N-Ac-Leukotriene E_4

Unique Vascular Activity in the Conscious Rat

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N-Acetyl-leukotriene E_4 (*N*-Ac-LTE_4) is a recently discovered metabolite of the cysteinyl leukotrienes (LT).[1] Although *N*-Ac-LTE_4 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-LTE_4 is not known. Experiments conducted in the pig show that *N*-Ac-LTE_4 has very weak actions on the cardiovascular and respiratory systems.[3] However, the formation of *N*-Ac-LTE_4 has not been shown as yet in the pig. Therefore, we have decided to examine the effect of *N*-Ac-LTE_4 in the rat, where $LTC_4/D_4/E_4$ have potent cardiovascular effects and *N*-Ac-LTE_4 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-LTE_4 (Merck Frosst) was administered to the

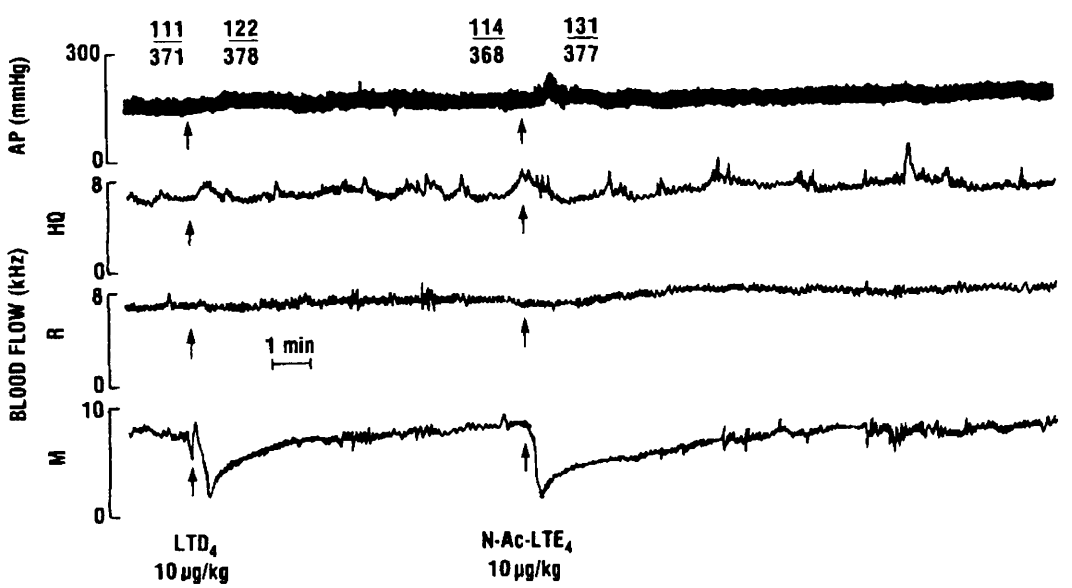

FIGURE 1. Authentic recording of the cardiovascular effects of *N*-Ac-LTE_4 in the conscious rat. AP = arterial pressure. M, R, and HQ represent the superior mesenteric, renal, and hindquarter circulation, respectively. Arrows represent the time of *N*-Ac-LTE_4 injection. Mean arterial pressure and heart 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-LTE_4 ($n = 6$) 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-LTE_4 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-LTE_4 on MBF to that of LTD_4 revealed a more prolonged effect of *N*-Ac-LTE_4 (FIGURE 2).

The data presented in this report clearly show that *N*-Ac-LTE_4 is a biologically active metabolite of LT. *N*-Ac-LTE_4 had a preferential effect on the mesenteric circulation with virtually no effect on the R and HQ circulation. In this regard, *N*-Ac-LTE_4 is more specific than LTD_4 or LTE_4, which produce significant renal and HQ vasoconstriction in comparable doses[4] in this same model.

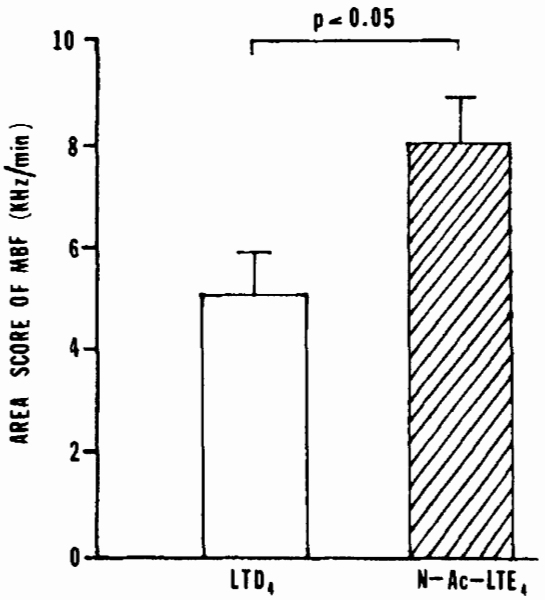

FIGURE 2. The areas score of the mesenteric blood flow response to *N*-Ac-LTE_4. The overall effect of *N*-Ac-LTE_4 is significantly larger than LTD_4 at $p < 0.05$ ($n = 6$).

The effects of *N*-Ac-LTE_4 in the rat are substantially different from those described in the pig.[3] The significant vasoconstrictor activity of *N*-Ac-LTE_4 in the rat, taken together with this LT being the primary bile metabolite, and the possible enterohepatic recycling of LT suggest that *N*-Ac-LTE_4 might play an important role in systemic effects of LT in this species. Furthermore, the possible role of *N*-Ac-LTE_4 in mediation of some of the overall LT effects also presents the need to evaluate LT antagonists against *N*-Ac-LTE_4 because the failure of some LT antagonists to effectively block *N*-Ac-LTE_4[3] might underlie their limited capacity to prevent or reverse LT-mediated pathological processes.

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