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## Natural Chemical Thwarts Estrogen's Heart Protection

In 2002, the National Institutes of Health stopped a large clinical trial when data revealed that women taking estrogen for symptoms of menopause had an increased risk of developing cardiovascular disease. New research suggests that higher risk may be partially explained by the presence of a naturally occurring chemical that blocks estrogen's protective effects on the heart.

The researchers theorize that women taking hormone replacement therapy may be at greater risk of developing heart disease because the chemical 27-hydroxycholesterol (27HC) inhibits the activity of estrogens circulating in the blood. 27-hydroxycholesterol is produced when the body breaks down cholesterol. Decreased estrogen, when combined with high cholesterol, atherosclerosis, or both, could lead to an increased risk of cardiovascular disease.

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Howard Hughes Medical Institute investigator David J. Mangelsdorf and his colleagues published their findings September 16, 2007, in an advance online publication of the journal *Nature Medicine*. Mangelsdorf is at the University of Texas Southwestern Medical Center. Other co-authors were from the New York University School of Medicine and the National Institute of Environmental Health Sciences.

Before this work, it was well known that estrogen may be cardioprotective, said Mangelsdorf, citing human and animal studies that have found estrogen signaling to be important for the maintenance and repair of vascular tissue and the widening of blood vessels. But the evidence was nil that there might be some endogenous antagonist to this protective system. Scientists did know that high levels of 27HC were associated with cardiovascular disease. As cholesterol levels increase, so does the level of 27HC in the body.

There had also been evidence that 27HC interacts with nuclear receptors, a family of proteins that includes estrogen receptors. When hormones or other regulatory molecules activate these receptors, they alter cellular processes by triggering gene activity.

The researchers decided to screen the dozens of known nuclear receptors to test whether any were affected by 27HC. In studies in cultured human cells, they discovered that 27HC specifically and efficiently competes with estrogen for binding to its receptors. In experiments with mice, they showed 27HC prevents estrogen from promoting the repair of damaged blood vessels.

Estrogen signaling also triggers the production of nitric oxide, which protects the cardiovascular system by relaxing blood vessels. The researchers found that 27HC interferes with nitric oxide production, both by blocking the activity of an enzyme needed for its synthesis, and by keeping the gene for that enzyme inactive.

Mangelsdorf and his colleagues found that 27HC specifically interferes with estrogen signaling in cardiovascular tissue. They found that 27HC had different effects on estrogen's action in liver, breast, and colon cells.

Mangelsdorf said that discovering that a single chemical has such well defined effects could offer scientists clues that would aid in developing drugs that affect estrogen receptors in specific tissues. The pharmacologic benefit of such selective estrogen receptor modulators is tremendous because one potential problem with hormone replacement therapy in postmenopausal women is that it stimulates growth of tissues in the breast and uterus, which can promote cancer, he said. Several such drugs with targeted cardioprotective effects are now being tested, he noted.

Mangelsdorf said that 27HC's damaging effects could explain why large clinical studies failed to link hormone replacement therapy to a decrease in heart disease among participants. Women who were recruited into trials such as the Women's Health Initiative study had gone through menopause an average of 12 years earlier, he said. Basically, they had lost the protective effect of estrogen long before; and if they already were at risk and were on their way to atherosclerosis, damage may already have been done due in part to the action of 27-hydroxycholesterol. Giving them estrogen after so long may have made things worse, since one effect of estrogen is that it tends to promote the release of blood clots.

Mangelsdorf said he and his colleagues will explore 27HC's effects in other tissues, as well as its detailed mechanism of action on estrogen receptors. Such studies could yield insights into how to better modulate the complex function of estrogen receptors for therapeutic benefit, he said.