Overall and Regional Hemodynamic Effects of Leukotriene D₄ in Spontaneously Hypertensive Rats

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SUMMARY Leukotriene D₄, a constituent of slow-reacting substance of anaphylaxis, elicits a pressor response followed by hypotensive shock in spontaneously hypertensive rats but not in other rats. Hemodynamic mechanisms underlying this pattern in spontaneously hypertensive rats, pithed and vagotomized to eliminate circulatory reflexes, were studied using radiolabeled microspheres. One minute after leukotriene D₄ administration (20 μg/kg i.v.), mean arterial pressure increased by 54 mm Hg, total peripheral resistance index increased by 68%, heart rate decreased by 34 beats/minute, and cardiac index was unchanged. Profound reductions of blood flow and increases of vascular resistance in the hepatosplanchnic area, skeletal muscles, and skin also occurred. Five minutes later, mean arterial pressure remained elevated (+35%), hematocrit rose (+17%), and total peripheral resistance index increased, which offset 40% decreases in cardiac and stroke volume indices. Ten minutes after leukotriene D₄ administration, during hypotension, cardiac and stroke volume indices and blood flow to all vascular beds declined further while total peripheral resistance index and hematocrit (+28%) continued to rise. In Wistar-Kyoto rats, administration of leukotriene D₄ caused less of a pressor response (+34 mm Hg) because vascular resistance was increased only in skeletal muscles, which was followed by a slight hypotension without any significant changes in cardiac and stroke volume indices, total or regional vascular resistance, and hematocrit. Thus, in spontaneously hypertensive rats the leukotriene D₄-induced pressor response appears to be caused by generalized vasoconstriction, and the subsequent hypotension appears to result not from vascular collapse but from reduced cardiac output. (Hypertension 7: 507-513, 1985)

KEY WORDS • leukotrienes • blood pressure • cardiac output • total peripheral resistance • regional blood flow • regional vascular resistance • spontaneously hypertensive rats • Wistar-Kyoto rats

A CUTE anaphylaxis is characterized by severe hemodynamic changes, cardiac arrhythmias, and myocardial ischemia. All these phenomena can be elicited by systemic or intracardiac administration of slow-reacting substance of anaphylaxis. Recently, leukotriene D₄ (LTD₄) and C₄ (LTC₄), 5-lipoxygenase metabolites of arachidonic acid, were identified as major constituents of slow-reacting substance of anaphylaxis and were shown to cause bronchoconstriction, vasoconstriction, cardiodepression, and increased venular permeability. After systemic administration of leukotrienes to some animal species, an initial arteriolar constriction and rise in blood pressure are followed by a transient hypotensive period. This biphasic response to LTD₄ and LTC₄ is characteristic of guinea pig, monkey, and sheep but is uncommon in various species of rats. Spontaneously hypertensive rats (SHR), however, are extremely sensitive to the cardiovascular effects of LTD₄. The hemodynamic effects of LTD₄ seem to involve peripheral organs as systemic injection of LTD₄ to pithed SHR in which the central nervous system is destroyed causes prolonged, irreversible hypotensive shock, cardiac depression, myocardial ischemia, conduction disturbances, and arrhythmias. In normotensive Wistar-Kyoto rats (WKY) only pressor phase and transient bradycardia and no or slight decrease in blood pressure were present. The hypotensive shock observed in the SHR appears to be a unique phenomenon, since the cysteinyl leukotrienes are only constrictor agents when tested on vas-
cular smooth muscles in vitro, and the moderate degree of pressor responses seen in vivo in other species would not be expected to produce prolonged hypotension and shock.

To further investigate the hypotensive cardiovascular responses of SHR to systemic LTD4, a microsphere technique was used to measure the cardiac output and blood flow to discrete organs during the pressor and shock states elicited by systemic LTD4 administration and compared with hemodynamic effects in normotensive WKY. Pithed, vagotomized rats were studied to exclude the possibly confusing effects of circulatory reflexes.

