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Assessment of Possible Role of Renin Angiotensin Aldosterone System in Obesity: Review Article

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ABSTRACT

Background: There has been a dramatic rise in the prevalence of obesity around the world, and it is now recognized as a major contributor to health problems. Secondary negative health issues, such as high blood pressure, cardiovascular disease, and type 2 diabetes, are more likely to affect those who are overweight and obese. Body fluid regulation and cardiovascular homeostasis are traditionally attributed to the renin-angiotensin-aldosterone system (RAAS), which is a hormone system. Recent studies have revealed the presence of active RAAS in many different tissues. Adipose tissue is one of these tissues where the RAAS has been found to have functional components.

Objective: Assessment of renin angiotensin aldosterone possible role in obesity.

Methods: PubMed, Google Scholar, and Science Direct were used to search for the terms angiotensin, obesity, and renin-angiotensin-aldosterone system. Although they only looked at the most recent or comprehensive study from July 2003 to July 2022, the authors also looked at references from relevant literature. Documents produced in languages other than English have been rendered invalid due to lack of translation-related information. Dissertations, oral presentations, unpublished publications, conference abstracts, and other items that did not deal with significant scientific research were all ignored.

Conclusion: Experiments suggest that the processes that drive adipose tissue development and metabolism in peripheral organs, as well as the effects of angiotensin on appetite and metabolism, contribute to the increased activity of the renin-angiotensin system in obesity. Although renin angiotensin aldosterone system antagonists are typically used to treat high blood pressure and heart failure, there is growing evidence that they may also be useful in managing obesity and other metabolic diseases.

Keywords: Angiotensin, Obesity, Renin angiotensin aldosterone system.

INTRODUCTION

There has been a dramatic rise in the prevalence of obesity around the world, and it is now recognised as a major contributor to health problems. Hypertension, cardiovascular disease, and type 2 diabetes are only some of the secondary diseases to which people who are overweight are more prone. While BMI has traditionally been used to define overweight and obesity, there is growing evidence that alternative measurements of body fat, such as abdominal adipose tissue and ectopic fat deposition, are also associated with the onset of serious health problems**.** In obesity, there are many hormones and cytokines such as angiotensin are secreted from fat cells. This state of metabolic disturbance not only seen in adipose tissue but it can also be seen in lean tissue such as liver and skeletal muscle **(1).**

Body fluid regulation and cardiovascular homeostasis are traditionally attributed to the RAAS, a hormone system. Recent research has shown that RAAS activity is present in a wide variety of tissues. Adipose tissue is one of these tissues where the RAAS has been found to have functional components.

Renin, angiotensinogen, rennin-angiotensin converting enzyme, angiotensin II, and angiotensin II receptors type 1 and type 2 are all expressed by adipocytes.

Additionally, to its classical systemic action, RAAS also has a paracrine (local) effect on adipocytes. Angiotensin I is created when renin cleaves angiotensinogen, while angiotensin II is created when angiotensin I is converted by angiotensin I converting enzyme. This is an example of the endocrine RAAS process **(2)**.

Traditionally, hypertension and heart failure have been treated with ACE inhibitors. The hypertensive effects of angiotensin II (ANG II) are mediated through AT1 receptors, which explains why AT1 receptor antagonist drugs (ARBs) are used to treat hypertension and heart failure. Both ARBs and ACE inhibitors are effective in lowering insulin resistance and reversing type 2 diabetes. It's possible that ANG II is doing this through directly affecting adipocytes, particularly by altering fat cell size **(3).**

Increasing the number of fat cells, known as adipocyte hyperplasia, has been associated with better glucose tolerance, whereas increasing the size of existing fat cells, known as adipocyte hypertrophy, has been linked to insulin resistance. This is because the metabolic rate of the brand-new adipocytes is higher than that of the old ones. Through an AT1 receptor-mediated mechanism, mature adipocytes act paracrinely (locally) to suppress the recruitment of preadipocytes **(3).**

When the RAAS is overstimulated, it causes the adipocytes to enlarge and the cellular triglyceride content to rise, which causes the body to store more fat. In studies where RAAS antagonist were used, body fat was regulated **(4).**

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Angiotensin II and nonalcoholic fatty liver disease (NAFLD) (Figure 1):

Through the generation of pro-inflammatory cytokines like TNF-α, AngII signaling in the liver can provoke an inflammatory state. Reactive oxygen species (ROS) generation in the mitochondria is also implicated. Hepatic stellate cells are activated by ROS and inflammatory cytokines, and as a result, they release pro-fibrotic cytokines and initiate the deposition of extracellular matrix, leading to fibrosis. Additionally, insulin resistance has been blamed for contributing to the onset of NAFLD. First, insulin resistance causes a rise in inflammation by stimulating adipocytes to produce more pro-inflammatory adipo-cytokines. Second, elevated lipolysis in central adipose tissue results in an influx of fatty acids into the liver, where they are esterified or oxidized, both of which are inefficient metabolic processes [(5)].

