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Is Intranasal Administration of Oxytocin Effective for Social Impairments in Autism Spectrum Disorder?

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Additional information is available at the end of the chapter

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1. Introduction

The neuropeptide oxytocin (OT) is synthesized in magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus and released from axon terminals in the neurohypophysis into the general circulation. However, OT is also released from somata and dendrites of magnocellular neurons into the brain [1]. OT release from axon terminals, somata and dendrites is regulated by not only activity-dependent Ca^{2+} influx, but also by mobilization of Ca^{2+} from intracellular Ca^{2+} stores [2, 3]. CD38, a transmembrane glycoprotein with ADP-ribosyl cyclase activity, plays a critical role in mobilization of intracellular Ca^{2+} , and therefore CD38 gene knockout (CD38^{-/-}) mice show low plasma OT concentrations [2]. On the other hand, CD38 is not responsible for the secretion of arginine vasopressin, which is another neurohypophyseal hormone [2].

Perioherally, OT promotes milk ejection in females and penile erection in males [4]. In addition, studies using OT gene knockout (OT^{-/-}), OT receptor gene knockout (OTR^{-/-}), or CD38^{-/-} mice, in which OT signaling would be disrupted, were performed to investigate the roles of OT in the central nervous system [5, 6].

While OT^{+/+} male mice showed a decline in the time investigating a female mouse during repeated pairings with full recovery following the introduction of a new female, OT^{-/-} male mice show no such decline [7]. The results suggested that OT^{-/-} male mice fail to develop social memory. Moreover, in a different experimental paradigm, OT^{-/-} mice showed the same sociability, which was reflected as more time spent with a novel mouse as compared to time spent with a novel object, and preference for social novelty, which is reflected as more time spent with a second novel mouse as compared to time spent with a non-stranger mouse, as

OT^{+/+} mice [8]. This experimental paradigm contains no memory component. Taken together, OT^{-/-} mice exhibit impairments specific to social memory rather than deficits in general sociability. In addition, OT^{-/-} infant mice show fewer call rates in ultrasonic vocalizations in response to maternal separation compared to OT^{+/+} infant mice [9], so OT^{-/-} mice may be less emotional in the mother-infant relationship.

When OTR^{-/-} dams retrieve their infant mice scattered in the home cage, they take a longer time and spend less time crouching over infant mice than OTR^{+/+} dams. OTR^{-/-} infant mice show decreased ultrasonic vocalizations as seen in OT^{-/-} infant mice [10]. While OTR^{+/+} mice spend a longer time exploring a cage occupied by an unfamiliar mouse than an empty cage, OTR^{-/-} mice spend the same time in exploring both cages [11]. Interestingly, forebrain-restricted OTR^{-/-} male mice show a decline in the investigation time with the same female mice during repeated pairings and show full recovery following the introduction of a new female as with OTR^{+/+} male mice [12].

CD38^{-/-} male mice also show no decline in the investigation time with the same female mouse during repeated pairings unlike CD38^{+/+} male mice [2]. CD38^{-/-} infant mice show fewer call rates in ultrasonic vocalizations in response to maternal separation compared with CD38^{+/+} infant mice [13].

OT^{-/-}, OTR^{-/-}, and CD38^{-/-} mice show similar impairments in social memory and emotional relationship to the dam on isolation. Thus, investigations performed in OT-related knockout mice suggested the possible roles of OT as a sociability hormone. OT signaling in the brain was expected to play an important role in sociality in humans and to contribute to the etiologies of psychiatric disorders with social deficits, such as autism, which has been suggested to involve low plasma concentrations of OT [14].

