Oxytocin and Animal Models for Autism Spectrum Disorder

Shlomo Wagner and Hala Harony-Nicolas

Abstract Autism spectrum disorder (ASD) is a group of complex neurodevelopmental conditions characterized by deficits in social communication and by repetitive and stereotypic patterns of behaviors, with no pharmacological treatments available to treat these core symptoms. Oxytocin is a neuropeptide that powerfully regulates mammalian social behavior and has been shown to exert pro-social effects when administered intranasally to healthy human subjects. In the last decade, there has been a significant interest in using oxytocin to treat social behavior deficits in ASD. However, little attention has been paid to whether the oxytocin system is perturbed in subgroups of individuals with ASD and whether these individuals are likely to benefit more from an oxytocin treatment. This oversight may in part be due to the enormous heterogeneity of ASD and the lack of methods to carefully probe the OXT system in human subjects. Animal models for ASD are valuable tools to clarify the implication of the oxytocin system in ASD and can help determine whether perturbation in this system should be considered in future clinical studies as stratifying biomarkers to inform targeted treatments in subgroups of individuals with ASD. In this chapter, we review the literature on genetic- and environmental-based animal models for ASD, in which perturbations in the oxytocin system and/or the effect of oxytocin administration on the ASD-associated phenotype have been investigated.

Keywords ASD animal models • Autism spectrum disorder (ASD) • Oxytocin

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1 Animal Models for ASD

1.1 Autism Spectrum Disorder (ASD)

ASD, which affects 1 in 68 children, is a group of neurodevelopmental conditions characterized by persistent deficits in social communication and interaction and in the manifestation of repetitive and stereotypic patterns of behaviors (American Psychiatric Association 2000). Beyond the basic characteristic features used as diagnostic criteria, the term ASD covers a large set of heterogeneous phenotypes that originate from a wide range of some recognized but mostly unrecognized etiologies. Those etiologies encompass genetic as well as nongenetic factors. The mode by which these factors affect brain molecular mechanisms, systems, and circuits, leading to the manifestation of the ASD-associated phenotype, is not fully understood. The pro-social peptide, oxytocin, is of a great interest in the ASD field; given the well-established knowledge about the role that oxytocin plays in modulating social behaviors (Harony and Wagner 2010) and the fact that social deficits are core symptoms of ASD. The question of whether the oxytocin system is affected in humans by ASD genetic or nongenetic risk factors is yet to be answered. Moreover, the effect of oxytocin on behavioral measures in individuals with ASD is in debate, mainly following the emergence of some equivocal results from clinical trials (reviewed by Guastella and Hickie 2016). Studies in human subjects are, with no doubt, essential for addressing any disease or disorder-related questions; however, they are extremely challenging as they are usually constrained by several factors. Those include the enormous heterogeneity in ASD, the lack of adequate tools to assess the integrity and functionality of the oxytocin system in the human brain, the insufficient availability and poor quality of postmortem brain tissues, and the restricted number of participating subjects.

Animal models for ASD are, therefore, valuable tools to help overcome these limitations. They provide us with unlimited access to affected brains that empower the discovery and investigation of mechanisms and circuits impaired in ASD.

Moreover, the relatively homogeneous genetic background of ASD animal models enables analyses of biological mechanisms in much higher resolution than that allowed by the heterogeneous human samples. ASD animal models also have a valued potential to enhance the discovery and development of new drugs and can be used to screen drugs approved in other medical conditions, which can be repurposed for ASD. To date, none of the drugs prescribed for individuals with ASD targets the core symptoms of the disorder; rather those are tailored to treat the co-morbidities and symptoms accompanying ASD in each individual, such as hyperactivity, anxiety, and self-stimulatory behaviors. Behavioral and psychological treatments are still considered a first line of intervention in ASD (Reichow and Wolery 2009; Seida et al. 2009; Warren et al. 2011). With the urgent necessity to develop pharmacological treatments that address the biological bases of the disorder, there is a need for valid animal models for ASD that could be reliable to inform translational studies.

1.2 Defining Validity of Animal Models for ASD

Similar to other fields of the medical sciences, the field of neurodevelopmental disorders, including ASD, applies three major criteria that relate to the validity of newly developed animal models. Those include face, construct, and predictive validity. In the context of neurodevelopmental disorders, *face validity* refers to the ability of a model to successfully capture aspects of the observed phenotype. Although it became a requirement for rodent models of ASD to show social deficits in order to demonstrate face validity, it is still open to debate whether the behaviors that we consider in rodents as social are truly related to the social deficits we observe in individuals with ASD. Moreover, there is little evidence showing that specific gene mutations produce one particular behavioral phenotype; rather, we are now aware that mutations in the same gene can lead to variable expressivity among affected subjects. For example, mutations in the ASD-associated gene *SHANK3* have been reported in individuals diagnosed with atypical schizophrenia (Gauthier et al. 2010) or intellectual disability (Gong et al. 2012; Hamdan et al. 2011). Therefore, face validity is based on a subjective assessment and is therefore prone to bias. *Construct validity* refers to the use of a proven biological cause in a model system, such as introducing a mutation/deletion in an ASD-associated gene or the exposure of an animal to an environmental factor associated with the disorder. This criterion also reflects current biases, as many of the models that were produced to mimic mutations in ASD candidate genes can be challenged, now that we know they are not true ASD genes. *Predictive validity* is a measure of the degree to which a treatment in a model system predicts effective treatment in humans. Despite the availability of animal models with face and construct validity, most of these models show little or no subsequent evidence for predictive validity. With the recent successful genetic discoveries of high confident ASD genes (De Rubeis and Buxbaum 2015), the field is now leaning towards choosing animal

models with construct validity, which will allow for unbiased findings of associated phenotypes. In order to obtain such unbiased findings, "construct validity-based models" should be characterized not only based on assessment of higher-order behaviors, but also based on assessment of neurological phenotypes, morphological and anatomical analyses of neural cells and brain regions, and examination of brain activity and connectivity, as suggested by Buxbaum et al. (2012).

