Review

EFFECT OF α- AMINOADIC ACID ON MÜLLER CELLS IN RETINA

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Summary

Research data on α-aminoadipic acid (α-AAA), a structural analogue of glutamate, which is toxic to glial cells, shows that: it has three isomers (L, D and DL); L- α-AAA is the most toxic on glial cells; the toxic effect depends on the dosage and postnatal moment of exposure; in retina, α-AAA shows transitional primary and secondary effects; there is no significant difference of the action of α-AAA on adult and newborn rat retina. The toxic effects of α-AAA can be used in a research on the Müller cells' function and to understand the mechanism of some retinal diseases, such as retinitis pigmentosa and diabetic maculopathy. The model of the α-AAA action on Müller cells can be successfully applied in research of the retinal transplantation.

Key words: retina, Müller cells, a-aminoadipic acid, postnatal development

Introduction

Alpha-aminoadipic acid (α-AAA) is a structural analogue of glutamate, which is toxic to glial cells (Fig. 1).

Alpha-AAA derives as a product of degradation of lysine [1, 2]. The deamination of lysine residues, forming allysine, may originate from six pathways [3]. The α-AAA amounts to 1.6 percent of the dry weight of the human organism [1 ,2]. High levels of α-AAA in serum and/or urine have been observed in many cases with neurological and other disorders. Some authors report cases with α-AAA excess in urine and plasma and cerebrospinal fluid in children, who died in the first three years of their lives [4-6]. The highest concentrations of α-AAA and deficiency of alpha-amino-adipate aminotransferase (kynurenine aminotransferase - KAT II) are found in the liver and kidney of young individuals post mortem [7, 8]. KAT II is present in the astrocyte-like cells of mammalian brains and takes part in the neutralization of α-AAA in the mammalian brain [2]. Alpha-AAA significantly increases in aging human skin, in diabetes in the absence of renal failure, and septicemia [3, 9]. The increased amount of-AAA in cerebrospinal fluid could be used as a mark to confirm the diagnosis of pyridoxine-dependent epilepsy [6, 10]. The mechanism of α-

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AAA formation in each of these conditions needs to be elucidated.

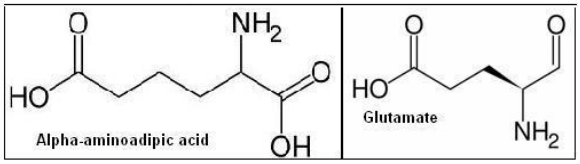

Figure 1. Chemical structure of alpha-aminoadipic acid (α-AAA) showing its similarity to glutamate (according to West EL et al., 2008)

Isomers of α-AAA and their different effects

D-α-AAA and L-α-AAA, the structural isomers of α-AAA, and a combination of these –DL-α-AAA have different effects on glial cells.

D-α-AAA selectively reduces the "off" component of the Müller cell light response and the d-wave of the electroretinogram, and does not cause appreciable histological damage to the Müller cells [11, 12]. The D-isomer appears to be toxic only for mitotic cells [13].

By contrast, the injection of L-α-AAA selectively abolishes the "on" component of the intracellularly recorded Müller cell light response, abolishes the b-wave of the electroretinogram, and causes severe glial swelling, reduces eye growth in non-occluded eyes of newly-hatched chicks. The electrical effect of L- α-AAA suggests that the initial loss of the b-wave is due to the action of the amino acid at a synaptic site via a mechanism distinct from the one causing subsequent histological damage to glial cells [11, 12]. The L-isomer of α-AAA competitively inhibits the transport of D-[3H]-aspartate, glutamine synthetase, and gamma-glutamylcysteine synthetase [14].

