There is a “new kid on the block” in the control of the renin-angiotensin system (RAS). The discovery of angiotensin (Ang)-converting enzyme (ACE2), a catalytic enzyme, that cleaves the octapeptide, Ang II into a septapeptide, Ang-(1-7),\(^1,2\) has opened up new vistas in the way we think about the regulation and biological effects of Ang II. ACE 2 was originally discovered in yeast\(^3\) as a gene product that codes for a protein that is a homolog of the more widely known protease ACE. ACE2 cleaves the C-terminal amino acid from Ang II and other peptides. For many years, the work of Ferrario and Chappell\(^4\) provided evidence that Ang-(1-7) operated in the central nervous system, as well as in the peripheral circulation to produce effects that were, in general, opposite to that of Ang II. Recently, the discovery that Ang-(1-7) binds to a specific membrane receptor, the mas receptor,\(^5\)\^-\(^7\) suggests that this metabolite may play a regulatory role in cell signaling and organ function. Clearly, the balance between the classic ACE and ACE2 will determine the physiological effect of activation of the RAS. Furthermore, the potential for therapeutic targeting of ACE2 and its role in the pathogenesis of various diseases such as hypertension and heart failure is intriguing.

To further understand the potential for ACE 2 in the brain to alter sympathetic function and drinking, 2 well-known effects of central Ang II, Feng et al, in this issue of *Circulation Research*,\(^8\) used adenoviral transfection techniques to overexpress ACE2 in the mouse brain. Overexpression was prominent in the subfornical organ (SFO), an area involved in sympathetic regulation and thirst in response to Ang II.\(^9\) This structure is heavily endowed with Ang type 1 receptors (AT1R). Because the SFO is devoid of a blood–brain barrier, it is well suited to “sense” both cerebrospinal fluid and circulating substances. Therefore, the SFO is an ideal structure to test the hypothesis that overexpression of ACE2 alters responses to Ang II. There are 2 striking results presented in this study. The first relates to the physiological responses to ACE2 overexpression when challenged by intracerebroventricular Ang II. Both thepressor and drinking responses were dramatically reduced in ACE2-transfected mice. The second and perhaps the most interesting result is that overexpression of ACE2 reduced AT1R expression in the SFO, as well as in isolated neuroblastoma cells.

Ang II signaling in most tissues is mediated by multiple pathways. The dominant pathway depends on tissue type and the function to be mediated. This is especially true in the central nervous system, where all of the components of the RAS exist. There is evidence that various components, such as angiotensinogen, may actually be predominant in glia,\(^10\) whereas others appear to predominate in neurons.\(^11\) A question that has been posed for many years is how the central RAS system is regulated. In fact, except for the kidney, this question is still valid for most tissues. Whatever the stimulus to activation of the central RAS (another fruitful area of investigation), there is growing evidence that augmented central Ang II activates a pathway that results in further upregulation of the AT1R,\(^12\)\^-\(^14\) and a decrease in the AT2R.\(^15\) This mechanism may be responsible for normal physiological regulatory processes to be transformed into a pathological process. For instance, in the setting of chronic heart failure, AT1R expression is upregulated in the rostral ventrolateral medulla\(^14\)\^-\(^16\) and most likely in the paraventricular nucleus of the hypothalamus as well.\(^17\) This process is completely dependent on binding of Ang II to the AT1R and to activation of a transcriptional pathway that most likely involves multiple transcription factors and their phosphorylation (see Figure). This effect can be mimicked by Ang II infusion in animals and by incubation with Ang II in cells.\(^14\) The fact that Feng et al\(^8\) demonstrated a downregulation in AT1R expression in the SFO following central ACE2 adenoviral transfection raises the question as to the physiological and pathological significance of this process. Is this effect dependent on the generation of Ang-(1-7)? If so, does it involve the mas receptor and do any of the downstream signaling steps involve components of the pathway shown in the Figure? These are critical questions whose answers will depend on novel tissue and cell specific transgenic models and specific inhibitors of both ACE2 and the mas receptor.

Finally, the relationship between AT1 and AT2 receptor expression in the brain may be of importance in the regulation of this system. A reciprocal relationship appears to occur for expression of these 2 receptors.\(^18\)\^-\(^19\) If expression of AT1 receptors influences AT2 expression, then the degree to which ACE2 is activated may play a determining role controlling the balance between these 2 receptors and their downstream signaling pathways. At this point, it is important to focus on how each of the components of the RAS is regulated in the brain to alter sympathetic neuronal function and ultimately peripheral vascular and cardiac function.

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The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Department of Cellular and Integrative Physiology, University of Nebraska Medical Center, Omaha.

Correspondence to Irving H. Zucker, PhD, Department of Cellular and Integrative Physiology, University of Nebraska Medical Center, 985850 Nebraska Medical Center, Omaha, NE 68198-5850. E-mail izucker@ummc.edu

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ACE

\begin{align*}
\text{Ang I} & \quad \text{Ang II} & \quad \text{Ang 1-7} \\
\downarrow & \quad & \downarrow \\
\text{AT1R} & \quad \text{AT2R} \\
\downarrow & \quad \\
pJNK & \quad \\
p-c-fos & \quad p-c-jun \\
\text{AP-1} & \\
\end{align*}

**Figure.** A schematic overview of the relationship between ACE and ACE2 and possible influences on AT,R expression in the brain. Ang II through the AT,R evokes an up regulation in AT,R expression via a transcriptional effect involving activator protein-1 (AP-1). ACE2 forms Ang-(1-7) from Ang II. Ang-(1-7) exhibits effects that are in opposition to Ang II. The data from the study of Feng et al\(^8\) suggests that overexpression of ACE2, and ostensibly Ang-(1-7), participates in downregulation of the AT,R. Solid arrows denote a positive effect; dashed arrow denotes a negative effect. pJNK indicates phosphorylated c-jun N-terminal kinase; p-c-fos, phosphorylated c-fos; p-c-jun, phosphorylated c-jun.

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Irving H. Zucker

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