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Linking oxytocin and arginine vasopressin signaling abnormalities to social behavior impairments in Prader-Willi syndrome

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ABSTRACT

Prader-Willi syndrome (PWS) is a genetic neurodevelopmental disorder. Global hypothalamic dysfunction is a core feature of PWS and has been implicated as a driver of many of PWS's phenotypic characteristics (e.g., hyperphagia-induced obesity, hypogonadism, short stature). Although the two neuropeptides (i.e., oxytocin [OXT] and arginine vasopressin [AVP]) most implicated in mammalian prosocial functioning are of hypothalamic origin, and social functioning is markedly impaired in PWS, there has been little consideration of how dysregulation of these neuropeptide signaling pathways may contribute to PWS's social behavior impairments. The present article addresses this gap in knowledge by providing a comprehensive review of the preclinical and clinical PWS literature–spanning endogenous neuropeptide measurement to exogenous neuropeptide administration studies–to better understand the roles of OXT and AVP signaling in this population. The preponderance of evidence indicates that OXT and AVP signaling are indeed dysregulated in PWS, and that these neuropeptide pathways may provide promising targets for therapeutic intervention in a patient population that currently lacks a pharmacological strategy for its debilitating social behavior symptoms.

1. Introduction

Prader-Willi Syndrome (PWS) is a genetic neurodevelopmental disorder that occurs in approximately 1 in every 10,000–30,000 births (Cassidy, 1997; Cassidy et al., 2012; Donaldson et al., 1994; Nicholls et al., 1998), and is caused by either deletion of the paternal allele of 15q11-q13 (Butler, 1990; Donlon, 1988; Knoll et al., 1989; Magenis et al., 1990; Nicholls et al., 1989b; Robinson et al., 1991), maternal uniparental disomy of chromosome 15 (Mascari et al., 1992; Nicholls et al., 1989a; Robinson et al., 1991), or defects in the chromosome 15 imprinting center (Buiting et al., 1995; Dittrich et al., 1996; Horsthemke, 1997). PWS is characterized by intellectual disability, physical attributes such as facial dysmorphism, short stature, hyperphagia and low metabolic rate with significant risk of obesity, as well as a variety of other maladaptive behaviors. Many of the features seen in PWS are thought to be due to hypothalamic dysfunction resulting in hormonal abnormalities (Correa-da-Silva et al., 2021; Tauber and Hoybye, 2021).

Social functioning is particularly impaired in PWS patients, with individuals showing pronounced deficits in social cognition and social interactions (Dimitropoulos et al., 2013; Dykens et al., 2017, 2019). Children with PWS exhibit deficits in facial emotion recognition, symbolic play, joint attention (e.g., when two individuals purposefully coordinate their mutual focus of attention on an object or an event), empathy, cooperation, and parent and peer interactions, which influence the ability to seek out social engagement and build quality relationships (Debladis et al., 2019; Dimitropoulos et al., 2013; Dykens et al., 2019; Key et al., 2013; Zyga et al., 2015; Zyga and Dimitropoulos, 2020). These social deficits are also evident early in development, significantly impact quality of life, and do not resolve over time (Dimitropoulos et al., 2019; Dimitropoulos and Schultz, 2007; Dykens

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et al., 2017).

The social impairments observed in PWS bear significant resemblance to those of autism spectrum disorder (ASD). Studies evaluating the incidence of ASD in children with PWS have shown a prevalence of between 12.3% and 41% for genetically confirmed PWS cases (Dykens et al., 2017; Veltman et al., 2005, 2004). Variation in ASD comorbidity incidence likely reflects differences in the methodology of ASD diagnosis, though the majority of children with PWS have some level of social skill difficulty (Dykens et al., 2017; Schwartz et al., 2021).

Efforts to better understand the biological basis of ASD's social impairments have implicated dysregulation of the two neuropeptides (i.e., oxytocin [OXT] and arginine vasopressin [AVP]) most critically involved in mammalian social functioning (Andari et al., 2010; Oztan et al., 2018, 2020; Parker et al., 2017, 2018, 2019; Zhang et al., 2016). Intriguingly, both neuropeptides are of hypothalamic origin (Zimmerman et al., 1984), and emerging evidence suggests that abnormalities in these neuropeptide signaling pathways may likewise contribute to PWS's social behavior impairments (Francis et al., 2014; Swaab et al., 1995; Tauber et al., 2011). The present article provides a brief primer on PWS, as well as a comprehensive review of the extant preclinical and clinical PWS literature – spanning endogenous neuropeptide measurement to exogenous neuropeptide administration studies – to better understand the roles OXT and AVP signaling may play in the social functioning of this patient population.

2. The genetic basis of PWS

The genetic locus responsible for PWS, located on a large maternally imprinted region of chromosome 15q11-q13, has been known since the 1970s and has been well described (Cassidy, 1997; Cassidy et al., 2012; Donaldson et al., 1994; Nicholls et al., 1998; Polex-Wolf et al., 2017). Approximately 65–75% of PWS cases are due to deletions on paternally inherited chromosome 15, 20–30% are due to maternal uniparental disomy, and 1–3% are due to imprinting defects (Cassidy, 1997; Cassidy et al., 2012). While the genetic locus and many of the associated genes have been explored, it has been difficult to elucidate the relationship between the genetic deficits and the clinical phenotype of PWS (Burnett et al., 2017; Polex-Wolf et al., 2017).

