N-Ac-Leukotriene E₄
Unique Vascular Activity in the Conscious Rat

G. FEUERSTEIN, a G. LETTS, b AND A-L. SIREN a

a Department of Neurology
Uniformed Services University of the Health Sciences
Bethesda, Maryland 20814

b Merck Frosst
Dorval, Canada H9R 4P8

N-Acetyl-leukotriene E₄ (N-Ac-LTE₄) is a recently discovered metabolite of the cysteinyl leukotrienes (LT). ¹ Although N-Ac-LTE₄ has been identified so far only in the bile, an enterohepatic cycle for LT has been suggested ² that might provide for some LT metabolites access to the systemic circulation. The biological significance of N-Ac-LTE₄ is not known. Experiments conducted in the pig show that N-Ac-LTE₄ has very weak actions on the cardiovascular and respiratory systems. ³ However, the formation of N-Ac-LTE₄ has not been shown as yet in the pig. Therefore, we have decided to examine the effect of N-Ac-LTE₄ in the rat, where LTC₄/D₄/E₄ have potent cardiovascular effects and N-Ac-LTE₄ is a primary metabolite of the LT.

Rats were anesthetized with ketamine-acepromazine. Next, a Doppler flow probe was implanted on the renal (R), mesenteric (M), and abdominal aorta (for hindquarter blood flow, HQ), and a PE-50 catheter was placed in the femoral artery for blood pressure (BP) monitoring. N-Ac-LTE₄ (Merck Frosst) was administered to the

FIGURE 1. Authentic recording of the cardiovascular effects of N-Ac-LTE₄ in the conscious rat. AP = arterial pressure. M, R, and HQ represent the superior mesenteric, renal, and hindquarter circulation, respectively. Arrows represent the time of N-Ac-LTE₄ injection. Mean arterial pressure and heart rate are given as numerator/denominator values, respectively.
conscious rat (0.1–30 μg/kg) and blood flow (BF) in the R, M, and HQ regions was continuously recorded, as was the systemic BP and heart rate.

N-Ac-LTE₄ (n = 6) produced only a moderate pressor response (5–15 mmHg). However, MBF was reduced in a dose-dependent manner (up to −50% at 30 μg/kg), along with an increase in the MVR: 300% (30 μg/kg). N-Ac-LTE₄ had no effect at all on the renal or HQ circulation in the dose range studied (FIGURE 1). Comparison of the duration of the effect of N-Ac-LTE₄ on MBF to that of LTD₄ revealed a more prolonged effect of N-Ac-LTE₄ (FIGURE 2).

The data presented in this report clearly show that N-Ac-LTE₄ is a biologically active metabolite of LT. N-Ac-LTE₄ had a preferential effect on the mesenteric circulation with virtually no effect on the R and HQ circulation. In this regard, N-Ac-LTE₄ is more specific than LTD₄ or LTE₄, which produce significant renal and HQ vasoconstriction in comparable doses in this same model.

The effects of N-Ac-LTE₄ in the rat are substantially different from those described in the pig. The significant vasoconstrictor activity of N-Ac-LTE₄ in the rat, taken together with this LT being the primary bile metabolite, and the possible enterohepatic recycling of LT suggest that N-Ac-LTE₄ might play an important role in systemic effects of LT in this species. Furthermore, the possible role of N-Ac-LTE₄ in mediation of some of the overall LT effects also presents the need to evaluate LT antagonists against N-Ac-LTE₄ because the failure of some LT antagonists to effectively block N-Ac-LTE₄ might underlie their limited capacity to prevent or reverse LT-mediated pathological processes.

REFERENCES