Autism spectrum disorder (ASD) is a diagnostic continuum, which encompasses autistic disorder (autism), childhood disintegrative disorder, Asperger's disorder, and pervasive developmental disorder not otherwise specified in the Diagnostic and Statistical Manual of Mental Disorders (DSM) [15] and is intended to be designated so in a new version (DSM-5). Qualitative impairments of social interaction (social impairments) would be regarded as the major core symptom of ASD with repetitive and restrictive behaviors as another core symptom. However, social impairments imply wide-ranging symptoms from lack of declarative pointing, immediate echolalia, and failure to develop reciprocal peer relationships to very slight deficits identified only by detailed examinations combined with diagnostic tools, such as an advanced task for theory of mind [16]. Individuals with ASD, therefore, may not be diagnosed until adulthood [17].

While symptoms designated and conceptualized as impairments of social interaction are indispensable to the diagnosis of ASD and are easily identified in mentally retarded subjects with typical ASD, such as autism, weaker phenotypes of social impairments would involve a complicated subject of considering the symptomatology of ASD. Behavioral signs of social impairments in ASD have been suggested to emerge as a decline in social engagement, such as gazing on faces and social smiles, between 6 and 12 months

of age [18]. These results imply that ASD is a nearly innate rather than acquired disease, although it could not be excluded that exogenous factors may exert adverse effects on newborns within the 6 months after birth. However, the clear boundary between the conditions with and without ASD could not be defined in research or from a clinical perspective. Autistic traits in the general population are common and show a continuous distribution [19]. Moreover, the symptom of social impairment has a different meaning in nature compared to all other medical symptoms. A fasting blood sugar level of 150 mg/dL in an individual with diabetes mellitus is an objective and independent measurement. Social impairments in an individual with ASD are by no means objective and independent, especially in the boundary region between the conditions with and without ASD. The term “social” has relevance to human “society.” Human society is the whole that has been shaped by innumerable iterated social interactions among humans from time immemorial, and cannot be defined from an external standpoint. While behaviors exhibited by individuals with ASD may look more or less deviant from the viewpoint of human society, they adapt themselves to human society unremarkably in some cases and deviate from it directly in other cases. Social impairments in ASD subjects cannot be anchored exactly in the context of real-life environments. Therefore, it is very difficult to determine how symptoms of social impairment should be evaluated in treatment of patients with ASD.

In this article, we first discuss the influence of intranasally administered OT on sociality in human adults. We further examine the results obtained from four studies in which the effectiveness of intranasally or intravenously administered OT was investigated in ASD subjects. Moreover, we discuss long-term clinical trials in progress, for which we searched the public databases, of intranasally administered OT in subjects with ASD in randomized, double-blind, placebo-controlled designs. Finally, we consider the improvements in social impairments in the treatment of patients with ASD.

2. Effectiveness of intranasally administered OT on social cognition and prosocial behaviors in healthy adults

We consider that reciprocal interaction with others would go through the processes of self-consciousness as a construct deeply embedded in human society, social cognition, and prosocial behavior. Self-consciousness (i.e., self-representation or self-reference) may be a key concept in considering the psychopathology of ASD [20]. Can individuals with attenuated self-consciousness distinguish self from others in a social context? Children and adolescents with ASD made fewer statements classified as the social not but physical, active and psychological category compared to non-ASD subjects [21]. Typical interaction with others may be realized only under the conditions of typical self-consciousness. While biological investigations of self-consciousness have been performed using functional magnetic resonance imaging in ASD and healthy individuals [22, 23], the effects of OT on self-consciousness in humans remain unclear.

Social cognition implies important factors underlying not just face-to-face exchanges with others but also even circumstances alone in a crowd. People may wonder “Who is he?” “What has my daughter been thinking?” or “That person is watching me”. All of this corresponds to social cognition. Prosocial behavior implies the favorable or unfavorable impressions that a person has toward others, and the following actions based on these impressions. People are impressed by others’ behaviors and may bring these impressions into actions: “He looks trustworthy. I will consult with him about which course to take after graduation,” “I hate people who discriminate against the weak. So, I will not talk to him.” These are prosocial behaviors.

