Kynurenic Acid AttenuatesIschemia Reperfusion Induced Acute Kidney Injury: A Comprehensive Review

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Abstract

Kynurenic acid was the first tryptophan metabolite to be isolated and characterized in mammals. It is synthesized from kynurenine which is catalysed by kynurenineaminotrasferase and is found in mammalian liver, kidney, intestine, and also in rat brain.The extracellular kynurenic acid is synthesized in astrocytes and is released in the extracellular space. Kynurenic acid restores the renal functions as they have antioxidant property. Along with this they are also reported to antagonize N-Methyl D-Aspartate receptors which gets activated during the ischemia reperfusion injury thereby making the drug (Kynurenic acid) a new approach for the treatment of acute kidney injury where the major cause of renal dysfunctioning is ischemia reperfusion. Also this drug can be considered for future study keeping the very important aspect in mind that NMDA receptors are abundantly found in kidney and the drug actively work by blocking both the NMDAR glycine binding site and alpha-7-nicotine receptor.

Keywords Kynurenic acid, Acute Kidney Injury, NMDA, tryptophan, Ischemia Reperfusion Injury

Introduction

Acute kidney injury (AKI) is defined as an abrupt deterioration in renal functioning typified by decreased glomerular filteration rate (GFR) and tubular dysfunction. (Bellomo *et al*., 2004). According to the Acute Kidney Injury Network, AKI is defined as a decrease in kidney function that is accompanied by a rise in serum creatinine of more than 0.3 mg/dL or 50% in just 48 hours.(Mehta *et al*., 2007).AKI is more common in elderly people, those with diabetes, hypertension, vascular disease, and those who already have renal impairment. AKI accounts for about 1% of hospital admissions, of which more than 7% worsen to cause further harm. AKI's long-term effects include the accelerated onset of end-stage renal disease and chronic kidney disease. AKI is most frequently caused by sepsis and shock in intensive care units. The mortality rate from sepsis is 20–50%, and it might reach 60% when there are hemodynamic changes. (Uchino *et al*., 2005).

Causes of AKI

AKI has three general categories of causes: pre renal, intrinsic renal, and post renal. The pre renal cause, which accounts for 40–70% of renal disorders, mostly includes decreased blood supply to the kidneys. (Hou *et al*., 1983; Kaufman *et al*., 1991). In 10 to 50 percent of kidney injury cases, the intrinsic renal failure is brought on by the direct renal parenchymal damage. (Kaufman *et al*., 1991; LianoandPascual, 1996).10% of renal patients have blocked urine flow as the post-renal cause of AKI. (LianoandPascual, 1996).

Pre renal

As pre and post glomerular arteriolar resistance fluctuates over a large range of mean arterial pressure, the renal blood flow and GFR remain essentially constant. The pre-glomerular arteriolar vasodilation caused by prostaglandins and nitric oxide and the post-glomerular arteriolar vasoconstriction caused by angiotensin I are the two key factors in renal autoregulation. AKI results from any perturbation in this equilibrium. The main pre-renal causes of AKI are atherosclerotic cardiovascular disease, renal hypoperfusion brought on by volume depletion, hypotension, or renal artery stenosis.(Hilton, 2006).

Intrinsic renal

Diseases that impact the glomeruli, tubules, vasculature, or interstitium are the primary causes of intrinsic acute renal failure. In sepsis, which is accompanied by many organ damage, it is frequently complex and prevalent. (Mehta *et al*., 2004).Nephrotoxins, heavy metals, crystallisation of uric acid and oxalate, and deposition of these substances are additional significant causes of intrinsic renal failure.

Post renal

Renal stones, issues with the bladder, and ureteral obstruction are the main causes of post renal failure. (Hilton, 2006).The main causes of renal failure are listed in table 1.

