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.

Johannes Flamm, funded by a Foundation of German Business grant, is a doctoral student in Prof. Zimmermann’s lab. His thesis is specifically focused on the development of a platform technology to transport proteins to their final destination by way of the CNS. The proteins he is seeking to transport must be pharmacokinetically reliable in therapeutic concentrations.

Intranasal administration is undergoing thorough investigation

The doctoral student and his supervisor both enjoy research activities with application potential. Zimmermann, who has worked for many years in preclinical Alzheimer’s research in industry and academia, states: “We are not looking for yet another trial where mice are administered droplets to the nose. We want to do it properly this time.” Zimmermann has tested many methods, all linked to the issue of how to bring drugs effectively into the brain. She considered the intranasal application of drugs a fairly promising method. However, most papers she read were limited to describing the effect a certain drug had, and did not measure the drug concentrations that actually reached the brain, stomach or lungs.

Prof. Zimmermann wanted to change this and so she contacted some of her colleagues for assistance: Prof. Chrystelle Mavoungou, a drug approval specialist, and Prof. Annette Schafmeister, an expert in aerosol technology. Martina Stützle, another doctoral student in Zimmermann’s team, is specifically focused on developing protein aerosols for intranasal nose-to-brain drug delivery.

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 bloodstream. However, only a handful of researchers are specifically studying the intranasal transport of drugs into the brain.

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.

Flamm will work with two model drugs: a low-molecular weight (200 Da) muscle relaxer (baclofen) and a peptide hormone (insulin). Insulin can cross the blood-brain barrier by way of transcytosis (i.e. receptor-mediated transport of macromolecules across the interior of a cell). The hormone is an important growth and differentiation factor in the CNS and improves, as Zimmermann herself has shown, the cognitive ability of Alzheimer’s patients, at least for a short period of time. In addition, studies with Alzheimer’s patients and healthy individuals have shown that intranasally administered insulin exerts distinct influences on central
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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