Angiotensin II Type 2 Receptor: A Target for Protection Against Various Disease conditions

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Abstract

The renin-angiotensin system's protective arm contains the angiotensin AT2 receptor (AT2R), which was first identified more than 30 years ago. Since its discovery, the AT2R has grown from a binding site with unknown function to a firmly established major effector that is a target for emerging medications. In most preclinical models, the AT2R represents an endogenous protective mechanism that can be altered to treat cancer, as well as lung, renal, cardiovascular, metabolic, cutaneous, and neurological illnesses. This page offers a thorough discussion of what we now know about the AT2R, including its discovery, location within the RAS, and general functions. The properties of the AT2R, including its structure, intracellular signaling, homo- and heterodimerization, and expression, are then thoroughly examined. We describe AT2R-selective ligands, ranging from naturally occurring peptides to synthetic peptides and nonpeptide compounds utilized as research tools. We conclude by outlining the AT2R's numerous protective effects in numerous experimental disease models, its known physiological roles, and the AT2R ligands that are currently being developed for clinical use. The current review highlights the contentious issues and knowledge gaps surrounding this receptor and sheds light on potential directions for AT2R research in the future.

Keywords: Stroke, Obesity, Metabolism, And Insulin Sensitivity, Cerebral malaria, Alzheimer’s disease

1. Introduction

The G protein-coupled receptors known as the angiotensin II receptors (ATR1) and (ATR2) have angiotensin II as their ligand. (1) They play a crucial role in the renin-angiotensin system because they transmit the signal that causes the major effector hormone, angiotensin II, to constrict blood vessels. [2] There are four distinct types of angiotensin II receptors: types 1 and 2, types 3 and 4, and type 5. The heart, blood arteries, kidney, adrenal cortex, lung, and circumventricular organs of the brain, basal ganglia, and brainstem all include the AT1 subtype, which mediates the vasoconstrictor effects. The angiotensin receptor is activated by the vasoconstricting peptide angiotensin II. The active receptor is responsible for activating phospholipase C, and it is also connected to Gq/11 and Gi/o. [3]

This raises the quantities of Ca2+ in the cytosol, which triggers cellular reactions including activation of protein kinase C. Furthermore, a variety of tyrosine kinases are active while adenylate cyclase is inhibited by an activated receptor. The AT1 receptor mediates the following effects: reduced renal blood flow, renal renin inhibition, renal tubular sodium reuptake, cardiac contractility, extracellular matrix formation, aldosterone synthesis and secretion, increased vasopressin secretion, increased peripheral noradrenergic activity, the proliferation of vascular smooth muscle cells. [4] The AT2 receptor, also known as angiotensin II receptor type 2, is encoded by the human AGTR2 gene. Angiotensin II is a potent pressor hormone and the primary modulator of aldosterone secretion. It is an important component of the volume of the cardiovascular system.[5].CGP 42112A is a selective agonist that increases the production of mucosal nitric oxide by stimulating AT2. [6] Further understudied subtypes are the AT3 and AT4 receptors. Angiotensin II metabolite angiotensin IV activates the AT4 receptor, which may be involved in controlling the release of oxytocin and the extracellular matrix in the central nervous system. [7][8][9][10][11][12][13][14]

2. AT2 receptor function in stroke neurological protective effects

Every year, millions of people worldwide sadly suffer from strokes. Ischemic strokes, which occur when there is insufficient blood supply to the brain, usually due to thromboembolism or

atherosclerotic obstruction, account for 88% of stroke cases. As a result, the brain is deprived of oxygen and nutrients, which causes rapid and irreversible necrosis in the center of the ischemic area but more gradual and perhaps reversible loss of neurons in the

penumbra, the region of the brain that surrounds the affected area. The sole approved treatments for ischemic stroke are thrombolytic agents, recombinant tissue plasminogen activator (rtPA), and endovascular clot retrieval/destruction techniques. These treatments aim to restore blood flow to the infarcted area.

