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Review Article

The link between angiotensin II-mediated anxiety and mood disorders with NADPH oxidase-induced oxidative stress

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Abstract: The renin-angiotensin system (RAS) and its active peptide angiotensin II (AngII) have major involvements not only in hypertension but also in mood and anxiety disorders. Substantial evidence supports the notion that AngII acts as a neuromodulator in the brain. In this review, we provide an overview of the link between the RAS and anxiety or mood disorders, and focus on recent advances in the understanding of AngII-linked, NADPH oxidase-derived oxidative stress in the central nervous system, which may underlie pathogenesis of mood and anxiety disorders.

Keywords: Renin-angiotensin system, angiotensin II, anxiety disorder, bipolar disorder, major depressive disorder, reactive oxygen species, NADPH oxidase

Introduction

The renin-angiotensin system (RAS) is essential for maintaining the balance between fluid intakes and blood pressure. Renin, typically produced in kidneys, cleaves an inactive peptide angiotensinogen into angiotensin I. Angiotensin I, a precursor of AngII with little physiological effects, is converted to AngII by the angiotensin I-converting enzyme (ACE) that is secreted by pulmonary and renal endothelial cells. AngII is known for its robust cardiovascular actions, not only increasing blood pressure by stimulating the Gq protein in arterial smooth muscle cells, but also stimulating kidneys to retain sodium and water via aldosterone released from the adrenal cortex. AngII is also widely expressed in the brain and plays important roles in the regulation of blood pressure. Injection of AngII into key brain nuclei produced hypertension, an effect blocked by the AngII antagonist saralasin or AngII type 1 receptor (AT_1R) deletion [1]. Although peripheral AngII does not cross the blood-brain barrier (BBB), the links between peripheral and central RAS are established through circumventricular organs (CVOs) that sense circulating AngII *via* AngII receptors. Effects of AngII are usually mediated by two well-characterized subtypes of AngII receptors, AT_1R and AT_2R [2]. AT_1Rs are highly expressed in the subfornical organs (SFO), paraventricular nucleus (PVN) [3], nucleus tractus solitarius (NTS) [4], hypothalamic-pituitary-adrenal axis (HPA) and amygdala nuclei [5]. Furthermore, two highly homologous AT_1R isoforms, termed $AT_{1A}R$ and $AT_{1B}R$, are expressed in the brain and may have different functions within the same region. In the mouse SFO, for example, $AT_{1A}Rs$ are involved in blood pressure regulation, while $AT_{1B}Rs$ mediate water drinking response [6]. AT_1Rs contribute to most of the harmful effects induced by AngII, such as hypertension, heart failure and mood disorders [1, 6]. AT_2Rs are significantly expressed during early development, but decline in the adulthood [2]. AT_1Rs and AT_2Rs are coupled with transduction signaling, including G proteins, phospholipases and NADPH oxidase [2, 4, 7-9]. However, pharmacological actions mediated by AT_2Rs may functionally oppose those induced by AT_1Rs. One example is that AT_1R-induced reactive oxygen species (ROS) are scavenged by AT_2R-induced nitric ox-

ide (NO). As a result, an imbalance between the AT_1R- and AT_2R-triggered signals may lead to hypertension [7, 8].

Evidence for the link between AngII and mood or anxiety disorders

Mood disorders

Clinically, two groups of mood disorders are widely recognized: (1) Major depressive disorder, a mental disorder characterized by depressed mood accompanied by anhedonia, feeling of guilty or hopelessness, change of appetite and weight; low energy, poor concentration, and suicidal ideation. This mood must represent a change from a person's normal mood; social, occupational, educational or other important functioning is impaired by the depressive symptoms. (2) Bipolar disorder, characterized by intermittent episodes of mania or hypomania, usually interlaced with depressive episodes. It is also a serious mood disorder clinically presented as unusual shifts in mood, energy and cognitive levels, with or without depressive episodes. Symptoms are different from the normal ups and downs, and may seriously damage relationships, job or school performance, and even cause suicide [10].

