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MATHEMATICAL MODEL OF DIRECT RENIN INHIBITION IMPROVES SYSTEMIC INSULIN RESISTANCE AND SKELETAL MUSCLE GLUCOSE TRANSPORT BY B-S DISTRIBUTION

GEETHA. T*, SANGEETHA. B.**

***Asst. Professor of Mathematics,**
K. N. Govt. Arts College for Women Thanjavur, Tamilnadu. South India.

****Lecturer of Mathematics,**
BDU (W) College. Orathanadu. Thanjavur, Tamilnadu. South India.

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ABSTRACT

R*enin is the rate-limiting enzyme in renin-angiotensin system (RAS) activation. We sought to determine the impact of renin inhibition on whole-body insulin sensitivity and skeletalmuscle RAS, oxidative stress, insulin signaling, and glucose transport in the transgenic TG(mRen2)27 rat (Ren2),which manifests increased tissue RAS activity, elevated serum aldosterone, hypertension, and insulin resistance. Young (aged 6–9wk) Ren2 and age-matched Sprague Dawley control rats were treated with aliskiren[50mg/kg d, ip]orplacebofor 21dandadministeredanipglucose tolerance test. Insulin metabolic signaling and 2-deoxyglucose uptake in soleus muscle were examined in relation to tissue renin-angiotensin-aldosterone system [angiotensin (Ang) II, mineralocorticoid receptor (MR), and Ang type I receptor (AT1R)] and measures of oxidative stress as well as structural changes evaluated by light and transmission electronmicroscopy. The hazard rate function has been applied to the renin levels.*

NOTATIONS

A-Steady-state system availability.
λ- Rate of failures (unplanned outages).
μ- Repair rate for unplanned outage.
μ2-Upgrade rate for planned outage.
T-Time to damage of renin level.

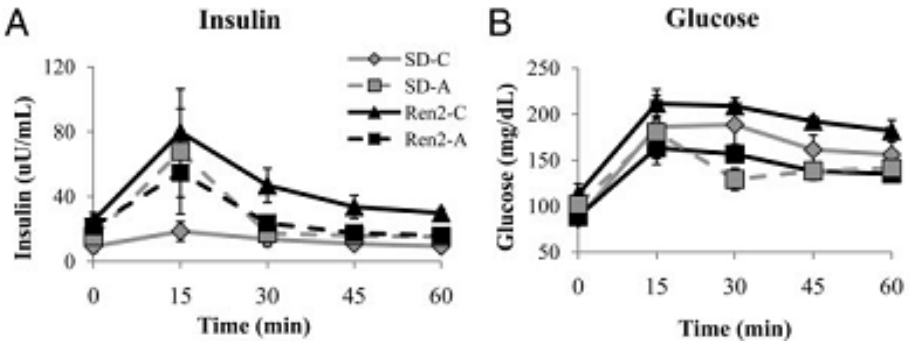
APPLICATION

Activation of the renin-angiotensin-aldosterone system (RAAS) has been linked to increased production of reactive oxygen species (ROS) in numerous tissues, including skeletal muscle and cardiovascular tissue. Excessive oxidative stressmay result in impairment of intracellular insulin signaling, constituting a potential pathway by which RAAS activation induces insulin resistance. Existent data suggest that angiotensin II (Ang II) and aldosterone signaling through an Ang type 1 receptor (AT1R) or ineralocorticoid receptor (MR), respectively, mediate these detrimental effects on skeletal muscle insulin metabolic signaling and glucose transport. One important mechanism by which activation of T1R and the MR inhibits insulin metabolic signaling is through activation of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzymatic complex. Resulting increases in ROS can activate redox sensitive serine (Ser) kinases which, in turn, can decrease insulin metabolic signaling [4, 5].

