

Vascular endothelial growth factor expression and angiogenesis induced by chronic cerebral hypoperfusion in rat brain.

Hai J, Li ST, Lin Q, Pan QG, Gao F, Ding MX.

Department of Neurosurgery, Tongji Hospital, Tongji University, Shanghai, People's Republic of China.
haijandoc@yahoo.com.cn

Abstract

OBJECTIVE: In a rat model, we studied the time courses of vascular endothelial growth factor (VEGF) expression and angiogenesis induced by chronic cerebral hypoperfusion in the brain, and we investigated the histological basis of normal-perfusion pressure breakthrough. **METHODS:** Twenty-one Sprague-Dawley rats were randomly divided into a control group (n = 3) and a model group assessed at various time points after the creation of a carotid artery-jugular vein fistula (12 h, n = 3; 24 h, n = 3; 72 h, n = 3; 7 d, n = 3; 21 d, n = 3; 90 d, n = 3). The time courses of the expression of VEGF messenger ribonucleic acid (mRNA) and protein in rat brain were analyzed with semiquantitative reverse transcriptase-polymerase chain reaction and Western blot assays, respectively. Immunohistochemical techniques were used to evaluate VEGF protein localization with rabbit polyclonal anti-rat VEGF, VEGF receptor (VEGFR) expression with rabbit polyclonal antibodies to VEGFR-1 and -2, microvascular density with mouse monoclonal anti-rat CD31, and astrocytic reactivity with polyclonal anti-gial fibrillary acidic protein, in cerebral cortical tissue of the right middle cerebral artery territory. **RESULTS:** Three alternative splicing forms, i.e., VEGF(188), VEGF(164), and VEGF(120), were observed in cerebral cortical tissue of the right middle cerebral artery territory in semiquantitative reverse transcriptase-polymerase chain reaction analyses. VEGF(164) mRNA was the predominant isoform expressed in rat brain. VEGF(188) mRNA and VEGF(120) mRNA were also detected but at very low levels (not statistically significant). Low levels of VEGF(164) mRNA were observed in the control brains. However, VEGF(164) mRNA levels were significantly increased in the model brains at 24 hours postoperatively, peaked by 7 days, decreased by 21 days, and returned to basal levels by 90 days after fistula formation. VEGF protein expression, as measured in Western blot assays, was also increased in rat brains in the model group from 24 hours to 21 days postoperatively but returned to control levels by 90 days after fistula formation. VEGF immunohistochemical analyses indicated that this increased expression was mostly associated with endothelial cells. Consistent with the VEGF protein expression findings, up-regulation of VEGFR-1 but not VEGFR-2 expression on endothelial cells in the model brains was observed. Microvascular density in the rat brains began to increase significantly 7 days after fistula formation in the model group, as assessed immunohistochemically, and the increase was maintained for 90 days. Although no prominent astrocytic reactivity was observed in the rat brains throughout the experiments, there was an absence of astrocytic foot processes surrounding some cerebral capillaries 90 days after fistula formation in the model group. **CONCLUSION:** These results demonstrated that chronic cerebral hypoperfusion could induce sustained up-regulation of VEGF mRNA and protein expression in rat brain, which was correlated with angiogenesis. An absence of corresponding astrocytic reactivity during angiogenesis may be an important factor accounting for structural deficits of the blood-brain barrier and the occurrence of normal-perfusion pressure breakthrough.

PMID: 14519228 [PubMed - indexed for MEDLINE]