COMPUTATIONAL STRATEGIES FOR NOSE-TO-BRAIN DRUG DELIVERY

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ABSTRACT

Intranasal drug delivery to the brain is a promising and powerful administration route for the direct access of drugs to brain areas and the subsequent treatment of various central nervous system related disorders (e.g., multiple sclerosis, Alzheimer's, Parkinson's or Huntington's disease, etc.), as the nose and brain compartments are closely connected via the olfactory and trigeminal nerve pathways. A major advantage of nose-to-brain drug delivery is that it can evade the extremely selective blood-brain barrier and diminish the amount of therapeutic drug dose to be administered owing to the efficient drug transfer mechanism to the brain. Therefore, the nasal cavity has been exploited as an entry point for the brain-targeted administration of various medications via the olfactory route (Figure 1) which can be distinguished into epithelial and neuronal pathways[1].

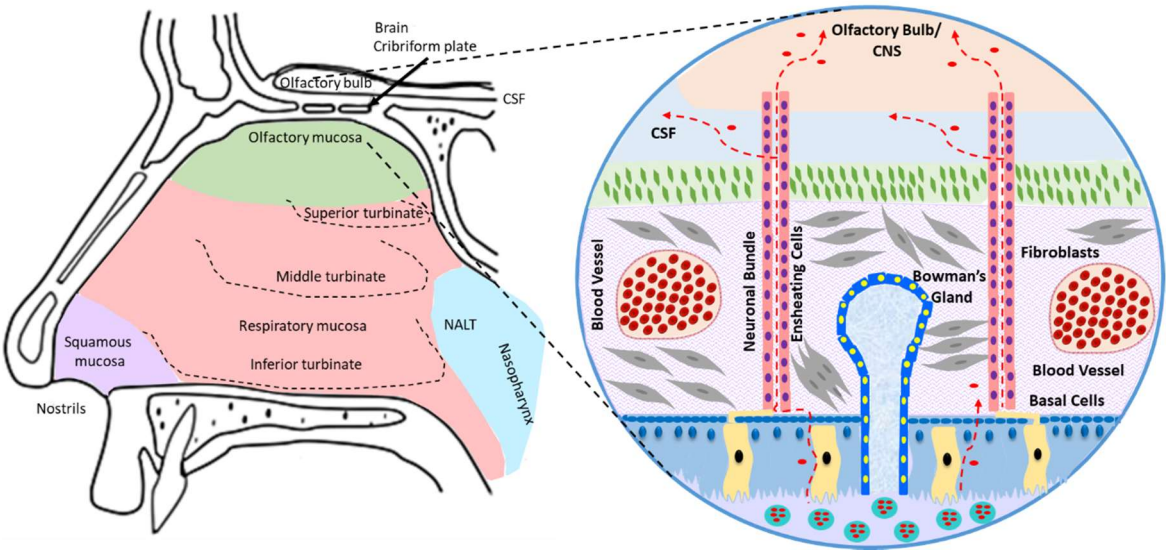

Figure 1: Nose-to-brain drug delivery via the olfactory route.

Further distinction of nose-to-brain drug transfer mechanisms derives from the extracellular and intracellular transport of administered remedies. Drug transfer via the mucus layer and the underlying epithelium sublayer can be effected by both the transcellular (i.e., via passive diffusion through the cellular membrane) and the paracellular route (through the tight junctions enclosed by supporting and/or adjacent neural cells). Advanced computational models including multi-scale mechanistic[2], pharmacokinetic/pharmacodynamic models, computational fluid dynamics, molecular and atomistic simulations, machine learning algorithms, etc. have been developed aiming at the elucidation and quantification of complex biological and physical nose-to-brain drug transfer mechanisms. The development of in-silico intranasal structural models to describe the systemic spatio-temporal variation of administered therapeutic ingredient in terms of drug formulation, administration mode (i.e., powder, gel, etc.), patient's specific nasal anatomy and physiological state

is of paramount importance to the advancement of personalized drug delivery systems and optimal design of existing and future drug formulations.

KEYWORDS: Nose-to-Brain Drug Delivery, Drug Transport Mechanisms, Model-based Design of Drug-delivery Systems

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