The P2Y₁ Receptor as a Target for New Antithrombotic Drugs: A Review of the P2Y₁ Antagonist MRS-2179

Anthony Baurand and Christian Gachet

INSERM U.311, Laboratoire de Biologie et de Pharmacologie de l’Hémostase et de la Thrombose, Etablissement Français du Sang-Alsace, Strasbourg, France

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ABSTRACT

MRS-2179 is a selective P2Y₁ receptor antagonist, a strong inhibitor of ADP-induced platelet aggregation in vitro and ex vivo. By i.v. administration to mice MRS-2179 increases resistance to thromboembolism induced by a mixture of collagen and epinephrine or by a tissue factor. Likewise, it significantly increases the time to thrombus formation in a ferric chloride-induced model of localized arterial thrombosis. MRS-2179 also confers resistance to localized venous thrombosis, which is dependent on thrombin generation and in which platelets play a relatively minor role as compared to stasis or activation of coagulation. These data provide considerable encouragement for the development of new P2Y₁ receptor antagonists. Nevertheless, the properties of MRS-2179 indicate that new compounds should be optimized in order to increase the half-life of the molecule in vivo and its selectivity and potency at the P2Y₁ receptor. Further directions include the synthesis of molecules with modifications of the nucleotide structure which replace the fragile moiety by a stable bond and should lead to a non-hydrolysable structure. In conclusion, P2Y₁ antagonists have been shown to be efficient antithrombotic agents. MRS-2179 is the first P2Y₁ antagonist with antithrombotic action. Its effectiveness demonstrates that the P2Y₁ receptor is a potentially promising target for drugs designed to treat thrombotic syndromes.