The gliotoxin DL-α-AAA inhibits cystine uptake through cystine/glutamate antiporter (system Xc^-) on the glial cells and elicits a reduction of cellular levels of glutathione. The antiporter usually transports glutamate outside and cystine inside, thereby maintaining cellular concentrations of glutathione. High concentrations of glutamate inhibit cystine uptake and lead to depletion of cellular levels of glutathione. The cystine uptake with carp retina is mainly Na^+-independent and Cl^--dependent as already described as a characteristic ion dependency of the Xc^-antiporter. DL-α-AAA induces a loss of electroretinographic b-wave 20–30 h after the treatment [15]. DL-α-AAA reduces responsiveness to glutamine synthetase (a differentiation marker of embryonic neural retina) induction by 60–90% due to preferential damage to Müller cells. The selective toxicity of DL-α-AAA for Müller cells is greatly reduced by carbonic anhydrase activity, another enzyme localized predominantly in Müller cells, but has not been reported to affect γ-aminobutyric acid transaminase and choline acetyl transferase in organ cultures of retina tissue from chick embryos [16].

D-α-AAA and DL-α-AAA, respectively, induce mild and extreme gliotoxic but not neurotoxic changes. The non-neurotoxicity of DL-α-AAA implies effective antagonism by D-α-AAA of the neurotoxicity of L-α-AAA. D-α-AAA is recognized as an effective antagonist of amino acid excitants and is thought to block specifically the excitatory receptor [17].

Effects of α-AAA in CNS

Astrocytes in the corpus striatum [18] and amygdala of adult rats [19], in postnatal mouse cerebellum [20, 21], in the arcuate hypothalamic nucleus of infant mice [22] , in cortical astrocytes [23], and in rat hippocampus [24] show clear structural degeneration (karyopyknosis in 50%), profound loss of glial fibrillary acidic protein and S100β-positive [19], inhibition of protein synthesis and associated lack of induction of HSP70 and HO-1 (heat shock or stress proteins) [23] 1 to 3 days after the injection of L-α-AAA or DL-α-AAA.

Rats develop severe limbic seizures between 1 and 6 h after L-α-AAA injection, characterized by generalized convulsions and significant decrease of kynurenine aminotransferase (KAT) activity in hippocampal brain tissue [25]. The hyperactive behaviour observed in KAT $II^{-/-}$ mice raised an interesting question as to whether the *α*-AAA level is increased in the knockout mouse brain and consequently contributes to the pathological mechanisms of the abnormal behavior [2].

As an endotoxin, α-AAA influences various elements of glutamatergic neurotransmission and kills primary astrocytes in the brain. Many studies have shown that a high concentration of α-AAA inhibits glutamate transport, blocks glutamine synthetase, prevents the uptake of glutamate into synaptic vesicles and functions as an *N*-methyl-d-aspartate (NMDA) receptor agonist. These effects can contribute to an increased excitatory tone because synaptic glutamate concentrations are elevated [19, 26].

Effects of α-AAA in rat retina

After α-AAA application (subcutaneous, subretinal or intravitreal) marked swelling Müller cells, astrocytes and oligodendrocytes but no changes in the microglia are observed [19, 26, 27,]. The downstream effects of α-AAA occur in a time-specific manner, resulting first in early gliotoxicity, followed by an apparent secondary neurotoxicity on photoreceptors, horizontal and ganglion cells [28-30].

Suggested modes of action include: inhibition of glutamate uptake, resulting in possible neuroexcitotoxicity; inhibition of cystine uptake through cystine/glutamate antiporter, leading to reduced levels of intracellular antioxidant glutathione and eventually causing cellular damage and oxidative stress [15, 25, 26, 31-34]. There are two possible reasons for the toxicity: firstly, the increasing concentration of the toxin would inhibit neuronal transport of glutamate, and secondly, the prolonged inhibition of either glial or neuronal transport would lead to elevated glutamate concentrations in the synaptic cleft, activation of post-synaptic receptors and a process of disruption of glutamatergic function [34].