RAAS activation involves production of preprorenin, followed by glycosylation and removal of a signal peptide, to form prorenin and finally renin. Ang I results from cleavage of angiotensinogen by renin, and Ang II is produced by the action of the angiotensin converting enzyme on Ang I. Increase in Ang II, in turn, stimulates aldosterone production. Renin is the rate-limiting enzyme in the generation of Ang II making it a particularly attractive therapeutic target for specific RAAS blockade at an early stage.

Corresponding Author: Geetha. T*, *Asst. Professor of Mathematics,
K. N. Govt. Arts College for Women Thanjavur. Tamilnadu. South India.

Aliskiren is a potent direct renin inhibitor, with high specificity for human and mouse renin. Because of this species specificity, aliskiren cannot be studied effectively in conventional rat models. To circumvent this issue, we used the transgenic TG(mRen2) 27 rat (Ren2), which harbors the mouse renin gene and is a model of excessive tissue renin-angiotensin system (RAS) activity and high plasma levels of aldosterone. This transgenic rodent model also develops hypertension and systemic insulin resistance. Use of the Ren2 rat allows for interrogation of the specific role of the RAAS because it contributes to hypertension and insulin resistance. We previously reported that AT1R, MR blockade and ROS scavenging treatment strategies improve whole-body glucose tolerance and skeletal muscle insulin-stimulated glucose transport in the Ren2 rodent model. Accordingly, in this investigation, it is hypothesized that in vivo direct renin inhibition would correct the skeletal muscle RAAS abnormalities [6]and attenuate tissue oxidative stress, thereby improving insulinmetabolic signaling, glucose transport, and systemic insulin sensitivity in young insulin-resistant Ren2 rats.



MATHEMATICAL MODEL

The probability density function (PDF) of a two-parameter BS random variable T corresponding to the CDF in (1) is given by

$$f(t;\alpha,\beta)=\frac{1}{2\alpha\beta\sqrt{2\pi}}\left[\left(\frac{\beta}{t}\right)^{1/2}+\left(\frac{\beta}{t}\right)^{3/2}\right]\exp\left[-\frac{1}{2\alpha^2}\left(\frac{t}{\beta}\right)+\frac{\beta}{t}-2\right].\quad 0<t<\infty,\alpha,\beta>0 \tag{1}$$

Consider now the monotone transformation

$$X=\frac{1}{2}\left[\left(\frac{T}{\beta}\right)^{1/2}-\left(\frac{T}{\beta}\right)^{-1/2}\right] \tag{2}$$

Or

$$T=\beta\{1+2X^2+2X(1+X^2)^{1/2}\} \tag{3}$$

then from (1), it readily follows that X is distributed as normal with mean zero and variance $(\alpha^2/4)$.[1, 2, 3].

To examine the shape of the hazard function, let us assume that the scale parameter $\beta = 1$, without loss of any generality. Let us consider the function

