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This Week's Citation Classic

Hamberg M, Svensson J & Samuelsson B. Thromboxanes: a new group of biologically active compounds derived from prostaglandin endoperoxides. *Proc. Nat. Acad. Sci. US* **72**:2994-8, 1975. [Department of Chemistry, Karolinska Institutet, Stockholm, Sweden]

Stimulation of human blood platelets results in the formation of thromboxane A_2 from platelet arachidonic acid. Thromboxane A_2 in very low concentrations causes clumping of human platelets and has a mediator role in hemostasis and in the generation of vascular disease. [The *SCI*® indicates that this paper has been cited in over 1,305 publications since 1975.]

Mats Hamberg
Department of Chemistry
Karolinska Institutet
S-104 01 Stockholm 60
Sweden

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"The discovery of the thromboxane family of compounds in 1974-1975 can be regarded as a logical outcome of our previous work on the mechanism of prostaglandin biosynthesis from certain polyunsaturated fatty acids carried out from 1965 to 1967.[1,2] This work led to the proposal of the existence of endoperoxide intermediates); however it was not until 1973 that such intermediates (prostaglandins G_2 and H_2) could be isolated.[3] The access to pure endoperoxides and the finding of their pro-aggregated activity on human blood platelets[3] necessitated a study on the metabolic fate of arachidonic acid in human platelets[4] and also made possible the work by Moncada and Vane which led to the discovery of prostaglandin I_2 (prostacyclin).[5]

"In platelets, two pathways of arachidonic acid metabolism were found. One was initiated by a novel lipoxygenase and resulted in the formation of 12-hydroxyeicosatetraenoic acid. This was the first example of a lipoxygenase-catalyzed reaction in animal tissue. Subsequently, several other lipoxygenases catalyzing dioxygenation of polyunsaturated fatty acids were found in animal tissue. Of special interest is arachidonic acid 5-lipoxygenase which catalyzes the first reaction in the formation of leukotrienes.[6]

"The second pathway of arachidonic acid metabolism in the platelets was initiated by the aspirin-sensitive enzyme, fatty acid cyclooxygenase, and resulted in the formation of thromboxane B_2 and a monohydroxy acid.[4] These two compounds were also formed from prostaglandin endoperoxides. The relatively complicated non-prostanoate structure of thromboxane B_2 suggested that its formation from prostaglandin endoperoxides occurred by more than one reaction. An intermediate having a fused oxetane-oxane ring structure appeared especially attractive. By a number of chemical studies including trapping experiments with nucleophilic agents, we were able to confirm the presence of an oxetane-oxane structure in the intermediate and to elucidate its complete chemical structure. The compound was called thromboxane A_2 and was found to be very unstable in aqueous medium ($t_{1/2}$ = 30 sec at 37°).

"At the same time, in collaboration with J. Svensson, who was carrying out his doctoral work at the department of chemistry, we observed a transient formation of very unstable potent pro-aggregating material upon incubation of platelet suspensions with arachidonic acid. This material was identified as thromboxane A_2 on the basis of its formation from prostaglandin endoperoxides, instability in aqueous medium, etc.

"Formation and action of thromboxane A_2 is the first example of physiological and pathological roles for the prostaglandin-thromboxane system in man. The finding of a new endogenously formed mediator in hemostasis and in the generation of vascular disease has stimulated a large number of biochemical, physiological, and clinical studies. This, I think, is the reason for the frequent citation of our paper."

1. **Samuelsson B.** On the incorporation of oxygen in the conversion of 8,11,14-eicosatrienoic acid into prostaglandin E_1. *J. Amer. Chem. Soc.* **87**:3011-13, 1965.
2. **Hamberg M & Samuelsson B.** On the mechanism of the biosynthesis of prostaglandins E_1 and $F_{1\alpha}$ *J. Biol. Chem.* **242**:5336-43, 1967.
3. **Hamberg M, Svensson J, Wakabayashi T & Samulsson B.** Isolation and structure of two prostaglandin endoperoxides that cause platelet aggregation. *Proc. Nat. Acad. Sci. US* **71**:345-9, 1974.
[The *SCI* indicates that this paper has been cited in over 790 publications since 1974.]
4. **Hamberg M & Samuelsson B.** Novel transformations of arachidonic acid in human platelets. *Proc. Nat. Acad. Sci US* **71**:3400-4, 1974.
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5. **Moncada S, Gryglewtki R, Bunting S & Vane J R.** An enzyme isolated from arteries transforms prostaglandin endoperoxides into an unstable substance that inhibits platelet aggregation. *Nature* **263**:663-5, 1976.
[The *SCI* indicates that this paper has been cited in over 1,260 publications since 1976.]
6. **Samuelsson B.** The leukotrienes: an introduction. (Samuelsson B & Paolelti R. eds.) *Leukotrienes and other lipnxygenase products.* New York: Raven Press, 1982. p. 1-17.