IOANA STAICU

Oxytocin in autism spectrum disorders:
role and potential application

Perspective

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder affecting a significant percentage of the population. Affected individuals present with limited interests and impaired communication and social interactions. Despite researchers' attempts, no specific pharmacotherapy has been developed, with behavioural interventions rendering the best results so far, yet their ability to alleviate social impairments remains rather limited. However, evidence suggests that oxytocin intake could improve social functioning in some of these individuals.

The aim of this paper is to evaluate the proposed mechanisms underlying dysregulation in the oxytocinergic system and to assess the results and discuss the limitations of several clinical studies involving oxytocin administration in ASD patients.

Keywords: autism; ASD; intranasal oxytocin; amygdala

INTRODUCTION

Autism spectrum disorder (ASD) is an umbrella term for a collection of neurodevelopmental disorders, characterized by a triad of the following symptomatology: persistent impairments in social interaction, impaired social communication and a narrow range of interests and repetitive behaviour (American Psychological Association, 2013), with symptoms starting typically in early childhood (World Health Organisation, 2018). What makes ASD particularly difficult to study is its incredible complexity, both in respect to the heterogeneity of symptoms and the underlying biological mechanisms, with each autistic individual offering a unique perspective on this pathology. In addition to the wide range of phenomena that describe it, ASD is often accompanied by comorbidities such as epilepsy, intellectual disability (Atladóttir et al., 2015) or macrocephaly (Campbell et al., 2014).

ASD is part of a cluster of disorders, namely the pervasive developmental disorders (PDD). It can be classified

according to severity of the symptoms and extent of support required (World Health Organisation, 2018). High-functioning individuals (formerly diagnosed as having Asperger's syndrome) have a higher chance of living an independent life, while for the low-functioning ones, the prognosis is usually poor, due to their impaired social functioning, stressing the need for effective treatments.

Available treatments for ASD are still limited, despite the number of years since its formal description by Leo Kanner and Hans Asperger in the 1940s, and the relatively high prevalence in the general population (approximately 1%, according to Elsabbagh et al., 2012). Early behavioural interventions seem to render the best results, with Applied Behavioural Analysis (ABA) and Early Intensive Behavioural Intervention (EIBI) as some of the most successful therapies, targeted specifically at improving social behaviours (Granpeesheh, Tarbox, & Dixon, 2009; Tonge, Bull, Brereton, & Wilson, 2014); however, these are particularly costly, time-consuming and require early intervention by highly skilled professionals. To this date, there is no pharmacological

therapy designed specifically for autism. Antipsychotic medication such as risperidone and aripiprazole are the most frequently prescribed to reduce aggresive behaviours, but are associated with serious side-effects and do not promote social functioning (McPheeters et al., 2011). However, a growing body of evidence points to a dysregulation in the oxytocinergic system of ASD patients, with studies showing mixed results in terms of intranasally administered oxytocin (OXT) improving some of the social impairments. This paper discusses oxytocine levels and its role in social behaviour, the genetic variation in OXT receptor in autism, as well as key brain regions affected in this pathology. Moreover, the results and limitations of several clinical studies testing OXT administration in ASD individuals will be examined.

OXT levels in autism

The neuropeptide OXT plays a pivotal role in social behaviours, promoting nurturing, bonding and parent-infant attachment, as

shown by human and other mammalian studies alike (Rilling & Young, 2014). The hypothesis of an OXT deficit in autism is rather prevalent, yet still a subject of debate. One of the very first studies examining this matter found that peripheral OXT levels in autistic individuals are significantly lower than those found in healthy populations (Modahl et al., 1998). Moreover, Alabdali et al (2014) showed OXT plasma concentrations negatively correlated with severity of autistic symptoms, as evaluated by either the Social Responsiveness Scale (SRS) or the Childhood Autism Rating Scale (CARS). Interestingly, Parker et al (2014) found that low OXT concentrations in plasma were predictive of impaired social interaction and a poorer theory of mind (the skill of discerning between one's state of mind and the others') in autistic individuals as well as in healthy controls. Their results also contradicted the OXT deficit hypothesis, as its levels did not significantly vary between groups (Parker et al., 2014). While there is no general consensus with regards to peripheral concentrations of OXT as a valid biomarker for ASD, it seems that it is a fair indicator of social impairment.

