By Rachel E. Gross

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Leer en español

Estrogen is the Meryl Streep of hormones, its versatility renowned among scientists. Besides playing a key role in sexual and reproductive health, it strengthens bones, keeps skin supple, regulates sugar levels, increases blood flow, lowers inflammation and supports the central nervous system.

"You name the organ, and it promotes the health of that organ," said Roberta Brinton, a neuroscientist who leads the Center for Innovation in Brain Science at the University of Arizona.

But appreciation for estrogen's more expansive role has been slow in coming. The compound was first identified in 1923 and was henceforth known as the "female sex hormone" — a one-dimensional reputation baked into its very name.

"Estrogen" comes from the Greek "oestrus," a literal gadfly known for whipping cattle into a mad frenzy. Scientifically, estrus has come to mean the period in the reproductive cycles of some mammals when females are fertile and sexually active.

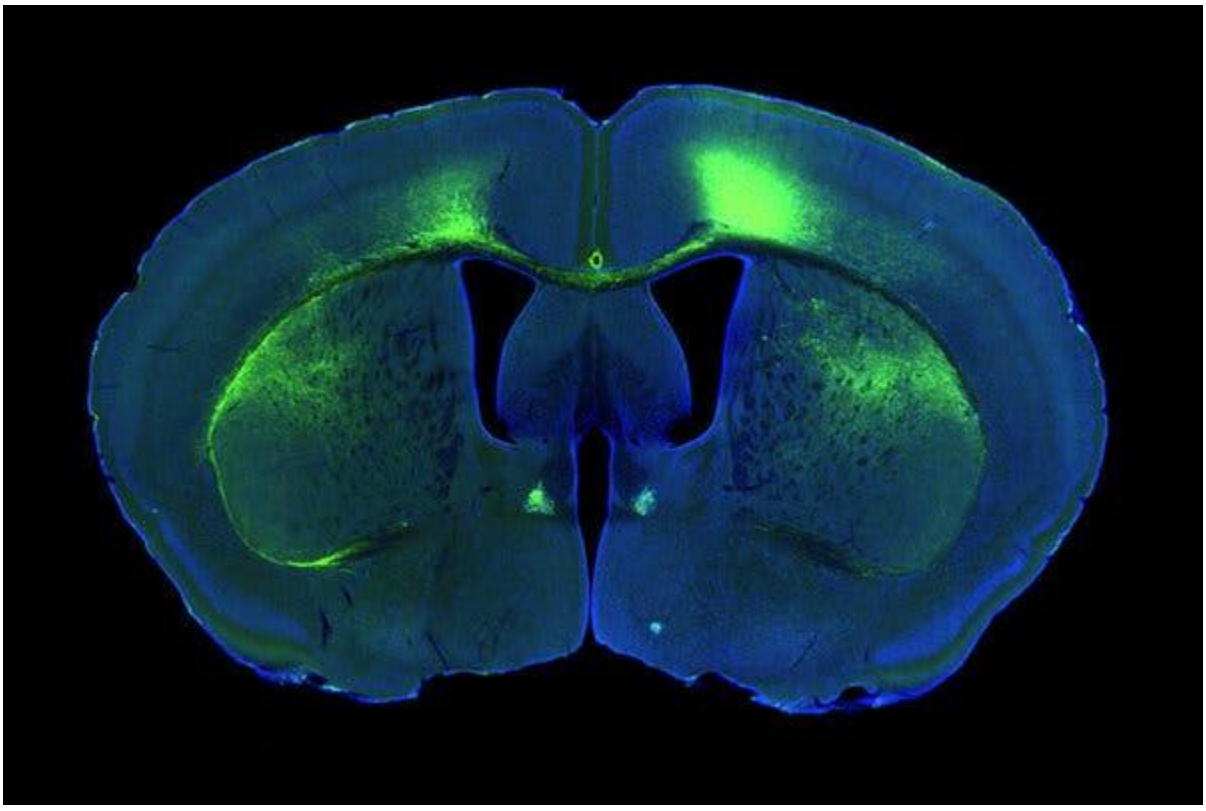
Women don’t enter estrus; they menstruate. Nevertheless, when researchers named estrogen, these were the roles it was cast in: inducing a frenzy and supporting female sexual health. Now, estrogen is gaining recognition for what may be its most important role yet: influencing the brain.

