New Product Highlights

Protease-Activated Receptor (PAR) modifying peptides

Protease-activated receptors (PARs) play important physiological roles in blood vessel wall biology, thrombosis and the cardiovascular system [1,2]. The consequences of PAR activation in vascular injury, inflammation, tissue injury and tumor microenvironment make them targets for pharmacological studies and drug discovery. PARs belong to the superfamily of G protein-coupled seven transmembrane domain receptors, but possess a distinctive activation mechanism. PARs are activated by proteolytic cleavage of the N-terminal peptide leading to exposure of the cryptic receptor-activating sequence, which then acts as a ligand that is tethered to the receptor molecule and that binds and activates the same receptor molecule. Four PAR subtypes, referred to as PAR-1 to PAR-4, have been identified to date, but other subtypes are suspected. PAR-1, PAR-3 and PAR-4 are activated by thrombin (also known as thrombin receptors), while PAR-2 is activated by trypsin, mast cell tryptase and coagulation factors VIIa and Xa.

PAR-1, PAR-3 and PAR-4 are expressed in platelets and are thought to act mainly in platelet activation. All three have been cloned and characterized as receptors for thrombin, the major serine effector protease involved in coagulation, vascular injury and inflammation. PAR-3 and PAR-4 are also expressed in a number of other tissues, especially in small intestine and pancreas. PAR-1 is known to be coupled to G_q and G_i while the G proteins coupled to other PARs remain to be identified. PAR-1 activation results in the stimulation of phospholipase C (PLC) activity, leading to the formation of inositol triphosphate (IP_3) and diacylglycerol (DAG) followed by calcium mobilization and activation of protein kinase C (PKC). Evidence has accumulated for the involvement of PAR-1 in the activation of tyrosine kinase (Src family), PI3 kinase (PI3K), protein kinase B (Akt) and mitogen-activated protein kinase (MAPK). The intracellular signaling mechanisms associated with PAR-3 and PAR-4 are the subject of ongoing investigations.

In contrast, PAR-2 is expressed at high levels in colon, pancreas, small intestine and kidney as well as in endothelial, epithelial and smooth muscle cells. This receptor is involved in digestive exocrine functions, triggering amylase secretion and pancreatic duct epithelial cell ion channel activation and is coupled to G_q and G_i such that its activation leads to both IP_3/DAG accumulation and adenosine 3',5'-cyclic monophosphate (cAMP) modulation.

It was discovered that synthetic short peptides modeled after the amino acid sequence of the proteolytically-exposed tethered ligands can activate PARs in the absence of proteases. These are sometimes called TRAPs (Thrombin Receptor-Activating Polypeptides). Table 1 summarizes the properties of this group of PAR modifying peptides, all of which have recently been introduced by Sigma-RBI.

Given what is known of the physiological roles of these receptors, PAR selective agonists and antagonists possess therapeutic potential in the management of human diseases. In addition, their receptor selectivity holds promise in making them ideal tools for elucidating the intracellular signaling mechanisms of these structurally related receptors.

References

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Peptide	EC_{50} (µM)	IC_{50} (µM)	Activity/Selectivity	References
SLIGRL-NH_2 (Prod. No. S 9317)	5	—	PAR-2 agonist at rat/mouse receptors; activates keratinocyte inositolphospholipid hydrolysis and calcium mobilization	3, 4, 5
SLIGKV-NH_2 (Prod. No. S 9192)	—	—	PAR-2 agonist; most potent at all species tested	5
AYPGKF-NH_2 (Prod. No. A 3227)	25 – 50	—	PAR-4 agonist; 10x more potent than natural ligands at mouse (GYPGKF) or human (GYPGQV) receptors	6
tcY-NH_2 (Prod. No. T 7363)	—	—	PAR-4 antagonist; inhibits endostatin release and platelet aggregation mediated by thrombin	7, 8
Mpr-F-Cha-Cha-RKPKPADK (Prod. No. M 2192)	20 (calcium signaling)	17 µM for PAR-1 mediated calcium signaling; 6.4 µM for thrombin-induced platelet aggregation	PAR-2 agonist/PAR-1 antagonist	9