Brain Uptake of the Glucagon-Like Peptide-1 Antagonist Exendin(9-39) after Intranasal Administration

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ABSTRACT

Exendin, a member of the glucagon-like peptide-1 family, and its antagonist exendin(9-39) affect cognition and neuronal survival after their intranasal delivery. Here, we examined the uptake of radioactively labeled exendin(9-39) (I-Ex) by the olfactory bulbs, brain (minus pineal, pituitary, and olfactory bulb), cerebrospinal fluid, and cervical lymph nodes (C-node) as well as levels in serum after intranasal or intravenous administration. We found that olfactory bulb uptake of I-Ex after intranasal administration was rapid, much greater than after i.v. administration, and was enhanced by about 60% with cyclodextrin (CD). I-Ex was also taken up by the remainder of the brain after intranasal administration, but this uptake was not enhanced by CD, nor did it exceed uptake after i.v. administered I-Ex. Uptake by the olfactory bulb was not dependent on Brownian motion but did involve active processes. Intranasal I-Ex reached the C-node by way of the blood. About one-sixth of the intranasal dose of I-Ex entered the blood. However, the vascular route accounted for little of the intranasal I-Ex that reached the brain and even less that reached the olfactory bulb. I-Ex after intranasal administration was found in the hippocampus, cerebellum, brain stem, and cerebrospinal fluid (CSF). Distribution patterns showed that intranasal I-Ex used the extraneuronal route of CSF rather than brain parenchyma to diffuse throughout the brain. These results show that intranasal administration is an effective means of delivering peptide to the brain, especially the olfactory bulb.

Glucagon-like peptide-1 (GLP-1) is produced by the gastrointestinal tract where it has effects on insulin, gastrointestinal motility, and appetite at peripheral receptors. GLP-1 and its receptor (GLP-1R) are also produced within the central nervous system (CNS). GLP-1R in the CNS mediates important effects on neuroprotection and cognition (During et al., 2003). This has raised the question of whether therapeutic agents targeted at GLP-1R can be delivered to the CNS in effective doses (Perry and Greig, 2002, 2003). Although other members of this peptide family cross the BBB by saturable and nonsaturable mechanisms (Banks et al., 1993, 2002; Dogrulkol-Ak et al., 2003), GLP-1 itself is a poor candidate for blood-to-brain delivery because it is rapidly degraded (Banks et al., 1997). In comparison, the GLP-1 homolog from the Gila monster, exendin, is stable and able to cross the BBB (Kastin and Akerstrom, 2003). One way to circumvent some of the problems with peptide delivery to the CNS may be by intranasal administration. We have found that an enzymatically resistant, synthetic analog of exendin, (Ser2)exendin(1-9), and its antagonist exendin(9-39) have biological effects on the CNS (cognition and neuroprotection) after intranasal administration (During et al., 2003).

A recent review by Frey (2002) has shown that many peptides and regulatory proteins can be delivered to the brain by intranasal administration. Additionally, Born et al. (2002) recently showed that insulin, melanocyte-stimulating hormone(4-10), and arginine vasopressin could be delivered to brain. All three substances occurred in the cerebrospinal fluid within minutes, and only arginine vasopressin was accompanied by elevations in its serum levels. This reinforces the idea that even if a substance can cross the BBB after intravenous administration, intranasal administration results in much higher brain/serum ratios. This, in turn, would favor effects in the CNS rather than effects at peripheral tissues. For example, Kern et al. (1999) was able to induce hypoglycemia by administering insulin by the intranasal route.

The disadvantages of a substance in its blood-to-brain de-

ABBREVIATIONS: GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; CNS, central nervous system; BBB, blood-brain barrier; I-Ex, radioactively labeled exendin(9-39); C-node, cervical lymph nodes; CSF, cerebrospinal fluid; CD, cyclodextrin; PE, polyethylene; PBS, phosphate-buffered saline; HPLC, high-performance liquid chromatography; ANOVA, analysis of variance; AUC, area under the curve.
livery can become advantages after its entry into the CNS. Rapid degradation in blood can be a major obstacle for delivery of a substance to the brain by intravenous administration, but it would limit the peripheral side effects of any of the substance that had entered the blood after its intranasal administration. In the absence of saturable transporters, large, water-soluble molecules cross the BBB poorly. This is true for blood-to-brain influx and also for brain-to-blood efflux. This means that once a large, water-soluble molecule has entered the CNS, as after successful intranasal or intrathecal delivery, the physicochemical properties that hindered its blood-to-brain delivery now act to retain it within the CNS (McCarthy et al., 2002). Peptides delivered by intranasal administration likely also have a longer residence time in brain than those delivered by i.v. administration. For example, vasoactive intestinal peptide can cross the BBB after intravenous administration and reach levels similar to those seen after intranasal delivery (Dogrulak-Ak et al., 2003; Dufes et al., 2003). However, 30 min after delivery, vasoactive peptide given by the nasal route but not by the i.v. route was still detectable in brain.

