STROKE

Kallikrein promotes hematoma expansion

Patients with hyperglycemia typically have a poor prognosis following intracerebral hemorrhage (ICH), but the biological processes that underlie this relationship are unknown. New research published in *Nature Medicine* indicates that hyperglycemia potentiates plasma kallikrein (PK)-mediated inhibition of hemostasis.

Hyperglycemia is generally considered to exacerbate hematoma expansion and hematoma volume is a determinant of poor outcome following ICH. Thus, an understanding of how hyperglycemia affects hematoma expansion could facilitate identification of drug targets for ICH therapy. Research conducted by Edward Feener and colleagues has implicated PK in blood–brain–barrier dysfunction following ICH. To further investigate the role of PK in ICH, Feener's group studied the effects of this protein in a rodent model of cerebrovascular injury.

Dorsal surface of brain 2 h after intracerebral injection of plasma kallikrein in nondiabetic and streptozotocin-induced diabetic rats. Image provided by Dr Edward Feener.

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In both rats and mice, intracerebral injection of autologous blood caused hematoma expansion. Such expansion was markedly greater in rodents with streptozotocin-induced diabetes than in nondiabetic animals. Intracerebral injection of PK was also associated with greater hematoma expansion in diabetic rats than in controls. By contrast, systemic administration of a small-molecule PK inhibitor or co-injection of autologous blood with a neutralizing PK-specific antibody was associated with attenuated hematoma expansion in diabetic rats compared with vehicle or control IgG. Moreover, diabetic transgenic mice that lacked functional PK had significantly smaller hematomas than diabetic control mice following intracerebral injection of autologous blood. “These findings suggest that PK is a key player in the impairment of hemostasis during hyperglycemia,” explains Feener.

Insulin treatment immediately before intracerebral injection of PK markedly attenuated PK-induced hematoma expansion in diabetic rats, whereas intraperitoneal injection of glucose exacerbated PK-induced hematoma growth in nondiabetic rodents. “These

results suggest that high blood sugar, rather than diabetes *per se*, is the critical factor that potentiates PK-induced hematoma expansion,” says Feener.

PK is involved in a number of physiological functions, such as the production of bradykinin and plasmin, but neither bradykinin receptor antagonist infusion nor plasmin infusion affected hematoma expansion in diabetic rats. Deactivated PK had similar effects on hematoma expansion to activated PK, indicating that the enzymatic activity of this protein does not underlie its antihemostatic properties. Further experiments indicated that PK can attenuate collagen-stimulated platelet aggregation—an important hemostatic process—in a dose-dependent manner, through binding of collagen and preventing platelets from interacting with this protein via glycoprotein IV. This process was in turn potentiated by glucose in a dose-dependent fashion.

“Our results suggest that only a subset of PK's actions may be directly mediated by its catalytic activity,” says Feener. By investigating the effects of PK in other models of ICH the researchers hope to aid the development of novel stroke treatments.

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Original article Liu, J. *et al.* Hyperglycemia-induced cerebral hematoma expansion is mediated by plasma kallikrein. *Nat. Med.* 17, 206–210 (2011)