An Insect-Based Ex Vivo Blood Brain Barrier Efflux Assay

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Drug efflux activity of ABC transporters, at the human blood brain barrier (BBB), constitutes a crucial challenge for central nervous system (CNS) drug development. Accordingly, early screening of CNS drug candidates is pivotal to sort out those whose brain uptake is substantially affected by efflux activity. In this context, affordable, simple, high-throughput and predictive screening models are required. It has recently been proposed that the grasshopper (locust) could be exploited as an ex-vivo model for drug BBB permeability assessment, as it has shown some similarities to vertebrate models. The p-glycoprotein (p-gp), encoded by the ABCB1 gene, is described as the most potent efflux pump that modulates drug brain disposition, so identification and characterization of such a transporter in the locust model is essential to demonstrate its utility and validity for drug development. The present work entails transcriptomic profiling followed by amino acid-based homology analysis of locust genes, in parallel to functional investigations using rhodamine 123 as a selective p-gp substrate. A protein with high sequence similarity to ABCB1 was found in the locust brain transcriptome, which indicates a conserved mechanism of brain efflux activity between insects and vertebrates. Functionally, the developed locust model showed a kinetic behavior comparable to those obtained from in vitro cell models such as the MDCKII cells expressing p-gp. Overall, the locust ex-vivo BBB model holds promise as a cheap model with a high-throughput screening potential in the early discovery phase of CNS drugs.

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