

Nose-to-Brain Delivery – A narrow shortcut towards the CNS

Fabio Sonvico^{1,2}

¹ Food and Drug Department, University of Parma, Italy

² Biopharmanet-TEC, University of Parma, Italy

Summary

In the field of nasal drug delivery, nose-to-brain delivery is among the most fascinating applications, directly targeting the central nervous system, bypassing the blood brain barrier. Its benefits include dose lowering and direct brain distribution of potent drugs, ultimately reducing systemic side effects. Recently, the interest in this administration strategy has increased due to the growing social and economic burden of neurological diseases, prompting several research group to explore therapeutics, formulations and devices specifically designed for this challenging delivery route [1].

This brief overview of results from our laboratory and others will report on the exploration of pharmaceutically active ingredients, such as antivirals, anti-inflammatory/anti-cancer agents, peptides and RNA therapeutics for which promising *in vivo* results were obtained exploiting the nose-to-brain route.

In the case of ribavirin, an broad spectrum antiviral agent active against both RNA and DNA viruses, it was demonstrated that a powder formulation in the form of soft pellets obtained from drug crystals and microparticles of functional ingredients was able to attain in the olfactory bulb of rats drug concentrations equivalent to the same dose of drug administered intravenously. When the olfactory bulb-to-plasma concentration ratios were calculated, significantly higher values were obtained for the nasal ribavirin powder formulation as a consequence of much lower plasma concentrations, supporting the claim of brain targeting and of reduced systemic side effects [2,3].

In another series of studies, simvastatin, a lipophilic statin with a plethora potential pleiotropic effects ranging from anti-inflammatory to neuroprotective and even anti-cancer, was encapsulated in hybrid lecithin-chitosan nanoparticles (LCNs) or chitosan-coated poly- ϵ -caprolactone nanocapsules (CPNs) in view of nose-to-brain delivery. LCNs were found to be mucoadhesive and biodegraded by specific enzymes in nasal secretions (*i.e.* lysozyme and phospholipase A2) demonstrating enhanced permeation on animal nasal mucosa and anti-inflammatory and neuroprotective action in an *ex vivo* model of psychosine-induced demyelination in cerebellar slices of mice. Moreover, simvastatin loaded in CPNs, but not the drug suspension, was able to reduce tumor growth in an orthotopic model of glioblastoma in rats when administered intranasally confirming the capacity of the nanocarrier to deliver the statin to the brain *in vivo* [4,5].

Mucus penetrating ultra-small micelles of TPGS were used to formulate cyclosporine A (CsA), a lipophilic undecapeptide with immunosuppressive, anti-inflammatory and neuroprotective properties. The micelles were tested in a model of LPS-induced neuroinflammation, in mice administering nasally a dose of 1.5 mg of CsA for three consecutive days using the oral treatment with the same amount of drug as control. A set of behavioral studies (novel object recognition, open field, tail suspension, buried food and tail hanging tests) demonstrated the superiority of nasal delivery of micelles over oral administration in terms of treatment of neuroinflammation induced memory and coordination impairment, as well as on anxiety and depressive symptoms [6].

Recently, the group led by Prof. Tamara Minko (Rutgers, the State University of New Jersey, USA) proposed a nose-to-brain liposome formulation for Alzheimer's disease that combined memantine, donepezil and beta-site amyloid precursor protein-cleaving enzyme (BACE-1) siRNA. The triple therapy was administered intranasally in APP/PS1 transgenic mice demonstrating accumulation of siRNA and liposomes in the brain tissue, reduction of BACE-1 mRNA expression and recovery of short-term memory evaluated by a Y-maze behavioral test [7].

Finally, some considerations related to the current gaps existing for the *in vitro*, *ex vivo* and *in vivo* development of nasal medicinal products aiming for CNS diseases treatment will be provided.

Key Message

Although nose-to-brain delivery is a viable approach for delivering potent therapeutics to the central nervous system (CNS), the development of new medicinal products is hindered by the inability to translate preclinical evidence to humans. New testing methods, dedicated formulations, and specific nasal devices that can target the olfactory region of the nasal cavity, as well as the careful selection of

molecular disease targets in the CNS, are expected to be instrumental in breakthrough product approvals in the coming years.

References

- [1] Boon PAJM, Berger T, Leonardi M, Marson T, Kallweit U, Moro E, Toscano A, Rektorova I, Accorroni A, Scheerens C, Boesch A, Crean M, Sander A, Lee S, Bassetti CLA. A roadmap toward promoting and improving brain health in Europe and closing the awareness and funding gap. *Eur J Neurol.* 2025; 32(1):e16589. doi: 10.1111/ene.16589.
- [2] Colombo G., Lorenzini L., Zironi E., Galligioni V., Sonvico F., Balducci A.G., Pagliuca G., Giuliani A., Calzà L., Scagliarini A. Brain distribution of ribavirin after intranasal administration. *Antiviral Res.* 2011; 92 408–414. doi:10.1016/j.antiviral.2011.09.012
- [3] Giuliani A, Balducci AG, Zironi E, Colombo G, Bortolotti F, Lorenzini L, Galligioni V, Pagliuca G, Scagliarini A, Calzà L, Sonvico F. In vivo nose-to-brain delivery of the hydrophilic antiviral ribavirin by microparticle agglomerates. *Drug Deliv.* 2018; 25(1):376-387. doi:10.1080/10717544.2018.1428242
- [4] Clementino A, Velasco-Estevez M, Buttini F, Sonvico F, Dev K. Hybrid Nanoparticles as a Novel Tool for Regulating Psychosine-Induced Neuroinflammation and Demyelination In Vitro and Ex vivo. *Neurotherapeutics*, 2021; 18:2608-2622. doi:10.1007/s13311-021-01109-3
- [5] Bruinsmann FA, de Cristo Soares Alves A, de Fraga Dias A, Lopes Silva LF, Visioli F, Raffin Pohlmann A, Figueiró F, Sonvico F, Stanisquaski Guterres S. Nose-to-brain delivery of simvastatin mediated by chitosan-coated lipid-core nanocapsules allows for the treatment of glioblastoma in vivo. *Int J Pharm.* 2022; 616:121563. doi: 10.1016/j.ijpharm.2022.12156
- [6] Guareschi F, Fonseca C, Silva S, Pescina S, Nicoli S, Buttini F, Sonvico F, Fortuna A. Therapeutic effect of cyclosporine A-loading TPGS micelles on a mouse model of LPS-induced neuroinflammation. *Eur J Pharm Sci.* 2025; 205:106994. doi: 10.1016/j.ejps.2024.106994
- [7] Lee D, Shen AM, Shah M, Garbuzenko OB, Minko T. In Vivo Evaluation of Nose-to-Brain Delivery of Liposomal Donepezil, Memantine, and BACE-1 siRNA for Alzheimer's Disease Therapy. *Int J Mol Sci.* 2024; 25(19):10357. doi: 10.3390/ijms251910357