Anxiety

Mild, brief anxiety caused by a stressful event (such as speaking in public) is a normal reaction to stress. But when anxiety becomes excessive, irrational and persistent, it becomes pathologic. Anxiety disorders commonly occur along with other mental or physical illnesses. Major types of anxiety disorders are: (1) Panic disorder is characterized by recurrent, unexpected attacks of terror, accompanied by a pounding heart, sweatiness, weakness, faintness, shakiness and dizziness. (2) Post-traumatic stress disorder presents as a cluster of symptoms such as re-experience, avoidance and hyperarousal developing after a person experiences or witnesses a traumatic event. Other anxiety disorders include obsessive-compulsive and generalized anxiety disorders [10].

Pharmacological and genetic links between AngII and mood disorders or anxiety

The hypothesis that the RAS is linked to mood disorders is based on early observations that the patient with hypertension and major depression was successfully treated for both conditions with the ACE inhibitor captopril [1, 11-13]. Captopril improved mood status and attenuated depressive symptoms, which was not associated with its antihypertensive action because other anti-hypertensive medications such as α-methyldopa and prazosin did not exert this mood elevating effect [11]. Antidepressant effects by other ACE inhibitors were also reported in patients with major depression or the depressive phase of bipolar disorder. Since plasma AngII does not cross BBB into the brain but the ACE inhibitor does, it is therefore implicated that the brain AngII plays a critical role in the ACE-sensitive mood disorders [12]. ACE expression is under control of ACE gene variants, which are due to an insertion/deletion (I/D) polymorphism resulting from the presence or absence of ~250-basepair fragments in the 16th intron of the ACE gene located on chromosome 17q23. Subjects with homozygous genotype DD display higher ACE activity, while those with homozygous genotype of II show decreased ACE activity. Significant associations of the DD allele with major depression and bipolar disorder were reported [1, 14-16]. Significant associations of two SNPs (rs4291, rs4295) located in the promoter area within the ACE gene were also identified in patients with major depression [17]. Moreover, the risk of suicidal behavior was higher for the subjects bearing the DD genotype than other variants [18]. In addition, the DD genotype was also linked with psychotic symptoms in bipolar and schizophrenic patients [19, 20]. For anxiety disorders, an association of another two SNPs (rs4311, rs4333) within the ACE gene was identified in patients with panic attacks [21]. However, the II allele was only associated with panic disorder in male patients, suggesting a gender-specific effect in the ACE I/D polymorphism [22]. More interestingly, the DD allele was associated with both high plasma AngII and NADPH oxidase-generated ROS in phagocytes in hypertensive patients [23]. In addition, variant genes for AT_1Rs are involved in major depression and anxiety disorders. AT_1R A1166C polymorphism CC gene was significantly associated with major depression [24]. Differences in AT_1Rs gene expression between strains were associated with their anxiety phenotypes [25]. Taken collectively, these results indicate that AngII and AT_1Rs are involved in mood and anxiety disorders.

AngII-induced emotional stress and anxiety disorders

Substantial evidence indicates the involvement of AngII in anxiety disorder mediated by the HPA and sympatho-adrenal axis [26]. AngII in the brain was associated with higher HPA axis activity, enhanced responses to stress and anxiety. Peripheral AngII also participated in emotional stress responses *via* the AT_1R activation within the forebrain, because peripheral administration of the AT_1R antagonist candesartan prevented peripheral and central sympathetic activations characteristic of isolation stress and abolishes the HPA activation during isolation [27]. In addition, AT_1Rs were expressed in the stress-sensitive brain structures including the dorsomedial hypothalamus (DMH) and amygdala [28]. The DMH plays a functional role in initiation of panic-like responses induced by lactate or AngII *via* the osmosensitive periventricular pathway that relays the signals to the forebrain limbic structures mediating anxiety responses. While injection of lactate or AngII into the DMH produced panic-like responses in panic-prone rats, co-injection with the AT_1R antagonist losartan into the DMH blocked these anxiety- and panic-like responses in panic-prone models [29, 30]. The amygdala, a region implicated in the conditioned fear, is rich in AT_1Rs. The AngII antagonist saralasin antagonized behavioral and physiological responses to the panicogen sodium lactate in rat panic models, indicating that AT_1Rs mediate panic attacks [31]. Therefore, these results led to the suggestion that both central and peripheral AngII are involved in the AT_1R-mediated stress or anxiety disorders.