In investigations, the disruption of Müller cell function has been evidenced by decreased glutamine synthetase activity and cellular retinaldehyde-binding protein (CRALBP) immunoreactivity, increased glial fibrillary acidic protein (GFAP) [31, 35-37] and loss of vimentin and the b-wave on the electroretinogram [29]. The delayed expression of *β*APP and B-cell lymphoma/leukemia-2 (Bcl-2) in developing Müller glial cells until 3–5 weeks post-injection is found. Normally, *β*APP and Bcl-2 express in the proximal part of the radial processes of Müller glial cells from the second postnatal week on. These changes may result in a rapid increase in the intracellular level of free Ca^{2+} and severe disruption of the process of turnover of neurotransmitter or production of antioxidant such as glutathione [36, 37].

Swelling, nuclear changes, marked loss of cytoplasmic substance [22, 28, 30, 31], disruption of the Müller cells' plasma membranes [29], followed by disruption of the outer limiting membrane (OLM) can be observed [27] in the first three days after the α-AAA application.

AAA treatment of early post-natal mice results in localized disruption of the contacts between Müller cells and photoreceptors [27, 28]. At hour six after application, vacuoles are detected in apical processes of the Müller cells at the margin of the OLM, and zonulae adherentes between Müller cells and photoreceptors are irregular or absent [27, 39].

The disruption of OLM is a possibility of photoreceptors to be displaced from their normal position and move to outer segments in the subretinal space.

Treatment with α-AAA (P1-P3) leads to clumps of photoreceptors, displaced through the inner segments, lying immediately beneath the retinal pigment epithelium (RPE) from the first days to the one month after treatment (Fig. 2, Fig 3, Fig. 4). The photoreceptor inner and outer segments are significantly disturbed, vacuoles are present and there is a loss of outer segments. In rat retina, the migration of photoreceptors (provided by Muller cells) to the outer nuclear layer (ONL) is completed at postnatal day 21 (P21). Even when α-AAA treatment is commenced as early as P3, several days prior to the formation of the ONL, the majority of photoreceptors migrate to their correct position and form inner and outer segments. Therefore, the signals for photoreceptor migration are either provided by the Müller cells prior to P3, or, alternatively, are derived from different intrinsic or extrinsic cues [27, 28, 39, 40].

Alpha-AAA can induce progenitor properties of Muller cells in the adult mouse. α-AAA induces the mature Müller cells to dedifferentiate, express the progenitor cell markers nestin and Chx10, migrate to the ONL, and divide and generate new photoreceptors. The acute neuronal injury leads to neuronal release of glutamate, which serves as a signal to stimulate neurogenesis from progenitor cells in the mature retina and CNS. It is not known whether glutamate activates progenitor cell properties by binding to receptors on Müller glia or entering the cells via glutamate transporters. Müller glial cells in the adult mouse retina can be reverted to a progenitor-like state and generate new neurons and photoreceptor cells [41-43].

A significant reduction in numerical density of cells with large somata in the ganglion cell layer is seen in the neonatally injected retinas at P56 (Fig. 3). In the ganglion layer, loss of immunoreactivity to vimentin is found, and a delayed expressed on *β*APP or Bcl-2 from 5 to 35 days after injection. In normal developing retinas, *β*APP and Bcl-2 is expressed primarily but transiently in a small number of neurons in the ganglion cell layer during the first postnatal week and in the endfeet [32, 38].

In contrast, no detectable changes in the

expression of βAPP and Bcl-2 are observed in the retina that has received α-AAA as adults. These results indicate that the gliotoxin α-AAA has long lasting effects on the expression of βAPP and Bcl-2 in Müller glial cells, as well as in neurons in the developing but not in mature retina. The loss of metabolic activity of Müller glial cells occurs long before any significant changes in the density and somal sizes of the cells in the GCL have provided evidence that the loss of neurons in retinas injected with α-AAA is likely to be secondary to toxic effect of α-AAA on the Müller glial cells during development [42, 43].

