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.

DHED

Evidence Summary

DHED, a prodrug that converts to 17β-estradiol exclusively in the brain, has therapeutic potential for cognitive decline, menopausal symptoms, and ischemia, but all data are preclinical.

Neuroprotective Benefit: DHED improves cognitive function in rodent models of aging/menopause and AD, but it has not been tested in people yet.

Aging and related health concerns: DHED has therapeutic potential for ischemia, hot flushes, and depression, without concerns for breast, uterine, and ovarian cancers, but no studies have tested it in humans.

Safety: Because DHED does not increase circulating estradiol levels, it does not carry cancer (breast, uterine, ovarian) and cardiovascular risks, though no evidence is yet available in humans.

What is it? DHED (10β, 17β-dihydroxyestra-1,4-dien-3-one) is a small-molecule bioprecursor prodrug that converts to 17β-estradiol in the brain after systemic administration, but remains inert in the rest of the body (Prokai et al., 2015). This is because DHED is a substrate for an enzyme (SDR; short-chain NADPH-dependent dehydrogenase/reductase) that is selectively expressed in the brain. DHED is inactive as an estrogen because it has no measurable affinity to the classical estrogen receptors. Because female hormones have wide-ranging effects throughout the body, chronic use of estrogens to treat menopausal symptoms can have adverse effects on peripheral tissues, including cancers of breast and reproductive organs (Taylor and Manson, 2011). Because of its brain-specificity, DHED capitalizes on estrogen's neuroprotective effects without the harmful peripheral side effects. Thus, the translational potential of DHED is being evaluated with the hopes that it may more safely treat neurological and psychiatric symptoms in women undergoing early and surgical menopause.

Neuroprotective Benefit: DHED improves cognitive function in rodent models of aging/menopause and AD, but it has not been tested in people yet.

Types of evidence:

- 2 laboratory studies, 1 in a mouse model of AD and 1 in a model of aging/menopause

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: Systemically administered DHED is rapidly taken up by the brain and conversion to 17β-estradiol occurs in all brain areas, with the cortical areas showing the highest levels (Prokai et al., 2015).

In a mouse model of AD (APPswe/PS1dE9 mice), DHED treatment (osmotic minipump, 2 µg/day) for 8 weeks reduced brain Aβ levels and improved cognitive performance (Tschiffely et al., 2016). Treatment started at 6 months of age when behavioral deficits first appear in this model. The magnitude of changes in cognitive scores and Aβ levels were comparable to the effects seen with 17β-estradiol.

In a rat model of aging and menopause (middle-aged and ovaries surgically removed), continuous administration of DHED (osmotic minipump, 4 µg/day) for 48 days significantly decreased working

memory errors, as measured by the delay match-to-sample plus maze test, compared to controls (Prokai et al., 2015).

DHED exerts its neuroprotective effects in manners similar to 17β-estradiol. DHED increased spine/synapse density in the hippocampal CA1 neurons, increased the number of cholinergic neurons in the medial septum and vertical diagonal band, and stimulated progesterone receptor expression in the hypothalamus (Prokai et al., 2015). The DHED effect on progesterone receptor expression was abolished when co-treated with an estrogen receptor antagonist, ICI 182780.

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. If this theory is true, DHED may only be protective at an early stage of AD (or before the appearance of neuropathology).

APOE4 interactions: Unknown.

Aging and related health concerns: DHED has therapeutic potential for ischemia, hot flushes, and depression, without concerns for breast, uterine, and ovarian cancers, but no studies have tested it in humans.

Types of evidence:

- 3 rodent studies, 1 on hot flushes, 1 on stroke, and 1 on depression

Ischemia: In a rat model of ischemic stroke (transient middle cerebral artery occlusion; tMCAO), DHED treatment reduced infarct volume in a dose-dependent manner, with concomitant attenuation of neurological deficits (ND score)(Prokai et al., 2015). The effective dose (ED_{50}) was about 15 μg/kg (s.c.). A significantly higher (~10-fold) dose of systemic 17β-estradiol was required to achieve the same level of protection. Furthermore, DHED exerted neuroprotective effects even after the stroke (up to 2 hours post-tMCAO).

Hot flushes: In a rat hot flush model, oral DHED treatment (30 and 100 µg/kg) blunted the tail-skin temperature rise (Merchenthaler et al., 2016). The dose used to achieve this effect for ethinyl-estradiol (EE, orally bioavailable estradiol) was much higher (200 µg/kg).
Depression: Rats treated with DHED (50 µg/kg, s.c.) once daily for 5 days expressed less anxiety-like behavior on a forced swim test (Prokai et al., 2015). DHED treatment had greater antidepressant effects compared to 17β-estradiol given at the same dose.

Safety: Because DHED does not increase circulating estradiol levels, it does not carry cancer (breast, uterine, ovarian) and cardiovascular risks, though no evidence is yet available in humans.

Types of evidence:

- 3 laboratory studies

Details. Systemic administration of DHED in rats does not trigger or inhibit endogenous estradiol formation in the brain and does not produce estradiol in the circulation and peripheral tissues (Prokai et al., 2015).

Uterus: UNAFFECTED. DHED does not increase uterine weight, an effect seen with systemic estrogen treatment, regardless of the route of administration (i.v., s.c., or oral) or the length of treatment (acute or continuous long-term, up to 48 days)(Prokai et al., 2015; Tschiffely et al., 2016). There were also no changes in the expression of a wide panel of estrogen-regulated uterine proteins with DHED treatment.

Breast cancer: UNAFFECTED. DHED treatment does not stimulate the growth of breast cancer cells in a mouse model of breast cancer (Prokai et al., 2015).

Liver: UNAFFECTED. In contrast to systemic 17β-estradiol treatment, which causes estrogen receptor activation in the liver, DHED treatment, even at high oral doses (>200 µg/kg), does not cause hepatic side effects (Prokai et al., 2015).

Sources and dosing: DHED has only been tested in mice and rats. In a mouse model of AD (APPswe/PS1dE9 mice), 2 µg/day (osmotic minipump delivery) of DHED was therapeutic (Tschiffely et al., 2016). In normal mice, doses ranging from 10-50 µg/kg (s.c.) showed anti-depressant effects (Prokai et al., 2015). In rats, doses ranging from 50-200 µg/kg (i.v.) showed neuroprotection in an ischemia

model (Prokai et al., 2015). Human equivalent doses based on body surface area range from 0.8-4.0 µg/kg (the human equivalent dose for the rat ischemia model was higher, ranging from 8-32 µg/kg).

Research underway: No clinical trials are underway.
Search terms:
Pubmed: DHED, Prokai (author), brain-selective prodrug