The OXT receptor gene in autism

The role of OXT in social behaviour is also supported by genetic findings. It appears that OXT receptor knock-out mice display aberrant characteristics in this respect, showing impaired social memory and recognition (Lee, Caldwell, Macbeth, Tolu, & Young, 2008) and deterioration of mother-offspring bonding (Nishimori et al., 2008). This motivated researchers to explore whether there are genetic differences in the OXT receptor gene (OXTR) in the autistic population. As such, a 2015 meta-analysis found four single-nucleotide polymorphisms (SNPs) in the OXTR significantly associated with ASD (rs7632287, rs237887, rs2268491, rs2254298) (LoParo & Waldman, 2015). One of them (rs237887) was particularly linked to face recognition memory in a sample of 198 families with a single autistic child, as reported by Skuse et al. (2014). The researchers found that the SNP was associated with poor recognition memory, which is characteristic of ASD, in patients as well as their immediate relatives (parents and siblings) (Skuse et al., 2014).

In addition to alterations in the DNA sequence, epigenetic mechanisms were also found to be involved with the expression of OXTR. Gregory et al. (2009) analyzed the methylation levels at the promoter region of the OXTR gene, which are predictive of a gene's expression. Using post-mortem brain tissue from autistic individuals, they found this region was heavily methylated in the autistic group, which subsequently correlated with a decreased expression of the gene when compared to controls (Gregory et al., 2009). A limitation of this study, though, is the small sample size, which consisted of only 8 patient-control pairs, yet there seems to be evidence for epigenetic mechanisms accounting for different expression of OXTR in ASD patients.

OXT and the amygdala

The amygdala, a key region with regards to social functioning and emotion processing, seems to also be affected in the ASD population, in terms of both structure and functional

connectivity with other brain areas. While there is evidence that children with ASD aged 2-4 years show amygdala enlargement correlated with social impairments (Nordahl et al., 2012), scans from older patients (8 years onwards), point to a gradual reduction in its volume, with the enlargement disappearing completely during adolescence (Barnea-Goraly et al., 2014). Preckel & Kanske (2018) hypothesized that early amygdala overgrowth could be a potential compensatory mechanism for social deficits, especially in the context of low OXT levels. Hennessey et al (2018) prompted for longitudinal neuroimaging studies, as the available data are either a one-time measurement, or only show how this brain structure evolves over the span of 1-4 years.

There also appears to be a decreased functional connectivity between the amygdala and several cortical regions (occipital, parietal and prefrontal cortices) in ASD adolescents when compared to controls (mean age = 16 years), as shown by a resting state fMRI study (Rausch et al., 2016). In addition to this, clinical studies point to exogenous OXT as an effective molecule

in both restoring activity in the amygdala and its connectivity to other regions (Watanabe et al., 2014), and promote pro-social behaviours (Anagnostou et al., 2014; Tachibana et al., 2013).

Intra-nasal administration of OXT - a potential treatment

As discussed so far, OXT shows a clear involvement in ASD, with its low peripheral levels linked to disrupted social functioning (Alabdali et al., 2014; Modahl et al., 1998; Parker et al., 2014); alterations in both gene sequence and expression of OXTR could serve as biological bases (Gregory et al., 2009; LoParo & Waldman, 2015; Skuse et al., 2014). Moreover, a link between the amygdala and social behaviours has been hypothesized to exist in the context of ASD (Nordahl et al., 2012; Preckel & Kanske, 2018; Rausch et al., 2016). As such, several researchers aimed to test whether intranasally administered OXT would benefit this population in terms of social functioning.

Promising results following acute or long-term OXT administration come from studies with various age groups. Anagnostou et al. (2014) reported on a case series of 15 ASD youths (aged 10-17) who received doses up to 0.4 IU/kg intra-nasal OXT for 12 weeks, twice a day. The patients showed improvements with regards to social cognition/function, theory of mind and face recognition when assessed at week 12, with some of the changes persisting up to another 12 weeks after treatment discontinuation (Anagnostou et al., 2014). Another study reported similar findings after 8 ASD males (aged 10-14) were exposed to increasing doses of intra-nasal OXT (8/16/24 IU), with each dose being administered daily for two months. Authors noted significant improvements in 6 of the children in terms of social and communication scores, but only in one of the three assessment tools used, namely the Autism Diagnostic Observation Schedule – Generic (ADOS-G) (Tachibana et al., 2013). In spite of the encouraging outcomes and lack of serious adverse effects, a major limitation of both of the studies is the sample size and the absence of a placebo group.