NADPH oxidase (NOX)-triggered oxidative stress

NOX

NOX is originally identified as a key component of innate host defense systems. The primary function of the phagocyte NOX is production of O_2^- and its secondary metabolite H_2O_2 to induce oxidative burst in phagocytes that enables the digestion of engulfed bacteria. NOX is also widely distributed in nonphagocyte cells [32, 33]. Normal tissues and cells defend themselves against ROS-induced damages through their scavenger systems such as superoxide dismutase (SOD), catalase and peroxidases to eliminate excessive ROS. However, under the circumstance of high ACE activities or continuous activation of AT_1Rs, ROS generation may exceed the antioxidant capacity, a condition termed oxidative stress occurs [2, 32-36].

NOX, along with other enzymes including nitric oxide synthase, xanthine oxidase or cytochrome P450, produce ROS as natural byproducts of the normal metabolism of oxygen [36-40]. ROS are small molecule metabolites of oxygen that participate in redox reactions *via* their high reactivity. Typical ROS include superoxide anion (O_2^-), H_2O_2, hydroxyl (HO^-), peroxynitrite ($ONOO^-$) and lipid peroxides (LOOH). O_2^- is considered as the "primary" ROS. One of the key endogenous anti-oxidative agents is the enzyme superoxide dismutase (SOD) that catalyzes O_2^- into H_2O_2. Other relevant endogenous enzymes involved in the metabolism of H_2O_2 are catalases and glutathione peroxidase (GPX) with glutathione (GSH) [37, 40]. Exogenous transition metal chelators, such as metal ions and EDTA complexes may also serve as one of the major anti-oxidant mechanisms in biological systems.

The structure of NOX2 includes two essential plasma membrane-bound subunits of NOX, $gp91^{phox}$ and $p22^{phox}$, forming a heterodimer termed flavocytochrome b_{558}, and cytoplasmic subunits of NOX including $p47^{phox}$, $p40^{phox}$ and $p67^{phox}$, translocating to the membrane upon stimulations and binding to flavocytochrome b_{558} during $gp91^{phox}$ activation. Complete complex assembly is necessary for complete NADPH oxidase activity. Electrons from NADPH are transferred through the enzyme to molecular oxygen to generate O_2^- [37, 40] (**Figure 1**). The catalytic subunit $gp91^{phox}$, also termed NOX2, has several homologues, NOX1, NOX3 through 5. NOX expressed in the brain is also region-specific [40, 41]. Several NOX isoforms are expressed in neurons. NOX2 is located in the SFO, PVN, NTS, RVLM, amygdala, striatum, thalamus, hippocampus, and cortex [4, 42-47]. ROS play important roles in the normal cellular signaling, which includes delivery of electrons across membranes and oxidative modification of proteins or DNA. Under environmental stresses or pathological circumstances, however, intracellular ROS levels increase dramatically, eliciting oxidative stress. Oxidative stress exerts deleterious effects on lipids, proteins or nucleic acids. Peroxynitrite ($ONOO^-$), for instance, one of ROS products due to reaction between O_2^- and NO, elicits tyrosine nitration in proteins. ROS are