The 15q11-q13 locus contains both protein-coding DNA genes and non-coding RNA genes. Animal models lacking single genes in the PWS locus have been developed and studied, and insights from these models have been integrated with genetic findings from clinical populations to better understand genetic contribution to the PWS phenotype. Deletions or mutations in Magel2 are associated with hypotonia, developmental delay, hypogonadism, hyperphagia, as well as robust social deficits (e.g., impaired social recognition in genetically modified mice and ASD in people) (Bischof et al., 2007; Boccaccio et al., 1999; Fountain et al., 2017; Mercer and Wevrick, 2009; Schaaf et al., 2013). The MKRN3 gene, also found in the PWS-specific region, is associated with abnormalities in reproductive timing due to effects on gonadotropin-releasing hormone (GnRH) production (Jong et al., 1999). Deficiencies in Necdin, the product of the NDN gene, result in reduction of GnRH-producing neurons in the hypothalamus, and consequently, reproductive abnormalities (Muscatelli et al., 2000). Deletions of the SNURF/SNRPN gene complex result in hypotonia and some growth restriction (Tsai et al., 1999; Yang et al., 1998). More recent work has implicated a possible role for SNORD116, a small nucleolar RNA C/D box 116 gene cluster on chromosome 15q11.2 (Burnett et al., 2017). Deletion of this region results in hyperphagia, obesity, hypogonadism, and growth hormone deficiency (de Smith et al., 2009; Ding et al., 2008; Sahoo et al., 2008), all features common in PWS; yet, there are mixed findings pertaining to the cognitive, emotional, and social behavioral abnormalities in the Snord116 deficient mouse model (Adhikari et al., 2019; Zieba et al., 2015). In sum, while several of these models recapitulate features of PWS, it is important to note that none do so consistently. Thus, these collective research efforts have shown that no one single gene is the cause of PWS. Instead, lack of expression of multiple genes in this locus leads to the disorder's characteristic phenotype (Polex-Wolf et al., 2017; Francis et al., 2014).

3. Possible etiologies of hypothalamic dysfunction in PWS

Global hypothalamic dysfunction has been identified as a core feature of PWS and as a causal factor in many of the phenotypic characteristics of the disorder (Correa-da-Silva et al., 2021; Tauber and Hoybye, 2021). The growth hormone deficiency, thyroid hormone deficiency, hypogonadism, and hyperphagia typical of the syndrome are thought to be hypothalamic in origin (Burman et al., 2001; Diene et al., 2010). Research using induced pluripotent stem cells has also enabled molecular investigation of PWS's neuronal dysfunction. As a result, deficiency in two factors, nescient helix–loop–helix 2 (NHLH2) and prohormone convertase 1 (PC1), encoded by the Proprotein Convertase Substilisin/Kexin Type 1 gene (PCSK1), have been implicated in the hypothalamic dysfunction seen in PWS. Neuronal induced pluripotent stem cells (iPSCs) were derived from PWS patients with microdeletions of the noncoding RNA gene SNORD116, located in the PWS critical region. These neurons show low levels of both NHLH2 and PC1 proteins, and transcriptomic analysis revealed decreased transcript of both NHLH2 and PCSK1, with the latter being one of the most suppressed genes in these cells (Burnett et al., 2017). The SNORD116 paternal knockout mouse model also shows low levels of hypothalamic PC1, as well as decreased expression in the pancreas and stomach (Burnett et al., 2017). In addition, humans with loss-of-function mutations in PCSK1 have a phenotype of hypothalamic dysfunction similar to those with PWS (Stijnen et al., 2016). Lower levels of prohormone convertase 2 (PC2), another prohormone convertase encoded by the PCSK2 gene, were also found in neuronal iPSCs from PWS patients (Eddiry et al., 2021).

Burnett et al. (2017) suggest that deletion of SNORD116 may result in a decrease in PC1 via modulation of NHLH2. NHLH2 is a basic helix-loop-helix neuronal transcription factor that positively regulates PCSK1 transcription (Fox and Good, 2008). In silico modeling shows SNORD116-mediated regulation of NHLH2, providing a mechanism by which SNORD116 deletion would result in decreases in NHLH2. These decreases would result in decreased transcription of PCSK1, leading, in turn, to lower levels of PC1. PC1 acts to cleave the pro-domain from hormones in the brain, adrenal, and pancreas, thereby increasing their activity (Seidah, 2011). SNORD116 paternal knockout mice show increases in proinsulin, pro-growth hormone-releasing hormone (proGHRH), and proghrelin. These decreases in PC1 may thus result in physiologically relevant disturbance of prohormone processing, which, in turn, may lead to hyperphagic obesity, hyperghrelinemia growth hormone deficiency, hypogonadotropic hypogonadism, and relative hypoinsulinemia (Burnett et al., 2017).

