Amphetamines show potential against Parkinson

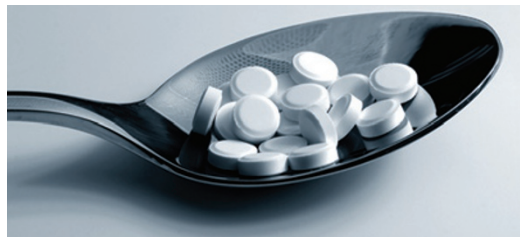
New research on Parkinson disease (PD) has yielded both a promising new mouse model for acute disease and the surprising finding that potential therapeutic compounds might be found among members of the amphetamine family, such as Ecstasy.

The effects of PD are gradual but devastating. Dopamine (DA) responsive neurons in locomotor centers of the brain die as a result of pathological mechanisms that still are not entirely well understood, and once this cell population drops below a critical threshold, the patient is subject to an array of debilitating physical symptoms that can include stiffness, tremor, and slowness of movement. There is only a limited range of pharmacological therapeutic options; compounding this problem has been the difficulty in generating relevant animal models for the disease, and mice have generally proven inadequate for the detailed study of DA-related locomotor disorders.

Marc Caron and his colleagues at the Duke University Medical Center (Durham, NC) had previously developed DAT-KO, a mouse strain deficient in the dopamine transporter (DAT), a protein essential for maintaining functional reserves of neurotransmitter. Now, in a new article from *PLoS Biology* (August), they show that by treating these DAT-KO mice with a compound that inhibits DA synthesis, it becomes possible to transiently establish conditions of extremely low DA—as low as 1 or 2% of control levels—and generate behavioral phenotypes that very closely resemble the symptoms of PD.

The depletion takes place rapidly and lasts as long as 16 hours, during which time the treated DAT-KO mice displayed a dramatic reduction in locomotion, body rigidity, and tremor. By comparison, wild-type mice treated with identical drug dosages showed no symptoms. The authors indicate that this highlights the importance of DA reservoirs—maintained through the action of DAT—for maintaining normal locomotor function even while DA synthesis is being modulated.

The authors recognized the potential of this model for determining the efficacy of treatments for acute PD and proceeded to test a variety of compounds. As expected,



L-DOPA, a natural DA precursor and popular treatment for PD, considerably ameliorated symptoms in these mice. Surprisingly, the authors found that amphetamine derivatives, which act via distinct and DA-independent signaling pathways, also showed some therapeutic benefits. In particular, MDMA—better known as Ecstasy—had a profound impact at high doses, restoring considerable locomotor activity to affected mice. These MDMA doses are too high to be considered practical for therapy, but this work suggests a new and potentially very valuable template for the design of future PD therapeutics—and a useful animal model in which to test them.

Michael Eisenstein

STEM CELLS REPLENISH EMPTY OVARIES

Contrary to long-standing scientific opinion, the female body doesn't put all of its eggs in one basket. A new study suggests that oocyte-depleted mouse ovaries may be replenished from stem cell reservoirs elsewhere in the body.

Recent years have seen dramatic challenges to some of the longest held beliefs in reproductive biology. "This field has been rooted in that concept that there's this fixed pool of eggs provided at birth," explains Jonathan Tilly, a researcher at Massachusetts General Hospital (Boston, MA). "That concept's been, I think, fairly widely accepted for the better part of the past five decades." It was thus a bit of a shock when, in 2004, Tilly's group presented evidence strongly supporting the continuous generation of new oocytes in the ovary throughout the mammalian reproductive life span. Their work built on earlier—but largely ignored—contrarian studies that suggest the existence of a reservoir of germline stem cells in the ovary.

But where have these cells been hiding? In a new study from *Cell* (29 July), Tilly's team presents a surprising possible answer. Initial experiments revealed a population of putative stem cells in the ovary, but their location and number—much too small for the scale of replenishment taking place—led Tilly's group to look for external sources. It immediately occurred to them that bone marrow (BM) stem cells were a strong candidate, because these cells have common lineage with primordial germ cells and are already known to replenish other organs, including the liver and heart. A number of transplantation experiments using recipient mice that have been chemically sterilized or are genetically incapable of producing mature oocytes seem to confirm this, showing that wild-type BM stem cells will rapidly differentiate to form a full spectrum of oocytes and follicles shortly after implantation. The authors suggest a model in which these stem cells may be transported by the peripheral blood to the ovarian medulla, where they can then mature into functioning oocytes and follicles.

Tilly's team is now working hard to confirm whether the oocytes generated from these BM stem cells are in fact fully fertile and functional. If they are, this could provide an important piece in a major puzzle of reproductive biology. Even if they aren't, though, this may not be the end of the story. "We think there still may be a role for these extranatal germ cells in supporting the ovaries through different means," says Tilly. "You actually need far more oocytes than what's needed for fertility to make the tissue work…so it may be that these cells, in lieu of having any fertility, [are] there to support the tissue."

Michael Eisenstein