# The nose may help the brain: intranasal drug delivery for treating neurological diseases

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`…intranasal drug delivery could be used to deliver both small- and large-sized drugs into the CNS by bypassing the BBB.'

While enormous progress has been made regarding our understanding of the pathogenic mechanisms of neurological diseases, there are only a small number of effective drugs for treating these illnesses. A key obstacle for developing effective drugs for treating neurological diseases is the blockage of drug entrance into the CNS by the BBB [1]. Less than 2% of all small-molecule drugs, and virtually no large-molecule drugs, can cross the BBB. Therefore, it is of critical significance to search for drug-delivery strategies that can effectively deliver drugs into the CNS. An increasing number of studies on both animals and human subjects have suggested that intranasal drug delivery could be used to deliver both small- and large-sized drugs into the CNS by bypassing the BBB. It appears increasingly reasonable to conduct clinical trials to determine if intranasal drug delivery may be used to treat neurological diseases.

In the 1970s and 1980s there were multiple studies suggesting that intranasal administration may enable substances to directly enter into the brain by pathways involving the olfactory epithelium and olfactory bulb [2]. In 1995 Thorne *et al.* reported the first quantitative study indicating that intranasal administration could deliver large-sized molecules into the brain by bypassing the BBB [3]. Intranasal administration of wheatgerm agglutinin-horseradish peroxidase (WGA-HRP) led to a significant presence of WGA-HRP in the olfactory bulb of rats, while there was no detectable amount of WGA-HRP in the olfactory bulb after intravenous injection of the same concentration of WGA-HRP. Since 1997, many studies have indicated that intranasal administration can enable large-sized molecules, such as IGF-1, FGF-2, TGF-β1, erythropoietin, IFN-β, HIV-1 Tat, insulin and leptin, to be transported into the CNS at least partially through direct nose-to-brain routes [2,4–9].

A number of studies using animal models of neurological diseases have demonstrated that intranasal delivery of large-sized molecules can produce beneficial effects. For example, intranasal nerve growth factor (NGF) administration can attenuate memory deficits and neurodegeneration in transgenic models of Alzheimer's disease (AD) [10]; administration of erythropoietin [8] or IGF-I [11] by the intranasal approach can significantly decrease ischemic brain damage; and intranasal delivery of growth factors can also increase neurogenesis in rat brains [9].

We have conducted studies to directly compare the efficacy of intranasal drug delivery with that of intravenous drug delivery in treating brain ischemia. Based on the cell-culture studies showing the protective effects of gallotannin (GT) and nobotanin B – two inhibitors of poly(ADP-ribose) glycohydrolase – against oxidative cell injury [12], we found that intranasal delivery of GT is much more effective than intravenous injection of GT in decreasing ischemic brain injury [13]. On the basis of the *in vitro* findings that nicotinamide adenine dinucleotide ($NAD^+$) treatment can prevent oxidative stress-induced cell death [14], we also found that intranasal $NAD^+$ administration can produce up to 90% decreases in infarct formation when given 2 h after ischemia, which is the most profound protection ever reported from drugs that have been administered hours after ischemic onset [15,16].

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By contrast, intravenous injection of $NAD^+$ at the same dose could not produce significant decreases in ischemic brain injury when the same number of rats was used. Collectively, our study has highlighted the distinct merits of intranasal drug delivery over intravenous drug injection in decreasing ischemic brain injury.

Multiple recent studies have also suggested that intranasal drug delivery could produce beneficial effects on human subjects. For example,

10.2217/14796708.3.1.1 2008 Future Medicine Ltd ISSN 1479-6708

intranasal oxytocin administration can increase confidence in human subjects [17]; insulin administration by the intranasal approach can improve the memory and mood of healthy adults [18]; and intranasal delivery of insulin can also improve the memory of AD patients without altering blood levels of insulin or glucose [6].

There are three likely mechanisms underlying the direct nose-to-brain drug delivery: there could be at least one intracellular transport-mediated route and two extracellular transport-mediated routes [2,5,6,8,9].

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The intracellular transport-based route is a relatively slow process, taking hours for intranasally administered substances to reach the olfactory bulb. The olfactory neurons in the olfactory epithelium could uptake the molecules by such processes as endocytosis, which could reach the olfactory bulb by axonal transport [2,5,6,8,9]. The two likely extracellular transport-based routes could underlie the rapid entrance of drugs into the brain, which can occur within minutes of intranasal drug administration [5,19]. In the first extracellular transport-based route, intranasally administered substances could first cross the gaps between the olfactory neurons in the olfactory epithelium, which are subsequently transported into the olfactory bulb. In the second extracellular transport-based route, intranasally administered substances may be transported along the trigeminal nerve to bypass the BBB [5,19]. After reaching the olfactory bulb or trigeminal region the substances may enter into other brain regions by diffusion, which may also be facilitated by a 'perivascular pump' that is driven by arterial pulsation. In addition, intranasally administered drugs may also partially enter into the CNS after the drugs enter into the systemic blood circulation from the nose [19].

