Expert Opinion

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Clinical trials of intranasal delivery for treating neurological disorders – a critical review

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Introduction: The intranasal delivery of therapeutics to the brain has achieved great success in preclinical studies. These findings are important because there are many neurological disorders without feasible treatments, due to a lack of effective drug delivery methods to the brain. Translating such intranasal delivery strategies from bench to bedside is an important step for curing these neurological diseases.
Areas covered: This review summarizes recent clinical trials that have investigated the intranasal delivery of drugs to the brain to treat neurological disorders and their potential mechanisms of action. In addition, the potential opportunities as well as challenges of intranasal delivery in clinical trials are discussed.
Expert opinion: The intranasal delivery of drugs to the brain is a novel method with great potential, and it may provide an extraordinary approach to overcome the existing barriers of drug delivery for treating some neurological disorders. Intranasal delivery of central nervous system therapeutics has shown promise in several clinical trials, which demonstrates both the need and importance of further research.

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Keywords: clinical trials, insulin, intranasal delivery, neurological disorders, orexin A, oxytocin

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1. Introduction

Intranasal drug delivery has a long history [1] in treating systemic or neurological disorders [2,3]. However, it was first established by Dr. William H. Frey II in 1989 that intranasal delivery could circumvent the blood–brain barrier (BBB) and facilitate drug delivery into the central nervous system (CNS) [4]. The reasons for developing the intranasal delivery of therapeutics into the CNS are that i) the intact BBB could prevent most foreign materials from entering the brain [5] and ii) molecules such as insulin may enter the CNS after systemic administration at a high dose but could cause severe side effects [6]. The basis of intranasal delivery is the special anatomy of nasal cavity, which has the olfactory region with specialized olfactory receptor cells in the roof. The olfactory neuron area is the only open window of CNS [7]. Intranasal delivery, unlike intravenous or intracerebroventricular injection, is a relatively novel route for drug administration [8]. The details of the technique are summarized in the review by Pires *et al.* [9]. It is simple and easy for patients to manage the procedure without the help of physicians; it is also noninvasive and safe for patients, which is very important in clinical trials especially for the placebo or sham controls, and most importantly, it could bypass the BBB and avoid the first-pass effect [9]. Accumulating basic and clinical evidence has verified that various substances, such as high-molecular-weight substances, water-soluble molecules, nucleic acids, viruses and cells, could enter the CNS of many species including humans after intranasal administration [10-18]. Animal studies have indicated that

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substances gain access via nasal, trigeminal, vascular or cervical node routes following intranasal delivery [19].

Several findings in animal studies have demonstrated that intranasally administered therapeutics could protect neurons against a number of insults and could treat neurological diseases such as ischemic stroke [20], Parkinson's disease (PD) [21] and Alzheimer's disease (AD) [22]. How to translate the results from the bench to bedside is a key point for applying this novel method in treating neurological disorders. A number of clinical trials have been launched to evaluate the feasibility of this strategy, and some clinical trials have obtained encouraging results. This paper reviews progress in the field.

2. Clinical trials of intranasal delivery in neurological disorders

Clinical trials of intranasal delivery begin with the finding that drugs administered intranasally could enter the human brain. Born *et al.* [23] first delivered three peptides, insulin (40 IU), vasopressin (40 and 80 IU) and melanocortin (10 mg), into human CNS via the nasal route. Intranasal administration of the three peptides resulted in elevation of their concentrations in cerebrospinal fluid (CSF). At the same time, there was no significant increase in any peptide concentration in serum or change in plasma glucose levels following the intranasal delivery of insulin. Afterward, other evidence demonstrated that other drugs could enter the human brain via the nasal route, such as perillyl alcohol (POH), orexin A and cholecystokinin (CCK).

2.1 Insulin

The effects of insulin, which is mainly used to control plasma glucose levels, in the CNS have been explored recently. Elevated levels of insulin in the CNS suppress food intake by affecting the hypothalamic structures [24], whereas low insulin levels could induce memory loss, particularly declarative memory. Systemically administered insulin can enter the CNS through insulin receptors in the BBB and then improve memory processing. However, intravenously administered insulin may cause severe side effects, such as hypoglycemia. Therefore, in preclinical studies, insulin was delivered to the CNS via intracerebroventricular injection to avoid influencing blood glucose levels [24,25]. However, the trauma and expensive fees of surgery may prevent the widespread clinical application of intracerebroventricular injection. Previous studies have demonstrated that intranasally administered insulin could enter the brain and treat neurological disorders in animal models [26].

