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Site-Specific Delivery of 17β-Estradiol into the CNS

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The beneficial effects of estrogens in the central nervous system (CNS) are the results of the synergistic combination of their genomic and non- genomic actions, making them potential broad-spectrum neurotherapeutic agents. Owing to detrimental peripheral hormonal burden and cardiovascular liability, clinical utilization of estrogens as safe neuropharmaceuticals cannot be realized until they can be delivered specifically and selectively to the intended sites of action. In this presentation focusing on the main human estrogen 17β-estradiol (E2), we show that 10β,17β-dihydroxyestra-1,4-dien-3-one (DHED) bioprecursor prodrug produces E2 only in the CNS while remaining inert in the rest of the body (Figure 1). DHED is synthesized through the stereoselective oxidation of the phenolic A-ring of E2 to a para-quinol that is selectively re-aromatized back into E2 by a CNS-specific target enzyme. This distinguishing prodrug metabolism occurs both in male and female animals regardless of the route of administration or the duration of treatment, thereby avoiding the unwanted off-target impacts associated with direct E2 therapies, such as stimulation of the uterus. The highly localized formation of E2 from DHED in the CNS will be shown through a selected series of bioanalytical assays and efficacy studies using animal models of estrogen-responsive maladies pertaining to the brain and the retina, especially in the context of neuroprotection. DHED also exhibits profoundly more favorable physicochemical properties compared to those of the highly lipophilic parent, E2, for transport through biological membranes such as the blood-brain barrier or the cornea. Therefore, a significantly more potent estrogen therapy can be achieved with DHED, further enhancing its therapeutic safety. Altogether, our DHED-based approach shows unprecedented selectivity to deliver E2 into the CNS, and thus, promises a high translational value for the successful and safe treatments of neurodegeneration, as well as neurological and psychiatric symptoms arising from estrogen deficiency.

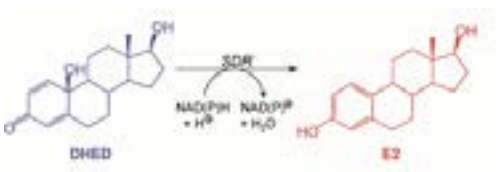

Figure 1. Schematic illustration of DHED's metabolism to E2 in the CNS. As an α,β-unsaturated carbonyl compound, DHED is a plausible substrate for a short-chain NADPH-dependent dehydrogenase/reductase (SDR) that is selectively expressed in the CNS [10].

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