JPP Journal of Pharmacy and Pharmacology

JPP 2004, 56: 3–17

Received October 2, 2003
Accepted November 14, 2003
DOI 10.1211/0022357022764
ISSN 0022-3573

Review Article

Is nose-to-brain transport of drugs in man a reality?

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Abstract

The blood–brain barrier that segregates the brain interstitial fluid from the circulating blood provides an efficient barrier for the diffusion of most, especially polar, drugs from the blood to receptors in the central nervous system (CNS). Hence limitations are evident in the treatment of CNS diseases, such as Parkinson's and Alzheimer's diseases, especially exploiting neuropeptides and similar polar and large molecular weight drugs. In recent years interest has been expressed in the use of the nasal route for delivery of drugs to the brain, exploiting the olfactory pathway. A wealth of studies has reported proof of nose-to-brain delivery of a range of different drugs in animal models, such as the rat. Studies in man have mostly compared the pharmacological effects (e.g. brain functions) of nasally applied drugs with parenterally applied drugs and have shown a distinct indication of direct nose-to-brain transport. Recent studies in volunteers involving cerebrospinal fluid sampling, blood sampling and pharmacokinetic analysis after nasal, and in some instances parenteral administration of different drugs, have in my opinion confirmed the likely existence of a direct pathway from nose to brain.

Introduction

In the last decade increasing interest has been expressed in the possibility of circumventing the blood–brain barrier for the delivery of drugs to the central nervous system by exploiting the potential direct transport pathway from nose to brain via the olfactory region. Such a pathway has been proven to exist in animal models, but it is still debatable whether a similar transport takes place in man. Hence, it is still debatable whether such delivery of drugs to the brain could be exploited therapeutically for diseases of the central nervous system (Mathison et al 1998; Illum 2000; Pardridge 2001; Thorne & Frey 2001; Minn et al 2002). This would be especially beneficial for drugs that do not cross the blood–brain barrier easily due to their physicochemical characteristics.

The vasculature of the central nervous system (CNS) is characterized by the existence of the blood–brain barrier that separates the brain interstitial fluid from the circulating blood. Apart from protecting the brain from agents in the blood that could impair neurological functions, the blood–brain barrier controls influx and efflux of substances to provide the brain with necessary nutrients and maintain proper homeostasis. The cells of the capillary epithelium in the brain are closely connected by complex tight junctions. These tight junctions completely encircle each endothelial cell like a belt and join both adjacent cells and contiguous borders of the same cell. In addition, each brain capillary is composed of two lipid membranes separated by 300 nm of endothelial cytosol, the luminal membrane facing the blood and the antiluminal membrane, facing the brain (Pardridge 1991).

Lipid soluble molecules are absorbed rapidly and efficiently across the nasal membrane into the systemic blood stream via the transcellular pathway with a plasma profile resembling that of an intravenous injection and with a bioavailability of up to 100%. Due to this rapid absorption such molecules do not normally show direct nose-to-brain transport, although this might be dependent on the site of deposition in the nasal cavity (Illum 2003). Once such lipophilic molecules reach the blood stream they can diffuse freely through the blood–brain barrier and reach the CNS. This diffusion is

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qualified by the degree of lipid solubility and molecular size, with smaller molecules passing through the membrane more easily than larger ones (Temsamani 2002).

Less lipophilic or polar molecules are not as readily absorbed across the nasal membrane into the systemic circulation, with bioavailabilities being in the order of 10% or less for low molecular weight and less than 1% for large molecular weight polar molecules such as peptide drugs (Illum 2000). Such molecules normally pass the nasal membrane via the paracellular pathway, through the tight junctions. This pathway is less efficient than the transcellular pathway and very dependent on the molecular weight of the molecule. Once in the systemic circulation, the hydrophilic molecules do not pass the blood–brain barrier easily unless aided by some form of receptor or carrier mediated transport mechanism (Schwartz et al 1990), whether naturally occurring (as is the case for insulin) or by a specific drug delivery approach (Pardridge 2001). Polar molecules do not rapidly diffuse across the nasal membrane into the systemic circulation and so they have a better chance of reaching the olfactory mucosa and from there being transported across into the CNS. This has been demonstrated in many animal studies (Illum 2000).

This review sets out to discuss recent relevant studies concerning the potential of drugs applied to the nasal cavity being at least partially transported via the olfactory pathway to the CNS. These studies have been published in the literature or have been provided as information at scientific meetings and largely concern investigations in man. Support in the understanding of the subject will be provided in the form of a brief overview of nasal morphology and physiological function.

The human nose

To comprehend fully the intricacies of nasal drug delivery and to evaluate whether nose-to-brain transport of drugs is a reality, it is important to have an understanding of the relevant morphological structures and physiological factors affecting these functions. Comprehensive reviews dealing with the morphology and physiology of the nose, to include the olfactory mucosa, have been published (Mygind 1978; Moran et al 1982; Hilger 1989) and hence only limited necessary details will be given here.

Structure and function of the human nose

An outline of the human nose is shown in Figure 1. The total surface area of the nasal cavity is approximately 150 cm^2 in a man and normally less in a woman. The cavity is divided longitudinally into two non-connected parts by the nasal septum. The two cavities open anteriorly to the facial site through the narrow (0.3 cm^2 in diameter) nasal apertures or "the nasal valve" at the top of the nostril and posteriorly to the rhinopharynx via the posterior nasal apertures. Each of the two nasal cavities are largely subdivided into three regions i.e. the nasal vestibule, the respiratory region and the olfactory region. The nasal vestibule (0.6 cm^2) is covered with stratified squamous epithelium (very similar to skin) and is the part of the nose one can reach with an index finger. The olfactory region in man is situated in the roof of the nasal cavity lying partly on the nasal septum and partly on the superior and middle turbinates. The olfactory mucosa covers a relatively small area of approximately 4 cm^2 or 3–5% of the area of the total nasal cavity (Morrison & Constanzo 1992). However, it has been suggested that the tips of the olfactory sensory neurons can stretch further into the nasal cavity and hence be accessible over a larger area (personal communication, N. Jones). As a comparison, in the dog the olfactory mucosa constitutes 77% and in the rat 50% of the total nasal area (Illum 1996).

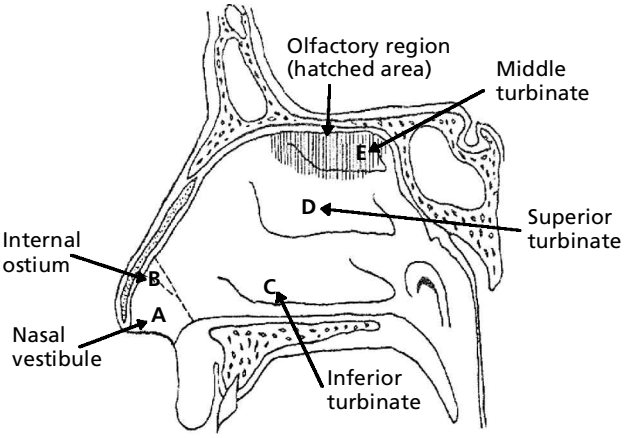

Figure 1 Schematic representation of the lateral wall of the human nasal cavity.

