PROTECTION FROM BRAIN DAMAGE AND BACTERIAL INFECTION IN MURINE STROKE BY THE NOVEL CASPASE-INHIBITOR Q-VD-OPH

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Introduction: Infarction size and infections are important determinants of stroke outcome. Aim: We investigated the effects of quinolyl valyl-O methylaspartyl [-2,6-difluorophenoxy]-methyl ketone (Q-VD-OPH) on stroke-induced brain damage, immunodepression, infections, and mortality. Q-VD-OPH is a new, non-toxic broad-spectrum caspase-inhibitor with improved potency. Materials/methods: We applied the mouse monofilament model of middle cerebral artery occlusion (MCAO). Q-VD-OPH was injected intraperitoneally. Blood was plated on blood agar plates. Tissues were evaluated with terminal transferase mediated nick end labeling (TUNEL), caspase-3 staining, and electron microscopy. Lymphocyte-subsets were analyzed by flow cytometry analysis. Results: A) Activation of caspase-3 was observed in brain, thymus and spleen after cerebral ischemia. B) Q-VD-OPH blocked TUNEL-staining (by 77%, $p < 0.05$) in the penumbra, but not in the ischemic core. Q-VD-OPH reduced caspase-3-positive cells in thymus and spleen by 60-70% and in stroke penumbra by 85% (all $p < 0.05$). C) Q-VD-OPH partially reduced stroke-induced apoptosis of lymphocyte subpopulations. D) Q-VD-OPH decreased bacterial counts in blood of MCAO mice about 4 orders of magnitude ($p < 0.001$). E) Infarction volume was 77.6 ± 31.5 mm3 without Q-VD-OPH and 47.8 ± 23.8 mm3 with Q-VD-OPH ($p = 0.0178$). Mortality in MCAO mice with vehicle treatment was 4 out of 12, whereas none of the Q-VD-OPH-treated animals died ($n=12$) ($p < 0.05$). Summary: Q-VD-OPH reduced ischemic brain damage, infarct volume and stroke-induced programmed cell death in lymphoid organs and lymphocyte subpopulations; it decreased susceptibility to post-stroke bacteremia, and improved survival. Conclusion: Q-VD-OPH may be a promising therapeutic agent in stroke.