

# NEUROLOGY REVIEWS®

## Intranasal Drug Delivery Bypasses the Blood–Brain Barrier

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**LAS VEGAS**—The nasal mucosa in the upper third of the nasal cavity provides a direct pathway from the external environment to the brain and, according to William H. Frey II, PhD, that pathway can be used to noninvasively deliver therapeutics into the brain. This pathway effectively bypasses the blood–brain barrier and avoids the systemic exposure and side effects associated with therapeutics that enter the bloodstream. At the 19th Annual Meeting of the North American Neuromodulation Society, Dr. Frey presented an in-depth look at intranasal delivery of therapeutics to the brain.



### **William H. Frey II, PhD**

“We have learned from experience that therapeutics sprayed into the nose or even given as nose drops can travel extracellularly and paracellularly along the olfactory axon bundles and along the trigeminal nerve pathway from the nose to the brain,” said Dr. Frey, who is Founder and Codirector of the Alzheimer’s Research Center at Regions Hospital and Senior Director of HealthPartners Neuroscience Research in St. Paul.

Therapeutics that can be delivered intranasally include proteins like insulin, small molecules, charged molecules, oligonucleotides, therapeutic cells like stem cells and Treg cells, nanoparticles, and microparticles. “You do not have to modify your drug or therapeutic in any way in order to do this, but this method only works for really potent therapeutics that are active in the picomolar, nanomolar, or very low micromolar concentration range,” Dr. Frey said.

This technique is being investigated in various disorders. “Most of the studies have been done in animal models, but the Alzheimer’s work has also been done in humans,” Dr. Frey said.

The Neuroanatomy of Intranasal Delivery

The cribriform plate of the skull separates the upper part of the nasal cavity from the brain. The primary olfactory nerves are located in the roof of the nasal cavity under the cribriform plate and include the olfactory sensory neurons and odorant receptors. Sniffing brings molecules into the nose, thus allowing them to bind to odorant receptors and send a signal. Intranasal delivery of therapeutics involves spraying therapeutics into the upper part of the nasal cavity to enable them to follow these olfactory axon bundles directly into the brain through foramina in the cribriform plate. Once across the cribriform plate, the therapeutics penetrate the subarachnoid space and enter the perivascular spaces of the brain's blood vessels.

When the heart pumps, a corresponding pulsation in the cerebrovasculature creates a perivascular pumping mechanism that moves the therapeutics throughout the brain. “They are near the blood vessels, but on the brain side of the blood–brain barrier throughout the brain,” Dr. Frey explained. Drugs also follow the trigeminal nerves that innervate the entire nasal mucosa and follow the trigeminal neural pathway through the trigeminal ganglion and into the brain and upper spinal cord.

“[This method] results in rapid delivery—within 10 minutes in mice, rats, and monkeys—to the brain and upper spinal cord,” Dr. Frey said. In humans, intranasal neuropeptides reach the CSF within 10 minutes.

## Stroke

Preclinical studies have examined intranasal therapy for stroke. Researchers gave rats a stroke by occluding the middle cerebral artery. Two hours of occlusion were followed by reperfusion. Ten minutes after the reperfusion was initiated, investigators administered nose drops containing insulin-like growth factor 1—a 7,600-Da neurotrophic protein naturally found in humans. Compared with controls, rats that received 150 mg of this peptide intranasally had an infarct volume or amount of brain damage that was reduced by 63%. Benefit was also seen when treatment was delayed for two or four hours.

## Brain Tumors

A different intranasal treatment uses GRN163, a polynucleotide that inhibits the enzyme telomerase. Telomerase is expressed highly in brain tumors and is required for the brain tumor cells to keep dividing. Investigators tagged the negatively charged large polynucleotide with a fluorescent label and administered it. They observed that GRN163 accumulated in the brain tumor over a period of four hours but did not accumulate in the normal brain. After 24 hours, GRN163 was completely cleared from the brain. Survival time was doubled following treatment with the intranasal polynucleotide.

## Neurodegenerative Disease

Iron accumulates abnormally in the brain in all of the neurodegenerative disorders. “Obviously, our bodies need iron, but the abnormal accumulation of free iron is damaging because it is a strong promoter of free-radical damage,” Dr. Frey said. Data also indicate that the key receptor for memory, the human brain muscarinic cholinergic receptor, is rapidly inactivated by free iron or free heme, which are present at increased levels in the brains of people with Alzheimer's disease. “We have a potent iron chelator, deferoxamine mesylate, that has been around for about 40 years. It has a high affinity for iron and it is a generic drug. It has been used to treat beta thalassemia, sickle cell anemia, and various conditions where too much iron is accumulated in the blood. When given intramuscularly over a period of two years to patients with Alzheimer's disease, it reduced their cognitive decline by 50%. That's a far bigger benefit than any drug on the market today for Alzheimer's disease,” Dr. Frey noted. But there were significant side effects at the injection site, and deferoxamine does not cross the

blood-brain barrier well. “Consequently, we’ve been developing and have patented intranasal deferoxamine to treat Parkinson’s disease, Alzheimer’s disease, stroke, and traumatic brain injury,” Dr. Frey said.

