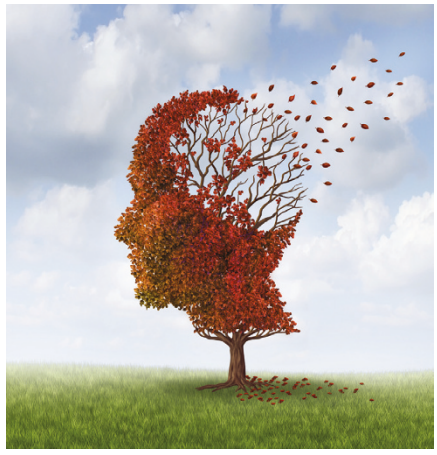
Refining HDAC inhibition to restore memory

Alzheimer disease is a progressive neurodegenerative disorder that impairs memory and mental function. It is the most common form of dementia, accounting for 60–70% of cases, and its prevalence is increasing worldwide, a trend that is expected to continue for the next few decades. Memory loss in Alzheimer disease is driven by the loss of synapses. Previous research has shown that memory can be partially restored in animal models of Alzheimer disease by inhibiting a family of enzymes called histone deacetylases (HDACs), which are involved in transcriptional control of gene expression. HDACs have many roles in the body, however, and manipulating them to improve memory might have unwanted effects on other systems. To minimize these off-target effects, some neuroscientists have suggested refining HDAC inhibition to focus on specific HDAC isoforms. But it is not known which isoforms have the greatest potential to affect memory nor how selective HDAC inhibition might affect synapse formation or function.

Researchers at The Scripps Research Institute (Jupiter, FL) led a study to address these questions. They tested the effects of HDAC inhibitors with different isoform selectivity on synaptogenesis and memory. "We wanted to find out which inhibitors were… the most effective in restoring memory function," said Courtney Miller in a press release. Miller is senior author on the paper describing the study (*Neuropsychopharmacol.* doi:10.1038/npp.2015.93; published online 22 April 2015).

Simultaneous inhibition of HDAC-1, HDAC-2 and HDAC-3 was most effective at stimulating synaptogenesis, whereas selective inhibition of HDAC-1 and HDAC-2 together or of HDAC-3 alone induced much less, even minimal, synapse formation. First author on the paper Gavin Rumbaugh observed, "We found evidence that better synapse growth was associated with less specific inhibition of… HDACs." Spinogenesis similarly responded more robustly to inhibition of three HDAC isoforms than to selective inhibition of HDAC-3. And in a transgenic mouse model of Alzheimer disease, simultaneous inhibition of HDAC-1, HDAC-2 and HDAC-3 restored memory whereas selective inhibition of HDAC-3 did not.



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Taken together, the results indicate that "the key to memory restoration was… synaptogenesis, which required simultaneous inhibition of multiple HDACs," explained Miller. The findings suggest that simultaneous inhibition of HDAC-1, HDAC-2 and HDAC-3 holds promise as a strategy to restore memory in Alzheimer disease, although more studies are needed to find a balance between treatment efficacy and off-target effects associated with HDAC inhibition.

Monica Harrington

TRANSGENERATIONAL EFFECTS OF BPA

Bisphenol A (BPA) is a synthetic industrial chemical found in many household goods and throughout polluted environments. In many animals, BPA can disrupt hormone signaling and even reproductive function, and this raises a concern that ubiquitous BPA exposure is negatively affecting the health of entire ecosystems and human populations. There is therefore much interest in understanding how BPA might affect humans and other animals at different levels of chronic or acute exposure.

Exposure to BPA *in utero* is known to affect reproductive function in developing mice, and recent studies have now shown that it can alter reproductive function for up to three generations (*Toxicol. Appl. Pharmacol.* **284,** 354–362; 2015). Researchers at the University of Illinois administered different dosages of BPA or a control substance to pregnant mice and then monitored female offspring in three subsequent generations for an array of developmental and reproductive parameters. The researchers administered the BPA orally, with the consideration that most humans are exposed to BPA through diet.

Immediate differences were apparent in the first generation of mice, which were exposed *in utero*, and some of these corroborated previous research: at the age of nine months these mice showed higher weights and lower indices for fertility and gestation. The most novel findings, however, arose as some effects persisted into the second and third generations of mice. At the age of nine months, mice of the second generation showed a markedly lower gestational index, and mice of the second and third generations showed lower fertility indices. Some effects even appeared unexpectedly in just the third generation. Mice whose grandmothers were exposed to BPA *in utero* showed delays in sexual development that were not seen in their mothers or grandmothers.

Some of the most pronounced effects were measured in mice whose progenitors received the lowest dose of BPA. Jodi Flaws, who led this study, acknowledged that this might seem counterintuitive, "but with endocrine-disrupting chemicals, it's sometimes the low doses that cause the most profound effects," she noted.

This particular finding emphasizes the importance of investigating chronic exposure to low levels of BPA. Research suggests that BPA has a relatively short half-life and is quickly metabolized in humans, but its pervasive presence can lead to near constant exposure for many people. Some studies have even found BPA in human ovarian follicular fluid, placental tissue and fetal plasma. As BPA percolates through foods, materials and environments it will be important to understand its lasting legacy in affected organisms and populations.

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