Renal and Systemic Hemodynamic Responses to Intravenous Infusion of Leukotriene C₄ in the Rat

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SUMMARY. We studied the systemic and renal hemodynamic effects of leukotriene C₄ (2 µg/kg per min for 5 minutes, iv) in the rat. During the period of its infusion, leukotriene C₄ produced a significant elevation of mean arterial pressure and reductions in cardiac output and renal blood flow, as measured by electromagnetic flow probes. These effects were abolished by FPL55712, a putative antagonist of sulfidopeptide leukotrienes, but not by saralasin or indomethacin. Leukotriene C₄ also resulted in an average loss of 20% in plasma volume which, during the postinfusion period, perpetuated the low cardiac output state and thus provoked the release of angiotensin II. This vasoactive peptide sustained the elevation in systemic vascular resistance and the reduction in renal blood flow over a 70-minute postinfusion observation period. Consequently, glomerular filtration rate fell by approximately 50%. These angiotensin II-mediated effects were abolished by saralasin. Indomethacin prevented the leukotriene C₄-induced loss of plasma volume and, thus, allowed for the significant recovery of cardiac output and renal blood flow during the postinfusion period, thereby preserving glomerular filtration rate. We conclude that leukotriene C₄ exerts direct systemic and renal vasoconstrictor, as well as cardiodepressant effects, during the period of its infusion. By virtue of its vasopermeability enhancing effect, leukotriene C₄ also results in an immediate loss of plasma volume, an effect which requires the presence of secondarily generated cyclooxygenase products and which perpetuates the hemodynamic abnormalities observed beyond the period of leukotriene C₄ infusion. (Circ Res 54: 492-499, 1984)

LEUKOTRIENES (LT) are products of arachidonic acid metabolism which are formed via the 5-lipoxygenase pathway (Samuelsson et al., 1979). The sulfidopeptide leukotrienes, 5S-hydroxy-6R,S-glutathionyl-7,9-trans-11,14-cis-eicosatetraenoic acid (LTC₄), 5S-hydroxy-6R,S-cysteinylglycyl-7,9-trans-11,14-cis-eicosatetraenoic acid (LTD₄), and 5S-hydroxy-6R,S-cysteiny1-7,9-trans-11,14-cis-eicosatetraenoic acid (LTE₄), together constitute the activity previously known as slow reacting substance of anaphylaxis (SRS-A) (Murphy et al., 1979; Lewis et al., 1980a, 1980b; Morris et al., 1980). These compounds elicit arteriolar constriction and augmentation of vascular permeability to macromolecules in postcapillary venules (Drazen et al., 1980; Lewis et al., 1980b; Dahlén et al., 1981), cardiodepression due to coronary arteriolar constriction (Burke et al., 1982; Letts and Piper, 1982; Michelassi et al., 1982; Smedgard et al., 1982; Pfeffer et al., 1983) and pulmonary bronchoconstriction (Dahlen et al., 1980; Hanna et al., 1981; Smedgard et al., 1982; Weiss et al., 1982; Weiss et al., 1983). A separate product derived from the 5-lipoxygenase pathway, 5S,12R-dihydroxy-6,14-cis-8,10-trans-eicosatetraenoic acid (LTB₄) (Borgeat and Samuelsson, 1979; Lewis et al., 1981) is a granulocyte chemotactic factor which increases leukocyte adhesion to endothelial surfaces and causes leukocyte-leukocyte aggregation (Smith et al., 1980; Goetzl and Pickett, 1981; Palmblad et al., 1981; Showell et al., 1982). The biosynthesis of LTC₄ and LTB₄ is carried out by activated neutrophils, eosinophils, and monocyte-macrophages in a number of mammalian species, including the rat (Lewis et al., 1980a; Bach et al., 1980) and the human (Borgeat and Samuelsson, 1979; Fels et al., 1982; Weller et al., 1983), and these products could play a role in mediating the microvascular, and possibly systemic, pathophysiological consequences of tissue injury (Lewis and Austen, 1981).

