since the first description of renin, angiotensinogen and angiotensin as well as converting enzyme and angiotensin receptors in the brain exactly 30 years ago,1-5 there was a heated debate, whether an endogenous intrinsic brain renin-angiotensin system (RAS) exists or not.6,7 For a long time, the “believers” of local angiotensin II generation by the brain RAS were in a minority. Even at a symposium 1981, celebrating the 10-year anniversary of the discovery of the brain RAS, there was skepticism and the question whether the “renin-like” enzyme in brain was identical with cathepsins, tonin, or other proteases was a matter of debate. Historically, it is interesting that the presence in the brain of other classically peripheral peptides such as insulin, glucagon, and substance P was accepted without identification of the local synthetic pathway and less controversial than angiotensin as neuropeptide. Open letters, public debates, and personal accusations nourished sometimes emotional controversy whether angiotensin could be generated locally in tissue. The brain was a model for angiotensin generating barriers, which is impermeable for proteins and peptides, made it more unlikely that the RAS components measured in the brain were contaminations from the plasma.

Angiotensin has extremely powerful effects on the brain that synergistically increase blood volume and blood pressure, eg, by stimulation of water intake and salt appetite, release of various pituitary hormones, increase of sympathetic tone, and decrease of baroreceptor reflex.7 The local generation of angiotensin II in the brain by an endogenous intrinsic RAS could therefore be extremely important for cardiovascular control and beyond.

With the advent of transgenic technology, novel approaches to study the mechanistic and functional aspects of the brain RAS became available. Renin and angiotensinogen could be overexpressed or ablated in experimental paradigms.

In this issue of Circulation Research, the group of Curt Sigmund8 analyzes a novel transgenic mouse model that overexpresses human renin driven by 75 kb of its own regulatory sequences. The expression of the transgene mimics the normal tissue-specificity and regulation of human renin in the periphery, albeit on a higher level due to multiple copies inserted in the genome.9 The animals are therefore valid models to study the distribution of renin in the brain. By immunocytochemistry, the authors show that human renin can be found in glial cells of the amygdala, cortex, thalamus, and hypothalamus, as well as in neurons of the dorsal cochlear nucleus and the hippocampus.8

This and other studies show that the brain mainly synthesizes a novel renin isoform encoded by an mRNA with an alternative first exon.8,10-13 The transcription of this isoform in humans starts far upstream of the previously described initiation site. A recent report supposed the novel exon 1A to be situated 1.3 kb upstream based on a partial sequence homology.13 However, a search in the Human Genome Database detects a 100% homologous sequence 6.2 kb 5’ of the canonical start site (own unpublished results). Moreover, there is no evidence that transcription really starts there and the promoter may map even further upstream. Thus, the structure and function of the new renin isoform is not yet understood, but it may be involved in intracellular angiotensin generation probably inside mitochondria.10

The analysis of transgenic animals overexpressing human angiotensinogen provided evidence against a role of alternative pathways in physiologically relevant angiotensin generation.14-16 Because human angiotensinogen cannot be cleaved by rodent renin, all these animal models remained without cardiovascular phenotype. Only when they were crossbred with animals carrying human renin transgenes, strong blood pressure effects were observed.15-17 It is unlikely, however still untested, that this species specificity also occurs for other angiotensin-generating enzymes. Thus, should an alternative metabolism of the human substrate by an enzyme other than renin exist in the rodent brain the animals should have become hypertensive even in the absence of human renin.

Functional Importance of the Brain Renin-Angiotensin System

In addition to the biosynthetic pathways, transgenic models also contributed to the study of the functional importance of angiotensin in the brain. Transgenic mice with overexpression of the human RAS in several tissues15 or in the brain alone18 become hypertensive, also the ones described in this issue.8 In these models, the high blood pressure can be reduced by intracerebroventricular injection of the angiotensin II receptor AT1 antagonist losartan, suggesting that brain renin is a major determinant of hypertension. Part of the effect seems to be mediated by vasopressin because intravenous injection of a V1 receptor antagonist also attenuates the
hypertensive phenotype. In contrast, ganglion blockade has no specific effect, indicating that the sympathetic nervous system is not primarily involved in this central angiotensin action.

Very recently, a transgenic mouse was presented with 8 times more angiotensin II in the brain but normal levels in the circulation. The peptide is liberated during secretion from an artificial chimeric protein expressed under the control of the brain-specific glial fibrillary acidic protein (GFAP) promoter. Also these animals are hypertensive.

The hypertension developed by transgenic rats carrying the mouse renin gene Ren-2, TGR(mREN2)27,29 is also partially dependent on the expression of the transgene in the brain. These animals generate up to tenfold more angiotensin II in the central nervous system than control rats.21 When they are anesthetized by chloralose-urethane, blood pressure drops to normal, arguing in favor of a neurogenic cause of their hypertension. Furthermore, when the central angiotensin generation in TGR(mREN2)27 is blunted by crossbreeding with transgenic rats carrying a brain-specific deficiency in angiotensinogen [TGR(ASrAOGEN)], a significant reduction in blood pressure is observed.23

The already mentioned transgenic rat model, TGR(ASrAOGEN), has provided numerous insights in the functionality of the brain RAS. These rats carry a transgene expressing an antisense RNA against angiotensinogen specifically in the brain under the control of the GFAP promoter.20 This causes a reduction of local angiotensinogen levels by 90% without affecting the circulating RAS. The rats are hypotensive and exhibit reduced vasopressin levels in the circulation, again supporting a central involvement of angiotensin II in vasopressin secretion. Furthermore, they show an increased baroreflex sensitivity due to an imbalance of the parasympathetic and sympathetic nervous system. Together with the findings that TGR(mREN2)27 and mice expressing an artificial chimeric protein increased baroreflex sensitivity due to an imbalance of the parasympathetic and sympathetic nervous system. Together with the findings that TGR(mREN2)27 and mice expressing an artificial chimeric protein18,19 show normal water intake. Thus, sudden elevation of central angiotensin II levels induces thirst but long-term overproduction may be compensated by other mechanisms regulating drinking behavior.

Although the drinking of water is unaffected by a permanent increase in brain angiotensin II, alcohol drinking is. Mice overexpressing rat angiotensinogen drink more and angiotensinogen knockout mice drink less alcohol than their respective controls in a free-choice paradigm.22 First evidence indicates that a modulation of dopamine release by angiotensin may mediate this effect.

Taken together, the study by Morimoto et al8 showing that human renin is expressed in brain areas relevant for cardiovascular and fluid homeostasis supports that it is a major angiotensin-generating enzyme in the brain. Furthermore, the increase of renin levels in this organ by targeted overexpression in transgenic animals causes hypertension by the local generation of angiotensin II. A contribution of other enzymes to central angiotensin generation can still not be completely ruled out, but the findings presented here allow us to sing, modified from Gene Kelly. “It’s renin in the brain!”

References


Key Words: renin-angiotensin system, brain, central mechanisms, transgenic animals
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Michael Bader and Detlev Ganten

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