The Journal of Pharmacology & Nutritional Sciences

(Pro)renin Receptor and Its Soluble Form in Metabolic Dysfunction: Friend or Foe?

Gertrude Arthur[1,*]

***Abstract*— (Pro)renin receptor is component of the renin angiotensin system which has been shown to be involved in several physiological and pathophysiological processes including blood pressure regulation and hypertension, water and electrolyte balance, kidney injury, obesity, and metabolic dysfunction. Enzymatic cleavage of prorenin receptor produces soluble prorenin receptor which can also activate the renin angiotensin system stimulate similar pathophysiological process like its full form receptor. This review explores findings on the role of prorenin receptor and soluble prorenin receptor in metabolic dysfunction and discusses the conflicting findings on soluble prorenin receptor in metabolic dysfunction.**

***Keywords*—Molecular, Genetic, & Biochemical Nutrition, Pharmacology**

I. Introduction

The (Pro)renin receptor (PRR) is a 350 amino acid trans-membrane receptor which was discovered a decade ago to be component of the renin angiotensin system (RAS) (Arthur, Osborn, & Yiannikouris, 2021; G. Nguyen et al., 2002; Nichols & Yiannikouris, 2022). In classical RAS physiology, PRR increases the catalytic activity of renin in cleaving Angiotensinogen (AGT) to Angiotensin I (Ang I) and gives enzymatic activity to the inactive form of renin; prorenin to catalyze the conversion of AGT to Ang I without the removal of its prosegment (Nguyen, 2007). When PRR is cleaved by enzymes such as furin, site 1 protease (S1P) and ADAM metallopeptidase domain 19 (Adam19), it produces a soluble form (sPRR) which is released into the plasma and urine (Arthur et al., 2021; G. Nguyen et al., 2002). sPRR has also been shown to activate the renin angiotensin system (Arthur et al., 2021). PRR is found in several organs of the body including the kidneys (G. Nguyen et al., 2002), adipose tissue (Achard, Boullu-Ciocca, Desbriere, Nguyen, & Grino, 2007), liver (E. Gatineau et al., 2021), heart (Hayakawa et al., 2015), brain (Mohsin et al., 2020), and the eyes (Alcazar, Cousins, Striker, & Marin-Castano, 2009). In these tissues, PRR mediates several different functions but research to date has tended to focus on its roles in blood pressure regulation and hypertension, water and electrolyte balance, kidney injury, obesity, and metabolic dysfunction (Arthur et al., 2021; Nichols & Yiannikouris, 2022). This mini review explores findings on how PRR and sPRR contribute to obesity and sheds light on the conflicting findings about the role of sPRR in obesity, glucose, and insulin homeostasis.

[1]Department of Pharmacology and Nutritional Science, College of Medicine, University of Kentucky, Lexington, KY, USA

***Corresponding author**: Gertrude Arthur, Department of Pharmacology & Nutritional Sciences, University of Kentucky, Lexington, KY 40536, USA, Email: Gertrude.arthur@uky.edu.

Received: March 6, 2023
Revised: April 8, 2023
Accepted: April 29, 2023
Published: May 3, 2023

Citation: Arthur, Gertrude (2023) "(Pro)renin Receptor and Its Soluble Form in Metabolic Dysfunction: Friend or Foe?," *Journal of Pharmacology & Nutritional Sciences*: Volume 1: Issue 1, Article 1. Available at: https://uknowledge.uky.edu/jpns/vol1/iss1/1.

