

Oxytocin intranasal administration as a new hope for hypogonadotropic hypogonadism patients



Mohammad Saied Salehi^{a,*}, Sareh Pandamooz^b, Homayoun Khazali^a

^a Department of Physiology, Faculty of Biological Sciences and Technology, Shahid Beheshti University, Tehran, Iran

^b Neuroscience Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

A B S T R A C T

Hypogonadotropic hypogonadism (HH) is a form of hypogonadism which also known as secondary or central hypogonadism. Congenital HH can occur due to defect in gonadotropin releasing hormone (GnRH) neurons, upstream regulators of GnRH neurons or pituitary gonadotropic cells. Testosterone or gonadotropins therapy are widely used to treat HH patients, however both have undesirable effects and GnRH treatment for HH patients is time and cost consuming. Direct delivery of therapeutics to the brain via the nasal route is located in the center of attention during the last decade and trial application of intranasal oxytocin as a method of enhancing social interactions are reported. It has been delineated that oxytocin stimulates GnRH release from the rat hypothalamic explants and intranasal applied oxytocin up-regulates GnRH expression in the male rat hypothalamus. Therefore application of intranasal oxytocin might be a new strategy to cure HH patients.

Introduction

Hypogonadotropic hypogonadism (HH) is a form of hypogonadism which also known as secondary or central hypogonadism. In male patients older than 14 years of age, HH is diagnosed with low testosterone level (less than 100 ng/dl) which is accompanied with low gonadotropins level [1]. The prevalence of HH has been estimated to range from 1:10,000 to 1:86,000 individuals [2]. HH may be due to congenital and/or acquired defects. Congenital HH can occur due to defects in gonadotropin releasing hormone (GnRH) neurons, upstream regulators of GnRH neurons or pituitary gonadotropic cells. Acquired defects can arise from structural defects (such as destruction of GnRH neurons by tumors) or reversible causes (including acute or chronic systemic illnesses). Decreased testicular volume, reduced libido, regression of secondary sexual characteristics and decreased spontaneous erections are more specific symptoms of HH [3].

Testosterone or gonadotropins therapy are widely used to treat HH patients, however they have undesirable effects. For instance administration of testosterone, while elevates the circulating androgens, suppresses gonadotropins secretion from the pituitary. In addition, exogenous testosterone can potentially increase the risk of prostate disease [4] and develop acne and oiliness of skin because of the androgenic effects on sebaceous gland [3]. Gynaecomastia occurs in up to a third of patients on gonadotropins treatment [5]. Pulsatile GnRH therapy is a programmable portable infusion pump which provide pulses of

subcutaneous GnRH into the abdominal wall. It has been reported that GnRH treatment leads to a higher testicular volume and a more rapid initiation of spermatogenesis compared with gonadotropin therapy [5,6]. Also Delemarre-van de Waal [7] reported that pulsatile GnRH can be used to induce puberty and fertility in adolescents HH patients and she concluded that in the congenital form of HH, GnRH therapy is the most adequate and successful treatment to initiate testicular development. However, GnRH therapy is available in few specialized centers and the costs of the delivery equipment and drug exceed 6000\$ per year! [8].

Oxytocin is a peptide hormone and neuropeptide which is synthesized by magnocellular neurons in the supraoptic and paraventricular (PVN) nuclei and stored at the axon terminals in the posterior pituitary. Oxytocin is also produced in parvocellular neurones of the PVN and its projections widely distributed throughout the brain [9]. Several lines of evidence have shown that oxytocin is involved in regulation of hypothalamic-pituitary-gonadal axis by affecting GnRH neurons. Oxytocin stimulates GnRH release from the rat hypothalamic explants [10] and central injection of oxytocin antisera completely abolished the pre-ovulatory luteinizing hormone (LH) surge in the rat [11]. In addition, about 10 percent of GnRH neurons in the rat medial preoptic area (mPOA) express oxytocin receptor and oxytocin fibers are located in the vicinity of these GnRH neurons [12].

Direct delivery of therapeutics to the brain via the nasal route is located in the center of attention during the last decade. Trial

* Corresponding author at: Department of Physiology, Faculty of Biological Sciences and Technology, Shahid Beheshti University Box 1983969411, Tehran, Iran.
E-mail address: ms_salehi@sbu.ac.ir (M.S. Salehi).