Methods and Materials

Male, 12- to 14-week-old SHR and WKY (Taconic Farms, Germantown, NY, USA) weighing 300 to 350 g were used in the study. Rats were anesthetized with halothane (2% in oxygen), the left jugular vein and carotid artery were cannulated with PE-50 catheters, and both vagi were cut at the cervical level. A cannula (PE-50 with PE-10 tip) was advanced into the left ventricle through the right carotid artery. Its position was confirmed by obtaining a typical left ventricular pressure tracing (Beckman R511A, Beckman Instruments, Inc., Fullerton, CA, USA), and the location of the tip was adjusted to avoid arrhythmias. The left femoral artery was cannulated with PE-50 tubing for collection of blood samples.

The rats were then intubated and pithed as previously described. This procedure abolishes all reflexes and enables direct study of the effects of vasoactive substances on the vasculature and heart. Immediately after pithing, artificial respiration was started with air enriched with oxygen and 30 minutes was allowed for blood pressure and heart rate to stabilize. Mean arterial pressure (MAP) and heart rate were recorded continuously.

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Cardiac output (ml/min)/injected radioactivity (cpm)/g cardiac output = organ radioactivity (cpm) x sampling rate (ml/min)/reference sample radioactivity (cpm)/body weight (kg). Organ blood flow per gram of tissue was calculated as follows: blood flow (ml/min/g) = organ radioactivity (cpm) x cardiac output (ml/min)/injected radioactivity (cpm)/g of tissue. Total peripheral resistance index (TPRI) and organ vascular resistance were calculated by dividing MAP by CI and corresponding organ blood flow, respectively. Hematocrit was determined before LTD4 administration, during the pressor phase (1 minute after LTD4), 5 minutes after LTD4 administration and during the hypotensive period (10 minutes after LTD4).

Statistical analysis was performed using one-way analysis of variance and Student-Newman-Keuls test for multiple comparisons for the evaluation of hemodynamic data within the groups or Student’s t test for comparisons between the groups of SHR and WKY and for hematocrit. All values in the text and figures are presented as means ± SEM, with p < 0.005 defining statistical significance.

Pure synthetic LTD4 was kindly supplied by Dr. J. Rokach, Merck Frosst Laboratories, Montreal, Quebec, Canada.

Results

Overall Hemodynamic Effects of Leukotriene D4 in Pithed Spontaneously Hypertensive Rats

In SHR, LTD4 (20 µg/kg i.v.) caused an immediate pressor response, which peaked at 30 seconds (+53.8 ± 1.8 mm Hg, p < 0.01; Figure 1, left panel), followed by a gradual decline of MAP (+24.1 ± 2.2 mm Hg at 5 minutes) and then severe hypotension by 10 minutes after LTD4 (−22.6 ± 2.2 mm Hg; p < 0.01). Before LTD4 administration, the CI of the pithed SHR was 247.3 ± 30.9 ml/min/kg (Figure 1), a value 15 to 20% lower than those reported for conscious SHR. During this 1-minute period of the pressor phase, CI...
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did not change significantly but there was a decrease in heart rate (−34 ± 5 beats/min, p < 0.01; see Figure 1) and an increase in left ventricular dp/dt (from 1400 ± 100 to 2184 ± 140 mm Hg/sec; p < 0.01). The stroke volume index was unchanged (see Figure 1). With the initial rise in MAP the TPRI increased from 0.31 ± 0.04 to 0.52 ± 0.07 mm Hg/ml/min/kg (see Figure 1).

Five minutes after LTD₄ administration, MAP remained elevated (+24.1 ± 2.2 mm Hg, p < 0.01; see Figure 1), cardiac and stroke volume indices decreased sharply (by 39%, p < 0.01, and 40%, p < 0.05, respectively), dp/dt fell by 30 ± 5% (p < 0.05), and TPRI increased further to 0.71 ± 0.07 mm Hg/ml/min/kg (p < 0.05; see Figure 1). Moreover, between 5 and 7 minutes after LTD₄ administration, MAP returned to the preinjection level and left ventricular dp/dt fell by 40% from baseline (p < 0.05).

During the subsequent hypotensive phase, TPRI rose further to 1.22 ± 1.21 mm Hg/ml/min/kg (p < 0.01; see Figure 1) and CI fell drastically to 25.0 ± 5.8 ml/min/kg (p < 0.01; see Figure 1), about 10% of the preinjection value. The decrease in cardiac output was associated with an eightfold decrease in stroke volume index and a 60% reduction in left ventricular dp/dt, but heart rate did not change.

