Through the nose directly into the brain: Biberach researchers are working on a novel way to apply pharmaceuticals

The blood-brain barrier prevents most drugs, and large biologics in particular, from entering the brain. This physiological barrier impairs the study of central nervous system (CNS) diseases such as Alzheimer’s, Parkinson’s and multiple sclerosis as well as the development of drugs. However, there is a hidden side entrance to the brain, which means that there is a way to circumvent this barrier.

This hidden side entrance is through the so-called regio olfactoria (olfactory region) on the roof of the nose where the cribriform plate of the ethmoid bone and cell layers of the nasal mucosa separate the nasal cavity (outside world) from the brain (cerebrospinal fluid). Olfactory nerve fibres run through the cribriform plate, making this structure an excellent gateway into the brain for certain drugs, including therapeutic proteins. Moreover, drugs can also diffuse from the nose into the CNS through the trigeminal nerve.

Demonstrating technical feasibility

Researchers led by Katharina Zimmermann, professor of molecular pharmacology at the Biberach University of Applied Sciences, now want to investigate whether this route can be used to administer drugs. They are also seeking to demonstrate the technical feasibility of the intranasal application of drugs, including big molecules such as therapeutic proteins. This would be an efficient, non-invasive way of administering highly specific antibodies. In addition, it would be associated with few adverse drug effects.

Flamm's task is no small one. He needs to find a way to bring a drug into the olfactory region without it being taken up by the entire body, where it can lead to undesired adverse drug effects. In addition, the immune system of the nasal mucosa is very active as it produces a large number of antibodies and lymphocytes that recognise and destroy foreign substances. The planned drug application system therefore must not, under any circumstances, activate the immune system.

Feasible, but not yet studied in detail: the path from the nose into the brain

Many researchers around the world are studying how drugs can travel from the nasal mucosa into the blood stream. However, only a handful of researchers are specifically studying the intranasal transport of drugs into the brain.

Johannes Flamm and Prof. Katharina Zimmermann have chosen the nose as a way of administering drugs into the brain. © Pytlik
nervous functions in humans. This is why the researchers from Biberach have decided to focus initially on insulin.

Nasal sprays do not work for proteins

Flamm and Zimmermann have been able to draw valuable conclusions from Stützle's work: proteins that are dispersed as an aerosol are very sensitive to the shear forces inside the aerosol generator. In order to apply proteins to the nose, they need to be specifically packed or formulated. This is not necessary for small chemical molecules, which are able to enter deep into the nasal cavity by way of gas-borne particles (aerosols) that are finely dispersed with a nasal spray. In addition, computer simulations carried out in cooperation with researchers from the University of Ulm and the Ulm University of Applied Sciences have shown that, when inhaled continuously, protein aerosols not only accumulate in the olfactory region as desired, but also in the nasopharynx where the mucosal immune system is located.

Pharmaceutical substances need to be protected against attack by nasal immune cells as they pass through the immunologically active areas inside the nose. In order to achieve this, Zimmermann and her team decided to work with 'packaging specialists' from the Stuttgart-based Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB who have developed a spray-drying procedure that enables them to load specific particles with pharmaceutical substances. Computer stimulations using standardised and idealised nose models of men and women of different ethnic origin have shown that it is possible to enclose the drug in transport vehicles with diameters of 100 or so micrometres and effectively transport them to the olfactory region. Experiments were carried out with a three-dimensional cast model of a human nasal cavity to substantiate computer simulations.

References:

Lorenzetti, Laura: Is the future of pharma about making good drugs great? Fortune, 27.2.2015.
Hidden high in the nasal cavity, but accessible to drugs - the olfactory region of the nose (frontal and lateral view).

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