Review

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Intranasal Oxytocin: Myths and Delusions

Gareth Leng and Mike Ludwig

ABSTRACT

Despite widespread reports that intranasal application of oxytocin has a variety of behavioral effects, very little of the huge amounts applied intranasally appears to reach the cerebrospinal fluid. However, peripheral concentrations are increased to supraphysiologic levels, with likely effects on diverse targets including the gastrointestinal tract, heart, and reproductive tract. The wish to believe in the effectiveness of intranasal oxytocin appears to be widespread and needs to be guarded against with scepticism and rigor. Preregistering trials, declaring primary and secondary outcomes in advance, specifying the statistical methods to be applied, and making all data openly available should minimize problems of publication bias and questionable post hoc analyses. Effects of intranasal oxytocin also need proper dose-response studies, and such studies need to include control subjects for peripheral effects, by administering oxytocin peripherally and by blocking peripheral actions with antagonists. Reports in the literature of oxytocin measurements include many that have been made with discredited methodology. Claims that peripheral measurements of oxytocin reflect central release are questionable at best.

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More than 100 neuropeptides are expressed in different neuronal subpopulations. Neurotransmitters are packaged in abundant small vesicles targeted to nerve endings, whereas peptides are packaged in large vesicles that are relatively sparse and that can be released from all compartments of a neuron. These vesicles carry a large cargo (~85,000 molecules of oxytocin), and peptides act at receptors with nanomolar affinity (1). Often, receptors are densely expressed at sites innervated by a few fibers that contain the peptide ligand, indicating that neuropeptides are more like hormones than neurotransmitters, acting at sites distant from their point of release, with organizational and activational roles rather than roles in information processing per se (2).

Some neuropeptides have a startling ability to evoke particular behaviors. Central injections (i.c.v.) of oxytocin trigger satiety and enhance sexual behavior in animal models; in rats and sheep, oxytocin injections can trigger maternal behavior (3,4); in monogamous voles, oxytocin injections facilitate pair bonding (5); and oxytocin receptor–deficient mice show disturbances in social behavior. There has been a deluge of reports more recently that oxytocin affects social behavior in humans when delivered as a nasal spray and in some studies when delivered peripherally (i.v.) (6). Such effects have several possible explanations. Oxytocin might enter the central nervous system, mimicking "neurohormonal" oxytocin release (2), or might act peripherally to affect behavior indirectly, via either oxytocin receptors or vasopressin receptors activated at high concentrations of oxytocin. Other possibilities are that reported effects reflect methodologic weaknesses and post hoc interpretation of outcomes with minimal statistical rigor.

OXYTOCIN AND THE BLOOD-BRAIN BARRIER

Most of the oxytocin in the body is stored in the posterior pituitary, which, in the adult rat, contains .5–1 μg oxytocin and similar amounts of vasopressin. This gland contains the nerve endings of magnocellular neurons whose cell bodies lie in the hypothalamus, but it lies outside the blood-brain barrier, so peptide released from these endings readily enters the blood. The rat pituitary contains enough vasopressin to maintain the normal plasma concentration of 1 pg/mL for 30 days and a concentration of 10 pg/mL, as seen during water deprivation, for 3 days (1).

There is no barrier to the passage of peptides between the blood and interstitial fluid of the body, so the distribution volume for oxytocin is much larger than the plasma volume (7). Oxytocin is stable in plasma (except in pregnancy, when oxytocinase is abundant) and is cleared from the blood via the kidneys and liver. In the rat, at intravenous doses of up to 500 ng/kg, oxytocin disappears from the blood with a half-life of 3–8 minutes (8). The half-life in cerebrospinal fluid (CSF) is longer: 28 minutes in the guinea pig (9) and 19 minutes in the rat (10). Oxytocin is thought to be cleared from CSF by a combination of flow into the subarachnoid space (11) and active transport into blood (12).

In humans, the pituitary oxytocin content (estimated by bioassay) is ~14 IU (28 μg) (13). Circulating concentrations are (as in the rat) ~1–10 pg/mL, and the pharmacokinetics after intravenous injection fit a two-compartment model, with a distribution volume of ~33 L, a distribution half-life of ~3 minutes, and an elimination half-life of ~20 minutes (14). As in the rat, ~1% of oxytocin is excreted in urine (15).

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After entering the blood, oxytocin rapidly penetrates extravascular fluid, but it does not cross the blood-brain barrier in appreciable amounts. In an early study, Ermisch *et al*. (16) gave rats intracarotid injections of radiolabeled oxytocin. Brain areas without an effective blood-brain barrier extracted up to 30-fold more peptide than other brain regions, but oxytocin failed to penetrate deeper into the brain. Brain areas that lack a blood-brain barrier are encapsulated by glial and endothelial cells that form tight junctions, preventing passage of peptides to and from deeper brain regions.

The effectiveness of the blood-brain barrier for oxytocin was measured by Mens *et al*. (10), who injected 5 μg subcutaneously in rats, increasing plasma concentrations 500-fold to ~38,600 pg/mL. Increases in CSF were modest; concentrations increased from ~40 pg/mL to ~150 pg/mL. The authors calculated that just .002% of the injected oxytocin had reached the central nervous system after 10 minutes, when CSF concentrations were maximal.

