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Review

Kynurenic acid and kynurenine aminotransferases in retinal aging and neurodegeneration

Robert Rejdak[1,2,3], Anselm Junemann[4], Paweł Grieb[3], Sebastian Thaler[1], Frank Schuettauf[1], Tomasz Chorągiewicz[2], Tomasz Żarnowski[2], Waldemar A. Turski[5,6], Eberhart Zrenner[1]

[1]Centre for Ophthalmology, University of Tübingen, Roentgenweg 11, D-72076 Tübingen, Germany

[2]Department of Ophthalmology, Medical University, Chmielna 1, PL 20-079 Lublin, Poland

[3]Medical Research Centre of the Polish Academy of Science, Pawińskiego 5, PL 02-106 Warszawa, Poland

[4]Department of Ophthalmology, Friedrich-Alexander University Erlangen-Nurnberg, Schwabachanlage 6, 91054 Erlangen, Germany

[5]Department of Experimental and Clinical Pharmacology, Medical University, Jaczewskiego 8, PL 20-090 Lublin, Poland

[6]Department of Toxicology, Institute of Agricultural Medicine, Jaczewskiego 2, PL 20-090 Lublin, Poland

Correspondence: Robert Rejdak, e-mail: rrejdak@yahoo.com

Abstract:
The kynurenine aminotransferases (KATs) KAT I and KAT II are pivotal to the synthesis of kynurenic acid (KYNA), the only known endogenous glutamate receptor antagonist and neuroprotectant. KAT I and II have been found in avian, rodent, and human retina. Expression of KAT I in Müller cell endfeet and KAT II in retinal ganglion cells has been documented. Developmental changes in KAT expression and KYNA concentration in the avian and rodent retina have also been found. Studies of retinal neurodegeneration have shown alterations in KYNA synthesis in the retina in response to retinal ganglion cell loss. In DBA/2J mice, a model of ocular hypertension, an age-dependent decrease of retinal KYNA and KATs was found. In the corpora amylacea in the human retina intensive KAT I and II immunoreactivity was demonstrated. In summary, these findings point to the potential involvement of KYNA in the mechanisms of retinal aging and neurodegeneration.

Key words:
kynurenic acid, kynurenine aminotransferase, neurodegeneration

Abbreviations: AMPA – 2-amino-3-(3-hydroxy-5-methyl-1,2-oxazol-4-yl)propanoic acid, CAm – corpora amylacea, CNS – central nervous system, EAA – excitatory amino acid, KAT – kynurenine aminotransferase, KYN – kynurenine, KYNA – kynurenic acid, NMDA – N-methyl-D-aspartate, ODN – oligonucleotide, PAS – periodic acid-Schiff, RGC – retinal ganglion cell, *t*-ACPD – *trans*-1-aminocyclopentane-1,3-dicarboxylic acid

The kynurenine pathway

Kynurenines, the metabolites of the kynurenine (KYN) pathway, are believed to play an important role in the physiology and pathology of the central

nervous system (CNS) [52, 79]. It has been shown that kynurenic acid (KYNA), a nonselective antagonist of glutamate receptors, has a high affinity for the glycine site of the N-methyl-D-aspartate (NMDA) receptor [6, 38]. It has been also documented that KYNA is a potent, noncompetitive antagonist of the α7 nicotinic acetylcholine receptor [34]. In addition, KYNA is a ligand for the orphan G protein-coupled receptor GPR35, which is predominantly located in immune cells and the gastrointestinal tract [89].

Endogenous KYNA is produced by the irreversible transamination of KYN by kynurenine aminotransferase I (KAT I) [4, 31] and kynurenine aminotransferase II (KAT II) [27]. The presence of KAT I has been demonstrated immunohistochemically in the rat brain, the medulla and the spinal cord [19, 37, 39], whereas KAT II was first identified by northern blot mRNA analysis in the human brain [58]. Immunohistochemical experiments using KAT I and KAT II antibodies [57, 58] have shown that both enzymes are present in the inner retina of the adult rat [67]. Recently, the existence of a third [26, 32, 97] and fourth enzyme [33] displaying KAT activity was reported. The biochemical properties of all four KATs were recently reviewed by Han and coworkers [30].

