The nose-brain pathway: Exploring the role of trigeminal nerves in delivering intranasally administered antidepressant

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Intranasal administration of PAS-CPP-GLP-2 results in its delivery to the brain via trigeminal axons of the trigeminal nerves. Therefore, it is thought to constitute a nerve-associated transcellular pathway for drug delivery. Credit: Prof. Chikamasa Yamashita from Tokyo University of Science

Intranasal (in.) administration has been garnering increasing popularity as a non-invasive approach to deliver drugs directly to the brain. This approach involves the respiratory or olfactory epithelia of the nasal mucosa through which the drugs reach the central nervous system (CNS).

Transport from the respiratory epithelium via the trigeminal nerve is considerably slower than transport from the olfactory epithelium route via the olfactory bulb (OB) or cerebrospinal fluid (CSF). However, only a small portion of the nasal mucosa in humans is made up of olfactory epithelium, propelling researchers to focus on improving in. drug delivery time through the predominant respiratory epithelium.

To facilitate this, a team of researchers including Professor Chikamasa Yamashita from Tokyo University of Science, Japan, developed a novel drug to test its uptake efficacy by the CNS.

To offer more insight, Prof. Yamashita states, "In a previous study, we combined functional sequences (namely, a membrane permeability-promoting sequence [CPP] and an endosomal escape-promoting sequence [PAS]) to glucagon-like peptide-2 (GLP-2), which is effective against treatment-resistant depression, so that it can be efficiently taken up by neurons. Using this, we aimed to construct a nose-to-brain system mediated by the trigeminal nerve in the respiratory epithelium."

While studying the uptake of this novel PAS-CPP-GLP-2 by the CNS, the team noted that its antidepressant effects via in. administration remained on par with intracerebroventricular (icv.) administration at identical doses. Therefore, Prof. Yamashita and his colleagues elucidated a nose-to-brain transfer mechanism to explain why intranasally administered GLP-2 derivatives show drug effects at the same dose as intracerebroventricularly administered GLP-2 derivatives.

The team’s findings have been documented in Journal of Controlled Release.

The team performed icv. and in. administration of PAS-CPP-GLP-2 into mice. The amount of drug transferred to the whole brain was quantified by enzyme-linked immunosorbent assay (ELISA).

Surprisingly, the ELISA revealed that a much smaller amount of intranasally administered PAS-CPP-GLP-2 reached the brain than intracerebroventricularly administered PAS-CPP-GLP-2. However, both icv. and in. administration showed efficacy at the same dose. This is attributed to the fact that icv. administration introduces drugs to the place of origin of CSF (ventricle), causing them to diffuse into the CSF and spread through the brain.
Since the CSF is present in the spaces outside the capillaries of the brain, the team saw that a large portion of PAS-CPP-GLP-2 was likely to stay here without being transported to its working sites of action. On the other hand, nasally administered GLP-2 derivatives were rapidly taken up by the trigeminal nerve of the respiratory epithelium, and efficiently reached the site of action while transiting neurons.

Prof. Yamashita explains, "This suggests that the peptide delivered to the site of action by icv. administration is present in large amounts in the brain but only in very small amounts, as it remains in the perivascular space. On the other hand, intranasally administered PAS-CPP-GLP-2, unlike icv. administration, may be transferred to the site of action without passing through the CSF or perivascular space."

These results prompted the team to identify the central transfer drug delivery route following in. administration. This route involved the principal sensory trigeminal nucleus, followed by the trigeminal lemniscus of the trigeminal nerve, and led to the drug's working sites. Finally, it was discovered that the migration of PAS-CPP-GLP-2 via nerve transit was the reason behind its pharmacological activity despite its low levels in the brain upon in. administration.

Prof. Yamashita explains, "This is the world's first drug delivery system that allows intranasally administered peptides to be delivered to the central nervous system via nerve cells, delivering peptides to the site of action with the same efficiency as icv. administration."

Speaking about the future applications of the team's findings, Prof. Yamashita concludes, "Current data suggests the possibility of extending the use of this system from treating depression to delivering drugs in patients with Alzheimer's disease. It is therefore expected to be applied to neurodegenerative diseases with high, unmet medical demand."

More information: Tomomi Akita et al, Involvement of trigeminal axons in nose-to-brain delivery of glucagon-like peptide-2 derivative,