

## **Protease nexin-2/amyloid beta-protein precursor: a cerebral anticoagulant?**

D D Cunningham

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Editorial

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In this issue of *The Journal*, Schmaier et al. (1) report the potent inhibition of blood coagulation factor IXa by protease nexin-2 (PN-2), which is a secreted isoform of the Alzheimer's disease amyloid  $\beta$ -protein precursor (A $\beta$ PP). A $\beta$ PP is the large, transmembrane parent protein of the amyloid  $\beta$ -protein (A $\beta$ ) that is found deposited in senile plaques in the neuropil and in the walls of cerebral blood vessels of individuals afflicted with Alzheimer's disease and certain related disorders (2). A $\beta$ PP is encoded by a gene on chromosome 21 that can give rise to alternatively spliced forms of the protein that contain or lack a 57-amino acid domain that is homologous to Kunitz-type serine protease inhibitors. The constitutive proteolytic processing of A $\beta$ PP that occurs under normal conditions results in secreted forms of the protein. The secreted isoforms that contain the Kunitz protease inhibitor domain are identical to PN-2 (3). The present paper by Schmaier et al. (1) provides biochemical evidence that PN-2 may serve as a cerebral anticoagulant. Along with other recent studies, it suggests the provocative hypothesis that excess PN-2 could lead to spontaneous intracerebral hemorrhage.

Hemostasis is regulated by a series of serine proteases, which in turn, are controlled by a group of serine protease inhibitors known as SERPINS. Antithrombin III, heparin cofactor II, protease nexin-1,  $\alpha_1$ -protease inhibitor, and C1-inhibitor are examples of SERPINS that can regulate proteases involved in blood coagulation. The recognition that tissue factor pathway inhibitor (TFPI), a Kunitz-type serine protease inhibitor, is a potent inhibitor of factor VIIa-tissue factor complex indicates that another class of serine protease inhibitors can also regulate hemostasis (4). The present finding of Schmaier et al. (1) that PN-2/A $\beta$ PP is a potent, tight-binding inhibitor of factor IXa indicates a second Kunitz-type protease inhibitor could regulate hemostasis. It is noteworthy that these two Kunitz-type protease inhibitors both regulate enzymes that activate factor X. Factor Xa, in turn, activates prothrombin to thrombin, the final protease in the coagulation pathway.

Several findings suggest that PN-2/A $\beta$ PP has an intimate interrelationship with the hemostatic system. PN-2/A $\beta$ PP is an abundant platelet  $\alpha$ -granule protein that is secreted upon platelet activation (5, 6). Moreover, PN-2/A $\beta$ PP is a potent inhibitor of coagulation factor XIa, a protease in the intrinsic pathway (6). The present finding by Schmaier et al. (1) that PN-2/A $\beta$ PP is also a potent inhibitor of factor IXa is particularly important because factor IXa is a major hemostatic enzyme whose deficiency leads to a severe bleeding state. PN-2/A $\beta$ PP has been recognized as a membrane-associated protein; thus, it

could function to modulate factor IXa activity on the surface of cells. This is an important point since studies have shown that physiologic activation of factor X occurs on the surface of endothelial cells and activated platelets. (7, 8).

Is there a relationship between the hemostatic function of PN-2/A $\beta$ PP and its presence in the brain? A rare disorder, hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D), is characterized by extensive cerebrovascular deposits of A $\beta$  and recurrent, often fatal spontaneous intracerebral hemorrhages by mid-life. Recent studies revealed that HCHWA-D patients have pronounced accumulations of PN-2/A $\beta$ PP (in addition to A $\beta$ ) in the walls of their cerebral blood vessels (9); Schmaier et al. (1) hypothesized that cerebral hemorrhage in these patients might result from excess PN-2/A $\beta$ PP, which could inhibit factor IXa and compromise physiologic blood coagulation. It remains to be determined if the mutation leading to HCHWA-D leads to excess accumulation of PN-2/A $\beta$ PP in the cerebral vasculature. Nevertheless, the studies of Schmaier et al. (1) underscore the importance of exploring the roles of PN-2/A $\beta$ PP in the regulation of cerebral hemostasis and exploring directly if alterations in PN-2/A $\beta$ PP in certain pathological conditions might imbalance proteolytic mechanisms involved in blood coagulation.

Dennis D. Cunningham

Department of Microbiology and Molecular Genetics  
University of California, Irvine

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