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A REVIEW ON ISCHEMIA REPERFUSION INDUCED ACUTE KIDNEY INJURY AND ROLE OF GABA IN RENAL DYSFUNCTION AND OTHER DISORDERS

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ABSTRACT

Acute kidney injury (AKI) is characterized by rapid loss of kidney function, associated with renal cell death. Epidemiology of AKI differs in developed countries from that in developing countries. In developed countries, the AKI predominates in the elderly people whereas in developing countries AKI is prevalent among young people and children. The various reasons for post-renal AKI include renal papillary necrosis, kidney stones, bladder tumor, carcinoma of cervix and prostrate hypertrophy. Ischemia reperfusion injury is the most common cause of Acute kidney injury. Ischemia causes impairment of renal functions by inducing renal vasoconstriction, renal tubular obstruction, tubular leakage of glomerular filterate and decreased glomerular permeability. GABA is the major inhibitory neurotransmitter in the brain and its role is extensively studied in various disorders including anxiety and epilepsy. The renoprotective effects of GABA has also been reported in animal model of glycerol-induced acute kidney injury. GABA released from renal tubular epithelium and transported with the urine might be involved in the modulation of contractility in the urinary tract.

Keywords: Acute kidney injury, Ischemia reperfusion, Oxidative stress, gamma amino butyric acid, angiotensin, Nitrous oxide

INTRODUCTION

Acute kidney injury (AKI) is characterized by rapid loss of kidney function, associated with renal cell death **[1]**. According to Acute Kidney Injury Network guidelines,

the AKI is defined as an abrupt reduction in kidney function that is associated with an increase in serum creatinine level either more than 0.3 mg/dL or 50% in 48 hours **[2]**. The AKI is among the most common complications observed in hospitalized patients and is more common among men and elderly people **[3]**. It is recognized that epidemiology of AKI differs in developed countries from that in developing countries. In developed countries, the AKI predominates in the elderly people whereas in developing countries AKI is prevalent among young people and children **[4]**. The AKI is categorized according to its primary risk factors, which may be pre-renal, intra-renal or post-renal. The pre-renal damage results from transient hypo-perfusion and is a functional response of structurally intact kidney to hypo perfusion. The various pre-renal reasons of AKI include hypotension, reduced effective circulating volume, renal artery stenosis and drugs including angiotensin converting enzyme inhibitors and non-steroidal anti-inflammatory agents especially selective cyclo-oxygenase-2 (COX-2) inhibitors. Various intrinsic factors leading to AKI include glomerulonephritis, ischemic tubular necrosis, myeloma cast nephropathy, uric acid and oxalate crystal deposition, aminoglycosides, radio-contrast media, heavy metals, thrombotic diseases and systemic lupus erythmatous. The various reasons for post-renal AKI include renal papillary necrosis, kidney stones, bladder tumor, carcinoma of cervix and prostrate hypertrophy **[5]**. Ischemia reperfusion injury (IRI) is the most common cause of AKI. The renal IRI observes ATP depletion, impaired solute and ion transport, loss of cellular polarity cytoskeletal disruptions and mitochondrial dysfunctioning in renal proximal tubular cells. Ischemia causes impairment of renal functions by inducing renal vasoconstriction, renal tubular obstruction, tubular leakage of glomerular filterate and decreased glomerular permeability. The kidney has remarkable regeneration capacity evidenced by complete recovery of renal function after IRI. However there remains a controversy about the mechanisms underlying renal recovery from AKI. The systemic effects of AKI involves multiple organs and lead to high mortality. The various disorders including congestive heart failure, acute respiratory distress syndrome and hepatic dysfunction are associated with AKI **[6]**. However, various studies have suggested that the proximal tubule is the most commonly affectedbecause of the presence of inducible type of microsomal mixed function oxidases(cytochrome P 450) which have been implicated in the toxic activation of various agents. This segment

is also rich in glutathione and glutathione metabolizing enzymes **[7]**.

