Thrombin and Antithrombin in Binswanger’s Disease

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Thrombin is multi-functional serine protease which has pivotal roles in hemostasis and thrombosis (1). In particular, thrombin is a key mediator for activation of both blood coagulation and platelets, and it is thereby of great importance in the pathophysiology of thrombotic diseases including cerebrovascular disease (CVD) (2). Recent studies have demonstrated that thrombin generation occurs in not only the acute phase but also the chronic phase of CVD. For example, Kario et al reported that the plasma levels of prothrombin fragment 1+2 (F$_{1,2}$), a sensitive marker of in vivo thrombin generation, are increased in the asymptomatic patients with lacunar infarction, especially multiple lacunar infarction and/or advanced periventricular lucency, suggesting the involvement of thrombin in the pathogenesis of these predisposing conditions for vascular dementia (3).

Increasing evidence points to the important roles of thrombin not only in CVD but also in neurodegenerative disorders such as Alzheimer’s disease (4). Thrombin induces retraction in neuroblastoma cells (5), astrocytes, and human fetal neurons (6). Excessive amounts of thrombin induce cell death of neurons and astrocytes (7). Nishino et al reported that thrombin infusion into the rat caudate nucleus causes increased reactive gliosis, infiltration of inflammatory cells, proliferation of mesenchymal cells, and induction of angiogenesis (8). In addition, thrombin may directly promote tissue damage in the central nervous system through an increase of vascular permeability and nitric oxide synthesis in glial cells (9).

Donovan et al have shown that thrombin causes apoptosis as evidenced by cleavage of DNA, fragmentation of nuclei, and prevention of death by inhibition of protein synthesis (10). They exhibited that thrombin receptor activating peptide (TRAP) also induces apoptosis, indicating that thrombin-induced cell death occurs via activation of thrombin receptor. The signal transduction cascade involves tyrosine and serine/threonine kinases, which have been revealed to be involved in the GTP-binding protein RhoA. Thrombin induces RhoA activity in astrocytes and hippocampal neurons, and inhibition of RhoA activity attenuated cell death, indicating that activation of RhoA by thrombin is necessary for thrombin-induced cell death. Tyrosine kinase inhibitors also block RhoA induction by thrombin, indicating that tyrosine kinase activity is necessary upstream of RhoA.

Smirnova et al studied calcium mobilization by thrombin in a model motor neuron cell line (11). They observed that thrombin dramatically increases intracytoplasmic Ca$^{2+}$ levels, which involved activation and cleavage of the proteolytically activated receptor for thrombin (PAR-1). They also demonstrated that nanomolar thrombin induces characteristic signs of apoptosis, and thrombin-induced apoptosis could be inhibited by a caspase family inhibitor, indicating that caspase activity is necessary downstream of PAR-1 (12).

These results suggest a sequential linkage of cellular events leading to apoptosis for the second messenger cascade induced by thrombin in neural cells. Continued elucidation of the signals underlying thrombin-induced apoptosis should facilitate therapeutic intervention against thrombin-induced cell death and lead to a better understanding of how to control the consequences of exposure of the brain to thrombin.

In this issue, Tomimoto et al reported the therapeutic efficacy of argatroban, a specific thrombin inhibitor, in four patients with Binswanger’s disease, that is, subcortical arteriosclerotic encephalopathy (13).

See also p 966.

They had already reported that argatroban ameliorated the neurological exacerbations in a patient with Binswanger’s disease and antiphospholipid antibody syndrome (APS) (14). Here, they report an additional three patients with Binswanger’s disease but without APS. In all of their patients argatroban improved cognitive function and gait disorders along with the reduction in the levels of hemostatic markers including thrombin-antithrombin-III complex (TAT), F$_{1,2}$, and cross-linked D dimer. They had previously observed increased levels of TAT in 9 patients with Binswanger’s disease with a subacute exacerbation of their focal or subcortical cerebral functions (15).

A similar observation was reported by Kario et al (16). They examined 17 patients with mild chronic peripheral artery occlusive disease, including 2 cases of vascular dementia, and categorized them into advanced CVD (multiple lacunar infarction and/or advanced periventricular hyperintensity) and non-CVD, and assessed the ratio of N-acetylaspartate to total creatine as an index of neuronal injury or death in the deep white matter area by proton MR spectroscopy before and after infusion of argatroban. The ratio was lower in the advanced CVD group than in the non-CVD group, and in the former group this decreased ratio was increased after argatroban therapy. In addition, two patients with vascular dementia showed clinical improvement with marked increases in the ratio as well as in the mini-mental score.

When markers of thrombin generation are significantly increased in peripheral blood samples, a substantial amount of
thrombin must be generated locally in the deep white matter of the brain in patients with Binswanger’s disease or vascular dementia. Then, generated thrombin may not only promote microcirculatory derangement by the formation of microthrombi as a consequence of platelet and coagulation activation but also directly induce neuronal cell death by activation of thrombin receptors in the brain of these patients.

Argatroban is approved for use in patients with chronic peripheral artery disease and acute atherothrombotic stroke in Japan. Argatroban is a direct thrombin inhibitor, which has been developed in Japan, and is a substituted derivative of arginine with specificity that depends on a stereospecific interaction between the carboxylamide substituent and a hydrophobic binding pocket of thrombin (17). A randomized controlled trial of argatroban of sufficient size may, therefore, clarify the role of thrombin in the pathophysiology of Binswanger’s disease, and may provide new information for therapeutic strategies for vascular dementia as well.

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Reference