Table 1. Various causes of AKI

- **Pre renal**
  - Hypotension
  - Reduced effective circulating volume
  - Renal artery stenosis
  - Drugs: angiotensin converting enzyme inhibitors, selective cyclo-oxygenase 2 inhibitors
- **Intrinsic**
  - Glomerulonephritis
  - Systemic lupus erythematous
  - Thrombotic disease
  - Ischemic acute tubular necrosis (ATN)
  - Nephrotoxic ATN

- Myeloma cast nephropathy
- Drugs: aminoglycosides, radio-contrast media, heavy metals
- Uric acid and oxalate crystal deposition

➢ **Post renal**

- Renal papillary necrosis
- Kidney stones
- Bladder tumor
- Carcinoma of cervix
- Prostatic hypertrophy
- Ureteral obstructions
- Pelvic malignancy

Renal ischemia reperfusion injury

Ischemia reperfusion injury (IRI) is a condition of decreased metabolite washout and tissue oxygen deprivation. The restoration of blood flow to the ischemic tissue is known as reperfusion. (Star, 1998).Even while tissues are receiving new nutrients and oxygen, reperfusion itself causes serious damage.(Bonventre, 1993).The renal IRI is seen in diseases such hydronephrosis, partial nephrectomy, cardiopulmonary bypass, sepsis, and renal transplantation, all of which are linked with severe morbidity and death. (Desai *et al*., 2005; Harnendez*et al*., 2008).Vasoconstriction, tubular and glomerular damage, as well as other processes, are all part of the complicated process known as renal IRI.(Bird *et al*., 1988).As a result of the production of various reactive oxygen species (ROS) by renal ischemia, including superoxide radicals (O2•), hydrogen peroxide, and hydroxyl radicals (OH•), neutrophils accumulate and lytic enzymes are released, resulting in increased oxidative stress and tissue damage. (Paller *et al*., 1984; Bonventre, 1993). The ROS are involved in intracellular and intercellular communication under normal circumstances.(Nose, 2000). In renal IRI, the O2 ion released during IRI combines with NO to create peroxynitrite (ONOO), which causes cellular damage by causing DNA strands to break and protein tyrosine residues to nitrate. The ONOO also produces OH, which is extremely harmful and worsens the cellular injury.(Beckman *et al*., 1990). Additionally, by nitrating and deactivating antioxidant enzymes like superoxide dismutase, ONOO increases the kidney damage. (MacMillan-Crow*et al*., 1996).Additionally, oxidative stress decreases the bioavailability of NO•, which causes vasoconstriction and microvascular thrombosis. (Gryglewski*et al*., 1986).This is clear from the fact that during the early stages of renal IRI, O2 increases prior to inducible nitric oxide synthase (iNOS) producing large concentrations of NO. (Araujo and Welch, 2006).Given that ONOO• scavanger ebselen has been shown to offer significant protection in models of ischemia renal failure, it has been established that ONOO• plays a key role in renal IRI. (Noiri *et al*., 2001).The production of ROS during reperfusion is linked to tissue injury. Lipid peroxidation is accelerated by the produced peroxy radicals, which take hydrogen atoms from lipids and cause a chain reaction.(Noguchi and Niki, 1998).The resulting lipid peroxides change membrane permeability and interfere with cellular processes

like membrane-bound ion pumps. Advanced glycosylation end products and extracellular signal-regulated kinase (ERK) are involved in the renal IRI-induced oxidative stress, which causes tissue damage.(Bas *et al*., 2009; Mansouri*et al*., 2011).An imbalance between endothelial NOS (eNOS) and iNOS expression in renal IRI, which increases iNOS and significantly contributes to the pathogenesis of renal IRI, occurs.(Goligorsky*et al*., 2002, 2004).Apoptosis is caused by the activation of caspase-3 and mitogen-activated protein kinase by the enzyme nicotinamide adenine dinucleotide phosphate oxidase. Additionally, profibrotic factors including nuclear factor kappa B and transforming growth factor- activated by renal IRI promote the production of monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8). (Morigi*et al*., 2002; Tang *et al*., 2003).MCP-1 is a powerful inducer of the recruitment of macrophages, which is thought to increase oxidative stress and have a role in the inflammation of the tubulointerstitial tissue.(Chow *et al*., 2007).