The Journal of Pharmacology & Nutritional Sciences

II. PRR AND sPRR IN OBESITY

The expression of PRR in adipose tissue was first demonstrated by Archard et al., where they showed that PRR is synthesized in the stromal portion of adipose tissues in humans and that its expression was greater in visceral adipose tissue than in subcutaneous adipose tissue (Achard et al., 2007). They also showed that PRR colocalizes in cell membranes and with renin which stimulates the phosphorylation of ERK1/2 signaling pathways (Achard et al., 2007). Since then, several studies have also demonstrated the presence of PRR in the adipose tissue (C. E. Gatineau, Gong, & Yiannikouris, 2019; Shamansurova et al., 2016; Wang et al., 2020; Wu et al., 2016). PRR is necessary for adipogenesis and hence the knockdown of PRR in the adipose tissue leads to lipodystrophy in mice (Shamansurova et al., 2016; Wu et al., 2016). Moreover, whole-body loss of sPRR reduced body weight in mice (Ramkumar et al., 2021) and infusion of sPRR increased body weight in male mice (C. E. Gatineau et al., 2019). In humans, obesity is known to increase adipose tissue PRR levels (Achard et al., 2007; Shamansurova et al., 2016) and elevate circulating sPRR (Nishijima et al., 2018). Consequently, weight loss after bariatric surgery reduced circulating sPRR (Nishijima et al., 2018). The functional role of PRR in adipogenesis is partly due to its role in Angiotensin II (Ang II) generation. Ang II is known to exert a trophic effect on adipocyte differentiation and adipose tissue growth which is mediated by Angiotensin type 1 receptor (AT1R) and ERK1/2 activation (Darimont, Vassaux, Ailhaud, & Negrel, 1994; Saint-Marc, Kozak, Ailhaud, Darimont, & Negrel, 2001). Moreover, independent of the RAS, PRR activates the mitogen-activated protein kinase (p38 MAPK) and ERK1/2 pathways (G. Nguyen et al., 2002). Through the activation of ERK1/2, PRR regulates peroxisome proliferator-activated receptor gamma (PPARG), known as the master regulator of adipogenesis (Prusty, Park, Davis, & Farmer, 2002; Wu et al., 2016). Hence, loss of PRR in adipose tissue reduces PPARG expression (Wu et al., 2016) and vice versa (Wang et al., 2020). Loss of PPARG also reduced plasma sPRR (Wang et al., 2020).

Mechanistic studies on sPRR mediated obesity are lacking but findings from a few studies suggest that sPRR could be acting through its full form receptor to influence adipogenesis. sPRR can increase protein expression of its full form receptor, PRR (E. Gatineau et al., 2021). In liver PRR-KO mice, increased sPRR expression in the adipose tissue stimulated adipogenesis (E. Gatineau et al., 2021). PRR inhibition using the handle region peptide (HRP), which is PRR antagonist decreased plasma and visceral adipose tissue leptin (Tan et al., 2014). Likewise, infusion of sPRR in male mice increased plasma leptin (C. E. Gatineau et al., 2019) and tended to increase subcutaneous adipose tissue signifying that sPRR could be working in concert with its full form to influence adipogenesis and drive obesity.

Contrary to these findings, Wang et al., showed that infusion of sPRR in male mice attenuated diet induced obesity and decreased gonadal white adipose tissue (Wang et al., 2020). This was quite a controversial finding as prior studies suggested otherwise. Interestingly, unpublished findings from our laboratory suggest that sPRR can indeed reduce gonadal white

https://uknowledge.uky.edu/jpns/vol1/iss1/1
DOI: https://doi.org/10.13023/jpns1123

The Journal of Pharmacology & Nutritional Sciences

adipose in male mice fed a high fat diet. In a transgenic mouse model, we expressed human sPRR in the adipose of male and female mice and kept these mice on a high fat diet for 20 weeks. Gonadal white adipose tissue was reduced in males and tended to decrease in females. The questions that are yet to be answered in these studies are:

1) What is the relative expression of PRR compared to sPRR?
2) Did the increase of sPRR affect the adipose tissue RAS especially Ang II?
3) Did the increase in sPRR affect ERK1/2 activation and is it dependent or independent of the RAS?

Overall, these studies show that PRR plays a central role in adipogenesis and obesity etiology. However, more studies are needed to understand the contribution of sPRR to obesity.

