Despite good progress in neurosciences and a corresponding high interest in brain delivery technologies, very few drugs have been marketed for such indications so far. This is not due to a lack of new central nervous system (CNS) drugs or ideas for improvement of drug transport to the brain, but to a negative interaction of sometimes much less sophisticated reasons. Qualified by its physical closeness, an interesting place for application of brain-active drugs is the nose. Recreational drugs such as nicotine, cocaine or amphetamines are commonly used in this way. However, nasal applications for delivery to the systemic circulation and/or brain have not been pursued by the pharmaceutical industry since the 1980s. This article aims to provide the reader with a selection of background information, emphasising the experiences of a specialised company in this area.

Problems with Brain-active Drug Delivery via the Nose
When targeting drug to the brain or the systemic circulation via the nose, it is necessary for the molecule to fit with the formulation and for the formulation to fit with the applicator.

The Molecule
The effect of some drugs on the CNS is unknown because they have not yet been administered by a suitable application route, formulation or dose. Furthermore, some drugs are known to affect the brain, but are generally thought not to cross/bypass the blood–brain barrier (BBB) because of their hydrophilic properties. An example of the latter is the molecule dopamine (DA), which, for example, is lacking in the brain of patients suffering from Parkinson’s disease (PD). It is believed that this catecholamine cannot cross the BBB, so instead its precursor 3,4-dihydroxyphenylalanine (L-DOPA) is used, which most probably is delivered to the brain by the type 1 large neutral amino acid transporter (LAT1). Although therapy with L-DOPA is the gold standard in the treatment of PD, it has some disadvantages, including the necessity of adding co-drugs, loss of efficiency and occurrence of side effects in long-term treatment.

Mattern Pharmaceuticals AG (Stans, Switzerland) has developed an efficient and safe nasal delivery system to transport the molecule DA to the brain. This was recently demonstrated in pre-clinical studies. Besides performing neurochemical analyses, the effects of intranasal administration of DA on the activity of dopaminergic neurons of the mesostriatal and mesolimbic systems and on motor activity in rats were investigated. The results indicate that the increase in DA is paralleled by an influence on dopaminergic functions and motor activity (see Figure 1). Comparing the percentages of the original dose remaining in the rodent’s brain 30–45 minutes after nasal administration of DA reached by other formulations (e.g. 0.12% found by Dahlin et al.,2) and by the new formulation (shown in Figure 1) reveals a promising approach by the latter.

Since DA is an important neurotransmitter in the brain, it contributes to the regulation of processes such as motor activity, reinforcement, emotion and cognition. Several neuropsychiatric disorders other than PD, such as schizophrenia, substance abuse, Huntington’s disease and attention deficit hyperactivity disorder (ADHD), are widely accepted to have a basis in a deregulation of dopaminergic transmission. Nasal application in this way may open the use of DA, a well-known and well-characterised molecule, for several new and interesting neurological indications.

The Formulation
Of course, the galenical formulation for nasal application has to be safe, especially in long-term treatment. Additionally, it also has to fit to the molecule – not only to its physico-chemical properties, but also to its clinical indication. Therefore, the solubility of a molecule should not be a naturally limiting factor since the dose for inducing brain activity might be lower than that for measurable blood levels. For example, Born et al.3 measured insulin levels after intranasal administration of the compound to subjects and found a significant and rapid increase in cerebrospinal fluid (CSF), but no such increase in blood. This increase in CSF was paralleled by an improvement in memory function.

A growing body of evidence suggests a modulatory role of neurosteroids (e.g. androgens and progestins) in the regulation of disorders influenced by receptors in the brain, such as depression, Parkinson’s disease, Alzheimer’s or even loss of libido. It is also known that brain cells concentrate steroid hormones to much higher levels than blood. Thus, the marked and rapid clinical effect observed after nasal application of such molecules is most probably due to the preferential transfer of the steroid to the brain. This has been confirmed by Mattern in a functional magnetic resonance imaging (fMRI) study4 in which testosterone, given as Noseafix®, rapidly – within 45 minutes – modulated amygdala reactivity. It is suggested that testosterone could positively influence mood and sexual function by modulating amygdala activity, the brain structure that is thought to influence mood and anxiety regulation and sexual arousal. Therefore, the immediate effect seen in the study might be important for a ‘Viagra-like’ onset of action. On the other hand, and depending on the indication, increasing the time over which the molecule is delivered to the brain might be equally important, because pharmacological effects in general are related to bioavailability to target tissues rather than to the administered dose.

