Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

17α-Estradiol

Evidence Summary

Compelling for its anti-aging, anti-inflammatory, and pro-cognitive properties, but the evidence is limited to preclinical studies.

Neuroprotective Benefit: Strong Aβ-decreasing, anti-inflammatory, and pro-cognitive properties of 17α-estradiol offer promise for neuroprotection, but evidence is limited to preclinical studies.

Aging and related health concerns: Very promising for its lifespan-extending and anti-inflammatory properties, but no data exist in humans yet.

Safety: Based on one safety trial in postmenopausal women and a few trials in people with hair loss, side effects were rare and mild; no clinical data exist for long-term treatment.

What is it? 17α-estradiol is a naturally-occurring isomer of 17β-estradiol, the primary female sex hormone in women. In contrast to 17β-estradiol, 17α-estradiol is thought to be a non-feminizing estrogen with significantly reduced binding affinity for the classic estrogen receptors ERα and ERβ (Toran-Allerand et al., 2002). 17α-estradiol is likely to be the predominant ligand for the estrogen receptor X (ER-X). 17α-estradiol is a minor component (~5%) of the hormone replacement medication Premarin™.

Neuroprotective Benefit: Strong Aβ-decreasing, anti-inflammatory, and pro-cognitive properties of 17α-estradiol offer promise for neuroprotection, but evidence is limited to preclinical studies.

Types of evidence: (bullet points)

- 0 meta-analyses or systematic reviews
- 0 clinical trials or observational studies
- 5 laboratory studies, 2 in AD mouse models, 2 in rats, and 1 in cell culture

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?: None available.

Human research to suggest benefits to patients with dementia: None available.

Mechanisms of action for neuroprotection identified from laboratory and clinical research: All studies examining the neuroprotective effects of 17α-estradiol have been carried out in rodents, and it is currently unknown whether similar benefits can be expected in people.

In a mouse model of Alzheimer's disease (AD), 17α-estradiol treatment for 6 weeks (~0.8 mg total across 6 weeks) decreased Aβ levels by 38%, which was greater than the effect seen with 17β-estradiol (27%) (Levin-Allerhand et al., 2002). In another study, middle-aged AD mice treated with 17α-estradiol for 60 days (sustained release of up to 1.5 mg total across 60 days) had significantly reduced inflammation (microglial activation) and neuronal loss in the hippocampus (Manaye et al., 2011). Cell culture studies also show that 17α-estradiol pretreatment prevents the increase in cellular calcium levels that result from an Aβ insult (Kawahara and Kuroda, 2001).

In rats, 17β-estradiol and 17α-estradiol were equally protective against cognitive deficits (induced by a drug, scopolamine) and both had significant antioxidant and anti-inflammatory activities (decreased

MDA and nitrite levels, increased SOD levels, and decreased TNFα) (Kaur et al., 2015). It is worth noting that 17α-estradiol appeared more effective than 17β-estradiol at reducing nitrite levels.

Roberta Diaz Brinton, PhD, has proposed the "healthy cell bias" hypothesis of estrogen actions in the brain, which suggests that estrogens are protective in healthy cells but may be harmful in diseased states (Yao et al., 2012). For example, in cell culture, 17β-estradiol is protective when applied prior to or during Aβ42 insult. It is not protective if applied after—and exacerbates Aβ42-induced apoptosis. It is currently unknown if this "healthy cell bias" extends to women and/or to 17α-estradiol.

APOE4 interactions: Unknown

Aging and related health concerns: Very promising for its lifespan-extending and anti-inflammatory properties, but no data exist in humans yet.

Types of evidence:

- 0 meta-analyses or systematic reviews
- 0 clinical trials or observational studies
- 5 laboratory studies, 2 on mouse lifespan, 1 on metabolism and inflammation, and 1 on ischemia
- 2 reviews

Lifespan: BENEFIT. The National Institute on Aging Interventions Testing Program (NIA ITP) is designed to test compounds such as 17α-estradiol that are purported to extend lifespan and/or delay onset of age-related diseases. This program is a collaborative effort that uses 1) parallel studies in males and females at 3 different sites, 2) genetically heterogeneous mice to guard against conclusions based on a single inbred genotype, and 3) enough samples to provide statistical power.

In the 2014 report, mice were fed 4.8 mg/kg/day of 17α-estradiol from 10 months of age (Harrison et al., 2014). While the median lifespan pooled across 3 test sites showed that 17α-estradiol increased lifespan by 12%, this effect was driven primarily by one test site that showed a 28% extension compared to the two other test sites that showed an increase by only 3%. Interestingly, median lifespan increased in males but not in females. The reasons for this sex-specific benefit are unknown. However, hepatic lipidosis (fatty liver) decreased in males from 27% to 6%, but was unchanged in females, which may partly explain the preferential benefits on male survival. A potential confound was the short lifespan of

the male controls at 2 out of the 3 test sites, while control female lifespan was long and comparable across 3 sites. While the reasons are unknown, the shorter lifespan in control males may have partly contributed to the proportionally larger lifespan extension with 17α-estradiol.

In a follow-up study published in 2016, the dose of 17α-estradiol was increased 3-fold to 14.4 mg/kg/day, which increased median lifespan by 19% in male mice (Strong et al., 2016). The effect was significant at all 3 sites (26, 9, and 23%). Similar to the previous study, there were no significant effects on female mice survival. Interestingly, males treated with 17α-estradiol lived longer on average than females (control or 17α-estradiol-treated). The potential mechanisms of action were not directly correlated with lifespan, but may include improved metabolic function and decreased inflammation, described below.

Weight loss/Metabolism: BENEFIT. Male mice receiving 4.8 mg/kg/day of 17α-estradiol from 10 months of age were on average ~10% lighter at 12, 18, and 24 months of age compared to controls (Harrison et al., 2014). Females treated with 17α-estradiol were ~7% lighter than controls.