However, they only work for a limited number of patients and are typically not able to completely treat neurological problems. As a result, agents that stop neurons from dying after an ischemic stroke are still required. In this study, we explore agonists of the angiotensin II (Ang II) type 2 (AT2) receptor as a possible target for treatment of this illness. The first concrete proof that AT2 receptors can prevent ischemic stroke came from studies comparing wild-type (Agtr2+) mice to AT2 receptor-deficient (Agtr2) mice, which showed notably larger cerebral infarcts and neurological deficits after permanent middle cerebral artery occlusion (pMCAO) . Additionally, this study demonstrated that a significant reduction in AT2 receptors can be observed in the neuroprotective effects of therapy with ARB [15]

. Furthermore, further studies revealed that the neuroprotection offered by ARBs was inhibited by an AT2 receptor antagonist. [16, 17] These findings provide credence to the theory that the neuroprotective properties of ARBs stem from Ang II's unopposed actions at AT2 receptors. Research revealed that in spontaneously hypertensive rats (SHR), endothelin-1 (ET-1)-induced ischemic stroke (a model of transient Vaso-occlusive stroke) was associated with dose-dependent reductions in cerebral infarct size and neurological deficits [18, 19]. A mouse investigation that

demonstrated a neuroprotective effect after intraperitoneal (IP) injections of CGP42112A were given at the time of reperfusion provided evidence for these conclusions. [20]

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Study evidence

According to I. Joseph et al. [23], we demonstrated in this study that the AT2R agonist C21, when given at a dosage that is selective for AT2R, is cerebroprotective during ischemic stroke (Jehle et al., 2012; Namsolleck et al., 2013; Pauli's et al., 2012). The degree of cerebral infarct and neurological deficits caused by ET-1-induced MCAO is limited by C21 pre-treatment administered centrally (ICV) or systemically (IP). Crucially, systemically administered C21 soon after the stroke also reduced the extent of the cerebral infarct and the neurological impairments caused by ET-1-generated MCAO; an AT2R antagonist reversed these effects. II. Alhusban et al. [24] found that C21 increased levels of the anti-inflammatory cytokine interleukin-10 (IL-10) near the ischemia border zone, A decrease in nitrative stress was linked to an increase in IL-10 near the ischemia border zone. III. et al. Fouda [25] It has been shown that nitric oxide (NO) signaling increases IL-10 levels in the kidney. Additionally, a study discovered that C21 may increase IL-10 synthesis from systemic immune cells. It is clear from the aforementioned description that a number of routes and processes contribute to the neuroprotective benefits of C21-induced AT2 receptor activation.

Ischemic stroke and AT2 receptor agonists: a promising new treatment or a lost cause? Given the potential for AT2 receptor agonists to be turned into potent treatments for ischemic stroke, two of the points made previously in this study should be emphasized. Specifically, numerous investigations conducted by various research groups have demonstrated the neuroprotective benefits of AT2 receptor agonists [26–35,23], and the mechanisms behind these effects seem to be intricate [28–33,23].
When assessing a medication as a potential treatment for ischemic stroke, it is important to maintain cerebral circulation after the stroke, particularly to keep blood and oxygen flowing to the penumbral area. [36] Despite evidence that daily ICV infusion of AT2 receptor agonists, peptide or C21, for days to weeks results in mild drops in blood pressure, especially during hypertension, acute administration of C21 (IV, oral, or N2B), as utilized in the neuroprotection studies, did not impact blood pressure. [37–39]
. Considering this, there is an additional noteworthy advantage to consider while creating AT2 receptor agonists for ischemic stroke. In summary In the fourteen years since the first evidence that activating AT2 receptors provided protection against ischemic strokes, a great deal of progress has been made in understanding the mechanisms underlying the neuroprotective effects of selective AT2 receptor activation in the brain. [40]

To effectively execute the STAIR and RIGOR guidelines [41, 42] and ascertain if AT2 receptor agonists are a viable therapeutic target for exerting neuroprotective effects in ischemic stroke, it is evident that additional preclinical research is required. In the event that AT2 receptor agonists do progress for clinical testing in ischemic stroke, the new confirmation that C21 is safe for use in humans places this selective AT2 receptor agonist in a great position for testing in human clinical trials.