The respiratory epithelium

The anterior part of the nasal cavity is covered with squamous epithelium that gradually changes posteriorly into the respiratory epithelium comprising a pseudostratified columnar epithelium. The cells of the respiratory epithelium are covered with microvilli. These provide this part of the nasal cavity with a relatively high absorptive capacity, due to an increase in the surface area, and make this the major site for systemic drug absorption. The respiratory epithelium consists of four major cell types, namely the ciliated (approximately 15–20% of the respiratory cells) and the non-ciliated columnar cells, the goblet cells and the basal cells. The cilia project 2–4 μm from the surface of the cells, are mobile and through a co-ordinated movement (synchronized beating, 1000 strokes min^{-1}) are able to propel the mucous layer, covering the respiratory epithelium, anteriorly towards the nasopharynx. Mucus is mainly derived from the goblet cells, interspersed between the columnar cells and is the major component of the mucous layer. The mucous layer consists of a low viscosity sol layer that surrounds the cilia and a more viscous gel

layer on top of the cilia. Hence, materials deposited on the mucous layer will gradually be cleared from the nasal cavity by this mucociliary clearance mechanism. For non-mucoadhesive materials this will generally result in a half-time of clearance of approximately 15–20 min (Illum 2000).

Epithelial cell barrier – tight junctions

The epithelial cells on the apical surface of the membrane are closely connected by intercellular junctions. The structural components and specialized sites of these junctions are generally known as the junctional complex. They are composed of three regions and are, in successive order from the apical surface towards the basal surface, the zona occludens (ZO) also known as the tight junction, the zonola adherens and the macula adherens (Madara 2000). These complexes create a regulatable semipermeable diffusion barrier between cells. It is clear that the tight junction is a dynamic structure that is selectively permeable to certain hydrophilic molecules (ions, nutrients and drugs). The permeability of the tight junction varies between the epithelial tissues in the body but is generally limited for molecules with a hydrodynamic radius larger than 3.6 Å and negligible to molecules with a radius larger than 15 Å (Stevenson et al 1988). It is difficult to relate these sizes to exact molecular weights since the size of a molecule, and especially peptides and proteins, will be determined by the physicochemical environment, and possible secondary and tertiary structures of the molecules. However, it has been shown in the literature that for molecules of a molecular weight of approximately 1000 Da and larger, the transport through tight junctions is normally very restricted (McMartin et al 1987).

The tight junction comprises a series of transmembrane and cytosolic proteins that interact not only with each other but also with the membrane and the cytoskeleton e.g. occludins, claudins and junctional adhesion molecule (Anderson & Van Itallie 1995; Denker & Nigram 1998) (Figure 2). The topology of occludin suggests that the amino and the carboxyl termini of this protein are situated in the cytoplasm of the cell with two extracellular loops projecting into the paracellular space between adjacent cells. The loops of the extracellular occludin from two neighbouring cells may interact in the extracellular space to promote sealing of the paracellular space. The cytoplasmic occludin interacts with tight junction-associated proteins present in the cytoplasm (ZO-1, ZO-2 and ZO-3) (Ward et al 2000). For example, the N-terminal of the ZO-1 interacts with the C-terminal tail of occludin and its C-terminal interacts with F-actin of the cytoskeleton and thereby couples the tight junction to the scaffold of the cytoskeleton. The ZO-2 interacts with the C-terminal of the occludin and the N-terminal of ZO-1. The claudins have been suggested to be major structural components of tight junction strands in line with occludins. The third transmembrane protein junctional adhesion molecule is different structurally to the occludins and claudins, and is immunoglobulin-like in form.

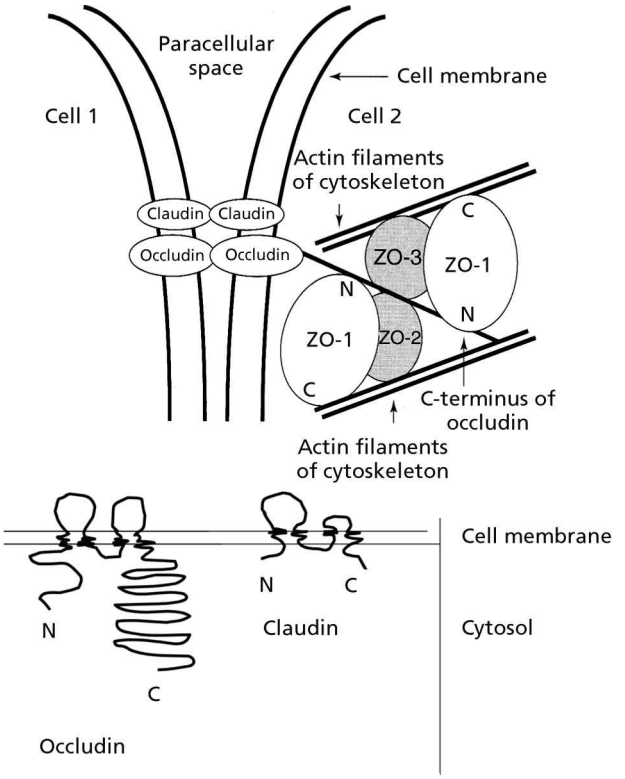

Figure 2 Schematic representation of the tight junction and the interaction of the transmembrane and cytosolic proteins (adapted from Ward et al (2000)).

The zona occludens is closely associated with the zonola adherens complex. The zonola adherens complex holds cells close together but does not form a tight barrier. The zonola adherens is made up of transmembrane proteins known as cadherins. Both zona occludens and zonola adherens structures act to anchor cytoskeleton components.

Many classical second messengers and protein kinases of signalling pathways such as tyrosine kinases, Ca^{2+} and protein kinase C (PKC) influence both the barrier properties and assembly of the tight junction. Hence increases in intracellular calcium can affect phosphorylation of myosin regulatory light chain contraction of perijunctional actin and cause increased paracellular permeability (Ward et al 2000). PKC plays a dual role in that it initiates tight junction synthesis under conditions that preclude tight junction synthesis (e.g. incubation in low calcium medium) and also appear to be involved in tight junction disruption in conditions that encourage tight junction formation (e.g. incubation in normal calcium medium). Hence PKC is strongly involved in the highly complex signal transduction process that regulates the tight junction. The phosphorylation of the tight junction proteins or the displacement (i.e. contraction or relaxation) of the perijunctional actin-myosin ring is generally the final effect of modulation of many of these signalling pathways. This has been shown by the fact that a disruption of the tight junction integrity by ATP depletion

induces a decrease in phosphorylation of the tight junction regulatory proteins. During ATP repletion the phosphorylation is increased again (Tsukamoto & Nigam 1999). Furthermore, the same signalling pathway that induces phosphorylation of the tight junction proteins may also modulate the actin cytoskeleton, which again has been shown to increase the transmembrane flux of sodium and mannitol. Recently, it has been shown that cationic polymer absorption enhancers, such as poly-L-arginine and chitosan, which predominantly work by transiently opening epithelial tight junctions, initiate this mechanism by activating the PKC signalling pathway (Natsume et al 2003).

The olfactory mucosa

The olfactory organ is unique in the CNS, since it is the only part in direct contact with the environment and hence exposed to volatile odorants and airborne (toxic) substances. The olfactory mucosa is located within the recesses of the skull, just under the cribriform plate of the ethmoid bone, approximately 7 cm from the nostril, at the top of the nasal cavity, lying partly on the nasal septum and partly on the superior turbinate (Figure 1). The olfactory region is not easily accessible anatomically in living human beings since to reach this area (for example in biopsy) an instrument must pass through a 1.5-mm crevasse between closely apposed nasal structures (turbinates and septum). The olfactory mucosa is above the normal airflow path, and hence odorants normally reach the sentive receptors on the neurons by diffusion. The size of the olfactory region in man has been quoted as 3.7 cm^2 (Jones 2001), 10 cm^2 (Proctor 1977) and as 2–10 cm^2 (Morrison & Constanzo 1990). The region is much smaller than, for example, that found in dogs (150 cm^2), indicating the importance of olfaction in the daily functions of dogs but not of man.