There have been many studies regarding the effects of OT on social cognition and prosocial behavior in healthy adults since the pioneering study by Kosfeld et al. [24] Interest in OT has increased due to the positive results obtained: e.g., strengthening of memory for faces [25] and increased emotional empathy [26] in social cognition, increased generosity [27] and trust [28] in prosociality. However, the results are inconsistent on closer inspection (for details, see [29]). For example, 259 healthy students participated in a study regarding the effects of OT on cooperative behavior in a randomized, double-blind, placebo-controlled design [30]. Participants played two economic games, which were a Coordination Game with strong incentives to cooperate and a Prisoner’s Dilemma game with weak cooperative incentives, after one-half of them talked together and the other half spoke to no-one. The former group receiving OT showed more cooperation only in the Coordination Game than participants receiving placebo. However, the latter group receiving OT showed less cooperation only in the Cooperation Game than participants receiving placebo. Prosocial behaviors on receiving OT proceeded in the opposite directions according to whether social information was presented previously.

Based on the review of Bartz et al. [29], of 14 studies investigating social cognition, nine (69.2%) showed that OT exerted a significant main effect on the outcome compared to placebo (Table 1). Eight of these nine studies suggested that the effect of OT was significantly modulated by situational differences or individual factors. However, there was a marginal trend between the distributions of two categorical variables of OT effect and modulated OT effect (Fisher’s exact test, $P = 0.095$).

			Modulated oxytocin effect		Fisher’s exact test
			Yes	No	
Social cognition	Oxytocin effect	Significant	8	1	P = 0.095
		Null	2	3	
Prosociality	Oxytocin effect	Significant	5	12	P = 0.006
		Null	12	3	

Table 1. Relationship between oxytocin effect and modulated oxytocin effect (designed according to [25])

Of 32 studies investigating prosocial behavior, 17 (53.1%) showed that OT exerted a significant main effect on the outcome compared to placebo. Five of these 17 studies suggested that the effect of OT was significantly modulated by situational differences or individual factors. On the other hand, 12 of 15 studies without a significant main effect of OT were significantly modulated by situational differences or individual factors. The distribution of two categorical variables was significantly different ($P = 0.006$). The more these factors affect study participants, the less the effects of OT emerge in them. That is, the effects of OT on sociality, especially prosocial behavior, may be affected by external factors in addition to the function of OT itself and, moreover, external factors may show paradoxical effects. For example, 66 healthy adults participated in a money game, in which they rated their emotions (envy and gloating) toward their opponents when they gained more or less money, in double-blind, placebo-controlled, with-in subject design [31]. Interestingly, OT increased the envy ratings when the participant gained less money and the gloating ratings when they gained more money compared to placebo.

While early research that suggested effectiveness of OT in psychiatric diseases such as social anxiety disorder and ASD generated considerable enthusiasm, the reasons for the inconsistent and paradoxical results of OT on sociality in healthy humans remain unresolved. However, the pathophysiology of ASD has not yet been elucidated and no effective treatments for social impairments in ASD exist. It would be useful to investigate whether OT can improve the core symptoms of ASD.

3. Effectiveness of intranasally or intravenously administered OT in ASD subjects

Four randomized, double-blind, placebo-controlled trials of short-term OT administration in subjects with high-functioning ASD have been published since 2003 (Table 2) [32–35].

Reference number	n	Male gender	Age (years)	Intelligence quotient	Medication method	Oxytocin dose	Outcomes
32	15	14	19–56	74–110	Intravenously	10U	Repetitive behavior scale
33	15	14	19–56	74–110	Intravenously	10U	Comprehension of affective speech
34	13	11	17–39	unknown	Intranasally	24 IU	Social ball tossing game
35	16	16	12–19	unknown	Intranasally	18 or 24 IU	Reading the Mind in the Eyes-Revised

Table 2. Randomized, double-blind, placebo-controlled trials of short-term oxytocin administration in subjects with high-functioning autism spectrum disorder

The designs were naturally different between these studies in terms of age and gender of participants, medication methods, doses of OT and outcomes, so no conclusions could be drawn regarding the treatment of ASD patients based on a single-dose design. However, OT

may play a role in alleviating repetitive symptoms [32] and modifying social impairments [33–35].

