Examination of blood-brain barrier (BBB) integrity in a mouse brain tumor model.

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Abstract
The present study evaluates, both functionally and biochemically, brain tumor-induced alterations in brain capillary endothelial cells. Brain tumors were induced in Balb/c mice via intracranial injection of Lewis Lung carcinoma cells into the right hemisphere of the mouse brain using stereotaxic apparatus. Blood-brain barrier (BBB) permeability was assessed at various stages of tumor development, using both radiolabeled tracer permeability and magnetic resonance imaging with gadolinium diethylene-triamine-pentaacetate contrast enhancement (Gad-DTPA). The expression of the drug efflux transporter, P-glycoprotein (P-gp), in the BBB at various stages of tumor development was also evaluated by Western blot and immunohistochemistry. Median mouse survival following tumor cell injection was 17 days. The permeability of the BBB to (3)H-mannitol was similar in both brain hemispheres at 7 and 10 days post-injection. By day 15, there was a twofold increase in (3)H-mannitol permeability in the tumor bearing hemispheres compared to the non-tumor hemispheres. Examination of BBB permeability with Gad-DTPA contrast enhanced MRI indicated cerebral vascular permeability changes were confined to the tumor area. The permeability increase observed at the later stages of tumor development correlated with an increase in cerebral vascular volume suggesting angiogenesis within the tumor bearing hemisphere. Furthermore, the Gad-DTPA enhancement observed within the tumor area was significantly less than Gad-DPTA enhancement within the circumventricular organs not protected by the BBB. Expression of P-gp in both the tumor bearing and non-tumor bearing portions of the brain appeared similar at all time points examined. These studies suggest that although BBB integrity is altered within the tumor site at later stages of development, the BBB is still functional and limiting in terms of solute and drug permeability in and around the tumor.


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