While deficits in prohormone convertase activity may account for some neuroendocrine disruption in PWS (Pan et al., 2005; Polex-Wolf et al., 2017; Stijnen et al., 2016), previous efforts have not systematically elucidated how hypothalamic processing disruption may relate to the social abnormalities exhibited by individuals with PWS. However, research has shown that PC1 is co-expressed with pro-OXT and pro-AVP in certain groups of neurons in the supraoptic nucleus (SON) and paraventricular nucleus (PVN) of the hypothalamus (Dong et al., 1997). When OXT levels are measured in the pituitaries of mice deficient in PC1, an 80% decrease in concentration has been found (Pan et al., 2005). Additionally, in a subset of PWS patients, a small study reported a link between PC2 deficiency and a hypothalamic AVP processing defect (Gabreëls et al., 1998). Thus, prohormone convertase deficiency may alter precursor processing of OXT and AVP in the hypothalamus which, in turn, may drive the pronounced social impairments evident in PWS patients.

4. OXT and AVP biology

OXT and AVP are structurally similar nonapeptides (i.e., they differ by only two amino acids) and are thought to have evolved due to duplication of a common ancestral gene (Donaldson and Young, 2008). Both molecules are synthesized as pre-prohormones and then processed into their active mature forms through enzymatic cleavage (Brownstein et al., 1980). Principal synthesis of these neuropeptides occurs in magnocellular neurons located in the SON and PVN of the hypothalamus. These neuropeptides are released into systemic circulation through posterior pituitary axon terminals following action potentials, and act as classic hormones to regulate a variety of physiological processes at distal target sites. OXT and AVP are also secreted from the dendrites of the magnocellular neurons into extracellular fluid, and from the axonal projections of parvocellular neurons, which project to the anterior pituitary, spinal cord, and various brain regions (Brownstein et al., 1980; Castel and Morris, 1988; Ludwig and Leng, 2006; Pow and Morris, 1989). In the brain, OXT and AVP act as neuromodulators to regulate a variety of species-specific behavioral functions (Baribeau and Anagnostou, 2015).

In mammals, OXT has a single receptor (OXTR) by which it exerts its classic physiological (e.g., uterine contractions; milk let-down) and social behavioral effects, whereas AVP has three receptor subtypes [AVPR1A, AVPR1B (also known as AVPR3) and AVPR2]. All of these receptors are G protein coupled (Barberis and Tribollet, 1996), and expressed in a variety of tissues throughout the body and brain (Thibonnier et al., 2001). Like their ligands, phylogenetic analysis has shown that these receptors originated from a gene duplication event of an ancestral vertebrate chromosome (Lagman et al., 2013). AVP's prosocial effects are predominantly mediated via central AVPR1A (Bielsky et al., 2004; Young et al., 1999), whereas its effects on stress-related anterior pituitary adrenocorticotropic hormone release and kidney-related water homeostasis are mediated through AVPR1B and AVPR2, respectively (Thibonnier et al., 2001). It should be noted that while OXT and AVP have the highest affinity for their own respective receptors, because of the high degree of structural homology between OXT and AVP, and the close evolutionary relationship between OXTR and the AVPR subtypes, there is significant "cross-talk" between each ligand and the various neuropeptide receptors (Song and Albers, 2018).

5. OXT and AVP regulation of mammalian social behavior

It is well established that both OXT and AVP regulate a wide range of species-typical mammalian social behaviors as reviewed in detail elsewhere (Baribeau and Anagnostou, 2015; Carter et al., 2008; Johnson and Young, 2017; Meyer-Lindenberg et al., 2011). OXT was first recognized as a "social" molecule over 40 years ago when it was implicated in the onset of maternal behavior in rats (Pedersen and Prange, 1979) and sheep (Kendrick et al., 1987), and subsequently, pair bond formation in female prairie voles (Williams et al., 1992). Approximately 15 years later, a "social" role for AVP was also identified: AVP was found to induce pair bonds in male prairie voles (Winslow et al., 1993), as well as paternal care in several vole species (Parker and Lee, 2001; Wang et al., 1994). Since, and of particular relevance for PWS, it has been found that reduced brain OXT or AVP signaling—either naturally occurring or experimentally induced—results in robust social behavior impairments in multiple species (Ferguson et al., 2000; Jin et al., 2007; Parker et al., 2018; Paul et al., 2016; Pedersen et al., 2006).

In addition to evidence from animal studies, research has also shown that OXT and AVP play a key role in regulating species-typical human social behavior. For example, intranasal OXT administration to neurotypical individuals improves emotion and facial recognition (Fischer-Shofty et al., 2010; Guastella et al., 2008b; Rimmele et al., 2009), enhances gaze to the eye region (Guastella et al., 2008a), promotes trust (Baumgartner et al., 2008; Kosfeld et al., 2005), and reduces behavioral and endocrine responses to social stress (Heinrichs et al., 2003; Meinlschmidt and Heim, 2007). Likewise, intranasal AVP administration to neurotypical individuals enhances various aspects of human social functioning including memory for emotional faces (Guastella et al., 2010), cooperative behavior (Brunnlieb et al., 2016; Rilling et al., 2012), and social communication ability (Thompson et al., 2004).

6. Preclinical studies of neuropeptide signaling in PWS models

Preclinical evidence for OXT and AVP's involvement in PWS comes principally from studies of mouse models lacking single genes in the PWS locus, specifically, *Necdin* and *Magel2*. This work has focused primarily on neuropeptide measurement ranging from assessment of neuron numbers and firing rates to quantification of mRNA expression and protein concentrations. The majority of these studies reported pronounced OXT signaling disruption, with more modest support found for AVP signaling abnormalities. Findings from this research are briefly summarized below, and experimental details are provided in Table 1.

