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

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Abstract

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.

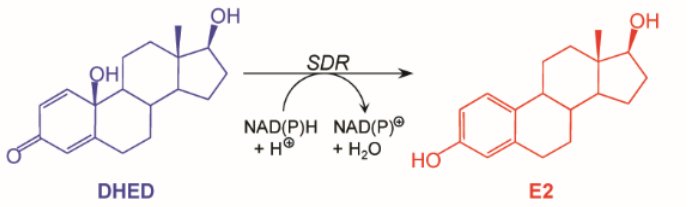


Figure 1. Schematic illustration of DHED's metabolism to E2 in the CNS. As an α,β-unsaturated carbonyl compound, DHED is a plausible substrate for a short-chain NADPH-dependent dehydrogenase/reductase (SDR) that is selectively expressed in the CNS [10].

Recent Publications

1. De La Cruz DL, Prokai L., Prokai-Tatrai K. (2021) The antagonist pGlu-βGlu-Pro-NH_2 binds to an allosteric site of the thyrotropin-releasing hormone receptor. Molecules 26:5397-5410.
2. Prokai-Tatrai K, Zaman K, Nguyen V, De La Cruz D, Prokai L. (2021) Proteomics-based retinal target engagement analysis and retina-targeted delivery of 17β-estradiol by the DHED prodrug for ocular neurotherapy in males. Pharmaceutics 13:1392-1409.
3. Prokai-Tatrai K, Nguyen V, Prokai L. (2021) [β-Glu^2]TRH is a functional antagonist of thyrotropin-releasing hormone (TRH) in the rodent brain. International Journal of Molecular Sciences 22:6230-6239.
4. Prokai-Tatrai K, Nguyen V, De La Cruz DL, Guerra R, Zaman K, Rahlouni F, Prokai L. (2020) Retina-targeted delivery of 17β-estradiol by the topically applied DHED prodrug. Pharmaceutics 12:456-467.
5. Prokai-Tatrai K. (2020) Prodrugs for CNS drug delivery. In: Recent Advancement in Prodrugs, CRC Press, eds. K. Shah NS, Chauhan DN, Chauhan P. Chapter 7, pp. 165-183.
6. Prokai-Tatrai K, Prokai L. (2019) A novel prodrug approach for central nervous system-selective estrogen therapy. Molecules 24: 4197- 4213.
7. Prokai-Tatrai K, De La Cruz DL, Nguyen V, Ross BR, Toth I, Prokai L. (2019) Brain delivery of thyrotropin-releasing hormone via a novel prodrug approach. Pharmaceutics 11:349-360.
8. Prokai-Tatrai K, Nguyen V, Prokai L. (2018) 10β,17α-Dihydroxyestra-1,4-dien-3-one: A Bioprecursor prodrug preferentially producing 17α-estradiol in the brain for targeted neurotherapy. ACS Chemical Neuroscience 11:2528-2533.
9. Merchenthaler I, Lane M, Sabnis G, Brodie A, Nguyen V, Prokai L., Prokai-Tatrai K. (2016) Treatment with a bioprecursor prodrug of 17β-estradiol alleviates hot flushes in rat models without peripheral hormonal side-effects. Scientific Reports, 6, Article number: 30721.
10. Prokai L, Nguyen V, Szarka S, Garg P, Sabnis G, Bimonte-Nelson HA, McLaughlin KJ, Talboom JS, Conrad CD, Shughrue PJ, Gould TD, Brodie A, Merchenthaler I, Koulen P, Prokai-Tatrai K. (2015) The prodrug DHED selectively delivers 17 beta-estradiol to the brain for treating estrogen-responsive disorders. Science Translational Medicine 7(297):297ra113.



Biography

Dr. Katalin Prokai-Tatrai is a Professor of Pharmacology & Neuroscience and Pharmaceutical Sciences at the University of North Texas Health Science Center at Fort Worth, USA. She is an award-winning researcher and educator at her institution. Her primary research interests have been on innovative and multidisciplinary projects focusing on medicinal chemistry-driven drug design and delivery into the CNS by the prodrug approaches. She has extensively published in a broad field of medicinal and pharmaceutical chemistry, including on the development of the very first CNS-selective delivery of estrogens based on a unique prodrug approach. She is an inventor on six issued US patents in the field of translational medicine and drug discovery. Dr. Prokai-Tatrai has been an editorial board member in numerous journals and has served as the academic editor of a successful special issue on neuroprotection in the International Journal of Molecular Sciences and as a section editor-in-chief in Life.

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Notes/Comments:

Invited by Ms. Hazel Walker as Keynote/Plenary Speaker