Alpha-AAA induces vascular telangiectasis and increases vascular permeability from 4 days to over 2 months post-injection in all three layers of the retinal vasculature, which co-localized with areas of Müller cell disruption. It is accompanied by increased expression of vascular endothelial growth factor and reduces expression of the tight junction protein claudin-5. These findings suggest that glial dysfunction is a primary contributor to the blood retinal barrier (BRB) breakdown in retinal vascular diseases. Müller glial dysfunction has been associated with retinal compromise including neuronal damage and breakdown of the inner BRB. Vascular changes induced by DL α-AAA are seen predominantly in regions of glial disruption, as reflected by reduced expression of glutamate synthetase and increased expression of glial fibrillary acidic protein and vimentin [39, 44, 45].

Müller glia may actually facilitate donor cell migration into the ONL of the recipient retina or play a role in supporting rod differentiation, and the transient toxic effects of α-AAA may impede or reduce these supportive functions. OLM disruption can facilitate movement of cells in the opposite direction, significantly enhancing the number of donor photoreceptors integrated into the recipient ONL after transplantation into the subretinal space [41, 46].

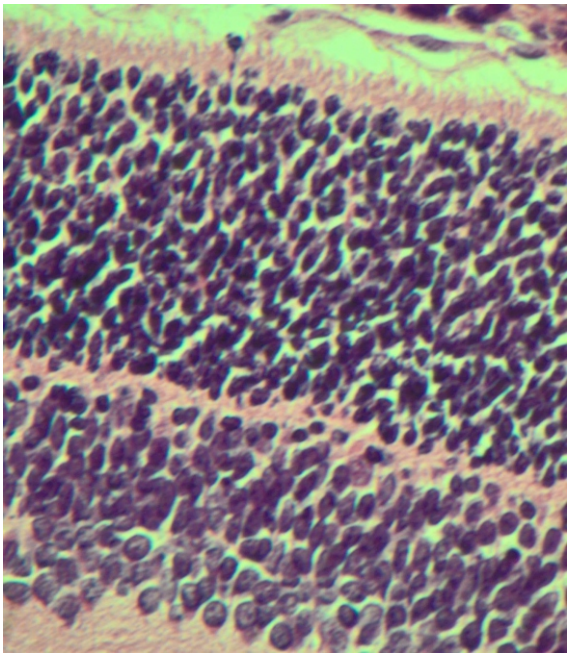

Figure 2. Displaced photoreceptor cell bodies through inner segment and disruption of the inner limiting membrane are seen 1 week after subcutaneous AAA applications in developing rat retina (Magnification x1000)