Then, a double blind, two-army study with 38 healthy subjects investigated declarative memory, attention and mood after intranasally delivering 160 IU of regular insulin per day for 8 weeks. In the study, delayed word list recall, which evaluates declarative memory, was significantly improved. In the intranasal insulin group, anger, as assessed by the Stroop test, and self-confidence were improved compared with the findings in the controls [27]. This is the first study that demonstrated that intranasal insulin improves memory in normal adult humans. A relative lack of insulin in the CNS is associated with obesity in humans, and intranasally delivered insulin is predicted to improve the memory of obese humans. A pilot study was designed to test this hypothesis. Regular insulin (160 IU per day) or placebo was intranasally administered to obese men over 8 weeks. Delayed word list recall and mood were significantly improved in obese men, and hypothalamic–pituitary–adrenal axis activity as assessed by circulating adrenocorticotropic hormone and cortisol levels were reduced in the intranasal insulin group without any significant reduction in body weight and body fat [28].

Intranasally delivered insulin may improve the declarative memory process, which is dependent on hippocampal function and is impaired in AD, and insulin levels are lower in the brains of AD patients [29]; therefore, intranasally administered insulin was used to treat *AD* [30,31], which was firstly proposed by Frey [32]. A single-site trial including 25 early AD or mild cognitive impairment patients evaluated the efficacy of the intranasal delivery of 20 IU of insulin per day for 21 days. The patients in the insulin-treated group benefited from the intranasal delivery of insulin as determined by memory, attention and functional status in the absence of side effects [33]. In another study, AD patients were divided into two groups based on the apolipoprotein E (APOE)-ε4 allele, which is a genetic risk factor for AD. Intranasally administered insulin improved the verbal memory of both APOE-ε4- and APOE-ε4+ subjects compared with intranasally administered placebo, and the effects were stronger for memory-impaired ε4- subjects than for memory-impaired ε4+ subjects [34]. The study demonstrates that some patients may not benefit from this therapy because of certain genetic factors, and further studies should consider these factors in clinical trials.

As intranasally delivered insulin has been proven to improve declarative memory in healthy adults and AD patients, some researchers investigated this treatment in other memory-impaired disorders. The 22q13 deletion syndrome (Phelan-McDermid syndrome) is characterized by a global development delay, absent or delayed speech, loss of verbal skills, generalized hypotonia, autistic behavior and phenotypic features [35]. Six children with 22q13 deletion syndrome received insulin (0.5 – 1.5 IU/kg/day) intranasally for 12 months. Gross and fine motor activities and cognitive functions were improved 6 weeks and 12 months after treatment. One patient displayed changes in balance, extreme sensitivity and general loss of activity, and another complained of intermittent nose bleeding [36].

A double-blind, placebo-controlled trial explored the effect of the intranasal delivery of single-dose (40 IU) insulin on cognition in 30 nondiabetic patients with schizophrenia. The Hopkins Verbal Learning Test and the Continuous Performance Test – Identical Pairs – were used to test verbal memory and sustained attention, respectively. The results

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demonstrated that intranasally delivered insulin was safe and well tolerated; however, intranasally delivered insulin did not have substantial effects on verbal memory or sustained attention in patients with schizophrenia [37].

2.2 Vasopressin

Arginine vasopressin (AVP) influences social behaviors in animal models and humans. As vasopressin could gain access to the brain via the nasal route, one study investigated the effect of the intranasal delivery of AVP on attention toward emotional facial expressions and its adverse effects. The results indicate that intranasally delivered AVP may influence aggression in males by biasing subjects to respond to emotionally ambiguous social stimuli as if they were threatened [38]. Another study used a similar design and found that intranasally administered AVP improved known judgments for previously seen happy and angry faces in comparison with neutral human faces, whereas it did not influence judgments for new faces [39]. Therefore, intranasally administered AVP could treat social disorders. In a descriptive study, 26 patients with *chronic aphasia after stroke*, which is one of the leading causes of death and long-term adult disability [40], were treated with intranasally delivered vasopressin. The results indicated that simple forms of speech and composite forms were improved using subendocrine doses of the neuropeptide in all cases, although there were no statistically significant differences between the sensory and integrative components of the organization of speech processes. Additionally, speech regulated by both brain hemispheres was improved [41].