The olfactory epithelium is a modified (pseudostratified) respiratory epithelium. It comprises olfactory sensory neurons, sustentacular cells (also called supporting cells) that ensheath the receptor neurons providing mechanical support and maintain the normal extracellular potassium levels needed for neuronal activity, and basal cells, which are able to differentiate into neuronal receptor cells and replace these every 40 days (Figure 3). The underlying lamina propria contains olfactory nerve fascicles and the mucus secreting tubuloalveolar Bowman's glands. The olfactory receptor cells are bipolar neurons with a round cell body. A single dendritic process extends from the cell body to the free apical surface where it terminates as a small knob-like swelling from which extends numerous (10–23) long and non-motile cilia. The olfactory sensory neurons taper into an unmyelinated axon which penetrates the basal membrane to join other axons and form large bundles in the lamina propria. The unbranched axons are ensheathed by glial cells, also called Schwann cells, and cross into the cranical cavity through small holes in the cribriform plate and synapse in the olfactory bulb. Approximately 1500 olfactory receptor cells on the bipolar sensory neurons converge on one mitral cell or tufted cell in the olfactory bulb (12.2 mm, range 6–16 mm, long). The mitral and the tufted cells

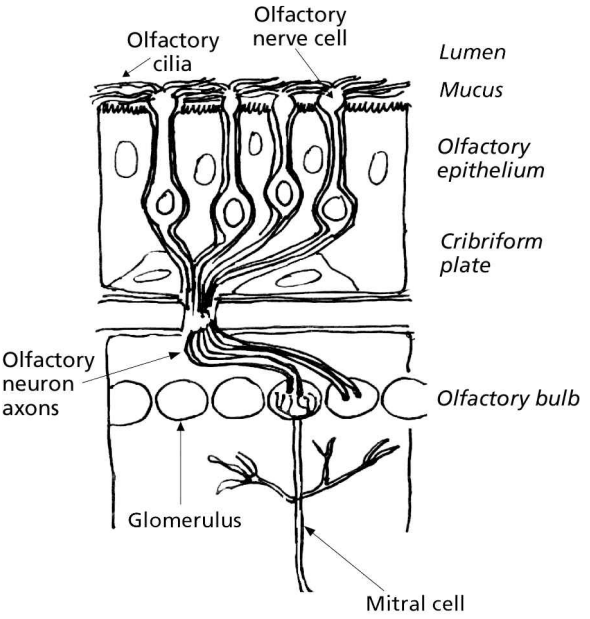

Figure 3 The structure of the olfactory epithelium (adapted from Firestein (2001)).

project a single primary dendrite to a single glomerolus and emit several dendrites within the external plexiform layer. From the olfactory bulb tract the main axons originate in the mitral or tufted cells and give off striae, which pass to the olfactory tubercle. The projections then go to the amygdala, the prepyriform cortex, the anterior olfactory nucleus and the entorhinal cortex as well as the hippocampus, hypothalamus and thalamus.

The olfactory epithelium is covered by a dense and viscous layer of mucus, which is secreted from the Bowman's glands and the supporting cells. Due to the non-motile cilia the mucus layer in the olfactory region is not cleared by a mucociliary clearance mechanism as in the respiratory epithelium. Over-production of mucus results in the mucus layer slowly moving into the respiratory region from where it is cleared by the normal mechanism of mucociliary clearance.

At the luminal surface in the olfactory epithelium the membranes of the adjoining receptor cells and supporting cells are connected by typical junctional complexes similar to those described for the respiratory epithelium (Engstrom et al 1989). The olfactory region is supplied with blood from the anterior and posterior ethmoidal branches of the ophthalmic artery supply and venous drainage is as for the respiratory system via the sphenopalatine foramen into the pterygoid plexus or via the superior ophthalmic vein.

Transport of drugs from nose to brain

The CNS

The CNS is protected against trauma by the cranium (skull) that encases the brain and the vertebral column that sur-

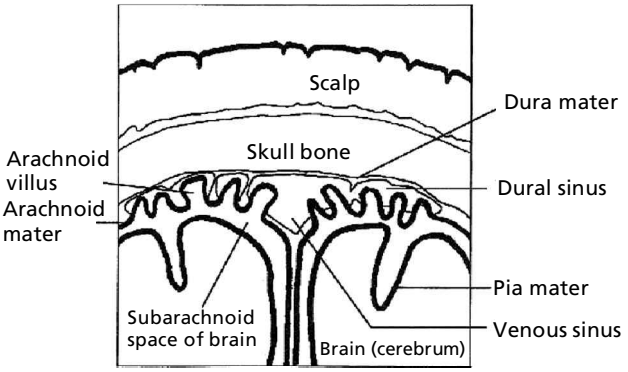

Figure 4 Relationship of meninges and cerebrospinal fluid to brain and spinal cord. Frontal section in the region between the two cerebral hemispheres of the brain, depicting the meninges in greater detail. (Adapted from Illum (2000).)

rounds the spinal cord. Three protective membranes, called the meninges, lie between the skull and the brain tissue (Pardridge 1991; Thorne & Frey 2001). Moving in the direction from the skull to the brain, these are the dura mater, the arachnoid mater and the pia mater. The dura mater consists of two layers, which are normally closely adherent. However, in some regions they are separated by blood-filled cavities, the dural sinuses or venous sinuses (Figure 4). Venous blood from the brain empties into these sinuses to be returned to the heart. The space between the arachnoid and pia mater, the subarachnoid space, is filled with cerebrospinal fluid (CSF) in which the brain is essentially suspended. Protrusions of arachnoid tissue, the arachnoid villi, penetrate through gaps in the overlying dura and project into the dural sinuses. It is across the surfaces of these villi that the CSF is reabsorbed into the blood circulating within the sinuses. The CSF is produced primarily by the four choroid plexi found in particular regions of the ventricle cavities of the brain. Once formed it flows through the four interconnected ventricles within the interior of the brain and through the spinal cord's narrow central canal, which is continuous with the last ventricle, and escapes from this fourth ventricle at the base of the brain to enter the subarachnoid space. When the CSF reaches the upper regions of the brain, it is reabsorbed into the venous blood through the arachnoid villi. It is known also that the CSF can drain from the subarachnoid space through the perivascular space surrounding the nerve bundles in the cribriform plate, and enters the olfactory submucosa where it drains into the nasal lymphatics (Pardridge 1991). This drainage constitutes less than 5% of the CSF.

Through the ongoing procedure of formation, circulation and re-absorption of the CSF, the entire volume of approximately 125–150 mL (in adults) is replaced more than three times a day (Sherwood 1989). In comparison the rat brain contains only 150 μL CSF and is replaced approximately 24 times a day. These differences in CSF renewal between rat and man could have a significant impact on interpretation of nose-to-brain drug delivery studies and together with the other anatomical differences depicted in Table 1 should always be carefully considered.

