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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.

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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., 1979, 1984; 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., 2009, 2011). 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

type 1, flavivirus, lysosomal enzyme (Procario et al., 2012; Wolf et al., 2012; Yun et al., 2012), herpes simplex virus, entering also along the vomeronasal chemosensory system (Mori et al., 2005; Tomlinson and Esiri, 1983) and the human influenza virus (Majde et al., 2007). Apparently, viral organisms have virtually 'open' access to the CNS along the olfactory system and pathways and for that reason most of the recent research activities in this field are aiming at prevention by intranasal vaccination as well as at intranasal protection mechanisms (Detje et al., 2009; Kang et al., 2012; Kim et al., 2012b; Lillie et al., 2012; Raghuwanshi et al., 2012; Weaver et al., 2012). Many of the viruses mentioned use the intra-axonal transport mechanisms of the olfactory pathways to gain entrance to the CNS although some use the trigeminal fibers as well (Perlman et al., 1990) or may even show a specific preference for entering the CNS via the trigeminal system (Mori et al., 2005; Perlman et al., 1993).

In addition to neuroanatomical tracers and viruses the use of alkali metal ions, like thallium and manganese, has been proposed to evaluate olfactory nerve injury since these ions are also transported intra-axonally via the olfactory pathways (Fa et al., 2010; Kim et al., 2012a; Kinoshita et al., 2008; Lehallier et al., 2012; Ruvin Kumara and Wessling-Resnick, 2012). The toxic effects of aluminum (Perl and Good, 1987a,b) and dental amalgam on the brain (Galic et al., 1999; Henriksson and Tjalve, 1998) are suspected to be caused by the direct nose-brain transport mechanisms (Maas et al., 1996; Stortebecker, 1989). Pathological prion proteins appear to avoid the olfactory and other cranial nerves completely despite the fact that the nasal cavity is a site for prion infection (Kincaid and Bartz, 2007; Sbriccoli et al., 2009).

Considering whether intra-axonal transport mechanisms could play a major role in the observed effects after intranasal application of neuropeptides like OT, the answer is: no or hardly. Firstly, dextran molecules applied intranasally were hardly detectable inside the olfactory axons despite extensive labeling of the connective tissue surrounding the nerve bundles (Jansson and Bjork, 2002). Secondly, because these transport mechanisms are too slow to explain the effects of IN-administration. Thirdly, because many different substances have been visualized after IN-administration and inside the CNS a specific correlation with the olfactory pathways has never been observed while the effects were not limited to olfactory effects. Finally, because IN-administration has been tested for many different substances and the observed effects were always specifically different in agreement with their physiological or endocrinological role suggested by other kinds of experiments. This variety of effects is hard to reconcile with the involvement of only a limited set of secondary or tertiary olfactory connections.

1.2.2. Peripheral transport via the blood stream after crossing the nasal mucosa

In a careful series of experiments, Merkus and van den Berg have shown that several IN-administered substances enter the systemic circulation to such an extent that increased CSF-levels can be explained as a secondary effect. Especially the evidence supporting the claim that IN-administration enhanced delivery in the human brain was questioned and considered as very weak or even virtually absent (in't Veen et al., 2005; Merkus and van den Berg, 2007; Van den Berg et al., 2003; van den Berg et al., 2004a,b). In their experiments a variety of substances was studied, like dextran, hydroxocobalamin, melatonin, estradiol and progesterone. Later studies by other investigators did not consistently support their findings, see (Dhuria et al., 2010), but their findings should at least warn us for drawing fast and unwarranted conclusions about 'direct brain delivery'.

In addition, an often neglected but functional vascular pathway appears to exist between the nose and the brain. Several of the venous vessels from the nasal cavity enter the cavernous sinus via the angularis oculi vein. The cavernous sinus is traversed by the internal carotid artery (human, rat) that splits into numerous small parallel vessels traversing the cavernous sinus in many other species (swine, sheep, camel, cat and dog) (Einer-Jensen and Larsen, 2000b; Skipor et al., 2003). Thus, following the 'counter-current-principle', carotid arterial blood can be cooled here to keep the brain temperature below deep body temperature during heavy exercise (for 'hunting' or 'being hunted') (Baker, 1982, 1995; Einer-Jensen and Larsen, 2000b; Skipor et al., 2003). Surprisingly, however, in addition to these temperature effects, chemical exchange between venous and arterial vessels appears to occur as well. Substances like neuropeptides, progesterone, tritiated water, tyrosine, propanol and diazepam are transferred from the nasal cavity into these cranial arteries, sprouting from the internal carotid artery. As a result of this local exchange, the levels of these substances may be considerably higher in the brain vasculature than elsewhere in the peripheral circulation (Einer-Jensen and Larsen, 2000a,b; Grzegorzewski et al., 1995; Krzymowski, 1992; Skipor et al., 1997, 2003, 2004). Other substances, however, failed to be transported along this route, like cocaine and the antimigraine agents sumatriptan and naratriptan (Einer-Jensen and Larsen, 2000a; Einer-Jensen et al., 2001).

Elevated levels of substances in specific brain vessels does not imply, however, that more of the substance involved enters the brain or the extracellular spaces, due to the BBB, which blocks the entrance of 98% of small and nearly 100% of large molecules (Dhuria et al., 2010; Pardridge, 2005). The much shorter half-live values, enzymatic degradation and binding processes in the vascular system are limiting factors for the effects of these vascular exchange mechanisms (Dhuria et al., 2010). However, this peculiar and only partially understood phenomenon of vascular exchange between venous vessels of the nasal cavities and facial regions with the cranial arteries leading to specifically elevated blood levels inside the brain, should not be completely neglected in the discussion about 'direct-brain-transport'.

However, most of the recent papers and reviews do not support the notion that nasal drug delivery employs mainly the systemic route (Charlton et al., 2007a,b, 2008; Chen et al., 2008; Costantino et al., 2007; Dhuria et al., 2009a, 2010; Graff and Pollack, 2005; Illum, 2004, 2007; Lochhead and Thorne, 2012; Pathan et al., 2009; Thorne et al., 2004; Wang et al., 2006). After careful evaluation of blood and CSF-levels of physicochemical factors and specific transport mechanisms, all recent reviews and reports reject the possibility that nasal delivery to the brain occurs only via the systemic circulation (Charlton et al., 2007b, 2008; Chen et al., 2008; Costantino et al., 2007; Pathan et al., 2009) but there are some additional considerations. The OT-levels in the CSF are for only 0.01% (Mens et al., 1983) derived from the OT-levels in the peripheral blood, which fact virtually excludes the possibility that IN-OT is effective along the peripheral route. There is anatomical evidence that intact olfactory and/or trigeminal nerves are necessary to obtain the effects after IN-administration (Johnson et al., 2010; Thorne et al., 2004). The fact that all IN-administered substances, that can be visualized, always seem to enter the cranial cavity via and along the olfactory bulb, with an occasional extra entrance site in the brainstem near the trigeminal system (see below), is hard to explain when all substances arrive and distribute themselves via the systemic circulation. These considerations make it highly improbable that 'nasal delivery', as a general rule, occurs via the general circulation but we have to keep in mind that under certain conditions and for certain substances, the systemic-route-contributions may play some role in the observed effects of IN-administration, especially if the substances easily cross the BBB.

1.2.3. 'Direct transport pathways' to the brain

Numerous studies agree that additional transport pathways, extra-axonal and extra-systemic and therefore called 'direct', must

exist between nasal and cranial cavities and/or between olfactory epithelia and olfactory and possibly other brain areas and/or the CSF-containing arachnoid space (Dhuria et al., 2010; Sakka et al., 2011). A variety of findings provides evidence for the existence of such additional pathways.

'Rapid access': several substances arrive at the olfactory brain regions considerably faster than expected on the basis of systemic or intra-axonal transport mechanisms. Arrival times of less than a minute have been observed for the olfactory bulbs (Born et al., 2002; Charlton et al., 2008; Illum, 2004; Thorne et al., 2004) while the highest brain levels after systemic administration as well as after intra-axonal transport are reached considerably later, up to hours in the case of intra-axonal transport (Dhuria et al., 2010).

Shifting the location of intranasal administration towards the olfactory part of the nasal cavity may enhance delivery to the brain while diminishing peripheral levels (Charlton et al., 2007b; Gao et al., 2007).

'Brain-concentrations' obtained after intranasal administration are frequently not accompanied by concomitant changes in peripheral levels (Charlton et al., 2007a; Costantino et al., 2007; Han et al., 2007; Hashizume et al., 2008; Jogani et al., 2008; Westin et al., 2006) and sometimes the latter did not change at all (Born et al., 2002; Dhuria et al., 2010).