Substances use various mechanisms to enter the brain after intranasal administration. For example, horseradish peroxidase leaks between the intercellular spaces of the nasal epithelium and uses extraneuronal pathways to reach deep areas of the brain (Balin et al., 1986). Horseradish peroxidase conjugated to wheat germ agglutinin, however, is taken up by the energy-dependent process of adsorptive endocytosis and uses intraneuronal and transneuronal pathways to reach various regions of the brain (Broadwell and Balin, 1986; Baker and Spencer, 1986). Molecular weight and lipid solubility are important characteristics for other substances (Frey, 2002), suggesting that those substances are crossing membranes by the nonsaturable, nonenergy-dependent mechanism of membrane diffusion.

Here, we investigated the distribution of exendin(9-39) radioactively labeled with iodine (I-Ex) into olfactory bulbs, whole brain, blood, and cervical lymph nodes (C-node) after intranasal and intranasal administration; the distribution of I-Ex within the brain and CSF after intranasal administration; and mechanisms of uptake and diffusion.

Materials and Methods

Radioactive Labeling of Exendin. Exendin was labeled by the iodobead (Pierce Chemical, Rockford, IL) method. Briefly, 1 mCi of 111I and an iodobead were incubated together in 100 μl of 0.2 M sodium bicarbonate buffer, pH 8.6. After 5-min incubation at room temperature with gentle agitation, 10 μg of exendin was added to the mixture and incubation continued for another 15 min at room temperature with gentle agitation. The radioactively labeled exendin (I-Ex) was purified on a column of Sephadex G-10 and eluted in 100-μl solutions and the I-Ex solution; both the CD and I-Ex had been dissolved in normal saline. Dead mice were studied within 10 min of death induced by an overdose of ethyl carbamate.

Tissue Collections. At the indicated times, the arterial blood was collected by severing the carotid artery. The mouse was decapitated and the C-node identified, removed, and weighed. The whole brain (without the pineal, pituitary, or olfactory bulb), right olfactory bulb, and left olfactory bulb were removed from the cranial vault and weighed. In some mice, the hippocampus, cerebellum, brain stem, and anterior one-third of the brain (excluding the olfactory bulb) were dissected and weighed. The arterial blood was centrifuged at 5000g for 10 min at 4°C and a 50-μl portion of the arterial serum was collected. The level of radioactive iodine in the serum and tissue samples was determined by counting in a gamma counter.

Intranasal Injections. Mice were anesthetized with ethyl carbamate, and the left jugular vein and right carotid artery were exposed. Mice were given by intranasal administration. In the absence of saturable transporters, large, water-soluble molecules cross the BBB poorly. This is true for blood-to-brain influx and also for brain-to-blood efflux. This means that once a large, water-soluble molecule has entered the CNS, as after successful intranasal or intrathecal delivery, the physicochemical properties that hindered its blood-to-brain delivery now act to retain it within the CNS (McCarthy et al., 2002). Peptides delivered by intranasal administration likely also have a longer residence time in brain than those delivered by i.v. administration. For example, vasoactive intestinal peptide can cross the BBB after intravenous administration and reach levels similar to those seen after intranasal delivery (Dogrulak-Ak et al., 2003; Dufes et al., 2003). However, 30 min after delivery, vasoactive peptide given by the nasal route but not by the i.v. route was still detectable in brain.

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The pellet, which contains the brain vasculature, and the supernatant, which contains the brain parenchyma, were carefully separated, and the radioactivity of each component was determined using a gamma counter. The parenchyma/serum and capillary/serum ratios (microliters per gram) were calculated by the equation ratio = (cpm Fr)/w/ (cpm/µl serum), where cpm Fr is the cpm in either the parenchyma or supernatant fraction, w is the weight of the cortex, and cpm/µl serum is the level cpm in a microliter of serum.

**Octanol-Buffer Partition Coefficient.** The lipophilicity of I-Ex was determined by mixing 10⁵ cpm of I-Ex in 0.5 ml of octanol with 0.5 ml of a 0.25 M phosphate-buffered solution (PBS; pH 7.6). This was mixed vigorously for 1 min, agitated for 10 min, and the two phases were separated by centrifugation. Aliquots of 50 µl were taken from each phase and counted in duplicate. This experiment was repeated. The partition coefficient was expressed as the log of the ratio of cpm (octanol phase) to cpm (PBS phase).