Knowledge of the manner in which drugs diffuse from the CSF into the brain parenchyma and the probability of this is important for the understanding of the significance of uptake of drug into the CSF after nasal application for treatment of CNS diseases. Unless receptors for the drug are present on the surface of the brain the drug will by necessity have to penetrate into the brain tissue. The rate of diffusion of drugs in the extracellular space of the brain can be expressed as $D^* = D/\lambda^2$, where D is the diffusion coefficient of the molecule in water and λ is tortuosity. Tortuosity is a dimensionless parameter reflecting the restrictions placed on the diffusion of the molecule by cellular elements and the connectivity of the extracellular spaces into which the molecule has access (Nicholson & Sykova 1998). Values of λ vary from 1.4 for small molecules to 2.5 for large molecules such as albumin. D is inversely related to the molecular size of the drug. It can be calculated that the time it takes for a small molecule such as glucose to diffuse 5 mm in the brain is approximately 11.7 h and for a molecule such as albumin 4.2 days!

The fact that there is a distinct difference between the bulk flow properties of the CSF and diffusional flow rates in the brain tissue creates a functional barrier between the CSF and the brain tissue (Pardridge 1991). This prevents complete equilibration between the two fluid compartments and consequently a significantly different drug concentration will normally exist between these two compartments.

Transport pathways

It is suggested in the literature that a drug administered nasally is able to reach the CNS (i.e. CSF and brain tissue)

Table 1 The characteristics of the rat animal model vs man in relation to nose-to-brain delivery of drugs.

The nasal cavity is approximately 180 cm^2 in man and approximately 10 cm^2 in rats.
The olfactory area constitutes approximately 3% of the nasal cavity in man, but 50% in rat.
The CSF volume is 160 mL in adult humans and 150 μL in rats.
The CSF volume is replaced every 5 h in man and every 1 h in rats.
The placement of the rat on its back in most experiments with easy access to the olfactory area influences CSF uptake.

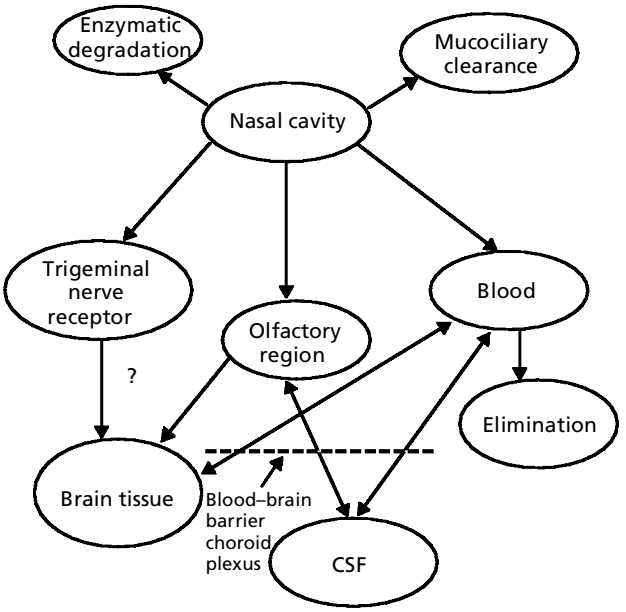

Figure 5 Suggested pathways from nose to brain.

by the various transport routes shown schematically in Figure 5. After nasal application, drug that has escaped enzymatic degradation and the normal rapid clearance by the mucociliary clearance system may be transported across the nasal membrane into the systemic circulation. As mentioned above, such absorption may for lipophilic drugs reach close to 100% (e.g. ~71% for fentanyl in man), but is normally less. The drug is subsequently eliminated from the blood by the normal clearance mechanisms. However, once the drug is in the blood it may (if it is sufficiently lipophilic or by exploiting specific transport mechanisms) cross the blood–brain barrier and reach the brain and the CSF (the so-called systemic pathway). Drug present in the CSF or the brain tissue will also be eliminated into the blood and cleared. Of special interest to the present review is the fact that a drug may be transported directly into the brain tissue (e.g. olfactory bulb) or the CSF by transport across the olfactory region of the nasal cavity (the so-called olfactory pathway). Recently, preliminary evidence has emerged that suggests that drugs may also be transported to the brain via trigeminal nerve receptors present in the nasal cavity (Thorne et al 2000). These receptors are responsible for most chemoperception apart from olfaction.

The various pathways that a drug can follow from the olfactory region of the nasal cavity to reach the CSF or the brain tissue have been discussed thoroughly (Mathison et al 1998; Dahlin 2000; Illum 2000; Thorne & Frey 2001), hence only a brief discussion will be given here.

Leaving the trigeminal pathway aside, the nasal pathway from nose to CNS is thought to involve one or a combination of two general mechanisms. The first is internalization of the drug into the primary neurons of the olfactory epithelium and transport by intracellular axonal transport to the olfactory bulb with subsequent possible distribution of the drug into more distant brain tissues. The second is absorption of the drug across the olfactory sustentacular epithelial cells, either by transcellular or paracellular mechanisms followed by uptake into the CSF or CNS.

Drugs transported intracellularly in the olfactory neurons (axonal transport) are thought to enter the neurons by mechanisms of endocytosis or pinocytosis. They travel along the axon and via the nerve bundle, transverse the cribriform plate and reach the olfactory bulb. As described in *The olfactory mucosa* above several dendrites are emitted further into the CNS from the tufted cells at the first order synapse in the olfactory bulb.

The existence of the axonal pathway has been described by several authors for transport of different materials from the olfactory region to the CNS e.g. gold particles (De Lorenzo 1970; Gopinath et al 1978), aluminium lactate (Perl & Good 1987) and wheat germ agglutinin–horseradish peroxidase (Shipley 1985; Baker & Spencer 1986; Itaya 1987; Thorne et al 1995). For the last material it was found that uptake into the neural cell was by receptor-mediated endocytosis and that horseradish peroxidase alone was not able to reach the olfactory bulb in significant quantities due to a different transport pathway (Thorne et al 1995). It has also been shown in the above experiments and in others that the axonal route of transport is very slow and that it can take up to 24 h before the drug reaches the CNS (Kristensson & Olsson 1971).

As opposed to the axonal pathway, the olfactory epithelial pathway for transport of drugs appears to be very fast, with drugs appearing in the CSF and in the brain a few minutes after nasal application. This has been shown among others for dihydroergotamine (Wang et al 1998), cocaine (Chow et al 1999), lidocaine (Chou & Donovan 1998) and cefalexin (Sakane et al 1991). The extracellular pathway, that transports polar drugs through tight junctions (see *Epithelial cell barrier* above) between sustentacular cells and olfactory neurons into the CSF, relies on a direct anatomic connection between the submucosa and the subarachnoid extensions, the perineural space surrounding the olfactory nerves, as they penetrate the cribriform plate (Figure 6) (Jackson et al 1979). The drug is thought to enter the perineural space either through loosely adherent perineural epithelium surrounding the axon ("open-cuff model"), or to enter through the epithelial cell junctions if the perineural epithelium is closely adherent to the axon ("closed-cuff model"). More lipophilic drugs passing though the epithelial cells transcellularly will reach the submucosa also and from there can likewise reach the perineural space. It has been shown in a rat model that large molecular weight drugs, such as protein nerve growth factor (MW 37 kDa) (Thorne & Frey 2001), insulin (MW 6 kDa) (Gizurarson et al 1996) and vasoactive intestinal peptide (VIP) (MW 3.5 kDa) (Gozes et al 1996) can be transported rapidly into the CSF and hence are able to exploit the olfactory epithelial pathway in line with small molecular weight drugs. Since most studies in animal models only cover limited periods of time (< 4 h), it is difficult to determine from the literature whether drugs that are transported initially by the olfactory epithelial pathway would also show exploitation of the axonal pathway.