Some of the first evidence for impaired OXT signaling came from a *Necdin*-deficient mouse model of PWS. Specifically, a significant decrease in the number of OXT-producing neurons in the lateral PVN was found in adult *Necdin*-deficient mice compared to wild-type mice (Muscatelli et al., 2000). Subsequently, investigators have studied neuropeptide biology in *Magel2* mutant mice across life span development. Beginning early in life, neonatal *Magel2* mutant mice exhibited a similar number of OXT-prohormone positive cells compared to wild type-littermates. However, *Magel2* mutant mice showed a significant accumulation of the OXT-intermediate form in the PVN and a significant decrease in mature OXT compared to wildtype controls. This evidence suggests that transformation of OXT intermediate forms to mature OXT is impaired in the hypothalamus of mutant neonates, leading to an accumulation of intermediate forms and a reduced amount of mature OXT (Schaller et al., 2010). Early life OXT transmission abnormalities are also evident post-synaptically, as a significant reduction in OXTR density has also been observed in neonatal *Magel2*-deficient mice compared to wild-type mice in the lateral periodontia (a feeding-related target) (Vaidyanathan et al., 2020).

Follow up research was conducted to assess whether the observed OXT processing defect was maintained during adulthood in *Magel2*-deficient mice. Although some evidence suggests that there may be compensatory changes in both OXT-producing cells and OXTR density in multiple brain regions during development (Meziane et al., 2015), other work suggests that the neonatal processing defect persists, as a significant reduction of mature OXT was found in both the hypothalamus and blood of adult *Magel2* mutant mice compared to adult wild-type mice (Chen et al., 2020). Convergent electrophysiological evidence likewise supports these abnormal protein findings, as a significant decrease in *ex vivo* OXT neuron activity with reduced synaptic excitation and increased inhibition currents in the PVN of adult *Magel2*-deficient mice has also been reported (Ates et al., 2019).

Somewhat parallel findings have been found for AVP in the *Magel2* mutant mouse across development. Although no significant difference was found between neonatal *Magel2* mutants and controls in AVP-prohormone or intermediate forms, a significant reduction of mature AVP in the hypothalamus as a whole was detected in neonatal mutants (Schaller et al., 2010). As with OXT, there also appears to be some evidence for compensatory developmental changes in mature hypothalamic AVP concentration (Meziane et al., 2015), but, again, other evidence suggests this deficit persists, as a significant reduction in mature AVP has been found in both the hypothalamus and blood of adult *Magel2* mutant mice compared to adult wild-type mice (Chen et al., 2020). Further, additional findings implicate more wide-spread AVP abnormalities: A separate study reported a significant decrease in the number and length of AVP fibers and number of AVPR1A, AVPR1B, and AVPR2 in the lateral septum of adult *Magel2*-deficient mice which, in turn, are associated with social discrimination deficits in these adult mutants (Borie et al., 2021).

Table 1
Preclinical endogenous neuropeptide measurement studies.