III. PRR AND SPRR IN GLUCOSE-INSULIN HOMEOSTASIS

Several studies have revealed PRR affects glucose and insulin homeostasis albeit differently in various organs. In the pancreas, knockdown of PRR in β-cells resulted in diabetes by reducing insulin secretion and impairing glucose sensitivity (Yin et al., 2013). However, in the muscle, inhibiting PRR using HRP in high fat fed mice after myocardial infarction improved insulin resistance (Fukushima et al., 2014). In fructose-fed mice, activation of prorenin increased skeletal muscle Ang II leading to insulin resistance whereas treatment with HRP ameliorated insulin resistance (Nagai et al., 2009). In the adipose tissue, knockdown of PRR improved fasting glucose and glucose sensitivity in male and female mice fed a high fat diet (Shamansurova et al., 2016). Deletion of PRR in brain neurons also reduced fasting blood glucose and improved glucose sensitivity (Worker et al., 2020). There is currently no study that has examined the role of liver derived PRR in glucose and insulin resistance. Overall, these studies show that PRR plays a significant role in insulin production and sensitivity.

The role of sPRR in glucose and insulin homeostasis is yet to be established. In humans, plasma sPRR positively correlates with gestational diabetes development in pregnant women (Bonakdaran, Azami, Tara, & Poorali, 2016) and men with type II diabetes and sleep apnea have higher plasma sPRR (Nishijima et al., 2016). The question is whether the elevated plasma sPRR is a biomarker or has a functional role in insulin resistance and diabetes. Studies in mice have shown the opposite effect. In severely obese mice, sPRR infusion improved glucose and insulin sensitivity by increasing adipose glucose transporter type 4 (Glut 4) and the phosphorylation of proteins kinase B (Akt) (Wang et al., 2020). New unpublished findings in our laboratory show that expression of human sPRR in the adipose tissue improves glucose sensitivity in high fat fed mice. Here, once again questions that remain to be answered are the relative tissue expression of PRR compared to the sPRR as well as the tissue RAS levels. Nevertheless, these findings suggest that PRR and sPRR work in contrast in glucose and insulin homeostasis, at least in mice.

The conflicting findings of sPRR on obesity and glucose and insulin homeostasis certainly draw various questions and avenues for continued research. The burgeoning question is whether sPRR is a friend or foe in metabolic dysfunction.

The Journal of Pharmacology &Nutritional Sciences

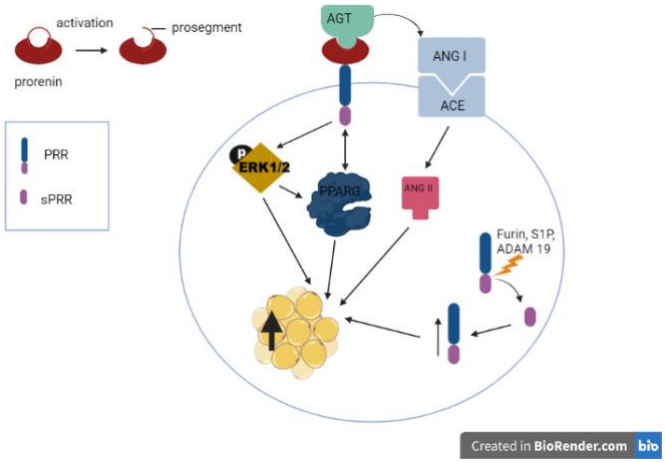

Figure 1. PRR mediates adipogenesis by increasing renin's catalytic activity to produce and Ang I and hence increase Ang II production. Moreover, PRR upregulates PPARG and vice versa. PRR also increases ERK1/2 activation. sPRR has been shown to increase its full-length receptor; PRR and this will inadvertently increase adipogenesis.