2.3 Oxytocin

Vasopressin could gain access to the human brain after intranasal administration [23]. Oxytocin and vasopressin have related structures differing by only two amino acids, which suggests a similar pharmacokinetic mechanism regarding the pathway to the brain for both peptides [42]. The neuropeptide oxytocin has an essential role in mammalian parturition and lactation. In addition, many recent preclinical data indicate that oxytocin can facilitate the development of social attachments and affiliations, including approach behavior, social support and social memory [43,44]. Therefore, oxytocin is used to study the mechanisms of social behavior and treat *social disorders* following intranasal delivery.

Heinrich *et al.* reported that the intranasal delivery of oxytocin causes a substantial increase in human trust, and this effect of oxytocin was not due to a general increase in the readiness to bear risks but was due to improvement in the willingness to accept social risks arising from interpersonal interactions [45]. A subsequent study used the Reading the Mind in the Eyes Test (RMET) to test how the intranasal delivery of oxytocin would improve interpersonal interactions in 30 healthy male volunteers. The results indicated that oxytocin improves performance on the RMET, which suggests that oxytocin confers the ability to infer the mental state of others from social cues of the eye region [46]. Another double-blind, randomized, placebo-controlled, between-subject study of 52 healthy male volunteers reported that the intranasal delivery of 24 IU of oxytocin increased the number of fixations and total gaze time toward the eye region of 24 neutral human faces [47]. In addition, the results were similar with previous findings.

In a later study, researchers studied the underlying mechanisms of the effects of oxytocin on approach behaviors. The study used functional magnetic resonance imaging (fMRI) to measure the neural responses to fearful, angry and happy expressions after the intranasal delivery of oxytocin and found that intranasally administered oxytocin facilitates social behavior through reducing the right-sided amygdala responses to facial expressions irrespective of their valence [48]. The same group used another trust and risk game to explore the underlying mechanism and found that the activities of the amygdala, midbrain regions and dorsal striatum in subjects receiving intranasally delivered oxytocin are reduced [49]. In addition to the reduction of amygdala activity, intranasally delivered oxytocin also decreased the level of salivary cortisol after a standard instructed couple conflict discussion [50].

All these findings suggest that intranasally administered oxytocin can treat mental disorders such as social phobia and autism, which are characterized by persistent fear or avoidance of social interactions. Guastella *et al.* used intranasally delivered oxytocin (24 IU) to treat social anxiety disorder in a randomized, double-blind, placebo-controlled trial with 25 patients. Participants in the oxytocin group exhibited improved positive evaluations of appearance and speech performance, whereas there were no significant differences in symptom severity, dysfunctional cognition and life impairment measures between the groups [51]. Another study explored the brain-based mechanism of the impact of intranasally delivered oxytocin on social anxiety disorder and found that oxytocin reduces amygdala activity in response to fearful faces in participants with social anxiety disorder [52]. In addition to social anxiety disorder, autism was also treated by intranasally delivered oxytocin in another clinical trial of 16 male young subjects from 12 to 19 years old, and the RMET was used to measure the emotion recognition. The data indicated that intranasally administered oxytocin improves performance on the RMET [53].

Some previous animal studies have indicated that intranasally delivered oxytocin may affect learning and memory function. In humans, intranasally administered oxytocin selectively influences memory performance depending on the type of memory test and the psychobiological relevance of the stimuli [54]. In this trial, three different memory tests – an implicit perceptual test, an implicit conceptual test and an explicit test – were used to test memory. Another trial used facial identity to investigate social memory and reported similar findings that intranasally administered oxytocin improved identity recognition memory for neutral and angry faces but not for happy faces [55]. However, one study suggested that intranasally administered oxytocin enhances

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the processing of positive versus negative emotional information in healthy male volunteers [56]. The reason for the conflicting findings may be that the two trials used different tests and investigated memory at different times after intranasal administration. Further investigation revealed that intranasally administered oxytocin could improve the recognition of previously presented faces, but the ability of recollecting faces was not changed [57].