In the renal IRI, physiologically active mediators such bradykinin, histamine, platelet activating factor, and pro-inflammatory cytokines like IL-1,6 and tumour necrosis factor (TNF-) are produced and released.(Couser, 1998; Chatterjee *et al*., 1999; Dahaandvan Kooten, 2000;Thurman, 2007).Because dialysis significantly benefits from removing inflammatory mediators from plasma, their significance in renal inflammation has been demonstrated. (InthornandHoffmann, 1996; Montoliu, 1997).Additionally contributing to renal inflammation are vasoactive substances like NO and arachidonic acid metabolites such cysteinyl leukotrienes. (Lieberthal, 1998; Patel *et al*., 2004).Also, pro-inflammatory proteins including vascular cell adhesion molecule-1 (VCAM-1) and intracellular adhesion molecule-1 (ICAM-1) are explicitly involved in renal IRI. (Muller *et al*., 1996; Molitoris and Marrs, 1999;Burne-Taney and Rabb, 2003).Through a highly specialised transport system that uses intracellular energy, the proximal tubular cells enable the movement of ions, water, and chemicals through the cell layer. This energy is disrupted during renal IRI, which causes adenosine triphosphate (ATP) levels to drop. This dysfunction of the Na+K+ATPase pump causes cell enlargement, intracellular disturbance, and ultimately cell death.(LieberthalandLevine, 1996;PadanilamandLewington,1999; Sheridan and Bonventre, 2000).Endothelial damage causes increased production of cell adhesion molecules such ICAM-1 on damaged endothelial cells, which further obstructs capillary and post capillary venules, resulting in endothelial damage and increasing microvascular permeability. (Friedewald and Rabb, 2004).Finally, many IRI-related events that resulted in tissue injury are outlined. in figure 1.

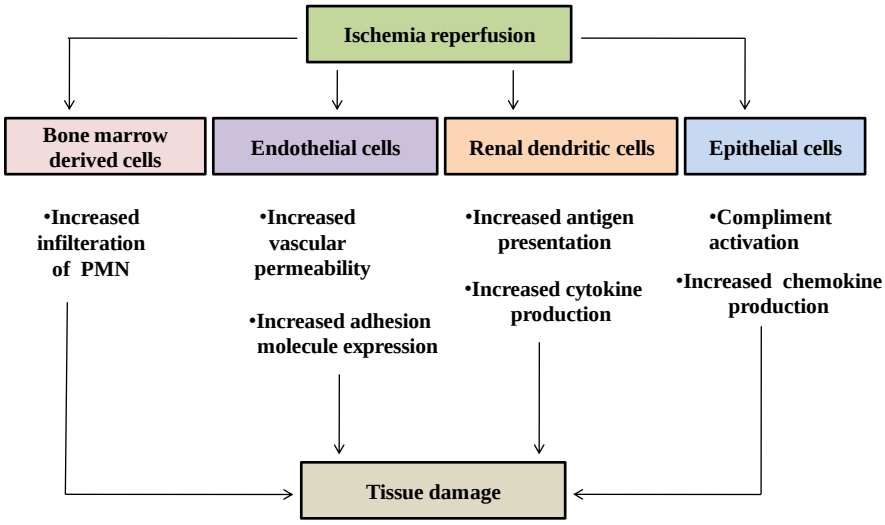

Figure 1. Mechanisms of IRI induced tissue damage.

Mechanisms of AKI

AKI is caused by a variety of vascular and tubular causes. The vascular factor comprises endothelial damage, leukocyte infiltration, and inflammatory mediators as well as renal vasoconstriction. Renal ischemia raises endothelins, which contribute to vasoconstriction and a lower GFR, while decreasing eNOS and vasodilatory prostaglandins. Inhibition of these culprits has proven protection against AKI, and overexpression of adhesion molecules has been observed in the outer medullary congestion. The tubular factors include tubuloglomerular feedback that is increased, tubular cast development, tubular blockage, and back-leak of glomerular filtrate.(Schrier*et al*., 2004).Additionally, the excretion of epithelial tubule cells and proximal tubule brush border membranes into urine (Thadhani*et al*., 1996).Reduced GFR results from the cast formation of viable and non-viable tubular cells, apoptotic, viable, and necrotic tubule epithelial cells, brush boundary membranes, and extracellular matrix, including fibronectin. (Kribben*et al*., 1999).During renal damage, it is seen that the calpase, caspase-1 (an inflammatory caspase), and caspase-3 (an executioner caspase) cysteine protease pathways are activated. Both a rise in cystolic calcium and a decline in calpastatin activate calpain. The inflammatory cytokine IL-8 is then stimulated by calpain's activation of caspase-1, and caspase-3 cleaves calpastatin to induce apoptosis. Since proximal sodium reabsorption is hampered and distal sodium chloride supply to the macula densa is ultimately increased by the intracellular rise in calcium, this further reduces GFR. (Schrier*et al*., 2004).Figure 2 provides a summary of the numerous tubular and vascular variables that contribute to AKI.