References

Achard, V., Boullu-Ciocca, S., Desbriere, R., Nguyen, G., & Grino, M. (2007). Renin receptor expression in human adipose tissue. *Am J Physiol Regul Integr Comp Physiol*, *292*(1), R274-282. doi:10.1152/ajpregu.00439.2005

Alcazar, O., Cousins, S. W., Striker, G. E., & Marin-Castano, M. E. (2009). (Pro)renin receptor is expressed in human retinal pigment epithelium and participates in extracellular matrix remodeling. *Exp Eye Res*, *89*(5), 638-647. doi:S0014-4835(09)00165-1 [pii]10.1016/j.exer.2009.06.014

Arthur, G., Osborn, J. L., & Yiannikouris, F. B. (2021). (Pro)renin receptor in the kidney: function and significance. *Am J Physiol Regul Integr Comp Physiol*, *320*(4), R377-R383. doi:10.1152/ajpregu.00259.2020

Bonakdaran, S., Azami, G., Tara, F., & Poorali, L. (2016). Soluble (Pro) Renin Receptor is a predictor of gestational diabetes mellitus. *Curr Diabetes Rev*. doi:CDR-EPUB-78391 [pii]

Darimont, C., Vassaux, G., Ailhaud, G., & Negrel, R. (1994). Differentiation of preadipose cells: paracrine role of prostacyclin upon stimulation of adipose cells by angiotensin-II. *Endocrinology*, *135*(5), 2030-2036. doi:10.1210/endo.135.5.7956925

Fukushima, A., Kinugawa, S., Takada, S., Matsushima, S., Sobirin, M. A., Ono, T., . . . Tsutsui, H. (2014). (Pro)renin receptor in skeletal muscle is involved in the development of insulin resistance associated with postinfarct heart failure in mice. *American journal of physiology: endocrinology and metabolism*, *307*(6), E503-E514. doi:10.1152/ajpendo.00449.2013

Gatineau, C. E., Gong, C. M., & Yiannikouris, C. F. (2019). Soluble Prorenin Receptor Increases Blood Pressure in High Fat–Fed Male Mice. *Hypertension*, *74*(4), 1014-1020. doi:10.1161/HYPERTENSIONAHA.119.12906

Gatineau, E., Arthur, G., Poupeau, A., Nichols, K., Spear, B. T., Shelman, N. R., . . . Yiannikouris, F. B. (2021). The prorenin receptor and its soluble form contribute to lipid homeostasis. *American journal of physiology: endocrinology and metabolism*, *320*(3), E609-E618. doi:10.1152/AJPENDO.00135.2020

Hayakawa, Y., Aoyama, T., Yokoyama, C., Okamoto, C., Komaki, H., Minatoguchi, S., . . . Minatoguchi, S. (2015). High salt intake damages the heart through activation of cardiac (Pro) renin receptors even at an early stage of hypertension. *PLoS ONE*, *10*(3), e0120453-e0120453. doi:10.1371/journal.pone.0120453

Mohsin, M., Souza, L. A. C., Aliabadi, S., Worker, C. J., Cooper, S. G., Afrin, S., . . . Feng Earley, Y. (2020). Increased (Pro)renin Receptor Expression in the Hypertensive Human Brain. *Frontiers in physiology*, *11*, 606811-606811. doi:10.3389/fphys.2020.606811

Nagai, Y., Ichihara, A., Nakano, D., Kimura, S., Pelisch, N., Fujisawa, Y., . . . Nishiyama, A. (2009). Possible contribution of the non-proteolytic activation of prorenin to the development of insulin resistance in fructose-fed rats. *Exp Physiol*, *94*(9), 1016-1023. doi:10.1113/expphysiol.2009.048108 expphysiol.2009.048108 [pii]

Nguyen. (2007). the (pro)renin receptor : pathophysiological roles in cardiovascular and renal pathology. *Curr Opin Nephrol Hypertension*, *16*, 129-133.

Nguyen, G., Delarue, F., Burcklé, C., Bouzhir, L., Giller, T., & Sraer, J.-D. (2002). Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. *The Journal of clinical investigation*, *109*(11), 1417-1427. doi:10.1172/JCI14276

Nichols, K., & Yiannikouris, F. (2022). The Role of (Pro)Renin Receptor in the Metabolic Syndrome. *Curr Hypertens Rev*, *18*(2), 117-124. doi:10.2174/1573402118666220216104816

Nishijima, T., Ohba, K., Baba, S., Kizawa, T., Hosokawa, K., Endo, F., . . . Sakurai, S. (2018). Decrease of Plasma Soluble (Pro)renin Receptor by Bariatric Surgery in Patients with Obstructive Sleep Apnea and Morbid Obesity. *Metabolic syndrome and related disorders*, *16*(4), 174-182. doi:10.1089/met.2017.0153

