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CDP-choline (citicoline) attenuates brain damage in a rat model of birth asphyxia

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To estimate protective potential of citicoline in a model of birth asphyxia, the drug was given to 7-day old rats subjected to permanent unilateral carotid artery occlusion and exposed for 65 min to a hypoxic gas mixture. Daily citicoline doses of 100 or 300 mg/kg, or vehicle, were injected intraperitoneally for 7 consecutive days beginning immediately after the end of the ischemic-hypoxic insult, and brain damage was assessed by gross morphology score and weight deficit two weeks after the insult. Caspase-3, α-fodrin, Bcl-2, and Hsp70 levels were assessed at 0, 1, and 24 h after the end of the hypoxic insult in another group of rat pups subjected to the same insult and given a single dose of 300 mg/kg of citicoline or the vehicle. Citicoline markedly reduced caspase-3 activation and Hsp70 expression 24 h after the insult, and dose-dependently attenuated brain damage. In the context of the well-known excellent safety profile of citicoline, these data suggest that clinical evaluation of the efficacy of the drug in human birth asphyxia may be warranted.

Key words: Bcl-2, birth hypoxia-ischemia, caspase-3, CDP-choline, heat shock protein 70, neuroprotection

List of abbreviations:
Bcl-2 – B-cell lymphoma protein 2
CDP-choline – cytidine-5'-diphosphocholine, citicoline
c.c.a. – common carotid artery
Hsp – heat shock protein
PD7 – postnatal day 7
PD21 – postnatal day 21

INTRODUCTION

Brain damage due to birth asphyxia is a leading cause of human neonate mortality as well as of cerebral palsy, epilepsy, learning disability and mental retardation in survivors (Vannucci 1997). Mechanisms of cell death triggered in the brain by perinatal hypoxia-ischemia are difficult to study in humans. However, the establishment of animal models believed to be clinically relevant such as the "Vannucci rat" (7-day old rat pup subjected to permanent unilateral common carotid artery (c.c.a.) occlusion and transient hypoxia (reviewed by Vannucci et al. 1999) enabled outlining several interrelated pathological processes which are likely involved in asphyxia-related CNS damage. Among them are: (1) activation of certain phospholipases leading to the breakdown of membrane phospholipids and build-up of platelet-activating factor in brain tissues, (2) disturbances of intracellular calcium homeostasis and activation of calpains, (3) activation of glutamate receptors, increased damage from free radicals, and (4) mitochondrial impairment leading directly to caspase-dependent and -independent apoptosis (Akisu et al. 1998, Peeters and van Bel 2001, Vexler and Ferriero 2001, Wang et al. 2001, Zhu et al. 2003, Hagberg 2004).

Ischemia/hypoxia-induced brain damage can be affected by induction of heat shock proteins (Hsp) such as Hsp70. These proteins act intracellularly as molecular chaperones and attenuate proteotoxic stress, and are usually considered neuroprotective and antiapoptotic (Yenari et al. 2005), both in adults and neonates (Ferriero et al. 1990, Matsumori et al. 2005). However, there is some indication that Hsp70 actually can promote brain

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