984.
7. Salari G, Braquet P and Borgeat P, Comparative effects of indomethacin, acetylenic acids, 15-HETE, nordihydroguaiaretic acid and BW 755C on the metabolism of arachidonic acid in human leukocytes and platelets. *Prostaglandins Leukotrienes Med* **13**: 53–60, 1984.
8. Kemal C, Louis-Flamberg P, Krupinski-Olsen R and Shorter AL, Reductive inactivation of soybean lipoxygenase 1 by catechols: a possible mechanism for regulation of lipoxygenase activity. *Biochemistry* **26**: 7064–7072, 1987.
9. Koshihara Y, Neichi T, Murota S-I, Lao Al-Na, Fujimoto Y and Takashi T, Caffeic acid is a selective inhibitor for leukotriene biosynthesis. *Biochim Biophys Acta* **6792**: 92–97, 1984.
10. Nielson CP, Beta-adrenergic modulation of the polymorphonuclear leukocyte respiratory burst is dependent upon the mechanism of cell activation. *J Immunol* **139**: 2392–2397, 1987.
11. Alanko J, Moilanen E, Vapaatalo H and Parantainen J, Effects of Caffeic Acid, noradrenaline and salbutamol on leukotriene production in polymorphonuclear leukocytes *in vitro*. XXXIII Nordic Meeting of Pharmacology, June 2–5, 1987, Kuopio. *Pharmacol Toxicol* **60**:(Suppl. III) 35, 1987.
12. Moilanen E, Alanko J, Seppälä E and Vapaatalo H, Effects of antirheumatic drugs on leukotriene B_4 and prostanoid synthesis in human polymorphonuclear leukocytes in vitro. *Agents Actions* **24**: 387–394, 1988.
13. Seppälä E, Pora O and Metsä-Ketelä T, A modified method for extraction and purification of prostaglandins with resin XAD-2. *Prostaglandins Leukotrienes Med* **14**: 235–241, 1984.
14. Zijlstra FJ & Vincent JE, Determination of leukotrienes and prostaglandins in (^{14}C) arachidonic acid labelled human lung tissue by high-performance liquid chromatography and radioimmunoassay. *J Chromatogr* **311**: 30–50, 1984.
15. Moilanen E, Alanko J, Juhakoski A and Vapaatalo H, Orally administered tolfenamic acid inhibits leukotriene synthesis in isolated human peripheral polymorphonuclear leukocytes. *Agents Actions* **26**: 83–88, 1989.
16. Goldstein DS, Feuerstein G, Izzo Jr JL, Kopin IJ and Keiser HR II, Validity and reliability of liquid chromatography with electrochemical detection for measuring plasma levels of norepinephrine. *Life Sci* **28**: 467–475, 1981.
17. Pace-Asciak CR, Catecholamine induced increase in prostaglandin E biosynthesis in homogenates of the rat stomach fundus. *Adv Biosci* **9**: 29–33, 1973.
18. Hammond ML, Kopka IE, Zambias RA, Caldwell CG, Boger J, Baker F, Bach T, Luell S, MacIntyre DE, 2,3-Dihydro-5-benzofuranols as antioxidant-based inhibitors of leukotriene synthesis. *J Med Chem* **32**: 1006–1020, 1989.
19. Aharony D, Smith JB, Silver MJ, Human platelet lipoxygenase requires ferric iron. *Fed Proc* **39**: 424, 1980.
20. Karthein R, Diez R, Nastainczyk W, Ruf HH, Higher oxidation states of prostaglandin H synthase. EPR study of a transient tyrosyl radical radical in the enzyme during the peroxidase reaction. *Eur J Biochem* **171**: 313–320, 1988.
21. Egan RW, Gale PH, Beveridge GC, Marnett LJ and Kuehl Jr FA, Direct and indirect involvement of radical scavengers during prostaglandin biosynthesis. In: *Advances of Prostaglandin and Thromboxane Research* (Eds. Samuelsson B, Ramwell PW and Paoletti R), Vol. 6, pp. 153–155. Raven Press, New York, 1980.
22. Sagone AL, Wells RM and DeMocko C, Evidence that OH· production by human PMNs is related to prostaglandin metabolism. *Inflammation* **4**: 65–71, 1980.
23. Laustiola K, Seppälä E, Vuorinen P, Salo M, Uusitalo A and Vapaatalo H, The effect of pindolol on exercise-induced increase in plasma vasoactive prostanoids and catecholamines in healthy men. *Prostaglandins Leukotrienes Med* **20**: 111–120, 1985.