Watanabe et al. (2014) proposed a more robust design, with 40 ASD adult males (aged >20) randomized in a double-blind, placebo-controlled trial. After receiving a single dose of either 24 IU intra-nasal OXT or a placebo, the participants were assessed by their ability to make decisions about social cues that had incongruent verbal and non-verbal content. It was previously observed that autistic patients have difficulty when asked to make non-verbal information-based judgements (NVJs). The authors noted that the group receiving OXT scored significantly better in terms of the number of NVJs and reaction time to these stimuli. Moreover, fMRI scans taken during the task showed a normalization in amygdalar activity, an increased activity in the medial prefrontal cortex and anterior cingulate cortex, as well as an enhanced connectivity between the two, which correlated with the OXT-induced behavioural effects (Watanabe et al., 2014).

Nevertheless, two randomized, double-blind, placebo-controlled trials failed to observe any benefits of administering OXT in ASD patients over placebo. Dadds et al (2014) compared

the effects of intra-nasally administering either 12 or 24 IU of OXT versus placebo in 38 ASD males (aged 7-16), once a day, for four consecutive days. The group receiving OXT did not significantly differ from the placebo group with regards to emotion recognition, social interaction skills and general behavioural adjustment. The authors noted, however, that their assessment of outcome measures differed from other studies with respect to time: while other trials evaluated patients while under OXT influence, theirs analysed the pre-post changes in the aforementioned outcome measures (Dadds et al., 2014). Guastella et al (2015) reported similar findings, with their study of 50 male ASD patients (aged 12-18) receiving either 18 or 24 IU of OXT or placebo intra-nasally, twice a day, over the course of 8 weeks. Patients were assessed using the Social Responsiveness Scale, as completed by their caregiver, and the Clinical Global Impression-Improvement Scale, as reported by a clinician. Other outcome measures consisted of assessment of presence, severity and frequency of repetitive behaviours, as recorded by a caregiver. Said outcomes were registered at baseline, at weeks 4 and 8 after commencing treatment, and at a 3 month follow-up.

The authors concluded that patients receiving OXT did not significantly improve on any of the outcome measures, yet caregivers' assessments seemed to be positively influenced by the belief that their patients were in the treatment group (Guastella et al., 2015).

DISCUSSION

In summary, OXT shows questionable potential in terms of improving social impairments in ASD. Evidence supporting its use comes from genetic studies showing polymorphisms in the OXT receptor gene (LoParo & Waldman, 2015; Skuse et al., 2014) and its decreased expression (Gregory et al., 2009), but also from altered activity in key brain areas associated with social behaviour (Nordahl et al., 2012; Preckel & Kanske, 2018; Rausch et al., 2016; Watanabe et al., 2014) and overall low levels of peripheric OXT (Alabdali et al., 2014; Modahl et al., 1998; Parker et al., 2014). Nevertheless, in spite of encouraging results from Anagnostou et al. (2014), Tachibana et al. (2013) and Watanabe

et al. (2014), studies with larger sample sizes and more robust designs failed to replicate their findings (Dadds et al., 2014; Guastella et al., 2015). A clear limitation of the studies with positive findings is the small number of subjects and lack of a control group (Anagnostou et al., 2014; Tachibana et al., 2013). Furthermore, an evident drawback of all discussed studies is the fact that the majority of the participants recruited was male. This could potentially introduce a gender bias and consequently lead to results that may not be relevant for females.

Possible explanations regarding the conflicting results could be the heterogeneity in the doses of OXT administered, as well as the different age groups studied. The latter aspect is particularly important, as age could influence the maturation of the amygdala and its functional connectivity with other brain regions, thus potentially determining the response of an ASD individual to OXT treatment. This calls for a more unified approach in terms of studying the effects of intra-nasal administration of OXT in this population. Another point to consider would be the necessity of follow-up studies to assess

the impact of OXT intake on brain development and potential side-effects that were not detectable at the time of the administration. Only two of the studies described conducted a follow-up assessment after discontinuation of treatment, around a similar time point (12 weeks): while they showed conflicting results, with Anagnostou et al. (2014) reporting positive findings and Guastella et al. (2015) noting no significant improvement, neither of them found any serious adverse reactions. However, it is important to know if there are any long-lasting changes of OXT administration on brain development, therefore patients should be monitored for a longer period of time after termination of treatment.