KYNA in the pathology of the CNS

Abnormal concentrations of KYNA in certain brain areas and/or cerebrospinal fluid have been recorded in subjects with several neurological and mental disorders such as Alzheimer's, Huntington's and Parkinson's diseases, multiple sclerosis, epilepsy, brain ischemia, depression and schizophrenia, and various pathophysiological consequences of disturbed KYNA metabolism have been hypothesized. For example, a lowered KYNA level in Parkinson's disease could enhance the symptoms of the disease [55], whereas an increased KYNA level in Alzheimer's disease could cause a blockade of NMDA receptors and contribute to the impairment of memory, learning and cognition [3]. The role of kynurenines in neurological and psychiatric disorders was the topic of recently published reviews [21, 49, 54, 61, 90, 94, 98].

Additionally, *in vivo* experiments have shown that the reduction of KYNA synthesis in the rat brain by nonspecific inhibitors can lead to neurotoxicity [86]. It was suggested that the preferential loss of layer III of the entorhinal cortex after the local injection of a nonspecific inhibitor of KYNA synthesis may be a significant factor in the pathophysiology of temporal lobe epilepsy [18].

The retina is a part of CNS, and glutamate appears to act as a major neurotransmitter in most types of retinal neurons [51]. Considering this, it seemed prudent to study the possible role of KYNA in retinal physiology and pathophysiology.

KYNA content in retinal ontogeny

Immunohistochemical experiments using KAT I and KAT II antibodies [57, 58] have shown that both enzymes are present in the inner retina of the adult rat [65]. Importantly, KYNA itself was identified and quantified in the retinas of adult rats [67]. The retinal KYNA concentration was 99.9 pmol/g wet weight and was therefore within the same range as in the rabbit vitreous body [100, 101]; it was also present in ranges similar to those observed in the rat, rabbit and human brain [53, 83].

Moreover, it was found that KYNA is already present in the rat and chicken retina at early stages of ontogeny. The experiments demonstrated changes in the KYNA content in vascularized rodent and avascular avian retinas during development. In rats, KYNA concentration peaked at birth and was 7 times higher than the concentration at E20, i.e., approximately 3 days before birth. During the first 2 weeks of life, KYNA again decreased markedly. In chickens, retinal KYNA concentrations measured at E16 were 30% higher than at E12 and twice as high as at P0. The KYNA content at P7 and P21 remained largely the same as at P0 [65] (Fig. 1). These data appear to agree with those reported by Beal and coworkers. They found that KYNA concentrations in rat fetal whole brain undergo a significant increase of approximately 4–5 fold prenatally, declined rapidly at 1 day after birth and reached adult concentrations at 7 days after birth [5].

In the immature brain, NMDA receptors are crucial for synapse development [73] and for modulation of neuronal migration [41]. Therefore, it has been suggested that a high level of the endogenous glutamate antagonist KYNA in the brain may provide antiexcitotoxic protection during birth, whereas the swift de-

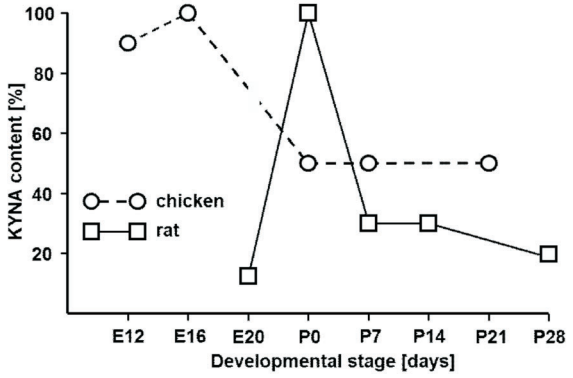

Fig. 1. Scheme depicting KYNA concentration at different developmental stages in the chicken and rat retina. Data are presented as the percentage of the highest recorded KYNA concentration (100%). The data in this figure are based on data published in [65]

cline in KYNA immediately after birth would assure minimal interference with developmentally essential postnatal glutamate receptor functions [13]. It has also been suggested that changes in KYNA availability may modulate the function of excitatory synapses [9]. Because glutamate receptors are already present at birth and show differences in spatial distribution and temporal expression in both rat [24, 25] and chicken retinas [78], it can be hypothesized that marked changes of KYNA metabolism in the pre- and postnatal period may modulate glutamate-mediated synaptogenesis and neurotransmission in the retina.

