Prostaglandins Leukotrienes and Medicine 14: 339 - 340, 1984

LEUKOTRIENE C_4 INDUCES VASOGENIC CEREBRAL EDEMA IN RATS

Keith L. Black, Section of Neurosurgery, University of Michigan Medical Center, Ann Arbor, Michigan 48109

Leukotriene C_4 (LTC_4) is reported to neither contract nor relax isolated human cerebral arterial strips (1), but in skin LTC_4 will increase vascular permeability in post capillary venules, increase blood flow (2) and elicit erythma and wheal formation (3). The present experiment was designed to determine whether LTC_4 could increase vascular permeability in the brain.

Materials and Methods. Wistar rats weighing 434 to 478 g were anesthetized with ketamine (87 mg/kg) and xylazine (13 mg/kg) injected intramuscularly. PE-10 polyethylene catheters were inserted into the femoral artery and vein. The arterial catheter was connected to a blood pressure transducer and systemic arterial blood pressure was continuously monitored. Buffered evans blue (0.75 ml) was injected into the femoral vein. A burr hole was made over the right parietal cortex. A 10 μl J & W Scientific Inc. syringe with a deactivated fused sillia needle (125 μm diameter) was mounted on the arm of a stereotaxic frame. With the aid of magnification the tip of the needle was manipulated 2.5 mm deep into the brain parenchyma. Rats were injected with either 10 μl of saline (n=5), or 10 μl of water (n=4), or 10 μl of 0.2 mg/ml LTC_4 (n=5) into the brain parenchyma, slowly over 5 min, 15 min after intravenous injection of evans blue. Rats were decapitated 1 h later and their brains removed and frozen. The frozen brains were coronally sliced through the plane of injection and at 2 mm intervals anterior and posterior to the first slice. The posterior surface of each slice was photographed and the % area of evans blue extravasation estimated with polar planimetry. LTC_4 was supplied by Dr. R. Rokach of Merck-Frosst Canada Inc. at a concentration of 0.2 mg/ml water.

Results and Discussion. Except for negligible blue staining along the insertion tract of the needle, none of the rats injected with saline or water had evidence of evans blue extravasation. In all rats injected with LTC_4 there was significant extravasation of evans blue in the area of injection. The area of evans blue extravasation ranged from 3.3 to 5.1 % of the area of the right hemisphere of the slices through the plane of LTC_4 injection. There was no significant differences in systemic blood pressure between groups. These findings suggest that leukotrienes could play an important role in the development of vasogenic cerebral edema. Cerebral injury associated with vasogenic edema will

stimulate leukocyte accumulation. Leukocytes, rich in lipoxygenase, could oxidize arachidonate to leukotrienes and thus produce vasogenic cerebral edema. Interestingly, the development of vasogenic edema after cerebral ischemia is delayed many hours despite an immediate 40 fold increase in free arachidonate. Even after restoration of oxygen, allowing the conversion of arachidonate to prostaglandins (4), vasogenic edema does not appear. This suggest that the brain itself may lack the ability to produce significant quantities of leukotrienes. Leukotriene production in the brain may, therefore, depend on the accumulation of leukocytes in the area of cerebral injury.

Elucidation of the role of leukotrienes in vasogenic cerebral edema may have important therapeutic implications. Inhibition of leukotrienes could ameliorate vasogenic cerebral edema in certain types of cerebral injury. A dose response study and a study to determine whether leukotriene inhibition can prevent vasogenic cerebral edema after leukotriene injection is currently in progress in our laboratory.

References

1. Holst H von, Granstrom E, Hammarstom S, Samuelsson B, Steiner L. Effect of leucotrienes C_4, D_4, prostacyclin and thromboxane A_2 on isolated human cerebral arteries. Acta Neurochir 62:117, 1982
2. Bisgaard H, Kristensen J, Sondergaard J. The effect of Leucotriene C_4 and D_4 on cutaneous blood flow in humans. Prostaglandins 23:797, 1982
3. Soter NA, Lewis RA, Corey EJ, Austen KF. Local effects of synthetic leukotrienes (LTC_4, LTD_4, LTE_4, and LTB_4) in human skin. J Invest Dermatol 80:115, 1983
4. Black KL, Hoff JT, Radin NS, Deshmukh G. Eicosapentaenoic acid: effect on brain prostaglandins, cerebral blood flow and edema in ischemic gerbils. Stroke 15 (In press)