Insulin resistance increased lipolysis of adipose tissue and dietary chylomicron remnants raises plasma free fatty acids (FFAs), which are then taken up by the liver and oxidized or esterified into triacylglycerol (TAG). De novo lipogenesis is activated, and the extra glucose is stored as triacylglycerol. An increase in hepatic lipid transport and/or de novo lipogenesis can lead to a buildup of excess TAG. This condition worsens when hepatic fatty acid oxidation decreases. In addition, the liver responds to an increase in TAG by secreting a greater quantity of extremely low-density lipoprotein particles**.** Liver cells absorb dietary chylomicron remnants or free fatty acids (FFAs) released by adipocyte lipolysis and deliver them to peripheral tissues. Therefore, increased plasma free fatty acids (FFA) are commonly observed in obese people, suggesting a link between obesity and fatty liver (Figure 2) [(7)].

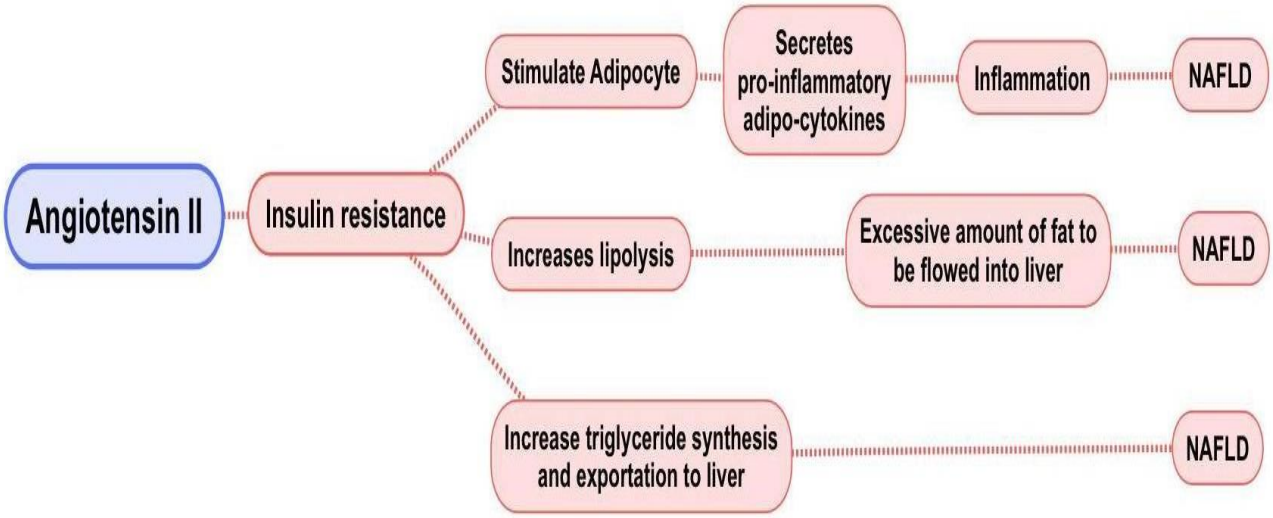

Fig. (1): Angiotensin and fatty liver [(6)]

Increased lipolysis in adipose tissue and subsequent elevations in fasting and postprandial plasma free fatty acids occur because of insulin resistance, which is another feature of obesity. Normally, insulin prevents fat breakdown. The inability of insulin to suppress lipolysis after a meal rises in obese people because of insulin resistance, leading to an increase in circulating free fatty acids. This occurs because AngII has an inhibitory effect on insulin function via increasing oxidative stress. Adipocyte size and tissue bulk are both increased by AngII's suppression of lipolysis [(8)].

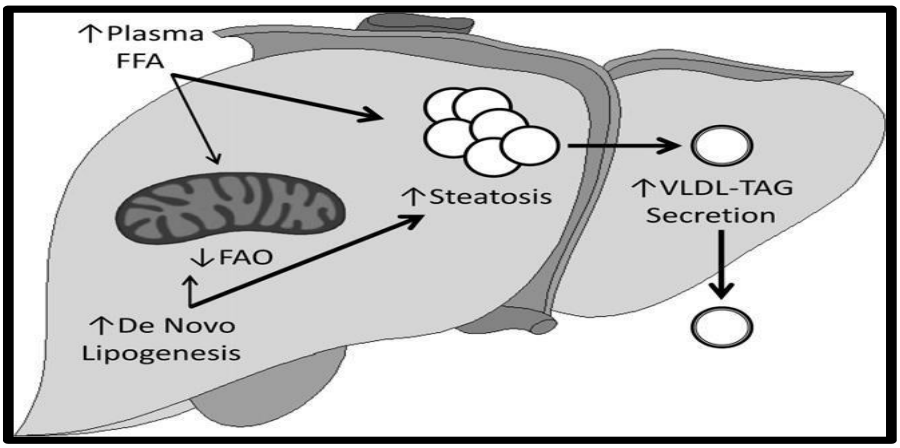

Fig. (2): Mechanisms of hepatic triacylglycerol accumulation [(7)].

