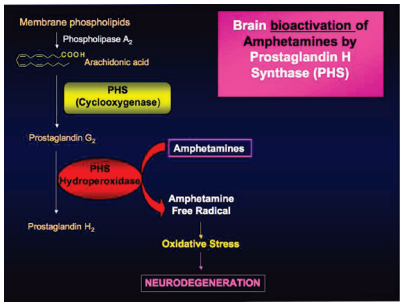
The Agony and the Ecstasy

3,4-Methylenedioxymethamphetamine (MDMA), which is better known as "ecstasy", is a psychoactive amphetamine derivative commonly used as recreational drug. Based on studies primarily in animal model systems, the neurodegenerative potential of MDMA has been proposed. However, this is a source of debate since there is currently a dearth of information on the mechanism by which neurodegenerative damage might occur. Jeng and Wells (DOI: 10.1021/cn900022w) hypothesize that a family of central nervous system enzymes, prostaglandin H synthases, directly bioactivate amphetamines to free radical intermediates that initiate reactive oxygen species formation and neurodegenerative oxidative DNA damage.



Here, they demonstrate that prostaglandin H synthase enzyme converts MDMA to a highly reactive compound capable of causing neurodegenerative DNA damage and that a chemical inhibitor of the enzyme abrogates the neurodegenerative effects of MDMA *in vitro*. The authors also show that MDMA can cause enzyme-dependent DNA oxidation and dopaminergic nerve-terminal degradation in various regions of the mouse brain. These results support MDMA-associated neurodegeneration resulting from the prostaglandin H synthase-catalyzed formation of a neurotoxic MDMA free radical intermediate.

Breaching the Blood−Brain Barrier

The blood−brain barrier is a "fortress" that strictly controls the entry of most peptides and proteins into the brain from the bloodstream. Thus, bioactive molecules that might be effective against brain disorders are prevented from entering the brain. Small fat-soluble compounds can penetrate the blood−brain barrier by passive diffusion, and a minute number of peptides and proteins do so through special gates located at the barrier.

To overcome the problem of limited penetration, scientists have attempted to convert neuropeptides into fat-soluble compounds or to link them to blood−brain barrier-penetrating proteins to permit entry into the brain. However, linking a neuropeptide to a fat-soluble "tail" or to a "shuttle" protein usually produces a therapeutically inactive product. Working with enkephalin peptides, Shechter et al. (DOI: 10.1021/cn100001j) provide a solution to this problem by using blood−brain barrier-permeable compounds that contain a weak chemical bond that allows the neuropeptide to detach in an active form from the inactive (but barrier-permeable) precursor after penetration into the brain. This proof-of-concept study might lead to similar strategies for design of bioactive compounds that penetrate the blood−brain barrier.

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