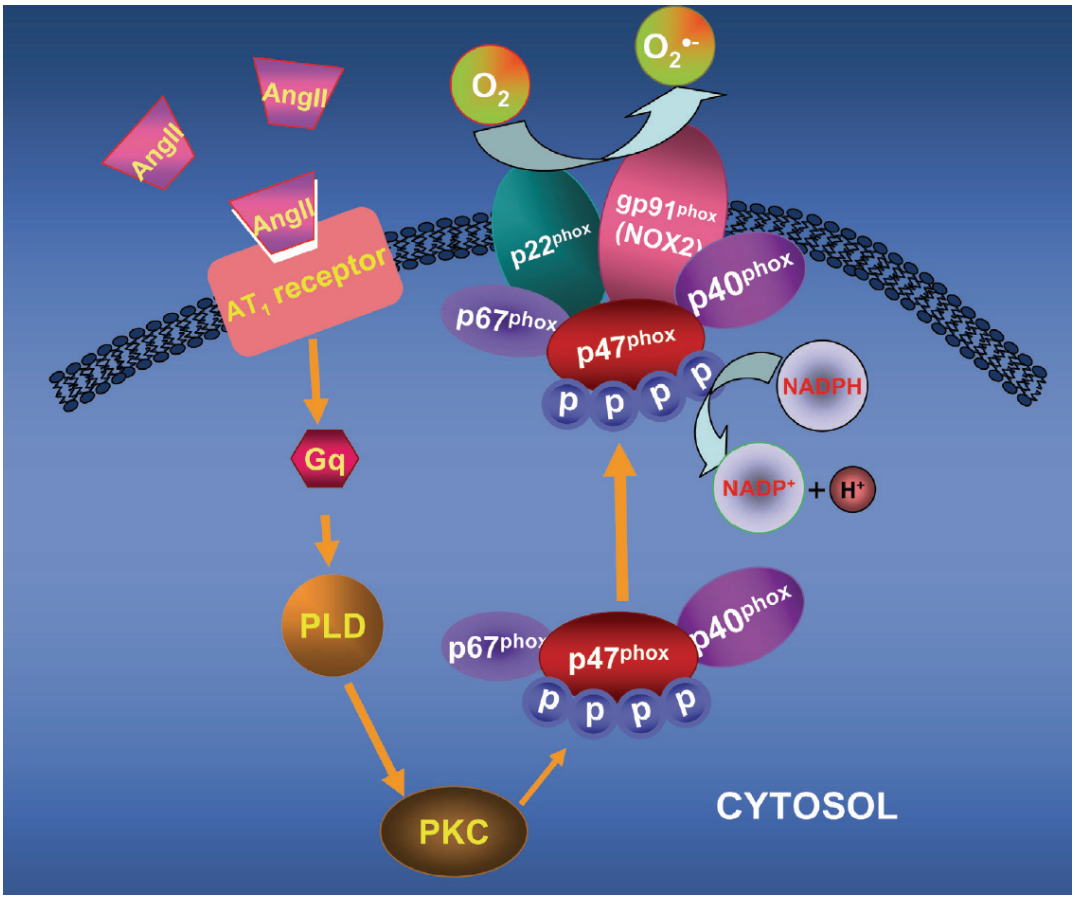

Figure 1. A schimatic signaling pathway for the AT_1-mediated, NOX2-derived ROS production. The AT_1R activation results in activation of phospholipase D (PLD) and protein kinase C (PKC), which then results in phosphorylation of $p47^{phox}$, the cytosolic regulatory subunit of NOX2. The phosphorylated $p47^{phox}$, along with other NOX2 subunits $p67^{phox}$ and $p40^{phox}$, translocate towards and bind to the plasma membrane-bound $gp91^{phox}$, the catalytic subunit of NOX2. Such multisubunit assembly results in activation of the whole NOX2 system, producing superoxide (O_2^{-}).

also able to oxidize many signaling proteins such as ion channels or neurotransmitter transporters [4, 33, 48], causing neurophysiological consequences.