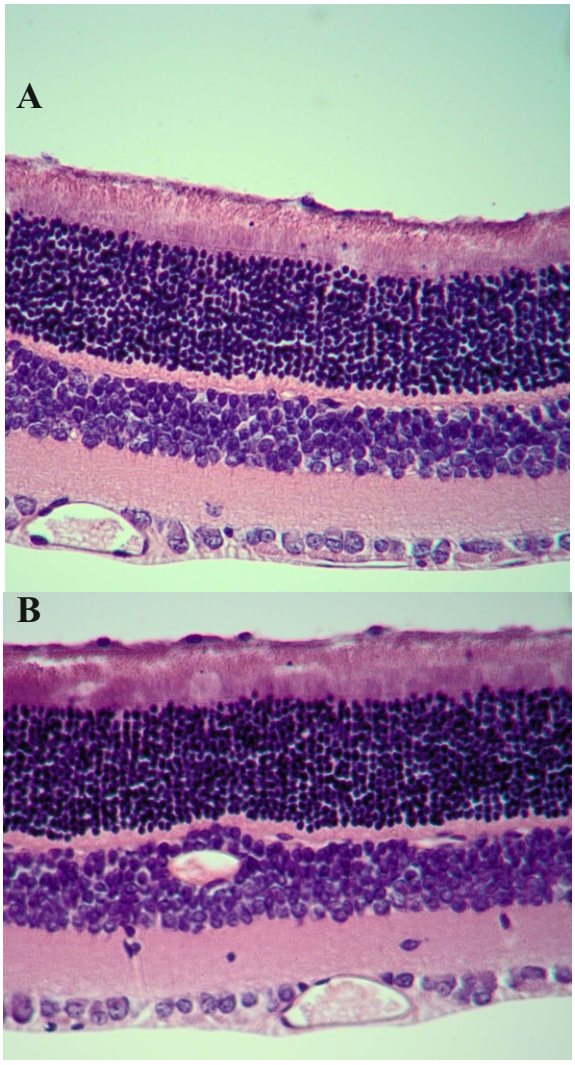

Figure 3. Displaced photoreceptor cell bodies in inner and outher segment, displaced may be amacrine cell bodies in IPL(A) and dilated blood vessels are seen at 16 days (B) after subcutaneous AAA applications in developing rat retina (Magnification x400)

The effects of *α*-AAA depend on the dosage and time. The morphological changes begin in the first three days after the application of *α*-AAA and recovery starts one week after administration. Photoreceptor organization appears largely normal two weeks following injection [28, 42]. Changes including reduction in numerical density in the ganglion cell layers are observed in the neonatally injected retinas at P56 [38]. One week after *α*-AAA treatment, retina shows significant recovery of OLM integrity, recovery of inner and outer segment organization, although small numbers of vacuoles are still present in the inner segment region. Disruption of the inner limiting membrane, loss of retinal layers, degeneration of the photoreceptor inner/outer segments and displaced photoreceptor cell bodies through inner segment is presented 3 weeks post high dosages of AAA injection (Fig. 3).

The different routes of administration including: intravitreal (20 μg/μl), subretinal (10 μg/μl) and subcutaneous (0.7–2.7 mg/g body weight) injection show some differences in toxicity of α-AAA. Retinae failed to recover normal histological morphology following subretinal injection, while subcutaneous injections have resulted in variable morphological changes. Intravitreal administration has caused modest and reversible morphological changes [27, 28, 30, 40].