De novo lipogenesis accounts for up to 30% of the hepatic lipid content in non-alcoholic fatty liver disease. The liver is already under stress, and any pathology that enhances de novo lipogenesis simply makes matters worse. Adipose tissue in both rats and humans contains the lipogenic hormone angiotensin II (AngII) [(9)].

AngII stimulates adipocyte lipogenesis by activating the angiotensin 2 receptor (AT2R), which in turn increases fatty acid synthase production and activity and the expression of the pro-lipogenic transcription factor AP2- binding protein-1c for sterol regulatory elements [(9)].

Fatty acid oxidation in the liver may be inhibited by angiotensin II (AngII), which is thought to occur in response to low adiponectin levels. Small changes in the electrochemical gradient caused by adiponectin result in significant increases in reactive oxygen species (ROS) generation, making adiponectin an effective anti-diabetic agent. The increased production of ROS in the mitochondria has been linked to the onset and progression of nonalcoholic fatty liver disease (NAFLD). Through a protein kinase C (PKC)-dependent mechanism, AngII increases the formation of mitochondrial ROS by oxidising electron transport chain proteins [(10)].

Angiotensin signaling:

AngII, an octapeptide, is the ultimate effector of the RAAS system on most biological actions including regulation of blood pressure. Traditionally, AngII has been thought to cause vasoconstriction and increased Na^+ retention, which raises blood pressure [(11)].

AngII signaling pathways have traditionally been divided into two categories:

- The classic G-protein coupled signaling pathways (e.g. Ca^{2+} and phospholipase C).
- Non-G-protein signaling pathways including:

(1) Receptor tyrosine kinases [EGFR],
(2) Non-receptor tyrosine kinases [Janus kinases (JAK)], (3) Protein kinase C (PKC) and
(4) Mitogen-activated protein kinase MAPKs [p38MAPK] are examples of serine/threonine kinases. Additionally, the pathologic effects of Ang II on the vasculature are often brought on by the activation of NADPH oxidases and production of ROS. Angiotensin II type 1 (AT1) receptor, a G-protein coupled receptor that is primarily responsible for mediating AngII activity, is found in the plasma membrane of the majority of cells [(12)]. The AT2R, a different AngII G-protein coupled receptor, has been discovered.

It has been shown in several studies that Ang II activates various pathways in a time-dependent manner. For instance, the G protein-dependent pathway is activated and produces inositol 1,4,5-triphosphate (IP3) in a matter of seconds, whereas MAP kinase and JAK/STAT are activated minutes to hours after the initial activation of the AT1R [(12)].

Researchers examined the efficacy of telmisartan (an angiotensin receptor blocker) and losartan (an angiotensin receptor blocker) in treating NAFLD, as predicted by the existing literature. There was no statistically significant difference between the two medications' improvements in liver enzymes after a full year of therapy. However, the researchers concluded that telmisartan may be more helpful in treating NAFLD in individuals with type 2 diabetes [(13)].

It has recently been shown that telmisartan can prevent the onset of multiple sclerosis, help those with diabetes and insulin resistance, and shield those who suffer from hypertension. In fact, telmisartan medication has consistently improved metabolic markers in animal trials [(14)].

Since an increase in visceral fat is connected to hypertension, dyslipidemia, and an irregular metabolic pattern, patients may benefit from telmisartan's ability to lower visceral-fat mass. Additionally, males with visceral fat have a higher chance of passing away young [(15)].

Effects of Angiotensin on Muscle Mass:

Dual energy X-ray absorptiometry shows that lean muscle mass accounts for most of the fat-free mass. Obesity is associated with a decreased lean body mass when compared to increased body mass accumulation of adipose tissue [(16)]. This was attributable to an increase in body fat mass caused by adipocyte hypertrophy and the consequent production of cytokines such as ANG II. ANG II reduces blood flow to the muscle while increasing blood vessel resistance. It was also shown that ANG II is linked to lower levels of insulin growth factor-1 (IGF-1), which has a well-known beneficial influence on the control of embryonic development, protein synthesis, and muscle hypertrophy [(17)].

It was discovered that lowering angiotensin II or its activity using angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers preserves human lean body mass. Increased muscle blood flow and a positive redistribution of cardiac output to the muscle are results of ACE inhibitors' reduction of local vascular resistance in arterioles and large conductance channels. ACE inhibitors also boost IGF-1 levels, which has a positive effect on muscle [(18)].

CONCLUSION

Experiments suggest that the processes that drive adipose tissue development and metabolism in peripheral organs, as well as the effects of angiotensin on appetite and metabolism, contribute to the increased activity of the renin-angiotensin system in obesity. Although these drugs are typically used to treat high blood pressure and heart failure, there is growing evidence that they may also be useful in managing obesity and other metabolic diseases.

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