1.3 Types of Animal Models for ASD

Models for ASD can be divided into three major categories: (1) *Genetic-based models*, which are produced by targeting an ASD-associated gene or chromosomal locus, through introducing point mutations, deletions, or duplications that can affect single or multiple genes. (2) *Environmental-based models*, which are produced by introducing an environmental factor that has been associated with ASD, such as chemical or infectious organisms. Many of these factors have been studied in the context of prenatal exposure of pregnant women. (3) *Behavioral-based models*, which are naturally occurring animal models, which present with behavioral deficits that parallel those observed in subjects with ASD.

In the following sections, we will first describe selected ASD animal models that fall in the first and second categories, and in which the oxytocin system has been implicated. Next, we will discuss findings that suggest a link between alterations in the oxytocin system and the behavioral deficits displayed by these models.

1.3.1 Fragile X Syndrome (FXS)

FXS is the most common inherited form of intellectual disability and one of the most prevalent genetic causes of ASD. FXS presents with a spectrum of physical abnormalities, cognitive impairment, and abnormal social behavior (Garber et al. 2008) and is caused by transcriptional silencing of the fragile X mental retardation (*FMR1*) gene, leading to the absence of the fragile X mental retardation protein (FMRP) (Gocel and Larson 2012; La Fata et al. 2014). FMRP is an RNA-binding protein, which binds to a distinct population of neuronal mRNAs, many of which are linked to ASD (Ascano et al. 2012; Darnell et al. 2011). The central function of FMRP is repression of translation, especially of synaptic-plasticity related genes (Darnell et al. 2011). FMRP also modulates mRNA trafficking, dendritic maturation, and synaptic plasticity (reviewed in Sidorov et al. 2013). Several animal models have been developed to understand the function of FMRP and the affected mechanisms in FXS. Those include *Fmr1*-knockout (KO) drosophila (Zhang et al. 2001), zebrafish (den Broeder et al. 2009), mouse (Kazdoba et al. 2014), and rat (Hamilton et al. 2014) lines. *Fmr1*-KO mice display a range of phenotypes similar to the human disorder, including ASD-like behaviors (social deficits and stereotypic/repetitive behaviors), audiogenic seizures, aberrant dendritic spine morphology, and macroorchidism

(Gkogkas et al. 2014; Huber et al. 2001; McKinney et al. 2005). *Fmr1*-KO mice also display enhanced long-term depression (LTD), mediated by metabotropic glutamate receptor in hippocampal slices (Bhattacharya et al. 2012; Dolen et al. 2007; Ronesi et al. 2012), reduced gamma-aminobutyric acid (GABAergic) synaptic transmission (Liu et al. 2013), elevated phosphorylation of translational control molecules, and increased rates of global mRNA translation (Gkogkas et al. 2014; Bhattacharya et al. 2012; Liu et al. 2013).

1.3.2 CNTNAP2

Recessive nonsense mutations in the contactin associated protein-like 2 (*CNTNAP2*) gene have been implicated in cortical dysplasia–focal epilepsy (CFDE) syndrome, which is a recessively inherited disorder in which 70% of affected individuals have ASD (Rodenas-Cuadrado et al. 2014; Strauss et al. 2006). Mutations have also been associated with seizures, epilepsy, and attention-deficit hyperactivity disorder (ADHD) (Elia et al. 2010; Mefford et al. 2010), which are prevalent in individuals with ASD. CASPR2, the protein encoded by the *CNTNAP2* gene, is a member of the neuroxin superfamily, a group of transmembrane proteins that mediate cell–cell adhesion through interacting with the neuroligin family of proteins, also associated with ASD (Betancur et al. 2009). CASPR2 is thought to play an important role in neural migration during development and subsequent laminar organizations (Strauss et al. 2006). Alterations in neural migration have been reported in individuals with *CNTNAP2* mutation and imaging studies in carriers of an alternative ASD risk allele of *CNTNAP2* have reported abnormal grey and white matter volumes, decreased frontal grey matter (Tan et al. 2010), and altered functional connectivity in frontal lobe circuits (Scott-Van Zeeland et al. 2010). Similar to humans with *CNTNAP2* mutations, *Cntnap2*-KO mice suffer from epileptic seizures, have neural migration abnormalities, and show deficits in ASD-associated behaviors, suggesting their face and construct validity as an animal model of a monogenic form of ASD (Brunner et al. 2015; Penagarikano et al. 2015).

