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Model of Pharmacoresistant Blood-Brain Barrier In-vitro for Prediction of Transfer of Potential Antiepileptic Drugs

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Abstract : The blood-brain barrier (BBB) is a key element regulating the transport of substances between the blood and the central nervous system (CNS). The BBB protects the CNS from potentially harmful substances and maintains a suitable environment for nervous activity in the CNS, but at the same time, it represents a significant obstacle to the entry of drugs into the CNS. Pharmacoresistant epilepsy is a form of epilepsy that cannot be suppressed using two (or more) appropriately chosen antiepileptic drugs. In many cases, pharmacoresistant epilepsy is characterized by an increased concentration of efflux pumps on the luminal sides of the endothelial cells that form the BBB and an increased number of drug-metabolizing enzymes in the BBB cells, thereby preventing the effective transport of antiepileptic drugs into the CNS. Currently, a number of scientific groups are focusing on the preparation and improvement of BBB models in vitro in order to study cell interactions or transport mechanisms. However, in pathological conditions such as pharmacoresistant epilepsy, there are changes in BBB structure, and current BBB models are insufficient for related research. Our goal is to develop a suitable BBB model for pharmacoresistant epilepsy in vitro and use it to test the transfer of potential antiepileptic drugs. This model is created by co-culturing immortalized human cerebral microvascular endothelial cells, human vascular pericytes and immortalized human astrocytes. The BBB in vitro is cultivated in the form of a 2D transwell model and the integrity of the barrier is verified by measuring transendothelial electrical resistance (TEER). From the current results, a contact cell arrangement with the cultivation of endothelial cells on the upper side of the insert and the co-cultivation of astrocytes and pericytes on the lower side of the insert is selected as the most promising for BBB model cultivation. The pharmacoresistance of the BBB model is achieved by long-term cultivation of endothelial cells in an increasing concentration of selected antiepileptic drugs, which should lead to increased production of efflux pumps and drug-metabolizing enzymes. The pharmacoresistant BBB model in vitro will be further used for the screening of substances that could act both as antiepileptics and at the same time as inhibitors of efflux pumps in endothelial cells. This project was supported by the Technology Agency of the Czech Republic (TACR), Personalized Medicine: Translational research towards biomedical applications, No. TN02000109 and by the Academy of Sciences of the Czech Republic (AS CR) – grant RVO 61388963.

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