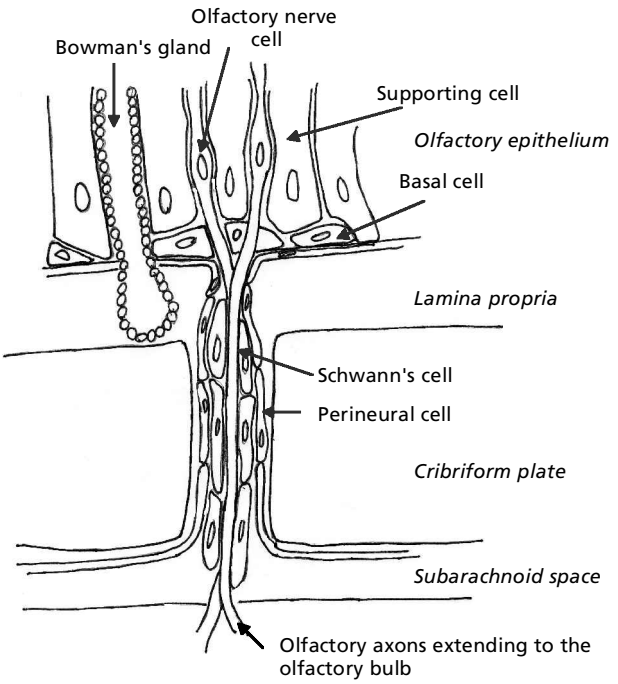

Figure 6 Anatomical connection between the olfactory epithelium and the CSF in the subarachnoid space (modified from Mathieson et al (1998)).

Transport of drugs in man

Animal studies

From the description of nose-to-brain studies in animal models in the literature it is evident that small molecular weight drugs of a suitable lipophilicity, and also larger hydrophilic molecules, can be transported from the nasal cavity into the CSF, the olfactory lobe and for some drugs further into the brain tissue. It is evident that if very lipophilic drugs, such as progesterone and estradiol, are administered to the nasal cavity, they will be absorbed rapidly and efficiently across the nasal membrane. They will provide a plasma concentration profile similar to that seen after an intravenous injection, and as such will not show a higher CSF or CNS uptake when given nasally as compared with an intravenous injection.

As background information a selection of studies performed on various drugs and in various animal models is given in Table 2 together with the key results. These studies will not be discussed further in this review, which is focused primarily on a discussion of results from nose-to-brain studies in man.

Human studies

Pharmacological evidence of nose-to-brain transport Most of the published studies evaluating nose-to-brain delivery of drugs in man do not describe the direct measurement of the rate and degree of transport into the CNS region but rather have measured indirectly the pharmacological effects of drugs on the CNS, e.g. the effect of the drug on event related brain potentials and working memory function. It should be mentioned that most of the published studies involving indirect measures originate from one research group in Lubeck, Germany, using peptides such as insulin, vasopressin and melanocortin. However, in the last few years studies have been published (or presented at meetings) where the appearance of drug in the CSF after nasal administration has been determined. Furthermore, a single study has reported the evaluation of the transport of radiolabelled drug into the brain using γ-scintigraphy measurements. A summary of these studies is given in Table 3.

Pietrowsky et al (1996a) found evidence that after nasal application of 20 IU arginine-vasopressin (AVP), in a cross-over study in 15 volunteers, a component (P3) of an event-related brain potential (ERP) was significantly increased whereas this was not the case after nasal administration of a placebo formulation or after an intravenous administration of 1.5 IU AVP. ERPs were recorded during a subject's performance of an auditory attention task. Furthermore, plasma concentrations of vasopressin during task performance were enhanced more after the intravenous administration of AVP than after nasal administration. Similar results were obtained by the same group after nasal and intravenous administration of cholecystokinin-8 (Pietrowsky et al 1996b) and performance of an auditory attention task (oddball task) in 20 volunteers in a double blind cross-over study recording the auditory event-related brain potentials. Further studies confirmed the results (Pietrowsky et al 2001).

Corticotropin-releasing hormone (CRP) has been shown to decrease gastric acid secretion after intracerebral administration. Kern et al (1997) reported on a double blind cross-over study involving 11 volunteers, assessing the effect of nasally and intravenously administered CRP on gastric pH. It was shown that after nasal administration of the drug the pH increased from 1.7 to 2.6 while after intravenous administration the pH value decreased to 0.9. The results indicated that a direct pathway from nose to brain existed. Derad et al (1998) evaluated the effect of angiotensin II on the central nervous functions of cardiovascular control after nasal and intravenous administration in 12 volunteers in a balanced cross-over design study. For intravenous and nasal administration of angiotensin II similar plasma levels were seen and both methods of administration resulted in comparable acute raises in blood pressure. However, subsequent blood pressure profiles were different for the two routes of administration. Nasally administered angiotensin II counteracted the decrease in noradrenaline (norepinephrine) levels observed after intravenous administration and enhanced the plasma level of vasopressin. It was concluded that the diverging pattern of effects suggested a direct transport of angiotensin II from nose to brain.

Smolnik et al (1999) evaluated the effects of acute and chronic nasal administration of the melanocortin melanocyte-stimulating hormone, adrenocorticotropin 4–10 (ACTH 4–10) on brain potentials and attention in 54 healthy subjects while the subjects performed an auditory selective attention task. The study was double blinded and

Table 2 Nose to brain delivery in animal models—selected studies.

Drug	Species	Sample	F	Outcome	Reference
Arginine–vasopressin	Dog	CSF	–	Similar CSF for intranasal and intravenous administration	Ang & Jenkins (1982)
Benzoylecgonine	Rat	Brain tissue	62.5%	$AUC_{olf.bulb}/AUC_{plasma}$ were 10–100 times higher after intranasal compared with intravenous administration	Chow et al (2001)
Cephalexin	Rat	CSF	–	CSF levels 100 times higher after intranasal as compared with intravenous administration	Sakane et al (1991)
Cocaine	Rat	Brain tissue	–	0–1 min significant higher $AUC_{olfbulb}/AUC_{plasma}$ for intranasal than for intravenous administration	Chow et al (1999)
Desglycinamide Arginine–vasopressin	Dog	CSF	–	Similar CSF for intranasal and intravenous administration	Ang & Jenkins (1982)
Desmopressin	Dog	CSF	–	Similar CSF for intranasal and intravenous administration	Ang & Jenkins (1982)
Dextromethorphan HCl	Rat	Brain tissue	78%	Brain concn after intranasal administration 65.7% of that after intravenous administration. No preferential CNS targeting after intravenous administration	Char et al (1992)
Diazapam	Rat	Brain tissue	–	At 10 min drug reached past olfactory bulb after intravenous administration	Gizurarson et al (1996)
Dihydroergotamine	Rat	Brain tissue	14%	Dihydroergotamine level in olfactory bulb 4 times higher after intranasal compared with intravenous administration	Wang et al (1998)
Dopamine	Mouse	Brain tissue	–	High levels after intranasal but not intravenous administration	Dahlin et al (2000)
Dopamine	Rats	CSF Brain tissue	68%	At 30 min the brain levels were higher after intranasal compared with intravenous administration	Dahlin et al (2001)
Insulin	Rat	Brain tissue	<1%	Brain/blood concn higher after intranasal compared with subcutaneous administration	Gizurarson et al (1996)
Lidocaine (lignocaine)	Rat	Brain tissue	100%	For most brain tissue ratio of concn after intranasal to after intravenous administration lower than 1	Chou & Donovan (1998)
Methotrexate	Rat	CSF	6.3%	The concn in the CSF was 13.7 times higher after intranasal compared with intravenous administration	Wang et al (2003)
Monosialoganglioside (GM1)	Rat	CSF	<1%	GM1 in CSF after intranasal but not after intravenous administration	Kumbale et al (1999)
Nerve growth factor	Rat	Brain tissue	<1%	Olfactory bulb levels after intranasal but not after intravenous administration	Frey et al (1995) Chen et al (1998)
Zidovudine	Rat	CSF	60%	At 15 min ratio of CSF/plasma concn higher for intranasal than for intravenous administration	Seki et al (1994)
WGA-HRP	Rat	Brain tissue	<1%	Levels of WGA-HRP in olfactory nerve and bulb after intranasal but not intravenous administration	Thorne et al (1995)

F, bioavailability; WGA-HRP, wheat germ agglutinin–horseradish peroxidase; CSF, cerebrospinal fluid.

