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Stages in Discovery: ACE2 and Stroke

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Rapid progress in relation to cardiovascular effects of Angiotensin 1–7 (Ang 1–7), the Mas receptor, and the angiotensin converting enzyme type 2 (ACE2) is an example of basic biomedical research which may eventually lead to an advance in care of patients.

When one of us (DH) first attended the meeting of the Council for High Blood Pressure Research about 1970, the future of studies of the renin/angiotensin system (RAS) seemed limited. It looked like there was not much more to be learned, and was not a promising area of research. That judgment was comparable to the initial impression that Furchgott's endothelium derived relaxing factor was not very important¹. Obviously, the renal/vascular/central RAS has proven to be important in normal cardiovascular regulation, pathophysiology, and as an enormously important therapeutic target.

Another chapter of the RAS story has been written over the past two decades as the ACE2 / angiotensin 1–7/mas receptor axis has emerged. The first stage was the discovery of Ang 1–7 by Ferrario², the role of ACE2 upon enzymatic formation of Ang 1–7 by Penninger³, and identification of the Ang 1–7 receptor, Mas, by Santos, Bader⁴. The second stage was the finding that administration of exogenous ang 1–7 is sufficiently potent to produce effects on the cardiovascular system, and that the endogenous system is sufficiently potent to affect responses to several pathophysiological states⁵.

One of the important effects of ACE2 / angiotensin 1–7/mas receptor axis is its effects on the brain and cerebral blood vessels. ACE2 and angiotensin 1–7 are important modulators of cerebrovascular function^{6, 7}. Treatment with angiotensin 1–7 appears to protect the brain from inflammation, apoptosis and oxidative stress induced by hypertension⁸. Angiotensin 1–7 also appears to play an important role in cerebrovascular disease. In stroke prone hypertensive rats⁹ and in a mouse model of rupture of intracranial aneurysms¹⁰, angiotensin 1–7 appears to increase survival. The ACE2 / angiotensin 1–7/mas receptor axis also appears to be modulated and be beneficial in models of ischemic stroke. Levels of angiotensin 1–7, and expression of ACE2 and Mas increase after middle cerebral artery occlusion (MCAO) in

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rats¹¹. Several groups have shown that intracerebroventricular (ICV) administration of angiotensin 1–7, administered before and during middle cerebral artery occlusion, may attenuate neuronal damage in rats after MCAO^{12–14}. Similarly, indirect approaches to increase brain angiotensin 1–7 levels have been developed using ICV administration of an ACE2 activator (diaminazene), which also appears to protect the brain against ischemic damage¹⁴. Thus, several lines of evidence suggest that the ACE2 /angiotensin 1–7/mas receptor axis plays a protective role in pathophysiology of cerebrovascular disease and stroke.

In the current issue of Hypertension, Bennion et al.¹⁵, extend previous studies and demonstrate that the ACE2 activator, diminazene, when given intraperitoneally, attenuates brain damage and neurological deficit after ischemic stroke. The authors used an MCAO model in which endothelin 1 is injected in the proximity of the MCA and induces vasoconstriction. Using this model, the authors report several findings. First, Brain ACE2 activity increases shortly after ischemic stroke. Second, circulating ACE2 activity is also increased 3 days after ischemic stroke. Third, inhibition of cerebral ACE2 by ICV injection of an ACE2 inhibitor (MLN-4760) did not increase infarct volume, but resulted in aggravation of neurological deficit after MCAO. Fourth, intraperitoneal injection of an ACE2 activator decreased infarct volume and neurological deficit after MCAO. Fifth, the beneficial effects of the ACE2 activator after MCAO were attenuated by ICV injection of a Mas receptor antagonist (A779). Collectively these results suggest that formation of angiotensin 1–7 and stimulation of Mas receptors is associated with the beneficial effects of ACE2 activation in ischemic stroke. The mechanisms by which ACE2 activation protects the brain after ischemic stroke are not clear, but appear to be independent of changes in blood pressure or cerebral blood flow. Protective effects of ACE2 may involve modulation of neuroinflammation, as suggested by previous studies. Importantly, although the authors used intraperitoneal injections, they demonstrated effects of the ACE2 activator in the brain. The finding is important with the potential for translation of these findings to the patient.

The long term impact of interventions that target ACE2 and angiotensin 1–7 in stroke are not clear. Is the early decrease in neurological deficit associated with better prognosis and survival? Is circulating ACE2 activity a valid marker of brain damage after stroke? Would increased circulating ACE2 activity be associated with better prognosis or would it be associated with systemic inflammation and increased shedding of ACE2 by TACE? Would systemic administration of angiotensin 1–7 protect the brain after brain ischemia?

The future? These studies suggest that ang 1–7/ACE2 Mas axis may protect against stroke. An ENORMOUS word of caution, however. Many studies have observed that a wide variety of interventions reduce the size of ischemic strokes in experimental models (especially in rats and mice). But these interventions have failed to reduce the size of strokes in humans. As a minimum, this area of research is clarifying mechanisms by which endogenous ang 1–7/ACE2 protect against stroke. We are far from knowing however whether ang 1–7 will be the first peptide to protect against stroke in humans.

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Figure 1.

Brain ischemia induces neuroinflammation, apoptosis and oxidative stress and causes brain damage. Recent studies revealed that brain ischemia may increase the circulating and local ACE2 activity. Increased ACE2 activity may lead to increased formation of angiotensin 1–7 and stimulation of Mas receptors, which may be neuroprotective. Similar effects can be obtained after local or intraperitoneal administration of an ACE2 activator (diminazene). Ang II: Angiotensin II; Ang 1–7: Angiotensin 1–7; ACE2: angiotensin converting enzyme type 2; ET-1: endothelin 1.