Article title	First author & publication year	Sample characteristics	Substrates & measurement techniques	Relevant findings
"Disruption of the mouse *Necdin* gene results in hypothalamic and behavioral alterations reminiscent of the human Prader–Willi syndrome"	Muscatelli et al. (2000)	*Necdin* mouse model Age and sex: adult males Mutant: n = 4 Wild-type: n = 4	Substrate: OXT Collection location: hypothalamus (PVN) Technique: IHC	-Significant decrease of 29% in the number of OXT-producing neurons were shown in lateral portion of the PVN in mutant mice compared to wild-type mice
"A single postnatal injection of oxytocin rescues the lethal feeding behaviour in mouse newborns deficient for the imprinted *Magel2* gene"	Schaller et al. (2010)	*Magel2* mouse model Age and sex: neonatal males and females Mutant: n = 6–14 Wild-type: n = 5–14	Substrates: OXT and AVP Collection location: hypothalamus (PVN), pituitary gland Techniques: EIA; IHC	-The number of OXT- and AVP- prohormone positive cells in the PVN was similar between mutant and wild-type mice. However, there was a 1.7-fold increase in the OXT-intermediate cells but not of AVP-intermediate cells in the PVN of mutant mice compared to wild-type mice -Significant reduction in OXT (36%) and AVP (20%) concentrations was found in the hypothalamus as a whole of mutant mice compared to wild-type mice -No significant difference was detected in the pituitary gland levels of OXT and AVP between mutant mice and wild-type mice
"An early postnatal oxytocin treatment prevents social and learning deficits in adult mice deficient for *Magel2*, a gene involved in Prader-Willi syndrome and autism"	Meziane et al. (2015)	*Magel2* mouse model Age and sex: adult males Mutant: n = 4–11 Wild-type: n = 4–10	Substrates: OXT, AVP, OXTR Collection location: anterior commissure to the posterior hypothalamus, hypothalamus (PVN), hypophysis, amygdala, lateral septum, dorsal vagal complex Techniques: EIA; mass spectroscopy; IHC; autoradiography	-Significant increase in OXT (34%) and AVP (21%) concentrations was detected in hypophysis, whereas only AVP (%15) concentration was increased in the hypothalamus of mutant mice compared to wild-type mice -Significant increase in the total number of OXT-positive neurons (26%) in the entire PVN but no accumulation of OXT-intermediate neurons was found despite the 22% more OXT-prohormone and -intermediate neurons in the rostral PVN in mutant mice compared to wild-type mice -Significant increases in OXT immunoreactivity were found in the medial amygdala (300%), the lateral septum (172%), and the dorsal vagal complex (33%) in mutant mice compared to wild-type mice -Significant decrease in OXTR density (26%) was detected in lateral septum of mutant mice compared to wild-type mice.
"Inactivation of *Magel2* suppresses oxytocin neurons through synaptic excitation-inhibition imbalance"	Ates et al. (2019)	*Magel2* mouse model Age and sex: adult (5–7 weeks old) males and females Mutant: n = 2–6 Wild-type: n = 2–7	Substrate: OXT Collection location: hypothalamus (PVN) Techniques: electrophysiology; confocal microscopy	-Significant decrease in baseline firing rates and frequency of action potentials in OXT neurons in the PVN of mutant mice compared to wild-type mice -Significant selective reduction in excitatory drive and increase in inhibitory drive onto OXT neurons in the PVN of mutant mice compared to wild-type mice -No deficit in the number of spiny protrusions from basal OXT neuronal dendrites in the PVN of mutant mice compared to wild-type mice
"Colocalization of *Oxtr* with Prader-Willi syndrome transcripts in the trigeminal ganglion of neonatal mice"	Vaidyanathan et al. (2020)	*Magel2* mouse model Age and sex: neonatal males and females Mutant: n = 8 Wild-type: n = 12	Substrate: OXTR Collection location: trigeminal ganglion, lateral periodontium, rostral periodontium, tongue, olfactory epithelium, whisker pads and brainstem Techniques: chromogenic in situ hybridization; autoradiography	-OXTR is co-expressed with *Magel2* and other PWS gene transcripts in the trigeminal ganglion of wild-type mice -Trigeminal ganglion neurons express OXTR but not *Magel2* in the mutant mice -Significant reduction in OXTR binding density in the lateral periodontia with intact levels in the rest of the head of mutant mice compared to wild-type mice
"Loss of MAGEL2 in Prader-Willi syndrome leads to decreased secretory granule and neuropeptide production"	Chen et al. (2020)	*Magel2* mouse model Age and sex: adult mice (sex unspecified) Mutant: n > 5 Wild-type: n = 5–6	Substrates: OXT, AVP Collection location: whole hypothalamus, plasma Techniques: Quantitative Proteomic/ Mass Spectrometry, EIA	-Significant reduction of OXT and AVP levels (~50%) in the hypothalamus of mutant mice compared to wild-type mice -Significant decrease in OXT and AVP concentrations in the plasma of mutant mice compared to wild-type mice
"Correction of vasopressin deficit in the lateral septum ameliorates social deficits of mouse autism model"	Borie et al. (2021)	*Magel2* mouse model Age and sex: adult males Mutant: n = 5–6 Wild-type: n = 5–6	Substrates: AVP, AVPR1A, AVPR1B and AVPR2 Collection location: lateral septum Techniques: IHC, autoradiography	-Significant decrease in overall AVP receptor densities in the somatostatin neurons of the dorsal lateral septum in mutant mice compared to wild-type mice -Significant reduction in the number and length of AVP fibers in the dorsal lateral septum of mutant mice compared to wild-type mice

AVP, arginine vasopressin; AVPR1A, arginine vasopressin receptor 1A; AVPR1B, arginine vasopressin receptor 1B; AVPR2, arginine vasopressin receptor 2; EIA, enzyme immunoassay; IHC, immunohistochemistry; OXT, oxytocin; OXTR, oxytocin receptor; PVN, paraventricular nucleus

7. Preclinical studies of neuropeptide administration in PWS models

Several studies have been conducted to assess the effectiveness of OXT or AVP administration to "rescue" social functioning impairments in *Magel2*-deficient mice (Borie et al., 2021; Meziane et al., 2015). These studies support both OXT and AVP as potential therapeutics for ameliorating behavioral abnormalities in gene-targeted mouse models of PWS. Findings from this research are briefly summarized below, and experimental details are provided in Table 2.

Adult mice lacking *Magel2* show social behavior and cognition deficits along with altered hypothalamic-hypophyseal OXT and AVP levels. Social recognition deficits in adult *Magel2*-deficient mice can be reversed by a single subcutaneous OXT injection. Moreover, *Magel2*-deficient mice treated with chronic subcutaneous injections of OXT as neonates showed improved social interaction and recognition abilities in adulthood (Meziane et al., 2015), providing evidence for the lasting therapeutic benefit of OXT when administered during an early "critical period" of development.

Therapeutic use of AVP on impaired social habituation and discrimination behaviors has also been studied in adult *Magel2*-deficient mice (Borie et al., 2021). A single AVP injection into the dorsal lateral septum (where AVP signaling is known to be impaired in this model), restored social discrimination in adult mutant mice. Moreover, a single AVPR1A antagonist injection into the dorsal lateral septum of C57BL/6 J wild-type mice decreased social novelty and discrimination (Borie et al., 2021), suggesting that septal AVP is a key factor in the pathophysiology of social deficits associated with *Magel2* deficiency.

