The (pro)renin receptor and body fluid homeostasis

Theresa Cao and Yumei Feng

Department of Physiology, Tulane Hypertension and Renal Center of Excellence, Tulane University School of Medicine, New Orleans, Louisiana

Submitted 26 April 2013; accepted in final form 11 May 2013

THE (PRO)RENIN RECEPTOR (PRR) is a 35-kDa single transmembrane protein that binds to both renin and prorenin, the precursor of renin. The binding of renin or prorenin to PRR promotes angiotensin (ANG) II formation, contributing to renin-angiotensin system (RAS) activation (11). On the other hand, activation of PRR mediates several ANG II-independent hypertrophy or proinflammatory signal activations (9). The presence of PRR mRNA and protein along with the other elements of the RAS system, renin or prorenin, in brain regions associated with cardiovascular function (5) allow the possibility of RAS activation to occur in the brain.

Brain PRR in Body Fluid Homeostasis

Brain ANG II has been shown to increase sympathetic nerve activity, blood pressure, thirst, sodium appetite, and release of arginine vasopressin (AVP) (13). However, functional intrinsic brain RAS has been debated due to the low levels of renin, suggesting that the enzymatic activity is not sufficient enough to mediate ANG II formation and the downstream effects (3, 8). On the other hand, circulating renin is unable to cross the blood-brain barrier (1, 8), suggesting the majority of ANG II is locally generated. The discovery of the PRR, as a new player in RAS, therefore, allows a novel pathway to locally generated ANG II in the brain. The question of whether neurons within the brain express functional PRR was addressed recently by our laboratory and others (6, 7, 15, 16). PRR mRNA levels were upregulated in the supraoptic nucleus (SON) of hypertensive animal models (6, 16). The increase in functional PRR in these specific brain regions in pathophysiological conditions associated with water-electrolyte balance, therefore, enhance the argument for an active role of functional PRR in the body fluid homeostasis.

One way that brain PRR has been suggested to affect body fluid homeostasis is through the activation of RAS. In a study conducted by Li et al. (6), brain PRR knockdown in the SFO in hypertensive human renin and angiotensinogen transgenic mice (RA) mice decreases levels of ANG II receptor type 1 (AT1R) expression and brain AVP mRNA and plasma AVP levels, suggesting an influence of PRR on AVP secretion in pathophysiological conditions. In another study conducted by Shan et al. (16), PRR knockdown in the SON of spontaneously hypertensive (SH) rats decreases mean arterial pressure, heart rate, and plasma AVP level. In the same study (16), human PRR (hPRR) was overexpressed in SON of Wistar-Kyoto (WKY) rats, which resulted in a twofold increase in plasma AVP and a threefold increase in urinary AVP. Additionally, there was an increase in urinary osmolality, decreased daily water intake, and daily urinary excretion (16). Although whether PRR regulates AVP by RAS pathway or RAS-unrelated signals was not addressed in this study, these findings emphasize the effect of PRR activation on AVP secretion and on body fluid homeostasis. An association between the PRR and AVP has also been found in humans (17). PRR was found colocalized with AVP in both PVN and SON in the human brain. Furthermore, PRR expression was found in all cell types in anterior pituitary but very low in the posterior lobe. The role of PRR in AVP secretion and, consequently its influence in water-electrolyte balance, therefore, is supported by animal models and human data.

Peripheral PRR in Body Fluid Homeostasis

The PRR gene is not been only expressed in the brain but also in other peripheral organs such as the heart, liver, pan-
creas, and the kidney (11). Recent studies show that PRR seems to play a role in RAS activation in peripheral organs. Prorenin has been uniquely found to mature into active renin only in the juxtaglomerular cells of the kidney (14), and PRR has been found to colocalize with renin in vascular structures (11), together suggesting a local role of PRR in the kidneys. Previous studies have also shown that renin has the ability to bind to human mesangial cells in vitro and resulted in hypertrophic effects and increased levels of plasminogen activator inhibitor-1; however, renin was not internalized or degraded (4, 10), supporting a functional role of a renin receptor, PRR, in the renal smooth muscle cells. In a study reported by Burckle et al. (2), human PRR was overexpressed in rat smooth muscle cells. The rat models developed higher systolic blood pressure and increased heart rate with aging, but the kidney function and plasma renin levels showed no significant change (2). There was, however, an increase in plasma aldosterone and the aldosterone-to-renin ratio, suggesting that PRR overexpression resulted in increased intra-adrenal RAS activation, therefore, aldosterone synthesis (2). The effects of aldosterone on sodium and water retention in addition to other indirect influences on water-electrolyte balance are well documented (12).

**Perspectives and Significance**

PRR, through both ANG II-dependent and ANG II-independent pathways, affects body fluid homeostasis (Fig. 1). PRR acts on both the central nervous system and the peripheral organs through the activation of renin or prorenin and the resulting catalysis of the RAS, affects ANG II formation, sympathetic activity, and the AVP synthesis and secretion and, therefore, affects water and electrolyte balance. On the other

---

**Fig. 1.** Central and peripheral effects of (pro)renin receptor (PRR) on body fluid homeostasis. PRR acts on both the central nervous system and the peripheral organs through the activation of renin or prorenin and the resulting catalysis of the renin-angiotensin system, affects ANG II formation, sympathetic activity, and the AVP synthesis and secretion and, therefore, affects water and electrolyte balance. See text for more information.
hand, the underlying mechanisms of RAS-unrelated PRR action on body fluid homeostasis need further investigation.

REFERENCES