Basal MAP, CI, and stroke volume index were lower in pithed WKY than in SHR (61.2 ± 1.2/72.1 ± 1.2 mm Hg, 140.9 ± 20.1/247.3 ± 30.9 ml/min/kg, and 0.59 ± 0.08/1.01 ± 0.12 ml/beat/kg, p < 0.01, respectively; see Figure 1). In addition, LTD₄ caused less of a pressor response in WKY (+36.4 ± 2.4 mm Hg; see Figure 1) and only a slight decrease in MAP at 10 minutes (−8.3 ± 0.6 mm Hg), significantly less than in SHR (p < 0.05; see Figure 1). No significant overall hemodynamic changes were observed in WKY at any time after systemic administration of LTD₄.

**Regional Hemodynamic Effects of Leukotriene D₄ In Pithed Spontaneously Hypertensive and Wistar-Kyoto Rats**

One minute after LTD₄ administration there was a significant increase in the amount of trapped microspheres in the lungs, and this resulted in a calculated increase in bronchial flow in both SHR and WKY (Figure 2A). Because the microspheres were injected into the left ventricle, no important delivery of microspheres through the pulmonary artery should have occurred. In SHR, the lungs also increased in weight from 0.45 ± 0.07% of body weight to 0.66 ± 0.02% (p < 0.05). None of the other organ to body weight ratios changed significantly after LTD₄ administration.

During the pressor phase (1–5 minutes) after LTD₄ administration there were no significant changes in

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**Figure 1.** Hemodynamic effects of systemic administration of LTD₄ (20 μg/kg i.v.) to pithed SHR and WKY. Arrow indicates LTD₄ injections. Asterisks denote statistical significance (Student’s t-test) as follows: *p < 0.005, **p < 0.01, ***p < 0.001. Each point represents a mean ± SEM of six rats.

**Figure 2.** Effect of LTD₄ (20 μg/kg i.v.) on blood flow (BF) and vascular resistance (VR) in the heart, lungs, and kidneys of pithed SHR and WKY. Asterisks denote statistical significance (Student’s t-test) as follows: *p < 0.005, **p < 0.01, ***p < 0.001. Each point represents a mean ± SEM of six rats.
coronary or renal blood flow and vascular resistances in SHR or WKY (see Figure 2A, B). During the depressor phase in SHR coronary, renal, and bronchial blood flow decreased 4-fold, 10-fold, and 42-fold respectively ($p < 0.01$; see Figure 2A) and renal vascular resistance rose 4-fold ($p < 0.01$; see Figure 2B). No changes occurred in blood flow to these beds in WKY.

The splanchnic organs showed a different pattern of blood flow changes. In SHR, 1 minute after LTD$_4$ administration, blood flow to the small intestine was drastically reduced from $1.10 \pm 0.12$ to $0.15 \pm 0.02$ ml/min/g ($p < 0.01$; Figure 3A) and splanchnic vascular resistance was markedly increased (from $0.68 \pm 0.06$ to $9.70 \pm 1.80$ mm Hg/ml/min/100 g, $p < 0.01$; Figure 3B). Blood flow to the spleen also decreased, and vascular resistance rose from $2.30 \pm 0.45$ to $12.13 \pm 1.21$ mm Hg/ml/min/100 g ($p < 0.01$; see Figure 3B). This same pattern of decreased blood flow and increased vascular resistance also was found in the hepatic circulation of SHR (see Figure 3A, B).

Five minutes after LTD$_4$ administration to SHR there was a partial recovery of the reduced blood flow to the liver, spleen, and small intestine that was attended by slight decrease of the markedly elevated vascular resistance in these areas (see Figure 3A, B). During the depressor phase vascular resistances in the small intestine, spleen, and liver continued to rise and correlated well with further reduction in blood flow to the respective organs (Figure 3A, B).

In WKY, blood flow to small intestine and spleen and vascular resistances in these areas did not change significantly at any time after LTD$_4$ administration (see Figure 3A, B, right panel). There was only a transient increase in hepatic blood flow during the pressor phase, without any alteration of the vascular resistance.