“We’ve shown that intranasal deferoxamine protects dopamine brain cells and improves movement in animals with Parkinson’s disease... We’ve shown that just a few nose drops of deferoxamine given before or after a stroke reduce brain damage in rats by 55%. We’ve shown that even in normal mice, it improves memory when given intranasally. And it also improves or reduces memory loss in Alzheimer transgenic mice.”

## Alzheimer’s Disease

Fludeoxyglucose ( $^{18}\text{F}$ ) PET scans reveal adequate uptake and utilization of glucose, the main energy source for brain cells, in the brains of healthy elderly controls. But the brains of patients with Alzheimer’s disease do not take up glucose normally, and their brain cells consequently have less energy. “A number of areas of the brain require insulin to take up glucose, and the hippocampus is one of those areas,” Dr. Frey explained. “Insulin signaling is reduced in the brains of patients with Alzheimer’s disease, causing what some have called type 3 diabetes, or diabetes of the brain, which leaves these brain cells starved for energy and not able to function normally.”

Dr. Frey obtained several patents on the direct intranasal delivery of therapeutics, including insulin, to the brain, and various clinical trials have been conducted. “Four trials in patients with Alzheimer’s disease and five trials in normal, healthy adults have demonstrated improved memory following intranasal insulin treatment, with no change in the blood levels of insulin or glucose,” Dr. Frey reported.

In one of the first trials, a single intranasal insulin treatment improved verbal memory for individuals with Alzheimer’s disease within 15 minutes. In a three-week trial, intranasal insulin enhanced memory, compared with placebo, and significantly improved attention and functional status in patients with Alzheimer’s disease. However, patients who carried the *APOE*  $\epsilon 4$  gene allele were not improved with intranasal regular insulin. “Only long-acting insulin detemir, given intranasally, has been shown to improve memory in patients who have the *APOE*  $\epsilon 4$  gene allele,” Dr. Frey said.

The longest completed trial lasted for four months and showed improved memory and function in patients who were given insulin twice per day in a nasal spray. It also showed that the treatment reduced the loss of glucose uptake and utilization in key brain regions, as seen in PET scans. A new six-month treatment trial is now underway at the HealthPartners Center for Memory & Aging in St. Paul.

## Mechanism of Action

One open question is whether intranasal insulin only provides symptomatic treatment (ie, improved memory and functioning in patients with Alzheimer’s disease) or also has the potential to change the underlying disease process. “We know it can provide energy to prevent brain cells from degenerating and allow the cells to produce materials to replace worn-out parts,” said Dr. Frey. “That result has been shown in humans using P-31 MRI. After administration of intranasal insulin, levels of brain cell adenosine triphosphate (ATP) and brain cell phosphocreatine increase significantly. We know that insulin, after it causes signaling, and glucose uptake occurs, causes the production of insulin-degrading enzyme to reduce the insulin signal so that the next time the signal comes in, it can be easily detected. That turns out to be the enzyme that degrades beta amyloid, which accumulates abnormally in the brains of individuals with Alzheimer disease. So, if you don’t have insulin signaling, you don’t make insulin-degrading enzyme, and you accumulate beta amyloid. Insulin also inhibits glycogen

synthase kinase 3 beta that phosphorylates tau to form Alzheimer neurofibrillary tangles. Insulin is also needed to maintain synaptic density, so it is possible that if humans were given intranasal insulin at the first sign of an insulin-signaling deficiency or a decrease in glucose uptake in the brain, it might be possible to delay, or maybe even prevent, the onset of this disease,” Dr. Frey said.

## Stem Cells

Dr. Frey and research collaborators in Germany, including Lusine Danielyan MD, discovered and patented that intranasal stem cells bypass the blood–brain barrier to reach the brain and treat Parkinson’s disease in rats. Adult bone marrow–derived stem cells have anti-inflammatory and neurotrophic properties. “After cell treatment, the proinflammatory cytokines in this inflammatory brain disease go down to normal levels. Our study showed highly significant improvement, compared with placebo, in motor function or movement,” Dr. Frey said.

Researchers in the Netherlands demonstrated that intranasal adult stem cells treat neonatal ischemia and neonatal brain damage. Other researchers at Emory University reported treatment of stroke with adult stem cells from bone marrow. Swedish researchers reported that intranasal Treg cells treat multiple sclerosis (MS). “These studies are all in animals,” Dr. Frey noted. Other researchers reported that neuronal stem cells induce recovery and remyelination in an animal model of MS. Brain tumors have also been treated in animals with intranasal stem cells. Recently, intranasal stem cell therapy was also reported to improve motor function and reduce lesion size in spinal cord injury in animals. “Noninvasive intranasal delivery can target therapeutics to the brain while reducing systemic exposure to facilitate the treatment of brain disorders,” said Dr. Frey.

—*Glenn S. Williams*

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