PATHOPHYSIOLOGY OF IRI INDUCED AKI

Complete or partial cessation of blood flow to a particular tissue followed by restoration is a serious process involving abnormal signal transduction and cellular dysfunction and initiates a cascade of reactions contributing to apoptosis or necrosis along with infiltration of inflammatory cells **[8]**. Renal IRI is observed in clinical conditions such as severe hypotension and subsequent resuscitation, kidney transplantation and aortovascular surgeries. The IRI induced AKI model in rats mimic these conditions that lead to acute renal damage. Marked sensitivity to hypoxia has been demonstrated in both proximal tubules and the medullary thick ascending limbs. The free radicals affect cell vitality by several mechanisms involving interference with the cell growth and proliferation, inflammatory response and immune process along with regeneration and tissue repair **[9]**. The mechanism responsible for post-ischemic apoptosis is attributed to the increasing activity of endonuclease through elevation of calcium entry into cells, or the release of reactive oxygen species. The reactive oxygen species (ROS) induces cellular death by causing DNA damage, oxidation of lipid membranes, direct activation of genes, or proteins responsible for apoptosis. The main components of oxidative stress in renal tissues include superoxide radicals, hydrogen peroxide and hydroxyl radicals. Moreover, nitric oxide (NO) and peroxynitrite radical have the capacity to induce oxidative damage **[10]**. The major sources of ROS generated during IRI include circulatory macrophages or neutrophils and the resident cells. A marked elevation in ROS is observed in IRI especially during the reperfusion phase. Normally, the tissues contain enough endogenous scavengers to protect against free radical damage. The enzyme superoxide dismutase (SOD) causes rapid removal of O_2^- whereas catalase and glutathione peroxidase inactivates hydrogen peroxide. However, during IRI, the supply of these endogenous scavengers may be depleted thus permitting cellular injury by oxygen free radicals **[11]**. The renal IRI observes marked decrease in reduced glutathione and catalase activity and increase in lipid peroxides measured in terms of thiobarbituric acid reactive substances. In normal conditions, NO is oxidized to the nitrite anion, but during hypoxia, this nitrite may be reduced back to NO by nitrite reductase action of deoxygenated haemoglobin, acidic disproportionation, or xanthine oxidoreductase **[12]**. The generation of NO

has been attributed to enzyme NO synthase (NOS) having three isoforms. The endothelial NOS (eNOS) plays a key role in maintaining normal renal functions. The NO can either ameliorates or exacerbates renal injury depending on the rate and site of its production. During ischemia, eNOS activity is compromised as a result of its essential dependence on oxygen. However, during ischemic conditions, the endogenous nitrite pool may serve as an important alternative source of NO in the heart, liver and kidney by providing NOS-independent NO generation **[13]**. The post-ischemic inflammatory process initiated by both endothelial and tubular cell dysfunction further adds to renal dysfunction. A number of different proinflammatory and immunomodulatory cytokines such as interleukins (IL) 1, 6 and 8, transforming growth factor-β(TGF-β), tumor necrosis factor-α(TNF-α), and monocyte chemoattractant protein-1 (MCP-1), are released into the renal tissue and the circulation. The serum levels of IL-6 have been shown to correlate with higher risk of death in patients with AKI. Another hallmark of IRI-associated inflammation includes activation of the complement system **[14]**. The complement cascade is represented by more than 30 plasma proteins that are mainly synthesized in the liver. Although, the renal hypo perfusion mainly causes functional and structural alterations of the tubular epithelium, various studies suggest the role of postischemic endothelial cell dysfunction in peritubular capillaries as an important contributing factor of renal dysfunction **[15]**. The TGF-β1 plays a key role in pathogenesis of fibrosis and is considered as the most important growth factor in the pathogenesis of glomerulosclerosis. It stimulates synthesis of an extracellular matrix in the mesangium and between epithelial cells. It is excreted during tissue damage and provides chemoattraction of inflammatory cells and thrombocytes which are responsible for fibrosis **[16]**. The role of enhanced renal sympathetic nerve activity (RSNA) during ischemic period and the renal venous norepinephrine overflow after reperfusion has been explored in various studies. It is observed that RSNA significantly increases during renal ischemia and post-ischemic renal damage is ameliorated by renal denervation or ganglionic blockade that act by suppressing the elevated renal venous norepinephrine levels immediately after reperfusion **[17]**.

GABA (Gamma aminobutyric acid)

GABA is the major inhibitory neurotransmitter in the brain and its role is extensively studied in various disorders including anxiety and epilepsy. GABA receptors have three subtypes, $GABA_A$, $GABA_B$ and $GABA_C$, out of which first two are extensively studied. The

$GABA_A$receptor is coupled to ligand-gated chloride ion channel and are widely distributed within the mammalian brain and peripheral organs including liver, heart, retina, uterus, spermatozoa, adrenal medulla, kidney, anterior and intermediate pituitary lobes, and pancreatic α-cells **[18]**. $GABA_B$ receptors are G protein coupled receptors and are widely distributed in the brain as well as in peripheral autonomic terminals **[19-21]**. The neuronal $GABA_A$ receptor is composed of five hetero-oligomer subunits that form a pentamericstructure with a chloride channel. The various binding sites for benzodiazepines, barbiturates, convulsants and neurosteroids have been identified on $GABA_A$ receptor subunits. GABA has been found to play an important role in various neurological disorders.

