Section A-Research paper

Role of renin-angiotensin-aldosterone system in the pathogenesis of depression

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Abstract

It was established that renin-angiotensin-aldosterone system (RAAS) controls blood pressure and body fluids peripherally. However, it was intriguing that central injection of angiotensin II (Ang II) also boosted the blood pressure and evoked thirst sensation suggesting that elements of the RAAS are also expressed in the brain. The role of the RAAS in hypertension and emotional disorders is well established. Evidence points to an association between elevated RAAS activity and depression, partly through the induction of neuroinflammation, and oxidative stress, and suppression of BDNF. Therefore, blocking the RAAS provides a theoretical basis for future treatment of depression.

Keywords: renin-angiotensin-aldosterone system, Depression

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Introduction

It was established that the renin-angiotensin-aldosterone system (RAAS) controls blood pressure and body fluids peripherally. However, it was intriguing that central injection of angiotensin II (Ang II) also boosted the blood pressure and evoked thirst sensation suggesting that elements of the RAAS are also expressed in the brain **(McKinley et al., 2003).**

The classical pathway:

Classically, renal juxtaglomerular cells produce renin that cleaves hepatic angiotensinogen into angiotensin I (Ang I). Then, pulmonary angiotensin-converting enzyme (ACE) cleaves Ang I into Ang II. Ang II activates both angiotensin II type 1 (AT_1) and angiotensin II type 2 (AT_2) receptors **(Zaman et al., 2002).**

The localization of AT_1 and AT_2 in many brain regions is well characterized **(Wright & Harding, 2011)**. However, the source of central Ang II is still puzzled. Ang II is highly hydrophilic and it cannot pass the BBB and the low concentration of renin centrally makes the central synthesis of Ang II is doubtful **(Van Thiel et al., 2017)**. Studies suggested that brain cells may possess their own active renin (renin-b or intracellular renin [icREN]) **(Grobe et al., 2008)** or contain non-renin pro-enzyme that can convert angiotensinogen (synthesized by astrocytes) into Ang II, **(Van Thiel et al., 2017)** or Ang II can cross the BBB when disturbed by hypertension **(Biancardi & Stern, 2016).**

Non-classical pathway:

Later studies revealed the complexity of the RAAS. Another pathway was discovered in which angiotensin-converting enzyme 2 (ACE2) (detected in the hippocampus and in the cerebral cortex) cleaves Ang II into angiotensin-(1–7) [Ang - (1-7)] that stimulates the Mas receptor **(Simões E Silva et al., 2013).**

*Opposing neurological functions of RAS system pathways (figure **1**):*

AT_1 activation is implicated in neurodegeneration directly via its vasoconstrictor effect or via initiating post-receptor cascades that result in neuroinflammation, oxidative stress and apoptosis **(Abiodun & Ola, 2020; Cosarderelioglu et al., 2020).**

On the other hand, activation of AT_2 receptor **(Mccarthy et al., 2009; Namsolleck et al., 2013)** and ACE2/Ang-(1-7)/Mas pathway is associated with neuroprotection counter regulating the effect of ACE/ ANG II/ AT_1 pathway **(Zheng et al., 2014; Tiwari et al., 2023).**