Table 3 Nose-to-brain delivery in man.

Functional evidence provided by changes in event related potential during performance of oddball task:
Arginine–vasopressin (n = 15) (Pietrowsky et al 1996a);
Cholecystokinin-8 (n = 20) (Pietrowsky et al 1996b);
Insulin (n = 18) (Pietrowsky et al 1996a or b?);
Adrenocorticotropin 4–10 (n = 54) (Derad et al 1998);
Insulin (n = 12) (Kern et al 2001);
Diazepam ((n = 8) ? (Lindhardt et al 2001).
Direct evidence of nose-to-brain uptake:
99mTc-DTPA–hyaluronidase (Okuyama 1997).
Direct evidence of nose to CSF uptake:
Insulin (n = 8) (Fehm et al 2000a, b);
Apomorphine (n = 5) ? (Quay 2001);
Melatonin/hydroxycobalamin (n = 8) ? (Merkus 2003);
Insulin, melanocortin, vasopressin (n = 36) (Born et al 2002).

placebo controlled. Acute nasal administration of ACTH 4–10 (1 mg) resulted in diminished focusing of attention whereas no effect was seen after sub-chronic administration of ACTH 4–10 (1 mg/day over 6 weeks). The authors proposed that the results indicated a direct action of the peptide on the respective brain functions. Although there was no parenteral control in the study, the authors considered that it was unlikely that the peptide would have been absorbed nasally into the blood stream to a significant degree and thence to the brain via the blood–brain barrier. These results were later complemented by a similar study in 60 volunteers (Smolnik et al 2000). Furthermore, nasally administered ACTH 4–10 (twice daily 0.5 mg for 6 weeks) reduced body fat by 1.68 kg and bodyweight by 0.79 kg, on average, as compared with no effect for two control formulations in three groups of healthy volunteers of normal weight, although no significant changes in serum concentration of ACTH 4–10 was found between 15 min before and 75 min after the nasal administration of the drug (Fehm et al 2001). Concurrently, CSF samples were collected via an intraspinal catheter that showed in five subjects an increase of ACTH 4–10 concentration from 0.67 ng mL^{-1} to 10.24 ng mL^{-1}. Hence, this study demonstrated that the melanocortin receptor pathway was involved in the regulation of body fat in man as had been shown previously for animals. It strongly supported the existence of a direct transport route for the drug from nose to brain in man.

Lindhardt et al (2001) performed a study in eight volunteers to assess the intranasal administration of diazepam as an alternative to intravenous administration for treatment of acute epileptic seizures. The effect of the drug was evaluated by measuring electroencephalographic (EEG) effects. Diazepam was given as nasal doses of 4 or 7 mg, or as an intravenous dose of 5 mg. The nasal bioavailability was indicated as approximately 45%. There was no significant difference between the EEG effects of the highest nasal dose and the intravenous dose whereas there was a significant lower effect of the 4-mg nasal dose. This indicated the importance of the plasma concentration and as expected did not seem to support direct nose-to-brain transport of this lipophilic drug. It should be mentioned that the study did not set out to evaluate the existence of this pathway.

Kern et al (1999) evaluated whether nasally administered insulin affected the auditory evoked brain potential (AEP) measured during the performance of an oddball task in a study of 18 volunteers (double blind cross-over design). A dose of insulin (20 IU) or a placebo formulation was administered into the nasal cavity every 15 min for 60 min. Blood glucose did not decrease and serum insulin was not elevated by the nasal administration of insulin. The nasal insulin was found to reduce the amplitudes of N1 and P3 components of the AEP and also increased P3 latency. The authors suggested that, due to the absence of any changes in serum insulin and blood glucose after nasal administration and in spite of the absence of an intravenously administered insulin control, the study indicated the presence of a direct pathway from nose to brain. In one study insulin was infused at high or low rates and the central nervous effects of insulin were evaluated. At high rates the subjects displayed enhanced performance in a Stroop test and expressed less difficulty in thinking than when given the low rate of insulin (Kern et al 2001). Hence, nasal insulin may be of interest in patients with alterations of brain insulin concentrations i.e. in dementia of the Alzheimer type as well as in diabetes mellitus.

Neuropeptides, such as growth hormone-releasing hormone (GHRH), do not readily pass the blood–brain barrier (Zlokovic et al 1990) and hence the central nervous effects (i.e. effects on sleep patterns) of the hormone are not pronounced after intravenous injection (Kupfer et al 1991). However, when the hormone was administered nasally in 12 young and 11 old individuals 30 min before bedtime, the cortisol nadir concentrations at the beginning of sleep and the sleep-induced elevation in GH concentrations during early sleep were both reduced as compared with a nasal placebo control (Perras et al 1999a). Moreover, the study suggested that after nasal administration GHRH increased rapid-eye movement (REM) sleep and slow wave sleep (SWS). The authors concluded that there was a co-ordinated influence of nasal GHRH on the central nervous regulation of sleep processes and of hypothalamic-hypophysiotropic secretory activity in all volunteers, and hence an indication of direct nose-to-brain transport of the drug. In another study, the same group (Perras et al 1999b) administered vasopressin nasally as 20 IU morning and night for three months to 26 volunteers (mean age 74.2 years) in a placebo-controlled double blind cross-over study. The nasal vasopressin treatment increased the total sleep time, time spent in SWS and time in REM sleep in the second half of the night as compared with control. Rather than mediated peripherally, it was suggested that the effects of vasopressin on sleep may reflect a direct central nervous system action of the peptide. Blood samples collected 30 min after nasal administration showed transport of drug from the nasal cavity into the systemic circulation, which was confirmed in later studies (Perras et al 1999b; Born et al 2002). Although an active transport of vasopressin across the blood–brain barrier had been demonstrated (Zlokovic

et al 1990), the authors suggested that the study indicated a direct transport of vasopressin from nose to CNS. This suggestion was supported by a previous study where there was a comparable increase in systemic blood concentration after nasal administration. Vasopressin had been shown to be essentially more potent in changing stimulus-evoked brain potentials than after intravenous administration in young healthy subjects (Pietrowsky et al 1996a).

Direct evidence of nose-to-brain transport As argued by Fehm et al (2000) these studies, although measuring pharmacodynamic effects rather than drug concentration in the CNS, provide compelling evidence that the intranasal administration of peptides results in an effect on the CNS that is not seen after intravenous administration of the drug. Hence it is most unlikely that it is due to the drug first passing into the blood stream from the nasal cavity and then crossing the blood–brain barrier. Due to the relatively fast onset of the effects on the brain potential and other CNS functions it can be concluded that the drugs were transported by an extracellular pathway across the olfactory epithelium.