Anatomical considerations: substances targeting the brain from the blood stream have specific access to the BBB-lacking 'circumventricular organs' (CVO's). These are small neurohaemal structures with numerous fenestrated capillaries, loosely apposed astrocytes and large perivascular spaces. They are functionally subdivided in sensory and secretory CVO's and involved in a variety of neuroendocrine and pathological functions including the production of neural stem cells (Benarroch, 2011; Bennett et al., 2009; Fry and Ferguson, 2007; Horsburgh and Massoud, 2012; McKinley et al., 2003; Siso et al., 2010). Their borderline towards the CSF is closed, however, by the tight junctions between the ependymal cells lining the ventricles (Suarez et al., 2010). The CVO's are monitoring the composition of the peripheral blood and provide access to numerous brain areas since they are extensively interconnected as well as reciprocally connected with hypothalamic and other brain areas involved in homeostatic functions (Benarroch, 2011; Suarez et al., 2010). But these 'entrance-portals' for humoral information have specific neuronal connections (Benarroch, 2011; Larsen and Mikkelsen, 1995; Larsen et al., 1991; Suarez et al., 2010) and the brain distribution of substances using them is radically different from what happens after IN-administration. In the latter case, whenever substances could be visualized, they entered the cranial cavity in its rostral, olfactory part, and encompassed more caudal brain regions with some delay and with steadily decreasing concentrations, most probably involving the CSF in the subarachnoid space (Charlton et al., 2008; Hashizume et al., 2008; Pathan et al., 2009; Thorne et al., 2004). Interestingly, several substances showed a second 'entrance' at the brainstem level, via peripheral branches of the trigeminal nerve innervating the nasal walls (Charlton et al., 2008; Hashizume et al., 2008; Pathan et al., 2009; Thorne et al., 2004). The specificity of these 'entrance-sites' is hard to reconcile with a systemic distribution of substances crossing the BBB via the CVO's.

In a recent study, the group of Frey (Danielyan et al., 2009) has shown that intranasally administered mesenchymal stem cells as well as human glioma cells were within an hour distributed not only into the olfactory bulb but to a variety of other brain areas as well. Migration occurred via the olfactory bulb as well as via the CSF with two additional potential migratory paths: the 'trigeminal route' and a 'perivascular route' (Danielyan et al., 2009) recently described as 'vasophilic migration' (Bovetti et al., 2007).

While the data in favor of 'direct pathways' from the nasal to the cranial cavity may be rather convincing, many questions remain to be answered both at the electronmicroscopical and at functional anatomical levels. Many details about these pathways or 'entrance-routes' are not fully elucidated yet and of the unanswered questions only a few can be addressed shortly in the scope of the present review.

The vast majority of studies concerning the morphological details of 'nose–brain-relationships' aimed at the olfactory and other routes for cerebrospinal fluid drainage and were 'looking for' possible mechanisms working in the 'opposite direction' (Bradbury and Westrop, 1983; Erlich et al., 1986; Gomez et al., 1985; Johnston et al., 2004, 2005, 2007a,b; Johnston, 2003; Kida et al., 1993, 1995; Koh et al., 2007, 2005, 2006; Li et al., 2005b; Nagra et al., 2006, 2008; Papaiconomou et al., 2004; Pollock et al., 1997; Walter et al., 2006a,b; Weller et al., 1992, 2008; Zakharov et al., 2003, 2004). Walter et al. (2006b) described in detail a putative model of labyrinthine channels, surrounding the olfactory fibers during their passage of the cribriform plate providing the CSF with a route for draining into the lymphatic system with the possible side-effect of stimulating antibody-production in the cervical lymph nodes (Walter et al., 2006a). Nerve-associated lymphatic vessels have been described, connecting lymphatic vessels in the dura mater on the cribriform plate, via the epineurium and close to the perineural sheath of the olfactory fibers downward into the nasal mucosa (Furukawa et al., 2008). These vessels seem to be present along all cranial nerves and may not only contribute to transport CSF, tissue fluid and free cells but provide also a morphological basis for routes of immune cell transfer and tumor metastasis (Furukawa et al., 2008). Anatomical investigations did not provide support for the possibility that these CSF-nose lymphatic connections are also used in the contrary direction (Jansson and Bjork, 2002; Sakane et al., 1995).

In addition, perivascular spaces, potentially driven by vascular pulsations, have been described not only as a possible route for lymphatic drainage of the brain (Li et al., 2005b; Pollock et al., 1997; Weller et al., 1992, 2008, 2009; Woollam and Millen, 1955) but also for the distribution of intranasally delivered substances (Dhuria et al., 2009a,b, 2010; Thorne et al., 2004, 2008).

Generally 'perineuronal spaces' surrounding the olfactory fibers are abundantly present and they form part of a complicated spatial 'rhinotopic' organization of the peripheral olfactory system (Clancy et al., 1994; Schoenfeld et al., 1994). Since there are about 1800 glomeruli in the mouse olfactory bulb (Rogers and Firestein, 2001) the continuous guidance of the new outgrowing OSN-axons via the proper fascicles (Nedelec et al., 2005) requires a complex control mechanism. Olfactory ensheating cells and olfactory nerve fibroblasts play a primary role (Field et al., 2003) and these cells maintain continuous open channels for regrowth of olfactory nerve fibers (Li et al., 2005a). Erythrocytes have been observed to traverse such channels all the way between the olfactory bulb and the mucosal lamina propria (Li et al., 2005a). A microscopical study applying IN-dextran molecules in the rat (Jansson and Bjork, 2002) showed clearly the transcellular uptake of the molecules through the epithelium followed by a fast transfer directly to the olfactory bulb via the connective tissue surrounding the nerve bundles. Within 2 min the dextran arrived at the olfactory bulb itself! These data fully supported the earlier findings of Sakane (Sakane et al., 1995). Paracellular uptake was not observed and considered unlikely. Intra-axonal transport of dextran was not observed either but some staining was observed in the Bowman ducts and glands. In the lymphoid tissue, underlying the epithelial layer, no staining could be detected (Jansson and Bjork, 2002).

To summarize the available evidence for 'open connections' between the cranial and nasal cavities, several potential routes have been described. Most studies focused at the 'brain to nose' direction as a release pathway for CSF-drainage but evidence that these connections are working in the opposite direction as well is

presently lacking. So, probably different parallel systems work side by side for 'draining the brain' and for 'accessing the brain'. Concerning direct transport pathways between nasal cavity and the central nervous system, there is agreement about the existence of extracellular pathways as a 'paracellular route' to reach the cranial cavity and the CSF (Charlton et al., 2008; Dhuria et al., 2010; Thorne et al., 2004).

Most recently, Neumann et al. (2013) reported the results of a microdialysis study in rats and mice and showed convincingly that IN-applied OT indeed reaches behaviorally relevant brain areas directly, without indications for the involvement of plasma or peripheral OT. For the final answers concerning the morphological and functional details an extensive series of physiological and ultrastructural studies will be required to elucidate further details.

For the present review we assume that 'direct-nose-brain-transport' occurs and in the next section we will focus on a small neuropeptide, oxytocin (OT) to see which brain areas and mechanisms are probably involved in the effects of intranasal administration of OT (IN-OT).

2. Intranasal administration of OT (IN-OT)

2.1. Introduction

About 230 papers applying IN-OT have appeared since the first report in 1958, by Newton and Egli (1958). Many early reports described the effects of IN-OT on inducing or sustaining labor (Cohen et al., 1962; DeVoe et al., 1967; Hendricks and Gabel, 1960; Hendricks and Pose, 1961; Hinde, 1963; Hoover, 1971; Laine, 1970; Stichbury, 1962; Suzumura et al., 1966) or lactation (Huntingford, 1961; Krupp et al., 1962; Luhman, 1963; Sandholm, 1968; Wenner, 1962). In later years the effects of IN-OT on obsessive-compulsive disorder (Ansseau et al., 1987; den Boer and Westenberg, 1992; Epperson et al., 1996), on post-traumatic stress symptoms (Haagsma et al., 2012; Olff, 2012; Pitman et al., 1993), on ejaculation latency (Burri et al., 2008; Ishak et al., 2008; Walch et al., 2001), on a sexually dimorphic spinal motor system (Lenz and Sengelaub, 2010) and possibly on obesity (Maejima et al., 2011) were studied as well. In the last decade the role of OT in social interactions, 'trust', 'mind-reading' and 'face-processing and -memory' has attracted most of the scientific and clinical attention (Baumgartner et al., 2008; Beetz et al., 2012; Di Simplicio et al., 2009; Ditzen et al., 2009; Domes et al., 2007b, 2010; Ebstein et al., 2009; Gouin et al., 2010; Guastella et al., 2008; Heinrichs et al., 2003; Hicks et al., 2012; Kosfeld et al., 2005; Meyer-Lindenberg, 2008; Nagasawa et al., 2012; Opar, 2008; Parker et al., 2005; Rimmele et al., 2009; Savaskan et al., 2008; Shamay-Tsoory et al., 2009; Smith et al., 2012; Theodoridou et al., 2009) leading to potential treatment of autistic symptoms (Domes et al., 2010; Meyer-Lindenberg, 2008; Meyer-Lindenberg et al., 2011; Opar, 2008). Quite recently, Neumann and Landgraf (2012) stressed the importance of the oxytocin-vasopressin-balance for social behavior.

OT is a nona-peptide, MW 1007 Da, isolated and characterized by (Du Vigneaud et al., 1953) and sequenced by the group of Archer (Michel et al., 1993). Its production occurs in the CNS in neurons mostly located in the paraventricular (PVN) and supraoptic (SON) hypothalamic nuclei, with some additional perivascular clusters in between. Inside the PVN, magnocellular and parvocellular subregions can be discerned containing different types of oxytocinergic neurons (Armstrong and Hatton, 2006; Armstrong et al., 1980, 2010; Buijs, 1978, 1990; Buijs et al., 1983; Carroll et al., 1968; Crowley and Armstrong, 1992; Sawchenko and Swanson, 1982; Sawchenko et al., 1984; Simmons and Swanson, 2009; Swanson and Claycomb, 1969; Swanson and McKellar, 1979). Concerning the effects of OT on peripheral organs as well as on the CNS, three different mechanisms have been described.