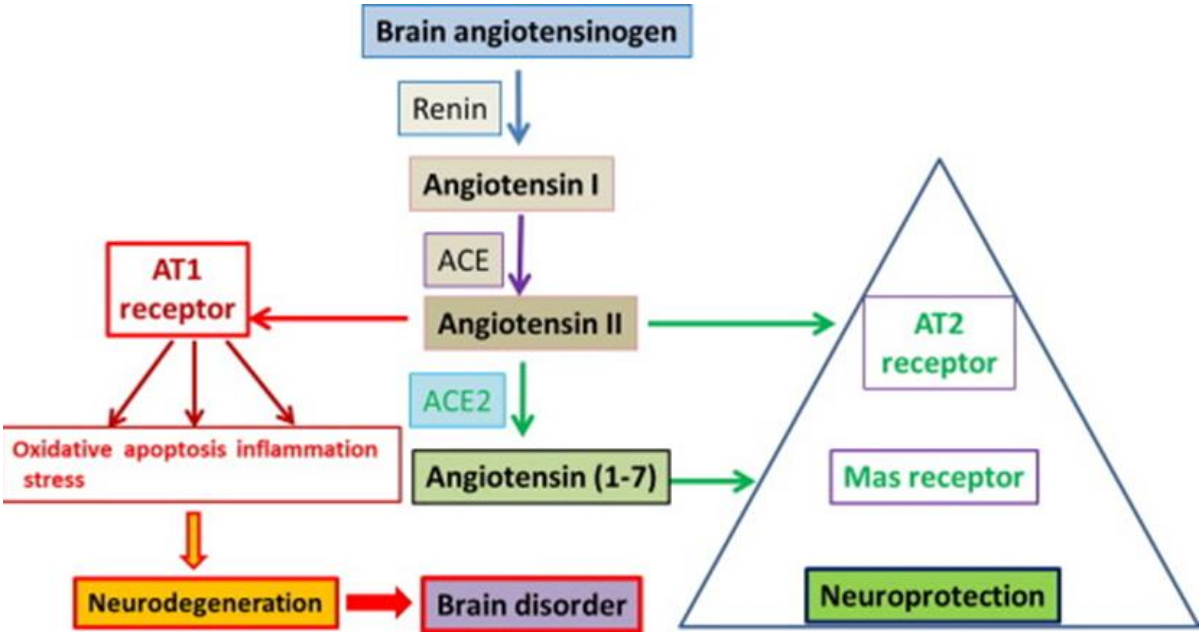

Figure (1): opposing neurological functions of RAAS (Abiodun & Ola, 2020)

Clinical and preclinical studies suggest that the RAAS is involved in the pathogenesis of depression and that targeting this system may be effective in the treatment of depression.

Clinical studies:

Despite the lack of randomized control trials that compare between the potential antidepressant effect of different RAAS inhibitors and traditional antidepressants, other types of studies provide good evidence to support the hypothesis. In a cross matched cohort study, Angiotensin receptor blockers (ARBs) were associated with the lowest risk of inducing psychiatric diseases among the different drug classes of hypertension **(Colbourne et al., 2021).** In a large population-based study that recruited 3 747 190 patients treated with different antihypertensive agents, the ACE inhibitors (enalapril and ramipril) could prove their efficacy in reducing the incidence of depression **(Kessing et al., 2020).** Furthermore, combining ACE Inhibitors or ARBs with calcium channel blockers (CCBs) reduced the risk of depression in patients with cardiovascular diseases in comparison to using CCBs alone in a large cohort study **(Lee et al., 2023).**

More evidence is obtained from studies trying to correlate depression with genetic polymorphisms in the RAAS. Depression is correlated with ACE polymorphisms such as: I/D, GG and A2350G genotypes which are associated with a higher ACE activity **(Vian et al., 2017)**. However, a meta-analysis found no significant correlation between depression and I/D, the most investigated allele **(Wu et al., 2012)**. Polymorphism of AT_1 receptor (A1166C, CC) was also correlated with higher sensitivity to Ang II, higher risk of depression and –interestingly- a better response to antidepressants **(Bondy et al., 2005; Saab et al., 2007)**.

On the other hand, van Sloten et al. **(van Sloten et al., 2022)** reported that neither ACE inhibitors nor ARBs were associated with lower risk of depression in elderly patients with hypertension**.** Furthermore, the use of ARBs was associated with a higher risk of suicide in elderly patients but the underlying mechanism is not well understood **(Mamdani et al., 2019**)**.**

Preclinical studies:

Lack of angiotensinogen lowered the risk of developing depressive symptoms in mice **(Okuyama et al., 1999)** while chronic infusion of Ang II triggered depressive- like effect in mice in the tail suspension test (TST) and in the forced swim test **(Park et al., 2020).** On the other hand, Intracerebroventricular injection of Ang-(1-7) showed anxiolytic and antidepressant like effect comparable with fluoxetine in transgenic rats with suppressed angiotensinogen **(Kangussu et al., 2013).** Likewise, central infusion of diminazene aceturate, an ACE2 activator, displayed antidepressant-like effect indicated by shortening the immobility time of mice in the TST and this effect was blocked with prior infusion of Mas receptor antagonist **(Nakagawasai et al., 2023).**

Aldosterone (which is released from adrenal cortex under control of Ang II, HPA axis and sympathetic nervous system) is another possible contributor in the pathogenesis of depression. Depression was more prevalent in Patients with primary aldosteronism compared to their controls **(Sonino et al., 2011).** Higher salivary aldosterone was associated with worse depressive symptoms in patients with major depressive disorder (MDD) **(Segeda et al., 2017).** Exogenous aldosterone evoked a state of anhedonia in rats presented by reduced sucrose preference in addition to evoking significant changes in the hippocampi similar to what depicted in MDD **(Hlavacova et al., 2012).** Conversely, Hallberg et al. **(Hallberg et al., 2011)** reported that the concentration of plasma aldosterone was lower in patients with MDD who attempted suicide in comparison to those who didn't and to the healthy participants**.** Over all, these inconsistent results require further high-quality studies to establish the association between aldosterone and depression. Inhibitors of the RAAS system could improve the depressive symptoms of diabetic rats without affecting the mean arterial blood pressure indicating that the antidepressant effect of these drugs does not depend on their blood pressure lowering effect. Members of the RAAS were found to mitigate pro-inflammatory cytokines and restore the synthesis of brain derived neurotrophic factor (BDNF) in the hippocampus improving the depressive symptoms in animal models of depression **(Lenart et al., 2019; Balogh et al., 2020)**.

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