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Current Perspectives on the Blood-Brain Barrier

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The blood-brain barrier (BBB) represents a critical protective interface between the circulatory system and the central nervous system, comprised of specialized brain endothelial cells, pericytes, astrocyte endfeet, and basement membrane components. The BBB's barrier properties are maintained through four key mechanisms: specialized tight junctions that regulate paracellular transport, specific influx and efflux transporters including ATP-binding cassette proteins and solute carrier transporters, minimal transcellular vesicle trafficking controlled by proteins like Mfsd2a, and restricted immune cell entry through glycocalyx-mediated protection. These mechanisms collectively ensure selective permeability while maintaining brain homeostasis. The lecture explores BBB development (barriergenesis), highlighting the critical role of transcytosis suppression in functional barrier formation. During maturation, the gradual suppression of caveolae-mediated transcytosis, particularly through Mfsd2a regulation, establishes the mature BBB phenotype essential for proper neurological function. Key age-related alterations include modifications in selective transport systems, pericyte dysfunction, basement membrane composition changes, and glycocalyx deterioration. Importantly, carrying the ApoE4 allele accelerates these age-related BBB changes. Clinical evidence demonstrates functional BBB breakdown in aging populations, particularly affecting the hippocampus, with implications for cognitive decline and neurodegenerative diseases. Therapeutic strategies encompass enhancing neurotoxicant clearance through P-glycoprotein modulation, protecting BBB integrity via ROS scavenging and angiotensin II receptor blockade, and improving drug delivery through various approaches including receptor-mediated transcytosis, physical stimulation methods, and engineered nanocarriers. Contemporary drug delivery strategies utilize multiple pathways: transcellular lipophilic transport, paracellular aqueous transport, carrier-mediated transport, efflux transporter modulation, and transcytosis mechanisms. Advanced delivery systems include liposomal formulations, polymeric materials, carbon and iron oxide nanoparticles, and biomass-derived materials, each optimized for efficiency, safety, and scalability. Understanding BBB dysfunction mechanisms and developing targeted therapeutic interventions remains crucial for treating neurological disorders and age-related cognitive decline, positioning the BBB as a central target for neurotherapeutic innovation.

Keywords: *Blood-brain barrier, Transcytosis, Receptor-mediated transcytosis, BBB shuttle, Drug delivery*