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The renin–angiotensin and “drinking” behavior

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Ganten et al. [1] were the first to show that renin may be present in the central nervous system. Interestingly, before that time, Epstein et al. [2] had already shown that angiotensin II (Ang II) introduced into the central nervous system initiates drinking. To my knowledge, the first experiment to show that central Ang II, as opposed to Ang II from elsewhere, was in any way related to drinking or any behavior was conducted by Antelman et al. [3]. These investigators determined if drinking elicited by central carbachol administration was dependent on the renin–angiotensin system, not in the brain but in the kidney. Rats were stereotaxically implanted with cannulae in the medial septal nucleus and then screened to determine whether or not they drank after carbachol. After a suitable period, all positive cholinergic drinkers were randomly assigned to one of three experimental groups: nephrectomized rats, ureterally ligated rats, and sham-operated rats. The operations were performed, and 9–11 h after surgery, all animals were stimulated with carbachol and given a 1-h drinking test. There was no effect of nephrectomy on cholinergic drinking. The renal Ang II had nothing to do with drinking. Thus, the Ang II resulting in drinking behavior had to come from elsewhere, produced locally in the brain for instance. Schinke et al. [4] elucidated the issue further. They generated a transgenic rat that expressed an antisense RNA against angiotensinogen (AGT) mRNA specifically in the brain, namely, the TGR(ASrAOGEN). The rats had lower blood pressure than controls. When Ang II was injected into their brains, their drinking response was attenuated. The rats also had a defect in generating a concentrated urine and were relatively deficient in their ability to release vasopressin.

Recently, Sakai et al. [5] generated double-transgenic mice expressing human renin (hREN) from a neuron-specific promoter and human AGT (hAGT) from its own promoter (SRA mice) to emulate this expression [4]. SRA mice exhibited an increase in water and salt intake and urinary volume, which were significantly reduced after chronic intracerebroventricular delivery of losartan. Ang II-like immunoreactivity was markedly increased in the subfornical organ (SFO). To further evaluate the physiological importance of de novo Ang II production specifically in the SFO, the authors utilized a transgenic mouse model expressing a floxed version of hAGT, hAGT(flox), so that deletions could be induced with Cre recombinase. They then targeted SFO-specific ablation of hAGT(flox) by microinjection of an adenovirus encoding Cre recombinase. The SRA(flox) mice exhibited a marked increase in drinking at baseline and a significant decrease in water intake after administration of AdCre/adenovirus encoding enhanced green fluorescent protein (GFP; AdCre/AdEGFP) but not after administration of AdEGFP alone. This decrease only occurred when Cre recombinase correctly targeted the SFO and correlated with a loss of hAGT and angiotensin–peptide immunostaining in the SFO. Sakai et al. provided strong gene-related evidence implicating de novo synthesis of Ang II in the SFO as an integral regulator of fluid homeostasis. Thus, in terms of water drinking behavior, we have learned that Ang II is important, the peptide is generated locally, brain renin probably participates as AGT must be converted to Ang, and the SFO is a major site of the action.

So much for water; the eccentric W. C. Fields never drank the stuff. Readers my age may know the reason why. In this issue, Sommer et al. [6] report on the brain renin–angiotensin system and ethanol consumption. Ethanol consumption can be programmed in rats by repeated cycles of exposure and withdrawal. The authors studied AGT, angiotensin-converting enzyme (ACE), and the Ang II receptor (AT1) expression in various brain regions. They found that AGT expression increased in medial prefrontal cortex, particularly in astroglia. The exposure time required 7 weeks. ACE was then blocked in the central nervous system by administration

of spirapril, an ACE inhibitor that is particularly blood–brain-barrier permeable. An alternative model was also studied, namely, the TGR(ASrAOGEN) was brought out of retirement. The readers will recall that the rat is transgenic for an antisense against AGT mRNA. Spirapril-treated rats and TGR(ASrAOGEN) drank less ethanol than controls. The current study is an extension of earlier work. Data are already available on Ang II-induced central signaling in terms of alcohol consumption. Maul et al. [7] characterized the role of central Ang II in alcohol intake first by using the same TGR(ASrAOGEN) rats. These rats consumed markedly less alcohol compared to their wild-type controls. Second, spirapril did not influence the alcohol consumption in the TGR(ASrAOGEN), but it significantly reduced alcohol intake in wild-type rats. Furthermore, the dopamine concentration in the ventral tegmental area (VTA) was markedly reduced in rats with low central Ang II, suggesting a role for dopaminergic transmission in Ang II-controlled alcohol preference.