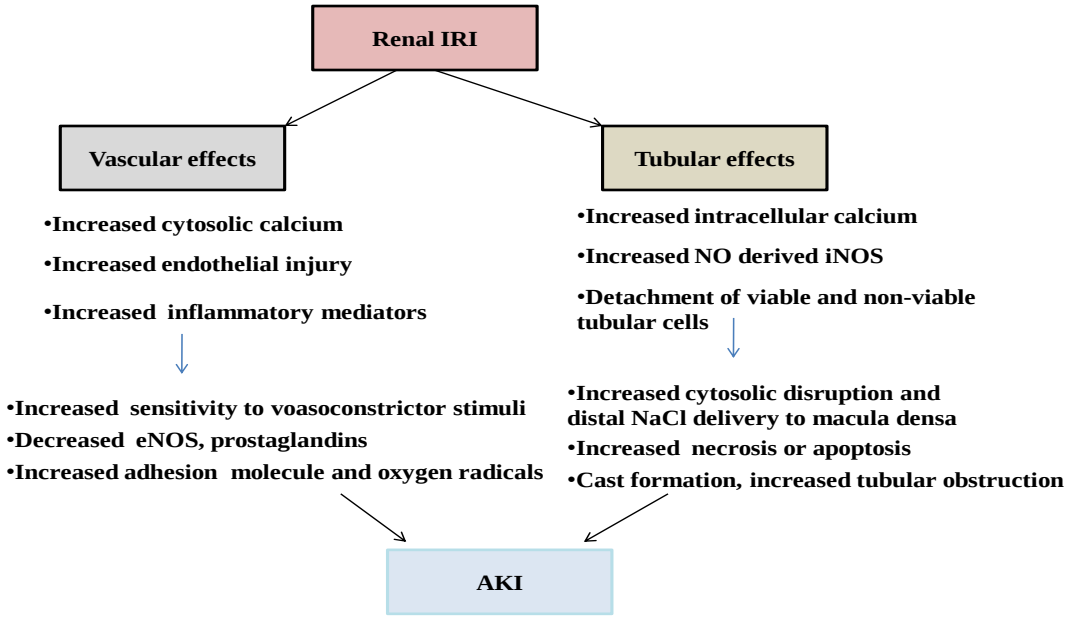

Figure 2.Mechanisms involved in IRI induced AKI.

N-Methyl-D-Aspartate Receptors (NMDAR)

The most sensitive agonist for the NMDAR class of ionotropic glutamate receptors is NMDA.(Hollmannand Heinemann, 1994).The only receptors that have an agonist site that is responsive to both glutamate and glycine are NMDARs. (Johnson and Ascher, 1987).When NMDAR is activated, an ion channel opens, allowing calcium ions to enter the cell and act as a second messenger, changing various brain functions as synaptic plasticity, excitotoxicity, and memory. Subunits of the NMDAR include NR1, NR2A, NR2B, NR2C, NR3A, and NR3B.(AvshalumovandRice, 2002; Leung*et al*., 2004; Isaac*et al*., 2007).Among these, NR2A and NR2B are discovered to differ from NR1 and NR3B due to their extended C-terminal lengths. Along with one or two NR2 or NR3 subunits, the NR1 subunit is a constant component of the NMDAR. Glycine is bound to the NR1 subunit of NMDAR, while glutamate is bound to the NR2 subunit. (Laube*et al*., 1997; Anson*et al*., 1998).Multiple indicators point to the presence of two NR1 and two NR2 subunits in the NMDAR complex. (Laube*et al*., 1998; Sobolevsky*et al*., 2009).Glycine binding modules are created when the NR3 subunit and NR1 subunit form a complex. (Chatterton*et al*., 2002).Four homologous pore-forming subunits combine to produce the tetrameric NMDAR complex. The subunits are made up of the C-terminal domain (CTD), the transmembrane domain (TMD), the agonist binding domain (ABD), and the vast extracellular N-terminal domain (NTD). The ABD permits glutamate or glycine to bind, the NTD takes part in subtype-specific assembly and regulation, and the TMD also has a re-entrant loop that filters the ion selectivity. The Y-shaped structure of the receptor is revealed by the crystal structure, with

TMD at the base, NTD at the top, and ABD in the middle.(Mayer, 2011).NMDAR activity is inhibited by the NR3A and B subunit. The body has multiple NMDAR isoforms, and the functional characteristics are determined by the differential expression of NR2 subunits and the splicing of NR1 transcripts. The membrane domain is in charge of the receptor's high calcium permeability and unitary conductance. Each subunit contains a cytoplasmic domain in addition. (Sobolevsky*et al*., 2009).