In the present studies, the direct and indirect effects of intravenously administered LTC₄ on mean arterial pressure (AP), cardiac output (CO), renal blood flow (RBF), systemic and renal vascular resistances (SVR and RVR), plasma volume (PV), and glomerular filtration rate (GFR) are described in the rat. By pretreating rats with the putative leukotriene receptor blocker, FPL55712 (Augstein et al., 1973; Fleisch et al., 1982), the cyclooxygenase inhibitor indomethacin (Vane, 1971), and the angiotensin receptor antagonist, saralasin (Streeten et al., 1976), the direct effects of LTC₄ could be separated from those of secondarily generated cyclooxygenase products and of angiotensin II.
Methods

LTC₄ was prepared by total organic synthesis, as previously described (Corey et al., 1980), and was stored under argon at ~80°C in 20 mM sodium phosphate buffer, pH 6.8: ethanol, 4:3 (vol/vol). For each experiment, the LTC₄ stock solution and the vehicle, lacking LTC₄, were diluted to final concentration in 0.9% sodium chloride solution. Indomethacin and sarasaline were purchased from Sigma Chemical Co. and FPL55712 was a gift from the Fisons Corp., Loughborough, U.K.

Experiments were performed on adult male Munich-Wistar rats (200–330 g) maintained on a standard rat pellet diet and allowed free access to water. Each rat was anesthetized with Inactin (100 mg/kg, ip) and placed on a heated surgical table so that body temperature was maintained at 36.5 to 37.5°C throughout the course of the experiment. Polyelectrolyte catheters (PE 50) were placed in the left femoral artery and vein. The arterial catheter was used for blood sampling and measurement of AP with an electronic transducer (model P23Db, Statham Instruments Division, Gould Inc.) connected to a direct writing recorder (model 7754A, Hewlett-Packard Co.). The venous catheter was used for infusion of homologous rat plasma as required to maintain euvelomia (Ichikawa et al., 1978). After a tracheostomy, PE 50 catheters were introduced into both jugular veins for the administration of a 7% inulin solution in 0.9% NaCl at the rate of 1.2 ml/hr, and for infusion of LTC₄ or vehicle. The left kidney was exposed via a subcostal incision and the left ureter was catheterized with PE 10 tubing. An electromagnetic flow probe (i.d. = 1.5 mm) was placed around the left renal artery and connected to a flowmeter (Carolina Medical Electronics, model 501), the output of which was displayed on a second channel of the Hewlett-Packard recorder. In rat groups designated IV and V, the tracheal cannula was connected to a small-animal ventilator, an anterior thoracotomy was performed, and an electromagnetic flow probe (i.d. = 2.0 mm, Statham) was placed on the ascending aorta for continuous monitoring of CO on a third channel of the Hewlett-Packard recorder.

After a 45- to 60-minute period during which AP, RBF, and urine flow, and CO were constant, two 15-minute clearance measurements were performed, and control values for AP, RBF, and CO were recorded. Vehicle or LTC₄ solution was then administered at a rate of 0.1 ml/min (2 µg LTC₄/kg per min) for 5 minutes. Hemodynamic indices were monitored continuously throughout the infusion of either vehicle or LTC₄ and observed for an additional 70-minute postinfusion period in groups I, II, III, and VII and for 15 minutes in groups IV and V. Clearance measurements were repeated during the postinfusion period.

The experimental groups were designated as follows:

Group IA: infusion of vehicle followed by a second infusion of vehicle (n = 6). Group IB: infusion of vehicle followed by infusion of LTC₄ (n = 12).

Group II: infusion of vehicle followed by LTC₄, each in the presence of sarasalain, 5 µg/kg per min, iv (n = 6).

Group III: infusion of vehicle followed by LTC₄, each in the presence of indomethacin, 2 mg/kg, over 10 minutes, followed by 2 mg/kg per hr, iv (n = 7).

Group IV: infusion of vehicle followed by LTC₄ in animals with thoracotomy and monitoring of CO (n = 7). In six animals, rat plasma (1.5–2 ml over 5 minutes was infused 15 minutes after LTC₄ infusion in order to restore hematocrit to pre-LTC₄ values (see below).

Group V: infusion of vehicle followed by LTC₄ in the presence of indomethacin in animals with thoracotomy and monitoring of CO (n = 4).

