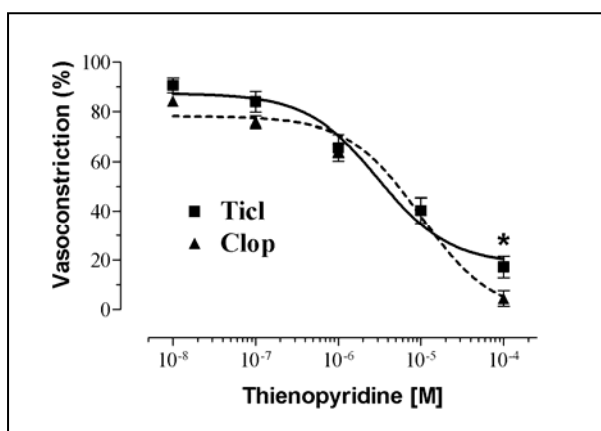


**DIRECT EFFECTS OF TICLOPIDINE AND CLOPIDOGREL ON RESISTANCE VESSEL *IN VITRO***

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Ticlopidine and clopidogrel are antiplatelet agents well known as ADP receptor antagonists *in vivo*. These compounds are believed to be inactive *in vitro* and it has been suggested that its activity is dependent on hepatic biotransformation into active metabolites. The mechanism of antiplatelet action appears to be the irreversible alteration of the platelet surface P2Y<sub>12</sub> receptor, resulting in a reduction of ADP-induced platelet aggregation. The aim of this research was to study *in vitro* direct effects of thienopyridines on resistance vessel. Rat caudal arterial rings were placed in a tissue bath containing Krebs-Ringer solution and their viability was assessed by 10  $\mu$ M phenylephrine and 30  $\mu$ M acetylcholine. Both ticlopidine and clopidogrel from 0.01  $\mu$ M to 1  $\mu$ M *per se* did not significantly change resting tension of arterial rings; only at 10  $\mu$ M they slightly decreased the basal tone of tissues. However, thienopyridines evoked direct relaxation of arteries precontracted by 80 mM KCl, 0.5  $\mu$ M phenylephrine or 0.5  $\mu$ M 5-hydroxytryptamine. Figure 1 shows concentration-effect curves obtained by ticlopidine (Ticl) and clopidogrel (Clop), in depolarized (80 mM KCl) rat caudal arteries; the pD<sub>2</sub> were 5.5 $\pm$ 0.2 and 5.0 $\pm$ 0.1, respectively. We also carried out experiments with thienopyridines in rat vascular smooth muscle cells (VSMC); in this experimental model, ticlopidine (1-10  $\mu$ M) decreased cell proliferation while clopidogrel (1-10  $\mu$ M) did not influence this one. However, higher concentrations of ticlopidine or clopidogrel increased VSMC proliferation. In the presence of 50  $\mu$ M ADP or 0.1  $\mu$ M 2-MethioADP, ticlopidine and clopidogrel never inhibited cellular proliferation. In contrast with the general assumption, authors [1] demonstrate direct inhibition of platelet aggregation by clopidogrel *in vitro*. Also our experimental observations suggest that thienopyridines directly, without hepatic biotransformation, induce relaxation of resistance arteries and influence cell proliferation. The data also indicate that their effects are not linked to P2Y receptors: other mechanisms must be involved at least at vascular level.



## Reference

1. Weber A.-A., Reimann S., Schrör K. (1999) Br. J. Pharmacol. 126: 415-420.