What is the underlying mechanism of the effect of intranasally delivered oxytocin on social memory? Some researchers delivered oxytocin to monozygotic twins with congenital Urbach–Wiethe disease, which is selective bilateral damage to the amygdala and found that learning and the ability to perform empathy tasks were impaired, whereas nonsocially reinforced learning and cognitive empathy were normal. These results indicated that intranasally delivered oxytocin facilitates learning and emotional empathy in men via modulating amygdala activity [58]. Additionally, intranasal delivery of oxytocin modulated electroencephalogram rhythms in the 8 – 10 Hz (low α/μ) and 15 – 25 Hz (δ) bands in 24 healthy subjects who were shown a point-light display of continuous biological motion of a walking person [59].

Previous results indicated that intranasally administered oxytocin might have antipsychotic properties [60,61]. Therefore, in a clinical trial, 15 schizophrenia patients received 40 IU of oxytocin twice daily for 3 weeks. The data suggested that the scores of the Positive and Negative Symptom Scale and Clinical Global Impression – Improvement Scale – were reduced after 3 weeks without adverse effects [62].

2.4 Perillyl alcohol

POH, composed of two isoprene units and produced by the mevalonate pathway, could inhibit the proliferation, migration and metastatic activity of glioblastoma multiforme cells *in vitro* and *in vivo* [63]. Orally administered POH exerted a tumoristatic effect in clinical trials, but it causes toxicities, such as nausea, early satiety and eructation, which will lead to problems with patient tolerance and compliance [64]. Therefore, POH (55 mg) was delivered intranasally to 29 *glioblastoma* multiforme patients four times a day, and progression-free survival was determined after 6 months. The results demonstrated that POH exhibits antitumor activity and that it is well tolerated by patients [65]. The same research group used computed tomography and MRI to establish tumor size and found that intranasally delivered POH could increase the regression of tumor size [66]. These studies indicate that intranasally administered POH is safe, noninvasive and efficient.

2.5 Orexin A

Orexin A (hypocretin-I) is a neuropeptide that is mainly expressed in neurons of the lateral hypothalamic and perifornical areas [67]. Preclinical studies demonstrated that intranasal delivery increases drug targeting to the brain and spinal cord by five- to eightfold because of direct transport from the nasal passages in rats [68]. In nonhuman primates, intranasally delivered orexin A produces a more pronounced reversal of sleep deprivation-induced changes in brain metabolic activity than intravenously delivered orexin A [69]. The possible pathophysiologic mechanism underlying olfactory dysfunction in narcolepsy is the lack of orexin A in the CNS. Therefore, in a double-blind, randomized, placebo-controlled, crossover design, orexin A was delivered intranasally to seven patients. Compared with the controls, patients exhibited significantly lower scores for olfactory threshold, discrimination and identification [70].

2.6 Cholecystokinin

CCK is a neuropeptide that colocalizes with dopamine (DA) in the neurons of the mesolimbic–frontocortical and nigrostriatal DA system, and it has been found to improve controlled stimulus processing and attention, as indicated by the late positive complex of event-related brain potentials (ERPs). Intranasally administered CCK induces a positive shift of ERPs without elevating blood plasma CCK levels in healthy subjects [71,72]. In *PD*, intranasally delivered CCK extends the auditory brain potential components without altering motor performance [73].

3. Ongoing clinical trials using intranasal delivery

Many clinical trials have demonstrated the efficiency of intranasally delivering drugs in treating neurological disorders. When we search 'intranasal delivery' on the Web site clinicaltrials.gov, we found a number of ongoing clinical trials. These ongoing trials may solve the existing problems and facilitate the widespread clinical application of intranasal delivery. Some features of these ongoing clinical trials are listed in **Table 1**. First, many new drugs will be used to treat neurological disorders. In addition, some of these neurological disorders are common diseases in the clinic, such as stroke and traumatic brain injury. Second, several objective outcomes will be added to evaluate the therapeutic effect. Third, insulin has the greatest potential to treat CNS disorders. Finally, most of the ongoing trials are Phase I/II trials. We look forward to the results of these clinical trials and encourage more trials to investigate intranasal delivery more deeply.

4. The limitations and perspectives of clinical trials of intranasal delivery

Clinical trials of the intranasal delivery of drugs to the brain are just emerging, and some limitations of this technology may require further studies.

4.1 Limitations

4.1.1 Pathway from the nose to the brain

None of the previous studies provided definitive evidence regarding the exact pathways of intranasally delivered drugs

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Table 1. Ongoing clinical trials of intranasal delivery.