In SHR, systemic administration of LTD$_4$ caused an immediate marked increase in vascular resistance in skeletal muscle (from $10.74 \pm 1.68$ to $69.40 \pm 8.97$ mm Hg/ml/min/100 g, $p < 0.01$; Figure 4B) and skin (from $7.03 \pm 1.19$ to $50.10 \pm 3.90$ mm Hg/ml/min/100 g, $p < 0.01$; see Figure 4B). Vascular resistance remained at these high levels in the skeletal muscle through the experimental period. Vascular resistance decreased in the skin after the initial rise at 1 minute but remained at the higher than preinjection levels during the period between 5 and 10 minutes (see Figure 4B), which resulted in persistent, severe reduction of blood flow (Figure 4A). In WKY, the skeletal muscle circulation was the only vascular bed significantly af-

**Figure 3.** Effect of LTD$_4$ (20 μg/kg i.v.) on blood flow (BF) and vascular resistance (VR) in small intestine, spleen, and liver (hepatic bed) of pithed SHR and WKY. Asterisks denote statistical significance (Student's $t$ test) as follows: *$p < 0.005$, **$p < 0.01$, ***$p < 0.001$. Each point represents a mean ± SEM of six rats.

**Figure 4.** Effect of LTD$_4$ (20 μg/kg i.v.) on blood flow (BF) and vascular resistance (VR) in skeletal muscle and skin of pithed SHR and WKY. Asterisks denote statistical significance (Student's $t$ test) as follows: *$p < 0.005$, **$p < 0.01$, ***$p < 0.001$. Each point represents a mean ± SEM of six rats.
fected by systemic administration of LTD₄ (p < 0.01). One minute after LTD₂ administration, blood flow to the skeletal muscles decreased markedly from 0.070 ± 0.010 to 0.030 ± 0.003 ml/min/g (p < 0.01; see Figure 4A) and vascular resistance rose from 9.61 ± 0.99 to 20.90 ± 2.45 mm Hg/ml/min/100 g (p < 0.01; see Figure 4B). These changes gradually subsided, and muscular blood flow normalized 10 minutes after LTD₄ administration.

Blood flow to the adrenal glands of SHR and WKY (1.87 ± 0.62 and 1.36 ± 0.35 ml/min/g respectively) was unchanged during the pressor phase (1.42 ± 0.19 and 1.41 ± 0.15 ml/min/g respectively at 1 minute), but decreased by 67% during the hypotensive period in SHR (0.68 ± 0.19 ml/min/g; p < 0.01).

Pithed SHR and WKY had similar basal hematocrits (43.0 ± 0.8 and 42.8 ± 0.7% respectively). One minute after LTD₂ injection, there was no change in hematocrit as compared to preinjection levels in any group of rats; however, 5 minutes after LTD₂ administration SHR showed a significant increase in hematocrit (+7.3 ± 0.2%; p < 0.01), and further hematocentrization was found during the depressor phase (hematocrit rose to 56.2 ± 0.1%; p < 0.001).

Discussion

The results of the present study demonstrate that systemic administration of 20 μg/kg of LTD₄ (4 × 10⁻⁴ mol/kg) to pithed SHR caused a biphasic cardiovascular response that was associated with severe derangements in overall and regional hemodynamics. The initial pressor phase was found to result from an intense vasoconstriction in most peripheral vascular beds, which contributed to a rise in total peripheral resistance. The findings are in agreement with the known vasoconstrictor effects of LTD₄ and LTC₄ (a precursor of LTD₄) in vitro⁴⁻⁷, ²⁶ as well as in vivo.⁴, ², ⁵, ⁷, ⁸, ¹⁸, ²⁷ The SHR, either pithed or conscious,¹⁰, ²¹ were much more sensitive to the cardiovascular effects of LTD₄ than were other strains of rats (e.g., normal Wistar or Sprague-Dawley and Wistar-Kyoto rats) that show smaller pressor responses and only transient and moderate decreases in blood pressure after systemic administration of LTD₄.

The most striking feature found during LTD₄-induced increase of blood pressure was the immediate, profound reduction in blood flow to the hepatosplanchnic area, especially to the small intestine (10-fold), in SHR. This reduction persisted throughout the pressor phase (up to 5 minutes) and progressed during the later development of the hypotensive phase.

