ROLE OF PLATELET cAMP AND PROSTAGLANDIN SYNTHESIS IN PLATELET AGGREGATION INHIBITION BY TICLOPIDINE HYDROCHLORIDE. J. Z. Eudy, D. Yang, L. A. Taylor and C. Fesmister. Institute of Biological Sciences, Syntex Research, Palo Alto, CA, USA.

Ticlopidine hydrochloride (T), 5-[6-(chlorophenyl) methyl]-3,5,6,7-tetrahydrothieno [3,2-d] pyridine hydrochloride, is a potent antiplatelet agent of unknown mechanism of action. T does not inhibit human platelet low Km, cAMP phosphodiesterase (PDE) in vitro, but does have some activity versus the low Km, cAMP-PDE (IC50=1.6x10^-6 M). Equivalent values for theophylline, a weak PDE inhibitor, are 1.6x10^-5 M and 4.2x10^-5 M, respectively. T has no synergistic effect in vitro on platelet aggregation inhibited by PGI2. PDE inhibitors do show synergy with PGI2 and other antiaggregatory PGs. In vivo in humans and animals, T inhibits ADP-induced aggregation. This inhibition is not altered by addition of SQ-22536 (1.6x10^-6 M), a purported inhibitor of adenylate cyclase activity, whereas drugs whose platelet inhibitory activity depend on elevation of platelet cAMP, e.g., PGI2, adenosine and diprydamide, have this inhibition partially reversed by SQ-22536.

PG synthesis is not required for the antiplatelet activity of T. Addition of aspirin (1.6x10^-6 M) in vitro to PRP from humans treated with T (500 mg/day) did not modify the aggregation response to ADP. In addition, POI2 is not essential for the antiaggregation effect of T. The inhibition of ADP-induced aggregation of PRP prepared from blood of T-treated humans just after collection and more than 30 minutes after, to allow for inactivation of POI2, were identical.

We conclude that neither elevated cAMP nor PG synthesis is essential for T activity.