Recombinant Tissue Plasminogen Activator Causes a Significant Increase in Endogenous Urokinase Following Experimental Focal Cerebral Ischemia.

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The aim of this study was to investigate the effects of different doses of exogenous recombinant human tissue plasminogen activator (rt-PA) on the endogenous cerebral plasminogen/plasmin system in focal ischemia. Ischemia was induced using the suture model in rats subjected to 3 h ischemia (i) and 24 h reperfusion (R). Each group of rats (n=6) received either treatment (0.9, 1, or 18 mg rt-PA/kg body weight) or saline (control group) at the end of ischemia. A sham-operated group of rats (n=6) was involved in the comparison. When using casein dependent plasminogen zymography of the ischemic and non-ischemic basal ganglia and cortex, compared with the contralateral non-ischemic area and the sham-operated controls, urokinase (u-PA) was significantly increased in the ischemic area. The cortex u-PA rose from sham 91% ± 7% to ischemia 176% ± 10% (p<0.005). Increasing rt-PA doses led to further elevation of u-PA activation. Thus, u-PA seems to play the major role in the endogenous plasminogen activator system following focal cerebral ischemia. This may be relevant for the development of edema and hemorrhage secondary to ischemic stroke.

Abnormal Vascular Responses and Cerebral Reperfusion Injury in Apo-E Deficient Mice on Western Diet.

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Background: Western diet fed apoE deficient mice demonstrate impaired endothelium-dependent relaxation in systemic vessels, and serve as a useful mouse model for atherogenesis. However, the effects of apoE gene deficiency and Western-diet on cerebral vascular function and reactivity, and the mechanism underlying these abnormalities are not well understood. These abnormalities may underlie the increased susceptibility of these animals to focal ischemia. Western diet-fed apoE knockout mice would show abnormalities in cerebrovascular function and reactivity, and serve as a useful mouse model for atherogenesis. The purpose of this investigation was to determine whether EPO and EMP-1 provide neuro- and vascular protection after temporary focal cerebral ischemia. Methods: Sixty-one animals were subjected to either 2 hours of middle cerebral artery occlusion (MCAO) followed by 48 hours of reperfusion (n=30) or 90 minutes followed by a 7 day survival (n=31). Animals received either EPO 5000 uc/kg, EMP-1 100 mcg/kg, or saline. In the acute study, infarct size and hemorrhage development were assessed and in the chronic study, infarct size and neurobehavioral outcome were endpoints. Results: There were no significant differences in infarct size at 48 hours but there was significantly more hemoglobin in the ischemic hemispheres of the EMP-1 treated animals (p<0.01). At 7 days, the EMP-1 treated animals exhibited significantly lower infarct size than either saline (p<0.001) or EPO (p<0.05) animals and the EMP-1 group was also significantly lower than saline (p<0.05). In addition, the EMP-1 treated animals had improved neurobehavioral scores, at least in the early days after the injury (p=0.012). Conclusions: EMP-1 may be superior to EPO in providing neuroprotection after focal cerebral ischemia. Although EPO and EMP-1 did not reduce infarct size at 48 hours, the significant decrease at 7 days may reflect a neurorestorative action. Whether the improved performance of EMP-1 over EPO is due to superior brain penetration is unknown at this time.

Intranasal Delivery of Nerve Growth Factor Bypasses the Blood-Brain Barrier and Protects Against Acute Ischemic Damage.

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Objective: Plenty of experiments in vivo and in vitro suggest that nerve growth factor (NGF) has significant neuroprotective actions on ischemic brain damage. However NGF is a protein with large molecular weight that does not cross the blood-brain barrier (BBB) efficiently. When administered through parenteral routines such as intravenous (IV) or intramuscular injection, it is difficult to reach the central nervous system (CNS). Intraparenchymal and intraparenchymal injection are effective to deliver NGF to CNS, it is invasive and not practical for clinical patients. Intranasal (IN) administration targeted the CNS bypassing the BBB. This study confirmed the reliability of IN pathway by comparing the distribution of NGF in different brain regions after IN and IV injection of NGF. The neuroprotective effects of ING on cerebral infarction were also observed. Methods: A blinded, vehicle-controlled study of ING and IV NGF on acute cerebral ischemia was performed using the intraluminal suture middle cerebral artery occlusion (MCAO) model. Experiment 1 Rats were randomly divided into IN NGF, IV NGF and untreated group (n=4). The NGF concentration in the brain following IN or IV treatment was measured by ELISA. Experiment 2 Rats were assigned to 4 groups: IN vehicle, IN NGF, IV vehicle, IV NGF (n=8 each). Treatments were initiated 30 min after the onset of MCAO and then again 24 h later. Three neurologic behavioral tests were used to assess the motor, sensorary and balance functions at 24th and 48th after MCAO. Corrected infarct volumes were determined 48h after MCAO. Results: Ofactory bulb in IN NGF group obtained the least infarct volume (P<0.001). The NGF concentration in the brain following IN or IV treatment was measured by ELISA. Experiment 2 Rats were assigned to 4 groups: IN vehicle, IN NGF, IV vehicle, IV NGF (n=8 each). Results: Treatment was initiated 30 min after the onset of MCAO and then again 24 h later. Three neurologic behavioral tests were used to assess the motor, sensorary and balance functions at 24th and 48th after MCAO. Corrected infarct volumes were determined 48h after MCAO. Results: Ofactory bulb in IN NGF group obtained the least infarct volume (P<0.001). The NGF concentration in the brain following IN or IV treatment was measured by ELISA. Results: Ofactory bulb in IN NGF group obtained the highest concentration, arriving at 325±2g/ml. The NGF concentration of ofactory bulb and hippocampus in IN NGF group is significantly higher than that in IV NGF and control group. The infarct volume was reduced significantly by 39% after IN NGF compared with vehicle. The balance function of IN NGF improved significantly at 24 and 48h (P<0.02 and P<0.04, respectively). Conclusions: ING could bypass BBB, reach the CNS, reduce infarct volume and improve neurofunctional outcome following MCAO in rats, which provides a simpler, safer and potentially more cost effective method of delivery.