Thyroxine (T-4) Transfer from Blood to Cerebrospinal Fluid in Sheep Isolated Perfused Choroid Plexus: Role of Multidrug Resistance-Associated Proteins and Organic Anion Transporting Polypeptides

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Abstract

Thyroxine (T-4) enters the brain either directly across the blood-brain barrier (BBB) or indirectly via the choroid plexus (CP), which forms the blood-cerebrospinal fluid barrier (B-CSF-B). In this study, using isolated perfused CP of the sheep by single-circulation paired tracer and steady-state techniques, T4 transport mechanisms from blood into lateral ventricle CP has been characterized as the first step in the transfer across the B-CSF-B. After removal of sheep brain, the CPs were perfused with I-125-T-4 and C-14-mannitol. Unlabeled T-4 was applied during single tracer technique to assess the mode of maximum uptake (U-max) and the net uptake (U-net) on the blood side of the CP. On the other hand, in order to characterize T-4 protein transporters, steady-state extraction of I-125-T-4 was measured in presence of different inhibitors such as probenecid, verapamil, BCH, or indomethacin. Increasing the concentration of unlabeled-T-4 resulted in a significant reduction in U-max%, which was reflected by a complete inhibition of T-4 uptake into CP. In fact, the obtained U-net% decreased as the concentration of unlabeled-T-4 increased. The addition of probenecid caused a significant inhibition of T-4 transport, in comparison to control, reflecting the presence of a carrier mediated process at the basolateral side of the CP and the involvement of multidrug resistance-associated proteins (MRPs: MRP1 and MRP4) and organic anion transporting polypeptides (Oatp1, Oatp2, and Oatp14). Moreover, verapamil, the P-glycoprotein (P-gp) substrate, resulted in similar to 34% decrease in the net extraction of T-4, indicating that MDR1 contributes to T-4 entry into CSF. Finally, inhibition in the net extraction of T-4 caused by BCH or indomethacin suggests, respectively, a role for amino acid "L" system and MRP1/Oatp1 in mediating T-4 transfer. The presence of a carrier-mediated transport mechanism for cellular uptake on the basolateral membrane of the CP, mainly P-gp and Oatp2, would account for the efficient T-4 transport from blood to CSF. The current study highlights a carrier-mediated transport mechanism for T4 movement from blood to brain at the basolateral side of B-CSF-B/CP, as an alternative route to BBB.

Keywords

Author Keywords: transport; thyroid hormone; blood-cerebrospinal fluid barrier; blood-brain barrier; efflux; uptake

KeyWords Plus: THYROID-HORMONE TRANSPORTERS; CARRIER-MEDIATED TRANSPORT; BRAIN-BARRIER; P-GLYCOPROTEIN; RAT-BRAIN; PRIMARY CULTURE; LEAD-EXPOSURE; CELLS; TRANSTHYRETIN; SYSTEM

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