Nishijima, T., Tajima, K., Yamashiro, Y., Hosokawa, K., Suwabe, A., Takahashi, K., & Sakurai, S. (2016). Elevated Plasma Levels of Soluble (Pro)Renin Receptor in Patients with Obstructive Sleep Apnea Syndrome in Parallel with the Disease Severity. *Tohoku journal of experimental medicine*, *238*(4), 325-338. doi:10.1620/tjem.238.325

Prusty, D., Park, B. H., Davis, K. E., & Farmer, S. R. (2002). Activation of MEK/ERK signaling promotes adipogenesis by enhancing peroxisome proliferator-activated receptor gamma (PPARgamma) and C/EBPalpha gene expression during the differentiation of 3T3-L1 preadipocytes. *J Biol Chem*, *277*(48), 46226-46232. doi:10.1074/jbc.M207776200 M207776200 [pii]

Ramkumar, N., Stuart, D., Peterson, C. S., Hu, C., Wheatley, W., Cho, J.-M., . . . Kohan, D. E. (2021). Loss of Soluble (Pro)renin Receptor Attenuates Angiotensin-II Induced Hypertension and Renal Injury. *Circulation Research*. doi:10.1161/CIRCRESAHA.120.317532

Saint-Marc, P., Kozak, L. P., Ailhaud, G., Darimont, C., & Negrel, R. (2001). Angiotensin II as a trophic factor of white adipose tissue: stimulation of adipose cell formation. *Endocrinology*, *142*(1), 487-492. doi:10.1210/endo.142.1.7883

Shamansurova, Z., Tan, P., Ahmed, B., Pepin, E., Seda, O., & Lavoie, J. L. (2016). Adipose tissue (P)RR regulates insulin sensitivity, fat mass and body weight. *Mol Metab*, *5*(10), 959-969. doi:10.1016/j.molmet.2016.08.009

Tan, P., Shamansurova, Z., Bisotto, S., Michel, C., Gauthier, M. S., Rabasa-Lhoret, R., . . . Lavoie, J. L. (2014). Impact of the prorenin/renin receptor on the development of obesity and associated cardiometabolic risk factors. *Obesity (Silver Spring)*, *22*(10), 2201-2209. doi:10.1002/oby.20844

Wang, F., Luo, R., Zou, C.-J., Xie, S., Peng, K., Zhao, L., . . . Yang, T. (2020). Soluble (pro)renin receptor treats metabolic syndrome in mice with diet-induced obesity via interaction with PPARγ. *JCI Insight*, *5*(7). doi:10.1172/JCI.INSIGHT.128061

Worker, C. J., Li, W., Feng, C.-Y., Souza, L. A. C., Gayban, A. J. B., Cooper, S. G., . . . Feng Earley, Y. (2020). The neuronal (pro)renin receptor and astrocyte inflammation in the central regulation of blood pressure and blood glucose in mice fed a high-fat diet. *American journal of physiology: endocrinology and metabolism*, *318*(5), E765-E778. doi:10.1152/ajpendo.00406.2019

Wu, C.-H., Mohammadmoradi, S., Thompson, J., Su, W., Gong, M., Nguyen, G., & Yiannikouris, F. (2016). Adipocyte (Pro)Renin-Receptor Deficiency Induces Lipodystrophy, Liver Steatosis and Increases Blood Pressure in Male Mice. *Hypertension*, *68*(1), 213-219. doi:10.1161/HYPERTENSIONAHA.115.06954

Yin, G.-s., Lin, S.-d., Xu, D.-c., Sun, R.-q., Lin, K., & Lin, C.-j. (2013). Handle Region Peptide Ameliorating Insulin Resistance but Not β Cell Functions in Male Rats Neonatally Treated with Sodium L-Glutamate. *International journal of endocrinology*, *2013*, 493828-493811. doi:10.1155/2013/493828