(1) The axons of the magnocellular neurons traverse the median eminence towards the posterior pituitary, where the terminals release their OT-contents directly into the peripheral blood circulation. This humoral mechanism may influence all receptive peripheral organs as well as all receptive parts of the CNS outside the BBB. More recent information has shown, however, that the magnocellular SON projects to a number of extrahypothalamic sites as well (Alonso et al., 1986) and that the magnocellular part of the PVN projects into the nucleus accumbens and other brain areas as well, using long varicose fibers (Ross et al., 2009a,b; Ross and Young, 2009). (2) The parvocellular oxytocinergic neurons, especially those in the paraventricular nucleus (PVN), do not participate in this peripheral release but take care of (part of) the neuronal connections of the PVN with several other parts of the CNS, including descending projections to the lower brainstem and all levels of the spinal cord in rat (Buijs, 1978; Buijs et al., 1983; Sawchenko et al., 1984; Simmons and Swanson, 2009; Swanson and McKellar, 1979) and mouse (Biag et al., 2012). This neuronal mechanism allows fast and specific messages towards circumscribed target-regions of the CNS. (3) Other neural release mechanisms are attracting attention since about a decade in addition to the 'regular' terminal and axonal release mechanism. Release of OT from soma and dendrites of neurons in the PVN and the SON has been studied in detail. Dendritic release of OT is regulated by specific mechanisms independently from the terminal (peripheral) release from SON (Landgraf and Neumann, 2004; Leng et al., 2008a; Leng and Ludwig, 2006; Ludwig, 1998; Ludwig and Leng, 2006; Waldherr and Neumann, 2007) and this dendritic release induces OT-release from neighboring dendrites as well, leading to a coordinated response of all OT-neurons in the activated nucleus (Moos and Richard, 1989; Morris and Ludwig, 2004; Yamashita et al., 1987). Additional excitatory mechanisms extend this activation to other hypothalamic OT neurons as well, bilaterally, most probably via a brainstem relay mechanism (Moos et al., 2004a,b) providing the 'OT-system' with a powerful release mechanism with special importance for the peripartum period (Neumann et al., 1996; Neumann, 2003). These mechanisms are extremely powerful since most of the OT content of the magnocellular neurons is located in their dendrites (Leng et al., 2005; Ludwig and Leng, 2006). Due to this coordinated dendritic release the extracellular levels of OT inside the PVN and/or the SON may increase to a thousand fold! Large amounts of this extracellular OT will reach the cerebrospinal fluid (CSF) either by intended release or by 'spilling over' of the huge ECF-concentrations alongside the CSF-compartment. The PVN borders the rostral tip of the third ventricle and its dendritically released OT may 'go with the flow' (Veening and Barendregt, 2010; Veening et al., 2010) of the CSF to arrive at caudal hypothalamic and brainstem destinations. The SON is located near the ventral surface of the hypothalamus and its contents may be released into the adjoining arachnoid space along the ventral surface of the brain.

Because transport via the ventricular CSF is relatively fast, it takes only 1 or 2 min from the lateral ventricles to reach the ventral medullar surface in rat or cat (Feldberg, 1976; Proescholdt et al., 2000) and because, as mentioned, half-life times in the CSF are considerably longer than in plasma (28 min versus 2 min!) and because numerous OT-receptive brain areas are bordering the ventricular system and arachnoid spaces (Campbell et al., 2009; Gimpl and Fahrenholz, 2001; Gimpl et al., 2008; Gould and Zingg, 2003; Schorscher-Petcu et al., 2009), we proposed that the CSF can be considered a 'message-carrier' for the endogenous OT-communication between PVN and SON and receptive target areas in the CNS (Veening and Barendregt, 2010; Veening et al., 2010). Such a diffuse way of brain communication has been coined 'Volume

Transmission', different from the well-known 'wiring transmission' and it plays an important role in the communication in the extracellular space including the CSF (Agnati et al., 1994, 1995, 2010; Agnati and Fuxe, 2000; Fuxe et al., 2007, 2010; Zoli et al., 1999). Details about such a role have been worked out before (Sewards and Sewards, 2003a,b) for the neuropeptides vasopressin and corticotrophin-releasing-factor and more recently for β-endorphin (Veening et al., 2012). Supporting evidence can be obtained from the numerous physiological and behavioural experiments with intracerebroventricular (icv) administration of OT showing that this route of administration generally requires much lower amounts of OT, while the effects were generally stronger and included effects that were not obtainable by peripheral administration (for a recent review: Veening et al., 2010). Neurons in the ventromedial hypothalamic nucleus, bordering the 3rd ventricle, were rapidly and strongly responsive to icv-administered OT (Leng et al., 2008b). Finally, it is good to keep in mind that CSF-levels of OT are different and independent and usually higher than plasma levels and that plasma-OT has virtually no access to the CSF-compartment because of the interposed blood-brain-barrier (BBB) (Amico et al., 1990; Ludwig and Leng, 2006; Mens et al., 1983).

Turning now to the fate of the OT administered intranasally, there are basically three possible functional pathways not necessarily mutually exclusive. The first is the vascular pathway, either directly from the nasal venules or indirectly via the lymphatic vessels descending through the cervical region and including specific transfer-mechanisms to the arterial vessels of the brain as discussed earlier. The second possibility has a neuronal character. If olfactory sensory neurons (OSN's) are responsive to OT, probably via their AVP1a receptors (Levasseur et al., 2004), their activity patterns may change leading to different neuronal activation patterns in the olfactory bulbs and succeeding 'brain stations'. The third possible 'pathway' consists of the numerous perineuronal spaces and paravascular routes, described earlier, by which OT may reach the CSF-filled subarachnoid space mainly at the level of the olfactory bulb but possibly at a trigeminal-brainstem level as well.

OT-effects along these pathways may be rather different. Via the 'vascular pathway', OT effects will be slow because of factors limiting the rate of access and peripheral levels will remain low (even in the case of venous-arterial transfer in the cavernous sinus); eventual peaks will have a short duration because of the short half-life-times of OT in the general circulation. In addition, brain effects via the vascular system will occur 'all over the brain' at about the same moment but the distribution via the CSF cannot be involved because of the BBB preventing the access.

Following the second 'pathway', neuronal access via the OSN's, effects on brain activity will be much more restricted and specific, limited as they are to the brain areas composing the main and accessory olfactory systems which have been described in detail (Shipley, 1985; Shipley and Ennis, 1996; Shipley et al., 2004).

If the third 'pathway' (perineuronal and perivascular spaces) forms the main access-route for OT, one may expect that the highest concentrations are observed in the rostral part of the cranial cavity, dorsal to the cribriform plate involving both the CSF and the rostral (olfactory) regions of the brain with the possibility of a second 'entrance' ventral to the brainstem along the trigeminal system. The relevant data from the literature will be discussed in relation to these possible 'pathways'.

A final point to be discussed here concerns the distinction between 'peripheral effects' and 'central effects'. Especially for OT it is appropriate to consider this distinction in some detail in view of the observed effects of the intranasal administration.

Several peripheral organs like heart, kidney and uterus, are sensitive for circulating OT because of the presence of OT-receptors. The receptor density is variable and can be up regulated considerably (12-fold) in the uterus at the end of gravity (Fuchs et al., 1984). Basal OT-levels are low and usually remain below 10 pg/ml in rat (Higuchi et al., 1986), sheep (Dawood et al., 1983) and man (Burri et al., 2008; Landgraf, 1985). Despite the gradual rise in OT-levels during pregnancy (sheep, Dawood et al., 1983), OT does not seem to be involved in the onset of parturition itself, since the steepest rise occurs only after vaginal extension in the expulsive phase (Higuchi et al., 1986; Landgraf et al., 1983). In the rat, peripheral OT-levels rise abruptly and steeply when suckling and milk ejection starts, followed by a rapid decline afterwards, as could be expected from the short peripheral half-life time of OT, in the order of 1 or 2 min (Higuchi et al., 1986; Mens et al., 1983; Robinson, 1983; Robinson and Jones, 1982). After parturition, however, the peripheral OT-decline is much slower (Higuchi et al., 1986) suggesting that a decline of peripheral levels of OT is not merely a passive matter of removal or proteolysis of circulating OT but includes the involvement central regulating mechanisms controlling the duration of the elevated levels of peripheral OT. These findings suggest that the flat but clearly elevated plasma OT-levels, extending over a period of more than an hour as observed in human males after a single intranasal administration of 65–100 μg OT (Burri et al., 2008; Landgraf, 1985), are most probably also the result of central mechanisms controlling the peripheral levels of OT. The observation that a 3–4 times lower dose of OT (25 μg) injected intramuscularly, results in 6–10 times higher peripheral levels whereas buccal administration was totally ineffective (Landgraf, 1985) supports the notion that the peripheral levels obtained after IN-OT are not simply reflecting its vascular uptake.

Very recently, Neumann et al. (2013) collected convincing evidence, in a microdialysis study on rats and mice, that IN-applied OT reaches distinct brain regions, like hippocampus and amygdala and they provided evidence that the rise in dialysate OT is almost entirely of central origin, without exclusion of the ventricular route.