8. Clinical neuropeptide measurement studies in PWS patients

Clinical evidence for neuropeptide dysregulation in PWS patients is drawn from postmortem brain tissue studies as well as assessment of central and peripheral OXT and AVP concentrations. The majority of these findings implicate significant abnormalities in neuropeptide signaling pathways in PWS patients, with variability in the direction of effects across studies. These discordant findings may be driven, at least in part, by factors that varied across studies, including: study population, control group, biological specimen type, and neuropeptide measurement technique. Findings from this clinical research are briefly summarized below, and experimental details are provided in Table 3.

Early clinical studies suggested altered hypothalamic OXT and AVP signaling in individuals with PWS (Gabreëls et al., 1998; Swaab et al., 1995). The first evidence came from a study which investigated OXT and AVP neurons in the PVN of postmortem hypothalamic tissue from adult individuals with PWS, and age- and gender-matched controls (Swaab et al., 1995). Morphometric assessment analysis showed that PVN volume was significantly smaller, and that total PVN cell number was significantly lower, in PWS cases. Subsequent analysis revealed that these reductions were specific to OXT neurons, since no group differences were found for AVP neurons. These results were replicated when PWS cases were compared to a larger independent group of control subjects (Swaab et al., 1995).

Another study used immunocytochemistry to quantify AVP precursor, processed AVP, and processed OXT in the magnocellular neurons of the SON and PVN in postmortem brain tissue from adult PWS cases and controls (Gabreëls et al., 1998). OXT staining intensity in PWS cases was comparable to controls. However, the intensity of processed AVP immunoreactivity varied among PWS cases. This variation in processed AVP was associated with variation in neuroendocrine polypeptide 7B2, which is localized close to the PWS deletion region on chromosome 15q13–14 (Roebroek et al., 1989). In PWS cases lacking 7B2, processed PC2 and AVP immunoreactivities were not detectable. However, these PWS cases showed normal AVP precursor immunoreactivity in the SON and PVN, suggesting an AVP processing defect (Gabreëls et al., 1998).

Investigation of cerebrospinal fluid (CSF) OXT and AVP concentrations provided gender specific results in PWS cases (Martin et al., 1998). Radioimmunoassay (RIA) analysis of lumbar CSF samples showed significantly higher OXT concentrations in adolescent and adult PWS cases compared to controls without PWS. This effect was even stronger when the analysis included only females. No significant difference was found in CSF AVP concentrations between the groups when both genders were included, but CSF AVP concentrations were significantly lower in female PWS cases if male subjects were excluded from the analysis (Martin et al., 1998).

Neuropeptide dysfunction in PWS has also been evaluated by measuring blood OXT concentrations in adolescent and adult PWS cases before undergoing growth hormone treatment (Höybye et al., 2003). RIA analysis of extracted blood samples showed a normal range of baseline plasma OXT concentrations, but when compared to their

Table 2
Preclinical pharmacological neuropeptide administration studies.

Article title	First author & publication year	Sample characteristics	Manipulation & outcome measures	Relevant findings
"An early postnatal oxytocin treatment prevents social and learning deficits in adult mice deficient for *Magel2*, a gene involved in Prader-Willi syndrome and autism"	Meziane et al. (2015)	*Magel2* mouse model Age and sex: neonatal and adult males Mutant: n = 10–14 (OXT); n = 10–14 (NaCl) Wild type: n = 12–14 (OXT); n = 12–14 (NaCl)	Manipulation: -Single s.c. injection of 10 mg/kg OXT or NaCl 1 h before behavioral testing (adult mutant and wild-type mice) -Daily s.c. injections of 2 μg OXT for 7 days, starting from 3 to 5 h after birth (neonate mutant and wild-type mice); behavioral testing performed in adulthood Outcome Measures: -Social recognition -Social interaction	-Single s.c. injection of OXT reversed social recognition deficit in mutant adult mice -Daily s.c. injections of OXT during early postnatal period restored normal social recognition and interaction in adult mutant mice
"Correction of vasopressin deficit in the lateral septum ameliorates social deficits of mouse autism model"	Borie et al. (2021)	*Magel2* mouse model Age and sex: adult males (3–4 months old) Mutant: n = 16 (AVP); n = 14 (NaCl) Wild-type: n = 11 (Manning compound AVPR antagonist); n = 15 (NaCl)	Manipulation: -Single injection of 30 μM AVP through cannula implanted in the dorsal LS for 9 min starting 5 min before social trial in mutant mice -Single injection of 10 nM AVPR antagonist through cannula implanted in the dorsal LS for 9 min starting 5 min before social trial in wild-type mice Outcome Measures: -Social habituation/discrimination	-AVP injection increased social discrimination in mutant mice compared to NaCl vehicle-injected mutant controls -AVPR antagonist vs NaCl injection decreased social novelty and discrimination in wild-type mice

AVP, arginine vasopressin; AVPR, arginine vasopressin receptor; LS, lateral septum; NaCl, sodium chloride; OXT, oxytocin; OXTR, oxytocin receptor; s.c., subcutaneous

Table 3
Clinical endogenous neuropeptide measurement studies.

