Oxytocin - A key to aetiology and treatment for Autism Spectrum Disorder

Rong Zhang [a,b,c,d,e]*

[a]Department of Neurobiology, School of Basic Medical Sciences, Peking University, Beijing, China
[b]Neuroscience Research Institute, Peking University, Beijing, China
[c]Key Laboratory for Neuroscience, Ministry of Education/National Health and Family Planning Commission, Peking University, Beijing, China
[d]Department of Integration of Chinese and Western Medicine, School of Basic Medical Sciences, Peking University, Beijing, China
[e]Autism Research Center, Peking University Health Science Center, Beijing, China

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The finding that the hypothalamic neuropeptide oxytocin (OXT) plays a key role in social cognition and behavior is one of the most significant discoveries in neuroscience. Since 1987, when work by Keith Kendrick in Cambridge firstly demonstrated that OXT played a central role in both maternal behavior and mother-infant bonds in sheep,[1] it has subsequently been reported to be deeply involved in enhancing socially relevant recognition, cognition, memory, reward, empathy, co-operation and attachment behaviors. Autism spectrum disorder (ASD) is a developmental disorder characterized by deficits in social interaction and communication as well as in restricted and repetitive behaviors and atypical sensory responses, and OXT is increasingly proposed as a key factor in ASD aetiology and a promising potential treatment. ASD is primarily a genetic disorder and it is known that miR-6126, which targets genes enriched in the OXT signaling pathway, is downregulated and that variants of OXT receptor (OXTR) are associated with ASD, such as rs7632287, rs237887, rs2268491, and rs2254298. Other OXTR variants, like rs2254298 and rs53576, may also modulate the efficacy of intranasal oxytocin in facilitating some aspects of social cognition processing relevant to ASD symptoms. However, there are several unsolved mysteries in this field. For example, why do autism animal models generated by targeting some other genes also show dysfunction in the OXT system even though mutations in OXT or OXTR themselves have a relatively-weak association with these genes. Although a meta-analysis has reported that peripheral OXT concentrations tend to be lower in autistic children,[2] findings concerning the efficacy of OXT therapy in ASD were inconsistent.[3,4] The article "Integrative Analysis Prioritized Oxytocin-related Biomarkers Associated with the Aetiology of Autism Spectrum Disorder"[5] in recent issue of *eBioMedicine* tries to answer the aforementioned question and allows us to rethink OXT-related translational medicine.

In this paper, 963 oxytocin-related genes (OTRGs) were included and 208 of them were defined as core OTGRs, carried by ASD probands as a higher coding de novo mutations (DNM) burden than the controls, especially loss-of-function (Lof) DNMs. The authors found: (1) of the de novo copy number variations (*dn*CNVs) in ASD probands, 28.98% were associated with OTRGs, and the genetic contribution of OTRGs was significantly associated with ASD aetiology in the order of *dn*CNVs> *inherited* CNVs (*ih*CNVs)>DNMs at the individual level; (2) the OTRG-associated *dn*CNV burdens were significantly higher in ASD probands with female gender and non-verbal intelligence quotient (NVIQ) ≤50. (3) 93.33% (28/30) of high- and 85.92% (122/142) of low positively contributed OTRGs (PC-OTRGs) involved in at least one of the four enriched pathways, namely "OXT signaling pathway", "GPCR ligand binding", "MAPK signaling pathway" and "signaling by receptor tyrosine kinases". Among the 30 high PC-OTRGs, *MAPK3* was the most prominent gene, followed by *SHANK3, NLGN4X* and *NLGN3*; (4) based on rare disrupted variations, 458 potential OXT-related molecular biomarkers were identified, including 172 PC-OTRGs and 286 ASD core genes connected to them, which carried functional DNMs and pathogenic CNVs that affected ~10% and ~1% of patients with ASD, correspondingly. About 66.98% of ASD core genes connected to 172 PC-OTRGs positively contributed to ASD aetiology, and 59.44% of ASD core genes were involved in chromatin organization, nervous system development and synaptic function.