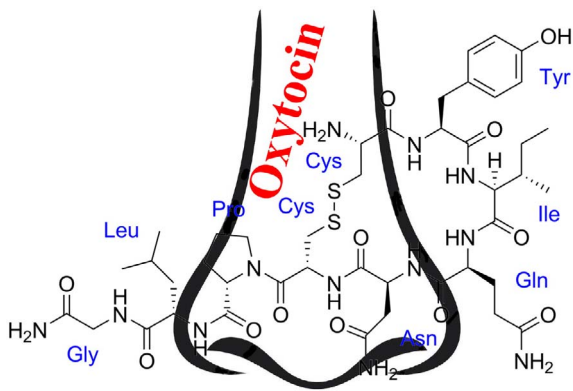


Fig. 1.

application of intranasal oxytocin as a method of enhancing social interaction in humans with social anxiety, autism, schizophrenia and borderline disorder to improve sociability and communication has been widely reported [13]. Since intranasal applied oxytocin reaches the brain [14] and it can affect neural networks upstream of GnRH neurons [15] it may influence various neurons in the central nervous system to help HH patients.

The hypothesis

Intranasal administration of oxytocin activates GnRH neurons which in turn stimulates gonadotropic axis by induction of synthesis and secretion of gonadotropins as well as gonadal testosterone. Therefore intranasal applied oxytocin might be a new strategy to cure HH patients.

Evaluation of the hypothesis

Recently we have demonstrated that intranasal administration of oxytocin for 10 continuous days could elevate hypothalamic GnRH expression by around 2 folds in healthy male rats [15]. Since GnRH treatment for HH patients is time and cost consuming, oxytocin treatment via the nasal route to induce GnRH expression might be very valuable. Intranasal applied oxytocin reaches the brain through several possible pathways such as vascular pathway, neuronal access via olfactory sensory neurons and perineuronal spaces and also paravascular routes [13,14]. It has been proposed that intranasal applied oxytocin through mitral cell layer of the olfactory bulb activates oxytocin neurons in the PVN and supraoptic hypothalamic nuclei which subsequently can impose long-term effects of oxytocin [13].

In rodents the great majority of GnRH cell bodies are located around the rostral POA; however small numbers of GnRH cells exist further caudal in the mediobasal hypothalamus (MBH). Although less than 10% of GnRH neurons are sufficient for GnRH secretion in pulsatile manner, it is unclear which of them are involved in generating pulses [16]. It has been proposed that oxytocin stimulates GnRH neurons from hypothalamus explant *in vitro* by releasing nitric oxide through activation of oxytocin receptor and nitric oxide synthase mediated mechanisms [17,18]. Furthermore, non-GnRH cells which express oxytocin receptor are detected in the proximity of GnRH neurons and raises the possibility that the effects of oxytocin on GnRH neurons can be either direct and/or indirect via upstream oxytocin-sensitive regulators of GnRH cells [12].

Although, it seems unlikely that this strategy can be useful for patients with defects in GnRH neurons, GnRH receptor or pituitary problems, it may shed light into the therapeutic strategies for treatment of HH patients with disorders of upstream regulators of GnRH neurons. In this regard, it has been reported that deletions and inactivating mutations in kisspeptin [19,20] or neurokinin B [21] signaling lead to HH.

Therefore, this hypothesis can be evaluated in kisspeptin or neurokinin B knockout mice to open new perspectives for therapeutic approaches based on this concept. Since pulsatile GnRH therapy was more effective in the congenital form of hypogonadotropic hypogonadism rather than acquired HH [7], this newly introduced hypothesis might be also more efficient in congenital HH. Furthermore, another possible condition that may be useful for testing this hypothesis is the serial measurement of circulating luteinizing hormone (as an indicator of GnRH release) following intranasal application of oxytocin to ensure that GnRH release is induced. In addition, defining the testicular volume and presence of spermatozoa in the semen/urine following oxytocin treatment in HH to evaluate this hypothesis (Fig. 1)

Conflict of interest statement

The authors declare that there is no conflict of interest regarding the publication of this paper.