Okuyama (1997) was the first to attempt a direct assessment of nose-to-brain transport of compounds in man. Using a radiotracer 99m-technetium-labelled diethylenetriamine-penta acetic acid (99mTC-DTPA) mixed with hyaluronidase sprayed deep into the nasal cavity, γ-scintigraphy was used to record the amount of activity appearing in the juxta-cribriform laminal intracranial space. The study was performed in a healthy 60-year-old man and in a 67-year-old anosmic female. The subjects were laid on their backs with their heads placed in a vertical position to enable the easy reach of the olfactory region with the spray droplets. The olfactory dysfunction in the female was limited to air-borne scenting. A significant rise in cerebral radioactivity was observed 5 min after introduction of the nasal spray in the female volunteer but not in the male. The penetration of the spray into the CNS in the anosmic subject may have been due to increased permeability of the olfactory epithelium in this patient; however, this was not confirmed by any examination of the subject or by any other means.

Later publications have not only studied the pharmacodynamic effects on the CNS of drugs administered nasally but have compared specific drug concentrations in the CSF after nasal drug and placebo administration. In a recent study, Born et al (2002) investigated the nasal administration of three different peptides, melanocortin 4–10 (MSH/ACTH 4–10), vasopressin and insulin (that had previously been well documented (as shown above) for their effects on brain functions such as learning, memory and body weight regulation), in 9 female and 27 male volunteers in a placebo controlled study. CSF and serum samples were obtained for 80 min after the nasal peptide or placebo administration via intraspinal (between L4 and L5) and intravenous catheters. The study included an intranasal placebo control but did not include a leg where the peptides were administered by any parenteral route. A summary of the results is shown in Table 4. Nasal administration of each peptide resulted in a significant increase in CSF concentration as compared with placebo for that peptide as expressed by the area-under-the-curve (AUC) values at 80 min (AUC_{0-80}) (in (ng mL^{-1}) $\times$ min; (pg mL^{-1}) $\times$ min; (pmol L^{-1}) $\times$ min) after administration. For MSH/ACTH 4–10 and insulin concurrent measurements of serum concentrations did not show a significant increase and in addition there was no decrease in glucose levels in the subjects receiving nasal insulin. For vasopressin the increase in CSF levels was accompanied by a significant increase in serum levels of vasopressin, indicating that transport from the nasal cavity of the drug into the systemic circulation had taken place. Although the data given in that paper should be interpreted with some caution due to the lack of a parenteral (intravenous) control, the fact that no increase in serum level was detected for MSH/ACTH 4–10 and insulin concurrent with the increase in CSF levels strongly indicated that these two peptides had reached the CSF via the olfactory region. It should be mentioned though that the endogenous levels of insulin in the serum (non-diabetic subjects) might have masked any small amounts of insulin reaching the systemic circulation from the nasal cavity and that, despite an initial delay, physiological increases in plasma insulin have been shown to produce significant elevations of CSF insulin levels by transport across the blood cerebrospinal fluid barrier (Wallum et al 1987; Schwartz et al 1990). Such transport from blood to CSF was thought to occur in part via a specific transport mechanism.

It has been shown that MSH/ACTH 4–10 is rapidly degraded in the plasma (Born et al 2002). Since the CSF levels were found to increase within 10 min of intranasal administration the authors suggested that the peptides reached the CSF by intercellular clefts in the olfactory epithelium to diffuse into the subarachnoid space. This is a probable explanation as discussed above. For vasopressin, it is difficult to decide whether some of the drug in the CSF originated from direct transport from nose-to-brain or all the drug reached the CSF via transport across the blood–brain barrier. It has been shown in dogs that arginine–vasopressin was transported across the blood–brain barrier from the blood to the CSF after intravenous injection (Ang & Jenkins 1982). Support for (at least some) drug reaching the CSF via the olfactory region is found in the studies by Pietrowsky et al (1996a, b, 2001), showing event related effects on the brain potential after nasal but not after intravenous administration of the drug.

Recently, a pharmaceutical company announced in a press release that a phase 1 clinical study in five subjects had shown that 20 min after nasal administration of apomorphine (0.5 mg) the CSF concentration was equivalent to 27–44% of the concentration found at the same time in the plasma. They reported that after subcutaneous administration the CSF levels were equivalent to only 2.5–4.3% of the plasma levels (Quay 2001). The CSF was sampled by spinal tap. The study has not yet been published as a full paper and hence complete details are not available. However, a major flaw in this study is apparent. The CSF

Table 4 The transport of peptides from nose to brain in man (Born et al 2002).

*Significant increases	CSF (mean AUC ± s.e.m.)	Serum (mean AUC ± s.e.m.)
MSH/ACTH(4–10)	(ng mL^{-1}) × min	(ng mL^{-1}) × min
Placebo	7.5 ± 8.9	8.8 ± 1.41
5 mg	21.51* ± 7.1	10.9 ± 0.26
10 mg	514.51* ± 195.4	10.9 ± 2.98
Vasopressin	(pg mL^{-1}) × min	(pg mL^{-1}) × min
Placebo	254.4 ± 65.6	207.4 ± 202.0
40 IU	1319.1* ± 821.8	1674.0* ± 931.8
80 IU	2481.9* ± 732.4	3749.0* ± 348.6
Insulin	(pmol L^{-1}) × min	(pmol L^{-1}) × min
Placebo	603.2* ± 34.6	3419.5 ± 106.1
40 IU	1091.1* ± 219.8	3414.3 ± 276.8

levels obtained after nasal administration were compared with data on the subcutaneous administration of apomorphine obtained from the literature and, hence, nasal administration and subcutaneous injections were not performed in the same group of subjects. Also, due to the very different volumes of CSF and blood, the concentrations obtained in the two different compartments cannot be directly compared. Furthermore, the CSF levels were compared at only one time point rather than comparing AUC values (over a short period of time). This is a problem, since it can be anticipated that apomorphine administered subcutaneously would have a different plasma profile to nasally administered apomorphine. Nevertheless, the study did indicate that at least some transport of apomorphine had occurred directly from nose to CSF.