**High-Performance Liquid Chromatography (HPLC).** Male ICR mice (2 months old) anesthetized with an i.p. injection of 0.2 ml of urethane (40% solution) were given 2 × 10⁵ cpm/mouse of I-Ex + CD by intranasal administration or 2 × 10⁵ cpm/mouse of I-Ex by intravenous injection. After 5 min, the whole brain, including the olfactory bulb, was removed and homogenized in 4 ml of ice-cold 1 M acetic acid. The homogenate was centrifuged at 5400g for 10 min at 4°C, and the resulting pellet was vigorously suspended in another 4 ml of ice-cold 1 M acetic acid, centrifuged, and the resulting supernatant was added to the first supernatant. The combined supernatant was lyophilized until use. Processing controls were performed by placing about 2 × 10⁵ cpm into a nonradioactive brain and handling as described for the other brains. The brain samples were reconstituted in 2 ml of trifluoroacetic acid in 2 ml of distilled water, vigorously mixed, and centrifuged at 5400g for 20 min at 4°C. Of the resulting supernatants, 0.1 ml was injected onto a size exclusion column for HPLC analysis and eluted with 50 mM NaPO₄ buffer at pH 6.85.

**Statistics and Calculations.** The Prism 4.0 program (GraphPad Software Inc., San Diego, CA) was used in statistical analysis. Regression lines were calculated by the least-squares method and are reported with their correlation coefficient (r), n, and p value. Means are reported with their standard error terms and n. Analysis of variance (ANOVA) was followed by Newman-Keuls post test. In two-way ANOVAs, time-matched values were compared with the Bonferroni post test. The percentage of the administered dose being taken up per gram of tissue (%Inj/g) was calculated with the equation ratio = (T cpm)/(w)(cpm/µl), where T cpm is the level of radioactivity in the tissue, w is the tissue weight in grams, and I is the number of cpm administered. The tissue/serum ratios were calculated in units of microliters per gram of tissue by dividing T cpm by w and the cpm per microliter of serum. Area under the curve (AUC) was calculated with the Prism 4.0 program.

**Results**

Figure 1, top, shows immediate entry of I-Ex into the olfactory bulb after intranasal administration (n = 4 animals/time point). There was no difference between left and right olfactory bulb (data not shown), so results were combined for this region. Some material was taken up by whole brain (which excluded the olfactory bulb, pineal, and pituitary), but at a much lower level.

Of the radioactivity extracted from brain and olfactory bulb, 87% eluted by HPLC in the position of I-Ex after intranasal administration and 94% for the processing control. The C-nodes also took up I-Ex, but accumulation was delayed compared with brain. Two-way ANOVA showed an effect of region [F(2,91) = 13.2; p < 0.0001], but not for time or for interaction. Intravenous injection produced a much different pattern, favoring C-node delivery (Fig. 1, bottom). Two anim-

![Fig. 1. Uptake of I-Ex by olfactory bulb (OB), brain, and C-node after intranasal or i.v. administration. For intranasal administration, I-Ex was combined with CD. Top, intranasal administration resulted in 2 to 2.5% of the administered dose being taken up per gram of olfactory bulb. Brain uptake is low and C-node uptake is intermediate. Bottom, i.v. administration resulted in high levels in the C-node but much lower levels in brain and olfactory bulb.](image-url)
brain was found in the brain parenchymal space and not sequestered by brain capillaries (Table 1). The log of the octanol/buffer partition coefficient was (2.92).

Because some I-Ex administered intranasally enters the blood, we evaluated the relative contribution of the vascular versus the intranasal route in olfactory bulb, whole brain, and C-node uptake by comparing tissue/serum ratios after i.v. versus intranasal delivery (n = 2–4 mice/time point). Figure 3 (top left) shows similar C-node/serum ratios for I-Ex given intravenously or intranasally with or without CD. Two-way ANOVA showed no differences with interaction or time. An effect was found for delivery route (p < 0.05), but Bonferroni post test showed no differences at any of the time-matched values. This is consistent with I-Ex reaching the C-nodes exclusively by the vascular route, even when administered intranasally. In comparison, the brain/serum ratios [delivery route: F(2,33) = 13.7, p < 0.001; time: F(6,88) = 2.6, p < 0.05; and interaction: not significant] ratios were much greater after intranasal than after i.v. injection, demonstrating that the vascular route played a minor role in the accumulation of I-Ex for these tissues (Fig. 3, top right and bottom panels).

