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Frontiers in Neurology (https://www.scopus.com/sourceid/21100212316?origin=recordpage) Open Access
Volume 8, Issue MAY, 23 May 2017, Article number 214

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 (Article)

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Abstract

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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, T_4 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 ^{125}I-T_4 and ^{14}C-mannitol. Unlabeled T_4 was applied during single tracer technique to assess the mode of maximum uptake (Umax) and the net uptake (Unet) on the blood side of the CP. On the other hand, in order to characterize T_4 protein transporters, steady-state extraction of ^{125}I-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).