Delivery to The Brain: The Last Frontier ?

The brain can be considered as the center of numerous command and control systems for many biological events. It does not surprise that it is guarded like The Crown Jewels: Unwanted materials are repelled, metabolized or otherwise neutered at the Blood-Brain Barrier (BBB), particularly if they are hydrophilic in nature. This has consequences for therapies that may require presence in a brain location for efficacy to be manifested. Getting drug to its site of activity can be a big ask.

The majority of drugs that have been developed over the past half-century, possibly longer, were assembled by chemical synthesis, purity being assured by isolation as crystalline solids. Adequate aqueous solubility was also desirable to ensure good dissolution and absorption from the GI Tract following oral dosage. Purity and solubility requirements could usually be met by using a salt form of the active ingredient. However, while aqueous solubility might have been appropriate for good (oral) "bioavailability" it hardly rendered them suited for brain entry. It has been estimated that 97% of hydrophilic structures do not surmount the BBB. Even in cases where hydrophobic structures are chosen, being formulated to enhance oral bioavailability they are likely to be metabolized, post-absorption to hydrophilic structures to facilitate their excretion. A small fraction may cross the BBB but drug distributed to other compartments may cause damaging side effects, particularly when dosing is chronic.

There is evidence that some non-steroidal inflammatory agents cross the BBB, albeit only at a fraction of the administered dose (Renner B et al: Arch Pharmacol (2010) **381,** 127-136). There is also observational evidence that NSAIDs can be effective in dementia-related conditions. However, side effects associated with NSAID's, present in other biological compartments could compromise their use where chronic dosage is required.

Delivering agents by inhalation via the oral/pulmonary /intranasal route is well established but, post-absorption, medications delivered in this way must also navigate the BBB, with attendant attrition or recycling. More creative modes of delivery may be warranted.

Is olfactory delivery worth considering?

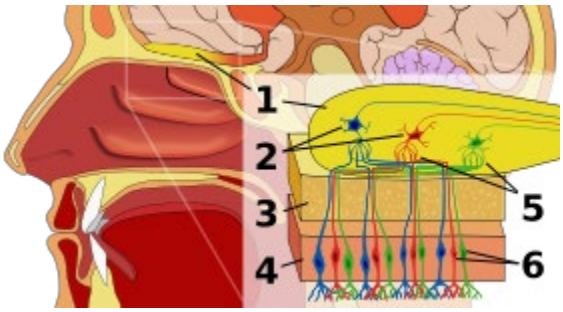
The olfactory route is designed to rapidly detect "odor" when volatile materials are inhaled. The system probably evolved as a "rapid alert" system for approaching danger, a means of evaluating the suitability of a potentially edible materials and many other situations. Historically, inhalation of vaporized agents has been used from ancient times in many cultures (and still used), whether for medicinal or recreational purposes. Nasal inhalation of powdered tobacco ("snuff") was common in many cultures for instance. Illicit drug use can also involve inhalation. "Crack", the free base form of cocaine is volatile, providing a more intense and rapid onset of effect than the salt foem, cocaine hydrochloride. More conventional agents such as perfumes and volatile oils (presumably) also find their way to brain receptors via the olfactory route. Yet, virtually no conventional medicinal agents are evaluated for such administration. It is conceptually feasible that "very little" material would be need to delivered by this route, to evince a desired effect.

The concept is worthy of investigation, at least from a preclinical "drug delivery" perspective. It would involve changed paradigms with respect to an overall evaluation program, from exploratory Discovery

activities, development and clinical programs. Equally importantly it could focus on repurposing existing therapeutic agents where their biology and physical characteristics might warrant exploratory studies.

Upper Nasal Tract Architecture

1: Olfactory bulb 2: Mitral cells 3: Bone 4: Nasal Epithelium 5: Glomerulus 6: Olfactory receptor cells.



It may be time to re-visit possibilities for olfactory delivery, particularly in the light of age-related brain-associated conditions that have defied the development of effective medications.