Group VI: red blood cell (RBC) volume determined using ⁵¹Cr-labeled cells (Sterling and Gray, 1950), both before and after vehicle administration and again after LTC₄ infusion (n = 8).

Group VII: FPL55712, 500 µg/kg per min, infused beginning 1 minute before and terminating 1 minute after the LTC₄ infusion (n = 5).

Since AP, RBF, and CO were constant for 45–60 minutes prior to LTC₄ or vehicle infusion, values for those parameters obtained immediately prior to LTC₄ or vehicle administration were considered as preinfusion controls. These measurements were compared to those observed at the end of the 5-minute LTC₄ infusion, as well as to those which were obtained 15 minutes after the end of this infusion (i.e., minute 20, on Figs. 1, 2, and 4). This last point was chosen to present postinfusion values for the purposes of statistical analysis since, at 20–75 minutes postinfusion, AP, RBF, and CO were constant. End infusion and postinfusion values within groups were compared with preinfusion values using a one-way analysis of variance with a Bonferroni correction for multiple preplanned comparisons. GFR, Hct, and RBC volumes were measured twice within each group: before LTC₄ infusion, and also during the postinfusion period (min 5–20). These two values were compared by paired Student’s t-test. In all comparisons, a P value of < 0.05 was required for statistical significance. Results are presented as means ± SEM.

Results

AP remained at preinfusion levels (106 ± 4 mm Hg) throughout the vehicle infusion period (maximally 108 ± 3 mm Hg, mean ± SEM, group IA). Administration of LTC₄ resulted in an immediate elevation in AP from a baseline of 114 ± 3 to 125 ± 3 mm Hg (P < 0.001, group IB) (Fig. 1A) and a return to control levels within 1–2 minutes of stopping the infusion. The presence of saralasin did not prevent an LTC₄-induced rise in AP from 122 ± 5 to 133 ± 5 mm Hg, (P < 0.005, group II), nor did indomethacin (107 ± 4 to 119 ± 4 mm Hg, P < 0.001, group III); neither treatment prolonged the LTC₄-induced elevation in AP beyond the infusion period. In contrast, the addition of FPL55712 to the infusion prevented any significant increase in AP from a baseline of 114 ± 3 to 125 ± 3 mm Hg (P < 0.001, group IV) (Fig. 1B).

RBF (6.9 ± 0.6 ml/min preinfusion) was not significantly affected by vehicle infusion (7.3 ± 0.6 ml/min immediately postinfusion, group IA). LTC₄ administration resulted in an immediate reduction in RBF from 6.5 ± 0.3 which progressed to 5.0 ± 0.3 ml/min (P < 0.001, group IB), at 5 minute and to a nadir of 4.3 ± 0.4 ml/min in the immediate postinfusion period, and was persistently depressed over the entire 65-minute period of subsequent measurements (Fig. 2A). Although the fall in RBF which occurred during the infusion of LTC₄ in the presence of saralasin (6.4 ± 0.3 to 5.4 ± 0.3 ml/min, P < 0.025, group II) or indomethacin (6.6 ± 0.3 to 5.7 ± 0.3 ml/min, P < 0.005, group III) was less than in the group not treated with these drugs (Fig. 2B), the difference was not statistically significant (P = 0.052, group II vs. group IA).
FIGURE 1. Time course of changes in AP before, during, and after infusion of LTC4 or vehicle. Panel A: comparison of groups IA (vehicle) (*), IB (LTC4) (.), II (LTC4 + saralasin) (.), and III (LTC4 + indomethacin) (▲). Panel B: comparison of groups IB and VII (LTC4 + FPL55712) (□). *P < 0.05 vs. measurements in preinfusion control period. Values are mean ± SEM.

0.3 ml/min, $P < 0.01$, group III) was significant, RBF returned to normal 5 minutes (indomethacin) and 15 minutes (saralasin) after stopping LTC4 infusion (Fig. 2A). LTC4-mediated changes in RBF were completely prevented by FPL55712 (6.7 ± 0.2 to 6.7 ± 0.2 ml/min, group VII) (Fig. 2B).