Neuroscientists have learned that estrogen is vital to healthy brain development but that it also contributes to conditions including multiple sclerosis and Alzheimer’s. Changes in estrogen levels — either from the menstrual cycle or external sources — can exacerbate migraines, seizures and other common neurological symptoms.

“There are a huge number of neurological diseases that can be affected by sex hormone fluctuations,” said Dr. Hyman Schipper, a neurologist at McGill University who listed a dozen of them in a recent review in the journal Brain Medicine. “And many of the therapies that are used in reproductive medicine should be repurposed for these neurological diseases.”

Today, the insight that sex hormones are also brain hormones is transforming how doctors approach brain health and disease — helping them guide treatment, avoid harmful interactions and develop new hormone-based therapies.

Estrogen, rising



A fluorescent micrograph of a mouse brain.Credit...Mark and Mary Stevens Neuroimaging and Informatics Institute/Science Source

In women, estrogen is manufactured mainly in the ovaries, with some also produced by the adrenal glands and fat cells. In men, estrogen is converted from testosterone in the testes and is crucial for sperm production, bone strength, liver function, fat metabolism and more.

But in both sexes, the brain also makes its own estrogen, underscoring its neurological importance. “The brain is partially an endocrine organ,” said Lisa Mosconi, a neuroscientist who directs the Women’s Brain Initiative at Weill Cornell Medicine.

It is rich in estrogen receptors, which blink on and off throughout life. These were once thought to be clustered around structures with specific reproductive functions, like the pituitary and hypothalamus. In fact “they’re everywhere,” said Dr. Mosconi, who developed a PET-scanning technique to see these receptors in a living brain. “We couldn’t even find a region that was completely empty,” she said.

In the brain, estrogen can bind directly to receptors within neurons and other cells, setting off a cascade of actions. It can also be broken down into metabolites, called neurosteroids, which exert their own far-reaching effects.

Some of these neurosteroids have already been spun off into their own therapies: Allopregnanolone, a metabolite of progesterone, is the basis of a drug used to treat certain kinds of epilepsy. The same metabolite is in a clinical trial as a potential regenerative therapy for Alzheimer’s disease.

In the womb, a mother’s estrogen helps organize an embryo’s neural circuits, direct the production of brain cells and influence the growth of different brain regions. During major transitions like puberty, pregnancy and menopause, estrogen helps prune and rewire the brain once more.

But researchers now know that estrogen is shaping the brain at all stages of life. It can modulate neuron firing, reduce inflammation, increase neuroplasticity, help turn glucose into energy, prevent plaque from building up and improve blood flow in the brain.

Not all of these effects are positive. In rodents, Dr. Schipper has found, long-term estrogen use can age certain parts of the brain. “None of these hormones only do one thing,” he said.

Pregnancy and the brain

A molecular model of an estrogen receptor and estradiol. Credit...Laguna Design/Science Source

Neuroscientists in the past knew estrogen had impacts beyond the reproductive system. But they opted not to study them: Before 2016, they generally excluded female animals from experiments, to avoid having to deal with differences in behavior and physiology associated with cycling hormones.

“How are you going to know if estrogens are neuroprotective if you don’t even do any experiments in females?” said Dr. Rhonda Voskuhl, a neurologist at the Comprehensive Menopause Program at the University of California, Los Angeles. “Give me a break.”

In 1998, Dr. Voskuhl was searching for a molecule that would protect the brain from the effects of multiple sclerosis, in which the immune system attacks nerve cells, stripping them of their protective coating. M.S. afflicts about a million Americans, most of them women.

Drugs already existed to lower inflammation and help prevent further nerve-stripping. But they could only do so much. “You’ve got to add something directly targeting the brain,” Dr. Voskuhl said.

Her hunt began with a clinical observation: Pregnancy was known to protect women against M.S. symptoms. During the third trimester, relapse rates drop by 70 percent; pregnancy, it seems, is at least as effective as the best medications. But this protection is temporary. After childbirth, the risk of relapse rises sharply.

Dr. Voskuhl knew that the immune system quiets down in pregnancy, presumably to protect the delicate, half-foreign graft that is an embryo. But she suspected there was more to it. “It makes sense that the mother would have something that’s not only anti-inflammatory but is neuroprotective,” she said.