Article title	First author & publication year	Sample characteristics	Substrates & measurement techniques	Relevant findings
"Alterations in the hypothalamic paraventricular nucleus and its oxytocin neurons (putative satiety cells) in Prader-Willi syndrome: a study of five cases"	Swaab et al. (1995)	Human adult study; postmortem tissue Age range: 22–64 y PWS: n = 5 Females: 3 Males: 2 Control: n = 5 Females: 3 Males: 2 (Additional 27 adult controls, i.e., 14 males and 13 females)	Substrates: OXT and AVP Collection Location: hypothalamus (PVN) Techniques: ICC	-Significant decrease in the volume (28%) of the PVN and the total cell numbers (38%) in the PVN was detected in the PWS cases compared to five matched controls -Significant decrease in the volume (54%) and the number (42%) of OXT neurons in the PVN was found in the PWS cases compared to five matched controls -The number of AVP neurons in the PVN was not significantly different in the PWS cases, but only the size of the nucleus was increased compared to five matched controls -Significant decrease in the number of OXT neurons and unaffected number of AVP neurons in the PVN of PWS cases remained consistent when compared to additional 27 controls
"Attenuation of the polypeptide 7B2, prohormone convertase PC2, and vasopressin in the hypothalamus of some Prader-Willi patients: indications for a processing defect"	Gabreëls et al. (1998)	Human adult study; postmortem tissue Age range: 19–88 y PWS: n = 7 Females: 4 Males: 3 Control: n = 11 Females: 5 Males: 6	Substrates: OXT and AVP Collection Location: hypothalamus (SON; PVN) Techniques: ICC	-Normal staining intensity for OXT was found in the magnocellular neurons of the PVN and SON in all PWS cases relative to controls -The magnocellular neurons of SON and PVN in two PWS cases who were deficient for neuroendocrine polypeptide 7B2 did not show processed AVP and prohormone convertase 2 immunoreactivity, but showed normal immunoreactivity for AVP precursor relative to controls -Two other PWS cases showed moderate processed AVP immunoreactivity along with some degree of 7B2 immunoreactivity in the magnocellular neurons of SON and PVN relative to controls -Remaining three PWS cases showed normal processed AVP immunoreactivity in the magnocellular neurons of SON and PVN relative to controls
"Cerebrospinal fluid levels of oxytocin in Prader–Willi syndrome: a preliminary report"	Martin et al. (1998)	Human adolescent and adult study Age range: 16–28 y PWS: n = 5 Females: 3 Males: 2 Control: n = 6 Female: 6 Male: 0	Substrates: OXT and AVP Collection Location: cerebrospinal fluid via lumbar puncture Technique: RIA (unspecified if sample extraction was performed)	- CSF OXT levels were significantly higher in the PWS cases compared to controls, and this finding was more prominent when males were excluded from the analysis -CSF AVP levels were not significantly different between the groups with both female and male subjects, but significantly lower in female PWS cases when excluding males from the analysis
"Peptides associated with hyperphagia in adults with Prader–Willi syndrome before and during GH treatment"	Höybye et al. (2003)	Human adolescent and adult study Age range: 17–32 y PWS: n = 17 Females: 8 Males: 9	Substrate: OXT Collection Location: peripheral blood Technique: RIA after solid phase extraction	-Baseline plasma OXT levels were within the normal range but considered low with relevance to their obesity - Significant negative correlation was found between plasma OXT and anorexigenic hormone leptin levels in serum at baseline
"Whole genome microarray analysis of gene expression in Prader-Willi syndrome"	Bittel et al. (2007)	Human infant, adolescent, and adult study; included postmortem tissue Age range: 1–45 y PWS: n = 10 Females: 3 Males: 7 Control: n = 6 Females: 3 Males: 3	Substrate: OXTR Collection Location: lymphoblastoid cells and frontal cortex brain tissue Techniques: microarray; qPCR	-Significant reduction in expression of OXTR in PWS cases relative to controls was found in both lymphoblastoid cells and frontal cortex
"Elevated plasma oxytocin levels in children with Prader–Willi syndrome compared with healthy unrelated siblings"	Johnson et al. (2016)	Human child study Age range: 5–11 y PWS: n = 23 Females: 10 Males: 13 Controls: n = 18 Females: 8 Males: 10	Substrate: OXT Collection location: peripheral blood Technique: multiplex sandwich immunoassays (no sample extraction)	-Plasma OXT levels were significantly increased in the PWS cases compared to healthy unrelated siblings of children with PWS -PWS diagnosis predicted the OXT levels in regression analyses with an overall model fit -Significant positive correlation between OXT levels and age was only found in females with PWS

AVP, arginine vasopressin; CSF, cerebrospinal fluid; GH, growth hormone; ICC, immunocytochemistry; OXT, oxytocin; OXTR, oxytocin receptor; PVN, paraventricular nucleus; PWS, Prader-Willi syndrome; qPCR, quantitative polymerase chain reaction; RIA, radioimmunoassay; SON, supraoptic nucleus

obesity status, these PWS patients had low plasma OXT concentrations, suggesting that altered anorexigenic OXT concentrations may play an important role in regulation of hyperphagia-induced obesity in PWS. Unfortunately, we do not know whether low plasma OXT concentrations in this study sample were also linked to impaired social functioning, as to our knowledge this relationship was not assessed.