In human studies, it has been shown that intranasally applied OT has potent effects on the amygdala and related brainstem regions (Baumgartner et al., 2008; Domes et al., 2007a; Kirsch et al., 2005; Meyer-Lindenberg, 2008) as well as on the sympathetic nervous system (Burri et al., 2008). The direct involvement of these brain areas in 'autonomic control' mechanisms implies that the effects of intranasally administered OT are by no means restricted to central effects but will result, 'indirectly' via these regulatory brain mechanisms, in a variety of peripheral effects as well. In that respect the peculiar findings obtained by the group of Nozdrachev (Kovalenko et al., 1995; Shtylik et al., 1995) need to be replicated. One of these articles in Russian reports in the English abstract: 'Following unilateral intranasal oxytocin administration, asymmetric alterations in some functional parameters of the adrenal glands, testis, lungs and heart, occurred. The lateralization of alterations was dependent on the side of oxytocin injection and the side of paired organ arrangement ….' (Shtylik et al., 1995). If such or similar findings can be replicated it would be fully clear and convincing that peripheral effects of intranasal oxytocin can not be the result of direct venous or lymphatic drainage of the nasal mucosa into the blood stream, because after passage of the heart the contents of the bloodstream do not contain any lateralized information any more. So, for the moment, despite the fact that IN-OT is reflected in human saliva (Weisman et al., 2012) and the numerous peripheral effects of 'central OT' (Borrow and Cameron, 2012), we consider, for the present discussion, all peripheral IN-OT effects as secondary to the induced changes in brain activity that include autonomic and endocrine mechanisms, via neuronal connections descending deeply into brainstem and spinal cord, possibly via lateralized pathways. These 'central effects' of IN-OT will therefore be the focus of the present review.

2.2. Entrance routes and distribution of IN-OT

The entrance routes of IN-OT have not been investigated so far and specific data are lacking. In a recent study, however, it was clearly shown in rats and mice that IN-applied OT reaches brain areas like hippocampus and amygdala (Neumann et al., 2013). OT is a nonapeptide with a molecular weight of 1007.19 g/mol or 1007 Da. A comparison with data obtained from other neuropeptides shows that its size is in the favored range of up to about 1000 Da, allowing efficient absorption (Costantino et al., 2007; Fisher et al., 1987; McMartin et al., 1987). Apart from its molecular size, however, many other factors determine the amount of OT becoming available to the brain after IN-administration, like lipophilicity and biochemical stability. (see for a review of all relevant physicochemical aspects Costantino et al., 2007).

Its relatively small size favors access to the brain via the 'direct transport pathways' as discussed earlier. Because the blood-brain-barrier is virtually closed for OT (Jones and Robinson, 1982; Mens et al., 1983) and because of its short half life time in the blood stream (Higuchi et al., 1986; Mens et al., 1983; Robinson, 1983; Robinson and Jones, 1982), it can be safely assumed that all OT, reaching and influencing the brain after intranasal administration, does arrive via the 'direct pathways'. In how far the olfactory access pathways are dominant over the trigeminal and other access routes remains to be investigated.

The time scale at which the IN-OT starts to affect brain activity and the local distribution over the brain after a few minutes, have not been investigated in detail so far. But in a recent dialysis study on rats and mice central OT levels were elevated after about 30 min (Neumann et al., 2013). Occasionally, in human studies, the behavioral effects of IN-OT were studied after about an hour (Burri et al., 2008). However, plasma levels of OT were elevated already within 20 min (Burri et al., 2008; Landgraf, 1985), whereas the central nervous effects of a neuropeptide of similar size (cholecystokinin, CCK-8, MW 1143) were most clearly obtained at 15–30 min after IN-administration (Pietrowsky et al., 2001). The finding that plasma OT-levels remain elevated for a long time (more than 80 min!) after a single intranasal administration (Burri et al., 2008; Landgraf, 1985) is rather surprising. In view of the short peripheral half-life values of OT, the sustained elevated levels can hardly be explained by continuous OT-uptake from the nasal membranes (Burri et al., 2008). Rather, they reflect a long-term peripheral release by activation of the OT neurons in the paraventricular and supraoptic hypothalamic nuclei induced by the intranasal administration of OT. Projections arising in the mitral cell layer of the olfactory bulb project directly to SON (Meddle et al., 2000; Smithson et al., 1989, 1992) and may be involved in such elevated levels for a longer period of time. Brainstem projections as well as paracrine mechanisms coordinating a bilateral response from SON and PVN (Belin et al., 1984; Bodineau et al., 2011; Moos et al., 2004b; Moos and Richard, 1989; Rossoni et al., 2008) may suffice for an elongated peripheral OT-response. Further investigations are necessary and currently available techniques provide ample opportunities to tackle the open questions in this field.

2.3. Time-scale and access speed of IN-OT

The data obtained by (Charlton et al., 2008; Thorne et al., 2004), as discussed below, show that IN-administration of radically different neuroactive substances was leading to very comparable results concerning the time-range of brain effects, starting at 1 and peaking between 15–30 min, and there is no reason to expect that the neuropeptide OT is behaving very differently. However, concerning the IN-effects of OT, several special OT-related aspects have to be considered because they are 'OT-specific' and not occurring after IN-administration of other substances except vasopressin. The following aspects may affect both the immediate effects of OT and the surprisingly long-term effects of IN-OT administration.

(1) The olfactory sensory neurons (OSN's) themselves are OT-receptive. OT exerts a massive stimulating effect on OSN's most probably via the V1a AVP receptor (Levasseur et al., 2004). Therefore, we assume that activity in the olfactory system will be increased immediately after IN-administration of OT starting in both main and the accessory olfactory bulbs.
(2) Given the favorable size of the OT molecule, its arrival at/around the olfactory bulb via the 'direct pathways' can be expected within a minute or two and this 'activation wave' would arrive at a perfect moment to increase and prolong the earlier, OSN-induced olfactory effects.
(3) OT molecules in the CSF surrounding the olfactory bulbs have 'free access' to the superficial and deeper layers of the bulbs because the CSF and the extracellular compartment of the brain are in open communication (Milhorat, 1975). While the BBB is virtually closed for OT (Mens et al., 1983), CSF-OT has free access to the bulbar extracellular space by diffusion or via paravascular spaces and possibly CSF-contacting neurons (see reviews by Veening and Barendregt, 2010; Veening et al., 2010). Therefore, OT arriving in the CSF surrounding the olfactory bulbs will contribute to their coordinated direct and indirect activation.
(4) Projections from the mitral cells of the main and accessory olfactory bulb reach the (dendrites of the) OT-neurons in the SON directly (Meddle et al., 2000; Smithson et al., 1989, 1992) in addition to the many possible indirect effects via the medial amygdala, the bed nucleus of the stria terminalis or the medial preoptic areas.
(5) Along the projections mentioned, olfactory stimulation induces activation of OT-neurons in the SON and these neurons may activate a larger population of OT-neurons in the SON via dendritic release mechanisms (Ludwig, 1998; Ludwig and Leng, 2006) or via the lower brainstem (Belin and Moos, 1986; Moos et al., 2004a,b) to include the contralateral SON and the PVN-OT-neurons as well (for a recent review: Veening et al., 2010).
(6) Interestingly, electrical stimulation of the PVN, elevating OT-levels in the CSF (Jones et al., 1983), as well as icv administration of OT have inhibitory effects on olfactory processing in the mitral cells of the bulb (Yu et al., 1996a,b). This inhibitory effect appears to be necessary for the behavioral switch occurring at the rapid onset of maternal behavior after parturition.
(7) OT, after arriving in the CSF around the olfactory bulb, will start spreading caudally via the CSF to 'cover' more caudal parts of the brain, as described for other substances (Charlton et al., 2008; Dhuria et al., 2010; Lochhead and Thorne, 2012; Thorne et al., 2008, 2004) implying that cortical and other OT-receptive areas will be affected at a later stage than the olfactory regions and by steadily decreasing gradients in OT-levels from rostral to caudal brain areas. Concentrations at the level of the cerebellum may still be considerable, however, as shown for the angiotensin-antagonist GR138950, where 'cerebellar levels' clearly surpassed the levels obtained after intravenous administration (Charlton et al., 2008).

Thorne et al. (2004) used a neuropeptide ([^{125}I]-IGF-I) with a MW about 7.5 times higher (7.65 kDa) than the MW of OT (1.007 kDa). IGF-I is different from OT, as IGF-I is passing the BBB much easier. However, highest peaks in the blood were reached about 6 h after intranasal administration, while highest brain levels were obtained within 30 min. In addition, consequences of intranasal administration were completely different from intravenous administration effects and the brain levels measured after IN-administration were about 100 times higher than after i.v. administration, virtually excluding the possibility that brain effects

were secondary to peripheral effects (Thorne et al., 2004). In their study a number of surprising, illuminating as well as puzzling findings were reported. Among them:

- Entrance of the cranial cavity occurred along two different cranial nerves: the olfactory nerve, innervating the olfactory part of the nasal cavity and the trigeminal nerve innervating also the respiratory part of the nasal epithelium.
- The olfactory entrance is the main route for the forebrain effects and the trigeminal entrance is mostly responsible for the brainstem and cerebellar effects.
- The levels of IGF-I in the CSF remained surprisingly low, at least at the level of the cisterna magna, but peak levels consistently preceded those in the bloodstream.
- Of the brain regions sampled, highest concentrations of radioactive IGF-I were observed in specific rostral brain regions (olfactory bulb, anterior olfactory nucleus, frontal pole and motor cortex), in the trigeminal nerve and in areas just below where the trigeminal nerve enters the brainstem (medulla and cervical spinal cord), with levels decreasing in the caudal direction from the olfactory bulb and in both directions from the caudal brainstem.

