Review

Biological Psychiatry

Oxytocin Treatment, Circuitry, and Autism: A Critical Review of the Literature Placing Oxytocin Into the Autism Context

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ABSTRACT

Observed impairment in reciprocal social interaction is a diagnostic hallmark of autism spectrum disorders. There is no effective medical treatment for these problems. Psychological treatments remain costly, time intensive, and developmentally sensitive for efficacy. In this review, we explore the potential of oxytocin-based therapies for social impairments in autism. Evidence shows that acute oxytocin administration improves numerous markers critical to the social circuitry underlying social deficits in autism. Oxytocin may optimize these circuits and enhance reward, motivation, and learning to improve therapeutic outcomes. Despite this, the current evidence of therapeutic benefit from extended oxytocin treatment remains very limited. We highlight complexity in crossing from the laboratory to the autism clinical setting in evaluation of this therapeutic. We discuss a clinical trial approach that provides optimal opportunity for therapeutic response by using personalized methods that better target specific circuitry to define who will obtain benefit, at what stage of development, and the optimal delivery approach for circuitry manipulation. For the autism field, the therapeutic challenges will be resolved by a range of treatment strategies, including greater focus on specific interventions, such as oxytocin, that have a strong basis in the fundamental neurobiology of social behavior. More sophisticated and targeted clinical trials utilizing such approaches are now required, placing oxytocin into the autism context.

Keywords: Biomarkers, Clinical trials, Developmental disorders, Hormones, Nasal spray, Personalized medicine

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Autism spectrum disorder is the collective term for multiple neurodevelopmental conditions characterized by qualitative impairments in social interaction and communication and restricted range of activities and interests (1). Many countries have reported increases in diagnosed prevalence over the past three decades, with recent estimates at 1 in every 68 individuals (2). Impairment in reciprocal social interaction can manifest as a failure to develop peer relationships, atypical responses to others' emotions, and/or lack of capacity to share enjoyment or interests with others (1). Autism is also frequently associated with behavioral difficulties such as hyperactivity, irritability, and aggression (3) and comorbidities with developmental, mental health, and physical problems (1,4). Autism is, for example, often accompanied by intellectual disability, epilepsy, gastrointestinal problems, and macrocephaly (4–6). It is, therefore, a major contributor to disability and distress to those affected by the diagnosis and results in significant costs for individuals, families, and governments (7).

Autism, sometimes colloquially referred autisms, is highly heterogeneous with different causes and trajectories across development. No single genetic factor accounts for a major proportion of those diagnosed (8), and although highly heritable, this is likely due to oligogenic and polygenic factors with numerous genetic and epigenetic components. Many genetic factors linked to autism also regulate synaptic functions of neurons underlying learning and plasticity, suggesting their role may be during critical periods of neuronal development in the womb and first years of life (9). Imaging studies also show a complex and varied trajectory clustering different subsets of autism (10) in terms of atypical brain anatomy (11), connectivity (12,13), and function (14). For example, autism is characterized by increased connectivity locally between neurons in the same cortical layer and reduced axonal projections between distant brain regions, suggesting disorganization and poor regional coordination as a feature (12,15,16). Research is, however, in its infancy in establishing neural profiles that predict subsequent functioning later in life or response to different interventions (10,14). Many aberrations in neural profiles are no longer apparent in older children and adults (11,17), also leading to a view that early life developmental changes are critical drivers of life-long impairment. Along with characterization of the brain changes across development, attention has been placed on understanding interactions with other contributors to the broad cognitive and behavioral phenotype, including interactions between gut (18), immune (19), metabolic (20), and circadian changes (21). Notably, these factors are also influenced by environmental variables and may jointly influence brain development and behavioral phenotypes at certain developmental stages.

