Stereospecific effects of the α-aminoadipic acid on the retina: a morphological and electrophysiological study

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Abstract. In both frog and chicken an intravitreal injection of the dextrorotatory (D)-isomer of α-aminoadipic acid (α-aaa) leads to a progressive disappearance of the ERG b-wave without affecting a and c components. Tectal evoked potentials (TEP) are no longer recorded. These physiological effects are concomitant with a specific glial cell damage, without any apparent damage to neurons. The levorotatory (L)-isomer at low concentrations is more gliotoxic than the D-isomer; the ERG b-wave is suppressed, while the amplitude of both a and c components is increased. TEPs are always recorded, i.e., a visual message is still generated in the retina and transmitted to the optic tectum when the Müller cells have been damaged and the b-wave is abolished. At higher concentrations the L-isomer suppresses TEPs and damages both glial and neuronal cells. Thus α-aaa appears to be a good tool for analyzing ERG components, especially subcomponents of the c-wave.

Introduction

DL-α-aminoadipic acid (α-aaa) was found to specifically destroy glial cells without affecting neurons neither in the retina (Pedersen and Karlsen, 1979; Szamier et al., 1981) nor in other structures of the central nervous system (Olney, 1971). An intravitreal injection of DL-α-aaa provokes severe damage to the Müller cells in frog or chicken retina. This morphological alteration is accompanied by a progressive disappearance of the ERG b-wave (Welinder et al., 1982); ganglion cell discharges however, as well as tectal evoked potentials (TEP) can be recorded, i.e., a visual message is still generated in the retina and transmitted to the optic tectum when the Müller cells have been damaged and when the ERG b-wave has disappeared (Bonaventure et al., 1981).

Moreover DL-α-aaa proved to antagonize the depolarizing action of aspartate (Biscoe et al., 1977; Hall et al., 1977; Evans et al., 1979; Wu and Dowling, 1978; Stone, 1979; Homma, 1981); this excitatory amino acid has been regarded as a transmitter between photoreceptors and second order neurons in the retina (Cervetto and McNichol, 1972; Dowling and Ripps, 1972; Sugawara and Negish, 1973; Wu and Dowling, 1978).
Thus the question arises to what extent gliotoxicity and possible interactions with aspartate play a role in the origin of the drug-induced electrophysiological effects. Therefore comparative morphological and electrophysiological analysis with the dextrorotatory (D)- and levorotatory (L)-isomers respectively seemed of interest. In the spinal cord the D-isomer of α-aaa was found to be more potent than the racemic form in blocking the excitatory amino acid receptor (Lodge et al., 1978; MacLennan et al., 1978). Conversely, the L-isomer is considered antagonist of glutamate and aspartate. Gliotoxicity and neurotoxicity are important for the L-form, while the D-isomer is only slightly gliotoxic and not neurotoxic (Olney et al., 1980).

Methods

This study was carried out in curarized frogs (n = 36) and chickens (n = 24), the latter being artificially ventilated. The animals received repeated injections of xylocaine at all critical surgical loci. The techniques of electrophysiological recordings as well as the histologic methods used were described previously (Bonaventure et al., 1981). Recordings were performed before and after intravitreal administration of the drug. Volumes of 30 μl (frog) or 50 μl (chicken) were injected at various concentrations (0.05 M to 0.3 M in phosphate-buffered saline) into the vitreous body. Control injections of saline never altered the ERG nor the TEP. The racemic and the L forms are commercially available (Sigma). The D-isomer was synthetized from the DL form according to the method described by Olney et al. (1980).

Morphological results

Chicken and frog eyes were removed at various intervals after injection of either isomer, just after having undergone an electrophysiological control test.

In both species intravitreal injection of the D-isomer in all concentrations applied provoked marked histologic lesions of Müller cells, already visible under the light microscope (Fig. 1B) and confirmed by electron microscopy. The damage was identical to that observed after injection of the racemic form (Bonaventure et al., 1981). Glial cells exhibited very marked alterations with a massive oedematous swelling of the cell bodies and processes. The plasma membranes appeared disrupted. A loss of electron density correlated with internal destruction of the cells was observed, together with a vacuolization of the cytoplasm and a swelling of the endoplasmic reticulum. The cell nuclei were swollen and appeared very clear; chromatin was condensed in heterogenous masses. No retinal element other than Müller cells was affected by D-α-aaa. About 7 h later Müller cells could be recognized again and after 24 hours they appeared quite normal. Thus the morphological damage induced by the D-isomer was reversible like that induced by the