In a later study, Charlton et al. (2008) showed that elevated levels of GR138950, an angiotensin antagonist (MW 611) with low BBB permeability, were present within a minute after IN-administration in the olfactory bulbs as well as in the surrounding CSF. More posterior cerebral parts of the brain showed elevated levels progressively later after 5 or 10 min, while in the cerebellar tissue highest levels were reached after about 30 min. Apparently, the spreading of the intranasally applied substance occurred in a rostral to caudal direction and from the autoradiographs of the tissue sections authors concluded that the CSF in between and surrounding the olfactory bulbs, the cerebral hemispheres and the cerebellum was mainly responsible for this distribution pattern because increased CSF levels tended to precede the elevated brain tissue levels (Charlton et al., 2008). Their study provided no indications for possible other 'entrance-points', like the trigeminal system, from where spreading might have occurred or for the possible involvement of the intraventricular CSF. The CSF is flowing rapidly in a caudal direction and probably contains messages for distant brain areas (Veening and Barendregt, 2010).

Such data were, however, recently provided (Johnson et al., 2010). Low molecular weight drugs (lidocaine, 234 Da, and a dye (IRDye 800), 962 Da) were applied intranasally to rats. Their data show that for these substances:

- the trigeminal nerve is an important route of access, in addition to the olfactory entrance;
- not only the brain(stem) but also peripheral oral, dental, nasal and facial structures innervated by branches of the trigeminal nerve are targeted after IN-application;
- after reaching the olfactory bulbs in about 10 min and the frontal poles of the cortex in about 15 min, the drugs spread in a caudal direction; meanwhile, the substances arriving at the ventral surface of the brainstem via the trigeminal nerve start spreading in a rostral direction;
- generally, ventral brain structures near the CSF showed higher concentrations of the IN-applied drugs than more dorsal non-CSF-contacting brain structures;
- structures like olfactory bulbs, anterior olfactory nucleus, hypothalamus, medial and ventral cortical areas, ventral pons and the trigeminal nuclei in the brainstem showed the highest concentrations of the IN-applied drugs;
- the brain distribution and time patterns observed after IN-application were totally different from the patterns observed after intravenous application.

Other publications like a monkey study using a large neuropeptide (Interferon-β, 20 kDa MW) (Thorne et al., 2008) as well as other recent reviews (Dhuria et al., 2010; Lochhead and Thorne, 2012) support the findings obtained from the studies mentioned.

Taking together the events described in the preceding part of our review, we recognize a specific cascade of events potentially occurring after IN-administration of OT. All available evidence suggests that vasopressin works along similar mechanisms but to different effects via other brain areas (Ferris, 2008; Levasseur et al., 2004). Similar cascades of neural activation mechanisms may occur after IN-administration of other neuropeptides or neuroactive substances as well, but generally we have no clear idea yet about their features and neuronal distribution.

Such cascading of events after IN-administration of OT may explain why the first effects may appear very rapidly, in a matter of minutes to reach a possible summit after 15–30 min as described for other neuroactive substances, with OT-blood levels remaining elevated for more than an hour. The last, peripheral, effect probably bears no relationship any more with the tiny amount of OT delivered to the nasal epithelium but seems to be fully resulting from activated internal OT-control mechanisms. The occurrence of such a variety of successive 'internal' effects involving probably all brain circuits in which OT usually operates, implies that CSF- and peripheral levels of OT hardly reflect what is really 'going on' after IN-administration and that the evidence obtained by measuring them can be, at the most, circumstantial. Nevertheless, the available data will be discussed in the next part of the review, the more so as such parameters, 'central' vs peripheral', are almost the only available ones.

2.4. OT-levels after IN-OT in Cerebrospinal Fluid (CSF) and blood

After intranasal administration of 24 I.U of OT (~48 μg) blood levels of OT start rising from about 7.5 to about 15 pg/ml X 10^3 within less than 20 min in male volunteers (Burri et al., 2008). Similar effects were observed in a recent study by Gossen et al. (2012). Such long-term elevations do not occur in CSF-levels after an orgasm at least not at the lumbar level of the spinal cord (Kruger et al., 2006). As mentioned before, there are several reasons to assume that these elevated peripheral OT-levels are not simply and merely the result of intranasal uptake and release into the vascular system but more probably of long-term activation of the intrinsic OT-mechanisms controlling the peripheral levels. Combined information obtained from both the CSF- and the peripheral OT-levels is necessary to draw permanent conclusions, about the possibly cascading effects of IN-OT administration. Interestingly, Born et al. (2002) observed that most neuropeptides did not induce elevated peripheral levels after IN-administration, but peripheral level of AVP remained elevated for more than 80 min. This is quite remarkable for neuropeptides with such short peripheral half-lifes, virtually without access to the brain itself. Given the fact that the BBB blocks the entrance of peripheral OT into the brain and that even the altered stress responses, induced by IN-OT in monkeys, are not directly affecting the peripheral adrenals but probably reflecting a central nervous effect on the adrenals (Parker et al., 2005) it is clear that we have to look for other parameters than the peripheral levels of OT to understand the effects of IN-OT.

Apparently, we need information about the brain- and CSF levels of OT after IN-administration, and for OT this information was completely lacking, until a recent paper from Neumann et al., who showed in a microdialysis study on rats and mice, that both central and peripheral OT-levels are elevated within 30 min and they

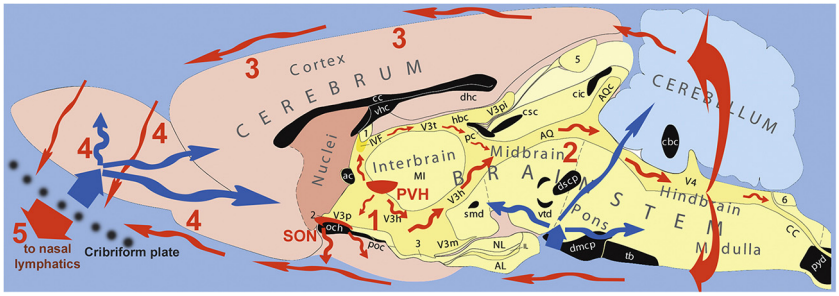

Fig. 1. The figure shows a midsagittal section of the rat brain (kindly provided by Prof. L.W.Swanson), with the fiber bundles, crossing the midline, indicated in black. The orange arrows indicate the flow of oxytocin (OT) from the natural hypothalamic sources: the paraventricular hypothalamic nucleus (PVN) and the supraoptic nucleus (SON). After (dendritic) release OT follows the flow of the cerebrospinal fluid (CSF) through the ventricular system and along the external surface of the brain. Eventually, more than 50% of the 'central' OT is leaving the cranial cavity along the olfactory fibers, through the cribriform plate into the nose lymphatics.
The blue arrows suggest the entrance of intranasally applied OT (in-OT), entering the cranial cavity and the CSF along the olfactory fibers but possibly also by following the trigeminal nerve. The scheme is based on assumptions obtained from other neuropeptide studies (like Thorne et al., 2004), since the entrance and distribution of in-OT itself has never been studied, yet. The arrows suggest a rostral to caudal distribution through the brain and CSF from the rostral entrance, supported by the OT entering the brainstem along the trigeminal fibers (but this entrance remains to be shown to be relevant for OT!). The more strongly 'inundated' parts of the brain appear to be the ventral parts and include the hypothalamus and amygdaloid regions. For further details, see text, and Veening et al. (2010) and Veening and Barendregt (2010). The numbers 1–5 indicate OT-receptive brain areas, containing OT-receptors.

argued convincingly that the central levels were not caused by the peripheral levels, but followed the rules of separate mechanisms (Neumann et al., 2013). Their findings support what is known for a variety of other substances, including several neuropeptides. From these data, two 'general rules' emerge: after IN-administration: (1) brain/CSF-levels tend to be higher than the peripheral levels, sometimes higher than the levels obtained after i.v.-administration; (2) peripheral levels rise more slowly and are generally preceded by steeper rising brain/CSF-levels. Such effects have been shown for neuropeptides and hormones like CCK-8 (Pietrowsky et al., 2001, 1996), vascular endothelial growth factor (VEGF) (Yang et al., 2009), MSH/ACTH (Born et al., 2002), insulin-like growth factor-1 (Thorne et al., 2004) and hexarelin (Yu and Kim, 2009), as well as for a variety of other substances like testosterone (Banks et al., 2009), estradiol (Ohman et al., 1980; Wang et al., 2006), ergoloid mesylate (Chen et al., 2008), gastrodin (Wang et al., 2007, 2008), cephalexin (Sakane et al., 1991), tetramethylpyrazine (Feng et al., 2009), and the angiotensin antagonist GR138950 (Charlton et al., 2008). This list can be extended easily but these suffice to illustrate that IN-administration of substances mostly results in faster peaks and/or higher brain concentrations than peripheral administration. Only in the case of vasopressin, peripheral levels tended to rise about as fast as the central levels and both levels showed long-term elevations (Born et al., 2002), remarkably similar to what has been observed in the peripheral OT-levels after IN-administration (Burri et al., 2008; Landgraf, 1985; Neumann et al., 2013). These findings suggest that the coordination between peripheral and central levels of vasopressin and OT is organized in a different way compared to other peptides/substances. There is no reason, however, to expect that OT behaves differently intracranially and we assume that after IN-OT-administration earlier and higher peaks of OT occur in the (rostral parts of) the brain, preceding the effects on peripheral levels of OT. However, experimental verification of these assumptions is absolutely necessary.