Given this heterogeneity, it is not surprising there is not a single medical treatment for the behavioral phenotypes of

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social impairment. Despite many promoted treatments in the community, often attached with significant cost, most have little evidence to support use (22,23) and are not specified for a subtype of autism. Most published therapeutic treatment trials are of small sample size, questionable methodological rigor (24–27), and like the diagnosis itself, based only on reports of observed behavior, as opposed to independent objective markers. Risperidone, aripiprazole have shown benefit in reducing hyperactivity, aggressive, self-injurious, and repetitive behavior (22,28) but are associated with significant negative side effects. Risperidone is, in fact, the most widely prescribed medical treatment for autism in the world today (29), even though it does not target social symptoms and is associated with weight gain, drowsiness, extrapyramidal side effects, and hormonal changes related to galactorrhea, amenorrhea, and gynecomastia (22,26,30,31). That it is prescribed frequently highlights the complexity of symptoms for people with autism, as symptoms that cause distress may not be related to social deficit components. Given the limitations of the existing scientific literature and complexities in presentation, many people often choose to trial accessible investigational therapies.

Some behavioral treatments show benefit in improving social responsiveness and interaction for children with autism (27,32), although they are usually associated with intensive weekly sessions of 20 to 40 hours per week accumulating over years (25,32). These interventions have grown in sophistication (33,34) since the work of Lovaas (35), in the way they engage children in rich social learning skills across development. For example, the Early Start Denver Model (36) focuses on social-cognitive development, including training in verbal and nonverbal communication, imitation, emotion sharing, joint attention, play, social orienting, and social attention by clinicians and caregivers (37). It is believed that the Early Start Denver Model is developmentally sensitive (38), providing better outcomes for children under age 6 who may learn more fundament skills to permit more complex social skills later in life. It has an explicit target of increasing the child's sensitivity to social reward and interest and affective engagement with others (36–41). This work demonstrates that young children with autism show considerable potential for learning and plasticity to change and improve developmental trajectories, although patient variables may moderate response. How such interventions can be delivered in a cost-effective manner to produce sustainable outcomes remains unclear (24,42), particularly in lower resourced communities.

OXYTOCIN AND AUTISM SPECTRUM DISORDERS

The neuropeptide oxytocin has garnered significant interest in the scientific and lay communities as an investigational treatment for autism. Oxytocin is a nine amino acid peptide, which is synthesized in the paraventricular and supraoptic nucleus of the hypothalamus and released into the bloodstream by the posterior pituitary gland. Mammalian nonhuman animal studies demonstrate the importance of oxytocin to social behaviors, including social recognition, memory, and attachment and reducing stereotyped behaviors such as exaggerated grooming (43–45). Across many studies, central administration of oxytocin agonists before social contexts enhances recognition and memory for peers, partner preference, and bonding, while reducing predatory aggression (46). Studies of transgenic animals show oxytocin receptor (OXTR) knockout mice lose capacity to respond to social cues, which is fully restored by infusion of 1.0 pg oxytocin into the medial amygdala before social encounters (47). Parenting models also highlight how oxytocin release is critical to bond formation during exposure to bonding cues, probably by increasing reward and sensitivity to these cues (suckling; parent-offspring touch, grooming) (48).

GENETIC VARIATION, OXYTOCIN PLASMA AS A MARKER FOR AUTISM SPECTRUM DISORDERS

There is growing evidence that allelic variation within the *OXTR* gene (including several single nucleotide polymorphisms and haplotypes) has evolutionarily importance to social cognition and function, although functionally important alleles are unresolved (49–52). Animal models established the importance of OXTR on social behavior and memory (43,53). In humans, some studies suggest genetic variability in the *OXTR* gene could increase risk for autism (49–52,54), but others show associations reflecting broader social-cognitive phenotypes (55–58). Examination of oxytocin plasma as a marker has also produced mixed results. Baseline plasma oxytocin may relate to functioning in autism (59), but a larger research body implicates peripheral oxytocin levels with social-cognitive trait dimensions (58). Given oxytocin release is highly responsive to social context shifts, we know little about its function in autism in response to social cues (e.g., touch, social reciprocity, and reward). We also acknowledge disagreement regarding reliable methods for sample processing, methods of measurement, and controversy regarding the relationship between circulating plasma, salivary, or urinary oxytocin and central levels.