With regard to social impairments, Hollander et al. investigated the effectiveness of intravenously administered OT on comprehension of affective speech in 15 subjects with ASD in a randomized, double-blind, placebo-controlled, cross-over design [33]. The task was fairly easy for the participants resulting in the same improvements of scores of those who were administered placebo in the first condition as those who were administered OT in the first condition. However, after an interval between the first and second conditions (days: mean = 16.07; SD = 14.26), the scores at baseline in the second condition were retained in the participants administered OT and dropped in those administered placebo. These results suggested that OT may play a role in social memory acquisition in social cognition in ASD subjects.

Andari et al. investigated the effectiveness of intranasally administered OT on trust and preference toward opponent players using a social ball tossing game in 13 subjects with ASD by randomized, double-blind, placebo-controlled, within-subject design [34] (No results of face perception tasks shown in the study are noted here). ASD subjects administered OT trusted more and showed stronger preference for good than bad opponent players regardless of the perception of monetary rewards. No significant differences were found under placebo conditions. These results suggest that OT may play a role in prosocial behavior in subjects with ASD. Moreover, it was noted that plasma OT concentration at 10 min after nasal administration of OT show a significant increase compared to baseline concentration.

Guastella et al. investigated the effectiveness of intranasally administered OT on emotion recognition using the Reading the Mind in the Eyes Test-Revised [36] in 16 subjects with ASD by randomized, double-blind, placebo-controlled, cross-over design [35]. The improved performance by OT compared to placebo was restricted to the younger participants aged 12 to 15 and easy items in the test. These results suggest that OT may play a role in emotion recognition in social cognition for ASD subjects, although age and task difficulty may act as modulators.

Taken together, short-term (continuous intravenous infusion over 4 h or nasal spray of certain doses at a time) administration of OT may show effectiveness on social cognition and prosocial behavior in ASD subjects with situational differences or individual factors as confounders taken into account. The next step should be to investigate whether long-term administration of OT modulates social impairments in ASD.

4. Long-term randomized, double-blind, placebo-controlled trials of OT in subjects with ASD registered in the public databases

We searched the public databases, i.e., Clinicaltrials.gov (<http://clinicaltrials.gov>), UMIN Clinical Trials Registry (<http://www.umin.ac.jp/ctr/index-j.htm>), and Australian New Zealand Clinical Trials Registry (<http://www.anzctr.org.au/>), for long-term clinical trials of OT in ASD. In other databases of EU Clinical Trials Register (<https://www.clinicaltrialsregister.eu/>) and ISRCTN Register (<http://www.isrctn.org/>), we could not obtain the detailed information about long-term clinical trials of OT in ASD.

Nine pioneering clinical trials are in progress (Table 3). Although there is considerable diversity in age and gender of participants, oxytocin doses and trial duration, primary and secondary outcome measures would be the most noticeable items and are discussed here.