1.3.3 15q11–13 Deletion/Duplication

The 15q11–13 chromosomal region includes several imprinted genes that are expressed either from the maternal of paternal inherited copy. Therefore, deletions or duplications in this region can lead to the manifestation of different disorders/syndromes, depending on the parental origin of the mutated allele. Angelman Syndrome (AS), for example, is a genomically imprinted disorder linked to this chromosomal region and is associated with ASD (Veltman et al. 2005). It is caused by the loss of imprinted genomic material of a maternal origin within the same locus, particularly the loss of the Ubiquitin-protein ligase E3A (UBE3A) gene (Margolis et al. 2015). UBE3A plays an important role in synapse development and plasticity (Greer et al. 2010; Yashiro et al. 2009), and mice with maternal

inherited disruption in this gene show altered spatial learning memory, in addition to increased susceptibility to seizures and deficits in motor coordination (reviewed in Jana 2012). $GABA_A$ receptor ($GABA_AR$) subunit genes, which modulate the GABAergic signaling pathways that has been previously associated with ASD (Blatt 2005), are also contained in this imprinted region. Those include *GABRB3*, *GABRA5*, and *GABRG3*. *Gabrb3*-null mice also show impaired learning and memory, increased susceptibility to seizures, impaired social behaviors, hyperactivity, and increased tactile sensitivity (DeLorey et al. 1998, 2008; Homanics et al. 1997). Prader-Willi Syndrome (PWS), on the other hand, is caused by the loss of imprinted genomic material of a paternal origin within the 15q11.2–13 locus (Veltman et al. 2005). This syndrome, which occurs in 1/10,000–1/30,000 births, is a multisystem neurodevelopmental disorder that presents with great variability and changing clinical features during the patient's life. Following infantile severe hypotonia and feeding difficulties, which take place at early developmental stages, individuals with PWS present later with unrelenting feelings of hunger and therefore an excessive eating that leads to life-threatening obesity (Angulo et al. 2015). Moreover, PWS patients display mild-to-moderate intellectual disability and behavioral alterations including many features of ASD, such as impaired social behavior, increased repetitive behaviors, as well as ritualistic behaviors (Bennett et al. 2015). The parentally expressed genes within the 15q11.2–13 region have been well studied and, although deletion of no one individual gene has been found to cause PWS, research has shown that the lack of expression of multiple genes may be central to the syndrome's expression. Specifically, five polypeptide-coding genes, namely *MKRN3*, *MAGEL2*, *MAGED1*, *NECDIN*, and *SNURF-SNRPRN*, have been shown to be centrally involved in PWS. Several mouse lines with null mutations in one of these genes were produced and investigated (reviewed in Bervini and Herzog 2013), with each displaying phenotype resembling some of PWS-associated deficits.

Finally, duplications in the 15q11–13 loci are also associated with ASD. When paternally derived, these duplications may show mild developmental and cognitive impairment or no phenotype, while, when maternally derived, they confer a high risk of ASD (>85%) (Cook and Scherer 2008). Modeling these duplications in mice shows an opposed phenotype to what we observe in human subjects. Mice with paternally derived duplication of the conserved linkage group on mouse chromosome 7 that parallels the human 15q11–13 loci display impaired social interaction, behavioral inflexibility, abnormal ultrasound vocalization, and increased anxiety. Maternally derived duplication shows no significant differences in these behaviors (Nakatani et al. 2009).

1.3.4 Valproic Acid (VPA) Exposure

Prenatal exposure of pregnant women to several chemicals and/or infections has been suggested to be associated with ASD, amongst which VPA is the most extensively studied. VPA is frequently prescribed as an anti-epileptic drug and is

known as human teratogen (Meador et al. 2008; Ornoy 2009). Prospective and retrospective human studies demonstrated that exposure of pregnant women to VPA increases their risk for having a child with ASD (Bromley et al. 2008; Christensen et al. 2013; Rasalam et al. 2005; Williams et al. 2001). VPA is a histone deacetylase inhibitor and is therefore thought to be posing its deleterious effect through the role it plays as an epigenetic modulator (Gottlicher et al. 2001). Notably, recent emergence of high-throughput sequencing technologies in a large ASD cohort has identified a set of chromatin-remodeling genes (De Rubeis et al. 2014; Iossifov et al. 2014), suggesting that perturbation of the epigenetic-remodeling machinery through genetic or environmental factors may underlie the pathophysiology of ASD in a subset of individuals with ASD. The prenatal embryonic development in rodents reflects the first and second trimester of pregnancy in humans, while the early postnatal developmental stages reflect the third trimester and the first several months of human life. Studies from rats and mice evolved to examine the effect of VPA exposure during several time points within these prenatal and postnatal developmental periods. Findings from prenatal exposure studies supported those from human studies and demonstrated that prenatal exposure to VPA leads to the manifestation of ASD-like behaviors including social behavioral deficits, increased repetitive and stereotypic behaviors, decreased sensitivity to pain, and increased anxiety (reviewed in Ergaz et al. 2016). Moreover, they showed that parental exposure to VPA could also lead to cellular and anatomical changes similar to those observed in postmortem brain tissues from individuals with ASD. Those included reduction in the size of the cerebellar hemispheres, decreased number of cerebellar Purkinje cells, and enhanced synaptic plasticity of the prefrontal cortex and amygdala (Dufour-Rainfray et al. 2010; Ingram et al. 2000; Tsujino et al. 2007). These studies also indicated that embryonic day 12.5 (E12.5) in mice (Kataoka et al. 2013) and E12 in rats (Kim et al. 2011) are the most vulnerable to VPA exposure. Findings from postnatal exposure studies, mainly on postnatal day 14 (P14), suggested that even a single postnatal exposure to VPA leads to the manifestation of social interaction deficits, increased anxiety, and depressive behaviors and results in enhanced cell death in the cerebellum and hippocampus (Yochum et al. 2008).

