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# DIPHENHYDRAMINE ACTIVE UPTAKE AT THE BLOOD-BRAIN BARRIER AND ITS INTERACTION WITH OXYCODONE IN VITRO AND IN VIVO

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## ABSTRACT

Diphenhydramine (DPHM) and oxycodone are weak bases able to form cations. We have demonstrated that oxycodone/proton antiporter is involved in the transport of cationic drugs across the blood-brain barrier (BBB).[1)] There is thus a possibility for a pharmacokinetic interaction between them by competition for the same uptake transport system. The present experiments were designed to study the transport of DPHM across the BBB and its interaction with oxycodone in vitro and in vivo.[2)] The interaction between the drugs was studied using conditionally immortalized rat brain capillary endothelial cells (TR-BBB13 cells). The in vivo relevance of the in vitro findings was studied in rats using brain and blood microdialysis. DPHM was transported into TR-BBB13 cells, and the transporter was energy-dependent and oppositely directed proton gradient dependent. Furthermore, mutual uptake inhibition by DPHM and oxycodone with $K_i$ values of 35 and 106 μM, respectively, suggesting that a common mechanism is involved in their transport. In rats DPHM showed 5-fold higher unbound concentration in brain interstitial fluid (ISF) than in blood, confirming a net active uptake. There was no significant interaction between DPHM and oxycodone in vivo. The in vitro experiments revealed that DHPM is transported by the oxycodone/proton antiporter. The 5-fold higher unbound concentration of DPHM in brain ISF than in blood indicates active transport of DPHM into the brain across the BBB. In vivo, however, no such interaction was observed due to much lower unbound concentrations in blood compared with the $K_i$ values found in vitro.