[Prostaglandins Leukotrienes Essential Fatty Acids, **51**, 95-99 (1994)] [Lab. of Pharmacology]

**Pharmacological studies of platelet-activating factor (PAF)-induced augmentation of response to histamine in guinea-pigs.**

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An acute increase in airway response to histamine produced by platelet activating factor (PAF) was investigated in guinea-pigs. Airway response to histamine was increased 8 min after injection of PAF without affecting the numbers of leukocytes in bronchoalveolar lavage fluid and airway capillary permeability. CV-3988 completely inhibited PAF-induced bronchoconstriction and airway hyperresponsiveness, while ONO-1078 and AA-861 had no effect. OKY-046, S-1452 and indomethacin inhibited PAF-induced bronchoconstriction more potently than PAF-induced airway hyperresponsiveness. $TXA_2$ may play a role in the onset of the airway hyperreactivity, but the role of $TXA_2$ in hyperreactivity may be less important than in PAF-induced bronchoconstriction.

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**Effect of the selective thromboxane $A_2$ receptor antagonist, S-1452, on antigen-induced sustained bronchial hyperresponsiveness.**

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Long-lasting bronchial hyperresponsiveness to i.v. acetylcholine was observed in actively sensitized guinea-pigs after aerosol ovalbumin exposure. The response became significant at 7 h post-challenge and persisted for at least 120 h. Pretreatment with the specific thromboxane (TX) $A_2$ receptor antagonist, S-1452, almost completely inhibited the onset of bronchial hyperresponsiveness. Lung vascular injury occurred transiently immediately after antigen challenge, the kinetics of injury being associated with those for the production of $TXB_2$ in bronchoalveolar lavage fluid, and the injury was dramatically suppressed by S-1452 pretreatment.

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**Effects of ZCR-2060 on allergic airway inflammation and cell activation in guinea-pigs.**

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The effects of 2-(2-(4-(diphenylmethyl)-1-piperadinyl)ethoxy)benzoic acid maleate (ZCR-2060) on allergic airway inflammation and inflammatory cell activation in guinea-pigs were studied. ZCR-2060 clearly inhibited the aeroantigen-induced increase of eosinophil numbers in bronchoalveolar lavage fluid. ZCR-2060 inhibited the platelet-activating factor (PAF)-induced chemotaxis of eosinophils and neutrophils, but did not inhibit the leukotriene $B_4$-induced chemotaxis of eosinophils and formyl-Met-Leu-Phe-induced chemotaxis of neutrophils. PAF-induced superoxide anion generation by eosinophils, neutrophils and alveolar macrophages was inhibited by ZCR-2060.