

THROMBIN: IS IT ON A PAR WITH SEIZURES AND EPILEPSY?

Thrombin Induces Long-Term Potentiation of Reactivity to Afferent Stimulation and Facilitates Epileptic Seizures in Rat Hippocampal Slices: Toward Understanding the Functional Consequences of Cerebrovascular Insults. Maggio N, Shavit E, Chapman J, Segal M. *J Neurosci* 2008;28(3):732–736. The effects of thrombin, a blood coagulation serine protease, were studied in rat hippocampal slices, in an attempt to comprehend its devastating effects when released into the brain after stroke and head trauma. Thrombin acting through its receptor, protease-activated receptor 1 (PAR1), produced a long-lasting enhancement of the reactivity of CA1 neurons to afferent stimulation, an effect that saturated the ability of the tissue to undergo tetanus-induced long-term potentiation. This effect was mediated by activation of a PAR1 receptor, because it was shared by a PAR1 agonist, and was blocked by its selective antagonist. An independent effect of thrombin involved the lowering of the threshold for generating epileptic seizures in CA3 region of the hippocampus. Thus, the experiments in a slice mimicked epileptic and cognitive dysfunction induced by thrombin in the brain, and suggest that these effects are mediated by activation of the PAR1 receptor.

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COMMENTARY

Several pathological conditions, including ischemic and hemorrhagic stroke, traumatic brain injury, tumor, and

infection are associated with disruption of the blood–brain barrier (BBB). Depending on the severity of compromise of the BBB integrity (e.g., complete compromise with hemorrhage vs partial compromise with vasogenic edema), a variety of blood constituents can come into direct contact with the brain. Although the short- and long-term effects of the brain's exposure to blood products are not well elaborated, clinical evidence clearly indicates that the direct interaction of blood products with brain tissue can initiate the pathogenesis of several brain dysfunctional and disease states—prominent among these are acute seizures and epilepsy.

Modeling the effects of BBB breakdown that lead to seizure generation has been advanced by recent studies demonstrating that BBB disruption in rat neocortex can be induced by focal application of a low concentration of bile salts, which results in a prolonged extravasation of serum components to the brain extracellular space (1,2). Cortical brain slice recordings show the development of an epileptiform focus within 4 to 7 days of BBB breakdown: propagation velocities of evoked epileptic potentials were increased 1 month after treatment, and the focus of epileptiform activity could persist up to 7 weeks posttreatment. The precise serum components responsible for generating the epileptiform focus could not be determined from these studies; however, epileptiform activity was induced by direct cortical application of native and denatured serum and an albumin-containing solution. These studies provided important, direct evidence that BBB breakdown could potentially trigger cortical reorganization and have a role in the pathogenesis of focal cortical epilepsy.

After BBB disruption, one of the constituents of blood that the brain may be exposed to is thrombin. Animal studies have demonstrated that thrombin can cause brain injury after intracerebral hemorrhage (3), including acute seizures (4). Thrombin is a serine protease that converts fibrinogen to fibrin in the final common pathway of the coagulation cascade; serine proteases are so named because of the critical presence of aspartate, histidine, and serine in the catalytic site (5). In addition to thrombin, other serine proteases found in the brain (e.g., tissue plasminogen activator and plasmin), regulate the consequences of several pathological processes, including neurodegenerative disorders and stroke. The effect of thrombin on cellular responses is mediated by protease-activated receptors (PARs), which are G protein-coupled receptors that function in hemostasis, thrombosis, inflammation, and proliferative responses secondary to tissue injury (6). PARs consist of PAR1, PAR2, PAR3, and PAR4 family members; they are widely expressed in the brain, including neurons, microglia, astrocytes, and oligodendrocytes, and can contribute to neuroprotection and/or neurodegeneration under pathological conditions (5). The signaling pathways linking PAR activation to diverse tissue responses have not been fully elucidated (6).

In their report on the effects of thrombin applied to hippocampal slices, Maggio et al. demonstrate that thrombin interacts with PAR1 to produce a long-lasting increase in spontaneous activity of CA3 pyramidal neurons and to lower the threshold for generating ictal-like discharges when coapplied with an increased K^+ or glutamate concentration that would otherwise not elicit ictal discharges. An independent effect of thrombin was the generation of a long-lasting enhancement of CA1 neuronal reactivity to afferent stimulation—an effect that saturated the ability of the tissue to undergo tetanus-induced, long-term potentiation. The results of these studies were interpreted to mimic the epileptic and cognitive dysfunction induced by thrombin in the human brain in pathological conditions.

The results of Maggio et al. raise provocative questions regarding the potential role of thrombin and PARs in a diversity of experimental models involving brain trauma (in particular, stroke and traumatic brain injury) associated with BBB opening and acute and chronic seizures. The present study demonstrates an acute, selective ictal effect of thrombin on PAR1 in CA3 neurons under experimental conditions that augmented excitability. Similar to the thrombin-induced electrobehavioral seizures observed in the studies of Lee et al. (4), the ictal effect of thrombin in the present study was observed only within hours of its application, and no conclusions can be drawn regarding whether thrombin, as a plasma-derived extravasate, is capable of a potential epileptogenic effect similar to that obtained in the bile salt-induced, BBB opening studies (1,2). Long-term, in vivo monitoring studies of the effects of thrombin administration to selected neocortical or hippocampal areas could address this issue.

Although PARs have been implicated to be new therapeutic targets for the treatment of neurodegenerative disorders (5), these receptors are relatively unexplored as potential targets for the prevention of provoked seizures and possibly, epileptogenesis. The study of Maggio et al. draws a potential link between seizures and brain disorders associated with BBB disruption, a link that can be further explored by preclinical studies and, as warranted, clinical trials that selectively target PARs for possible antiseizure or antiepileptogenic effects.

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