GFR (0.90 ± 0.10 ml/min) was unaffected by administration of vehicle (0.91 ± 0.10 ml/min, group IA). In contrast, LTC4 infusion resulted in a reduction in GFR from 0.90 ± 0.10 to 0.46 ± 0.12 ml/min ($P < 0.005$, group IB) (Fig. 3). The LTC4-induced fall in GFR was prevented by saralasin infusion (1.01 ± 0.03 pre-LTC4 vs. 0.94 ± 0.01 ml/min post-LTC4, group II), pretreatment with indomethacin (0.98 ± 0.08 preinfusion vs. 0.98 ± 0.10 ml/min postinfusion, group III) and the presence of FPL55712 (0.95 ± 0.01 preinfusion vs. 1.10 ± 0.12 ml/min postinfusion, group VII) (Fig. 3).

A significant reduction in CO from 35.4 ± 1.8 to 26.5 ± 2 ml/min occurred 1–2 minute after the initiation of the LTC4 infusion. By the end of the LTC4 infusion, CO had fallen to a minimum of 23.5 ± 0.8 ml/min ($P < 0.01$, group VI) and remained depressed for the remaining 15 minutes of observation (Fig. 4A). The reduction in CO was accompanied by a rise in SVR from 2.7 ± 0.2 to 4.5 ± 0.2 mm Hg/ml per min ($P < 0.05$) at 5 minutes and to 3.7 ± 0.3 mm Hg/ml per min ($P < 0.025$) at 20 minute (Fig. 4B). Pretreatment with indomethacin (group V) prevented the fall in CO during LTC4 infusion (34.6 ± 4.4 preinfusion to 28.8 ± 5.0 ml/min immediately postinfusion), as well as during the postinfusion observation period (32.2 ± 4.0 ml/min) (Fig. 4A). The responses of AP, RBF, and GFR to LTC4 infusion in animals subjected to thoracotomy, without or with indomethacin pretreatment (groups IV and V, respectively), were similar to those of animals treated under the same protocol, but without thoracotomy (groups IB and III, respectively).

Vehicle administration had no effect on hematocrit (Hct) (47.6 ± 0.6 preinfusion vs. 47.3 ± 0.7 vol% postinfusion, group IA), whereas infusion of LTC4 resulted in an immediate and sustained increase in Hct (47.4 ± 0.7 vs. 51.9 ± 0.9 vol%, $P < 0.001$, group IB) (Fig. 5). The rise in Hct after LTC4 infusion
was also seen in the saralasin-treated animals (47.3 ± 0.4 vs. 51.8 ± 0.4 vol%, P < 0.001, group II) and in animals subjected to thoracotomy (45.7 ± 0.6 vs. 49.6 ± 1.0 vol%, P < 0.001, group IV). Animals pretreated with indomethacin, and either without thoracotomy (48.0 ± 0.6 to 48.8 ± 0.7 vol%, group III) or with thoracotomy (43.5 ± 1.2 to 43.3 ± 1.5 vol%, group V), or animals receiving FPL55712 (47.5 ± 0.7 vs. 47.4 ± 0.7 vol%, group VII) did not have a rise in Hct (Fig. 5).

Measurements of RBC volume and Hct before and after LTC4 infusion in group VI demonstrated that the former parameter remained constant (7.9 ± 0.1 preinfusion to 7.6 ± 0.2 ml postinfusion), while Hct increased from 49.4 ± 0.6 to 53.4 ± 1.0 vol% (P < 0.005). Thus, calculated PV was significantly reduced, on the average from 8.2 ± 0.3 to 6.5 ± 0.4 ml (P < 0.005) (Fig. 6). In six of the seven animals in group IV, PV losses were replaced 15 minutes after cessation of LTC4 infusion by restoring Hct in each animal to its pre-LTC4 level. This replacement of PV effected an almost complete recovery of CO, SVR, RBF, and RVR (Fig. 7).

