Morphine-potentiated platelet aggregation in in vitro and platelet plug formation in in vivo experiments

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摘要

Abstract

The detailed mechanisms underlying morphine-signaling pathways in platelets remain obscure. Therefore, we systematically examined the influence of morphine on washed human platelets. In this study, washed human platelet suspensions were used for in vitro studies. Furthermore, platelet thrombus formation induced by irradiation of mesenteric venules with filtered light in mice pretreated with fluorescein sodium was used for an in vivo thrombotic study. Morphine concentration dependently (0.6, 1, and 5 μM) potentiated platelet aggregation and the ATP release reaction stimulated by agonists (i.e., collagen and U46619) in washed human platelets. Yohimbine (0.1 μM), a specific 2-adrenoceptor antagonist, markedly abolished the potentiation of morphine in platelet aggregation stimulated by agonists. Morphine also potentiated phosphoinositide breakdown and intracellular Ca2+ mobilization in human platelets stimulated by collagen (1 μg/ml). Moreover, morphine (0.6-5 μM) markedly inhibited prostaglandin E1 (10 μM)-induced cyclic AMP formation in human platelets, while yohimbine (0.1 μM) significantly reversed the inhibition of cyclic AMP by morphine (0.6 and 1 μM) in this study. The thrombin-evoked increase in pHi was markedly potentiated in the presence of morphine (1 and 5 μM). Morphine (2 and 5 mg/g) significantly shortened the time require to induce platelet plug formation in mesenteric venules. We concluded that morphine may exert its potentiation in platelet aggregation by binding to 2-adrenoceptors in human platelets, with a resulting inhibition of adenylate cyclase, thereby reducing intracellular cyclic AMP formation followed by increased activation of phospholipase C and the Na+/H+ exchanger. This leads to increased intracellular Ca2+ mobilization, and finally potentiation of platelet aggregation and of the ATP release reaction.