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Effect of JNK Inhibition on Post-ischemic Inflammation

Corinne A. Benakis[1], Christophe Bonny[2], Lorenz Hirt[1]

[1]Neurology Department, CHUV (University Hospital of Canton de Vaud), Lausanne, Switzerland; [2]Xigen Pharmaceuticals, Lausanne, Switzerland

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INTRODUCTION

The c-Jun-N-terminal kinase signaling pathway (JNK) is activated during ischemia and plays an important role in apoptosis and inflammation. We have previously demonstrated that D-JNKI1, a specific JNK inhibitor, is strongly neuroprotective in animal models of stroke. We presently evaluated if D-JNKI1 modulates post-ischemic inflammation.

METHODS AND RESULTS

D-JNKI1 (0.1 mg/kg) or vehicle (saline) was administered intravenously 3 h after 45 min middle cerebral artery occlusion (MCAo) in outbred CD1 mice. Lesion size at 48 h was significantly reduced in the treated group. Activation of JNK (phosphorylation of c-Jun) was observed in neurons as well as in Isolectin B4 positive microglia 48 h after MCAo. We quantified microglial cells (CD11b) by measuring the average intensity of CD11b labelling (infra-red emission) within the ischemic tissue. No significant difference was found between groups. Cerebral ischemia was modelled *in vitro* by subjecting rat organotypic hippocampal slice cultures to oxygen (5%) and glucose deprivation for 30 min. In *vitro*, D-JNKI1 was found predominantly in NeuN positive neurons of the CA1 region and in few Isolectin B4 positive microglia. 48 h after OGD microglia were activated whereas resting microglia were found in controls and in D-JNKI1-treated slices. The secretion of inflammatory mediators was analysed *in vivo* (immunohistochemistry) and *in vitro* (Luminex technology) 48 h after induction of ischemia. Preliminary results suggest a decrease in interleukin-1-beta (IL-1-beta) and monocyte chemoattractant protein-1 (MCP-1) after treatment, respectively.

CONCLUSION

Our *in vivo* study shows that D-JNKI1 reduces the infarct volume 48 h after transient MCAo and does not act on the activation and accumulation of microglia. In contrast, *in vitro* data show a modulation of microglial activation after treatment.

All together, our data suggest that D-JNKI1 does not act directly on microglia. Further experiments will show whether D-JNKI1 reduces inflammatory mediators in the brain and in peripheral tissue or systemic circulation.

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