What is the connection between alcohol intake and the renin–angiotensin system or with hypertension? An association between hypertension and alcohol abuse has long been recognized, and manipulations of the renin–angiotensin system in laboratory animals has been shown to alter their consumption of ethanol [*8*]. Procedures that decrease the renin–angiotensin system increase ethanol consumption. Paradoxically, inhibitors of angiotensin converting enzyme also diminish drinking. Several possible explanations for this observation have been proposed. However, observations on the relationship between stress-induced drinking and the antidipsogenic action of a fragment of adrenocorticotropic hormone suggest another possibility. ACE may be involved in the metabolism of this peptide and thereby could also exert a non-Ang II-related influence on drinking behavior.

Nonetheless, clinicians know that for control of hypertension, cessation or at least reduction in alcohol intake is a first step in treatment [*9*]. Pharmacologic treatment should be withheld until after 2–4 weeks of abstinence from alcohol. Alcoholism can result in autonomic neuropathy and cardiomyopathy that can lead to a fall in blood pressure. Prevailing evidence suggests that ACE inhibitors may be the most appropriate pharmacologic treatment for alcohol-addicted patients.

The brain renin–angiotensin system (►Fig. 1) appears here to stay [10]. Exactly how renin figures into the equation remains difficult to say. A splice variant appears to be expressed particularly in brain [11]. However, documenting the existence of the functioning protein and showing its central action has been fiendishly difficult. Nevertheless, two groups have shown in the mouse [12] and in the rat (Gratze et al., unpublished observations, 2007) that rodents transgenic solely for the human renin gene (hREN) exhibit polyphagia and become obese, compared to controls. Eating, as is drinking, would appear to be a central behavior. hREN has no preferred mouse or rat substrate to our knowledge. Whether or not Ang II is the final mediator of any central nervous system responses is also unclear. Strong argument has been made for a central aminopeptidase that degrades Ang II to the heptapeptide Ang [2–8], which is also known as Ang III. Fournie-Zaluski et al. [*13*] reported that brain Ang III exerts a tonic stimulatory effect on blood pressure in the desoxycorticosterone (DOCA)-salt rat that is characterized by a depressed systemic but a hyperactive brain renin–angiotensin system. The group developed RB150, a prodrug of the specific and selective aminopeptidase A (APA) inhibitor, EC33. RB150 is able to cross the blood–brain barrier to inhibit brain APA and to block the formation of central Ang III. A single dose of systemic RB150 markedly reduced blood pressure for up to 24 h in these rats. Drugs that influence the renin–angiotensin system in the brain could be of great interest. AT1 receptor blockers penetrate only modestly. Spirapril seems the best ACE inhibitor in that regard. Little information is available on the direct renin inhibitor, aliskiren. The drug is very hydrophilic and is a substrate for P-glycoprotein so its central effects may be modest. In any event, the brain renin–angiotensin system continues to remain heady stuff.

Respectfully,

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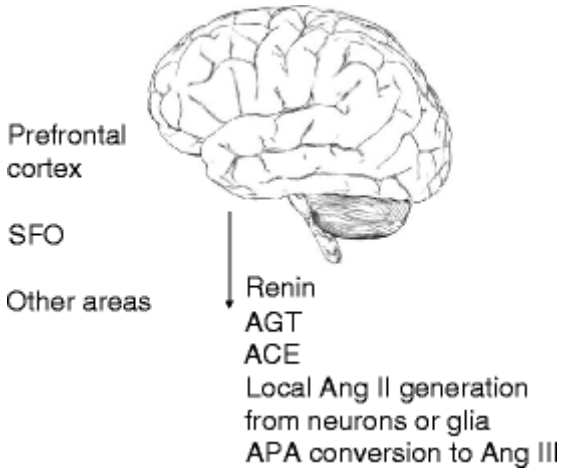

►Fig.1. In the brain, Ang II exerts effects on drinking, salt appetite, ethanol intake, and blood pressure. Since AGT central nervous system depletion exerts an effect, renin seems to be necessary and Ang II is probably generated locally rather than being taken up from the circulation. Renin may exert an independent effect on eating behaviors. The subfornical ogan (*SFO*) seems well worked out as an Ang II-regulated thirst center.