$$Є(t)=t^{1/2}-t^{-1/2} \tag{4}$$

For which

$$Є'(t)=\frac{1}{2}\left(t^{-1/2}+t^{-3/2}\right)$$

$$=\frac{1}{2t}\left(t^{1/2}+t^{-1/2}\right) \tag{5}$$

$$Є''(t)=-\frac{1}{4t^2}\left(t^{1/2}+3t^{-1/2}\right) \tag{6}$$

And also

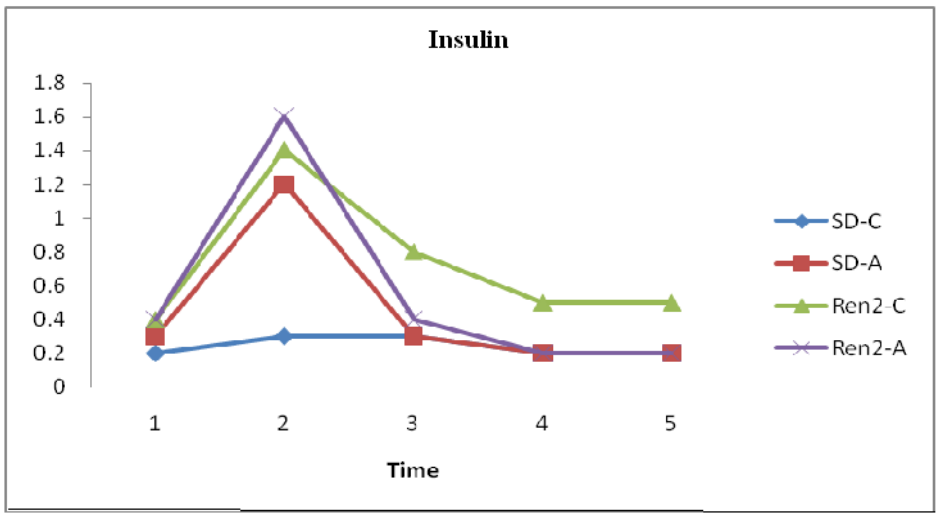
$$Є^2(t)=t+\frac{1}{t}-2 \tag{7}$$

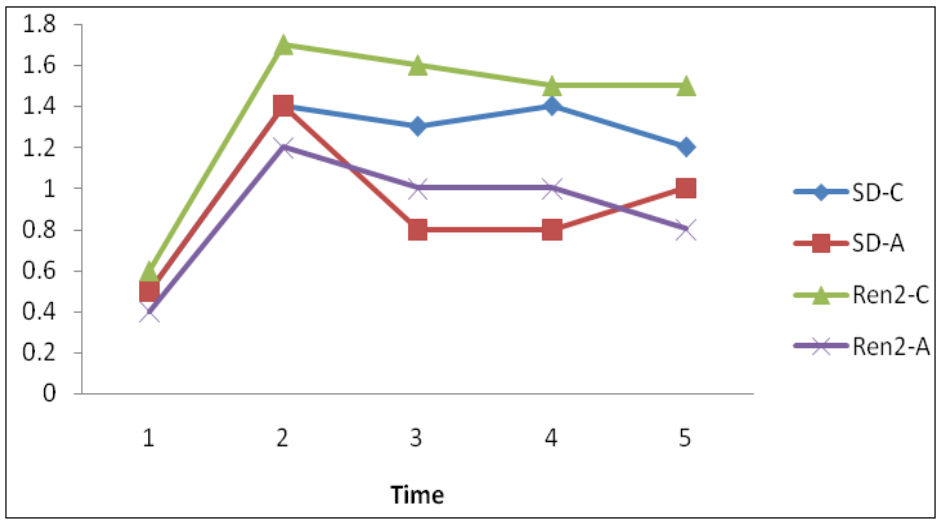
The density function of the BS distribution in (2) (for β = 1) is then

$$f(t;\alpha) = \frac{1}{\alpha\sqrt{2\pi}}\epsilon'(t)\ \exp-\frac{1}{2\alpha^2}\epsilon^2(t) \qquad (8)$$

This, in conjunction with the expression of the distribution function in (1), gives the hazard function as

$$h(t;\alpha) = \frac{f(t;\alpha)}{1-F(t;\alpha,1)} = \frac{\frac{1}{\alpha\sqrt{2\pi}}\varepsilon'(t)\exp-\frac{1}{2\alpha^2}\varepsilon^2(t)}{\sqrt{\phi\left(-\frac{\varepsilon'(t)}{\alpha}\right)}} \qquad (9).$$





CONCLUSION

It is explored the effect of direct renin inhibition on insulin-stimulated glucose transport in skeletal muscle in a rodent model of increased tissue RAS activation, elevated plasma levels of ldosterone, and enhanced oxidative stress. Also it is observed that young transgenic rats over expressing the mouse renin gene are insulin resistant compared with age-matched SD litter mates. Insulin metabolic signaling and glucose transport in Ren 2 skeletalmuscle were improved by in vivo treatment with a direct renin inhibitor, as previously observed with treatment with an AT1R and MR blockade. When this result is applied to the hazard rate of B-S distribution, we found that the notably reduced hazard rate level for renin.

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