ID	Drugs	Participants	Phase	Outcomes
NCT01212679	NGF	TBI	II	Neurological functions
NCT01206322	Insulin	DM	II	Regional perfusion and vasoreactivity
NCT00916201	Insulin	Schizophrenia	I	Psychopathological scores
NCT00438568	Insulin	MCI/AD	II	Changes in cognition
NCT00581867	Insulin	AD	II	fMRI activation
NCT00145482	Insulin	MCI/AD		Cerebral glutamate concentration
NCT01123317	Oxytocin	Schizophrenia		rCBF
NCT01002300	Oxytocin	Dementia/Pick's disease		Performance on emotion recognition tasks
NCT00748956	NPY	Mood and anxiety disorders	I	Levels of NPY in CSF and plasma
NCT00069069	E-selectin	Stroke	I	Maximum tolerance dose of E-selectin

AD: Alzheimer's disease; CBF: Cerebral blood flow; DM: Diabetes mellitus; MCI: Mild cognitive impairment; NGF: Neurotrophic growth factor; NPY: Neuropeptide Y; TBI: Traumatic brain injury.

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to the brain in humans. Previous preclinical research indicated that drugs may enter the brain through the olfactory route, trigeminal nerve and cervical lymph nodes following intranasal administration; however, whether drugs are distributed in similar patterns in humans remains to be answered. We hypothesize that there may be a pathway from the nose to the brain with some indirect phenomena that intranasally delivered drugs cause the elevation of drugs in CSF but not in plasma [23,74]. One study investigated the intranasal administration of melatonin (0.4 mg) and hydroxocobalamin (1.5 mg) to three and five patients, respectively. The results demonstrated that intranasally delivered melatonin and hydroxocobalamin led to a rapid increase in their levels in blood and CSF, but there were no significant differences in drug levels between intranasal and intravenous administration [75]. The reasons may be as follows: i) nonpeptide drugs are better absorbed into the systemic circulation, but peptides were not used in this study; ii) there were only three patients involved in the study, and the data may not reflect the true situation; iii) the volumes and times of sample collection were different among the groups and iv) the different methods to measure the blood concentration and CSF measurements and imaging should be both included.

4.1.2 Lack of a standard procedure of intranasal delivery

Experiment data demonstrate that different procedures of intranasal delivery, such as head position [76], device for delivery [77], the volume of drugs [78], absorption enhancers (vasoconstrictor) and pharmaceutical dosage form (nanoparticles) [79], may cause different outcomes (**Table 2**). The procedures of intranasal delivery vary among different clinical trials. What is the optimal head position of humans? What are the total volume of drugs and the volume of each drop? How much time is needed between drops? What is the best device, Impel Neuropharma, Optionose, Kurv, WolfMAD or something else? In ongoing studies, there are differences among different trials using both the same and different drugs. To facilitate the widespread application of intranasal delivery, a standard procedure is necessary.

4.1.3 The design of the clinical trials

Some clinical trials obtained negative results using intranasally delivered drugs to treat neurological disorders [37]. How to interpret these differences is essential for the application of intranasal delivery. Are the drugs inefficient, or are they unable to reach the brain following intranasal delivery? Are the samples of these clinical trials too small, or are the outcomes not sufficiently sensitive? To answer these questions, first, the control group should be designed strictly and reasonably. For example, intravenous delivery should be included in the trials to exclude the possibility of drugs not reaching the brain. However, many trials did not include a control group for differing reasons [33]. Second, because most clinical trials are Phase I/II trials, there are not many subjects in these clinical trials. Finally, many trials did not have objective outcomes. All of the biases may result in different conclusions.

4.2 Perspectives

4.2.1 Deeper research on mechanism of nose-to-brain drug transport

Intranasal delivery is a novel method with some limitations for drug delivery. To resolve the problems in the clinical trials, we should focus on a number of factors. First, we should investigate the pathway from the nose to the brain. Although many studies have reported some potential routes, no available report has presented direct evidence of these pathways in humans [17]. Because of the development of molecular imaging, we can use this technology to clarify the pathway of intranasal delivery. Then, we should investigate more appropriate drugs for intranasal delivery. Many drugs have been studied in clinical trials, and some drugs that have proven effective in animal models have not been tested in clinical trials. Additionally, we should investigate the strategy in additional neurological disorders. The aim of intranasal delivery to the brain is to treat CNS disorders; therefore, the safety and efficacy of intranasal treatment needs to be assessed for a

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Table 2. Intranasal delivery procedures in clinical trials.