SINGLE DOSE OXYTOCIN ADMINISTRATION ON SOCIAL COGNITION IN NEUROTYPICAL POPULATIONS

In neurotypical adults, a large body of research suggests benefits of oxytocin nasal spray for improving social cognition [for review, see (60)], including eye gaze, emotion recognition, affective voice recognition, and interoceptive awareness, along with neural underpinnings of these benefits (61). Oxytocin effects can be sensitive to social contexts, even to increase defensive tendencies (62,63), and individual differences moderate effects (64,65). A recent meta-analysis using whole-brain analysis showed strong effects on the left insula, which is important given its recognized role in social cognition (66), but task-specific effects have been reported on the caudate and putamen (during social learning tasks) and the temporal lobes, amygdala, and prefrontal and anterior cingulate cortex (during social stimuli and face processing) (61), as well as enhancement of functional coordination between some of these regions during social interactions (67). Replication across gender and age remains an ongoing issue, but most findings support oxytocin's role in reducing threat and uncertainty (68) and improving empathy, synchrony, reward, and communication during processing of social cues and interactions (61,66,69).

THE IMPACT OF A SINGLE DOSE OF OXYTOCIN IN AUTISM SPECTRUM DISORDERS

In adults with autism, Hollander *et al.* (70,71) first showed acute intravenous oxytocin reduced repetitive behavior and learning of affective speech. Nasal administration studies followed to show oxytocin improved emotion recognition (72), higher order social cognition (73), eye gaze, social interaction (74), and physiological responses to affective sounds (75). For example, Andari *et al.* (74) showed oxytocin increased eye gaze, oxytocin plasma, and social decision making within a cooperative social ball-tossing computer game, by reducing attempts to engage the uncooperative player. This was the first evidence that oxytocin improves social awareness and effective decisions in online social situations. Separately, we reported the first evidence of benefit to youth with autism, showing that oxytocin enhanced emotion recognition (72).

In adults with autism, imaging studies show intranasal oxytocin increases right anterior insula (73) and activity and coordination in the medial prefrontal cortex, with the latter associated with improved performance on a false-belief task (76). Domes *et al.* (77) showed that oxytocin administration increased right amygdala, fusiform gyrus, and inferior occipital gyrus activity during presentation of facial stimuli, which is opposite to effects in neurotypical control studies (61). The individual difference literature has highlighted how autism traits may moderate response (64,78) and some have argued that oxytocin might increase salience and reward for social cues, specifically for individuals with a lack of awareness for these cues. Finally, Gordon *et al.* (79) reported that oxytocin administered to young autistic children increased activity in the striatum, middle frontal gyrus, the medial prefrontal cortex, right orbitofrontal cortex, and superior temporal sulcus during social judgment making.

Overall, published studies support the benefits of oxytocin to social neurocognition, circuitry, and social processing in neurotypical adults, adults with autism, and youth and children with autism. This evidence is consistent with a view that oxytocin could enhance social salience and awareness for, reward and responsiveness to, and learning of social cues. A recent meta-analysis of trials and effect sizes utilizing oxytocin nasal spray in psychiatric disorders revealed that autism was the candidate psychiatric disorder with the most potential to benefit (80). Based on single dose studies, oxytocin shows promise to improve diagnostic symptoms of social awareness and use of appropriate social approach behaviors in context, appropriate use of eye contact, gestures, and understanding and recognition of facial expressions (1). One study to date suggests oxytocin may also reduce repetitive behaviors.

THE EFFECT OF OXYTOCIN AS AN EXTENDED TREATMENT FOR AUTISM SPECTRUM DISORDERS

Open-label case studies and uncontrolled cohort studies suggest potential benefits of nasal oxytocin to treat observed autism symptoms using repeated dosing (81,82). Two published randomized placebo-controlled trials provided nasal oxytocin over an extended period to evaluate this. The first gave 24 International Units (IU) of intranasal oxytocin or a placebo twice daily for 6 weeks to 19 adults with autism (83). Measures included caregiver reports of social responsiveness and repetitive behavior, social cognition tests, and clinician ratings of symptoms severity. This study showed benefit on secondary measures of emotion recognition and quality of life but not on primary domains of social reciprocity or repetitive behavior. We published a trial of oxytocin (18 or 24 IU) or a placebo nasal spray in 52 youth with autism (aged 12 to 18) given twice daily for 8 weeks (84). Across all social cognition, caregiver, and clinician assessments, there was no benefit of oxytocin. Parental reports of social responsiveness were, however, likely influenced by expectation. Regardless of whether their child was assigned to the oxytocin or placebo condition, parents who believed their child received oxytocin reported greater change in social responsiveness. This may offer some explanation for reported benefits in open-label studies.