2 Oxytocin in Animal Models for ASD

2.1 Possible Implication of the Oxytocin System in Behavioral Deficits Displayed by ASD Animal Models

A causal link between oxytocin and ASD has been suggested by Modahl and colleagues in 1992 (Modahl et al. 1992). Since then, this causality has been intensively discussed in the literature (see for example Green and Hollander 2010; Hammock and Young 2006; Insel et al. 1999; Lee et al. 2015; Lukas and

Neumann 2013; Olza Fernandez et al. 2011; Preti et al. 2014; Romano et al. 2015), yet with no definite conclusion. To examine the potential link between oxytocin and ASD, one approach is to study the consequence of impairment in the oxytocin system on behavior. This can be done, for example, by studying the effect, on behavior, of mutations in the genes encoding for oxytocin (*Oxt*) or its receptor (*Oxtr*). While such effects have been investigated in a limited number of human studies (Bittel et al. 2006; Gregory et al. 2009), it has been well studied in animal models. Multiple lines of genetically modified mice, bearing null mutations in genes encoding for *Oxt*, *Oxtr*, or regulators of the oxytocin system, such as the ADP-ribosyl cyclase CD38 (Higashida et al. 2012), were produced and thoroughly investigated. Ferguson and colleagues were the first to report that *Oxt*-deficient mice display a specific impairment in social recognition memory (Ferguson et al. 2000), an observation that was later confirmed in several lines of *Oxt* and *Oxtr*-deficient mice (Crawley et al. 2007; Lee et al. 2008; Takayanagi et al. 2005). Interestingly, a similar deficit was also observed in *CD38*-deficient mice, in which the release of oxytocin, from nerve terminals, is affected (Jin et al. 2007). These mouse lines also show deficits in multiple parameters of social behavior, such as male aggression (Takayanagi et al. 2005), maternal behavior (Higashida et al. 2010; Pedersen et al. 2006), and social interaction (Pobbe et al. 2012; Sala et al. 2013). Moreover, they display deficits in behavioral and physiological parameters related to other domains of ASD symptoms, such as separation-induced pup vocalization (Takayanagi et al. 2005; Higashida et al. 2010), which is thought to represent linguistic skills in animal models, cognitive flexibility, which is related to stereotyped behavior, as well as, in susceptibility to seizures (Sala et al. 2011). Interestingly, a recent study showed that heterozygous *Oxtr* mice (Sala et al. 2013) display some social behavior deficits, suggesting that these behaviors are sensitive to *Oxtr* gene dosage. Taken together, these findings provide strong evidence that impairment in oxytocin system in mice leads to the manifestation of a range of ASD-related symptoms, which extends beyond the social memory deficit, initially reported in these models (see Crawley et al. 2007). The findings also support the face validity of these mouse lines as model for ASD. Notably, the behavioral deficits exhibited by *Oxt*-null, *CD38*-null, and *Oxtr*-null mice could be reverted by exogenous application of oxytocin or the Oxtr agonist TGOT (Table 1).

A second approach to examine the potential link between oxytocin and ASD is to apply an opposing strategy and examine if the oxytocin system is impaired in valid animal models of ASD (those fulfilling construct and preferably face validity as well). This approach has been specifically applied in studying animal models for PWS. As discussed earlier in Sect. 1.3.3, individuals with PWS present with several characteristic phenotypes and with ASD-associated behaviors, including social behavior deficits and increased repetitive behaviors. Notably, those patients exhibit a significant decrease in the number of oxytocin-expressing neurons in the hypothalamic paraventricular nucleus (PVN) (Swaab et al. 1995), and there is strong evidence that this alteration in brain oxytocin production is underlying the excessive obesity of PWS patients (reviewed in Sabatier et al. 2013). Mouse models for PWS show a similar phenotype. *Maged1*-deficient mice develop progressive obesity,

Table 1 Summary of animal models displaying deficits in ASD-associated behaviors and impairment in the oxytocin system

Model	Observed deficits	Effect on Oxt system	Oxt administration method *Unless otherwise noted	Effect of Oxt administration	Reference
Oxt-KO adult male mice	Impaired social memory	No Oxt production	Acute ICV	Reversal of social memory loss	Ferguson et al. 2000
CD38-KO male and female mice	Increased locomotion, impaired maternal behavior and social memory	Impaired Oxt release	Acute subcutaneous and ICV	Reversal of impaired maternal behavior and social memory	Jin et al. 2007
Oxtr-KO adult male mice	Impaired social preference and social memory, increased aggression, decreased cognitive flexibility	No Oxtr production	Acute ICV	Reversal of all deficits (via the AVP1a receptor)	Sala et al. 2011
Oxtr-Het adult male mice	Impaired social preference and social memory	Reduced Oxtr production	*Acute ICV TGOT (Oxtr agonist) administration	Reversal of all deficits	Sala et al. 2013
Maged1-KO adult male mice	Reduced sexual behavior, social interactions, and ultrasonic vocalization towards females. Impaired social memory and increased self-grooming and anxiety	Reduced number of Oxt neurons and reduced level of mature Oxt production in the hypothalamus	Acute subcutaneous	Reversal of impaired social memory	Dombret et al. 2012
Magel2-KO new born mice	High mortality and impaired suckling	Reduced levels of mature Oxt in the hypothalamus	Acute subcutaneous injection, 3-5 hours after birth	Reversal of impaired suckling and mortality	Schaller et al. 2010
Magel2-KO male mice	Atypical social interactions, impaired recognition and spatial memory	Increased number of Oxt neurons and mature Oxt in the hypothalamus, and decreased Oxtr binding specifically in the lateral septum	Daily subcutaneous injections during PND 1-7	Reversal of all impairments in adulthood, including the anatomical modifications	Meziane et al. 2014