KAT in retinal ontogeny

In 2003, it was shown that KAT I is present in the avascular chicken retina during ontogeny and is localized in Müller cell endfeet. KAT I enzymatic activity measured at E16 was 58% higher than at E12 and 48% higher than at P0. KAT I activity measured at P7 was more or less at the same level as at P0 [68]. Given that it has been proven that KAT I activity contributes to the formation of KYNA [27], these data correspond with a previous finding that KYNA concentrations in the chicken retina were significantly higher at E16 than at E12 and rapidly decreased to adult levels by postnatal day 7. Because KAT I enzymatic activity is high in late embryonic stages, it was suggested that it can play a neuromodulatory role in the chicken retina during the late phase of embryogenesis [68].

Next, it has been shown that both KAT I and II are present in the rat retina during differentiation and that these 2 enzymes display different patterns of spatial distribution and temporal expression. The pronounced expression of both enzymes in early developmental stages generally paralleled previous results showing that KYNA, the product of both enzymes, is present in both vascularized rat and avascular chicken retinas during development [65]. A high level of expression of KAT I and II in the retina occurs almost exclusively within the first 2 postnatal weeks and may be related to the process of synapse formation in the retina. At the time of eye opening, approximately P15–P17, the expression patterns of KAT I and II are already very similar to those observed in adult retinas [64].

It has been suggested that changes in KYNA may modulate the function of excitatory synapses [9]. Because glutamate receptors, which are preferential targets of KYNA, are already present at birth and show differences in spatial distribution and temporal expression in the rat retina [24, 25], developmental changes in KAT levels and KYNA content may play a role in glutamate-mediated neurotransmission during differentiation. It was documented that excitatory amino acid (EAA) antagonists can trigger apoptosis in the developing mammalian brain [59] and that KAT I plays a role in the regulation of programmed cell death [15]. Considering these findings, it is conceivable that KAT and KYNA may control apoptosis in the retina during early development.

The decrease in the cellular expression of both KATs found in our study during postnatal life may also be explained by a significant increase in the total rat retinal content of glutamate during the postnatal period, synchronous with the generation and maturation of glutamatergic cells [28]. Data exist showing that glutamate diminishes KYNA synthesis in brain and retinal slices, and a regulatory influence on endogenous KYNA concentration has been suggested [85, 99].

Regulation of KYNA synthesis in retinal slices

It has been demonstrated that retinal slices incubated in the presence of the KYNA precursor KYN synthesize KYNA in a concentration- and time-dependent

manner [99]. Similar results were obtained in previous studies with brain slices [83, 85, 87]. The presence of KYNA in the incubation medium suggests that it is freely liberated from cells to the external milieu. The inhibitory effect of glutamate, aspartate and NMDA on KYNA synthesis in bovine retinal slices has also been clearly demonstrated. The most effective agent was glutamate; aspartate was 10 times less active, and NMDA exerted an inhibitory effect only at high mM concentrations [99]. Kainic acid and 2-amino-3-(3-hydroxy-5-methyl-1,2-oxazol-4-yl)propanoic acid (AMPA) have turned out to be ineffective as inhibitors in the retina, spinal cord and cortex [85, 87]. NMDA has been shown to reduce KYNA synthesis in the retina but was ineffective in the spinal cord and cortex [85, 87]. However, NMDA was tested only up to a concentration of 0.5 mM in the brain and spinal cord. Although *trans*-1-aminocyclopentane-1,3-dicarboxylic acid (*t*-ACPD) did not affect KYNA synthesis in the retina and spinal cord, it was effective in the cortex at a comparable concentration [85, 87, 99] (Tab. 1).

Furthermore, differences in the inhibitory effectiveness of glutamate agonists on KYNA production in the brain, spinal cord and the retina have been observed. Glutamate was found to inhibit KYNA production in the retina, the astrocytes [16] and C6 glioma cells [40]. Aspartate also reduces the formation of KYNA in brain slices [87]. However, aspartate in brain slices was only slightly more effective than glutamate [85, 87]. In contrast, glutamate was 10 times more active in the retina than aspartate. Such a high susceptibility of retinal KYNA production to the inhibitory action of glutamate may indicate the presence of distinct regulatory mechanisms.

