2-Cl-MGV-1 reduces neuronal apoptosis in the remote brain regions and ameliorates cognitive deficits after cortical infarct in hypertensive rats

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Objectives

Focal cortical infarction causes neuronal apoptosis in the ipsilateral nonischemic thalamus and hippocampus, which is potentially associated with poststroke cognitive deficits. TSPO (translocator protein) is critical in regulating mitochondrial apoptosis pathways. We examined the effects of the novel TSPO ligand 2-Cl-MGV-1 on poststroke cognitive deficits, neuronal mitochondrial apoptosis, and secondary damage in the ipsilateral thalamus and hippocampus after cortical infarction.

Methods

One hundred fourteen hypertensive rats underwent successful distal middle cerebral artery occlusion (n=76) or sham procedures (n=38). 2-Cl-MGV-1 or dimethyl sulfoxide as vehicle was administrated 2 hours after distal middle cerebral artery occlusion and then for 6 or 13 days (n=19 per group). Spatial learning and memory were tested using the Morris water maze. Secondary degeneration and mitochondrial apoptosis in the thalamus and hippocampus were assessed using Nissl staining, immunohistochemistry, terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL), JC-1 staining, and immunoblotting 7 and 14 days after surgery.

Results

2-Cl-MGV-1 administration significantly improved spatial cognitive impairment ($P<0.05$) without amelioration of motor deficits after MCAO compared to vehicle. Infarct volumes did not significantly differ between the two groups at 7 or 14 days post-MCAO (both $P>0.05$). Increased TSPO expression was correlated to neuronal loss and microglia proliferation in the ipsilateral thalamus at 7 and 14 days after MCAO.

Figure 1. 2-Cl-MGV-1 attenuated cognitive deficits tested by Morris Water Mazes at 8-14 days after focal cerebral infarction. * $P<0.05$ compared to the sham-operated controls; # $P<0.05$ compared to the vehicle group.

Figure 2. Increased expression of TSPO was correlated with neuronal loss and glia activation in the ipsilateral non-ischemic thalamus after cortical infarction.

After 2-Cl-MGV-1 treatment, neuronal death and glial activation were remarkably decreased in the ipsilateral thalamic anterior nuclei and hippocampus post-MCAO ($P<0.05$).

Figure 3. 2-Cl-MGV-1 ameliorated secondary damage in the ipsilateral anterior thalamic nuclei after focal cerebral infarction.

Figure 4. 2-Cl-MGV-1 reduced neuronal apoptosis in ipsilateral anterior thalamic nuclei after focal cerebral infarction.

The collapse of mitochondrial transmembrane potential was prevented within the thalamus. Cytoplasmic release of apoptosis-inducing factors and cytochrome c, Caspase cleavage and the numbers of TUNEL⁺ or Nissl atrophic cells were reduced within the thalamus and hippocampus. This was accompanied by upregulation of Bcl-2 and downregulation of Bax ($P<0.05$).

Figure 5. 2-Cl-MGV-1 inhibited the collapse of mitochondrial transmembrane potential in the ipsilateral thalamus after focal cerebral infarction.

Figure 6. 2-Cl-MGV-1 reduced cytoplasmic release of apoptosis-inducing factors and cytochrome c in the ipsilateral thalamus after focal cerebral infarction.

Figure 7. 2-Cl-MGV-1 reduced the cleavage of Caspase-3 and Caspase-9 in the ipsilateral thalamus after cortical infarction.

Figure 8. 2-Cl-MGV-1 upregulated the levels of Bcl-2 and downregulated the levels of Bax in the ipsilateral thalamus after cortical infarction.

Conclusions

2-Cl-MGV-1 reduces neuronal apoptosis via mitochondrial-dependent pathways and attenuates secondary damage in the non-ischemic thalamus and hippocampus, potentially contributing to ameliorated cognitive deficits after cortical infarction.