In a recent meeting in London, Merkus (2003) presented results from a study in 28 postoperative neurology (ICU) patients in which the patients had been given either hydroxycobalamin or melatonin by the nasal or the intravenous routes of delivery. The study has recently been published (Merkus et al 2003). As part of the ICU operation the patients were fitted with a CSF drain from the site of the operation. Arterial blood (4 mL) and CSF (2 mL) samples were taken concurrently for up to 180 min. The patients were lying flat on their backs and remained fully conscious during the study with hyperextension of the neck during nasal application. A commercially available single dose spray was used for the application. Of the 28 patients only eight fully completed the study due to problems with sampling, analytical problems and for medical reasons; five patients received hydroxycobalamin and three patients received melatonin. The results presented for each drug showed a comparison of the AUC values (in (pmol L^{-1}) × min) for the CSF and the plasma obtained after nasal and intravenous administration. Unfortunately no plasma or CSF concentration–time profiles were provided. For the lipophilic drug melatonin (log P = 1.65; MW 232.3), the CSF ratio ((AUC CSF i.n./AUC plasma i.n.)/(AUC CSF i.v./AUC plasma i.v.)) was given for each patient together with the individual AUC values. For this drug there was no difference in the AUC values for plasma and CSF whether the drug was given nasally or intravenously. Likewise, when calculating the mean CSF ratio on the basis of the individual CSF ratios for each patient CSF ratios a value of 0.71 was obtained, indicating that less drug reached the CSF after nasal application than after intravenous application. For the less lipophilic drug hydroxycobalamin (log P = not available; MW 1346) the results showed that the AUC value for the CSF was higher when the drug was given by slow infusion via the intravenous route than when it was administered nasally. At the same time the plasma AUC showed that the drug was well transported across the nasal membrane into the systemic circulation (the bioavailability can be calculated to 19.5%). It was evident that the drug was able to cross the blood–brain barrier. When calculating the CSF ratio for this drug (given as 1.0) the authors based their calculation on the mean AUC values (n = 5) for CSF and plasma rather than the individual patient CSF ratio values. The latter is the correct procedure. If instead the CSF ratio value is calculated on the basis of the individual patient CSF ratio values (the quoted zero CSF values were changed to 25 pmol L^{-1}, as is the limit of detection for the assay, for calculation purposes), then the mean CSF ratio is 1.61 rather than 1.00, indicating direct nose-to-brain transport! In my opinion, it is not possible to judge whether nose-to-brain uptake has taken place based simply on a comparison of AUC values for CSF and AUC values for plasma alone, and without considering the rate of uptake and especially when the AUC values are calculated from time 0 to time 180 min. For the 15-min intravenous infusion, most of the AUC value could be attributed to the clearance of the drug from the plasma, which in the case of hydroxycobalamin was slow ($t_{½}$ ~3 h) (Van Asselt et al 1998). It is known that a direct nose-to-brain transport normally shows a peak CSF concentration within the first 5 min followed by a rapid clearance from the CSF. Hence, with a first sample point at 5 min a possible initial high CSF concentration (due to direct nose-to-brain transport) may not have been detected, as demonstrated previously for cocaine (Chow et al 1999). Hence, the AUC for the CSF would be very similar to

that seen after intravenous infusion (due to blood–brain barrier transport of the systemically absorbed drug). Moreover, if the AUC values were calculated for the first 15–30 min only (AUC_{0-15} or AUC_{0-30}) it may have been easier to detect possible differences in terms of relatively higher CSF concentrations after nasal administration.

On the basis of the results obtained with melatonin and hydroxycobalamin, Merkus et al (2003) concluded that there was no evidence of a direct nose to CSF pathway in man in contrast to what had been shown by Born et al (2002) for other drugs. Although it is difficult to judge, without having access to all results from Merkus et al (2003), the following could be argued. Firstly, on the basis of individual patient CSF ratios for the hydroxycobalamin, it seems that there is an indication of direct nose-to-brain transport. Secondly, a simple comparison of relative AUC_{0-180} values for CSF for the two treatments, without reference to possible differences in the rate of transport into the CSF for the two routes of delivery, cannot be considered to be a valid approach. Thirdly, due to its relatively high lipophilicity, melatonin would not be expected to show significant direct nose to CSF transport; rather, as shown by Merkus et al (2003), the drug will pass rapidly into the systemic circulation and from there cross the blood–brain barrier and reach the CSF. Fourthly, the less lipophilic and larger drug hydroxycobalamin was shown to be sufficiently lipophilic for a high amount ($F = 19.5\%$) of drug to reach the systemic circulation, as shown by the plasma AUC. The intravenous data showed that the drug could cross the blood–brain barrier and reach the CSF. As indicated by the recalculated CSF ratios, it was highly likely that the drug that reached the CSF, apart from originating from the blood, also passed directly from the nose to the CSF. This might have been more evident if samples had been taken earlier than 5 min after application of the drug. Fifthly, it should be considered that the positioning of the subjects during nasal dosing was very different to that used by Born et al (2002), where the subject were sitting in an upright position during dosing. In summary, it could be argued that the drugs chosen by Merkus et al (2003) were not entirely appropriate due to their high nasal absorption and that the study was inconclusive in terms of whether a direct nose-to-brain pathway exists.

Therapeutic benefit The major proportion of the studies described above, where drugs were administered to the nasal cavity in man, showed either indirectly (in terms of pharmacological effects on the CNS) or directly (in terms of elevated drug levels in the CSF) that the existence of a nose to CNS pathway in man is a distinct possibility or even a reality. However, it is evident from animal experiments that the fraction of drug reaching the CNS from the nasal cavity is small (much less than 1%) (Table 5). No studies have so far tried to measure or estimate the fraction of drug reaching the CNS in man. Recently, it was shown in a mouse model that P-glycoprotein attenuated brain accumulation of certain nasally administered drugs (P-glycoprotein substrates) such as verapamil, ritonavir and quinidine and that the co-administration of P-glycoprotein inhibitors enhanced the brain uptake of such drugs by up to sixfold (Graff & Pollack 2003). These results have recently been confirmed in an in-vitro model employing bovine excised olfactory tissue (Kandimalla & Donovan 2003). The authors concluded that P-glycoprotein localised on the apical surface of the olfactory mucosa played an important role in preventing P-glycoprotein substrates from reaching the CNS after nasal administrations. Hence, for some drugs an efflux mechanism may constitute a natural barrier to high brain deposition after nasal administration.

Table 5 Quantitation of nose-to-CNS absorption.

Monosialoganglioside (GM1) in rats
"bioavailability" in CSF after intravenous 0.005%
"bioavailability" in CSF after subcutaneous 0%
(Kumbale et al 1999)
Nerve growth factor in rats
"bioavailability" in CSF after intravenous 0.023%
"bioavailability" in CSF after subcutaneous 0.001%
(Chen et al 1998)
[^{3}H]Dopamine in mice
"bioavailability" in brain after intravenous 0.120%
(Dahlin et al 2000)

For most drugs, except for very potent molecules, nose-to-brain drug delivery may not constitute a therapeutically interesting method of reaching the brain for treatment of the various diseases of the CNS. Thus it is evident that in situations where it is paramount to target receptors in the brain, for example for treatment of Alzheimer's or Parkinson's diseases or the treatment of pain (unless may be for very potent drugs), it would be necessary to develop drug delivery systems capable of improving the delivery of the drug from the nasal cavity to the brain. Such systems would most likely involve bioadhesive excipients and delivery devices allowing a targeting of a larger fraction of the nasal formulation to the olfactory region. On the other hand, in some cases, where the transport of drugs from the nasal cavity to the brain may not be beneficial to the patients due to possible adverse reactions and toxic effects, it may be necessary to find appropriate delivery systems that decrease direct transport from the nose to the brain. Such delivery systems would most likely contain absorption enhancing systems that would provide a rapid and efficient transport of the drugs across the nasal membrane into the systemic circulation.

Conclusion and future directions

On the basis of a critical evaluation of the studies described in the currently available literature on nose-to-brain delivery of drugs in man, it can be concluded that the existence of an olfactory pathway (axonal and epithelial) is a more than distinct possibility and in my opinion a reality. The results are supported by numerous studies in

animal models showing transport of polar molecules from nose to brain. It is evident that better planned and more controlled studies should be performed to obtain scientifically valid and conclusive results. It is of importance to evaluate in man the therapeutic benefit that can be obtained for drugs, other than very potent drugs such as some neuropeptides, by this method of brain delivery compared with other methods of targeting the brain receptors. Future studies should evaluate the possibility of improving the effectiveness of nose-to-brain transport by drug delivery and drug formulation approaches.

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