# Forage Findings

## Expanding the Definition of EDCs

Endocrine-disrupting chemicals (EDCs) can derail hormone signaling pathways in vertebrates by interacting with estrogen receptors. These same receptors can also serve as unintended docking sites for phytoestrogens, weakly estrogenic chemicals produced by plants to deter herbivores, attract beneficial insects, and recruit symbiotic nitrogen-fixing soil bacteria. Now Jennifer E. Fox, currently of the Center for Ecology and Evolutionary Biology at the University of Oregon, and colleagues report that environmental EDCs and phytoestrogens also share the ability to influence phytoestrogen signaling systems in a manner parallel to EDCs' effects in vertebrates—evidence that these chemicals may have broader biological and ecological impacts than previously appreciated [***EHP* 112:672–677**].

The team focused on the symbiosis between alfalfa and the soil bacterium *Sinorhizobium meliloti*. Alfalfa secretes luteolin and apigenin, phytoestrogens that attract and direct *S. meliloti* to infect the plant's roots, setting the stage for symbiosis. Luteolin also interacts with a bacterial receptor, nodulation D (NodD) transcriptional activator protein, and induces transcription of bacterial *nod* genes. These genes direct formation of root nodules, where *S. meliloti* draws carbon from the plant while providing it a useable source of nitrogen by converting atmospheric nitrogen to ammonia. Plants that have little or no nodulation do not thrive, and crop yields suffer.

The team examined whether EDCs that can bind to vertebrate estrogen receptors and interfere with normal hormone action would also influence luteolin–NodD receptor signaling. They added environmentally relevant concentrations of 62 natural and synthetic environmental EDCs to bacterial cultures, then assayed for receptor-controlled transcription. They also investigated whether NodD receptors bore a molecular resemblance to vertebrate estrogen receptors.

Of the 62 chemicals tested, 45 significantly inhibited *nod* gene activation and luteolin–NodD receptor signaling. The inhibitors represent a variety of chemical classes: organochlorine pesticides, herbicides, polyaromatic hydrocarbons, plastics by-products, polychlorinated biphenyls, hormone-active compounds such as diethylstilbestrol, and phytoestrogens produced by several plants. One chemical, bisphenol A, also induced *nod* gene expression, but only in the absence of luteolin. After comparing the amino acid sequences of NodD and estrogen receptors and the nucleotide sequences of their genes, the team did not find the two proteins to be similar.

**Field of bad dreams?** Research with alfalfa shows that EDCs affect organisms besides vertebrates.

Fox and colleagues conclude that EDCs do affect luteolin–NodD receptor signaling, which implies that the effects of these chemicals are not confined to vertebrates expressing estrogen receptors. They suggest that the current definition of endocrine disruption should be broadened to encompass unconventional environmental targets. **–Julia R. Barrett**

# EMFs and DNA Effects

## Potential Mechanism Elucidated

For many years, scientists have suspected that long-term exposure to extremely-low-frequency electromagnetic fields (EMFs) may be associated with increased risk of neurodegenerative diseases such as Alzheimer disease, Parkinson disease, and amyotrophic lateral sclerosis. Some studies have shown that EMF exposure can damage DNA in a variety of human and animal cells, while others have shown no significant effect. Now Henry Lai and Narendra P. Singh of the University of Washington offer support for speculation that environmental exposure to EMFs is hazardous and that the effects may be cumulative [***EHP* 112:687–694**]. They also offer a potential cellular mechanism for cell damage associated with EMF exposure that may help explain anomalies reported earlier in the literature.

**Not just hot air.** Environmentally relevant levels of EMF exposure, such as those encountered near hair dryers, may cause DNA damage through a two-part mechanism.

Lai and Singh's findings support the so-called free radical hypothesis, which posits that extremely-low-frequency EMFs increase free radical activity in cells, thereby causing DNA damage and disturbing other cellular processes and functions. They and others had shown earlier that free radical damage can lead to cellular necrosis and apoptosis. Such effects are particularly troubling in neurons, because these cells cannot divide and are not replaced when they die—thus the potential link to neurodegenerative diseases.

Lai and Singh exposed groups of rats for 24 or 48 hours to a 60-hertz magnetic field at an intensity of 0.01 millitesla (mT)—a low intensity within the levels that a person could encounter in the environment, for example near electric blankets and hair dryers. They treated some of the groups with one of three drugs, two that are known to decrease cellular free radicals and a third, an iron chelator, that has been implicated in the generation of free radicals.

They found significantly more DNA single- and double-strand breaks in the brain cells of undosed rats that were exposed longer, indicating that the effects were cumulative. In previous research, they had exposed rats to a 0.1-mT field for 2 hours with no detectable increase in DNA double-strand breaks. This suggests a complicated interaction between intensity and duration of exposure in the biologic effects of EMFs, and could explain negative results in other studies.

Among the dosed rats, all three drugs protected against EMF-induced DNA damage. The team therefore proposes that EMF-induced effects arise through a two-stage process. Exposure first upsets iron homeostasis in certain cells, releasing free iron into the cytoplasm and nucleus. This leads to the generation of hydroxy radicals that damage DNA, lipids, and proteins. Lipid damage in the cellular membrane then leads to calcium leakage from internal sites in the cell, triggering the second step: an increase in the synthesis of the free radical nitric oxide. Nitric oxide can also cause more iron-mediated free radicals to be generated.

At that point, say Lai and Singh, if antioxidation processes fail, the cell will undergo necrosis or apoptosis. Thus, the outcome depends on the interaction of a variety of factors, including the preexisting oxidative status of the cell and the parameters of the exposure. The pair speculate that, considering the role iron seems to play in the process, iron-rich human brain tissues such as glial cells, neurons, and myelin may be more susceptible to EMF-induced damage. **–Ernie Hood**

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