3.Obesity, Metabolism, And Insulin Sensitivity [43]

Overview Because obesity results in hyperinsulinemia, dyslipidemia, and hyperglycemia (diabetes), all of which signal inflammation and the destruction of cells and organs, obesity plays a major role in metabolic dysfunction and impairs organ function. Additional research has demonstrated that diabetes and obesity increase the expression of AT2R in both adipose and non-adipose tissues, including the kidney and blood vessels, indicating a larger function for these conditions. Hyperglycemia is one factor that contributes to an increase in AT2R expression. 86 Understanding how AT2R affects metabolism, insulin sensitivity, and renal-cardiovascular function in relation to these conditions is therefore crucial. Ongoing study is being done on this subject.

Study evidence:

According to a recent study, 12 weeks of C21 therapy in normal mice decreased the amount of adipocytes and improved insulin receptor signaling in terms of Akt activity in the liver and adipose tissues. Rats treated with C21 exhibited unaltered insulinemia, increased glucose tolerance, and decreased glycemia with improved insulin sensitivity when compared to untreated controls.88 degrees Numerous investigations that employed animal models of diabetes and insulin resistance demonstrated the significance of AT2R in these diseases. For example, in rats with insulin resistance produced by a high-fat/high-fructose diet, C21 treatment promoted adipocyte differentiation and enhanced adipose insulin sensitivity. [15]

These changes were linked to an increase in Proliferator-activated receptor (PAR) expression mediated by PI3K/Akt. PAR is a transcription factor that has been shown to improve insulin sensitivity by altering the expression of many genes related to insulin receptor signaling. [15] Another study employing type 2 diabetic mice shows that, partly due to adipocyte differentiation and pancreatic beta-cell protection, AT2R activation with C21 improved PPAR activity and insulin resistance. Studies have demonstrated that antioxidative stress, anti-apoptosis, improved microvascular perfusion, efficient delivery of insulin to tissues, including muscles, and an increase in adiponectin are also linked to AT2R-mediated improvements in insulin resistance, glycemia, and pancreatic function. In the previously described studies, AT2R activation also reduced the quantities of cytokines that cause inflammation, such as TNF.Given that inflammation is a contributing factor to insulin resistance, AT2R's anti-inflammatory activity represents likely additional pathway enhancing insulin sensitivity and metabolism.

4.Obesity [43,44,45]

The excessive or abnormal buildup of fat that can be harmful to one's health is called obesity. Body mass index (BMI) is a straightforward weight-for-height metric that's frequently used to categorize persons who are overweight or obese. It is calculated by dividing a person's height in meters squared by their weight in kilograms (kg/m2). AT2R activation reduces obesity and adiposity. For example, we observed that male mice treated with C21 had reduced adiposity and improved lipid metabolism, most likely through decreased lipid synthesis and increased lipid breakdown. This research indicates AT2R is a new goal to combat adiposity and obesity. It shows that pharmacological AT2R activation prevents the obesity, dyslipidemia, inflammation, and insulin resistance brought on by a high-fat diet. Results specifically showed that AT2R agonist treatment enhanced plasma dyslipidemia indicators and inhibited the increase of adipocyte size in HFD-fed mice.

Conclusion [45]

Activation of AT2R seems to be a promising therapeutic strategy for managing obesity and obesity-associated conditions like inflammation and insulin resistance.

5. Cerebral malaria [46,47]

Brain endothelial cells adhering to Plasmodium falciparum-infected red blood cells (Pf-iRBCs), breakdown of the blood-brain barrier, and cerebral microhemorrhages are characteristics of cerebral malaria. Cerebral malaria is the most dangerous neurological side effect of Plasmodium falciparum malaria infection. Its primary clinical signs on peripheral blood smears are coma and asexual forms of the parasite.