Tab. 1. Effect of excitatory amino acids on KYNA synthesis in the retina, brain and spinal cord

	Retina	Brain	Spinal cord	References
Glutamate	↓	↓	↓	85, 87, 99
Aspartate	↓	↓	↓	87, 99
NMDA	↓	=	=	85, 87, 99
AMPA	=	=	=	85, 87, 99
Kainate	=	=	=	85, 87, 99
t-ACPD	=	↓	=	85, 87, 99

↓ – inhibition; = – no effect

KYNA synthesis in response to retinal ganglion cell loss

The loss of the retinal ganglion cell (RGC) is a hallmark of many ophthalmic diseases, including glaucoma, retinal ischemia and optic neuropathy. Recent studies have indicated that glutamate affects the RGC predominantly through NMDA receptors [80]. Moreover, it has been suggested that kainate and AMPA receptor subtypes may contribute to RGC loss [60, 75]. Thus, because dysfunction of KYNA synthesis in the brain may be an important factor in neuronal degeneration [22, 77], it has been hypothesized that KYNA is relevant to the mechanisms of RGC loss. Pursuing this line of thought, it has been reported that the number of RGCs decreased significantly 2 days after intraocular NMDA injections. At the same time, retinal KYNA markedly increased to 124% of control values [66]. It can be speculated that an increase of KYNA during the initial phases of excitotoxic injury provides enhanced neuroprotection. This may also be a factor in endogenous anti-excitotoxic defense mechanisms in the CNS [88]. Such a lesion-induced increase in retinal KYNA might result from an enhanced influx of blood-borne KYN after compromise of the blood-retina barrier [29] or from increased cerebral biosynthesis of KYN at the lesion site [70]. Other factors, such as compounds released from damaged and dying neurons, which are known to play an active role during the initial period after excitotoxic insult [45], activated microglia and/or infiltrating macrophages might also play a role [50]. Interestingly, Ceresoli-Borroni and colleagues reported a dramatic increase of striatal KYNA content 2 days after intrastriatal quinolinate injections [12]. A similar effect was also observed after intrastriatal ibotenate injection [11].

It has been found that the retinas of NMDA-treated eyes displayed a marked decrease in the number of RGCs 7 and 14 days after injection, compared to both the control and the number observed 2 days after the NMDA injection. Correspondingly, KYNA concentrations decreased to 70% of control values at days 7 and 14 [66]. Given that immunohistochemical studies have shown preferential localization of KAT II on RGC, it appears that loss of RGCs might account for the decrease in retinal KYNA content [66].

In contrast, KYNA content increases in the brain 7 days after the intrastriatal or intrahippocampal ap-

plication of NMDA agonist quinolinate. This has been attributed to massive gliosis following neuronal cell death induced by neurotoxin [12, 92]. In the brain, KAT has been found mainly in glial cells, and it appears that they are responsible for most KYNA formation there [69, 81]. In the retina, neuronal damage due to neurotoxin administration induces reactive proliferation of Müller cells [20]. It can be speculated, however, that these cells produce only limited amounts of KYNA, given that they contain KAT I almost exclusively [67], which has optimum activity at the non-physiological pH of 9.5. This may explain the decrease in KYNA concentration in retinas lesioned with NMDA.

It has been suggested that KYNA deficiency is causally related to the pathology of excitotoxic brain diseases [77]. *In vivo* studies have shown that reduced KYNA synthesis in the rat brain caused by nonspecific inhibitors can lead to neurotoxicity [35, 86]. On the other hand, it has been found that an increased concentration of brain KYNA may be neuroprotective. In experimental brain ischemia, neuroprotection was observed following systemic administration of KYNA [1, 71] or its precursor KYN [56]. Similarly, systemic KYN administration offers some protection against NMDA-induced degeneration of RGCs and also reduces visual discrimination deficits in adult rats [95].

The neuroprotective properties of KYNA are usually explained by its ability to block the EAA receptor functions, but this is still a subject of debate. Under physiological conditions, KYNA concentrations are far lower than those required to antagonize the EAA receptor functions found in *in vitro* electrophysiological studies. However, several studies confirmed that the increase of endogenous KYNA following the administration of its bioprecursor KYN results in biochemical and/or behavioral changes, which can be functionally linked to the interaction of KYNA with glutamate receptors or α7 nicotinic receptors [42, 72, 74, 93].

KYNA in a mouse model of glaucoma

Genetically dependent hypertension glaucoma in the DBA/2J mouse strain was described by John et al. [36]. These mice develop progressive ocular abnormalities, with pigment dispersion, iris transillumination, iris atrophy and anterior synechia. Nine months after birth, intraocular pressure was elevated in most of the DBA/2J mice, and glaucomatous changes, including a progressive loss of 40% of RGCs, optic nerve atrophy and optic nerve cupping, were evident.