Functions of NMDAR

The NMDAR performs a variety of neurophysiological functions in the body. Strong depolarization and glutamate release are necessary for NMDAR to function synaptically, enabling the integration and decoding of incoming synaptic activity. (Seeburg*et al*., 1995).High calcium ion influx allows the receptor to translate the synaptic input pattern into a long-lasting change in synaptic strength. (Mayer *et al*., 1984; Nowak*et al*., 1984).According to the long-term potentiation (LTP) phenomenon, which Bliss and Lomo first described in 1973, an intense burst of synaptic input causes excitatory synapses to become stronger over time. (Bliss and Lomo, 1973).The NMDAR plays a crucial part in the hippocampus area's production of LTP. Along with NMDAR, which creates the action potential, voltage-gated sodium and calcium channels also play a role in the active conductance of dendrites. (Sprustone*t al*., 1995;Stuart*et al*., 1997).NMDARs are investigated for their function in ischemic brain injury in addition to their roles in cognition and memory. (Rothmanand Olney, 1986).On a chronic model of inflammation and neuropathic pain, NMDAR antagonist has anti-nociceptive effects. (Qu*et al*., 2009).In monoarthritic rats, NMDAR in the spinal cord modifies the expression of NOS isoforms.(Infante*et al*., 2007).Additionally, glutamate-mediated protection involves inducing COX-2, which reduces neuronal mortality brought on by excitotoxicity, leading to an upregulation of COX-2 expression in neurons via the glutamatergic route. (Strauss andMarini, 2002).For many neurological conditions, including stroke, hypoxia, ischemia, head trauma, Huntington's, Parkinson's, and Alzheimer's diseases, epilepsy, neuropathic pain, mood disorders, alcoholism, and schizophrenia, the NMDAR is a significant therapeutic target. (Qu*et al*., 2009; Dhanwan*et al*., 2011; Gonda, 2012; Moojen et al., 2012; Tayeb*et al*., 2012). Additionally, they have had limited clinical success due to their poor efficacy and undesirable side effects, which include catatonia, ataxia, nightmares, hallucinations, and memory problems.

Pharmacology of NMDAR

Glutamate functions as a powerful NMDA agonist at the NMDAR's particular binding site. Another such agonist that binds selectively to NMDARs is homoquinolinate, a derivative of the endogenous agonist quinolate. (Grimwood*et al*., 2002).L-aspartate and sulfur-containing amino acids like homocysteate, in addition to glutamate and quinolinate, act as agonists at NMDAR. (Hollmannand Heinemann, 1994; Kew and Kemp, 2005).Numerous substances operate at the glycine binding site and are NMDAR agonists. One of the most powerful agonists of the glycine binding site is D-serine produced from neurons.(Kartvelishvily*et al*., 2006; Panatier*et al*., 2006).One such substance, 1-aminocyclopropane carboxylic acid, functions as a high affinity full

agonist and a low affinity competitive antagonist, respectively, at the glycine and glutamate sites. (Nahum-Levy *et al*., 1999).In astrocytes, kynurenic acid is produced endogenously and is thought to regulate NMDAR in vivo. (Poeggeler*et al*., 2007).The kynurenic acid is an antagonist that competes with the NMDAR and nicotinic alpha-7-acetylcholine receptor for the glycine site. (Erhardt*etal*., 2009).

Role of NMDAR in peripheral organs including kidney

NMDAR has been found in a variety of peripheral organs, including cells from the pancreas, the urogenital tract, the microvasculature, and even lymphocytes and megakaryocytes. (Yang *et al*., 2008).Additionally involved in gastric motility, the NMDAR is expressed by both osteoblasts and osteoclasts. (Chenu*et al*., 1998; Watanabe *et al*., 2008).Additionally, NMDAR receptors are found on taste buds, and blocking them increases hunger and food intake. (Dingledine and Conn, 2000; Covasa*et al*., 2003).They are crucial to the growth of the embryo. Additionally, NMDAR is expressed in the lung tissues, and when activated, it worsens lung damage. (Shen*et al*., 2010).