Compared with traditional drug-delivery approaches, intranasal drug delivery has multiple significant advantages. First, large-sized drugs could be delivered into the brain by bypassing the BBB; second, potential side effects of the drugs on the peripheral system could be minimized; third, smaller amounts of drugs are required to produce the desired concentrations of drugs in the CNS, which can reduce treatment cost; fourth, the noninvasiveness of intranasal drug delivery can minimize the pain patients suffer; and fifth, intranasal drug delivery may be conducted by patients themselves or other nonprofessionals, which could minimize the delay of medical treatment.

Understanding of the direct nose-to-brain routes may also promote our understanding of the pathogenic mechanisms of neurological diseases. For example, the presence of herpes simplex virus type 1 in the brain of carriers of *APOE4* may be a significant risk factor of AD. It is conceivable that elucidation of direct nose-to-brain routes in humans could shed light on the mechanism of virus entrance into the CNS.

In summary, cumulating evidence has suggested that intranasal drug administration could enable drugs to directly enter into the CNS through olfactory pathways or the trigeminal nerve. A number of studies on both animals and human subjects have also demonstrated that intranasal delivery of various types of molecules can produce beneficial effects on the brain. These studies have suggested the great potential of intranasal drug delivery for treating various CNS diseases.

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## Future perspective

Although major progress has been made regarding intranasal drug delivery, there is still a distinct lack of information regarding this important topic. The studies searching for this information are urgent due to the rapid increases in the aging population and the number of patients with neurological diseases around the world. The following future studies may be of particular interest.

First, it is essential to search for the mechanisms underlying the direct drug transport from nose-to-brain after intranasal drug delivery, particularly those mechanisms in humans.

Second, methods for intranasal drug administrations to treat neurological diseases must be improved. Previous studies have suggested potential pathways to further increase the efficacy of intranasal drug delivery. For example, it was reported that carriers of drugs such as methoxy poly(ethylene glycol)-poly(lactic acid) nanoparticles, can further increase the efficacy of intranasal drug delivery into the brain [20]; the

optimal body positions for intranasal drug delivery have been investigated [19]; and some tools for intranasal drug administration have also been invented [19]. Future investigation along these research directions is warranted to optimize the intranasal drug-delivery approach.

Third, it appears increasingly necessary to conduct clinical trials to determine if intranasal drug delivery may be used to treat neurological diseases, which has been distinctly insufficient. Future studies on this topic may suggest that utilizing intranasal drug delivery could be a critical advance for establishing effective therapeutic strategies for neurological diseases.

When I was a small child in China, many people who were older than me provided me with the following serious advice: please do not scratch the infectious sites near your nose, as the toxins may get into your brain. This advice had become an amusing fairy tale in my mind even before I entered college. However, with the increasing number of studies suggesting the amazing effects of intranasal drug delivery on the brain, it is increasingly likely that this age-old tale linking the nose to the health of the brain may become a true story.

### Acknowledgements

*The author would like to thank Dr Guangwei Wei, Mrs Dongmin Wang and Dr Peng Zhang for their contributions to the author's experimental studies regarding intranasal drug delivery.*

### Financial & competing interests disclosure

*This work is supported by a VA MREP Award and by grants from the Department of Defense and American Heart Association Western States Affiliate. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.*

*No writing assistance was utilized in the production of this manuscript.*

**Executive summary**

- Because a key obstacle for developing effective drugs for treating neurological diseases is the blockage of drug entrance into the CNS by the BBB, it is of critical significance to search for drug-delivery strategies that can effectively deliver drugs into the CNS.
- Intranasal drug delivery has been shown to produce significant beneficial effects on the brains of both animals and human subjects.
- There are three likely mechanisms underlying the direct nose-to-brain drug delivery. There could be at least one intracellular transport-mediated route and two extracellular transport-mediated routes.
- Clinical trials must be conducted to determine if intranasal drug delivery may be used to treat neurological diseases. Future studies on this topic may suggest that applying intranasal drug delivery could be a critical advance for establishing effective therapeutic strategies for neurological diseases.

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