References

- [1] Layman LC. Hypogonadotropic hypogonadism. *Endocrinol Metab Clin North Am* 2007;36(2):283–96.
- [2] Fraietta R, Zylberstein DS, Esteves SC. Hypogonadotropic hypogonadism revisited. *Clinics* 2013;68(Suppl. 1):81–8.
- [3] Surampudi P, Swerdloff RS, Wang C. An update on male hypogonadism therapy. *Expert Opin Pharmacother* 2014;15(9):1247–64.
- [4] Guay AT, Bansal S, Heatley GJ. Effect of raising endogenous testosterone levels in impotent men with secondary hypogonadism: double blind placebo-controlled trial with clomiphene citrate. *J Clin Endocrinol Metab* 1995;80(12):3546–52.
- [5] Schopohl J, Mehlretter G, von Zumbusch R, Eversmann T, von Werder K. Comparison of gonadotropin-releasing hormone and gonadotropin therapy in male patients with idiopathic hypothalamic hypogonadism. *Fertil Steril* 1991;56(6):1143–50.
- [6] Schopohl J. Pulsatile gonadotrophin releasing hormone versus gonadotrophin treatment of hypothalamic hypogonadism in males. *Hum Reprod* 1993;8(Suppl. 2):175–9.
- [7] Delemarre-van de Waal HA. Application of gonadotropin releasing hormone in hypogonadotropic hypogonadism—diagnostic and therapeutic aspects. *Eur J Endocrinol* 2004;151(Suppl. 3):U89–94.
- [8] Han T, Bouloux P. What is the optimal therapy for young males with hypogonadotropic hypogonadism? *Clin Endocrinol (Oxf)* 2010;72(6):731–7.
- [9] Burbach JPH, Luckman SM, Murphy D, Gainer H. Gene regulation in the magnocellular hypothalamo-neurohypophysial system. *Physiol Rev* 2001;81(3):1197–267.
- [10] Selvaie D, Johnston CA. Central stimulatory influence of oxytocin on preovulatory gonadotropin-releasing hormone requires more than the median eminence. *Neuroendocrinology* 2001;74(2):129–34.
- [11] Johnston CA, Lopez F, Samson WK, Negro-Vilar A. Physiologically important role for central oxytocin in the preovulatory release of luteinizing hormone. *Neurosci Lett* 1990;120(2):256–8.
- [12] Caligioni C, Oliver C, Jamur M, Franci C. Presence of oxytocin receptors in the gonadotrophin-releasing hormone (GnRH) neurones in female rats: a possible direct action of oxytocin on GnRH neurones. *J Neuroendocrinol* 2007;19(6):439–48.
- [13] Veening JG, Olivier B. Intranasal administration of oxytocin: behavioral and clinical effects, a review. *Neurosci Biobehav Rev* 2013;37(8):1445–65.
- [14] Neumann ID, Maloumy R, Beiderbeck DI, Lukas M, Landgraf R. Increased brain and plasma oxytocin after nasal and peripheral administration in rats and mice. *Psychoneuroendocrinology* 2013;38(10):1985–93.
- [15] Salehi MS, Khazali H, Mahmoudi F, Janahmadi M. Oxytocin intranasal administration affects neural networks upstream of GnRH neurons. *J Mol Neurosci* 2017;62:356–62.
- [16] Herbison AE. Physiology of the adult gonadotropin-releasing hormone neuronal network. In: Plant TM, Zeleznik AJ, editors. *Knobil and Neill's physiology of reproduction*. 4th ed. San Diego: Academic Press; 2015. p. 399–467.
- [17] Rettori V, Canteros G, Renoso R, Gimeno M, McCann S. Oxytocin stimulates the release of luteinizing hormone-releasing hormone from medial basal hypothalamic explants by releasing nitric oxide. *Proc Natl Acad Sci USA* 1997;94(6):2741–4.
- [18] Selvaie D, Johnston C. Interaction between norepinephrine, oxytocin, and nitric oxide in the stimulation of gonadotropin-releasing hormone release from preovulatory rat basal hypothalamus explants. *J Neuroendocrinol* 2004;16(10):819–24.
- [19] de Roux N, Genin E, Carel J-C, Matsuda F, Chaussain J-L, Milgrom E. Hypogonadotropic hypogonadism due to loss of function of the Kiss1-derived peptide receptor GPR54. *Proc Natl Acad Sci USA* 2003;100(19):10972–6.
- [20] de Tassigny XdA, Fagg LA, Dixon JP, Day K, Leitch HG, Hendrick AG, et al. Hypogonadotropic hypogonadism in mice lacking a functional Kiss1 gene. *Proc Natl Acad Sci USA* 2007;104(25):10714–9.
- [21] Topaloglu AK, Reimann F, Guclu M, Yalin AS, Kotan LD, Porter KM, et al. TAC3 and TACR3 mutations in familial hypogonadotropic hypogonadism reveal a key role for Neurokinin B in the central control of reproduction. *Nat Genet* 2009;41(3):354–8.