AngII, the brain NOX and psychiatric disorders

In the brain, NOX distributes in somatodendritic and axonal profiles in the NTS, hippocampus and prefrontal cortex. NTS dysregulation may disrupt cardiorespiratory homeostasis that not only leads to hypertension, but also is involved in anxiety disorders. Within the NTS, the ultrastructural analysis revealed an anatomical link between $AT_{1A}R$ and NOX2. $AT_{1A}Rs$ were identified in somatodendric, pre- and post-synaptic axon terminal profiles containing NOX2 [4]. These results implicate that NOX2 may be functionally coupled with pre- and postsynaptic $AT_{1A}R$ signaling. Within the hippocampus, dual labeling of $p67^{phox}$ subunit with the presynaptic marker synaptophysin suggested a close association between NOX and presynaptic sites, which are coupled with glutamate release triggered by NOX-derived ROS [4, 45, 47]. The NMDA receptor-dependent activation of the extracellular signal-regulated kinase (MAPK) was blocked by the NOX inhibitor diphenylene iodonium or absent in $p47^{phox}$ null mice, indicating that NOX-derived ROS are required for MAPK activation [47]. Within the prefrontal cortex, NOX2 also served as a major source of ROS that control glutamate release and were associated with behavioral alterations after acute ketamine exposure [33, 49].

NOX plays important roles in the AngII-linked hypertension [2, 7, 8]. It is accepted that the

AngII-linked neurogenic hypertension is attributed, at least in part, to the ROS produced by the brain NOX [7, 33, 35]. The transduction signal pathways underlying the AngII-induced ROS production *via* NOX in the brain have recently been addressed [4, 8, 33-37]. Moreover, continuous activation of the brain RAS impairs cognitive functions by NOX-derived ROS. In human renin and human angiotensinogen gene chimeric transgenic mice, AngII expression was significantly increased in both the brain and plasma. More interestingly, an increase in the avoidance rate in these chimeric double transgenic mice was associated with an increase in the brain O_2^- production derived from the NADPH oxidase. The AT_1R antagonist olmesartan or the O_2^- scavenger tempol improved the cognitive function and oxidative stress in these mice, suggesting that continuous activation of the brain renin-angiotensin system impairs cognitive functions *via* both AT_1Rs and NADPH oxidase (NOX)-derived ROS [34].

Accumulating evidence also supports the hypothesis that NOX-derived ROS are involved in the pathophysiology of anxiety and bipolar disorders [12, 33, 34, 50-53]. Anxiety and mood disorders are closely linked to NOX-mediated oxidative stress [54-58]. Two separate genes encoding glyoxalase 1 and glutathione reductase in correlation with oxidative stress metabolism were involved in anxiety-like behavioral phenotypes. Overexpression of glyoxalase 1 and glutathione reductase in the mouse brain results in increased anxiety-like behaviors. However, Inhibition of glyoxalase 1 expression by siRNA decreases anxiety-like behaviors [56]. Moreover, anxiety disorder was linked to intracellular ROS levels in central neuronal and glial cells [55]. The oxidative stress inducer L-buthionine-(S,R)-sulfoximine produces anxiety-like behaviors, which were antagonized by the NOX inhibitor apocynin and PDE_2 inhibitor [57]. NOX2-derived oxidative stress is involved in the development of anxiety disorder after social isolation. The oxidative stress indicator oxidized nucleic acid 8 -hydroxy-2'-deoxy-guanosine was increased following social isolation. The oxidative stress could be in part due to NOX2 activation in microglia, because the pretreatment with apocynin prevented both behavioral and pathological alterations induced by social isolation [58]. The roles of oxidative stress in bipolar disorder and schizophrenia are also addressed. The level of tyrosine nitration that reflects the levels of an endogenous ROS $ONOO^-$ was significantly higher in bipolar patients than in healthy controls [59]. In addition, a link between an increased NOX activity and resultant superoxide production in interneurons of the ketamine-induced schizophrenic model was reported [60]. NOX expression and activity were upregulated in the temporal region of mild cognitive impairment patients [61]. ROS and NOX also played a critical role in the pathogenesis of Alzheimer's dementia [62, 63].

Perspective

It is widely accepted that the interplay of genetic, developmental and environmental factors contributes to the pathogenesis of anxiety and mood disorders. AngII generated in the brain by the brain RAS functions as a peptidergic neuromodulator and has many neuropsychopharmocological effects. As of the genetic aspect, it has been determined that the ACE DD gene polymorphism may serve as a susceptibility gene for mood disorder since it reproduces the phenotype that is associated with the high ACE activity, high AngII concentration and/or high NADPH oxidase activity in the brain of subjects with hypertension and mood disorder.

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