(continued)

Table 1 (continued)

Model	Observed deficits	Effect on Oxt system	Oxt administration method *Unless otherwise noted	Effect of Oxt administration	Reference
Cntnap2-KO juvenile (4-6w) male and female mice	Impaired social interactions, hyperactivity, increased repetitive preservative behaviors, and hypersensitivity to sensory stimuli	Reduced Oxt expression in the PVN	Acute intraperitoneal or intranasal, or subchronic intranasal in juvenility (PND 7-21)	Reversal of the social behavioral impairment and elevation of Oxt expression in the PVN	Peñagarikano et al. 2015
Grin1-KO adult male and female mice	Hyperactivity and impaired sensorimotor gating and social preference	Not examined	Acute or subchronic (4 injections across 8-9 days) intraperitoneal	Reversed the hyperactivity but not the impaired sensorimotor gating. The subchronic treatment reversed the impaired social preference	Teng et al. 2016
Oprm1-KO adult male mice	Reduced ultrasonic vocalization towards females	Higher levels of Oxtr expression in specific brain regions	Acute intranasal	Restoration of normal ultrasonic vocalization	Gigliucci et al. 2014
Stx1a- KO adult male mice	Impaired social memory	Lower Oxt level in the CSF, impaired Oxt release from amygdala slices	Acute ICV	Restoration of social memory	Fujiwara et al. 2016
Shank3-deficient rat	Impaired attention and long-term social recognition memory and deficits synaptic plasticity in the Hip-mPFC circuit	Not examined	Acute ICV	Rescue of attention, social recognition memory, and synaptic plasticity deficits	Harony-Nicolas et al. 2017

Abbreviations: Oxt- Oxytocin, Oxtr- Oxytocin receptor, KO-Knockout, Het-Heterozygous, ICV- Intracerebroventricular, CD38- cluster of differentiation 38, Maged1-Melanoma antigen family D1, Magel2- Melanoma antigen family L2, Cntnap2- Contactin-associated protein-like 2, Grin1-Glutamate Receptor, Ionotropic, N-Methyl D-Aspartate 1, Oprm1- Opioid Receptor Mu 1, Stx1a- Syntaxin-1A, Hip-Hippocampus, mPFC-medial prefrontal cortex

reduced social interactions and social memory, deficient sexual behavior, as well as increased anxiety and self-grooming. Interestingly, these mice show a significant decrease in the production of mature oxytocin in the brain and acute subcutaneous administration of oxytocin can rescue their social memory deficits (Dombret et al. 2012). *Magel2*-deficient mice exhibit feeding difficulties as well as deficits in social behavior and learning (Meziane et al. 2015; Schaller et al. 2010). Similar to *Maged1*-deficient mice, *Magel2*-deficient pups show a significant reduction in the production of mature oxytocin in the PVN, while intermediate forms of the peptide are enhanced (Schaller et al. 2010). In adulthood, these mice have a higher number of oxytocin-expressing neurons, higher levels of mature oxytocin in the PVN, and increased innervation of target brain areas by these cells. These observations suggest that the oxytocin system is plastic and may compensate for impairments displayed by newborns. Notably, daily subcutaneous administration of oxytocin in the first postnatal week was sufficient to prevent the deficits in social behavior and learning abilities in adult *Magel2*-deficient male mice. Moreover, this treatment restored the normal processing and maturation of oxytocin in the adult PVN (Meziane et al. 2015). *Necdin*-deficient mice show a significant reduction in the number of oxytocin-producing neurons in the hypothalamus (Muscatelli et al. 2000). Overall, these studies make PWS a strong case for a genetic disorder with common lines with ASD, where impairment in the oxytocin system exists and where administration of the oxytocin peptide can reverse the behavioral deficits.

An additional example for this opposing approach comes from studies on the *Cntnap2*-mouse model (Penagarikano et al. 2015), presented in Sect. 1.3.2. In their study, Peñagarikano and colleagues showed that the expressional level of oxytocin in the PVN and the oxytocin levels in brain extracts of *Cntnap2*-KO mice are both significantly low, as compared to WT mice. They also found that a single intraperitoneal or intranasal application of oxytocin was sufficient to transiently rescue deficits in social behavior exhibited by *Cntnap2*-deficient mice. Moreover, they showed that chronic treatment of young *Cntnap2*-deficient mice, with intranasal oxytocin application between days P7 to P21, not only alleviated the social behavioral deficits displayed by this mouse model in adulthood, but also restored the normal level of oxytocin-expression in PVN neurons and the brain oxytocin levels at P30. Thus, similar to findings evolving from studies on the *Magel2*-deficient mice, this study in *Cntnap2*-deficient mice also reports promising results for a beneficial early-life intervention with oxytocin.