To determine the extent to which diffusion alone is important in uptake of I-Ex after intranasal administration, we studied mice that had been dead for about 10 min, overdosed on the same anesthesia that we used for the rest of the studies. Figure 4, top, shows that almost no radioactivity could be found in the C-nodes. Some uptake was found in the right olfactory bulb (the side of administration) and a lesser amount in the left olfactory bulb and brain. Two-way ANOVA showed statistically significant differences for time, group, and interaction, all at p < 0.001. Figure 4, bottom, shows that accumulation of I-Ex by even the right olfactory bulb from dead mice was small in comparison with living mice (open circle olfactory bulb is the same data as in Fig. 1). These results show that diffusion based on Brownian motion alone cannot explain the uptake of I-Ex by CNS tissues after intranasal administration.

<table>
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<th>TABLE 1</th>
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<td>Capillary depletion after intranasal administration of I-Ex + CD or i.v. administration of I-Ex</td>
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<td>Means are given ± S.E., n = 3/group. Units are microliters per gram.</td>
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3.24, p < 0.05; and interaction: F(12,33) = 2.10, p < 0.05] and especially the olfactory bulb/serum [delivery route: F(2,88) = 13.7, p < 0.001; time: F(6,88) = 2.6, p < 0.05; and interaction: not significant] ratios were much greater after intranasal than after i.v. injection, demonstrating that the vascular route played a minor role in the accumulation of I-Ex for these tissues (Fig. 3, top right and bottom panels).

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Brain distribution was determined 5 min after giving I-Ex + CD by the intranasal route (n = 5 mice; Fig. 5). ANOVA
showed a statistical difference among the brain regions: $F(4,18) = 50.1; p < 0.001$. Olfactory bulb was much higher than any other tissue and was statistically different from all other tissues ($p < 0.001$). None of the other tissues differed from one another, even when ANOVA and Newman-Keuls was run without olfactory bulb data.

Uptake into cerebrospinal fluid was measured after bilateral intranasal administration of I-Ex CD into eight mice. Cerebrospinal fluid, olfactory bulb, and whole brain were collected 5 min later. Cerebrospinal fluid (Fig. 6) values were intermediate between olfactory bulb and whole brain values. One-way ANOVA showed a statistical difference ($F(2,19) = 15.5; p < 0.001$) with olfactory bulb differing from cerebrospinal fluid ($p < 0.001$) and brain ($p < 0.001$) but with no difference between cerebrospinal fluid and brain.

**Discussion**

These studies evaluated the effectiveness of intranasal administration in the delivery of I-Ex to the CNS. Previous work has shown that intranasal administration of exendin can affect CNS function (During et al., 2003). That work also showed that the antagonist was effective after intranasal delivery. We choose to characterize the antagonist rather than the agonist for two reasons: because of steric blocks on the agonist, the antagonist was easier to label; being larger, the antagonist should have a more difficult time being taken up by the nasal route and so would be more important to investigate as a proof of concept that intranasal administration was a viable route for CNS delivery of these molecules. Here, we found that, as assessed by AUC, the intranasal route was about 4 times more efficient than the intravenous route in the delivery of I-Ex to the olfactory bulbs. Capillary depletion and HPLC of radioactivity extracted from the CNS confirmed that intact I-Ex was taken up into the CNS after intranasal administration. Injection with CD increased uptake of I-Ex by the olfactory bulb by about 60%. The rest of the brain also took up I-Ex after intranasal delivery, but inclusion of CD did not improve uptake. Intranasal delivery and i.v. injection produced equivalent uptakes in the delivery of I-Ex to whole brain.

Radioactivity occurred in blood, raising the possibility that the I-Ex found in the CNS after intranasal delivery entered by a vascular route. To explore this possibility, we assessed uptake of I-Ex by a peripheral tissue, the C-nodes. We found that intranasal administration produced a lower uptake of I-Ex by the C-nodes in comparison with the olfactory bulbs but that i.v. administration produced a greater uptake.

One pathway by which intranasal I-Ex could be taken up by the C-nodes is by way of the primitive lymphatics, which drain from the cribriform plate to the C-nodes (Kida et al., 1993; Boulton et al., 1999). Alternatively, intranasal material entering the CNS could enter the blood after cerebrospinal fluid reabsorption or by direct absorption into the blood.
Therefore, I-Ex could be taken up by C-nodes by pathways that are either dependent on or independent of the blood. To further compare the contributions of vascular delivery and nasal absorption, we expressed results as tissue/serum ratios. After i.v. injection, the sole route of uptake for all tissues is vascular. To the extent that uptake by a tissue depends on the vascular route, the tissue/serum ratios will be similar after i.v. or intranasal delivery. To the extent that the vascular route is not a contributor to tissue uptake, tissue/serum ratios will be much higher after intranasal than after i.v. administration.