The abnormalities of GABAergic function leading to reduction of GABAmediated inhibition, activity of glutamate decarboxylase, binding to $GABA_A$ and benzodiazepine sites, reduced levels of GABA in cerebrospinal fluid and brain tissue have been observed in animal models and patients of epilepsy **[22]**. The absence of GABA signalling results in loss of inhibitory neuronal firing that normally prevents the spread of paroxysmal discharge. The abnormal GABAergic function may significantly affect neuronal migration, differentiation, synaptogenesis and circuit formation **[23]**. Moreover, the downregulation of GABAergic function is critical in autism spectrum disease (ASD) associated with epilepsy **[24]**. The $GABA_A$ aswell as $GABA_B$ receptors are reduced in restricted regions of the cerebral cortex in ASD patients **[25]**.

Alzheimer disease is the most common type of dementia and is characterized by cognitive and behavioural deficits including psychological symptoms such as dementia include delusions, hallucinations, aggression, aberrant motor behaviour, sleep disruptions, agitation, depression, and apathy **[26, 27]**. Potentiating GABAergic inhibition potentially counteracts elevated glutamate excitation and decrease excitotoxicty in cortical circuits **[28]**. $GABA_A$ receptors are responsible for synaptic transmission of dopamine, serotonin, and acetylcholine. Increased interstitial GABA leads to conversion of glutamate to GABA by glutamic acid decarboxylase that results in chronic depolarization and neuronal degeneration, that is a major etiological pathway involved in Alzheimer disease **[29, 30]**.

Neurogenic inflammation within the meninges is the common cause of migraine headaches **[31]**. The neurogenic inflammation develops due to release of vasoactive neuropeptide from perivascular trigeminal nerve fibres and is characterized by plasma protein extravasation, platelet

aggregation, mast cell degranulation and endothelial activation **[31]**. The targeting of multiple subtypes and subunits of GABA in the CNS has been found to be effective in the treatment of migraine **[32-34]**. Zellweger syndrome is a fatal inherited peroxisomal deficiency disorder that is mediated by downregulation of GABAergic system through diazepam binding inhibitor and is characterized by multiple disturbances in lipid metabolism, profound hypotonia and neonatal seizures, and distinct cranio-facial malformations in the patients. It involves the deficiency of functional peroxisomes and disruption of peroxisomal beta-oxidation, thereby causing accumulation of branched and long-chain fatty acids, abnormal bile acids, and leukotrienes leading to decrease in lipid components of brain **[35, 36]**.

ROLE OF GABA IN PERIPHARAL DISORDERS

ANTIHYPERTENSIVE ROLE

The paraventricular nucleus (PVN) of the hypothalamus is involved in the regulation of sympathetic outflow. The changes in GABAergic tone within the posterior hypothalamus modulates sympathetic outflow to the cardiovascular system **[37, 38]**. The impairment of GABAergic system of paraventricular nucleus neurons contributes to the elevation of sympathetic nerve activity leading to hypertension **[39 40]**. $GABA_A$ as well as $GABA_B$ receptors play a role in regulation of the increased sympathetic nerve activity during hypertension.

ROLE IN ENDOCRINE DISORDERS

GABA serves as a neurotransmitter or neuromodulator in the autonomic nervous system and as a hormone in peripheral tissues. GABA is widely distributed in endocrine tissues including the pituitary, pancreas, adrenal glands, uterus, ovaries, placenta and testis. Moreover, GABA is involved in the pathophysiology of endocrine disorders such as diabetes mellitus and diseases of reproductive tracts **[41]**. GABA is present in pancreatic islets in similar concentration as that of in the brain **[42]**. The presence of GABA and its synthesizing and metabolizing enzymes in pancreatic cells suggests the role of GABA in regulating pancreatic cell function. Its concentration has been observed to decrease in pancreatic tissue in experimental and human diabetes. Other studies depict that $GABA_B$ activation increases the release of insulin and glucagon. It has been investigated that $GABA_A$ receptors present at alpha cells are responsible for lowering glucagon release **[43, 44]**.

The GABA receptors are present in the female and male reproductive tracts and both $GABA_A$ as well as $GABA_B$ receptors are present in ovary, testis, testicular interstitial cells, seminal vesicles and the

prostate gland **[45, 46]**. It regulates the release of estradiol and progesterone from rat ovary. Modulation of GABA receptors by tetrahydro-progesterone and gonadal steroid effects uterine motility through $GABA_A$ receptors **[47, 48]**. The acrosomal and sperm functions of progesterone had been also found to be regulated by GABA. The GABA agonists including benzodiazepines are reported to stimulate the production of testosterone in leydig cells **[49, 50]**.