2.2 *Oxytocin and Developmental Processes Associated with ASD*

Oxytocin could affect developmental processes that may underlie the etiology of ASD, suggesting that oxytocin manipulations in subjects with ASD during early life stages may be beneficial even if there is no evidence for perturbations in the

oxytocin system. The brain excitation/inhibition balance provides a strong example for a developmental process that can be affected by oxytocin. A prominent hypothesis in the field suggests that imbalance between excitatory and inhibitory neurotransmission in the brain, especially in cortical areas, is involved in ASD pathophysiology (Yizhar et al. 2011). In general, inhibitory neurotransmission in the brain is mediated by the neurotransmitter GABA, while excitatory neurotransmission is mediated by glutamate. The most important mechanism by which GABA exerts its inhibitory action is by binding to the $GABA_AR$. This highly abundant receptor forms a channel in the plasma membrane that opens upon GABA binding, mainly to chloride ions (reviewed in Farrant and Kaila 2007). Usually, the electrochemical gradient across the cell membrane drives the negative chloride ions into the cell through the activated $GABA_AR$, thus creating a negative charge transfer that hyperpolarizes the cell membrane and inhibits neural activity. This hyperpolarizing action of activated $GABA_ARs$ depends on the ratio of chloride concentrations between the two sides of the plasma membrane, which dictates the membrane potential in which the chloride influx reverses to become efflux. This membrane potential is termed the reversal potential of the $GABA_AR$ (E_{GABA}).

In most cases of mature neurons in the brain, the chloride concentration is much higher in the extracellular than in the intracellular space, thus causing E_{GABA} to be in the hyperpolarizing range of -60 to -80 mV. This gradient of chloride ions is created by the balance between the activities of the chloride importer NKCC1 and the chloride exporter KCC2 (Payne et al. 2003). It is well known that, unlike mature neurons, newborn neurons tend to be excited, rather than inhibited, by GABA (Ben-Ari et al. 1994; Cherubini et al. 1991). This GABA-mediated excitation is caused by downregulation of KCC2 in newborn neurons, resulting in relatively high intracellular chloride levels (Yeo et al. 2009). This imposes a depolarizing E_{GABA} of ~ -40 mV and drives neuronal excitation in response to $GABA_AR$ activation by GABA. Nevertheless, during development (around birth in rats and mice), a continuous KCC2-mediated process of chloride extrusion hyperpolarizes E_{GABA}, thus creating a gradual shift of GABA action from excitatory during developmental stages to inhibitory in the mature brain (Fig. 1). This "GABA switch" is best studied in rat hippocampal pyramidal neurons, where GABA becomes strictly inhibitory by the end of the first postnatal week. It was shown by Rivera and colleagues that, in these cells, an upregulation of KCC2 expression, until reaching the level of mature neurons, occurs in rats between P5 and P9 (Rivera et al. 1999). This process correlates with the excitatory-to-inhibitory GABA switch, which could be blocked using KCC2 antisense RNA. Following this study, Tyzio et al. (Tyzio et al. 2006) showed that around birth (E20 to P0), there is a rapid and transient decrease in intracellular chloride (from 18 to 4 mM), which causes a marked hyperpolarization of E_{GABA}, leading to inhibitory responses to the $GABA_AR$ agonist. They also demonstrated that this process is induced by oxytocin-mediated inhibition of NKCC1 activity. Accordingly, offspring of pregnant rats, treated with oxytocin

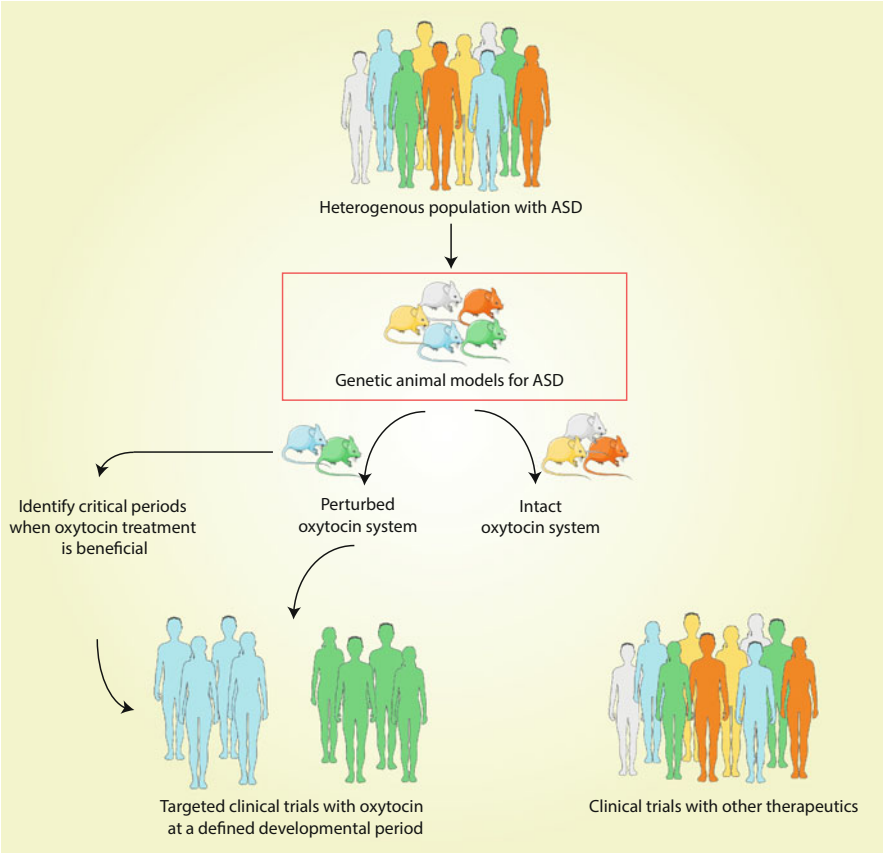

Fig. 1 Animal models with genetic mutations mimicking those identified in individuals with ASD can be leveraged to enhance our understating of the pathophysiology underlying the ASD phenotype and to inform future targeted clinical trials in subgroups of individuals with ASD. Genetic animal models for monogenic forms of ASD (depicted by similar colors in human and mouse) can be employed to study the impact of specific ASD-associated mutations on the integrity and functionality of the oxytocin system and to identify the developmental periods when oxytocin treatment is most beneficial in these models. Findings from preclinical studies in monogenic animal models can inform targeted clinical studies in subgroups of ASD individuals with the same mutation that would be most helped by oxytocin treatment, and will define the most beneficial developmental period for intervention