For example, the similar C-node/serum ratios after administration of I-Ex by intranasal or i.v. administration are consistent with a vascular route of delivery. In comparison, extremely high olfactory bulb/serum ratios show that the vascular route played little role in the uptake of intranasal I-Ex. For brain, the vascular route was a minor contributor to the uptake of intranasal I-Ex.

We then addressed the extent to which nasal uptake depended on diffusion and nonenergy-dependent processes by giving intranasal I-Ex to mice that had been dead for about 10 min. With that short a period after death, we reasoned that post-mortem fluid shifts in brain would not yet have occurred, and so Brownian motion as a source of diffusion would still be operational. Because the vascular route and cerebrospinal fluid reabsorption are not operational in the dead mice, there should be no uptake by C-nodes.

We confirmed a virtual absence of uptake of I-Ex by the C-nodes. These are small tissues (8–20 mg), so even a few counts multiplied to cpm per gram of tissue can produce seemingly large results. A reliable level of counts was only found in the right-sided olfactory bulb (the side of administration), and this was markedly lower than that found in live mice. In the dead mice, there was a marked difference in I-Ex levels between the right and left olfactory bulb. This shows that Brownian diffusion plays a small part in uptake and distribution by the nasal route.

We explored the route by which intranasal I-Ex finds its way beyond the olfactory bulbs by assessing uptake by various brain regions and cerebrospinal fluid. After intranasal administration, substances enter the brain by two broad categories of mechanisms: extraneuronal and intraneuronal pathways (Frey, 2002). The intraneuronal pathways involve axonal transport and are too slow to account for the rapid...
uptake seen here. Extraneuronal pathways can involve either diffusion through the interstitial fluid of brain parenchyma or diffusion through the cerebrospinal fluid. To determine whether one or the other of these pathways was dominant for I-Ex, we investigated patterns of diffusion in brain tissue. None of the brain regions (except for the olfactory bulb) were statistically different from one another, but the arithmetic hierarchy was anterior brain > brain stem > cerebellum > hippocampus. The brain stem, furthest from the olfactory bulb, was not much different from the anterior one-third of the brain (ant brain), whereas the hippocampus, closest of all tissues to the olfactory bulb except the anterior brain, was arithmetically the lowest.

This pattern suggests brain distribution is occurring through the cerebrospinal fluid. Once substances are introduced into the cerebrospinal fluid, they are more or less evenly distributed throughout the cranial cerebrospinal fluid compartment. However, material introduced into cerebrospinal fluid outside the ventricular system would distribute more slowly into the third and fourth ventricle (the route needed to reach the hippocampus), because that requires diffusion against the current of cerebrospinal fluid flow. Therefore, the pattern of uptake seen here closely mirrors that predicted based on cerebrospinal fluid fluidodynamics. This conclusion is reinforced by the finding that the concentration of I-Ex in cerebrospinal fluid was intermediate between that of olfactory bulb and whole brain. This pattern of delivery has important implications for the biological activities of substances given by the nasal route. Substances do not diffuse very deeply from the cerebrospinal fluid into brain tissue. For example, concentrations in brain tissue 1 mm from the lateral ventricles may only be about 5% of those in the cerebrospinal fluid (Maness et al., 1996). In contrast, a substance crossing the vascular BBB is immediately distributed throughout the CNS. Therefore, intranasal and i.v. administration are likely to result in very different intraparenchymal brain distribution profiles and, as such, different pharmacodynamic profiles.

These experiments show that nasal administration is a particularly good route for delivering peptides to the olfactory bulb in mice. It also resulted in peptide being taken up by other brain regions. Results may not be so dramatic in man, however, where diffusion distances are greater and the olfactory bulbs make up a smaller percentage of brain weight. At the least, nasal administration represents a method by which peptide-brain interactions can be studied in rodent models.

In conclusion, we found that intranasal administration was an effective means of delivery of I-Ex to the brain, especially the olfactory bulb. Uptake into the olfactory bulb and distribution throughout the CNS was not a passive process and was not greatly influenced by the small amount of I-Ex entering the blood after intranasal delivery. Distribution beyond the olfactory bulb into the remainder of the brain was likely mediated through cerebrospinal fluid. These results are consistent with nasal administration as an effective means of delivering peptides to the CNS.

References


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