2.5. Conclusions

Based on evidence from the literature and recent findings (Neumann et al., 2013), we conclude that OT delivered intranasally gains access to rostral and possibly other brain areas via 'direct pathways' from the nasal epithelium that have not yet been fully defined but probably affect the 'intrinsic OT-sources', the magnocellular OT-neurons in the paraventricular and supraoptic hypothalamic nuclei as well. The finding that peripheral OT-levels remain elevated for more than an hour after intranasal administration strongly suggests the 'secondary' involvement of the magnocellular OT-system in addition to the central effects of IN-OT.

Our conclusions concerning the fate and effects of intranasally applied OT are shown in Fig. 1.

3. Behavioral and clinical effects of IN-OT

3.1. Behavioral effects of IN-OT

A search on PubMed shows that about 230 publications have appeared describing the effects of intranasally applied OT, about 50 of them appeared in 2011, and almost 80 in 2012. While induction of labor and breastfeeding were the main goal in the initial experiments, the focus of attention has shifted considerably over the last two decades.

3.1.1. Human behavioral and physiological effects

Limiting ourselves to the human studies over the last few years, the main outcomes concerned effects on fear and (social) anxiety (Fischer-Shofty et al., 2009; Guastella et al., 2009; Xu et al., 1996), trust, social stimuli and rejection (Alvares et al., 2010; Baumgartner et al., 2008; Norman et al., 2010), responsiveness during play (Naber et al., 2010), empathy (Bartz et al., 2010a; Hurlemann et al., 2010; Shamay-Tsoory et al., 2009; Tai et al., 1996), recognition of facial expressions and biological motion (Bartz et al., 2010b; Goldman et al., 2011; Perry et al., 2010), prosocial effects (Macdonald and Macdonald, 2010; Meyer-Lindenberg, 2008), stress (Ditzen et al., 2009; Nelson and Yu, 1996). In addition, memory systems (for faces) (Perry et al., 2010), effects on cardiac control (Norman et al., 2011; Zhu et al., 1996) and clinical syndromes like autism (Andari et al., 2010; Guastella et al., 2010), schizophrenia (Feifel et al., 2010; Yuan et al., 1996) and borderline disorder (Naber et al., 2010; Simeon et al., 2011) received extensive attention. Some studies reported the possible effects on peripheral organs (pregnancy rates and male sexual functions and orgasm) (Ishak et al., 2008; Ochsenkuhn et al., 2010; Walch et al., 2001) as well as stress reduction (Quirin et al., 2011). In a recent review, Neumann and Landgraf (2012) stressed the important aspects of the oxytocin-vasopressin-balance for many aspects of social behaviour.

Animal behavior. Despite the frequent application of other substances via the intranasal route in rats, the behavioral effects of IN-OT have been studied less extensively. In 2005, Parker et al. applied 50 μg OT intranasally in adult female squirrel monkeys to study its effects on the stress-induced activation of the

hypothalamic-pituitary-adrenal (HPA) axis (Parker et al., 2005). The anti-stress effects of IN-OT were reflected by lowered ACTH levels without affecting cortisol levels suggesting a central point of action. In more recent studies in marmoset monkeys, Smith et al. (2010) demonstrated that daily treatment with 50 μg for 30 days facilitated pair-bond formation and social relationships, while clear reinforcement effects were obtained in rhesus macaques (Chang et al., 2012). Quite recently it was shown that IN-applied OT reaches the amygdala in rats and mice, while the prosocial effects of OT were also observed in rats (Lukas et al., 2013; Neumann et al., 2013). Finally, the effects of chronic IN-OT were studied in adolescent male prairie voles (Bales et al., 2012). After an initial 'prosocial' effect, the long-term changes showed a deficit in partner preference and pair bonding, containing the warning that "Long-term developmental treatment with OT may show results different to those predicted by short-term studies" (Bales et al., 2012).

Generally, the number of IN-studies in rodents is very sparse but in mice the effects of chronic application of a neuroprotective octapeptide (NAP) have been studied. The animals showed a clear decrease in anxiety-like behavior, as well as a reduction in the accumulation of amyloid peptide in a mouse model of Alzheimer's disease (Alcalay et al., 2004; Matsuoka et al., 2007)

3.2. Clinical effects of IN-OT

3.2.1. 'Peripheral effects' of IN-OT

As mentioned above, the slow but sustained rise in peripheral OT-levels after intranasal application most probably reflects the superimposed effect of activation of the 'intrinsic' OT-system of the brain in addition to the IN-OT accessing the peripheral vascular system directly. We assume that the 'peripheral effects' of IN-OT reported in the earliest studies contained a strong 'central component', activating lactation and labor. Soon after the initial reports about the effects of IN-OT on lactation (Newton and Egli, 1958; Stern, 1961) the effects on labor were described (Borglin, 1962; Salvatore, 1963) and in the next 20 years many aspects of the labor-inducing effects of IN-OT were investigated (Andreasson et al., 1985; Hohmann et al., 1986; Hoover, 1971; Lundin et al., 1986), concurrent with the marketing of the intranasal OT-spray 'syntocinon' for the specific clinical indication of labor induction (Engstrom, 1958). Occasional recent reports about the effects of IN-OT on lactation concern the possible specific applications for mothers of preterm infants (Fewtrell et al., 2006) and for tetraplegic mothers (Cowley, 2005).

Only a few studies addressed the effects of IN-OT on male sexual functioning. Apart from a single case report describing positive effects in male anorgasmia (Ishak et al., 2008), other studies reported equivocal or no detectable effects on ejaculation time and seminal parameters in normal healthy man (Burri et al., 2008; Walch et al., 2001).

About 30 years after the first clinical reports of IN-OT effects on lactation and uterine contractions, attention shifted more towards the mental and psychic effects of IN-OT in both males and females. The first reports, about effects in obsessive-compulsive disorder (Ansseau et al., 1987; den Boer and Westenberg, 1992) were not especially promising but will be discussed in the next section.

3.2.2. 'Central effects' of IN-OT

Starting in the eighties, studies applying IN-OT focused on psychological/behavioral parameters like autism (Israel et al., 2008; Opar, 2008), face memory (Domes et al., 2010; Rimmele et al., 2009; Savaskan et al., 2008), face judgment (Domes et al., 2007a,b; Guastella et al., 2008; Theodoridou et al., 2009), social behavior, prosocial effects and trust (Baumgartner et al., 2008; Ebstein et al., 2009; Guastella et al., 2009; Kirsch et al., 2005; Kosfeld et al., 2005; Meyer-Lindenberg, 2008; Opar, 2008), emotion processing (Di Simplicio et al., 2009; Ditzen et al., 2009), stress-responsivity (Heinrichs et al., 2003; Meinlschmidt and Heim, 2007; Pitman et al., 1993) and other memory aspects (Heinrichs et al., 2004; Lukas et al., 2013).The main effects on these parameters can be summarized as 'prosocial' (Meyer-Lindenberg, 2008) and agree very well with data obtained in animals. The results of the three IN-OT experiments in monkeys in the literature (Chang et al., 2012; Parker et al., 2005; Smith et al., 2010) are completely in line with the human data (see Section 3.1). For additional animal experimental data we have to turn to experiments involving icv-administration of OT and such data support the prosocial function of OT as evidenced by numerous recent reviews (Adkins-Regan, 2009; Bora et al., 2009; Donaldson and Young, 2008; Insel, 1992; Insel et al., 2001; Lee et al., 2009; Lukas et al., 2011, 2013; McEwen, 2004; Neumann, 2008, 2009; Pfaus, 2009; Ross and Young, 2009; Sanchez-Andrade and Kendrick, 2009; Veenema and Neumann, 2008; Veening et al., 2010; Young et al., 2005, 2002; Young and Wang, 2004).

A simple 'positive prosocial' label for all effects of OT is too much of a simplification, however, since OT-effects appear to depend on early experiences and show sexual dimorphism (Carter et al., 2009; Domes et al., 2010; Yamasue et al., 2009).

In conclusion, the experimental and clinical effects of IN-OT are clear and all of them pointing in the same 'prosocial' direction in line with the evidence after icv-administration of OT in animals. We conclude that further investigations on the role of IN-OT are certainly worthwhile and one of the main questions to be addressed will necessarily be: which brain areas are OT-receptive and responsible for the observed OT-effects.

3.3. Distribution of OT-receptors in the brain

The distribution of OT-receptors (OTR) in the brain has been studied extensively (for a review, see Gimpl and Fahrenholz, 2001) with a variety of techniques, not only in the rat (Freund-Mercier et al., 1987; Tribollet et al., 1989, 1992b; Vaccari et al., 1998) but also in mouse (Gould and Zingg, 2003; Yoshida et al., 2009), guinea pig (Tribollet et al., 1992a), rabbit (Tribollet et al., 1992b), Merione (Rabhi et al., 1999), marmoset (Schorscher-Petcu et al., 2009) and human brain (Loup et al., 1991, 1989). Many additional papers are available wherein the presence of OTR in specific brain areas was studied in detail (Bale et al., 2001, 1995; Blanks et al., 2007; Blume et al., 2008; Ebner et al., 2005, 2000; Engelmann et al., 1998; Ingram and Moos, 1992; Knobloch et al., 2012; Neumann, 2008; Neumann et al., 2000a,b; Neumann and Landgraf, 2012; Viviani et al., 2011), mostly in combination with the use of OT-(ant)agonists or some kind of manipulation to induce a change in the local density of OTR, but discussing them would go far beyond the scope of the present review. From the papers mentioned above, the following four important notions can be derived:

- The diversity and variability in density of OTR is impressive, both between different brain areas in a single brain, as well as between brains of different species. The latter aspect implies that simple extrapolations of findings from one species to another are virtually impossible.
- The variability over time is also impressive, because desensitization processes and internalization of OTR may occur in a few minutes but similar rapid increases in OT-binding have been observed as well (Gimpl and Fahrenholz, 2001).
- The variability over time is region-specific as it has been shown that specific factors (castration or administration of steroids like estrogen, testosterone, progesterone and glucocorticoids) all have their own region-specific effect on the distribution of OTR and these effects may be even completely contrary in species like mouse and rat (for a review: Gimpl and Fahrenholz, 2001).