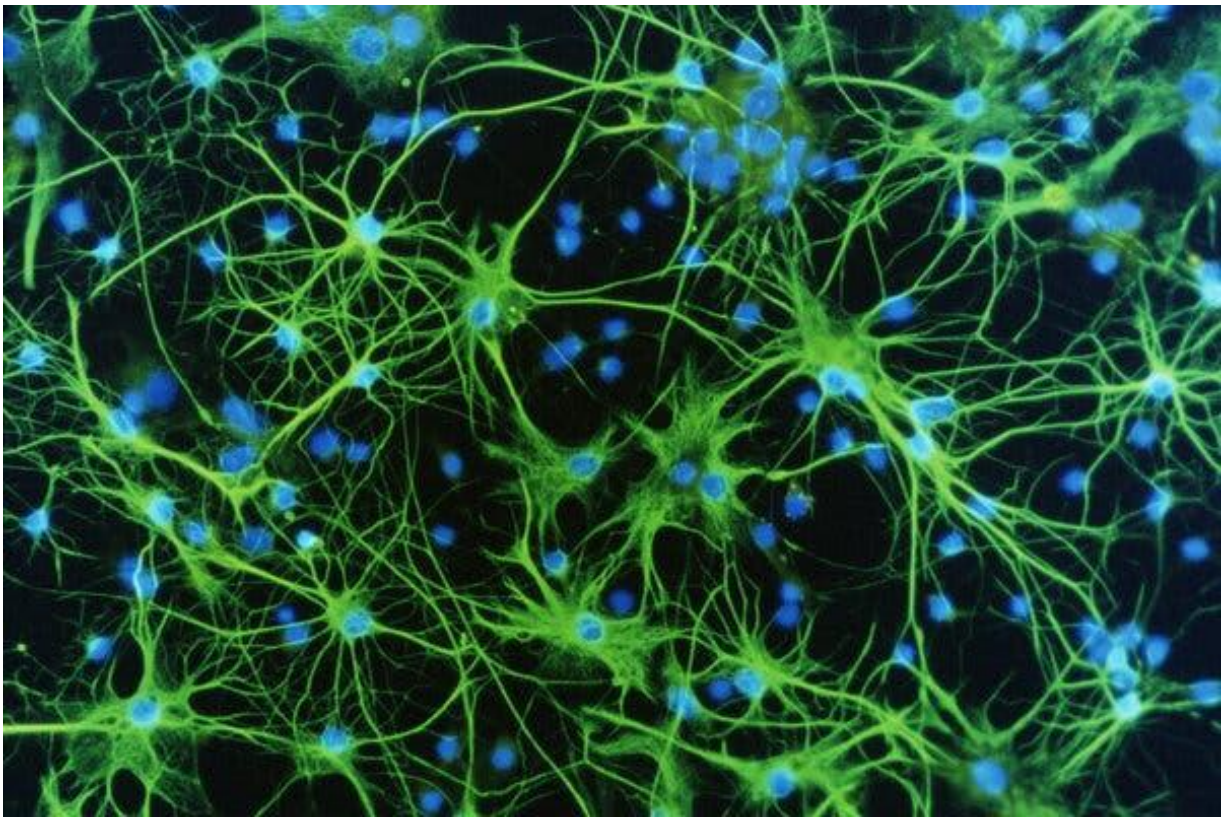
That substance turned out to be estriol, a form of estrogen primarily produced by the placenta. In 2016, in a randomized clinical trial of 164 women, Dr. Voskuhl showed that estriol treatment given over two years significantly reduced relapses of M.S. It also appeared to improve cognition and reduce atrophy of gray matter.

Estriol was known to be safe: Menopausal patients in Europe have been using it for decades. And unlike estradiol, it doesn’t bind strongly to receptors in the breast, meaning it doesn’t come with the same long-term breast cancer risk. It could even potentially be used in men, Dr. Voskuhl said. “It’s a gift to scientists,” she added.

Dr. Voskuhl is now studying whether the finding holds not just for M.S. patients but for all women undergoing menopause. She has developed a patented hormone therapy, PearlPAK, that contains estriol and is being sold by the company CleopatraRX, for which she is the medical advisor.