One study examined the potential of oxytocin to combine with social skills training (85). Dadds *et al.* (85) recruited 35 youth (aged 8 to 16) to four sessions of 1-hour social skills training with emotion recognition training. Drug administration preceded training by 30 minutes for two sessions and 2.5 hours for two sessions. For two sessions, a family observation coding session took place before training, while for two sessions observation took place after training. This study did not show benefit of oxytocin on any measure. Despite hyperbolic media reports of this null finding, consideration must be given to the variable times training was provided after dosing, the limited total oxytocin doses ($n = 4$), and the use of a social training procedure that currently lacks evidence of efficacy in the format provided to the age range. Research is needed to confirm and extend these initial findings. In summary, we can, however, conclude that benefits from single-dose studies have not translated to benefits when examining the literature of extended oxytocin treatment.

PLACING THE DEVELOPMENT OF OXYTOCIN INTERVENTION INTO THE AUTISM CONTEXT

This field is now delicately poised with claims oxytocin may provide the first targeted treatment for social impairments in autism pitted against assertions that it has little or no therapeutic value (86,87). This diversity in views is not surprising given major limitations of the existing evidence base; the initial hype, expectation, and the real need for a therapeutic; and the phenotypic heterogeneity presented by persons with autism and associated conditions. Fortunately, there are a growing number of trials underway to further evaluate potential benefits of oxytocin in larger samples. Despite this, there remains a need for much greater debate about what might be required for optimal evaluation of therapeutics in autism and oxytocin nasal spray specifically. Otherwise, when heterogeneous populations are tested (by age, gender, intelligence, social function, target behaviors, and other concurrent neurological or neurodevelopmental disorders), we will likely see mixed outcomes possibly demonstrating moderate improvements for some participants on some selected measures, with little guidance for individuals about who are likely to benefit, when, and why. Such problems may not result from a failure of the therapeutic but failure of adequate clinical trial design, drug delivery, and patient selection to target circuitry appropriately. Greater focus is

required on understanding the important subject variables, neurobiological and developmental windows of opportunity that might mediate response, the therapeutic relevance of oxytocin for the range of symptoms that cause distress and result in treatment seeking, and the sensitivity of outcome measures employed to determine benefit.

PATIENT SELECTION AND TRIAL DESIGN

There is much discussion about how genetic and epigenetic factors (e.g., methylation status of OXTR) might mediate response to oxytocin and learning interventions. It is further hoped developmental profiles emerge to cluster autism subtypes that could be used as variables to predict response. In regard to common patient characteristics, gender appears to moderate oxytocin effects (88), including neural response to nasal oxytocin, but it remains unclear how this might effect a therapeutic response for people with autism (89). Almost all autism oxytocin studies have exclusively recruited male subjects due to its overrepresentation in autism (1). The autism field is generally lacking in terms of understanding the characteristic female autism profile (90), which could then be used to inform trials of therapeutics. Also, a majority of people with autism show some intellectual impairment (1), but the existing research evaluating the circuitry markers associated with autism (e.g., physiological, imaging, immune, cognitive measures) and studies validating the sensitivity of outcome measures typically excludes those with moderate to severe intellectual impairment. This leaves open debate about whether a lack of measure sensitivity drives any observed reduced responsiveness to intervention in this important patient group. Repetitive and self-injury behavior is also a core feature of autism and its presence may moderate response to social intervention (91). Such behavior may cause more distress than other symptoms, characteristically fluctuates within a smaller subpopulation, is related to other important variables such as nonverbal intelligence, and limits response to social intervention (91). While one acute study suggests benefit of oxytocin to repetitive behaviors (70), this is not a main focus of oxytocin intervention. It also remains unclear how observed benefit to repetitive behavior might relate to the different circuitry that can guide it, including obsessive-compulsive or stereotyped behaviors, anxiety, impulsivity, and hyperactivity (91).

