PA-7

Differential Effects of Minocycline on Caspase- and Calpain-dependent Cell Death After Oxidative Stress

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Minocycline is known to protect neurons from microglia-mediated cell death in many experimental models of brain diseases including ischemic stroke, Huntingtons disease (HD), amyotrophic lateral sclerosis (ALS), traumatic brain injury, multiple sclerosis, and Parkinsons disease. When the activity of caspases was assessed using their fluorescent peptide substrates, activation of caspase-2, 3, 8, and 9 was evident within 2 8 hr following oxidative insult with 0.5 mM hydrogen peroxide in PC12 cells. Minocycline significantly attenuated activation of these caspases up to 18 hr, resulting a significant increase in the cell viability as assessed by MTT assay as well as trypan blue staining. However, cleavage of alpha-spectrin and a cdk5 activator p35, which are known to be substrates for calpain, remained unchanged in the presence of minocycline, suggesting that minocycline did not block caspase-3-independent cell death or necrosis. Moreover, co-treatment with minocycline and a calpain inhibitor calpeptin synergistically inhibited hydrogen peroxide-induced cell death. These data suggest that minocycline directly inhibited apoptosis, but not necrosis, after oxidative insult in PC12 cells