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Review

Intranasal administration of oxytocin: Behavioral and clinical effects, a review

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ABSTRACT

The intranasal (IN-) administration of substances is attracting attention from scientists as well as pharmaceutical companies. The effects are surprisingly fast and specific. The present review explores our current knowledge about the routes of access to the cranial cavity. 'Direct-access-pathways' from the nasal cavity have been described but many additional experiments are needed to answer a variety of open questions regarding anatomy and physiology.

Among the IN-applied substances oxytocin (OT) has an extensive history. Originally applied in women for its physiological effects related to lactation and parturition, over the last decade most studies focused on their behavioral 'prosocial' effects: from social relations and 'trust' to treatment of 'autism'.

Only very recently in a microdialysis study in rats and mice, the 'direct-nose-brain-pathways' of IN-OT have been investigated directly, implying that we are strongly dependent on results obtained from other IN-applied substances. Especially the possibility that IN-OT activates the 'intrinsic' OT-system in the hypothalamus as well needs further clarification.

We conclude that IN-OT administration may be a promising approach to influence human communication but that the existing lack of information about the neural and physiological mechanisms involved is a serious problem for the proper understanding and interpretation of the observed effects.

Contents

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1. Introduction

1.1. Intranasal (IN-) administration

The intranasal route of administering substances is attracting a steadily increasing amount of attention. A simple search of the literature tells us that by now almost 13,000 scientific papers have been published where IN-administration of a large variety of substances was reported. The number of papers per year shows a continuing rise from a mere 12 in 1970 to more than 100 in 1980, to almost 200 in 1990 via more than 400 in 2000, up to more than 1600 in the most recent years. The main reason for the increasing popularity of IN-administration is based on its proven efficacy to deliver substances into the brain and the Cerebrospinal Fluid (CSF). At least two aspects make this route of delivery of substances to the brain more and more interesting. First, as a way to circumvent the 'Blood-Brain-Barrier' (BBB), that prevents many substances (including proteins and neuropeptides) to access the extracellular fluid surrounding the neurons and glial cells of the brain. The BBB is formed by the endothelial layer of the cerebral blood vessels and protects the Central Nervous System (CNS). It is a dynamic interface with a range of interrelated functions, consisting of effective tight junctions, transendothelial transport systems and enzymes, together composing the physical, transport and enzymatic regulatory functions of the BBB. The BBB forms part of the 'neurovascular unit' comprising pericytes or vascular smooth muscle cells, glial cells (astrocytes) and neurons, together controlling the permeability of the BBB and local vascular blood flow (Abbott and Friedman, 2012; Banks, 2012; Berezowski et al., 2012; Daneman, 2012; Pardridge, 2005; Zlokovic, 2011). The BBB is not a closed barrier but its permeability is a regulated function and in addition some 'leakage' may occur via the circumventricular organs (Ermisch et al., 1985). However, the possibility to target the brain and its functions directly without the limitations posed by the BBB (see below), opens new perspectives for clinical treatment of pain, psychiatric symptoms, degenerative brain diseases as well as brain-tumors.

The second consideration to apply IN-administration of neuropeptides is the elongation of the half-life values and efficacy of the substances administered. Due to enzymatic degradation, the half-life time of oxytocin (OT) in the blood is only less than 2 min, while in the extracellular space of the brain and in the CSF this time amounts up to 28 min (Mens et al., 1983; Robinson, 1983; Robinson and Jones, 1982). Similar differences in half-life values have been observed for other substances, particularly neuropeptides like β-endorphin (Burbach et al., 1984, 1979; Houghten et al., 1980), which makes intranasal administration of substances considerably more effective by keeping CNS-concentrations locally higher over a longer period of time.

A quick search of the available literature shows that by now the effects of IN-administration of at least 50 different substances have been reported, including a large variety of neuropeptides, some steroids, DNA-plasmids and siRNA (Bortolozzi et al., 2011; Han et al., 2007; Perez et al., 2012; Renner et al., 2012) and even mesenchymal stem cells and human glioma cells have been applied via the nose (Danielyan et al., 2011, 2009). In addition, intranasal cooling can be used to induce brain hypothermia (Covaciu et al., 2011). Since all applied substances apparently induce different effects on (aspects of) brain functioning, we have to pay some attention to the mechanisms involved in brain delivery of substances via the intranasal route and to the specificity of targeting the brain along the available routes of access. For the present purpose, a short survey will suffice since numerous reviews have been considering specific aspects of IN-administration over the last few years (Banks, 2006; Bos et al., 2012; Carnes and Robinson, 2008; Charlton et al., 2008; Dale et al., 2002; Dhuria et al., 2009a, 2010; Domes et al., 2010; Graff and Pollack, 2005; Grassin-Delyle et al., 2012; Guindon et al., 2007; Illum, 2003, 2004; Jogani et al., 2008; Liu et al., 2012; Merkus and van den Berg, 2007; Meyer-Lindenberg, 2008; Mygind and Andersson, 2006; Pathan et al., 2009; Strachan, 2005; Striepens et al., 2011; Thorne et al., 1995; Van Ijzendoorn and Bakermans-Kranenburg, 2012; Viero et al., 2010).

1.2. Mechanisms involved in the uptake of IN-applied substances

Basically, there are three possible ways how substances applied on the mucosal wall of the nasal cavity may reach the cranial cavity and (parts of) the brain itself. Since these routes-of-access are not mutually exclusive, they deserve a short description in order to evaluate in how far OT, the main substance of interest for the present review, is using selectively one or a combination of these possible mechanisms. These possibilities are: (1) intra-axonal and transneuronal transport mechanisms via the olfactory pathways; (2) via the peripheral blood stream and the Blood-Brain-Barrier (BBB) after crossing the mucosal walls of the nasal cavity; (3) via perineuronal and other spaces along the olfactory fibers and other cranial nerves to enter the arachnoid space and CSF surrounding the brain.

1.2.1. Intra-axonal and transneuronal transport via olfactory pathways.

Several studies in the rat have shown that neuroanatomical tracers can be transported from the olfactory sensory neurons (OSN) in the epithelium covering the nasal cavities to the olfactory bulb as well as, after transneuronal transport, to all second order olfactory regions. Apparently, transport occurs in both anterograde and retrograde directions, revealing all central olfactory connections (Paxinos, 2004; Shipley, 1985). These findings were confirmed in other species at the electronmicroscopical level in the rat (Baker and Spencer, 1986) as well as after gene transfer of a plant lectin as a transneuronal tracer in transgenic mice to target the olfactory system in order to study its connectivity (Horowitz et al., 1999). Anterograde labeling of the olfactory bulb was observed after all survival times studied starting with 1 day (Baker and Spencer, 1986; Shipley, 1985) but for transneuronal labeling longer survival times were necessary, up to 7 days (Shipley, 1985).

Viruses have been widely used as transneuronal neuroanatomical tracers and interestingly for our present purpose many of them appear to infect the CNS via olfactory and/or trigeminal connections arising in the olfactory mucosa. Early investigations showed that a variety of viruses like Borna disease virus (Morales et al., 1988; Shankar et al., 1992), mouse hepatitis virus (Barnett and Perlman, 1993; Barthold, 1988; Perlman et al., 1995), corona virus (Perlman et al., 1990) and mouse rabies virus (Lafay et al., 1991) enter the CNS along the olfactory pathways. Some recent additions are adenovirus

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