Oestrogen is gaining recognition for what may be its most important role yet. **Rachel E. Gross** has the story

BRAIN HORMONE

Oestrogen 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 in the US.

Now, oestrogen is gaining recognition for what may be its most important role yet: influencing the brain.

Neuroscientists have learned that oestrogen is vital to healthy brain development but it also contributes to conditions including multiple sclerosis and Alzheimer's. Changes in oestrogen 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 in the US, 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.

In women, oestrogen is manufactured mainly in the ovaries, with some also produced by the adrenal glands and fat cells. In men, oestrogen 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 oestrogen, 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 in the US. It is rich in oestrogen receptors.

GENDER BIAS: Neuroscientists knew of oestrogen's far-reaching impact but opted not to study it till recently. istock.com/fizkes

In the brain, oestrogen 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 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 also in a clinical trial as a potential regenerative therapy for Alzheimer's disease.

In the womb, a mother's oestrogen helps organise 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, oestrogen helps prune and rewire the brain once more.

But researchers now know that oestrogen is shaping the brain at all stages of life.

Neuroscientists in the past knew oestrogen 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 behaviour and physiology associated with cycling hormones.

In 1998, Dr Rhonda Voskuhl, a neurologist at the Comprehensive Menopause Program at UCLA, US, was searching for a molecule that would protect the brain from the effects of multiple sclerosis. MS afflicts about 1 million Americans, most of them women.

Her hunt began with a clinical observation: pregnancy was known to protect women against MS symptoms. After childbirth, the risk of relapse rises sharply.

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 is not only anti-inflammatory but is also neuroprotective," she said.

That substance turned out to be estriol, a form of oestrogen primarily produced by the placenta. In 2016, in a randomised clinical trial of 164 women, Voskuhl showed that estriol treatment given over two years significantly reduced relapses of MS. It also appeared to improve cognition and reduce atrophy of grey 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. Voskuhl said. "It's a gift to scientists," she added.

Voskuhl is now studying whether the finding holds not just for MS patients but for all women undergoing menopause.

Nowhere is the role of oestrogen 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. Oestrogen loss is a primary reason, some neuroscientists believe, that Alzheimer's afflicts twice as many women as men.

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

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

In February, Mosconi started a $50 million research programme 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 oestrogen-related brain changes, and figure out whether hormone therapy given during a critical time window could help lower their risk.

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