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Role of nitric oxide and peroxynitrite in methamphetamine

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DESCRIPTION

Methamphetaraine (METH), a potent psychomotor stimulant drug, is known on the street as “speed”, “crystal meth”, or “crank”. Over the last 50 years, epidemics of METH abuse have occurred in many parts of the world, including Sweden, the United Kingdom, Japan, and the United States. To this day, abuse of METH continues, with recent surveys indicating that METH abuse is on the rise. It is a potent, indirectly acting sympathomimetic amine and is self-administered by experimental animals and abused by humans. Although the abuse liability of METH and its congeners was recognized shortly after its discovery, a concerted effort to assess its long-term effects in the central nervous system was made only in the last 15 years. Administration of METH has profound effects on central nervous system functions. Because of the increased frequency of METH abuse, elucidation of its consequent neurochemical, biochemical and molecular impact is important. Some of the potentially dangerous effects of METH on the brain of humans are known. Of particular interest are reports that monoaminergic systems are especially sensitive to administration of this potent stimulant. Our understanding of the duration of these effects and their consequences may provide valuable insight and guidance for treatment and prevention programs. METH neurotoxicity may be an example of a more general process of terminal degeneration or cellular damage that occurs during aging, injury, or the alteration of brain metabolism. The social problems caused by the abuse of METH and its congeners may be caused or compounded by their neurotoxic effects.

Methamphetamine Anb Catecholamines

METH is known to have the potential to damage brain Dopamine (DA) and serotonin (5-HT) systems. Laboratory animals given repeated high doses of METH show large, long-lasting depletions of brain DA and 5-HT, as well as reduction of Vaux and marked long-term reductions in the activity of tyrosine hydroxylase and tryptophan hydroxylase, the concentrations of DA and 5-HT metabolites, and the number of DA and 5-HT transporters. Anatomic studies indicate that loss of presynaptic DA and 5-HT axonal markers is related to damage of distal DA and 5- HT axon projections METH neurotoxicity is also evidenced by morphological changes showing that cells in DA and 5-HT regions are argyrophilic after METH exposure and immunohistochemistry showing swelling and fragmentation of axons in the short-term, and decreased immunoreactivity in the long-term. METH neurotoxicity has been demonstrated in mice, rats, guinea pigs, cats, and rhesus monkeys. Moreover, the toxic effects of METH on brain DA and 5-HT systems in non-human primates persist for up to 4 years, suggesting that they may be permanent, at least in rhesus monkeys given repeated high doses. DA, TH and the DA transporter are reduced in the post-mortem striatum of chronic METH users. METH appears to elicit its effects by acting as a weak base and collapsing the pH gradients of acidic dopamine-containing synaptic vesicles, resulting in redistribution of the neurotransmitter to the cytoplasm where it may undergo either auto-oxidation or metabolism by monoamine oxidase. The METH-induced reductions in forebrain aromatic monoamines were first reported in 1968 for brain DA levels and in 1971 for brain tyrosine hydroxylase activity, Gibb and colleagues also published early reports of such effects, but it was not until these effects were shown to be extremely long-term in primates and rats that they began to be studied in earnest. Since that time, METH neurotoxicity has been investigated using a variety of exposure paradigms. These can be divided into two categories: chronic and acute. Chronic dosing typically exposes animals to a prolonged series of doses or to continuous exposure by osmotic minimum. Conversely, acute dosing exposes animals to one or several high doses, usually by intraperitoneal injection. It is this second, acute approach that has been most employed. Gibb and colleagues involved up to five

injections of 10-15 mg/kg METH at 6-h intervals. A related paradigm exposes animals to four injections of between 4 and 10 mg/kg METH, at 2-h intervals. Seiden and colleagues have developed a rather different approach, involving one, or at most two, injections at very high-dose levels, often 50 or 100 mg/kg METH. These acute exposure techniques can produce substantial mortality, and can have pronounced short-term physiological effects. Such effects have been described both in laboratory animals and in human sufferings from METH toxicity or related congeners. Neuro toxic doses of METH may also transiently increase glutamate release, as seen with neostriatal microdialysis. These increases in extracellular glutamate take the form of gradual rise, normally occurring 4-6 h after METH administration. The METH exposure paradigm can also have long-term effects on brain aromatic monoamines, lasting from days to years. There are reductions in brain levels of DA, 5-HT, their major metabolites, and enzymes related to their synthesis. The DA and 5-HT uptake sites are also reduced in other aromatic monoamine-enriched brain regions, with DA depletions generally more pronounced in the neostriatum. METH-induced decreases in aromatic monoamine content are sometimes accompanied by silver degeneration of an axonal nature, by hypertrophy and an apparent proliferation of astrocytes. Histological studies also document a reduction in tyrosine hydroxylase-positive axons, in 5-HT-positive terminals, in aromatic monoamine fluorescence, and in labeled DA- and 5-HT- uptake sites. Most laboratories report more immediate (within several hours of the last dose of METH) drops in striatal DA when multiple doses of more than 5 mg/kg METH are administered. However, this immediate depletion of DA may be due to a partially reversible inhibition of tyrosine hydroxylase produced by the high doses of METH. Therefore, there may be two other mechanisms by which METH can decrease striatal DA levels, without destroying DA terminals. One mechanism occurs almost immediately and involves the inactivation of tyrosine hydroxylase, and the other has a slower time course of onset that may involve decreased levels of tyrosine hydroxylase in the DA terminals owing to a reduction in synthesis in the nigral cell bodies.