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Classification of methamphetamine and terminal degeneration

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DESCRIPTION

Endogenous tumor suppressor gene like p53 plays an important role in both apoptosis and cell-cycle arrest. The inactivation of p53 gene occurs in almost half of all human tumors and is considered a critical event in the pathogenesis of many cancers. DNA damage caused by a number of agents including free radicals causes accumulation II of p53 protein with subsequent induction of apoptosis in the damaged cells. The products of this gene may also play a role in the CNS and are likely to be involved in the regulation of neuronal ceil death during development, after injury, and in neurodegenerative disorders. For example, kainic acid, a potent excitotoxin, induces neuronal cell loss and a concomitant increase in p53 expression in rat brain, suggesting that p53 is required in cell death pathway in CNS. The role of p53 protein in METH-induced neurotoxicity has been revealed by the attenuation of METH induced serotonergic neurotoxicity in p53-knockout mice. Furthermore, METH-induced decrease in DA transporters is attenuated in these p53 knockout mice and METH did not cause any decrease in the DA transporter mRNA and the number of TH-positive cells in substantia nigra pars corapacta and the ventral tegmental area of homozygous p53-knockout mice. Also p53- knockout mice has been protected against METH-induced decrease in striatal DA D1 receptors. These evidences provide strong support for the role of the tumor suppressor, p53, in the deleterious effects of METH. The proto-oncogene bcl-2 was initially characterized because of its ability to inhibit apoptosis. Hcl-2 is widely expressed in the nervous system. Bcl-2 expression inhibits apoptosis in neural cells induced by a variety of stimuli. Bd-2 inhibits oxidative neural cell death induced by the glutathione depletion and protects cells from the lethal effects of hydrogen peroxide. Bcl-2 is an antiapoptotic protein located in the outer mitochondrial membrane and it has been shown to either detoxify or decrease the 12 production of reactive oxygen species. There is a direct antioxidant effect of bcl-2 in PC12 rat pheochromocytoma cells. Neural cells expressing bcl-2 have elevated levels of reduced glutathione/oxidized glutathione and NADH/NAD”^, indicating a shift in cellular redox potential to a more reduced state. Bcl-2 also causes the redistribution of glutathione to the nucleus. Substantial evidence implicates the role of reactive oxygen species and the status of glutathione in METH-induced neurotoxicity. Mice overexpressing bcl-2 have been protected against MPTP-induced neurotoxicity and cells overexpressing hcl-2 have been protected against METH-induced apoptosis.

The large and growing body of evidence for the major role of OONO' in a wide variety of human diseases has naturally led to a search for drugs that can detoxify the powerful oxidant. Peroxynitrite is known to undergo acid-catalyzed decomposition by two distinct pathways. Isomerization to nitrate is a major decay route, but a significant portion of the decomposition produces a species with reactivity related to that of a hydroxyl radical. Recently, it has been reported that certain water-soluble iron (III) porphyrins are highly active OONO' decomposition catalysts and that they function by catalyzing the isomerization of ONOO" almost exclusively to nitrate under physiological conditions. These iron porphyrins have profound activity in biological models of ONOO* related disease states and have been investigated as therapeutic agents for 13 diseases in which ONOO" has been implicated. The catalysis of ONOO" by these iron porphyrins dramatically increase the rate of ONOO' isomerization, preempting the formation of oxidizing radical species and generating the harmless nitrate anion. Various Selenium (Se) containing compounds such as ebselen (2-phenyl-1,2-benzisoselenazol-3(2//)-one) react with peroxynitrite very efficiently. Ebselen, selenocystine and selenomethionine protected DNA single-strand break formation caused by ONOO' more effectively than sulfur-containing analogs. Recent evidence established a protective function for the selenium-containing enzyme glutathione peroxidase as well as ebselen and selenomethionine against peroxynitrite, Seleniumcontaining compounds have been hypothesized to act as peroxynitrite reductases. Asahi reported that nitric oxide and its derivative ONOO',

directly inactivate the enzyme, glutathione peroxidase, in a specific manner *via* the production of selenyl sulfide. Therefore, the use of Se or Se-containing compounds might prove a positive approach to counter the oxidations and nitrations resulting from the generation of peroxynitrite.