Drugs	Diseases	Drop size	Volume per time	Interval	Total times	Enhancers or device	Ref.
Insulin	Normal	0.1 ml	0.4 ml	24 h	4	No	[27]
Insulin	Obese	0.1 ml	0.4 ml	6 h	56	No	[28]
Insulin	AD	2 ml	2 ml	12 h	42	ViaNase	[33]
Insulin	AD	0.1 ml	0.4 ml	Unknown	1	No	[34]
Insulin	22q13 deletion syndrome	0.1 ml	0.1 ml	24 h	365	Aero Pump	[36]
Oxytocin	Normal	4 IU	24 IU	-	1	No	[45]
Oxytocin	SAD	3 IU	24 IU	1 week	5	No	[51]
POH	Glioma	55 mg	55 mg	6 h	112	No	[65]
Orexin A	Narcolepsy	0.1 ml	2 ml	-	1	No	[70]
CCK	PD	0.08 ml	0.32 ml	Unknown	1	No	[73]

AD: Alzheimer's disease; CCK: Cholecystokinin; PD: Parkinson's disease; POH: Perillyl alcohol; SAD: Social anxiety disorder.

variety of brain diseases. Finally, we should improve the efficiency of transportation from the nose to the brain. The experimental data indicate that the amount of drugs reaching the brain from the nose is still small compared with the dose of application. Improving the efficiency may be essential for widespread application.

4.2.2 *Create a standard protocol for intranasal delivery*

Because the protocols of intranasal delivery vary among different laboratories and different protocols may cause different outcomes, a standard protocol is necessary. A simple and stupid standard may be good at the moment for widespread application even though later on modifications for further improvement might be necessary. We should determine the procedures according to the following factors: the position of the patients; the total volume of medium for each drug; the volume of each drop; the interval between each drop; the device for delivery; and how many times the procedure should be performed. We suggest the establishment of an organization to solve this problem because an organization may provide a platform to communicate with individual researchers.

4.2.3 *Design the clinical trials more appropriately*

As we discussed previously, there are many limitations of the available clinical trials, and we should more appropriately design clinical trials. As there are many Phase I/II trials with impressive results, we could begin Phase III trials using the most potent drugs such as insulin and oxytocin. We should create more strict criteria to exclude confounding factors. Some researchers mentioned that many trials did not have a control group such as an intravenous drug delivery group. In the future, researchers should consider the inclusion of a control group. The outcomes of many clinical trials were not objective, and we should detect the area of injury in the CNS via imaging technology, pathology or serum factors to assess the effect of the intranasal delivery of drugs. For example, we may calculate the infarct size of stroke patients using imaging technology before and after the intranasal delivery of some drugs.

5. Conclusion

In summary, clinical trials of intranasal delivery have achieved great success in therapy and in uncovering underlying mechanisms of neurological disorders.

6. Expert opinion

6.1 Why should we focus on the drug delivery?

The goal of drug development is clinical application. However, in 2006, a systematic review reexamined the extracted data for 1026 neuroprotective strategies tested in 8516 experiments relevant to stroke, which were published in about 3500 articles between 1957 and 2003 and found that none of them demonstrated significant improvement of neurological functions in clinic [80]. An important one of many causes of the problem is that drugs could not enter the brain to exert the neuroprotection. To address this issue, the Stroke Therapy Academic Industry Roundtable Preclinical Recommendations group added the method of drug delivery to the criteria for the future neurological disease researches [81]. Therefore, we should focus drug delivery in the field of developing CNS drugs.

6.2 Why do we need intranasal delivery?

In clinical practice, physicians need a safe, easy and efficient method to deliver drugs into the CNS. Because of the BBB, most drugs cannot enter the CNS via general drug delivery routes. Intracerebroventricular or intraparenchymal injection appeared to be the choice to deliver drugs to the CNS, but despite its effectiveness, this method is invasive. When we see holes in the heads of patients, we understand the necessity of alternative delivery methods. The risks of intracerebroventricular or intraparenchymal injection can be ignored for a single procedure, but neurological disorders such as PD are progressive and chronic. These patients need to take drugs

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repeatedly or even daily. Intranasal delivery is a good alternative method due to its noninvasive character and its feasibility even in patients.

