The Cerebral Vascular Diversity and Identification of Vascular Targets Capable of Crossing the Blood Brain Barrier

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The blood-brain barrier (BBB) is the major site responsible for regulating exchange of nutrients, metabolites and inorganic molecules between blood and central nervous system (CNS). It also prevents the invasion of pathogens and its selectivity is an important obstacle for the treatment of various diseases in CNS since it precludes transposition of drugs and other therapeutic agents across the BBB. Therefore, our goal is to understand the vascular diversity of the CNS and to identify peptides that cross the BBB. Our expectation is that such knowledge will help the development of novel approaches to deliver therapeutic agents to the CNS. For that purpose, we employed Phage Display in vivo. A peptide phage display library was injected into mice and after 30 minutes or 24 hours circulation phage bound to the brain vasculature were isolated, amplified and reinjected into mice. Three rounds of selection were performed before randomly selected bacterial colonies were analyzed by DNA sequencing to identify the peptide displayed by the phage particles. Among the identified peptides, 15% had a peptide motif (termed "Peptide-1") rich in hydrophobic amino acids. We next show that Peptide-1 phage binds selectively to blood vessels in the brain, muscle and optic nerve, but not in other tissues such as small intestine, kidney and pancreas. In conclusion, we have identified by in vivo Phage Display a peptide that binds specifically to blood vessels of the CNS. Studies to identify the receptor in the brain vasculature for Peptide-1 and whether it crosses the BBB are ongoing.

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