- In many brain areas a serious mismatch has been observed between the presence and abundance or the lack of OT-IR fibers and the local density of the OTR (Gimpl and Fahrenholz, 2001).

These notions together make it fully clear that a general discussion of the OTR that could be reached by IN-applied OT is not an appropriate approach because the behavioral effects are probably strongly dependent on the species studied as well as on the individual hormonal state at a given moment. Therefore, we may better focus first on the distribution patterns of OT entering the cranial cavity after intranasal application as well as on experimental findings showing effects IN-OT in specific brain areas. Since such studies have not been published yet for OT itself, we have to rely on other available studies showing detailed distribution patterns over time.

We conclude that, given the variety of substances applied leading to similar distribution and time patterns that IN-application of OT most probably influences:

- Rostral brain structures (olfactory structures, rostral cortical areas) within minutes.
- Ventrally located brain structures bordering the CSF are more strongly influenced than dorsally located brain structures distant from the CSF.
- Superficial ventral brainstem areas if OT appears to be transported along the trigeminal nerve as well.

If these assumptions about the OT-distribution turn out to be true, as remains to be shown, many behavior-relevant brain areas showing medium to high densities of OT receptors (Gimpl and Fahrenholz, 2001; Gould and Zingg, 2003; Vaccari et al., 1998) are directly accessible to IN-OT. To mention a few of the rostral, ventral and superficial brain regions involved: olfactory bulbs and anterior olfactory nuclei, piriform, periamygdaloid and entorhinal cortices, central and corticomedial amygdaloid nuclei, anterior cingulate cortex, ventral subiculum, hypothalamic nuclei, especially the ventral ones like supraoptic, arcuate and ventrolateral ventromedial nuclei, ventral tegmental and pontine nuclei, and possibly the trigeminal nuclei in the caudal brainstem. In how far some of the brain regions surrounding the ventricular system, like paraventricular and other hypothalamic nuclei, bed nucleus of the stria terminalis, nucleus accumbens, lateral septal and dorsal hippocampal regions, the periaqueductal gray, the raphe nuclei locus coeruleus and the solitary complex, are also directly accessible for the IN-applied OT, remains to be investigated. If not, one or more of the brain areas mentioned earlier, may influence the neural activity in the latter group of nuclei. The impressive effects of OT in the olfactory bulbs in the rat either by direct administration on maternal behavior (Yu et al., 1996a) or on social recognition memory after vaginocervical stimulation (Larrazolo-Lopez et al., 2008) show clearly how the olfactory bulbs are participating in extensive neural circuits, involved in the induction of major behavioral and physiological changes. It is tempting to consider the possibility that activation of the dendritic release mechanisms in the magnocellular OT-neurons of the paraventricular hypothalamic nucleus could provide a signal towards other brain regions surrounding the ventricular system (Veening et al., 2010). Some well-designed Fos-studies would certainly bring us further, at this point.

3.4. 'Mirror-neurons'

An intriguing group of neurons has been described as 'mirror neurons' (Rizzolatti and Craighero, 2004; Rizzolatti et al., 1996). Originally proposed as a mechanism that unifies action perception and action execution, located in a parieto-frontal mirror network (Rizzolatti and Craighero, 2004; Rizzolatti et al., 1996; Rizzolatti and Sinigaglia, 2010), the mirror system turned out to play a crucial role in understanding the intention of a motor act (Ortigue et al., 2010; Rizzolatti and Fabbri-Destro, 2010; Rizzolatti and Sinigaglia, 2010). For that reason, the mirror system is supposed to play a major role not only in social relations, language and music processing and also in autism as reviewed in numerous recent reviews (Bonaiuto and Arbib, 2010; Brang and Ramachandran, 2010; Craig, 2009; D'Ausilio, 2009; Enticott et al., 2010; Heyes, 2010; Newlin and Renton, 2010; Oberman et al., 2007; Perkins et al., 2010; Rizzolatti and Fabbri-Destro, 2010; Rizzolatti and Sinigaglia, 2010; Wan et al., 2010; Williams, 2008).

Interestingly, oxytocin is apparently linked to (part of) the mirror system. Electrophysiological studies in humans associated the suppression of EEG μ/α-bands with perception of biological movement execution as well as social stimuli (Cochin et al., 1999; Gastaut and Bert, 1954; Oberman et al., 2008) and it has been shown that IN-OT modulates this rhythm during perception of biologically relevant motions (Perry et al., 2010). The OT system may be seriously disturbed in autistic children (Green et al., 2001; Modahl et al., 1998) and shifting the balance between vasopressin and OT may restore the emotional balance (Neumann and Landgraf, 2012). Recently, it was also proposed that olfactory bulb dysgenesis could lead to a dysfunctioning mirror neuron system and dysregulation of autonomic functions as a neural basis for autism via the so-called 'emotional pathway' and that OT is seriously involved in the underlying neural mechanisms (Brang and Ramachandran, 2010).

Of course, many questions remain to be answered, especially about the possible OT-receptivity of (part of) the mirror neurons or the OT-receptive brain areas like the amygdala, that may have direct access to the mirror system. The pertinent relations between autism, mirror system and oxytocin are immediately obvious from the literature, but at the anatomical and physiological level many questions remain to be clarified.

3.5. Localization of brain effects of intranasally applied OT

3.5.1. Brain areas involved in the effects of OT

The starting point for the effects of intranasally applied OT can be localized in the olfactory system itself. The olfactory sensory neurons (OSN) themselves contain vasopressin-receptors, which are activated by OT as well via the V1a receptor (Levasseur et al., 2004) which implies that OSN-activity may be influenced directly upon IN-OT-administration. Consequently, the olfactory bulbs are necessarily and directly involved. Since the original studies of Kendrick and Keverne (Kendrick et al., 1988, 1991, 1997; Keverne and Kendrick, 1994) the studies of Yu et al. (1996a,b) and most recently of (Arakawa et al., 2010; Fang et al., 2008; Larrazolo-Lopez et al., 2008; Sanchez-Andrade and Kendrick, 2009; Wacker and Ludwig, 2011) it is obvious that the olfactory bulbs play a crucial role. While Yu et al. (1996b) found clear indications that transport via the CSF played a role in the effects of paraventricular hypothalamic OT, icv manipulations turned out to be much less effective than direct bulbar administration (Yu et al., 1996a). Inside the olfactory bulb, both mitral and granule cells appear to be involved in the induction of short- and long -term potentiation (Fang et al., 2008; Osako et al., 2000, 2001; Yu et al., 1996b). The mitral cells project directly to the supraoptic nucleus (Hatton and Yang, 1989, 1990; Meddle et al., 2007, 2000) in addition to the more extensively explored projections to anterior olfactory nucleus, piriform cortex and medial and cortical amygdaloid nucei (Ghosh et al., 2011; Kang et al., 2011a,b; Miyamichi et al., 2011; Nagayama et al., 2010; Shipley, 1985; Sosulski et al., 2011). Quite recently it was reported that the amygdaloid region of rats and mice clearly shows elevated levels of OT after IN-administration (Neumann et al., 2013). These areas have direct and reciprocal connections with hypothalamic brain areas like the medial preoptic nucleus (Coolen et al., 1997;

Usunoff et al., 2009; Veening and Coolen, 1998) or the principal nucleus of the bed nucleus of the stria terminalis (Gu et al., 2003) of which structure the projections cover many of brain structures related to various kinds of social behavior. Many of the brain areas controlling sexual behavior are directly involved in this set of projections (Coolen and Hull, 2004; Gu and Simerly, 1997; Hull, 2011; Hull et al., 2004; Northcutt and Lonstein, 2009; Olivier et al., 2007; Triemstra et al., 2005). Given that amygdaloid projections contact the ventral striatum, especially the accumbens nuclei, composing an essential part of the reward mechanisms (Ferguson et al., 2001; Ikemoto, 2007; Mucignat-Caretta, 2010; Novejarque et al., 2011) from where the cingulate and other parts of the frontal cortex are within immediate reach (Del Arco and Mora, 2008; Ishikawa et al., 2008; McGinty and Grace, 2008; Rigoard et al., 2011; Wang et al., 2011), it is clear that the olfactory pathways have fast access to numerous behavioral mechanisms, in a matter of seconds. In addition, it has been shown that oxytocin-dopamine interactions have a direct effect on maternal behavior in the rat (Shahrokh et al., 2010).

Ferguson et al. (2001) concluded that direct activation of the medial amygdala is necessary and sufficient for social recognition in the mouse; this conclusion can hardly be surprising given the excellent central position of the medial amydala in the networks involved.