In relation to age, oxytocin could have an important role for autism early in life (92). It is well-established that there are critical development periods for social intervention (93). Some argue that early social-training interventions shape the brain's receptiveness to the social world to mitigate the severity of autism symptoms (94,95) and reduce the compounding negative influence of social impairment (96). There seems to be a very strong rationale to combine oxytocin with social-learning interventions to improve outcomes in early development. To illustrate, a well-replicated oxytocin effect is improved eye gaze. Reduced eye gaze and joint attention are one of the first markers of autism (97), documented in children as young as 12 months of age (98), and it predicts later diagnosis and functioning (99). Older children who then perform poorly on related emotion-recognition tasks also perform poorly on measures of social skills (100) and have a worse long-term prognosis (101). Theoretical models (38,94,98,102) propose that initial deficits in engaging with social stimuli from an early age (through mechanisms such as eye gaze and joint attention) compound existing social deficits across development, as the social responses that are required become more complex. Individuals may then increase their withdrawal from social-learning opportunities. Thus, we propose that evaluation of early intervention with novel treatments that target the oxytocin system should be a research priority, to combine with early social-learning interventions to enhance attention, reward, and the intensity of social learning. Alternatively, such interventions could be given to parents during parent-training to enhance the interactive process (103).

OXYTOCIN MANIPULATION IN AUTISM SPECTRUM DISORDERS

In the absence of social-learning therapies, nasal oxytocin may improve endogenous regulation through repeated administration. There is little human evidence (or evaluation) to support this assumption. Numerous reviews elsewhere have discussed limitations of standard nasal delivery devices and non-optimized formulas to absorption for central nervous system impact (104,105). Dose-finding and delivery comparison studies are desperately needed. Delivery considerations for people who have difficulty tolerating the spray could be a major source of variation, with few devices optimized for children, youth, or those with communication disabilities. We have observed in our own unpublished data that children with poor verbal communication have greater difficulty tolerating nasal sprays. Different medical interventions may be needed to activate central oxytocin release, different delivery methods, or use of an adjunctive medical intervention with oxytocin to activate critical circuits (105–107). Alternatively, environmental manipulations known to facilitate oxytocin regulation could be considered and evaluated as an alternative to drug administration (e.g., tactile and attachment based therapies) (108). The critical point being that mechanistic human work needs to be done before one is in a position to disregard oxytocin-targeting interventions.

SOCIAL IMPAIRMENT AND OXYTOCIN RESPONSE IN AUTISM SPECTRUM DISORDERS

In the autism field, limitations of observer reporting scales as outcome measures of social responsiveness (109) and repetitive behavior (110) are further accentuated by the typical absence of self-report, particularly in pediatric settings. Our recent meta-analysis of pharmaceutical and dietary supplements in pediatric autism clinical trials (A. Masi, 2015, unpublished data) showed that placebo effects are a significant source of bias in both caregiver and independent observer ratings, including trained clinicians. Clinical trials need to establish different physiological, biological, and cognitive makers of change to predict observed functioning. For example, studies have suggested the potential of inflammatory biomarkers in drug discovery (55,111). Oxytocin influences inflammatory processes (112,113), some of which may be important for autism, disease recovery, and social behavior (114). There has, however, been no investigation of such

markers in clinical trials or integration with a set of neurobiological measures to guide patient selection and treatment response.

Research priority should be given to linking objective markers of response to oxytocin intervention, to broader measures of therapeutic response, and patient selection. This has only attracted limited discussion. This problem is further accentuated by limitations of laboratory models that do not account for the complicated and heterogeneous nature of autism and the human condition. Such models do not easily cross from the laboratory to effective clinical treatments for all. Thus, greater emphasis on the specific neurobiological circuitry that is being targeted by oxytocin and, hence, the predicted pattern of clinical response within certain groups of subjects is required.