receptor antagonist before labor, did not show this transient hyperpolarization of E_{GABA} and maintained excitatory responses to $GABA_AR$ activation. The authors suggested that, by this action, the oxytocin, which is secreted in high level from the mother's brain around labor, acts to protect the fetus brain from hypoxic-ischemic damage during delivery. In a recent paper (Tyzio et al. 2014), the same group explored the developmental shift in E_{GABA} in two animal models of ASD: the

genetic model of FXS; the *Fmr1-KO* mouse, and the pharmacologically induced model of ASD; the prenatally VPA-exposed rats, discussed in Sects. 1.3.1 and 1.3.4, respectively. They found that, in both animal models, E_{GABA} did not go through the hyperpolarization process characterizing the period of the first weeks after birth and was found significantly more depolarized during P30 as compared to control animals. Moreover, the transient robust hyperpolarization of E_{GABA}, observed in WT mice and rats around P0, was completely abolished in VPA rats and significantly weakened in FXS mice. The depolarized E_{GABA} could be corrected to hyperpolarized levels by blocking NKCC1 activity, either using the NKCC1 blocker bumetanide or via oxytocin application. In accordance with the depolarized E_{GABA}, pyramidal neurons in hippocampal slices, derived from both animal models, responded with excitation to $GABA_AR$ agonist, whereas the neurons derived from control animals typically responded with inhibition. Moreover, the frequency of spontaneous glutamatergic excitatory postsynaptic currents (EPSCs) was significantly higher in both models, suggesting a hyper-excitable neuronal network. The enhanced network activity could also be blocked by bumetanide, suggesting a role of depolarized E_{GABA} in this phenomenon. Interestingly, a maternal pretreatment of pregnant VPA-exposed rats or FXS mice, with bumetanide in their drinking water 1 day before delivery, restored hyperpolarized E_{GABA}, reduced the excitatory effect of $GABA_AR$ agonist, and decreased the spontaneous glutamatergic network activity measured from hippocampal pyramidal neurons at P15. Thus, the blockade of the NKCC1 activity during the critical period around delivery appears to have a positive long-lasting effect on the abnormal excitation/inhibition balance in both ASD animal models. The authors then tried to examine the effect of the same bumetanide treatment on the behavioral abnormalities displayed by the two ASD animal models. They focused on the isolation-induced ultrasonic vocalizations that pups (at P4) emit when separated from their mothers, which are abnormal in both models, and found that maternal bumetanide pretreatment rescued this phenotype and restored the control characteristics of these vocalizations. In a follow-up study (Eftekhari et al. 2014), the authors also looked at social behavior in adult subjects of these models and found that maternal pretreatment with bumetanide does improve distinct deficits of social behavior displayed by these ASD models. Notably, the authors found that maternal pretreatment of naïve pregnant animals with the orally applicable oxytocin receptor (Oxtr) antagonist SSR126768A, a day before delivery, exerted a very similar influence on hippocampal E_{GABA}, GABA response, and spontaneous network activity as found for the VPA-exposed rats and FXS mice. Moreover, this treatment caused deficits in the ultrasonic vocalizations of separated naïve pups, as well as in sociability of adult rats and mice that resembled the deficits characterizing the ASD models. Thus, the authors propose that failure of the oxytocin-mediated process that regulate the changes in E_{GABA} around birth causes the development of ASD symptoms in several ASD animal models and, thus, may also be involved in ASD etiology. Moreover, they suggest that bumetanide treatment at the early developmental stages, mainly when the shift of GABA action from excitatory to inhibitory takes place, may rescue at least some of the ASD symptoms. Notably, bumetanide

treatment in young children is now in clinical trials and promising preliminary results have recently evolved and have been published by the same group (Hadjikhani et al. 2015; Lemonnier and Ben-Ari 2010; Lemonnier et al. 2012, 2013).

The suggestive involvement of impairment in the oxytocin-mediated developmental GABA switch in ASD was further supported by several recent studies. First, the delay in the hyperpolarizing shift in $E_{GABA,}$ during the first 2 weeks of life in *Fmr1*-KO mice, was recently confirmed by in an independent study and shown to be correlated with a developmental upregulation of NKCC1 expression at P10 (He et al. 2014). Second, analysis of the expression of chloride cotransporters in cerebrospinal fluid from young patients (2–19 years old) with Rett syndrome, also associated with ASD, showed significantly reduced levels of KCC2 and KCC2/NKCC1 ratio, as compared to a control group (Duarte et al. 2013). Finally, Leonzino et al. (2016) reported a delayed GABA switch in cultured hippocampal neurons derived from *Oxtr*-deficient mice at E18, as compared to WT controls. This delayed switch correlated with the impaired ability of the *Oxtr*-KO neurons to increase their KCC2 expression levels after being cultured for 5 days in vitro (DIV5), as compared to the 20–30-fold increase observed in *Oxtr*-WT neurons at DIV5. In addition, the delayed GABA switch correlated with high frequency and amplitude of spontaneous excitatory synaptic currents of the cultured network, as previously described by Tyzio and colleagues (Tyzio et al. 2014) for the *Fmr1*-KO mice and VPA-exposed rats. Accordingly, a reduced level of KCC2 was observed in hippocampal neurons derived from *Oxtr*-deficient mice at P6 and P60, as compared to WT controls, suggesting a long-lasting effect of *Oxtr* deficiency on KCC2 activity. The authors also found that *Oxtr*-KO cultured neurons also failed to increase the phosphorylation of KCC2 on Ser940, a post-translational modification that promotes KCC2 incorporation into the plasma membrane. Notably, the authors reported that, in *Oxtr*-WT neurons, oxytocin application increased KCC2 phosphorylation only in a very early and restricted time window (DIV3 and DIV4 but not at DIV5 or DIV6).