The marked increase in splanchnic vascular resistance appears largely to account for the initial pressor response to LTD₄. In contrast, the renal vascular bed seemed to be unaffected by systemic administration of LTD₄. This finding may indicate a differential sensitivity of the various vascular beds to LTD₄ in SHR. Similar differential effects of LTD₄ on organ blood flow recently were found in dog after direct injections of leukotrienes into the mesenteric or renal arteries.¹⁰ Conversely, LTD₄ has been shown to cause renal vasoconstriction in isolated rat kidney.²⁹ The reduction in renal blood flow observed in our study during the hypotensive period could be a late consequence of shock.

In WKY, only muscular circulation was altered by, and most vascular beds appeared to be much less responsive to, systemic administration of LTD₄. This differential pattern of regional blood flow changes in the hypertensive and normotensive rats suggests differences between the two strains in the type and density of LTD₄ receptors on vascular smooth muscle or the known differences in the vascular sensitivity to pressor substances.

Recently, LTD₄ and LTC₄ have been reported to be potent coronary vasoconstrictors,⁶, ¹², ¹⁵, ²⁶, ²⁷ We did not observe a significant increase in coronary resistance during the pressor phase in either WKY or SHR in the period preceding hypotension; however, despite a marked increase in afterload, especially in SHR, coronary blood flow did not change, which suggests an increase in coronary vascular resistance.

The results of our study indicate that cardiac output was not affected at the peak of the pressor phase. These data do not agree with those of Pfeffer et al.,¹⁷ who reported that LTD₂ and LTC₄ caused reduced cardiac output as early as 30 to 60 seconds after systemic administration to anesthetized Sprague-Dawley rats. The maintenance of cardiac output during the initial pressor phase in our model could be explained by increased myocardial contractility or increased left ventricular filling or both. A few studies have indicated a positive inotropic action of LTD₄ on guinea pig atria²⁶; others have reported cardiodepression¹², ¹⁵, ²⁶ or no effect of LTD₂ on contractility after systemic administration of a high dose of LTD₄ to Sprague-Dawley rats.¹⁳

We found that dp/dt was increased by 60% shortly after LTD₄ administration to SHR, which suggests an increase in contractility especially as the heart faced a simultaneous increase in afterload in this period. Peripheral venoconstriction, however, would have shunted blood toward the heart, increased filling volume, and thereby enhanced left ventricular emptying and thus dp/dt by a Starling effect of LTD₄ on cardiac myocytes. In support of LTD₄-induced venoconstriction, it has been recently suggested that lipoxygenase metabolites alter contractile processes of isolated canine veins to an even greater degree than those of arteries.²⁹ In addition, in our study the administration of LTD₄ to SHR caused a significant decrease in heart rate that also could have contributed to a transient increase in contractility by the Starling effect. The slowing of the heart rate in pithed SHR, which are devoid of reflexes, suggests a negative chronotropic action of LTD₄. Some in vitro studies have also indicated that LTC₄ and LTD₄ reduce the spontaneous rate of isolated guinea pig and rat hearts.¹⁶

Our study clearly indicates that the hemodynamic response pattern to LTD₄ changes dramatically with time. Five minutes after LTD₄ administration, MAP remained elevated and total peripheral resistance continued to rise whereas CO, stroke volume, and dp/dt were markedly reduced. This phase could correspond
to a state of depressed contractility, as several studies have indicated that LTD₄ reduces cardiac contractility either by its direct action on cardiac muscle or through some ischemia-dependent mechanism.⁹,¹²-¹⁶ Administration of LTC₄ (a precursor of LTD₄) into the right atrium of ketamine-anesthetized monkeys has been reported to evoke acute pulmonary as well as systemic hypertension,²³ although immediate changes in pulmonary pressure were not found in normal Wistar¹³ or Sprague-Dawley¹¹ rats. This finding suggests that increased pulmonary vascular resistance after LTD₄ may occur in SHR because of a direct effect on the pulmonary vasculature, as well as the indirect effect of developing congestive heart failure.

According to this scheme, in response to intense vasoconstriction induced by LTD₄, compensatory mechanisms for maintaining CO in the face of increased afterload eventually fail and pulmonary edema and hypotension ensue. As a result, lung weights increase due to pulmonary vascular disruption and leakage of plasma into the extracellular space produces hemoconcentration. It is unlikely, however, that the reduction in CO in response to LTD₄ was due solely to a prolonged elevation of afterload as vasoconstriction of a similar degree and duration caused by norepinephrine infusion in pithed SHR did not cause cardiac failure (unpublished observations, 1984).

