DHED, A Brain Specific 17βE2 Prodrug, Affects Gonadal Steroid Receptor Expression but not Metabolic Function

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Gonadal steroid hormones including estrogen and progesterone play an important role in reproductive and metabolic function over the lifespan. The decline of circulating sex hormones during menopause is associated with many symptoms including weight gain and hot flushes, thought to be mediated through the central nervous system. Hormone replacement therapy (HRT) is the clinical gold standard to alleviate these symptoms and contains estrogens such as 17 Beta estradiol (17βE2). However, peripheral estrogen receptor activation by HRT can increase the risk of reproductive cancers in some patients.

Specifically in the context of weight gain, 17βE2 is known to exert protective effects against metabolic dysfunction, mediated by the arcuate nucleus of the hypothalamus. Therefore, restricting 17βE2 actions to the brain could serve as a safer mechanism of HRT in the treatment of metabolic dysfunction. 10b,17B-dihydroxyestra-1,4-dien-3-one (DHED), is a prodrug of 17βE2 which is enzymatically converted to estradiol exclusively within the brain. DHED has demonstrated positive benefit in rodent models of hot flushes, cognitive decline and stroke and critically does not act on estrogen sensitive tissues in the periphery. We hypothesised that DHED treatment in female mice would act within the hypothalamus to provide the same beneficial metabolic effects as 17βE2, while avoiding peripheral actions.

Female mice placed on a high fat diet to induce metabolic dysfunction were split into either control, DHED, or 17βE2 treatment groups. Uterus weight, body weight, food intake and glucose tolerance was recorded along with estrogen and progesterone receptor expression in the brain. Findings to date indicate that while DHED influences the expression of steroid receptors in the hypothalamus and avoids uterine proliferation in periphery, the prodrug does not elicit the same protective metabolic effects as 17βE2. Further optimisation of delivery route and drug dosage may be required to fully establish whether DHED can provide protection against metabolic dysfunction.