Activated protein C can protect against age-related cardiac ischemia and reperfusion injury, preclinical study finds

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A University of South Florida Health (USF Health) preclinical study offers molecular insight into how activated protein C (APC) may

improve aging patients' tolerance to reperfusion injury—a potentially adverse effect of treatment for ischemic heart disease.

The research, published online Dec. 21 in *Circulation Research*, suggests that drugs derived from APC may limit ischemia and reperfusion-induced heart damage (reperfusion injury for short) and thereby help preserve cardiac function in older hearts.

Advanced age is a major risk factor for ischemic heart disease, often caused by a buildup of plaques in coronary arteries that narrows the vessels and restricts the supply of oxygenated blood to the heart. This "hardening of the arteries" can eventually trigger a heart attack.

Blood thinners, clot-buster medications, and other drugs, as well as procedures such as coronary artery bypass surgery and balloon angioplasty, are commonly used to restore blood flow to oxygen-starved (ischemic) heart muscle tissue. Paradoxically, especially in older patients , these necessary revascularization treatments can worsen cellular dysfunction and death around the site already damaged by a heart attack, or coronary artery disease. No effective treatments currently exist to prevent age-related reperfusion injury.

"Our research focuses on trying to determine why older hearts are at greater risk for reperfusion injury than younger hearts," said lead author Di Ren, Ph.D., a research associate in the Department of Surgery, USF Health Morsani College of Medicine. "Our goal is to find targeted therapeutic strategies to help older people improve their resistance to the pathological condition of ischemia and reperfusion stress."

"The preliminary evidence in this paper suggests that treatment with activated protein C has the potential to strengthen the cardiac tolerance of aging patients to reperfusion injury from surgery, minimally invasive procedures, or drugs, and (thereby) increase heart attack prevention or

survival," said the study's principal investigator Ji Li, Ph.D., a professor of surgery at the USF Health Heart Institute.

APC, a protein circulating in blood, has both anticoagulant (blood clot prevention) and anti-inflammatory functions that can help protect cells from disease and injury. Endothelial protein C receptor (EPCR)—located both on cells lining blood vessels and on the surface of cell membranes, including heart muscle cells—is associated with increased APC production and regulates APC's subsequent cell signaling (or cell communication).

In this mouse model study, the researchers analyzed how APC exerts cardiac protection during ischemia and reperfusion. The groups of mice observed included young and old "wild-type" mice with all their genes intact, and young "knock-in" EPCR R84A/R84A mice genetically modified to make their EPCR receptors incapable of interacting with the APC protein as well as their wild-type littermates without the EPCR R84A/R84A mutation.

Naturally occurring APC or one of two laboratory-engineered APC derivatives were administered to the mice with heart attack-induced ischemia before reperfusion. One derivative (compound APC-2Cys) selectively activated a signaling pathway to promote cell protection without inhibiting blood clotting (coagulation). The other derivative (compound APC-E170A) selectively triggered a signaling pathway promoting only anticoagulation.

Among the team's key preclinical findings:

- The stress of Ischemia and reperfusion injury induced "shedding" of EPCRs in young and old wild-type mice—that is, a greater number of these receptors were cut from the heart muscle cell membrane and then moved into the bloodstream. This EPCR

shortage (deficiency) in the heart can impair activated protein C signaling critical for favorably regulating energy metabolism and anti-inflammatory responses, preventing cell death, and stimulating other activities needed to protect cardiac muscle cells.

- While the hearts of the old and young wild-type mice both showed EPCR shedding, older hearts experienced a more severe EPCR deficiency and decline in APC signaling activity in response to reperfusion injury. No APC signaling was detected in the EPCRR84A/R84A mice, because APC was blocked from binding to the cell membrane receptor.
- Administering APC or its derivatives helped reduce heart damage inflicted by ischemia and reperfusion, particularly in the old mice. Digging deeper, the researchers discovered that by stabilizing (maintaining) EPCR on the cardiac cell membrane, APC strengthens the aging heart's resistance both to heart attack-related ischemia and to injury associated with restoring coronary artery blood flow.
- Furthermore, APC and the APC-2Cys signaling derivative, but *not* the APC-E170A anticoagulant-selective signaling (a potential bleeding risk), helped preserve cardiac function. All cardioprotective effects of APC were weaker in young mice in which EPCR was eliminated; their hearts looked and performed like that of older mice.
- The researchers detailed how APC treatments improve cardiac function by regulating both acute (short-term) and chronic (longer-term) metabolic pathways. They demonstrated that enzyme AMPK (AMP-activated protein kinase) mediates an acute adaptive response to cardiac stress immediately following heart attack, while enzyme AKT (protein kinase B) regulates chronic metabolic adjustments to reperfusion stress over time. APC treatment led to better enzyme activity and more efficient energy balance needed to contract cardiac muscle cells and pump

blood from the heart to the rest of the body.

"APC is beneficial for ischemia-reperfusion injury both in the acute and chronic stages, so appropriate APC derivatives might be used both as preventive and therapeutic drugs," Dr. Li said.

More information: Di Ren et al, Activated Protein C Strengthens Cardiac Tolerance to Ischemic Insults in Aging, *Circulation Research* (2021). DOI: 10.1161/CIRCRESAHA.121.319044

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