In addition to other peripheral organs, the kidney's existence of NMDAR is widely known. (Ma *et al*., 2002; Tanaka *et al*., 2004; de Araujo*et al*., 2005).The glomeruli, brush boundary membrane, and outer medulla of the nephron all contain the NMDAR. In the brain, the nNOScolocalizes with NMDAR and is notably expressed in renal macula densa cells. (Deng *et al*., 2002).NMDAR agonists and antagonists are both thought to protect the kidneys from IRI-induced AKI in rats. The NMDAR agonist's protective impact is achieved by its vasodilatory effect in response to constitutive NOS, which mediates vasodilation. (Deng *et al*., 2002).In IRI-induced AKI, the NMDAR antagonist is also said to be renoprotective. (Yang *et al*., 2008).Calcium influx and overload, increased ROS production, and COX-2 overexpression are all caused by NMDAR activation.(Biber*et al*., 1981; Choi, 1992; Monyer*et al*., 1992; Conn and Pin, 1997; Tian*et al*., 2008).Additionally, NMDAR activation uses the endothelin-NO route to cause cell damage. (Leung *et al*., 2004).

Various target sites of NMDAR

The NMDAR has a variety of target sites, including sites for glutamate binding and sites for glycine and polyamine modulation. It is widely known that binding of glycine and glutamate results in calcium influx and channel opening. A non-essential amino acid is glutamate. Glutamate is the name for the carboxylate anion and the salts of glutamic acid. It is an essential component of cellular metabolism and is crucial for the body's removal of extra or waste nitrogen. It is among the most prevalent excitatory neurotransmitters in vertebrates' nervous systems. The significance of glutamate receptors in synaptic plasticity demonstrates its importance for cognitive processes in the brain, including memory and learning. At glutamatergic synapses in the hippocampus, neocortex, and other regions of the brain, the LTP is a type of plasticity. Excitotoxicity brought on by glutamate is a result of the ischemic cascade and is linked to stroke, amyotrophic lateral sclerosis, lathyrism, autism, mental retardation, and

Alzheimer's disease.(Hynd*et al*., 2004; Sapolsky, 2005).Additionally, it lessens the antinociception that morphine causes and is known to cause hyperalgesia.(Srivastava*et al*., 1995).With the arrival of calcium, glutamate or NMDA binding causes the channel to open. The glutamate binding site's competitive antagonists, 2-amino-5-phosphopentonoate (AP-5) and 2-amino-7-phosphonoheptanoic acid (AP-7) work to counteract glutamate's effects on NMDARs. (van den Bos*et al*., 1992; Abizaid*et al*., 2006).

Kynurenic Acid as a treatment drug

The first tryptophan metabolite to be identified and characterised in animals was kynurenic acid. (Ellinger, 1904; Homer, 1914).It is extensively researched in mammalian liver, kidney, gut, as well as rat brain. It is synthesised from kynurenine, which is catalysed by kynurenine aminotransferase (figure 3).(Minatogawa*et al*., 1974; Okuno*et al*., 1980).

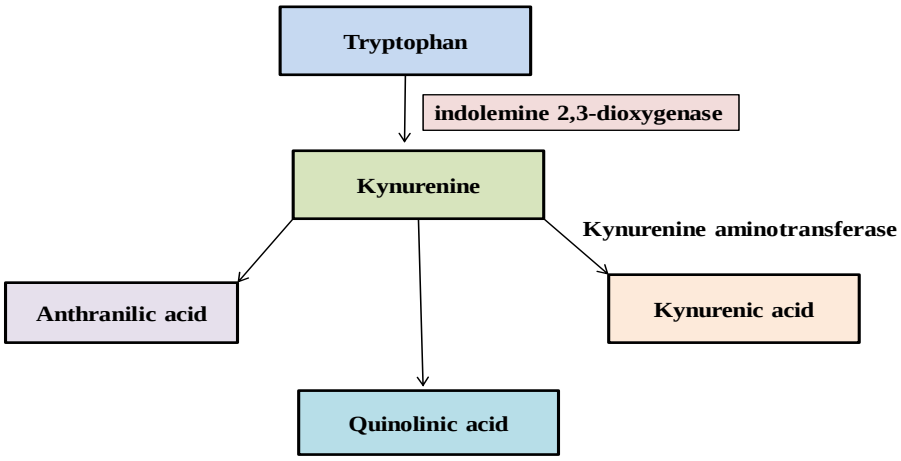

Figure 3.Synthesis of kynurenic acid.