The leukotrienes, especially LTD₄, are known to directly enhance the permeability of venules in guinea pig¹⁸ and hamster cheek pouch.¹⁷ In the present study, the first significant increase in hematocrit (+7%) occurred with the reduction of CO, stroke volume, and dp/dt 5 minutes after LTD₄ administration. This hemoconcentration appears to be indicative of plasma extravasation into the extracellular space and decreased circulatory volume, which would impair venous return and contribute to the reduction of CO. By 10 minutes after LTD₄ administration hemoconcentration became even more pronounced (+28%), as were the cardiovascular derangements in SHR.

Recently, Bahr et al.²⁰ have reported that systemic administration of LTC₄ to Wistar rats caused a significant increase in hematocrit (about 8%). In another model of one-kidney, one clip hypertensive rats, we found similar and transient hemoconcentration following LTD₄ administration, but the rats recovered from that and no hypotension was observed.³¹ The presence of marked hemoconcentration in response to LTD₄ in SHR but not WKY or renovascular hypertensive rats³¹ may indicate a significant difference in vascular permeability between these groups of rats. Indeed, SHR have been shown to possess various abnormalities in the microcirculation, such as increased arteriolar rigidity or venular distention and tortuosity early in life,³² which may render this segment of the circulation particularly vulnerable to LTD₄ action. In SHR, microcirculation may represent a locus minoris resistentiae for cardiovascular effects of LTD₄ and contribute to the lack of recovery of cardiac output.

In the present study the calculated bronchial blood flow was increased during the pressor phase of LTD₄ action in both SHR and WKY. As bronchial to pulmonary artery precapillary anastomoses have been described in rat lungs,³³ increased bronchial blood flow may have influenced pulmonary circulation to provide more blood to alveolar capillaries. Whether LTD₄ augments such shunting is unknown. Normally, increased flow through these shunts counterbalances transient inadequacies of pulmonary blood flow; however, in a situation involving enhanced venular permeability, such as that evoked by LTD₄,⁴⁸ that appears to occur in SHR (hemoconcentration) an increase in pulmonary capillary pressure could enhance plasma extravasation into the lungs. This possibility is supported by the 25% increase in lung to body weight ratios during the pressor phase and the 34% increase during the depressor phase in SHR; no such changes were observed in any other organ nor in WKY. It also cannot be ruled out that microspheres could have been trapped excessively in the lungs during venular engorgement or even disruption, which led to erroneously high calculated values for bronchial blood flow.

In conclusion, our results indicate that the immediate cardiovascular effects of systemically administered LTD₄ consist of intense vasoconstriction of the splanchnic, muscular, and cutaneous regions, marked elevation of total peripheral resistance, and increased blood pressure in SHR, whereas in WKY a less intense pressor response was precipitated by muscular vasoconstriction alone. In SHR, this response is followed by a second phase of irreversible hypotensive shock. The depressor phase is associated with a progressive fall in CO, which results from myocardial failure, decreased effective plasma volume, and myocardial ischemia; however, no peripheral vascular collapse occurs because all these phenomena appear during persistent arteriolar constriction that is most pronounced in mesenteric and muscular vascular beds. This secondary phase present in SHR may not be the result of the continuous action of LTD₄ as LTD₄ is rapidly metabolized; moreover, we have previously shown that the hypotension is not reversed by the slow-reacting substance antagonist FPL-55712.²⁰ This depressor phase does not appear to depend on prostaglandin release as we were unable to prevent it by cyclooxygenase inhibition.²¹ Therefore, it appears likely that the hypotensive shock that follows the pressor phase of LTD₄ action in SHR is a result of severe tissue damage caused by intense vasoconstriction and plasma leakage, which resembles that seen during the irreversible stage of anaphylactic shock.¹-³ Hypertensive rats have been previously shown to respond to experimental myocardial infarction with much greater impairment of cardiac performance than normotensive rats.²⁴ It is still not clear why SHR are more prone to the cardiovascular effects of LTD₄, but such sensitivity might be important in pathophysiological states mediated by cysteinyl-leukotrienes (e.g., acute anaphylaxis).

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