Discussion

In the present study, the intravenous administration of LTC4 to Munich-Wistar rats led to an increase in SVR which, despite a progressive fall in CO (Fig.

\begin{figure}
\includegraphics[width=\textwidth]{fig3}
\caption{Comparison of GFR before (open bars) and after (hatched bars) infusion of LTC4 or vehicle in groups IA (vehicle), IB (LTC4), II (LTC4 + saralasin), III (LTC4 + indomethacin), and VII (LTC4 + FPL55712). *P < 0.05 vs. control. Values are mean ± SEM.}
\end{figure}

\begin{figure}
\includegraphics[width=\textwidth]{fig4}
\caption{A: time course of changes in CO before, during, and after infusion of LTC4 (group IV) (A), and LTC4 + indomethacin (group V) (O). Panel B: time course of changes in SVR before, during, and after infusion of LTC4 (group IV) (A), and LTC4 + indomethacin (group V) (O). *P < 0.05 vs. control. Values are mean ± SEM.}
\end{figure}

\begin{figure}
\includegraphics[width=\textwidth]{fig5}
\caption{Comparison of Hct before (open bars) and after (hatched bars) infusion of LTC4 or vehicle in groups IA (vehicle), IB (LTC4), II (LTC4 + saralasin), III (LTC4 + indomethacin), IV (LTC4 in animals subjected to thoracotomy), V (LTC4 + indomethacin in animals subjected to thoracotomy), and VII (LTC4 + FPL55712). *P < 0.05 vs. control. Values are mean ± SEM.}
\end{figure}
FIGURE 6. Comparison of plasma volume before (C) and after (E) infusion of LTC4 in group VI animals. *P < 0.05 vs. C for mean ± SEM.

FIGURE 7. Percent changes in Hct, AP, CO, RBF, SVR, and RVR from preinfusion control period (C), to 20 minutes after LTC4 infusion (E), and 10–15 minutes later, following PV replacement (E'), *P < 0.05 vs. C.

A), resulted in a net increase in AP of ~10 mm Hg (Fig. 1A). The likelihood that this effect is due to a direct action of LTC4 is suggested by its occurrence in the presence of saralasin (group II) or indomethacin (group III), the coincidence of its time course with that of LTC4 administration, and its abrogation by the LTC4 end-organ antagonist, FPL55712 (Fig. 1, A and B). The normalization of AP in the post-LTC4 infusion period is attributable to the balance between decreased CO and increased SVR, as has been reported previously (Pfeffer et al., 1983). The fall in CO during and after LTC4 infusion was not significant in the presence of indomethacin (Fig. 4), and was thereby probably evoked by a secondarily generated cyclooxygenase product (Fig. 4).

Despite an increase in renal perfusion pressure during LTC4 administration, in parallel with the increase in AP, there was a significant reduction in RBF due to a marked increase in RVR. Since the fall in RBF and the calculated rise in RVR is blunted, but not abolished, by either indomethacin or saralasin (Fig. 2), it is presumed to result from the combined effects of LTC4 and secondarily released endogenous vasoconstrictors. That the major proportion of the rise in RVR persists in the presence of saralasin and indomethacin (Fig. 2A), but is abrogated by FPL55712 (Fig. 2B) suggests that direct LTC4-mediated vasoconstriction is the principal underlying mechanism. This finding substantiates recent observations by Rosenthal and Pace-Asciak (1983) who demonstrated potent vasoconstriction of the isolated, perfused rat kidney by LTC4 and LTD4 which was inhibitable by FPL55712 but not by indomethacin or OKY-1581, a presumed inhibitor of thromboxane synthesis. In the post-LTC4 infusion period, no recovery in RBF was noted (group IB), whereas complete recovery occurred in animals infused with LTC4 and saralasin simultaneously (group II) or pretreated with indomethacin before LTC4 infusion (group III) (Fig. 2A). The recovery of renal perfusion in these animals indicates that the direct action of LTC4 on RVR is limited to the period of its infusion. Further, the capacity of saralasin to abolish this effect completely suggests that endogenously released angiotensin II mediates the persistent increase in RVR in the postinfusion period. The capacity of indomethacin to produce a recovery of RBF implicates the action of one or more cyclooxygenase products in the same cascade that leads to angiotensin II release and renal vasoconstriction. Finally, since the leukotriene antagonist FPL55712 abolished the fall in RBF which occurred during the infusion of LTC4 and, also, that occurring during the postinfusion period (Fig. 2B), it is likely that a primary effect of LTC4 is required for the persistent secondary events to ensue.