Astrocytes produce extracellular kynurenic acid, which is then discharged into the extracellular space.(Poeggeler*et a*l., 2007).Poor blood-brain barrier translocation from peripheral to central nervous system (Swartz*et al*., 1990;Fukui*et al*., 1991).However, by irreversible transmission of kynurenine, its immediate precursor, kynurenine, can successfully penetrate the blood–brain barrier to create a dose–dependent increase in kynurenic acid content. (Robotka*et al*., 2008).Due to its ability to block both the alpha-7-nicotine receptor and the NMDAR glycine binding site, kynurenic acid functions as a neuroprotectant.(Hilmas*et al*., 2001).Additionally, it reduces the release of TNF- from mononuclear cells treated with lipopolysaccharide and functions as a chemokine by regulating leukocyte endothelial contacts in the vasculature under

physiologically relevant circumstances.(Wang *et al*., 2006).Because of the antagonistic interaction between kynurenic acid and the glutamate system in the amygdale, kynurenic acid has an effect on the epileptogenic process.(Szyndler*et al*., 2012).It has been discovered to be crucial in regulating brain plasticity and cognition.(Potter *et al*., 2010).Kynurenic acid treatment intracerebrally or systemically reduces quinolinic acid-induced seizures in mice and rats. (Lapin, 1976,1980).It lessens the rat brain's excitotoxic neuronal damage. (Foster *et al*., 1984).The kynurenic acid produced by glial cells has a high rate of turnover and greatly builds up with ageing. (Moroni*et al*., 1988).In the rat locus coeruleum, extracellular kynurenic acid concentration increases have behavioural effects such as decreased locomotor activity, mild analgesia, seizure control, and the protection of excitotoxic neuronal damage. (Carpenedo*et al*., 1994; Nemeth *et al*., 2004).In both in vitro and in vivo models of focal or generalised ischemia, kynurenic acid has been shown to lessen post-ischemic brain damage. (Cozzi*et al*., 1999; Carpenedo*et al*., 2002).Additionally, it lessens neurodegeneration in various transgenic models of the diseases Huntington and Alzeimer. (Zwilling*etal*., 2011).The kynurenic acid reduces the number of fatalities in the septic shock model and possesses direct antioxidant properties. (Lugo-huitron*et al*., 2011).

Future Prospect of Kynurenic Acid

It is seen that increased urinary glycolysis intermediates and alters purine and tryptophan catabolism in mice with histopathological AKI. These pathways are potential diagnostic and therapeutic targets for postoperative AKI in this high-risk cohort(Davidson, J.A et al., 2022). Modest to severe AKI following newborn heart surgery is related to changes in the blood metabolome, particularly major changes in the purine, methionine, and kynurenine/nicotinamide metabolism. Hence there can be scope for metabolic investigations in the evaluation of lower-stage injury since some infants with moderate AKI showed comparable metabolic changes(Davidson, J.A et al., 2021).Animal research and human observational studies of AKI and CKD have both revealed dysregulatedKynurenine pathway (KP) metabolites. The magnitude and direction of modifications in the KP depend on the aetiology of the injury in AKI. From the onset of the disease to its advanced stages, KP metabolites are altered in CKD, including uremia and its related vascular effects. The activation of the KP and redirection to certain sub-branches are currently being studied for the treatment of various illnesses, especially in light of the immunomodulatory capabilities of some KP metabolites. Further knowledge of the KP may aid in the development of biomarkers and specialised treatments for specific kidney diseases (Wee, H.N et al., 2021)

Conclusion

The KYN pathway is a promising target in kidney disease prevention and treatment. Although many questions remain to be answered, future studies should explicitly explain the role of the KYN pathway in the pathogenesis of renal disorders, especially AKI. Searching for novel agents

modulating KYN pathway activity may contribute to the introduction of new drugs for kidney diseases and signifcantly improve patient prognosis

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