OXYTOCIN PENETRATION OF THE BRAIN AFTER INTRANASAL ADMINISTRATION

Two routes have been proposed for the passage of peptides from nose to brain. The first postulates internalization of peptide into olfactory or trigeminal neurons, followed by axonal transport and exocytosis. There is doubt about whether peptides survive internalization, and Born *et al*. (17) dismissed this as requiring hours for substances to reach the brain by axonal transport. Oxytocin might pass through intercellular clefts into the subarachnoid space, but transport across the arachnoid membrane is not an important route for the entry of solutes into brain (18). The arachnoid is a multilayered epithelium with tight junctions between cells of the inner layer that form an effective seal; valve-like villi project into the sagittal sinus through the dura mater and allow CSF movement only from the brain to blood. However, if vast amounts of peptide accumulate in the subarachnoid space, the concentration difference across the blood-brain barrier might support nonspecific passage. The slow disappearance of oxytocin from blood after intranasal application suggests that large amounts reach an extravascular pool from which it slowly leaches into the circulation.

Ang and Jenkins (19) studied the brain penetration of radiolabeled vasopressin given intravenously and measured how much label was still associated with intact peptide. Vasopressin, similar to oxytocin, is a nonapeptide with a sulfur bridge, differing in just two amino acids, and has similar bioavailability. Plasma vasopressin disappeared with the expected bi-exponential decay, whereas CSF levels of the label were maximal after 50 minutes; this peak was <1% of the peak in plasma, and none of the label in CSF was associated with intact peptide. The investigators also gave labeled vasopressin intranasally, sampling CSF and plasma 40 minutes later. The concentration of label in CSF was ~5% of that in plasma, but although 16.5% of the label in plasma was associated with intact peptide, none of the label recovered from CSF was.

Since then, six studies have measured CSF levels of oxytocin or vasopressin following intranasal application. After giving 40 IU (80 μg) to human subjects, Born *et al.* (17) reported CSF levels increased within 10 minutes from ~5 to ~10 pg/mL, increasing to ~20 pg/mL at 60 minutes. They administered as a bolus more than twice the pituitary vasopressin content, justifying this dose on the basis that most probably passes through the nose without being absorbed. Estimating the CSF volume as 300 mL, it seems that ~4.5 ng of vasopressin reached the CSF: .005% of the given dose—assuming that the increase was due to administered peptide and not endogenous release triggered indirectly.

Striepens *et al*. (20) measured CSF oxytocin in 11 patients given 24 IU oxytocin intranasally. Although Born *et al*. (17) saw an increase after 10 minutes (albeit with vasopressin, at a larger dose), Striepens *et al.* saw no increase at 45 minutes or 60 minutes. However, three patients sampled at 75 minutes had CSF levels 64% higher than control subjects (at ~30 pg/mL). In the same month, these authors submitted an article on functional magnetic resonance imaging changes in subjects tested 30 minutes after intranasal administration of oxytocin (21). The article does not cite the CSF data or the fact that the functional magnetic resonance imaging measurements were made at times when CSF oxytocin was unchanged.

Neumann *et al*. (22) gave 20 μg of oxytocin intranasally to rats (20 times the pituitary content) and found no change in CSF oxytocin after 45 minutes. However, they found a doubling of oxytocin levels in microdialysates of brain regions collected at 30–60 minutes, correlated with a fourfold increase in plasma. Intracranial microdialysis inevitably ruptures blood vessels around the probe, so these measurements might reflect local passage into the brain from damaged vessels.

Dal Monte *et al*. (23) gave 48 IU oxytocin (~10 μg/kg body weight) intranasally to macaques using either a spray or a nebulizer. The CSF oxytocin levels were increased from ~35 to ~90 pg/mL after 40 minutes. On the (very) conservative assumption that the CSF/extracellular fluid volume in the macaque is 40 mL, the additional content at this time is 2.2 ng—.002% of the administered dose.

Chang *et al*. (24) gave 25 IU oxytocin to two macaques and reported an increase in CSF from ~20 to ~50 pg/mL at 35 minutes. In a larger study, Modi *et al*. (25) gave 24 IU oxytocin (~5 μg/kg body weight) to macaques by spray or aerosol; only the aerosol produced a significant increase in CSF (from ~20 to ~60 pg/mL). Again assuming a CSF volume of 40 mL, the additional content at this time is 1.6 ng—.003% of the administered dose. Spray and aerosol increased plasma oxytocin levels. Intravenous administration of the same dose increased plasma levels to ~60,000 pg/mL with no increase in CSF.

All seven studies administered enormous amounts of peptide intranasally—in every case more than the pituitary content as a bolus—yet found only modest increases in CSF; two studies found no increase. At most, .005% of intranasally injected oxytocin reaches the CSF within 1 hour. Intranasal application achieves higher concentrations of peptide in blood than in CSF, and as basal concentrations in plasma are lower than in CSF, the proportional change in blood is much greater.

HOW MUCH OXYTOCIN MUST ENTER THE BRAIN FOR A BEHAVIORAL EFFECT?

Although intranasal application seems inefficient, doses of oxytocin that have become conventional in human studies all

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