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Abstract

Back to Hit List

Grant Number:	1R01NR005208-01
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PI Title:	
Project Title:	INFLAMMATORY AND THROMBOTIC CELL INTERACTIONS IN STROKE

Abstract: DESCRIPTION: Stroke is the leading cause of serious long-term adult disability and remains the third leading cause of death in the United States. An increasing number of patients with stroke (cerebral ischemia) are experiencing a timely return of blood (reperfusion) to the ischemic brain. Paradoxically, the return of blood to the ischemic brain may cause additional injury to the brain vessels and surrounding cells. This is known as cerebral ischemia-reperfusion injury. The initial events in cerebral ischemia-reperfusion injury are complex and involve inflammatory (leukocytes) and thrombotic platelet) cell activation by multiple mediators that are released during ischemia and reperfusion. The contributions of each of these cell types to cerebral reperfusion injury have been studied separately. However, little is known about the in-vivo mechanisms and the functional significance of leukocyte-platelet interactions after stroke. There is convincing in-vitro evidence that when activated leukocytes and platelets interact with each other, their inflammatory and thrombotic cell responses are exaggerated. These exaggerated responses may be associated with additional brain cell injury after stroke. Therefore, the specific aims of this proposal are to 1) determine the magnitude of leukocyte-platelet interactions and the relationship between leukocyte-platelet interactions and blood cell activation after experimental stroke, 2) determine the effects of leukocyte-platelet inhibition on leukocyte and platelet activation, leukocyte-platelet interactions, functional neurologic outcome, and the size of cerebral infarction after experimental stroke, and 3) determine the relationship between leukocyte and platelet interactions in humans with acute stroke. Aim 1 will be accomplished in an animal model of middle cerebral artery occlusion by directly observing leukocyte-platelet interactions in the microcirculation of the reperfused brain using in-vivo microscopy, and by using flow cytometry to test the magnitude of leukocyte-platelet aggregation and the activation state of leukocytes and platelets. Animal models will be used in Aim 2 to test the inhibition of leukocyte adhesion molecule Mac- I and platelet receptor OPlib/Iha on leukocyte-platelet inhibition, leukocyte and platelet activation, functional neurologic outcome, and cerebral infarction size. In Aim 3, flow cytometry will be used to assess the magnitude and mechanisms of leukocyte-platelet aggregation and the degree of activation of leukocytes and platelets in humans with acute stroke. The information gained

from this translational research will more clearly characterize the inflammatory and thrombotic blood cell interactions after stroke. This information will aid in the development of optimal therapies for the treatment of stroke that will subsequently limit brain cell injury and disability, and will aid in formulating nursing research questions and interventions related to the care of people with acute stroke.

Thesaurus Terms:
cell aggregation, inflammation, stroke, thrombosis
brain circulation, leukocyte activation /transformation, microcirculation, platelet aggregation, reperfusion, selectin
clinical research, flow cytometry, human subject, laboratory mouse, laboratory rat, transgenic animal

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