題名:Apoptosis of Cultured Astrocytes Induced by the Copper and Neocuproine Complex Through Oxidative Stress and JNK Activation.

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摘要:Astrocytes play a critical neurotrophic and neuroprotective role in the brain, and improper function of these cells may contribute to the onset of neurodegenerative diseases. Because astrocytes are known to be enriched with Cu chaperone proteins, it is important to understand the factors that may lead to cytotoxic effects of Cu on astrocytes. In this report, we demonstrated a dramatic potentiating effect of neocuproine (NCP), a membrane permeable metal chelator, on Cu, but not Fe or Pb, in inducing apoptosis of cultured astrocytes. It was estimated that individually, CuCl2 and NCP only weakly exhibited cytotoxic effects on astrocytes, with EC50 of 180 and 600mM, respectively. However, NCP at a nontoxic concentration of 10mM markedly reduced EC50 of Cu to 0.35mM (physiological concentration) and Cu (10mM) reduced EC50 of NCP down to 0.06mM. The mechanisms underlying these dramatic potentiation effects are elucidated. NCP increased the

intracellular concentration of Cu in astrocytes and a nonpermeable
Cu chelator, bathocuproine disulfonate was able to abolish all of
the apoptotic signaling. Cell death was determined to be via
apoptosis due to increased reactive oxygen species production,
mitochondrial dysfunction, depletion of glutathione and adenosine
triphosphate, cytochrome c release, c-Jun N-terminal kinase,
and caspase-3 activation, and poly-ADP-ribose polymerase degradation. This finding, coupled with our previous reports,
suggests that metal chelators (NCP, dithiocarbamate and disulfiram)
should be cautiously used as they may potentiate a cytotoxic effect of endogenous Cu on astrocytes. Their clinical
implications in the etiology of neurodegenerative diseases deserve
further investigation.