The website claims that PearlPAK can address “memory and cognitive health issues caused by menopause.” But that is the hypothesis Dr. Voskuhl is trying to test, by annually monitoring women on PearlPAK with cognitive tests. The need was too urgent, she said, for women to wait for the unlikely event that the N.I.H. or a pharmaceutical company will fund a randomized clinical trial. “I’m just taking the way we do things in M.S. and trying to apply it to menopause,” she said.

A fraught legacy



A microscopic view of immunofluorescent brain nerve fibers.Credit...N. Kedersha/Science Source

This would not be the first time estrogen therapy has been suggested as a cognitive cure-all for menopausal women. “Before 2000, it looked like estrogen was a panacea,” Dr. Schipper said.

At that time, the hormone was thought to protect the aging brain against stroke and Alzheimer’s, an idea supported by numerous animal studies and a few observational human studies.

The tide turned in 2003. The Women’s Health Initiative Memory Study, a landmark clinical trial tracking long-term effects of hormone therapy in postmenopausal women, found that older women in the study taking estrogen — as opposed to estrogen plus progesterone — had twice the risk of dementia compared with those on a placebo.

Doctors stopped prescribing estrogen to postmenopausal women, and women stopped taking it out of fear. The attitude among many scientists was: “Why study it? Nobody’s going to take estrogen anymore, so there’s no point,” said Margaret McCarthy, a neuroscientist at the University of Maryland. “It was terrible for the research.”

Later it became clear that this finding held only for women who started on estrogen therapy at 65 or older, at least 10 years past their last menstrual period. For women 50 to 55, a meta-analysis found, estrogen’s effect on dementia risk was neutral. Younger women were not included in the Women’s Health Initiative.

“Timing is everything,” said Dr. JoAnn Manson, a W.H.I. investigator and a neuroendocrinologist at Brigham and Women’s Hospital who led the meta-analysis. “There is growing evidence that there is a critical window for exposure to estrogen in terms of having cognitive benefits.”

Researchers now had to go beyond the idea that estrogen was neuroprotective and ask a more nuanced question: Exactly when, and how, does this hormone protect the brain?