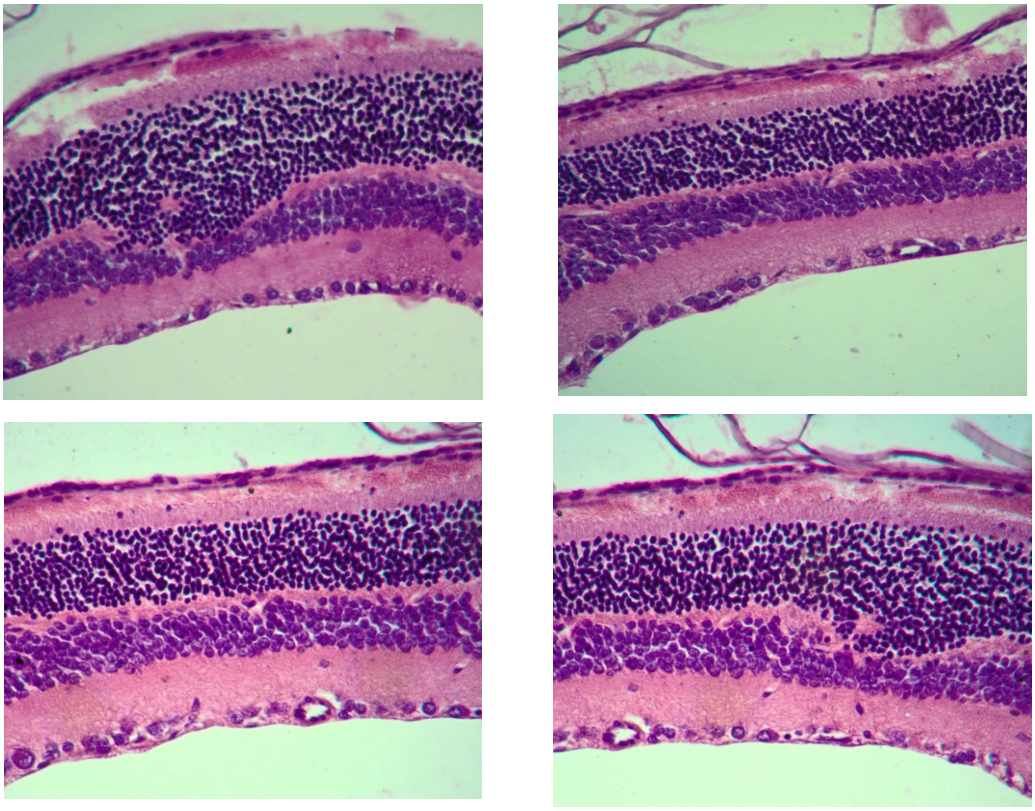

Figure 4. Displaced photoreceptor cell bodies in inner and outer segment, amacrine cell bodies may be displaced in IPL. Dilated blood vessels are seen 1 month after subcutaneous AAA applications in developing rat retina (Magnification x400)

Effects of α-AAA acid in retina of other animals

The gliotoxic efficacy (the reversible suppression of glutamate synthetase and electroretinographic b-wave activities) of L-*α*-AAA is two-fold higher than that of DL-*α*-AAA in carp (*Cyprinus carpio*) retina *in vivo* [47], in isolated guinea pig retinal glial cells [48], and in both frog and chicken [49]. L *α*-AAA reduces the level of carbonic anhydrase activity, another enzyme localized predominantly in Müller cells. Susceptibility of Müller cells to *α*-AAA is found to increase with embryonic development of the retina in cultures of retina tissue from chick embryos [50, 51].

DL-α-AAA has had a dose-dependent toxic effect on 661W photoreceptors and induces vascular telangiectasis in monkeys [45, 52] and has produced a mixed glial-neuronal lesion that affected inner neuronal structures of chick embryo retinas [51] but in the adult retina *α*-AAA does not affect retinal neurons. It is widely used to selectively abolish Müller cells [49]. Alpha-AAA specifically inhibits the retina visual cycle and not the canonical pigment epithelial visual cycle, blocks cone pigment regeneration and single-cell and whole-retina cone dark adaptation in isolated salamander retina. The inhibition of chromophore recycling by *α*-AAA leads to 50% reduction in the sensitivity of dark-adapted cones [53]. Injecting DL-α-AAA into vitreal chamber causes a marked decrease in myopic diopters and downregulation of retinal vimentin protein in Müller cells of guinea pig [54, 55].

Cystoid macular oedema (CME) is a condition seen in the end stages of many diseases of the outer retina, such as retinitis pigmentosa and diabetic maculopathy. Microscopic examination of pathological specimens has shown that CME represents an intra-cytoplasmic swelling (oedema) of Müller cells in the foveal region, which is similar to the effects of α-AAA [56, 57, 58].

Conclusions

L-αAAA shows the most toxic effect on the glial cells and has a primary (on glial and Müller cells) and a secondary effect (on photoreceptors and ganglion cells).

There are no significant differences in the action of *α*-AAA in adult and newborns retina of rats. The first morphological changes in retina begin during the first three days after application and reach the peak on 72 h. Recovery of the retina is first seen one week after *α*-AAA injection, lamination recovers and photoreceptor inner and outer segments regain nearly normal orientation. Photoreceptor organization appears largely normal two weeks after injection in retina or brain in mature rats. However, in newborn rats the pathologic changes persist even after postnatal day 28, when periodic clumps of displaced photoreceptor nuclei in subretinal space are seen.

The toxic effects of α-AAA are dosage and time-dependent.

The different routes of administration, including intravitreal, subretinal and subcutaneous injection, show some differences in toxicity of α-AAA. The subretinal injection has the most toxic effect; and that of the intravitreal is modest. Subcutaneous injection results in a variety of morphological changes, though it is the easiest to apply.

The toxic effects of α-AAA can be used to study in details the Müller cells functions and to understand the mechanism and the treatment of some retinal diseases, such as retinitis pigmentosa and diabetic maculopathy.

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