In rats treated with LTC4 (group IB), GFR fell by nearly 50%, as shown by comparison of inulin clearances in the pre- and postinfusion periods (Fig. 3). That no change in GFR was noted in rats that...
received LTC$_4$ in the presence of saralasin (group II), indomethacin (group III), or FPL55712 (group VII) (Fig. 3) implies that the presence or absence of a persistent fall in renal perfusion (Fig. 2A) was critical. Further, since the fall in GFR in group IB was proportionately greater than the fall in renal plasma flow (i.e., filtration fraction fell on the average from 0.27 to 0.21), another mechanism, in addition to the fall in RBF, must pertain. The efficacy of saralasin in abolishing the LTC$_4$-mediated fall in RBF and GFR, coupled with a previous demonstration of the capacity of angiotensin II to lower the glomerular capillary ultrafiltration coefficient (Kf) (Blantz et al., 1976), suggests that an angiotensin II-mediated fall in Kf may be the additional factor. Confirmation of this possibility awaits precise quantification of the renal microcirculatory changes following LTC$_4$ infusion. FPL55712, by preventing all of the LTC$_4$-mediated changes in renal and systemic hemodynamics, also prevented the fall in GFR.

Acute hemoconcentration accompanied the administration of LTC$_4$ in all animals except those treated with indomethacin or FPL55712 (Fig. 5) and was due largely to a fall in circulating PV (Fig. 6). The average 20% loss of PV is consistent with the known potency of LTC$_4$ for increasing the permeability of postcapillary venules to fluid and macromolecules (Drazen et al., 1980; Lewis et al., 1980b; Dahlen et al., 1981) and significantly contributes to the hemodynamic abnormalities observed in the postinfusion period. That indomethacin prevents LTC$_4$-infused PV losses, as evidenced by a stable hematocrit in groups III and V (Fig. 5), is not only consistent with the capacity of LTC$_4$ to stimulate cyclooxygenase product generation by some cells and tissues (Feuerstein et al., 1981; Folco et al., 1981; Cramer et al., 1983), but also extends previous reports regarding potentiation of leukotriene-mediated local vasopermeability by certain cyclooxygenase products (Williams and Piper, 1980; Wedmore and Williams 1981; Soter et al., 1983). By preventing PV losses, indomethacin prevents a significant fall in CO in the post-LTC$_4$ infusion period (Fig. 4A), and, so, presumably prevents the release of endogenous angiotensin II. Thus, systemic, coronary, and renal vascular resistances promptly return to their respective control levels as evidenced by the normalization of SVR (Fig. 4B) and RBF (Fig. 2A) and preservation of GFR (Fig. 3). This is further supported by observations on saralasin-treated rats (group II) wherein PV losses occur and CO is presumably depressed, but RVR, RBF, and GFR remain stable during the postinfusion period. That the LTC$_4$-evoked losses of PV are of primary importance in mediating the postinfusion hemodynamic abnormalities is substantiated by their reversal with PV replacement (Fig. 7).

In summary, the intravenous administration of LTC$_4$ in the rat produces striking intrainfusion and postinfusion pathophysiological responses (Fig. 8). During intravenous infusion, the direct vasoconstrictor actions of LTC$_4$ on coronary, renal, and systemic arteriolar beds, respectively, decrease myocardial performance and CO, decrease RBF, and increase AP. Postinfusion responses result from LTC$_4$-mediated increases in vascular permeability which are secondarily dependent upon cyclooxygenase product generation and are blocked by in-
domethacin. When unopposed, the fall in PV perpetuates the depression in CO and in RBF. Endogenously released angiotensin II sustains an increase in RVR, thereby exacerbating the depression in RBF. GFR declines—in part, due to the fall in RBF, and, in addition, due to a likely, but as yet unproven, reduction in $K_t$, presumably mediated by angiotensin II (Blantz et al., 1976).

