Role of NF-?B in platelets: impaired activation responses by NF-?B inhibitors

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We have previously demonstrated that specific inhibition of NF-?B activation with Bay 11-7082 (Bay) impairs platelet function, suggesting a novel non-genomic role of this transcription factor on platelet activation. In the present study, the mechanisms involved in the action of Bay were further analyzed. Filopodia and lamellipodia formation associated to cytoskeleton reorganization are the first morphological changes observed on stimulated platelets. Both phenomena were significantly decreased in the presence of Bay (detected by actin polymerization, fluorescent microscopy). Platelet stimulation with classical agonists induced NF-?B activation (determined by binding of NF-?B to its DNA regulatory sequences by ELISA, n=3), which was prevented by treatment with Bay. Aggregation (measured by light transmission aggregometry), intraplatelet ATP release (luminescence), and TXB_2 generation (ELISA) were not modified by incubation with Bay indicating that cyclo-oxigenase pathway is not affected. However, generation of TXB_2 mediated by agonists that induce endogenous araquidonic acid synthesis, as well as cytosolic PLA_2 activity (colorimetric assay) were inhibited 64±8% and 25±7% respectively in the presence of Bay (n=3, $p<0,05$). The effects observed with Bay appear to be specifically related to NF-?B since another inhibitor of this transcription factor not structurally related to Bay (Ro 106-9920) mimicked all antiaggregating effects obtained with Bay. These results suggest that NF-?B, probably through interaction with PLA_2, is required to generate platelet effector responses.

Key words: platelets, NF-?B, phospholipase A_2.