21-aminosteroid

see 21-aminosteroids for severe traumatic brain injury

see also Tirilazad.

Earlier in vitro studies demonstrated the remarkable potency of the lazaroid compounds to prevent oxidant-induced early cell injury. However, the ability of lazaroid compounds to limit oxidative injury in vivo(including renal ischemia-reperfusion) has been less certain, and the early clinical trials using lazaroids to limit CNS injury or organ injury in the setting of transplantation have not been promising. Lazaroid compounds are potent inhibitors of lipid peroxidation, and their inability to influence other key injury processes, particularly during the late stages of cell injury, might partly explain the limited clinical efficacy. To test this, renal tubular (LLC-PK1) cells were incubated with 250 micromH(2)O(2)for 135 min, in the presence or absence of 2-methyl aminochroman (2-MAC, U-83836E), a lazaroid with potent ability to inhibit lipid peroxidation, or desferrioxamine, (DFO) an iron chelator with broader antioxidant efficacy. Cell injury, lipid peroxidation, DNA damage and ATP depletion were measured in the early (immediately after H(2)O(2)incubation) and late (24 h after H(2)O(2)incubation) stages of cell injury. In the early stage, 2-MAC suppressed H(2)O(2)-induced lipid peroxidation and LDH release, but not the DNA damage, ATP depletion or loss of cell replication. In contrast, DFO suppressed all of the measurements. In the late stages, despite continued suppression of lipid peroxidation, only DFO maintained significant cytoprotection against H(2)O(2), and this was accompanied by reduced DNA damage, higher ATP levels and preservation of cell proliferation. Thus, the inability of the lazaroid compound 2-MAC to sustain cytoprotection in the later stages of cell injury might provide at least a partial explanation for the inefficiency of lazaroids to limit tissue injury in clinical and certain in vivo settings [1)].

Twenty-two immature and 44 mature rats were divided equally into two groups. The experimental group received two injections of 3 mg/kg of U-74006F (Tirilazad) at a 2 hour interval. The control group received the same volumes of a citrate buffer. A 5 mm segment of the sciatic nerve was subjected to a crush load of 100 g for 2 hours. Motor function (sciatic functional index) was assessed to day 48 postoperatively. There was total paralysis of the crushed limb in all rats the first week after crushing. The experimental group had a statistically significant improvement in motor function compared with the controls on days 14, 21, 25, and 28 for the mature rats and on days 11 and 14 for the immature rats. The mature controls attained complete recovery on day 42 and had a significantly slower recovery rate than the immature controls, which had recovered fully by day 25. The recovery rates were almost similar among mature and immature groups pretreated with U-74006F, both of which had fully recovered motor function by day 28. The results indicate that pretreatment with U-74006F can significantly promote peripheral nerve function after low-load crush injury and that the age of the animal influences the rate of peripheral nerve recovery [2)].

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see U74389F.

The 21-aminosteroid U74389G exhibits a radioprotectant effect on normal brain tissue, but does not appear to protect the tumor in an in vivo rat radiosurgery model. We believe that the observed beneficial effects on healthy brain led to significant prolongation of animal survival; perhaps, by limiting the adverse effects of high-dose radiosurgery. This radioprotectant should be evaluated in randomized clinical trials in patients with malignant brain tumors [3) 4)].

Radiation protection was studied in a rat brachytherapy brain injury model. Radiation lesions were produced by stereotactic placement of high-activity iodine-125 seeds on the frontal lobe of F-344 rats. A minimum dose of 80 Gy was delivered to a 5.5-mm-radius volume. Radiation damage was evaluated 24 h after removal of the seeds by T1-weighted gadolinium-enhanced magnetic resonance imaging on a 1.5-T unit. Computerized three-dimensional reconstruction of the lesions seen on magnetic resonance imaging was performed to calculate the volume of radiation injury. Two experiments were performed with rats of different weights (mean, 300 g; mean, 180 g). All animals underwent surgical placement of an indwelling internal jugular catheter before brachytherapy. Treated animals received the 21-aminosteroid U-74389F 5 mg/kg intravenously every 6 hours during the implant and for 24 hours after the removal of the iodine-125 seed. Control animals were administered vehicle only. In both experiments, a statistically significant reduction in volume of radiation damage was observed in the U-74389F-treated group compared with the control group [5)]

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