Taken together, these studies support the role of oxytocin in mediating the GABA switch during early development and suggest that failure of this switch, due to different causatives, leads to the manifestation of ASD symptoms in animal models. Such a failure may underlie ASD pathophysiology in, at least, a subset of individuals with ASD, a hypothesis that requires further investigation.

2.3 *Oxytocin to the Rescue in Animal Models with ASD-Associated Behaviors*

The role that oxytocin plays in regulating mammalian social behavior is very well established (Heinrichs et al. 2009). Therefore, whether or not oxytocin is implicated in processes that could potentially underlie ASD pathophysiology and are essential

during early developmental, treatment with oxytocin can still be considered for ameliorating ASD-associated behavioral deficits in adulthood. In fact, several animal studies that examined the effect of oxytocin on social behavior, where deficits in the oxytocin system have not been reported or, more likely, never tested, have reported an ameliorative effect. For example, Teng and colleagues examined the effects of either a single or subchronic (four times over 8–9 days) intraperitoneal administration of oxytocin on ASD-related behavioral deficits exhibited by two inbred mouse lines, BALB/cByJ and C58/J (Teng et al. 2013). They found that the subchronic treatment in young adults (around P30) had a significant improving effect on the social behavioral deficits, displayed by both lines, and that oxytocin treatment decreased the motor repetitive behavior displayed by the C58/J mice. In a follow-up study the same group has also reported similar effects of subchronic oxytocin treatment in a genetically modified model for ASD, the *Grin1*-defiecient mice, which lacks the *N*-methyl-D-aspartate receptor NR1 subunit (Teng et al. 2016). It should also be noted that acute oxytocin application was reported to rescue social deficits in other genetically modified mouse lines that exhibit impaired social behavior. For example, in *Oprm1*-KO mice, which lack the mu 1 opioid receptor, a single intranasal delivery of oxytocin rescued the deficit in ultrasonic vocalization towards females exhibited by adult males (Fujiwara et al. 2016; Gigliucci et al. 2014). Similarly, a single intracerebroventricular administration of oxytocin restored the impaired social memory displayed by *Stx1a*-KO adult male mice lacking Syntaxin 1a (Fujiwara et al. 2016; Gigliucci et al. 2014) (see Table 1 for a summary of these findings). We have recently reported the generation and characterization of a transgenic rat model for Phelan McDermid Syndrome and ASD, the *Shank3*-deficient rat model (Harony-Nicolas et al. 2017) and demonstrated that the introduced *Shank3* mutation leads to synaptic plasticity deficits in a brain circuit implicated in social behavior and to impaired attention and long-term social recognition memory. Importantly, we found that intracerebroventricular injection of oxytocin could rescue the synaptic plasticity deficits and ameliorate the impaired behavior (Table 1) (Harony-Nicolas et al. 2017). It is yet to be determined whether the oxytocin system is affected by *Shank3*-deficiency and whether perturbation in this system may contribute to the observed phenotype.

3 Concluding Remarks

The possible link between oxytocin and ASD and the potential therapeutic effect of oxytocin in treating social behavioral deficits have been extensively discussed and investigated in the past two decades. Despite the advances in our knowledge, there are still no explicit conclusions on whether the oxytocin system is disturbed in some individuals with ASD and if the efficacy of oxytocin treatment is strictly dependent on the functionality of the oxytocin system. Addressing these questions in human studies is extremely challenging, mainly due to the lack of predictive biomarkers to identity relevant subgroups and the limited number of diverse postmortem samples.

Animal models for ASD have been used as a powerful tool to help overcome these limitations and discoveries from these models are now paving the way towards a better understanding of the link between oxytocin and ASD. In this chapter, we summarized findings that evolved (1) from animal models, where components of the oxytocin system were genetically targeted, leading to ASD-associated deficits, (2) from validated ASD animal models, where impairments in the oxytocin system were detected, and (3) from ASD animal models, where oxytocin administration was found to alleviate ASD-associated impairments. These findings suggest that the oxytocin system may be affected directly or indirectly by genetic and nongenetic factors associated with ASD, which could disturb oxytocin production, oxytocin trafficking, or oxytocin release within the brain. They also suggest that developmental processes modulated by oxytocin may be impaired in ASD.

Future studies should leverage additional monogenic models for ASD to enhance our understating on the impact of mutations in ASD-associated genes on the integrity and functionality of the oxytocin system and to identify developmental periods when oxytocin treatment is most beneficial. Findings from these studies will be of translational significant, as they will (1) inform future clinical trials in subgroups of individuals with ASD that may be most helped by oxytocin treatment and (2) point to critical periods for treatment (Fig. 1).

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