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BRAIN RESEARCH

Research Report

Ultrastructure of blood–brain barrier and blood–spinal cord barrier in SOD1 mice modeling ALS

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ABSTRACT

The purpose of this study was to determine the ultrastructure of the blood–brain barrier (BBB) and blood–spinal cord barrier (BSCB) in G93A SOD1 mice modeling ALS at different stages of disease. Electron microscope examination of brainstem, cervical and lumbar spinal cords was performed in ALS mice at early and late stages of disease. Our results show disorganized mitochondrial cristae and degenerating mitochondria in endothelial cells and neuropil, swollen astrocyte foot processes, swollen and degenerating capillary endothelial cells, astrocytes and motor neurons and extensive extracellular edema. In spite of progressive extracellular edema in neural tissue, capillary endothelial cell tight junctions appeared to remain intact in early and late symptomatic animals. Results show that disruption of BBB and BSCB was evident in areas of motor neuron degeneration in G93A mice at both early and late stages of disease. Capillary rupture was observed in brainstem in early symptomatic G93A mice. Capillary ultrastructure revealed that endothelial cell membrane and/or basement membrane damage occurred, followed by vascular leakage.

1. Introduction

The blood–brain barrier (BBB), blood–spinal cord barrier (BSCB) and blood–cerebrospinal fluid barrier (BCSFB) control the exchange of substances between the blood and brain/spinal cord. BBB and BSCB components such as the capillary endothelium, endothelial cell tight junctions, capillary basement membrane and astrocyte play essential roles in maintaining cerebral

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homeostasis (reviewed in Pardridge, 1999; Nag, 2003; Ballabh et al., 2004). Impairment of this cellular machinery may cause BBB or BSCB breakdown leading to edema in many brain and spinal cord diseases or injuries.

In amyotrophic lateral sclerosis (ALS), which is characterized by multifactor motor neuron degeneration in the brain and spinal cord, there is some evidence that BCSFB permeability may be affected. Increased levels of albumin, IgG and C3c have been found in the cerebrospinal fluid (CSF) in ALS patients (Leonardi et al., 1984; Annunziata and Volpi, 1985; Apostolski et al., 1991; Meucci et al., 1993). Moreover, IgG was detected in spinal cord motor neurons of ALS patients, localizing in the rough endoplasmic reticulum and microtubules (Engelhardt et al., 2005). Ultrastructural examination of post-mortem spinal cord samples also showed that IgG was taken up in endothelial cells in the ventral horn of ALS patients. The high molecular weight (150,000 Da) of IgG makes it unlikely that this molecule could cross an intact brain capillary endothelium. However, some studies showed that insulin-like growth factor (IGF)-1, IGF binding protein-2 or nitric oxide (Pirttila et al., 2004) as well as levels of the growth hormone and insulin (Bilic et al., 2006) were not elevated in CSF of ALS patients in comparison with those of controls. Pirttila et al. (2004) suggested that since "a large portion of these proteins in CSF may originate from blood, and BBB