It can be concluded that more research needs to be conducted in order to establish whether or not OXT is an efficient pharmacological treatment for ASD patients.

REFERENCES

Alabdali, A., Al-Ayadhi, L., & El-Ansary, A. (2014). Association of social and cognitive impairment and biomarkers in autism spectrum disorders. *Journal of Neuroinflammation*, *11*(4). https://doi.org/10.1186/1742-2094-11-4

Anagnostou, E., Soorya, L., Brian, J., Dupuis, A., Mankad, D., Smile, S., & Jacob, S. (2014). Intranasal oxytocin in the treatment of autism spectrum disorders: A review of literature and early safety and efficacy data in youth. *Brain Research*, *1580*, 188–198. https://doi.org/10.1016/j.brainres.2014.01.049

Association, A. P. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.).

Atladóttir, H., Schendel, D. E., Parner, E. T., & Henriksen, T. B. (2015). A Descriptive Study on the Neonatal Morbidity Profile of Autism Spectrum Disorders, Including a Comparison with Other Neurodevelopmental Disorders. *Journal of Autism and Developmental Disorders*, *45*(8), 2429–2442. https://doi.org/10.1007/s10803-015-2408-7

Barnea-Goraly, N., Frazier, T.W., Piacenza, L., Minshew, N.J., Keshavan, M.S., Reiss, A.L., Hardan, A. Y. (2014). A preliminary longitudinal volumetric MRI study of amygdala and hippocampal volumes in autism. *Prog. Neuro-Psychopharmacology Biol. Psychiatry*, *48*, 124–128. https://doi.org/http://dx.doi.org/10.1016/j.pnpbp.2013.09.010

Campbell, D. J., Chang, J., & Chawarska, K. (2014). Early generalized overgrowth in autism spectrum disorder: Prevalence rates, gender effects, and clinical outcomes. *Journal of the American Academy of Child and Adolescent Psychiatry*, *53*(10), 1063-

1073.e5. https://doi.org/10.1016/j.jaac.2014.07.008

Dadds, M. R., MacDonald, E., Cauchi, A., Williams, K., Levy, F., & Brennan, J. (2014). Nasal oxytocin for social deficits in childhood autism: A randomized controlled trial. *Journal of Autism and Developmental Disorders*, *44*(3), 521–531. https://doi.org/10.1007/s10803-013-1899-3

Elsabbagh, M., Divan, G., Koh, Y., Kim, Y. S., Kauchali, S., Marcín, C., … Fombonne, E. (2012). Global Prevalence of Autism and Other Pervasive Developmental Disorders. *Global Perspectives on Autism*, *5*(3), 160–179. https://doi.org/https://doi.org/10.1002/aur.239

Granpeesheh, D., Tarbox, J., & Dixon, D. R. (2009). Applied behavior analytic interventions for children with autism: A description and review of treatment research. *Annals of Clinical Psychiatry*, *21*(3), 162–173.

Gregory, S. G., Connelly, J. J., Towers, A. J., Johnson, J., Biscocho, D., Markunas, C. A., … Pericak-Vance, M. A. (2009). Genomic and epigenetic evidence for oxytocin receptor deficiency in autism. *BMC Medicine*, *7*, 1–13. https://doi.org/10.1186/1741-7015-7-62

Guastella, A. J., Gray, K. M., Rinehart, N. J., Alvares, G. A., Tonge, B. J., Hickie, I. B., … Einfeld, S. L. (2015). The effects of a course of intranasal oxytocin on social behaviors in youth diagnosed with autism spectrum disorders: A randomized controlled trial. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *56*(4), 444–452. https://doi.org/10.1111/jcpp.12305

Lee, H.-J., Caldwell, H. K., Macbeth, A. H., Tolu, S. G., & Young, W. S. (2008). A Conditional Knockout Mouse Line of the Oxytocin Receptor. *Endocrinology*, *149*(7), 3256–3263. https://doi.org/10.1210/en.2007-1710

LoParo, D., & Waldman, I. D. (2015). The oxytocin receptor gene (OXTR) is associated with autism spectrum disorder: A meta-analysis. *Molecular Psychiatry*,