ROLE IN INFLAMMATION

The immune cells are able to synthesize GABA. The antigen presenting cells express functional GABA receptors. The increased GABAergic activity ameliorates paralysis in experimental model of autoimmune encephalomyelitis along with reduction in inflammation. The GABAergic agents act directly on antigen presenting cells decreasing mitogen activated protein kinase signals thus leading to reduction in inflammatory responses to myelin proteins. Multiple sclerosis is an inflammatory, demyelinating neurodegenerative disease, is associated with diminished serum levels of GABA **[51-53]**. GABA is reported to be beneficial in the healing process of cutaneous wounds. The protective role of GABA is attributed to its inhibition of anti-inflammatory property and fibroblast cell proliferation and is compared to the epidermal growth factor treatment. The healing effect of GABA is remarkable and starts at the early stage of wound healing that result in significant reduction of the whole healing period **[54]**.

ROLE IN OTHER DISORDERS

The membrane depolarization and secretion in adrenal medullary cells is one of the secondary roles of GABA. Glutamic acid decarboxylase, a GABA synthesizing enzyme, and vesicular GABA transporter are expressed in rat adrenal medullary cells. It has been indicated that increased calcium signals in the adrenal medullary cells evoked by nerve stimulation are reported to get suppressed in response to GABA, and this suppression is attributed to the shunting effect of the GABA-induced increase in conductance **[55]**.

Ligand gated GABA receptors mediating inhibitory neurotransmission are expressed on the apical plasma membrane of alveolar epithelial type II cells. GABA is responsible for significant increase in chloride efflux in the type II epithelial cells. The $Na^+K^+2Cl^-$ co-transporter at the basolateral membrane is responsible for entry of chloride ion into the cell that accumulates chloride ion gradient for extrusion at the apical side in the epithelial cells of lungs. The role of GABA in the cystic fibrosis transmembrane conductance regulator has been identified on the apical membrane of alveolar epithelial cells which

plays an important role in cAMP-stimulated alveolar fluid clearance **[56-58]**.

ROLE OF GABA IN RENAL DYSFUNCTION

The presence of GABA receptors on kidney and their role in regulation of renal function is well recognized. $GABA_A$ receptor subunits exist in renal tubular epithelial cells as well as proximal tubules. Moreover, the sequences of the $GABA_A$ receptor subunits are similar to those of their neuronal system. GABA increases chloride uptake in renal proximal tubular cell and the concurrent addition of GABA blocker picrotoxin blocks chloride uptake. These functional studies confirm the presence of active $GABA_A$ receptor in the rat kidney. GABA administration in rats is documented to inhibit progression of tubular fibrosis and atrophy thus indicating role of GABA receptors in renoprotection. The GABA activates postsynaptic $GABA_A$receptors that leads to suppression of ischemic depolarization **[59**, **60]**. Picrotoxin, a well-known $GABA_A$ antagonist, binds presumably near the mouth of the chloride channel and inhibit neuronal GABA-activated chloride current **[61]**.

It has been demonstrated that preventive effect of GABA on ischemic AKI through the suppression of enhanced renal sympathetic nerve activity induced by renal ischemia is presumably mediated via $GABA_B$ receptor stimulation in central nervous system, rather than peripheral $GABA_B$ receptor. The enhancement of renal sympathetic nerve activity and its consequent effect on norepinephrine overflow from nerve terminals is considered to be involved in the development of the IRI induced AKI. In addition, it has been observed that ischemic AKI is ameliorated by renal denervation or ganglionic blockade **[62]**. Moreover, GABA is known to suppress the electrical renal nerve stimulation-induced norepinephrine release from isolated rat kidney without affecting basal release thus indicating that GABA can modulate peripheral as well as central neurotransmission. The renoprotective effects of GABA has also been reported in animal model of glycerol-induced acute kidney injury **[63, 64]**. Several other mechanisms underlying the GABA-induced suppressive action on peripheral sympathetic nervous system have been proposed, including ganglionic blockade and inhibition of transmitter release from the nerve terminals **[63, 65]**. The GABA has been documented to manage hypertension associated with chronic renal failure. The renal injury is reported to witness decrease in the activity of antioxidant enzymes along with elevation of lipid peroxidation. The administration of GABA attenuates oxidative stress through

an increase in superoxide dismutase and catalase, and decrease in lipid peroxidation in renal tissues **[64, 66]**. Moreover, it is suggested that GABA released from renal tubular epithelium and transported with the urine might be involved in the modulation of contractility in the urinary tract **[66]**.

CONCLUSION

The complexities created by systemic effects of AKI contribute to the in effectiveness of the various treatments given to manage AKI. Therefore there is a need to develop therapeutic strategies that limit to the treatment of AKI alone but also be broadened to the treatment of systemic effects of AKI. However, various studies have suggested that the proximal tubule is the most commonly affected because of the presence of inducible type of microsomal mixed function oxidases (cytochrome P 450) which have been implicated in the toxic activation of various agents.

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