Registered identifier	Registered date	Estimated enrollment	Age (years)	Gender	Intellectual disability
NCT01417026	11 August 2011	68	12–17	Male	Profound mental retardation excluded
NCT01337687	10 December 2010	34	18–55	Both	Excluded
NCT01256060	22 November 2010	84	12–18	Both	Excluded
UMIN000003812	7 January 2010	20	10–14	Male	Not excluded
UMIN000005211	8 March 2011	60	>15	Both	Excluded
UMIN000007122	1 February 2012	20	18–54	Male	Excluded
UMIN000007250	9 February 2012	30	15–44	Male	Restricted to subjects with intellectual disability
ACTRN12611000061932	17 January 2011	40	3–8	Both	Not excluded
ACTRN12609000513213	29 June 2009	40	12–18	Male	Excluded
Registered number	Oxytocin doses per day	Oxytocin duration	Primary and secondary outcome measures		
NCT01417026	24 IU	5 days	Part/Whole Identity Test, Reading the Mind in the Eyes Test, social attention, reward/motivation, perception, and cognition tasks		
NCT01337687	48 IU	8 weeks	Clinical Global Impressions Scale- Severity and Improvement. Yale Brown Obsessive Compulsive Scale, Repetitive Behavior Scale— Revised, Diagnostic Analysis of Nonverbal Accuracy—2		
NCT01256060	0.8 IU / kg	12 weeks	Diagnostic Analysis of Nonverbal Accuracy, Social Responsiveness Scale, Clinical Global Impressions Scale— Improvement, Repetitive Behavior Scale— Revised, Child Yale-Brown Obsessive-Compulsive Scale		
UMIN000003812	Maximum 24 IU	12 months	Child Behavior Checklist, Autism Diagnostic Observation Schedule, Childhood Autism Rating Scale		
UMIN000005211	Unknown	Unknown	Aberrant Behavior Checklist, Childhood Autism Rating Scale, Zung Self-Rating Depression Scale, State-Trait Anxiety Inventory		
UMIN000007122	48 IU	6 weeks	Autism Diagnostic Observation Schedule, Childhood Autism Rating Scale 2, Psychological paradigms to test social cognition and behavior		
UMIN000007250	16 IU	8 weeks	Childhood Autism Rating Scale, Clinical Global Impressions, Aberrant Behavior Checklist, Global Assessment of Functioning, Interaction Rating Scale Advanced		
ACTRN12611000061932	Maximum 12 IU	5 weeks	Positive social interaction, Severity of repetitive behavior, Clinical Global Impressions, Preferential attention to social stimuli, Developmental Behavior Checklist, Social behavior scale		
ACTRN12609000513213	12–18 IU	8 weeks	Social Responsiveness Scale, Reading the Mind in the Eyes Test, Repetitive Behavior Scale, Clinician Global Assessment		

Table 3. Randomized, double-blind, placebo-controlled trials of intranasally short-term oxytocin administration in subjects with high-functioning autism spectrum disorder based on the public databases

The Social Responsiveness Scale provides quantitative measurements of social impairments in ASD by assessing domain of sociality such as social awareness and social information processing [37], and has been used as an outcome measure for interventions [38, 39]. The Reading the Mind in the Eyes Test [36] measures an aspect of social cognition by having the subjects assess emotion through the look of an actor's eye in photographs and has been adopted in many experimental trials [35, 40]. The Diagnostic Analysis of Nonverbal Accuracy Scale measures receptive and expressive abilities for receiving and sending emotions in faces, gestures, postures, and prosody [41], and has been used in the researches of not only ASD [42] but also of other mental disorders [43]. The Childhood Autism Rating Scale helps to identify subjects with ASD and determine symptom severity and has been commonly used in research and clinical settings. The scale assesses various domains of symptoms in ASD, including social impairments. The Autism Diagnostic Observation Schedule is a tool for assessment of symptoms of ASD through structured and semi-structured activities with subjects and provides scores in communication, social, and restricted and repetitive domains [44]. This tool has been regarded as the gold standard for assessing and diagnosing ASD. The Interaction Rating Scale Advanced assesses a practical index of social skills using five-minute video recorded interaction session [45]. It is interesting to note that this new tool may provide a validated measure of social impairments of ASD. The evaluations mentioned above provide quantitative values of social impairments of ASD based on caregivers' self-reports or behavioral observations.

At present, there is no commonly used assessment of symptoms in ASD, especially social and communication domains, for any interventions in contrast to the Positive and Negative Symptom Scale in schizophrenia and Hamilton Rating Scale for Depression in major depressive disorder, which are widely used as almost definitive measures. In the well-known research in which risperidone, a second-generation antipsychotic, was shown to be effective for reduction of irritability in subjects with ASD, the authors stated that they were unable to identify a validated measure for the core symptoms of ASD, i.e., social impairments [46].