Comparing the bioavailability of testosterone after intranasal (IN) (Noseafix) versus intravenous (IV) application, Mattern found that testosterone entered both brain and blood after both types of administration. The i.n. route had a bioavailability of about 75%, but favoured brain uptake. About two-thirds of the testosterone entering brain after IN administration was taken up directly across the cribriform plate and about one-third first entered the blood.5 This result is in line with what has been found for DA

Nose-to-brain Delivery – the Royal Road to Improve Central Nervous System Disorders

a report by
Mattern Pharmaceuticals AG
Nasal Delivery

It is known that in healthy individuals endogenous secretion follows stable rhythms, which may facilitate secretory efficiency and/or communication with downstream targets. These rhythms appear to be functionally connected and are important to their respective systems, as evidenced by the disorders and disease states that can result from the loss of pulsatile activity. Testosterone production, for example, has a circadian rhythm of 24 hours. As the master clock for these rhythms is located in the suprachiasmatic nuclei of the hypothalamus, changes at this level may affect the circadian clock and, consequently, endocrine rhythmic functions.

Typically, healthy young men have a high testosterone level in the morning, which steadily drops throughout the day, while in elderly or hypogonadal patients this rhythm is considerably blunted and/or shifted in time. This indicates that rhythms are critical for optimal body functioning, and obviously the most physiological way to treat hypogonadism (androgen deficiency) would be to apply testosterone in a way that imitates the rhythm seen in healthy young men. However, it seems that current methods of testosterone replacement tend to result in permanently increased concentrations of circulating testosterone, which is significantly different from the physiological profile in normal men. The consequences of ‘unopposed’ high circulating levels of testosterone, however, are unknown at present but may well result, for example, in oligo- and/or azoospermia and infertility (hypo- or pituitary feedback control of testosterone levels and spermatogenesis). To evaluate the similarity of nasal administration with normal circadian rhythm, the kinetic profile of testosterone given once in the morning as Nasobol® is set against a typical profile of a healthy young man. It is obvious that the concentration–time curve of testosterone in serum following nasal application imitates the natural endogenous course.

The Application Device

The choice of a suitable device for application is often underestimated. This implies considerations with regard not only to the physico-chemical properties of the formulation, but also to the clinical indication and regulatory points. Thus, a suitable device delivers the formulation in a reliable way (dose uniformity, stability), is easy to use – especially in view of the indication (handicapped persons) – and is not problematic in the registration process. Product development quite often focuses on molecule and formulation only. In intranasal delivery this might considerably delay the time to market because the choice of marketable devices is quite limited, especially for non-aqueous formulations.

Conclusion

The identification of ways to increase the bioavailability of drugs in the brain opens possibilities for the causal treatment of diseases associated with a deficiency in neurosteroids and neurotransmitters in the brain. Despite several limitations, intranasal delivery seems to be the most promising application to improve CNS disorders, including brain injuries, by medicine. However, during product development it is mandatory to consider on the one hand the inter-relation between drug, formulation and applicator, and on the other hand the influence of chronobiology on effect and side effects of the medication.

1. Joseph P. Huston et al., (Intranasal dopamine application increases dopaminergic activity in the neostriatum and nucleus accumbens and enhances motor activity in the open field, article submitted).
time curve

Figure 2: Kinetics After One Application of Nasobol® versus Testosterone Profile of a Healthy Young Man

Values are expressed as mean (± SEM) percent of baseline, with the mean of the six baseline samples taken as 100%. The arrow indicates the time-points of the administration.

* Significant difference from the vehicle group, p<0.05.

-50 -40 -30 -20 -10 0 10 20 30 40 50 60 70 80 90 100 110 120

0 2 4 6 8 10 12 14 16 18 20 22 24

0 200 400 600 800 1,000

Healthy young men

Mean concentration–time curve

Testosterone (pg/dl)

Time (h)
One of the leading research companies in the field of psychoneuroendocrinology based on intranasal drug delivery.

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