John et al. noted that the DBA/2J mice may represent a useful model for studying the mechanisms of RGC death and for evaluating strategies of neuroprotection against glaucoma [36]. It has also been noted that this RGC loss model is responsive to pharmacological treatment, e.g., RGC loss is blocked by the glutamate antagonist memantine when administered intraperitoneally [76].

It has been demonstrated that, in the retinas of DBA/2J mice, KYNA concentrations change during aging parallel to time-dependent RGC loss [62]. Retinal KYNA concentrations found in both C57BL/6 and DBA/2J mice in the early stages (3 months) were in the same range as those observed in rat and chicken retinas [65]. KAT I and KAT II were also found in the inner retina in both strains of mice. In the retinas of 3-month-old DBA/2J mice, KYNA concentrations were similar to those observed in the control animals. KYNA was markedly decreased in the retinas of 6-month-old animals and amounted to only 60% of control values by the 11th month of life. In contrast, the level of KYNA in C57BL/6 mice did not change in 3, 6, or 11-month-old animals. It is now assumed that KYNA concentrations reflect KYNA synthesis, given that KYNA storage in the brain has not been documented [83]. Comparing our data with those of other authors, we found that KYNA decreased by 24% between 3 and 6 months of age and by 46% by the age of 11 months. Schuettauf and colleagues found that RGC numbers decreased 16% between the ages of 3 and 6 months and 56% by the age of 9 months [76]. John and coworkers found a decreased thickness of the nerve fiber layer in older DBA/2J mice; however, the authors omitted measurements of nerve fiber layer thickness, and their qualitative assessments lack a clear age correlation [36]. It has already been suggested that KYNA deficiency is causally related to the pathology of excitotoxic brain diseases [77]. Therefore, it seems that the drop in retinal KYNA synthesis may be a contributing factor in the mechanisms of RGC loss, independent of increased intraocular pressure.

In agreement with biochemical findings, immunohistochemical experiments also demonstrated that the

cellular expression of both KAT I and KAT II in the inner retina decreases more during the aging of DBA/2J mice than in control animals [62]. Because immunohistochemical studies have shown a preferential localization of KAT I and KAT II on Müller cell endfeet and RGCs, respectively [64, 67], it can be postulated that KAT malfunction leads to KYNA loss, which in turn is partially responsible for the RGC loss.

Glutamate has been shown to diminish KYNA synthesis, and it has therefore been suggested that glutamate has a regulatory influence on endogenous KYNA contents [87]. Since that time, reports of increased glutamate in the vitreous in spontaneous disorders similar to glaucoma in dogs [8], quail [17] and in the aqueous humor of rats after optic nerve crush [96] have been published. It is conceivable that the decrease of KYNA synthesis observed in the retinas of DBA/2J mice during aging [62] may be the result of increased glutamatergic transmission.

The cellular expression of glutamate transporters has been studied by various researchers to gain new insights into a possible excitotoxic mechanism of neurodegeneration in the retinas of DBA/2J mice. Given that high levels of glutamate can be toxic to RGC [46, 48], effective buffering of extracellular glutamate by retinal glutamate transporters is essential for protecting RGCs.

In conclusion, a decrease of KAT I and KAT II cellular expression and decrease of KYNA content have been found in the retinas of DBA/2J mice during aging. Thus, our results suggest that decreased cellular expression of KYNA-synthesizing enzymes and KYNA deficiency may have relevance to the mechanisms of retinal degenerative diseases such as glaucoma and optic neuropathy.

Selective retrograde transfection of RGC with oligonucleotides against KAT II

Recently, it has been shown that RGCs can be transfected in a retrograde manner by means of oligonucleotide (ODN) injections into the superior colliculus in rats [82]. It was found that this method, like intravitreal ODN administration, induces downregulation of KAT II expression in RGCs [82]. We observed downregulation of KAT II expression lasting for up to 7 days after both routes of ODN administration.

The study also demonstrated that the retinal content of KYNA decreased in a dose-dependent manner, and a concentration of 100 μM was found to be the most effective. ODNs of this concentration induced a significant decrease of retinal KYNA content [82]. KYNA concentrations measured in the retinas of eyes injected with scrambled ODN as a control were similar to those in untreated rat eyes [64]. Retrograde transfer of specific ODNs induced downregulation of KAT II expression in RGCs, providing a new method of RGC transfection. This approach may facilitate the investigation of retinal gene expression, architecture and circuitry.