In addition to the genetic findings, OXT was influenced by biological and social factors in the embryonic and early postnatal stages, including sex hormones, neurotransmitters and growth factors

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*Corresponding author at: Neuroscience Research Institute, Peking University, Beijing, China.
E-mail address: zhangrong@bjmu.edu.cn

(serotonin, alpha- melanocyte stimulating hormone, cholecystokinin, brain derived neurotrophic factor *etc*). Social or physical stimulation (sucking, touching, eye-contact) will also influence the development or functional status of the OXT system.[6] It is important to pay attention to the influence of maternal factors in the development of children and mothers themselves, since not only children but also their mothers have been reported to show low levels of plasma OXT which were negatively associated with the autistic symptoms of children.[7] The mothers of children with ASD were also reported to have a higher rate of cesarean section[8] and a lower rate of lactation,[9] which may influence the mother-infant bonding and lead to the potential risk for development of OXT system through epigenetic modification. Therefore, the interaction of genetics and environment with OXT will be the next hotspot for aetiology, molecular diagnosis and precision therapy of ASD.

Finally, the paper presents a full view of OXT-related biomarkers for ASD in the real world, which is helpful to understand the central role of OXT in the genetic aetiology of ASD. Furthermore, it contributes to the understanding that a pharmacological intervention strategy based on OXT should conform to the requirements of precision medicine, so as to increase the response rate at the individual level. In fact, a recent double-blind, randomized, crossover design trial performed by the team of Keith Kendrick in China has shown that intranasal OXT treatment followed by positive social interactions can improve symptoms in autistic children when given every other day with 24 IU. Meanwhile, rs2268491 SNP OXTR genotype showed modulating effects with greater Social Responsiveness Scale-2 improvements and OXT concentration changes.[10] This study took into account of practical factors, such as drug dosage and frequency, and administrate OXT as an adjunction to experience of positive social interaction, thus providing a new and successful model for OXT therapy. More trials will be needed to extensively consider more genotypes and clinical phenotypes (sex, language and NVIQ) in future.

Declaration of interests

The author declares no competing interests.

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References

1 Kendrick KM, Keverne EB, Baldwin BA. Intracerebroventricular oxytocin stimulates maternal behaviour in the sheep. *Neuroendocrinology*. 1987;46:56–61. https://doi.org/10.1159/000124796.

2 John S, Jaeggi AV. Oxytocin levels tend to be lower in autistic children: a meta-analysis of 31 studies. *Autism*. 2021;25:2152–2161. https://doi.org/10.1177/13623613211034375.

3 Sikich L, Kolevzon A, King BH, et al. Intranasal oxytocin in children and adolescents with autism spectrum disorder. *N Engl J Med*. 2021;385:1462–1473. https://doi.org/10.1056/NEJMoa2103583.

4 Yatawara CJ, Einfeld SL, Hickie IB, Davenport TA, Guastella AJ. The effect of oxytocin nasal spray on social interaction deficits observed in young children with autism: a randomized clinical crossover trial. *Mol Psychiatry*. 2016;21:1225–1231. https://doi.org/10.1038/mp.2015.162.

5 Wang T, Zhao T, Liu L, et al. Integrative analysis prioritised oxytocin-related biomarkers associated with the aetiology of autism spectrum disorder. *EBioMedicine*. 2022;81:104091. https://doi.org/10.1016/j.ebiom.2022.104091.

6 Zhang R, Xu XJ, Zhang HF, Han SP, Han JS. The role of the oxytocin/arginine vasopressin system in animal models of autism spectrum disorder. *Adv Anat Embryol Cell Biol*. 2017;224:135–158. https://doi.org/10.1007/978-3-319-52498-6_8.

7 Xu XJ, Shou XJ, Li J, et al. Mothers of autistic children: lower plasma levels of oxytocin and Arg-vasopressin and a higher level of testosterone. *PLoS One*. 2013;8:e74849. https://doi.org/10.1371/journal.pone.0074849.

8 Liu KY, Teitler JO, Rajananda S, et al. Elective deliveries and the risk of autism. *Am J Prev Med*. 2022:68–76. https://doi.org/10.1016/j.amepre.2022.01.024.

9 Soke GN, Maenner M, Windham G, et al. Association between breastfeeding initiation and duration and autism spectrum disorder in preschool children enrolled in the study to explore early development. *Autism Res*. 2019;12:816–829. https://doi.org/10.1002/aur.2091.

10 Le J, Zhang L, Zhao W, et al. Infrequent intranasal oxytocin followed by positive social interaction improves symptoms in autistic children: a pilot randomized clinical trial. *Psychother Psychosom*. May 11, 2022:1–13. https://doi.org/10.1159/000524543.