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Poster presentation

Neurotransmitter release and histological changes following perinatal asphyxia in rats and the neuroprotective action of lamotrigine

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Background

Perinatal asphyxia remains a frequent cause of a variety of brain disorders including cerebral palsy, epilepsy, mental retardation, learning disability and attention deficit disorders. Excessive amounts of glutamate, aspartate and other neurotransmitters are released into the extracellular space during perinatal asphyxia and may contribute to neuronal loss and brain injury in several regions of the developing brain, especially in the hippocampus. Lamotrigine, a novel antiepileptic drug, is believed to act by reducing excitatory amino acids release due to an inhibition of Na+ channels. The purpose of our study was to investigate the acute effects of lamotrigine administration on the release of glutamate, aspartate, glutamine and GABA. Its potentional cerebroprotective action on the rat's hippocampus after perinatal asphyxia was also studied.

Materials and methods

In 7-day old rats a hypoxic-ischemic injury to the left cerebral hemisphere by left common carotid artery ligation (ischemia) was induced, followed by a one-hour exposure to hypoxia (8% oxygen). Animals (n = 30) were classified into three treatment groups and immediately after hypoxia were given intraperitoneally: (1) saline (control group), (2) lamotrigine at 10 mg/kg, (3) lamotrigine at 20 mg/kg. Seven days after the insult, histological analysis (by light and electron microscopy) was performed to determine neuronal death in the CA1, CA3 and CA4 regions of the left hippocampus and the dentate gyrus. Total percentage of damaged neurons was used as parameter for the evaluation of the neuroprotective effect. Determination of the amino acids, glutamate, aspartate, glutamine and GABA was performed in the same regions and at the same time by an HPLC technique followed by fluorimetric detection.

Results

The most significant post-asphyxia neuronal injury was identified in CA1 region and to a lesser extend in dentate gyrus and in CA3, whereas CA4 appears to be the least affected region. The percentage of the damaged neurons was significantly reduced by lamotrigine (10 mg/kg) only in the CA1 region, but at the relatively high dose of 20 mg/kg it was also significantly reduced in the CA3 region and in the dentate gyrus. Glutamate and aspartate were significantly elevated seven days after the insult probably indicating overstimulation by excitatory amino acids. The GABA levels were also increased but did not reach significant values. Lamotrigine significantly reduced glutamate and aspartate levels but only at the highest dose used (20 mg/kg). Neither concentration of lamotrigine significantly altered glutamine or GABA.

Discussion

Lamotrigine, especially at high doses, is capable to decrease the release of the excitatory amino acids glutamate and aspartate and it has neuroprotective effects in the hippocampus of rats after perinatal asphyxia. Administration of the drug alone or in combination with other agents, immediately after the insult, could be used in clinical trials to ameliorate the brain damage that is caused by the toxic action of excitatory amino acids.

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