17α-estradiol alleviates age-related metabolic and adipose tissue dysfunction in mice (Stout et al., 2016). In aged male mice (18 and 20 months old), 17α-estradiol prevents the increase in body mass and visceral adiposity by decreasing leptin, energy intake, fasting glucose, insulin and liver triglycerides, and increasing insulin sensitivity. In the brain, 17α-estradiol increases hypothalamic mRNA levels of anorexigenic genes (ERα, leptin receptor, melanocortin 4 receptor, POMC). Some of the effects of 17α-estradiol, such as increased AMPK activity and reduced mTOR activity, are similar to those seen with caloric restriction (Newman et al., 2016).

Inflammation: BENEFIT. In aged male mice (18 months old), 17α-estradiol treatment for 15 weeks decreased inflammation in adipose tissue (TNFα, IL-6, MCP-1, IL-1α, IL-1β)(Stout et al., 2016).

Ischemia: BENEFIT. In a rat model of ischemia (middle cerebral artery occlusion), 17α-estradiol pretreatment (24 hours prior to occlusion) significantly improved survival rate and substantially reduced brain lesion size by 55-81% (Simpkins et al., 1997). The magnitude of benefit was similar to that observed with 17β-estradiol pretreatment. 17β-estradiol post-treatment (40 min post-occlusion) also decreased mortality and lesion size—17α-estradiol was not tested in these experiments.

Safety: Based on one safety trial in postmenopausal women and a few trials in people with hair loss, side effects were rare and mild; no clinical data exist for long-term treatment.

Types of evidence:

- 1 phase I double-blind randomized controlled trial testing safety in postmenopausal women
- 1 double-blind randomized controlled trial in people with alopecia (in German; not accessible)
- 1 open-label, phase 4 study in women with female pattern hair loss
- 2 mouse lifespan studies

Details. Drug interactions are unknown and only a few studies have been carried out in humans.

In a small phase I safety study of 8 healthy postmenopausal women, single ascending oral doses of 17α-estradiol (MX-4509; 50, 100, and 200 µg, 7 days in between doses) were well-tolerated and no adverse events were reported (Dykens et al., 2005). All biochemistry, hematology, urinalysis, vital signs, and ECG measurements were within normal ranges. There was also no detectable conversion of 17α-estradiol to 17β-estradiol, the latter of which more strongly activates ERα, which in turn can promote tumorigenesis in the breast and reproductive organs (Higa and Fell, 2013).

Topical application has also been tested. In a double-blind randomized controlled study in 51 people with hair loss, topical application of 0.025% 17α-estradiol for 6 months did not cause any side effects, though the paper was in German and only the abstract was accessible (Orfanos and Vogels, 1980). In a more recent open-label non-comparative clinical trial in 53 women with female pattern hair loss, daily topical application of 0.025% 17α-estradiol (Ell-Cranell® alpha 0.025%) was well-tolerated for 8 months (Kim et al., 2012). Side effects included an itching sensation and irritation at the application site—no systemic reactions were observed.

In male mice, 17α-estradiol (14.4 mg/kg/day) does not appear to be feminizing (Stout et al., 2016). It did not significantly alter gonadal or seminiferous tubule mass, though means were lower in the 17α-treated compared to controls. No group differences were found in testosterone and 17β-estradiol levels. However, this study was not part of the ITP study and may have not had sufficient power to detect changes in male reproductive organs or hormone levels.

In female ovariectomized mice, 14.4 mg/kg/day of 17α-estradiol, the higher dose used in the ITP study, increased uterine weight to levels comparable to those of surgically-naïve controls (Strong et al., 2016). Compared to 17β-estradiol, 17α-estradiol is a significantly weaker agonist to the classical estrogen

receptors (ERα and ERβ), but at sufficient high concentrations it likely activates these receptors and modulate reproductive and other estrogen receptor-mediated functions in both males and females. The finding on uterine weight raises concerns for potential uterotrophic effects such as endometriosis and cancer. The dose that generates the best anti-aging benefit without initiating the feminizing/tumorigenic effects is currently not known. It is worth noting that most deaths in the mice used in the NIA ITP studies are attributable to some form of neoplasia (abnormal growth). More research on the role of 17α-estradiol on oncogenesis is needed.

Sources and dosing: The hormone is not on the market in the US. In the phase I safety trial in postmenopausal women, single ascending doses of 50, 100, and 200 µg were used and well-tolerated (Dykens et al., 2005). For treatment of hair loss, topical formulations with 0.025% 17α-estradiol (Ell-Cranell® alpha 0.025%) improved hair counts and diameter and side effects were mild (Orfanos and Vogels, 1980; Kim et al., 2012). In mice, doses of 4.8 mg/kg and 14.4 mg/kg have been used, with the latter producing more consistent results in increasing lifespan in males (Harrison et al., 2014; Stout et al., 2016). However, the higher dose also increased uterine weight in females (Strong et al., 2016). The human equivalent doses based on body surface area are 0.62 mg/kg and 1.87 mg/kg, respectively.

Research underway: No clinical trials are under way. NIH is currently funding Dr. Michael Stout at the University of Oklahoma Health Sciences Center for preclinical work on the effects of 17α-estradiol on diabetes and inflammatory disorders (K99AG051661).

Search terms:
Pubmed, Google: 17α-estradiol, 17αE2, alphatradiol

- + dementia (9), + cognitive (6), + ApoE4 (0), + Alzheimer's (23), + aging (13), + safety (11), + inflammation (4), + alopecia (3), + lifespan (1)

Clinicaltrials.gov, NIHRePORT: 17α-estradiol, 17αE2

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.