Antithrombotic and Anticoagulant Peptides that Inhibit Signaling Via Specific G Protein Subunit Switch Regions

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Technology description

A novel approach for pharmacologic blockade of thrombosis and platelet aggregation, these peptides have applications as both a therapeutic and as a research tool to study the links between G protein signaling and disease proceses.

In the last decade the incidence of thrombo-embolic diseases in which anti-platelet drugs may have been beneficial was estimated to be: 2,500,000 patients affected by coronary artery diseases, 873,000 patients with cerebrovascular disease, (i.e., stroke or transient ischemic attack) and 2,000,000 patients with peripheral arterial occlusive disease.

Even though G protein signaling pathways are known to be intimately involved in the genesis of thromboembolic events, it has not been possible to pharmacologically target G proteins as a means of decreasing blood platelet function.

With the exception of receptor-derived peptides and Gα subunit C-terminal peptides, which modulate receptor-G protein coupling, the field been limited to drug candidates that interfere with different downstream kinases or other downstream G protein effectors.

The problem with this is approach is that many of the different G protein downstream effectors are shared and control multiple cellular functions. Consequently, such inhibition would not be specific to a selected G protein signaling pathway.

Gα subunits are known to contain conformationally sensitive regions called switch regions (SR) which participate in G protein signaling events. Switch regions 1 and 2 (SR1, SR2) are structurally and functionally analogous to the small GTPase Ras while switch 3 region is unique to heterotrimeric G proteins.

SR1 contains critical sites for binding GTP and Gα subunits, and both SR1 and SR2 interact with GEF proteins. Thus, Gα subunit switch regions represent a potentially important pharmacological target for specific modulation of G protein function.

UIC inventors reasoned that direct control of specific G proteins involved in cellular signaling and disease might be obtained by interfering with the initial G protein signal transduction event, rather than by interfering with the secondary downstream consequences of this transduction process. Thus, peptides were generated that specifically inhibited SR1 and SR2 of different G protein subunits based on differential amino acid sequences.

These G protein subunit-specific peptides inhibit platelet signaling and function by blocking the ability of individual G protein Gα subunits to activate their specific downstream effectors.

Application area

A therapeutic for (1) the prevention and treatment of thrombotic diseases, such as stroke, and (2) the prevention of thrombosis after cardiovascular procedures.
A research tool applicable for pharmaceutical companies or academia interested in studying the links between specific G protein signaling events and development or prevention of disease processes.

Advantages

This technology provides a novel approach for pharmacologic blockade of thrombosis and platelet aggregation.
The peptide is a selective inhibitor of the switch region domain of GPCR-G protein interaction.

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