There is a high death rate, and a small percentage of survivors experience long-term neurocognitive impairments due to head trauma. In this article, we review studies that have added to our current understanding of the genesis of brain injury and discuss potential for neuro-protection and improved outcomes. Research has demonstrated that activation of the type 2 receptor (AT2) reversed the effects of Pf-iRBCs on -catenin activation, preventing the breakdown of HBMEC monolayers. This is because ruptured Pf-iRBCs cause activation of -catenin in human brain microvascular endothelial cells, which disrupts inter-endothelial cell connections (HBMECs). The deleterious effects of P. falciparum on endothelial integrity were shown to be significantly modulated by -catenin, as evidenced by the inhibition of -catenin-induced TCF/LEF transcription in the nucleus of HBMECs.

6.Severe Acute Respiratory Syndromecoronavirus-2 (Sarscov-2) [43,50]

The SARSCoV-2 virus is the infectious agent that causes coronavirus illness (COVID-19). The majority of virus-infected individuals will recover from mild to moderate respiratory infection without the need for additional care. Nonetheless, a small percentage will get really sick and need medical care. Serious sickness is more likely to strike the elderly and those with underlying medical disorders such as diabetes, cancer, cardiovascular disease, or chronic respiratory diseases. With COVID-19, anyone can get sick, get very sick, or pass away at any age.

Study evidence

According to this study, AT2R interacts with MasR and other GPCRs, including the angiotensin AT1 and bradykinin BK1 receptors. It has been proposed that this interaction could be a method by which AT2 enhances biological processes and cellular signaling. AT2 increases biological reactions and cellular signaling. AT2 and MasR, two members of the RAS's protective arm, have comparable beneficial effects in a range of renal-cardiovascular diseases, such as blood pressure reduction, natriuresis, and vasodilation. This study examines the functional reliance of AT2R-MasR in connection to SARS-CoV-2 viral infection. When ACE2 is suppressed by binding to SARS-CoV-2, Ang (1-7) is depleted. However, AT2R can be pharmacologically activated by coming into touch with MasRAs of right now, it is known that SARSCoV-2 enters cells by using ACE2 as a receptor, which lowers ACE2 activity. TAT2R reduces Ang II and AT1R signaling, which has advantageous effects as well. This rationale has led to the use of the AT2R agonist C21 in phase 2 double-blind, randomized, placebo-controlled clinical trials involving people with COVID-19.This would imply that C21 could be included in therapy regimens for COVID-19 patients.

7.Alzheimer's disease [47]

Alzheimer's disease is an age-related, neurological, progressive, and irreversible brain disease with multiple contributing factors. It causes slow cognitive decline, behavioral abnormalities, psychological disorders, dementia, and eventually death from complete brain loss years before symptoms show up. The two primary histological features of Alzheimer's disease are the breakdown of synaptic connections in the brain and the growth of neurofibrillary tangles (NFT), which are composed of hyperphosphorylated tau. Age-related plaques are caused by misfolded aggregates of the amyloid-(A) protein. These alterations are linked to oxidative stress, chronic neuroinflammation, and mitochondrial dysfunction; in turn, these alterations lead to neurovascular degeneration and advanced dementia.

Role of AT2R: Compound 21(C21/M024):

Numerous studies have shown that C21 therapy improves memory and cognition. According to research on animals, long-term C21 treatment preserved all aspects of cognitive function, including short-term working memory, associative learning, spatial reference, cognitive flexibility, and non-spatial recognition. Some of the proposed mechanisms of AT2R mediated cerebrovascular protection and cognitive preservation by C21 include increased cerebral blood flow and decreased accumulation, as well as the suppression of chronic reactive microgliosis and neuroinflammation. Conclusion: Using C21, a direct AT2R agonist, could be another effective tactic. Preclinical and experimental evidence seem to strongly support the use of this medicine in the prevention of dementia, suggesting that it would be a worthwhile candidate for further investigation in clinical trials.

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