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Neuroprotection in acute cerebral ischemia by acetylsalicylic acid

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ASA is widely accepted for secondary prevention of ischemic stroke. Its multiple pharmacological action sites include the anti-platelet aggregation effect, inhibition of the COX-pathway, comprise attenuation of glutamate release and anti-inflammatory properties such as inhibition of NF-κB expression. We hypothesised that a multiple application strategy is superior to a single bolus administration due to various pharmacological actions of ASA which might have an impact on infarct development during the acute and sub-acute stage of stroke. The mechanism involved might be that ASA attenuates the neurotoxic increase of glutamate in ischemic brain tissue.

We used the filament method for temporary middle cerebral artery occlusion and administered ASA or saline post-ischemically at subsequent time points: at 30 min, 6 hours, 24 hours, 2 days, 3 days, and 4 days after MCAO. On day 5 after MCAO, animals were sacrificed and infarct size determined using TTC staining. We also used microdialysis method to measure the concentration of glutamate in infarct and non-infarct hemisphere during MCAO. Endpoints of this study were infarct size and neurological outcome at day 5 after stroke onset, as well as glutamate concentration in infarct and non-infarct hemisphere in acute

stage of ischemia stroke. The aim of this study in rats was to assess whether repeated ASA injections both in the acute and chronic stage of ischemia were neuroprotective. The strategy of repetitive ASA application reduced infarct size and improved neurological function significantly if a high dose of 40 mg/kg ASA was used. No effect was observed when the same dosage was applied only once as a bolus at 30 min following tMCAO. Neither did repeated i.p. injections of a low dose of 20 mg/kg ASA yield a neuroprotective effect. Using striatal microdialysis, we also demonstrated that glutamate release in the infarct core is reduced by i.p. high dose of 40 mg/kg ASA administration started 30 min after stroke onset.

In conclusion, ASA in a high dosage of 40 mg/kg administered both in the acute stage of ischemia and repeatedly in the chronic stage is neuroprotective. A lower dosage or a one bolus application is less effective. ASA as a primary treatment strategy in ischemic stroke might act biphasically: In the acute stage, ASA may attenuate glutamate-mediated neurotoxicity by decreasing the concentration of glutamate in infarct region. In the chronic stage by anti-inflammatory mechanisms such as inhibiting the COX-pathway, delayed expression of iNOS, and down-regulation of NF-κB.