24. Vapaatalo H and Karppanen H, Blood glucose, serum GOT and tissue catecholamines in rats after combined ethanol-tranquilizer administration. *Agents Actions* **1**: 206–210, 1970.
25. Holzbauer M and Sharman DF, The distribution of catecholamines in vertebrates. In: *Catecholamines* (Eds. Blaschko H, Muscholl E), pp. 110–185. Springer, Berlin, 1972.
26. Robert A, Cytoprotection by prostaglandins. *Gastroenterology* **77**: 761–767, 1979.
27. Peskar BM, Hoppe U, Lange K and Peskar BA, Effects of non-steroidal anti-inflammatory drugs on rat gastric mucosal leukotriene C_4 and prostanoic release: relation to ethanol-induced injury. *Br J Pharmacol* **93**: 937–943, 1988.
28. Zabrodin ON, The effect of dopa and tyrosine on the healing of ulcerations of the gastric wall and norepinephrine content therein. *Biull Eksp Biol Med* **72**: 32–35, 1971.
29. Ford-Hutchinson AW, Leukotriene involvement in pathologic processes. *J Allergy Clin Immunol* **74**: 437–440, 1984.
30. Mathé AA, Hedqvist P, Strandberg K and Leslie CA, Aspects of prostaglandin function in the lung. I and II. *N Engl J Med* **296**: 850–855 and 910–914, 1977.
31. Yen S and Morris HG, An imbalance of arachidonic acid metabolism in asthma. *Biochem Biophys Res Commun* **103**: 774–779, 1981.
32. Schwartzberg B, Shelov SP and Van Praag D, Blood leukotriene levels during the acute asthma attack in

children. *Prostaglandins Leukotrienes Med* **26**: 143–155, 1987.
33. Mathé A and Knapp PH, Decreased free fatty acids and urinary epinephrine in bronchial asthma. *New Engl J Med* **281**: 234–238, 1969.
34. Barnes PJ, Fitzgerald G, Brown MJ and Dollery CT, Nocturnal asthma and changes in circulating epinephrine, histamine and cortisol. *New Engl J Med* **303**: 263–267, 1980.
35. Aso K, Sakamoto N, Farber E, Deneau D, Krulig D and Wilkinson D. The synthesis of prostaglandins E_2 and F_2 in psoriatic skin. *J Invest Dermatol* **60**: 111, 1973.
36. Voorhees JJ, Duell EA, Stawiski M and Harrell R, Cyclic nucleotide metabolism in normal and proliferating epidermis. In: *Advances in Cyclic Nucleotide Research* (Eds Greengaard P and Robinson GA), Vol. 4, pp. 117–162. Raven Press, New York, 1974.
37. Savery F, Karassik S and Gast J, A comparative evaluation of the antipsoriatic effect of l-dopa versus placebo in psoriasis. *Curr Ther Res* **20**: 130–133, 1976.
38. Gillispie MN, Kojima S, Owasoyo JO, Tai HH and Jay M, Hypoxia provokes leukotriene-dependent neutrophil sequestration in perfused rabbit hearts. *J Pharmacol Exp Ther* **241**: 812–818, 1987.
39. Jones C, Roebuck M and Walker D, The effect of adrenal medullary activity on the sensitivity to catecholamine stimulation of the sympathetic system in fetal sheep. In: *Catecholamines: Basic and Peripheral Mechanisms* (Eds. Usdin E, Carlsson A, Dahlström A and Engel J), pp. 121–128. Alan R. Liss, Inc., New York, 1984.
40. Kiwak KJ, Moskowitz MA and Levine L, Leukotriene production in gerbil brain after ischemic insult, subarachnoid hemorrhage, and concussive injury. *J Neurosurg* **62**: 865–869, 1985.
41. Tsukahara T, Taniguchi T, Miwa S, Shimohama S, Fujiwara M, Nishikawa M and Handa H, Presynaptic and postsynaptic alpha 2-adrenergic receptors in human cerebral arteries and their alteration after subarachnoid hemorrhage. *Stroke* **19**: 80–83, 1988.
42. Anichkov SV, Zavodskaya IS, Moreva EV and Korkhov VV, Effect of dioxyphenylalanin (DOPA) upon development of experimental neurogenic gastric ulcers. In: *Peptic Ulcer* (Ed. Pfeiffer CJ), pp. 307–311. Munksgaard, Copenhagen, 1971.