6.3 Why do we need clinical trials of intranasal delivery?

Filling the gap between what we know and what we do is translation, which describes the transformation of knowledge through successive fields of research from basic science discovery to public health impact. However, less than 25% of highly promising biomedical discoveries result in published randomized clinical trials, and less than 10% of the discoveries have been established in clinical practice in the last 20 years [82]. There are three phases of translation medicine: translating basic science to clinical efficacy; efficacy to clinical effectiveness; and finally effectiveness to health-care delivery [83]. Moreover, clinical research is the core component of the translation column [84]. As mentioned previously, intranasal delivery could deliver many types of substances, particularly high-molecular-weight molecules, to the CNS in animal models directly and efficiently. A resulting question is whether this method works in humans. Born *et al.* [23] performed an experiment and demonstrated that peptides could gain access to the human brain. The results inspired many other studies, and many clinical trial data supported this opinion in the years following their initial finding. Although there are many problems or limitations for intranasal delivery, researchers are anxious to treat neurological disorders via intranasal drug delivery because many neurological disorders such as stroke are difficult to treat.

6.4 What is the situation of clinical trials of intranasal delivery?

For someone who wants to know the process of clinical trials of intranasal delivery and join the area, there may be some advice based on the findings of our laboratory and other researchers as follows. First, the following conclusions should be drawn: i) drugs such as insulin may cause severe side effects via routine delivery methods or fail to cross the BBB; ii) drugs such as brain-derived neurotrophic factor [85] should prove efficient and safe in treating disorders; iii) the underlying mechanisms of drugs in treating neurological disorders are well investigated; and iv) intranasally delivered drugs could enter the brain in animal models. Second, we investigated the intranasal delivery of drugs in a small number of healthy volunteers to determine whether the selected drug could enter the brain. Usually, we collect CSF and blood samples to measure the concentration of drugs and calculate the area under the curve. Third, additional numbers of volunteers are needed to test whether the intranasal delivery of such drugs is safe and leads to improvements in function such as cognition. Fourth, we selected one disorder on the basis of the animal experiment data and intranasally delivered drugs to several patients to investigate the efficiency of this therapy. Fifth, we explored the possible mechanisms of the intranasal delivery of drugs. For example, we used fMRI to measure amygdala activity following the intranasal administration of oxytocin. Sixth, if the intranasal delivery of such drugs did not alleviate diseases, we analyzed the reason. For example, AD patients with APOE $\varepsilon 4+$ had better improvements in impaired memory than $\varepsilon 4-$ subjects following the intranasal delivery of insulin [86]. Finally, we introduced intranasal delivery to treat other diseases using the pathophysiology of diseases and pharmacological mechanisms of drugs. After we treated AD patients using intranasally delivered insulin, patients with schizophrenia were intranasally administered insulin to assess the healing effect.

6.5 What should we do in the future?

Great success in the clinical application of intranasal delivery has been achieved in recent decades, although some problems remain as discussed in the text. The problems are divided into three categories: the technique of intranasal delivery, the pathway of intranasal delivery and the design of clinical trials. Intranasal administration is a simple technique for physicians and patients. Some data demonstrated that different methods might cause different outcomes, and no guideline to direct how to perform intranasal delivery is available. We suggest that researchers work together to create such a guideline and apply it following standard procedures. The pathway of intranasal delivery is a key research field and a constant focus of debate. In fact, there is lack of direct evidence indicating the pathways of intranasal delivery in humans, but with the development of molecular imaging, drugs could be labeled with some tracers, permitting the monitoring of drugs from the nose to the brain until their elimination from the body. In previous decades, increasing numbers of clinical trials in the field of intranasal delivery have been performed. However, the numbers of subjects in these clinical trials have been very small, and the designs of some studies were incomplete. Therefore, multicenter, randomized, double-blind, controlled trials are encouraged in the coming years and the spectrum of the applied methods should be optimized.

Some researchers have mentioned that a new technology may face one of three problems: it is not true; it is not new; or it is not important. In previous years, intranasal delivery has proven to be a novel and important method of drug delivery in treating CNS disorders. It appears that intranasal delivery has overcome the three aforementioned problems. Moreover, clinical trials of intranasal delivery have achieved great success, and these findings may facilitate the widespread application in intranasal drug delivery in the clinic.

Declaration of interest

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