20(5), 640–646. https://doi.org/10.1038/mp.2014.77

McPheeters, M. L., Warren, Z., Sathe, N., Bruzek, J. L., Krishnaswami, S., Jerome, R. N., & Veenstra-VanderWeele, J. (2011). A systematic review of medical treatments for children with autism spectrum disorders. *Pediatrics*, *127*(5), e1312-21. https://doi.org/10.1542/peds.2011-0427

Modahl, C., Green, L., Fein, D., Morris, M., Waterhouse, L., Feinstein, C., & Levin, H. (1998). Plasma Oxytocin Levels in Autistic Children. *Biological Psychiatry*, *43*(4), 270–277. https://doi.org/10.1016/s0006-3223(97)00439-3

Nishimori, K., Takayanagi, Y., Yoshida, M., Kasahara, Y., Young, L. J., & Kawamata, M. (2008). New aspects of oxytocin receptor function revealed by knockout mice: sociosexual behaviour and control of energy balance. *Progress in Brain Research*, *170*(08), 79–90. https://doi.org/10.1016/S0079-6123(08)00408-1

Nordahl, C.W., Scholz, R., Yang, X., Buonocore, M.H., Simon, T., Rogers, S., Amaral, D. . (2012). Increased rate of amygdala growth in children aged 2 to 4 years with autism spectrum disorders: a longitudinal study. *Arch. Gen. Psychiatry*, *69*, 53–61. https://doi.org/http://dx.doi.org/10.1001/archgenpsychiatry.2011.145

Organisation, W. H. (2018). *International Classification of Diseases* (11th ed.).

Parker, K. J., Garnera, J. P., Libovea, R. A., Hydea, S. A., Hornbeaka, K. B., Carsona, D. S., … Hardana, A. Y. (2014). Plasma oxytocin concentrations and OXTR polymorphisms predict social impairments in children with and without autism spectrum disorder. *Proceedings of the National Academy of Sciences*, *111*(33), 12258–12263. https://doi.org/10.1073/pnas.1402236111

Preckel, K., & Kanske, P. (2018). Amygdala and oxytocin

functioning as keys to understanding and treating autism: Commentary on an RDoC based approach. *Neuroscience and Biobehavioral Reviews*, *94*, 45–48. https://doi.org/10.1016/j.neubiorev.2018.08.012

Rausch, A., Zhang, W., Haak, K. V., Mennes, M., Hermans, E. J., Van Oort, E., … Groen, W. B. (2016). Altered functional connectivity of the amygdaloid input nuclei in adolescents and young adults with autism spectrum disorder: A resting state fMRI study. *Molecular Autism*, *7*(1), 1–13. https://doi.org/10.1186/s13229-015-0060-x

Rilling, J. K., & Young, L. J. (2014). The biology of mammalian parenting and its effect on offspring social development. *Science*, *345*(6198), 771–776. https://doi.org/10.1126/science.1252723

Skuse, D. H., Lori, A., Cubells, J. F., Lee, I., Conneely, K. N., Puura, K., … Young, L. J. (2014). Common polymorphism in the oxytocin receptor gene (OXTR) is associated with human social recognition skills. *Proceedings of the National Academy of Sciences*, *111*(5), 1987–1992. https://doi.org/https://doi.org/10.1073/pnas.1302985111

Tachibana, M., Kagitani-Shimono, K., Mohri, I., Yamamoto, T., Sanefuji, W., Nakamura, A., … Taniike, M. (2013). Long-Term Administration of Intranasal Oxytocin Is a Safe and Promising Therapy for Early Adolescent Boys with Autism Spectrum Disorders. *Journal of Child and Adolescent Psychopharmacology*, *23*(2), 123–127. https://doi.org/10.1089/cap.2012.0048

Tonge, B. J., Bull, K., Brereton, A., & Wilson, R. (2014). A review of evidence-based early intervention for behavioural problems in children with autism spectrum disorder: the core components of effective programs, child-focused interventions and comprehensive treatment models. *Current Opinion in Psychiatry*, *27*(2), 158–165.

https://doi.org/10.1097/YCO.0000000000000043

Watanabe, T., Abe, O., Kuwabara, H., Yahata, N., Takano, Y., Iwashiro, N., … Yamasue, H. (2014). Mitigation of sociocommunicational deficits of autism through oxytocin-induced recovery of medial prefrontal activity a randomized trial. *JAMA Psychiatry*, *71*(2), 166–175. https://doi.org/10.1001/jamapsychiatry.2013.3181