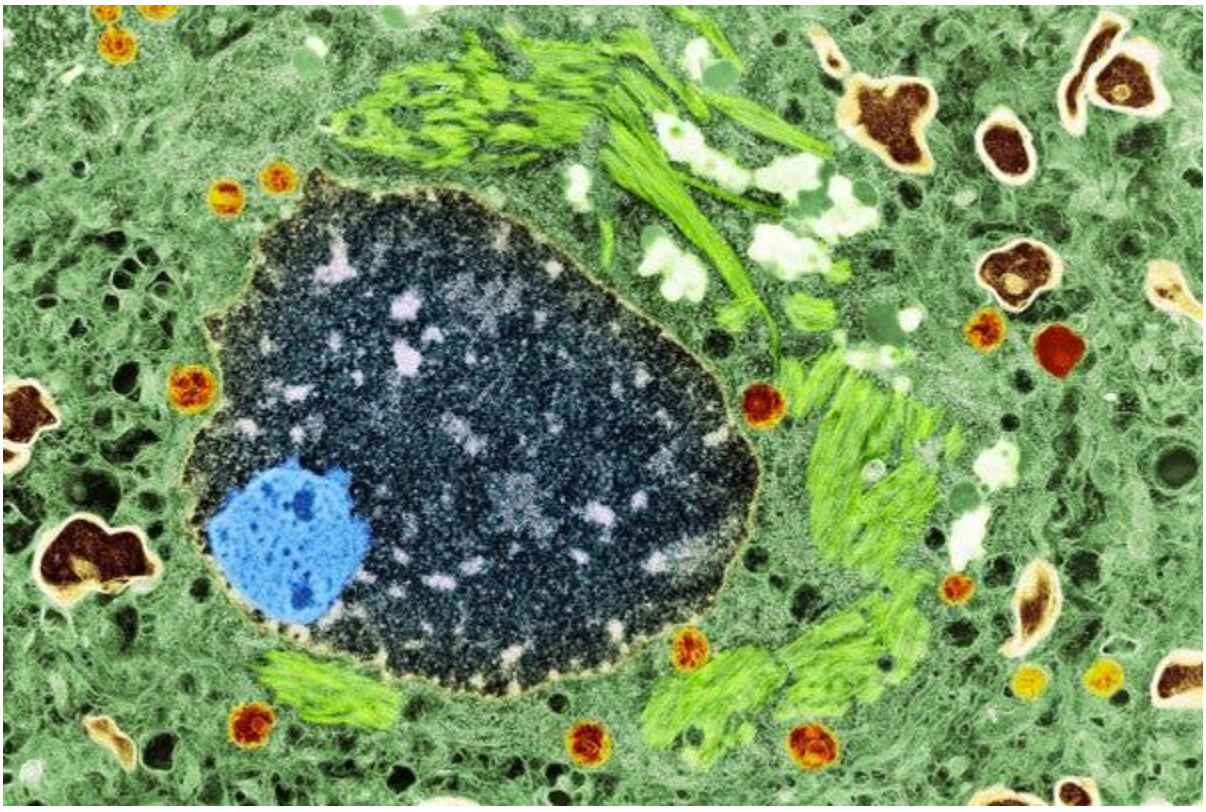
Zeroing in on Alzheimer’s origins

Nowhere is the role of estrogen in brain health more apparent than in menopause, when its retreat may contribute to the cognitive symptoms that women in midlife know and hate: hot flashes, interrupted sleep, brain fog. Estrogen loss is a primary reason, some neuroscientists believe, that Alzheimer’s afflicts twice as many women as men.

As estrogen levels decline, the brain’s metabolism shifts. Up until menopause, the brain runs largely on glucose, which estrogen helps convert into energy. At menopause, the brain begins relying on alternate fuels, including its own white matter, Dr. Brinton has found in animal studies.

“It’s a starvation response,” she said. “This has nothing to do with reproductive capability, but everything to do with the brain undergoing a transition state.”

This shift could mark when vulnerability to Alzheimer’s begins — and, theoretically, when estrogen therapy or another intervention could help prevent cognitive decline. But Dr. Brinton had no way to see it in a human brain. In 2014, she approached Dr. Mosconi, a neuroimaging expert, for help.



A transmission electron micrograph of a neuron in Alzheimer's disease.Credit...Thomas Deernick, NCMIR/Science Source

At that point, doctors could measure estrogen levels only in the blood. But millions of Americans were on some kind of estrogen-based therapy, Dr. Mosconi realized, and nobody knew what it was doing to their brains. "It's ridiculous," she said. So she developed an imaging technique to see estrogen receptors in the brain, by repurposing a tracer used for detecting the same receptors in breast cancer.

In 2024, she and Dr. Brinton were surprised to learn that, after menopause, the number of estrogen receptors in the brain appeared to drastically increase, perhaps in an attempt to grab more of this hormone. But, intriguingly, the more estrogen receptors a woman had, the worse her memory and cognitive scores were.

In February, Dr. Mosconi started a $50 million research program funded by Wellcome Leap called Cutting Alzheimer's Risk Through Endocrinology. She hopes to identify which women are most at risk of Alzheimer's because of estrogen-related brain changes, and figure out whether hormone therapy given during a critical time window could help lower their risk.

Filling in a neurological blind spot

As researchers gain a more nuanced understanding of how sex hormones affect the brain, some physicians worry that the knowledge is taking too long to reach clinics. "It affects my practice significantly," Dr. Schipper said. "It should affect every neurologist's practice."

For example, Dr. Schipper might treat a patient with menstrually related epilepsy by increasing her epilepsy medication during the late luteal phase of her period, when spiking estrogen levels increase the likelihood of seizures.

He would also avoid prescribing her Dilantin, a common anticonvulsant, he said. Many neurologists are unaware that Dilantin speeds up the metabolism of the liver, causing it to break down the hormones in birth control; even if the patient is on birth control, she could accidentally get pregnant. "It never crosses their mind," Dr. Schipper said.

Similarly, Dr. Jelena Pavlovic, a neurologist at the Albert Einstein College of Medicine in New York City, found that women with menstrually related migraines are more vulnerable to headaches right after their uterine lining sheds, when estrogen levels drop sharply. Understanding that link allows her to give preventative treatment when it will be most effective.

"We really need integration of women's health issues into neurology," said Dr. Pavlovic, who is one of the few neurologists specializing in headache disorders and sex hormones.

Dr. Voshkul, whose work also spans gynecology and neurology, agreed. When doctors who treat brains don't share knowledge with doctors who deal with hormones, and vice versa, she said, patients suffer.

"The answers are there," she said. "If they talk to each other, the answers are there."

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