

Early neutrophilic expression of vascular endothelial growth factor after traumatic brain injury.

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Abstract

The formation of edema after traumatic brain injury (TBI) is in part associated with the disruption of the blood-brain barrier. However, the molecular and cellular mechanisms underlying these phenomena have not been fully understood. One possible factor involved in edema formation is vascular endothelial growth factor (VEGF). This growth factor has previously been demonstrated to increase the blood-brain barrier permeability to the low molecular weight markers and macromolecules. In this study, we analyzed the temporal changes in VEGF expression after TBI in rats. In the intact brain, VEGF was expressed at relatively low levels and was found in the cells located close to the cerebrospinal fluid space. These were the astrocytes located under the ependyma and the pia-glial lining, as well as the epithelial cells of the choroid plexus. In addition, several groups of neurons, including those located in the frontoparietal cortex and in all hippocampal regions, were VEGF-positive. The pattern of VEGF-immunopositive staining of neurons and choroidal epithelium suggested that in these cells, VEGF binds to the cell membrane-associated heparan sulfate proteoglycans. Following TBI, there was an early (within 4 h post-injury) increase in VEGF expression in the traumatized parenchyma associated with neutrophilic invasion. The ipsilateral choroid plexus appeared to play a role in facilitating the migration of neutrophils from blood into the cerebrospinal fluid space, from where many of these cells infiltrated the brain parenchyma. VEGF-immunopositive staining of neutrophils resembled haloes and was found ipsilaterally within the frontoparietal cortex and around the velum interpositum, a part of the subarachnoid space. These haloes likely represent the deposition of neutrophil-derived VEGF within the extracellular matrix, from where this growth factor may be gradually released during an early post-traumatic period. The maximum number of VEGF-secreting neutrophils was observed between 8 h and 1 day after TBI. In addition, from 4 h post-TBI, there was a progressive increase in the number of VEGF-immunoreactive astrocytes in the ipsilateral frontoparietal cortex. The maximum number of astrocytes expressing VEGF was observed 4 days after TBI, and then the levels of astroglial VEGF expression declined gradually. Early invasion of brain parenchyma by VEGF-secreting neutrophils together with a delayed increase in astrocytic synthesis of this growth factor correlate with the biphasic opening of the blood-brain barrier and formation of edema previously observed after TBI. Therefore, these findings suggest that VEGF plays an important role in promoting the formation of post-traumatic brain edema.

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