To illustrate, imaging studies suggest numerous potential markers. Oxytocin influences *N*-acetylaspartate in the ventromedial prefrontal and anterior cingulate cortex to possibly improve social cognition performance (76). This finding is particularly fascinating, given evidence of a lack of coordination, organization, and formation underlying brain development in autism (12), with implications for improving social learning. Similarly, other studies suggest that oxytocin might enhance cortical information transfer while simultaneously lowering background activity (115), which is interesting given failure to focus on socially salient features while being distracted by background noise is a likely feature of autism. In addition, there might also be immediate physiological and behavioral markers to indicate potential therapeutic response to oxytocin, such as improved ability to integrate and coordinate social cues (e.g., joint attention, interoceptive awareness, ability to interpret complex social scenes, emotion regulation under social stress) to predict improvement in clinical observational measures of social responsiveness over time (e.g., observations of social responsiveness). Studies show that oxytocin increases physiological and behavioral synchrony in dyadic interactions with caregivers (e.g., joint attention, eye gaze, heart-rate variability) (76,103,116), coined by Feldman (117) as biobehavioral synchrony. Nonverbal social tasks and related physiology measures may be particularly useful as markers of social responsiveness in young children, before more complex, higher order social skills are required. Using this approach, we propose that those who do not show the predicted neural, behavioral, and physiological response would be unlikely to show a clinical response. Such a framework provides opportunity to more quickly establish optimal intervention approaches to manipulate these circuits (e.g., dose-finding studies, head-to-head device comparisons, etc).

SAFETY

Despite recognition that interventions for autism are optimally provided early in life, debate has been on safety and potential harm of oxytocin administration to young children (86). Some studies in rodents have suggested direct injection of large oxytocin doses to very young animals (118–120) might have long-lasting negative consequences for social behavior. In possible support, large cohort studies have suggested a very small but significant risk for the future development of autism later in life following oxytocin administration to mothers during labor (121). Such findings have been hotly debated (122). Trials to date show no reports of concerning or significant side effects that require intervention, although we note some tolerability issues for a minority of patients during the first administration. Reports of initial aggression or hyperactivity that subsides from discontinuation have been made in our studies in a small number of participants (A.J.G., 2015, unpublished data). Further discussion is required articulating the useful markers of a negative response. We propose that if repeated administration damages social circuits, one would expect deficits in circuitry initially enhanced by oxytocin (e.g., reduced eye gaze, joint attention, social de-synchrony). Oxytocin may also, independently, alter defensive anxious-arousal responses as a dark side of oxytocin (123). This could be expressed as increased anxiety or agitation symptoms (e.g., potentially as irritability, repetitive behavior) and emotion regulation difficulties under stress. Human data evaluating the costs and benefits of oxytocin administration and its safety for young children are now urgently required.

CONCLUSIONS

While there are many treatments for autism, most are poorly evaluated and do not apply to the broad range of presentations characterizing all people with autism. Oxytocin may have potential to provide a first medical treatment to improve social impairments for some. This review has highlighted the complexity of evaluating the efficacy of oxytocin for persons with autism, which presents as a set of neurodevelopmental disorders with a range of neurobiological trajectories and symptoms causing distress. Evaluation will require a range of personalized approaches to better identify neural targets and associated responses for addressing who might obtain benefit, what developmental stage and how (e.g., through learning, direct manipulation), and effective delivery routes, doses, or methods to optimize response of these circuits. The challenge is unlikely to be met by a single trial resulting in a simple answer (it works or does not work) and therefore may not resolve questions of therapeutic efficacy for autism quickly. In meeting this challenge, however, the evolving research provides an opportunity to detail sophisticated frameworks for understanding, evaluating, and potentially treating social impairments in autism that has not been offered before. These research applications are urgently required.

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health professionals and the community supported by governmental, community agency, and pharmaceutical industry partners (Wyeth, Eli Lilly, Servier, Pfizer, AstraZeneca) for the identification and management of depression and anxiety. He has received honoraria for presentations of his own work at educational seminars supported by a number of non-government organizations and the pharmaceutical industry (including Servier, Pfizer, AstraZeneca, and Eli Lilly). He is a member of the Medical Advisory Panel for Medibank Private and also a Board Member of Psychosis Australia Trust. He leads an investigator-initiated study of the effects of agomelatine on circadian parameters (supported in part by Servier) and has participated in a multicentre clinical trial of the effects of agomelatine on sleep architecture in depression and a Servier-supported study of major depression and sleep disturbance in primary care settings.

ARTICLE INFORMATION

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