The physiological alterations that occur during LTC4 infusion appear to be a direct consequence of the LTC4, and are presumably mediated by a specific ligand-receptor interaction as has been recently described for a cultured smooth muscle cell line (Krilis et al., 1983). If this is the case, the antagonism of these direct effects by FPL55712 could not have been anticipated from previous studies of either receptor-ligand binding (Krilis et al., 1983) or physiological responses, as assayed in guinea pig pulmonary parenchymal strips in vitro (Drazen et al., 1980). In both experimental settings, FPL55712 was not a potent antagonist for LTC4-tissue interactions. Indeed, the potent antagonistic effects of FPL55712 on LTD4-mediated pulmonary parenchymal strip contraction and the lack of LTD4 competition for the LTC4 receptor on the smooth muscle cell line and a subcellular fraction from rat lung homogenate have been used as arguments for the existence of separate LTC4 and LTD4 receptors (Drazen et al., 1980; Pong et al., 1983; Krilis et al., in 1983). Therefore, the present observations raise the possibility that such vascular LTC4 receptors as might exist have a different order of ligand specificity than those previously appreciated in nonvascular smooth muscle or that the conversion of LTC4 to LTD4 is responsible for evolving the observed physiological responses.

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References


Palmblad J, Malmstedt C, Uden A-M, Radmark O, Engstedt L, Samuelsson B (1981) Leukotriene C4 is a potent and stereo-
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cific stimulator of neutrophil chemotaxis and adherence. Blood 58: 658-661
Pfeffer MA, Pfeffer JM, Lewis RA, Braunwald E, Corey EJ, Austen
Pong S-S, DeHaven RN, Kuehl FA Jr, Egan RW (1983) Leuko-
triene C4 binding to rat lung membranes. J Biol Chem 258: 9616-9619
Rosenthal A, Pace-Asciak CR (1983) Potent vasoconstriction of
the isolated perfused rat kidney by leukotrienes C4 and D4.
Can J Physiol Pharmacol 61: 325-328
Samuelsson B, Borgeat P, Hammarstrom S, Murphy RC (1979)
Introduction of a nomenclature: Leukotrienes. Prostaglandins
17: 785-787
Showell HJ, Naccache PH, Borgeat P, Picard S, Vallerand P,
Becker EL, Sha’ai RI (1982) Characterization of the secretory
activity of leukotriene B4 toward rabbit neutrophils. J Immunol
128: 811-816
S, Samuelsson B (1982) Leukotriene C4 affects pulmonary and
B4: A potential mediator of inflammation. J Pharm Pharmacol
32: 517-518
Soter NA, Lewis RA, Corey EJ, Austen KF (1983) Local effects of
synthetic leukotrienes. (LTC4, LTD4, and LTE4) in human skin.
J Invest Dermatol 80: 115-119
Sterling K, Gray SJ (1950) Determination of the circulating red
cell volume in man by radioactive chromium. J Clin Invest 29:
1614-1619
Streeten DHP, Castellian AW, Micalizzi ER, Dalakos TC, Anderson
GH Jr, Freiberg GM, Keenan RE (1976) Saralasin (Sar1-
ala8-angiotensin II): Pharmacology and clinical use in angioten-
sin-dependent hypertension. Contrib Nephrol 3: 52-59
Vane JR (1971) Inhibition of prostaglandin synthesis as a mech-
anism of action for aspirin-like drugs. Nature [New Biol] 231:
232-235
Wedmore CV, Williams TJ (1981) Control of vascular permeability
of polymorphonuclear leukocytes in inflammation. Nature 289:
646-650
Weiss JW, Drazen JM, Coles N, McFadden ER Jr, Weller PF, Corey
EJ, Lewis RA, Austen KF (1982) Bronchoconstrictor effects of
leukotrienes in humans. Science 216: 196-198
Weiss JW, Drazen JM, McFadden ER Jr, Weller P, Corey EJ, Lewis
RA, Austen KF (1983) Airway constriction in normal humans
produced by leukotriene D4: Potency, time course, and effect of
acetylsalicylic acid. J Am Med Assoc 249: 2814-2817
Weller PF, Lee CW, Foster DW, Corey EJ, Austen KF, Lewis RA
(1983) Generation and metabolism of 5-lipoxygenase pathway
leukotrienes by human eosinophils: Predominant production
of leukotriene C4. Proc Natl Acad Sci USA 80: 7626-7630
Williams TJ, Piper PJ (1980) The action of chemically pure SRS-
A on the microcirculation in vivo. Prostaglandins 19: 779-789

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