In addition to some studies mentioned before (Meddle et al., 2000; Smithson et al., 1989, 1992) showing the existence of direct olfactory projections to the supraoptic nucleus, it is worthwhile to mention that amygdaloid projections to the paraventricular hypothalamic nucleus not only arise in the central amygdaloid nucleus (Gray et al., 1989; Marcilhac and Siaud, 1997) but, direct or indirect, also in the medial amygdaloid nucleus (Dayas et al., 1999; Saphier et al., 1988) and these relationships are apparently reciprocal (Krukoff et al., 1994). Elevated OT-levels in the amygdaloid region of rats and mice after IN-administration (Neumann et al., 2013) have direct access to a variety of brain mechanisms.

Considering the experimental literature, several of the brain areas mentioned were clearly reactive upon intranasal administration of OT, as we will see in the next part.

3.5.2. OT-receptors and changes in brain activity

Changes in brain activity after IN-OT have been reported many times. Wamboldt and Insel (1987) studied the effects of icv-OT on maternal behavior and demonstrated the functional connection of the olfactory and the OT-systems. In 2005, Parker et al. (2005) showed that the ACTH-depressing effects of IN-OT in monkeys affected brain regions without involving the adrenals directly. In the same year, Kirsch et al. demonstrated in humans for the first time that IN-OT modulates the neural circuitry for social cognition and fear. Their fMRI studies not only showed a depression of amygdaloid activation after fear-inducing visual stimuli but also a reduced coupling between amygdala and brainstem regions implicated in the autonomic and behavioral manifestations of fear. These effects were corroborated by Domes et al. (2007a), especially in the right amygdala of men with modulating effects on prefrontal and temporal cortical areas and in the brainstem. In a later study, however, Domes et al. (2010) reported that in women the BOLD-signal was enhanced in the left amygdala, the fusiform gyrus and the superior temporal gyrus in response to fearful faces and in the inferior frontal gyrus in response to angry and happy faces. They conclude that future studies should include both sexes to determine a possible sexual dimorphism in the neural effects of OT. A similar activation of the left fusiform gyrus was observed in a study relating genetic variations in the OT-system with autism (Sauer et al., 2012).

Gamer et al. (2010) showed that a differential pattern of amygdala activation occurs: a decrease in the lateral and dorsal regions of the anterior amygdala (after fearful faces) concurred with an increase in the posterior amygdala related to gazing shifts and an enhanced coupling to the superior colliculus.

Perry et al. (2010) showed that IN-OT had a significant suppressive effect on the low alpha/mu band (8–10 Hz) across the scalp, and related this modulation of EEG-rhythms to social tasks mediated by the mirror-neuron system.

Labuschagne et al. (2010) observed a bilateral amygdala activation after showing fearful faces and extended their observations in 2011 (Labuschagne et al., 2011) by showing that in generalized-social-anxiety-disorder (GSAD) patients the medial prefrontal cortex and the anterior cingulate cortex become seriously activated after showing sad faces and this activation was strongly reduced after IN-OT.

Also in 2011, Rilling et al. (2011) observed that not only the left amygdala increased activity after reciprocated cooperation and IN-OT but also the caudate nucleus. In addition the functional connectivity between amygdala and the anterior insula was enhanced. Finally, Strathearn (2011) stressed the role of the dopamine reward system in the effects of OT on maternal neglect and in line with these ideas Riem et al. (2012) showed that activation of the reward system by laughing infants reduced amygdala activation but enhanced functional connectivity between the amygdala and the orbitofrontal cortex, the anterior cingulate, the hippocampus, the precuneus, the supramarginal gyri and the middle temporal gyrus, after IN-OT. When confronted with a crying infant, however, amygdala activation was also reduced but now in combination with an increased activation of the insula and the inferior frontal gyrus pars triangularis (Riem et al., 2011).

The preceding overview clearly shows that the effects of IN-OT reach the amygdala and from there not only fear related connections project to the dorsal vagal complex and the PAG (Siegel et al., 1997; Veening et al., 1984; Viviani et al., 2011) but also to a wide array of other brain areas. Recently, Neumann et al. (2013) reported the results of a microdialysis study in rats and mice and showed clear temporary increases in OT-levels in brain areas like hippocampus and amygdala, in full support of many of the effects reported in the preceding section.

3.5.3. Direct and indirect influences of IN-OT

For the induction of IN-OT effects on brain activity, as described in the preceding section, various access routes are available, on one hand via OT-receptors, on the other hand via neuronal connections which are not necessarily oxytocinergic.

Concerning the location and distribution of the OT-receptors, extensive information is available for many species (see Section 3.3) including the human brain (Loup et al., 1989, 1991). While a direct projection has been described from the OT-neurons in the paraventricular hypothalamic nucleus to the olfactory bulb (Yu et al., 1996a,b) the density of the OT-innervation of the amygdala is relatively weak and was described recently in relation to fear responses (Knobloch et al., 2012) and the mismatch with the numerous amygdaloid OT-receptors can be bridged only by Volume-Transmission as shown by the experiments of Yu et al. (1996a,b) and as discussed by others (Herkenham, 1987; Leng et al., 2005; Ludwig and Leng, 2006; Veening et al., 2010). Interestingly, the plasticity of the oxytocin receptors is impressive as they are strongly influenced by estrogen-, corticosteroid- and cholesterol levels (Burger et al., 2000; Gimpl et al., 2000; Insel et al., 1992; Ivell et al., 2001; Liberzon and Young, 1997; McEwen, 1988; Mitchell and Schmid, 2001; Muth et al., 2011; Terenzi et al., 1999; Uchoa et al., 2009; Witt et al., 1991; Zingg et al., 1998) as well as cocaine and fluoxetine (Johns et al., 2004) but also by peripheral OT-levels around parturition (Meddle et al., 2007) in a region-specific way. Most importantly, all relevant brain areas mentioned are in the possession of the relevant receptors (Gimpl and Fahrenholz, 2001; Gould and Zingg, 2003).

In view of the fear-reducing effects of IN-OT, mentioned earlier, Viviani and Stoop (2008) showed that OT effects on GABA-ergic interneurons were inhibitory for vasopressin neurons located in another part of the central amydaloid nucleus. Such a mechanism would explain not only some of mutually inhibitory effects of both nonapeptides but also provide functionally differentiated exits of the CeA to affect specific distant brain regions (Viviani et al., 2011; Viviani and Stoop, 2008). Recently, much detailed information has become available about differential axonal projections from the main olfactory system of the mouse into the olfactory cortical areas suggesting a wider and more specific distribution of olfactory information than previously expected (Ghosh et al., 2011; Kang et al., 2011a,b; Miyamichi et al., 2011; Nagayama et al., 2010).

These references show that it is not useful to consider the direct effects of OT, by neural- or by volume-transmission and the indirect effects via non-OT connections as separate entities. Whatever the source may be, olfactory or not, activation of the medial and central amydaloid nuclei easily induces activation of the BNST, septal regions and medial preoptic areas (Coolen et al., 1997, 1998; Fernandez-Fewell and Meredith, 1998; Kelliher et al., 1999; Meredith, 1998; Robertson et al., 1991; Swann et al., 2001; Veening and Coolen, 1998; Veening et al., 2005) and in addition, the medial prefrontal cortex (Ninan, 2011) as well as the dopaminergic mesocorticolimbic reward system (Shahrokh et al., 2010).

4. Conclusions and perspectives

Considering all available evidence as discussed in the preceding sections, we conclude that the fear reducing effects of IN-OT are most convincing and certainly deserve further investigation. These effects have obvious consequences for affiliative behavior and social interactions including the memory aspects involved. We agree with Churchland and Winkielman (2012) that it is less appropriate to describe the effects in terms of an 'anti-autism-' or an 'anti-schizophrenia-' drug as this description is too limited to encompass the wide range of neural effects, potentially possible after activation of the olfactory connections in combination with the central and medial parts of the amygdaloid complex. As discussed, these brain areas have numerous entrances to a variety of forebrain and brainstem areas, and may even increase aggression under the proper circumstances (Hahn-Holbrook et al., 2011). Future connectivity studies will provide a wealth of additional information concerning the specific role of particular areas of the human brain under specific testing conditions.

Concerning potential animal experiments, a whole array of questions is waiting for answers and many of them can be approached with the presently available techniques. At the electron-microscopical level many questions are open concerning the character, the location and the cerebral and extracerebral spaces connecting the olfactory nasal and the olfactory brain regions. Not only these transport mechanisms need more attention but also the mechanisms involved in the further distribution of IN-applied-OT. The application of labeled OT may be necessary to study these mechanisms in more detail, and such studies have to start within the first minute after the IN-administration. For a better idea about the possible involvement of the CSF and/or the intercellular spaces or the distribution of IN-applied-OT, it may be useful to study larger animals like sheep as well, since such studies have provided unique information about the distribution of other neuroactive substances like GnRH and melatonin.

Finally, we need more information about possible 'cascading effects' of intranasally applied OT, since there are several indications that the peripheral release of OT gets stimulated as well, even over a considerable time-span, and this potential cascade of central IN-OT inducing peripheral release of OT as well, certainly deserves more attention in future human and animal studies, including measurement of OT-levels in blood and CSF over time after IN-OT administration.

We conclude that further studies of the effects of IN-OT are necessary, fascinating and important, not only as a mechanism to treat clinical symptoms, related to fear, anxiety, autism, affiliation and other socially disturbing factors, but also because it may provide new insights in the access roads into the brain as well as in additional distribution mechanisms inside the human and animal brain.

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