Abstract: Although recombinant tissue plasminogen activator (rt-PA) is successfully used for thrombolysis in human stroke, it may increase the risk of haemorrhagic complications. It was shown that the matrix metalloproteinase (MMP) system is critically involved in basal lamina degradation after middle cerebral artery occlusion and reperfusion following rt-PA administration. We describe the effects of different doses of rt-PA (saline, 0.9, 9, or 18 mg rt-PA/kg body weight) on the MMPs, their specific inhibitors (TIMPs), and also their inducer protein EMMPRIN following experimental cerebral ischemia (3 hours [h], 24 h reperfusion, suture model) in rats. The amount of MMP-2 and -9 was measured by gelatine zymography, TIMP-1 and -2 by reverse gelatine zymography, and the content of EMMPRIN and the basal lamina component collagen type IV by Western blotting. The amount of both MMPs steadily rose with increasing doses of rt-PA (p<0.05). In contrast, their endogenous inhibitors TIMPs decreased (p<0.001). A balance between the proteases and their inhibitors was achieved at the low dose of 0.9 mg/kg rt-PA in the rats, which significantly coincided with the demonstrated protection of collagen type IV degradation at this dose. The inducer protein EMMPRIN increased in parallel to its substrate MMP-2. Exogenous rt-PA leads to an increase...
of the MMP-inducing system by EMMPRIN, and a rise of the degrading MMPs follows. However, at low to moderate doses of rt-PA the microvascular basal lamina was protected, probably due to inhibition of MMP-2 and MMP-9 by the upregulation of their inhibitors. This strongly supports use of the lowest effective dosage of rt-PA available.