KATs in corpora amylacea in the human retina and optic nerve

Corpora amylacea (CAm) are homogenous or laminated oval structures frequently found in the brain and peripheral nerves. In the eye, CAm are observed not only in the optic nerve head, the nerve fiber layer, and the ganglion cell layer, but also in the inner plexiform and inner nuclear layers [43, 91]. Ultrastructurally, CAm consist of a filamentous tangle within an axonal swelling [2, 91]. It has been suggested that CAm formation results from impaired axonal flow [47].

CAm are the only structures associated with degeneration in the retina and optic nerve that are also visible by light microscopy. Nevertheless, their nature remains mysterious. To date, only limited data have been gathered concerning the mechanisms of their formation.

In CNS, CAm are regarded as a hallmark of aging and are thought to be associated with neurodegeneration [14]. However, little is known about their role in normal and pathological circumstances. Studies on the structure of the CAm have shown that their rich acid polysaccharide content makes them best demonstrable by periodic acid-Schiff (PAS) staining. CAm contain, in addition to glucose polymers, aging, stress, and proinflammatory proteins [7]. However, previous studies have emphasized their surprising lack of immunoreactivity [44].

Rejdak et al. were the first to demonstrate immunoreactivity on the part of KAT I and KAT II in CAm in

the human retina and optic nerve. CAm expressing both enzymes were observed in all cases in the retina and in the prelaminary, laminary and retrolaminary regions of the optic nerve [63]. Various staining patterns of KAT I were found to depend on the location of CAm. In general, there was more pronounced staining in the retrolaminar part of the optic nerve. The immunoreactivity of KAT II was less pronounced than that of KAT I, with no association to the staining variety or localization of CAm. All CAm-expressing KATs were found to be PAS-positive, thus demonstrating that KAT-stained structures are CAm [63]. These findings in PAS-stained sections agree with previous results reported by Kubota and colleagues [43].

It has been well documented that CAm have no pathognostic significance, although they accumulate under certain conditions and in certain pathological processes [44]. Numerous contributing factors have been suggested for the formation of CAm, such as (1) the components of degraded cells and (2) metabolites originating in cerebrospinal fluid, blood, the mesenchyma of the pia mater and the adventitia of the vessel wall [44]. Importantly, hypoxic/ischemic injury has been shown to potentiate the enigmatic biological pathway leading to the formation of CAm during aging. Botez and Rami [7] have speculated that damaged mitochondria and proteins induced *de novo* or overproduced during cellular insults may be sequestered by CAm. Assuming that the formation of CAm represents an arrangement for the management of products escaping normal cell catabolism [10], greatly increased numbers of CAm in the optic nerve and retina may reflect increased metabolic activity caused by repetitive cellular stress [7]; the presence of KAT I and II in CAm might also suggest a role of those enzymes in mechanism(s) of endogenous cellular protection against insult.

Interestingly, data from some brain studies have suggested that CAm possess, to some extent, a relatively high affinity for accumulating "protective" substances (such as Bcl2, AP1, heat shock proteins, etc.), which may rescue nerve cells from the devastating effects of ischemia or aging [7, 14, 23]. So far, immunohistochemical investigations have demonstrated anti-tau-2 immunoreactivity in CAm in the retina, optic nerve and brain tissue [47].

The presence of KATs in CAm in the human retina and optic nerve suggests that KYNA synthesis may be involved in the mechanisms of retinal aging and neurodegeneration, which lead to CAm formation. Future studies will be required to follow this up and provide a better understanding of the involvement of tryptophan metabolism in the development of degenerative retinal products; this might also result in a better understanding of the biological role and significance of CAm.

Summary and Conclusion

The kynurenine aminotransferases (KATs) were found in the avian, rodent, and human retinas, specifically in Müller cell endfeet (KAT I) and in retinal ganglion cells (KAT II). KATs are critical enzymes in KYNA synthesis. Changes of KAT activity and KYNA concentrations are dependent on developmental stage of rodent and avian retina. Production of KYNA, the only known endogenous glutamate receptor antagonist, in the retina is altered in response to retinal ganglion cell loss. In DBA/2J mice, a model of ocular hypertension with progressive loss of retinal ganglion cells, the activity of KATs and the concentration of KYNA decrease in an age-dependent manner. In the human retina, immunoreactivity of KATs was also found in CAm, the only known structures associated with degeneration in the retina. In summary, these findings demonstrate the potential involvement of KYNA in the mechanisms of retinal aging and neurodegeneration.

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