might be expected to damage the epithelium). Nevertheless, studies in rats are important and provide useful information on the pathways and mechanisms of drug absorption both into the systemic circulation and CNS.

The olfactory mucosa is composed of the olfactory epithelium and its underlying lamina propria. The routes by which the molecules cross the olfactory epithelium have yet to be fully elucidated, but a number of possible pathways have been suggested (Fig. 38.1). An intracellular, axonal pathway has been proposed where substances are taken into the olfactory sensory neurons (OSNs) via adsorptive, receptor-mediated or non-specific fluid phase endocytosis and transported within the cell along the axon to the olfactory bulb. Another pathway involves substances crossing the other cells of the olfactory epithelium (e.g. sustentacular (supporting) cells) via transcellular or paracellular passive diffusion to reach the lamina propria. Tight junctions exist between cells in the olfactory epithelium but the regular turnover of cells in the epithelium may lead to loosening of the tight junctions, helping the paracellular transport of larger molecular weight substances.

Once at the lamina propria, entry into the CNS is believed to occur, via diffusion or convection, extracellularly along the perineural space (which is the space surrounding the olfactory nerve bundles), through the cribriform plate and into the cerebrospinal fluid (CSF) or olfactory bulb. However, a proportion of molecules is also likely to enter the blood vessels of the systemic circulation or lymphatic vessels and will therefore be prevented from entering the CNS by this direct route. Of the two routes into the CNS, it has been suggested that intracellular transport along the axon of the OSN would be too slow to account for the experimental results observed and that the other extracellular pathway is the most likely.

Immunohistochemical studies have found the efflux transporter P-gp localized to the endothelial cells lining the olfactory bulb and the olfactory epithelium. P-gp is able to reduce entry into the CNS of those drugs which are substrates for the transporter. Since drugs need to be inside the epithelial cell to interact with the binding site of P-gp, this will mainly affect those drugs crossing the supporting cells of the olfactory epithelium via the transcellular route.

Interestingly, the trigeminal nerve which innervates the respiratory epithelium of the nasal cavity also feeds into various areas of the brain and could potentially be exploited for nose to brain drug delivery. However, so far, this route has not been implicated as providing a pathway for CNS drug delivery.

It should be noted that in the many studies of drug transport (low molecular weight drugs and peptides and proteins) from the nose to the brain, the amount of drug reaching the CNS is small compared to the amount administered to the nasal cavity, generally less than 1%. One major problem is the inaccessibility of the olfactory region of the nasal cavity coupled with the poor permeability of certain types of molecule (including peptides and proteins) across the olfactory epithelium. There is a need for a formulation containing an acceptable nasal permeation enhancer and a bioadhesive material which can be delivered from a nasal device that is able to target the formulation to the olfactory region.

Nasal delivery systems

Nasally administered medicines can be formulated as ointments or creams but most usually as a liquid (solution, gel or suspension) or as a powdered solid (Tables 38.1 and 38.2). The formulation issues with each of these dosage forms have been considered in previous chapters. With multi-dose liquid dosage forms, the possibility of 'suck-back' exists which is when a portion of the administered dose is sucked back into the remaining liquid in the delivery device. As a consequence, multi-dose liquid dosage forms can require the inclusion of antimicrobial preservatives to prevent the growth of contaminating microorganisms. There is evidence that some of these preservatives can cause irritation to the nasal mucosa and/or damage the cilia and therefore compromise mucociliary clearance, especially if used over a long period. Strategies to minimize or obviate such effects include the use of alternate nostrils, if chronic daily dosage is required, and the use of pressurized containers or unit-dose delivery systems (Table 38.8) which do not require the inclusion of a preservative. There is a move towards delivery systems that deliver an accurate metered dose and away from dosage forms such as nasal drops, which require considerable skill, dexterity and even flexibility (in terms of mobility) to apply uniformly across the mucosa. Smaller doses (< 100 μL) tend to persist longer than larger doses which may drip from the nostril after delivery.

Powdered solids tend to remain in the nasal cavity for longer periods than liquids, since a preliminary hydration step generally occurs before mucociliary clearance reaches maximal efficiency. This can prolong