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Poster Presentation

Role of Thrombin in Inflammatory Central Nervous System (CNS) Diseases

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Abstract

Thrombin is a multifunctional enzyme which has key roles in coagulation cascade and inflammatory events. The pro-inflammatory functions of thrombin occur by different mechanisms including increasing mast cell degranulation, up-regulating the expression of cell adhesion molecules (CAMs) and promoting the secretion of inflammatory chemokines and cytokines. Dysregulated signaling functions of thrombin contributes to the pathogenesis of pro-inflammatory diseases such as coronary thrombosis, pulmonary emboli, atherogenesis, and cancer and of special interest in this poster in central nervous system (CNS) associated inflammatory diseases. In support of the proinflammatory signaling function of thrombin in inflammatory CNS disease several reports demonstrated that PAR-1activation by thrombin elevates concentration of pro-inflammatory mediators like arachidonic acid, increases neutrophil chemoattractant-1, IL-1 and IL-8 in astrocytes. Similarly, PAR-1 has pro-inflammatory role in oligodendrocyte by inducing the expression of TNF-α and MMP-9. Furthermore, thrombin with activation of PAR-4 can induce pro-inflammatory signaling pathways including mitogen-activated protein kinase (MAPK) and nuclear factor-kappa B (NF-kβ) in microglia cell line. PAR-4 also increases the expression and release of TNF-α from microglia leading to up-regulation of inducible nitric oxide synthase (iNOS) and as a consequence, incense in degeneration of dopaminergic neurons occurs. Consistently, thrombin plays a key role in the pathogenesis of neuro-degenerative diseases including stroke, multiple sclerosis Alzheimer and Parkinson. In support of these findings, it has been shown that administration of thrombin inhibitors including hirudin and a-NAPAP could decrease CNS inflammation related disease. Understanding the detail of pro-inflammatory signaling functions of thrombin and designing novel therapeutic agent to targeting this inflammatory serine protease can be a useful strategy for treatment of CNS inflammatory disorders, however the unfavorable pharmaceutical activities, toxicity, and risk of bleeding of these compounds needs to be further investigated.

Keywords: CNS thrombin system, Alzheimer's disease, Parkinson's disease, Thrombin, Inflammatory CNS disease

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