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W06-3
Molecular and cellular mechanisms of ecstasy-induced neurotoxicity

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The amphetamine derivative 3,4-methylenedioxymethamphetamine (MDMA or "Ecstasy"), as well as its N-desmethyl and N-ethyl analogues, 3,4-methylenedioxyamphetamine (MDA) and 3,4-methylenedioxyethylamphetamine (MDEA) are popular recreational drugs of abuse. A growing body of concern has been associated with these drugs, because of their possible neurotoxic effects on human abusers. Following acute or repeated administration to laboratory animals these agents have been shown to induce serotonergic toxicity characterized by neurochemical changes, like long-term brain reductions in the levels of serotonin (5-hydroxytryptamine, 5-HT) and its metabolite 5-hydroxyindoleacetic acid (5-HIAA), reductions in 5-HT uptake sites and tryptophan hydroxylase (rate limiting enzyme for 5-HT biosynthesis) and, also, by histochemical and immunocytochemical evidences of sertonergic terminal loss. In addition, degeneration of other brain cells in several brain areas such as the cortex, hippocampus, and striatum is also observed. Meanwhile, in human "ecstasy" abusers, there are evidences for deficits in serotonergic biochemical markers, which correlate with long-term impairments in memory and learning. There are several mechanisms, frequently interrelated, that contribute to MDMA-induced neurotoxicity, namely the formation of MDMA neurotoxic metabolites, the uptake of MDMA or its metabolites by the 5-HT-transporter, monoamine oxidase metabolism of dopamine and 5-HT, dopamine auto-oxidation, activation of 5-HT_{2A} receptors, mitochondrial impairment, phosphorylation of heat shock proteins and subsequent decrease of its chaperone activity, glutamate excitotoxicity, hyperthermia, formation of reactive oxygen and nitrogen species, and neuroinflammation. This presentation aims to give an updated view on the cellular and molecular mechanisms involved in MDMA neurotoxicity.

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W06-4
Substituted amphetamine-induces neurotoxicity and alterations in blood–brain-barrier function

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Purpose: Substituted amphetamines such as METH and MDMA are most widely abuse drugs. These drugs are capable of producing potent addictive behavior and neurotoxicity in rodents, non-human primates. In the present study we evaluated if an acute injections of METH and MDMA induced neurotoxicity and blood–brain barrier (BBB) dysfunction. *Methods*: Animals were injected with an acute dose of either METH or MDMA (40 mg/kg, i.p.) and allow surviving 4 h after drug administration. Monoamines levels in different brain regions were evaluated. The BBB permeability, brain edema and ion content (Na, K, Cl) and cell injury were examined. *Results*: METH and MDMA produced significant hyperthermia and changes in monoamines levels in different regions of the rat and mouse brains. BBB permeability showed massive extravasations and Evans blue in several brain regions. The magnitude and intensity of Evans blue staining after MDMA injections were more prounced in mice compared to rats. Morphological examination showed distorted neuronal and glial cells, activation of astrocytes, as evident with upregulation of GFAP immunoreactivity. HSP72 immunostaining was most prounced in the nuclei of neurons compared to cytoplasm. Similar results on BBB leakage and brain pathology were found after 4 h METH administration. These data suggest that psychostimulants such as METH and MDMA are capable to disrupt BBB permeability to proteins and induce brain edema formation and neurotoxicity which might associate with oxidative stress and free radicals capable to induce brain pathology through modifying the BBB function.

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W06-5
Molecular interaction between cocaine and opioids. Implications on Speedball's toxicity

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Cocaine and heroin are co-abused by humans, in a combination known as speedball. Besides pharmacodynamic interactions between the two drugs, a chemical interaction was described to occur in cocaine:heroin solutions, involving the formation of a cocaine:morphine adduct, which may have specific biological effects. We have described that cocaine and heroin induce neurotoxicity in rat cortical neurons. We compared the neurotoxic effects of the drugs per se with the effects of their sequential and simultaneous combinations.

Cortical neurons exposed to the mixture presented a higher increase in intracellular calcium concentration, mitochondrial dysfunction and cell death by necrosis, in contrast with cells sequentially exposed to heroin and cocaine, which released cytochrome c to the cytosol and presented higher loss of metabolic viability. These results suggest that cocaine:morphine adducts affect neuronal mitochondrial function. We studied the direct effects of cocaine, morphine and their combination in isolated rat liver mitochondrial function. Cocaine and cocaine:morphine combination promoted the increase in proton leak, respiratory chain complex I inhibition and the decrease in mitochondrial potential. Our results indicate that molecular interactions between cocaine and opioids affect the toxicity of speedball.

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