37) The Effect of Ion Channel Blockers on Ischemic Brain Damage.
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It has been assumed that ischemia causes loss of calcium homeostasis and subsequent rise in intracellular calcium leads to neuronal damage. Some reports have indicated that calcium channel blockers may decrease ischemic neuronal damage, while others could not. The effect of two ion channel blockers, 1) NC-1100 (calcium channel blocker, pyperazine ethanol derivative), 2) MK-801 (non-competitive NMDA antagonist) on delayed neuronal death incurred on rat hippocampus was investigated using two vessel occlusion model.

<<material and methods>> Male 18-week-old SHR (spontaneously hypertensive rats) were used. The animals were fasted overnight and anesthetized with 2% halothane in a nitrous oxide/oxygen mixture (70%/30%) and ventilated mechanically throughout the procedure. A silicon catheter was inserted into the vena cava through the right jugular vein. Tail artery was cannulated to monitor blood pressure and blood gases. Cerebral ischemia was induced for 10 min by bilateral common carotid artery occlusion in combination with systemic hypotension (50 mmHg) by infusion of trimethaphan camphor sulphonate and exsanguination. At the end of 10 min of ischemia, reperfusion was performed by release of the carotid clasps and infusion of the shed blood. Rectal temperature was monitored and maintained at 37°C from the beginning of ischemia and during reperfusion period (ca 60 min). Arterial blood gases and PH was maintained within normal physiological range. Treated group was given NC-1100 (3 mg/kg) i.v. or MK-801 (2 mg/kg) i.v. just before the induction of ischemia. Control group was given normal saline. The numbers of normal neurons /mm (neuronal density) in the hippocampal CA1 sector were counted at day 1,2,3,4, and 7 after ischemia in treated and control groups. The local cerebral blood flow of hippocampal CA1 region was measured by hydrogen clearance method before and after ischemia in treated (NC-1100) and control group.

<<Results>> Neuronal density of CA1 region was not significantly decreased at day 1,2,3,4, but markedly decreased at day 7 after ischemia in control group. Treatment of NC-1100 (3 mg/kg), or MK-801 (2 mg/kg) significantly suppressed reduced neuronal density at day 7 after ischemia, compared to control group. NC-1100 did not significantly affect local cerebral blood flow in ischemia and reperfusion, compared to control group.

<<Conclusion>> Delayed neuronal death at day 7 after ischemia was suppressed by pre-treatment of NC-1100 or MK-801. NC-1100 had no effect on cerebral blood flow in ischemia and reperfusion. It was also reported that MK-801 did not increase cerebral blood flow. These data indicates that the effect of NC-1100 or MK-801 on delayed neuronal death may be mediated by suppression of calcium influx to neurons, not by improvement of local cerebral blood flow.