A key question is whether these outcome measures could be used to sensitively assess improvements in sociality, which may only be subtle changes. This question remains unanswered before publication of the results of these trials.

5. What are the improvements of social impairments in the treatments of patients with ASD?

Social impairments in ASD have fundamentally different meanings from personality characteristics, such as introversion, interpersonal tension, or aloofness. Infants or preschool children with ASD may indicate very unique and impressive behaviors in the social context, which substantially reflect the disparity between typically developing children and children with ASD in social interaction. Here, we will describe pointing behaviors as an illustration.

When one points at something, others are invariably around. When one points at something, one invariably attempts to convey any information to others around. A toddler pulls his/her mother's sleeve, points to a miniature car on a shelf, and then looks at his/her mother's face (requesting pointing). When a preschool child sees a rainbow in the sky after rain, he/she runs up to his/her mother, takes her to the garden, and points to the rainbow while looking at her (declarative pointing). Liszkowski et al. found that twelve-month-old infants show different attitudes according to experimenter's reactions when infants point declaratively [47]. When experimenters responded to infants' declarative pointing but attended an incorrect referent with positive attitude, infants repeated pointing to redirect the experimenters' attention. When experimenters identified the correct referent with negative attitude, infants did not repeat pointing. When experimenters identified the correct referent and shared interest in it, infants appeared satisfied. Pointing is a prototypical behavior of interpersonal exchange, i.e., sociality.

Toddlers with ASD display a reduced incidence of declarative pointing compared to typically developing toddlers [48]. Declarative pointing constitutes a significantly diagnostic sign as well as social interest and joint attention for early detection of ASD [49]. Individuals with ASD have an innate disability in the social domain.

We consider that it would be essential to refer to one's own self and others if social impairments in ASD are discussed, because our own selves are embedded in a society full of others [20]. Individuals with ASD may be unable to mentalize the inner states of typically developing individuals, and this raises the question of whether typically developing individuals can mentalize the inner states of individuals with ASD. "Theory of mind" tasks would be regarded as tasks in ASD with "altered" self-consciousness proposed by individuals with "intact" self-consciousness.

According to the standpoint of traditional German psychopathology, self-consciousness (*Ichbesitsein* in German) is formally comprised of four prototypical representations. First, one's own self is identical at all times. Second, one's own self is always consistent. Third, all of one's own acts belong to one's own self. Finally, one's own self differs from others' own self. These representations deeply embedded in social interactions are intrinsically self-evident and underlie interpersonal exchange of sociality. While one exists almost without reflection on these representations in daily life, severe disruption of self-consciousness would have fairly serious consequences, such as dissociative identity crisis, doppelganger, xenopathic experiences and delusions of possession. Interestingly, children with ASD performed significantly less well on the self-test question than the other-person test question using tasks in which participants have to reflect an awareness of one's own prior belief [50]. These results suggest that individuals with ASD represent altered self-consciousness as mentioned above: "all of one's own acts belong to one's own self."

Although self-consciousness have been investigated using functional magnetic resonance imaging in ASD and healthy individuals [22, 23], the effects of OT on self-consciousness in humans have not been examined.

It is essential but difficult to answer questions regarding improvements of social impairments associated with treatment of patients with ASD. However, it may be useful to

assess self-consciousness, although there is as yet no suitable test to examine representations of self-consciousness available in ASD research.

6. Conclusion

We hypothesized that OT signaling in the central nervous system may play a significant role in the pathophysiology of ASD based on studies using OT-related knockout mice, effectiveness in social context of OT to healthy subjects, and the results of short-term administration of OT on social impairments in ASD subjects. Long-term clinical trials of OT in ASD subjects are currently in progress. It is difficult to determine how symptoms of social impairment should be assessed in interventions in patients with ASD, although investigation of self-consciousness may provide important insights regarding this issue.

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