Medical Xpress

Study may explain why stroke risk in women changes after menopause

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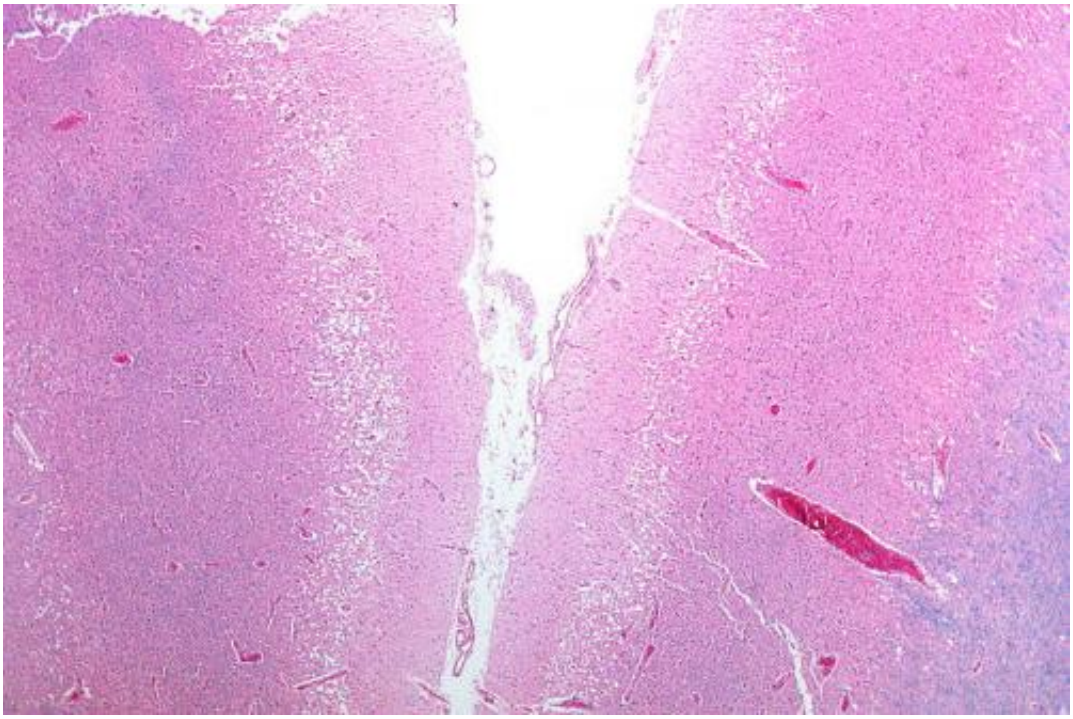

Micrograph showing cortical pseudolaminar necrosis, a finding seen in strokes on medical imaging and at autopsy. H&E-LFB stain. Credit: Nephron/Wikipedia

Risk of stroke in women may come down to a compound the body produces from estrogen known as 2-methoxyestradiol (2-ME). Furthermore, the compound's therapeutic potential may extend beyond treating stroke in women to healing brain injuries in men, a new study in *American Journal of Physiology—Endocrinology and Metabolism* reports.

Microglia, the immune cells of the brain, maintain the brain and protect it from infection by consuming damaged cells and bacteria—a process called phagocytosis—and releasing toxic molecules to induce injured cells and bacteria to die. The same processes help "clean up the mess" after brain injury, such as after stroke or a head impact, says Edwin Jackson, PhD, of the University of Pittsburgh and the study's collaborating investigator. However, overactive microglia may kill brain cells that otherwise would have survived the injury, worsening instead of healing the damage, Jackson explains.

Mouse microglial cells exposed to 2-ME multiplied less and had reduced immune activity: 2-ME stopped phagocytosis and the release of toxic molecules by microglia. "2-ME prevented microglia from becoming overly active," Jackson says.

The findings help explain why risk of stroke in women changes after menopause. Menopause occurs when the ovaries stop producing the female sex hormones estrogen and progesterone. Prior to menopause, women have a lower risk of stroke compared to men. After menopause, women are at a higher risk. "Our study shows that microglia can metabolize (change) estradiol into 2-ME. So the female advantage before menopause may be in part the result of microglia making 2-ME from estradiol. Once estradiol levels collapse with menopause, the female advantage is lost. Administration of 2-ME could restore the female advantage," Jackson says. Estradiol is an estrogen and the primary female sex hormone.

The use of 2-ME is not limited to women. "Although 2-ME is derived from estradiol, 2-ME is not estrogenic and can be used in both women and men," Jackson notes. Because 2-ME "calms" microglia, it may be useful in treating or preventing other brain injuries including traumatic brain injury and chronic traumatic encephalopathy—the injury commonly found in professional football players and athletes in other

contact sports, he says.

According to Jackson, current research on 2-ME supports that the compound is safe. "Unlike estradiol, 2-ME has anti-cancer activity, is cardio-protective and has beneficial activity in models of pulmonary artery hypertension. In fact, a slow-release formulation of 2-ME was developed and validated in a phase I clinical trial for pulmonary artery hypertension."

The next step is to corroborate 2-ME's effects, says Raghvendra Dubey of the University of Zurich and the study's lead investigator. These findings in cells "provide important leads which need to be further confirmed using in vivo (animal) models of brain injury," he says.

The article "2-Methoxyestradiol, an endogenous 17β-estradiol metabolite, inhibits microglial proliferation and activation via an estrogen receptor-independent mechanism" is published ahead-of-print in the *American Journal of Physiology—Endocrinology and Metabolism*.

More information: 2-Methoxyestradiol, an Endogenous 17β-Estradiol Metabolite, Inhibits Microglial Proliferation and Activation via an Estrogen Receptor-Independent Mechanism. *American Journal of Physiology - Endocrinology and Metabolism*. Published 5 January 2016 Vol. no. , DOI: 10.1152/ajpendo.00418.2015

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