In another study, non-extracted plasma OXT concentrations following overnight fasting were significantly increased in children with PWS undergoing growth hormone treatment compared to age- and gender-matched control siblings of individuals with PWS (Johnson et al., 2016). In particular, these analyses showed a significant age-related increase in plasma OXT concentrations in female PWS cases. These counterintuitive findings in blood OXT concentrations could be due to ongoing growth hormone treatment at the time of blood sample collection. However, these blood samples did not undergo an extraction procedure before immunoassay , an important step in obtaining accurate OXT values (Leng and Sabatier, 2016; McCullough et al., 2013; Szeto et al., 2011), calling into question the validity of these (and other) unextracted blood sample findings in people with PWS.

Lastly, to better understand genetic alterations in several possible candidate genes that may contribute to the clinical manifestation of PWS, including OXT and OXTR, whole genome microarray and qPCR analysis were performed on lymphoblastoid cells and postmortem frontal cortex tissue from adolescent and adult PWS cases and age and gender-matched controls. PWS cases were shown to have almost undetectable levels of OXT in both tissue types (i.e., a weak probe signal on the microarray) as well as decreased OXTR gene expression levels, providing further evidence for dysfunctional OXT signaling pathways in PWS (Bittel et al., 2007).

9. Clinical studies of neuropeptide administration in PWS patients

Nine independent studies to date have tested the therapeutic effect of OXT or a related compound, carbetocin (an oxytocin analogue), on ameliorating behavioral impairments in individuals with PWS. Although all treatment trials have administered OXT or carbetocin through nasal spray, and all trials have thus far reported good safety and tolerability profiles, the therapeutic benefit of OXT in PWS has been equivocal, perhaps due to the remarkable variability in study design, length of treatment, drug dose, age group, gender, PWS genetic subtype, and outcome measures across trials. These findings are briefly summarized below, and experimental details are provided in Table 4. Interestingly, despite emerging evidence that central AVP administration "rescues" social deficits in *Magel2*-deficient mice (Borie et al., 2021), and intranasal AVP treatment appears to be safe, well tolerated, and improve social abilities in people with ASD (Parker et al., 2019), AVP has not yet been evaluated as a potential treatment for PWS, and thus no AVP treatment studies are reviewed here.

9.1. Oxytocin administration and behavioral functioning

Single dose OXT vs. placebo administration was found to improve trust, sadness, and disruptive behaviors, but not social skills, in adults with PWS (Tauber et al., 2011). These promising single dose OXT data paved the way for investigating the effects of longer-term OXT treatment in adolescents and adults with PWS. However, 8-week OXT treatment showed no significant benefit on compulsivity, social behaviors, or hyperphagia, but instead resulted in increased temper outbursts, particularly at higher doses of OXT (Einfeld et al., 2014). The authors of this study speculated that the increased temper outburst behaviors observed at higher OXT doses could be due to AVP receptor occupancy, since AVP receptor activation has been shown to increase negative emotional arousal in rodents under some circumstances (Albers, 2012). However, it is worth noting that individuals with ASD also frequently exhibit temper outburst behaviors (Adler et al., 2015; Research Units on Pediatric Psychopharmacology Autism Network, 2005), but increased temper outburst behaviors were not previously associated with higher doses of OXT administration in a large sample which included at least some similar aged individuals with ASD (Sikich et al., 2021). Additionally, a meta-analysis of intranasal OXT treatment trial findings found OXT to be safe and well tolerated in people with ASD (Cai et al., 2018). Thus, whether the observed PWS response to OXT treatment is disease-specific (i.e., high-dose OXT induces temper outburst behaviors in people with PWS but not in those with ASD), a false positive due to chance inclusion of non-representative individuals in the trial's small sample, or due to age-related developmental effects rather than dose per se (see below), is unknown.

Subsequent OXT treatment trials have been conducted in children with PWS, with varying results, reviewed here by duration of treatment. Five-day OXT treatment in children with PWS showed no significant change in behavior, but trends were observed for improvement in hyperphagia, socialization, anxiety, and repetitive behaviors (Miller et al., 2017). Following a 4-week OXT treatment, age-specific effects were detected: Children under 11 years showed significant improvements in social and food-related behaviors, as well as improvements in anger, sadness, and conflicts, whereas children over 11 years of age showed decreased happiness and increased anger and sadness (Kuppens et al., 2016). It remains unclear why older children did not benefit from OXT treatment. Perhaps lack of efficacy was due to puberty-related changes in the OXT system that may prevent older children from responding to OXT treatment.

Another study examined the effects of daily 8-week OXT vs. placebo treatment on hyperphagia and repetitive behaviors in children and adolescents with PWS. This trial reported modest significant improvement in hyperphagia and repetitive behaviors following placebo but not OXT treatment (Hollander et al., 2021). Although both male and female children and adolescents were included in this trial, randomization was not gender-balanced and the study was not adequately powered to examine PWS genetic subtype, age, or gender effects. These findings highlight the need for larger, well-powered studies to better understand the effects of OXT treatment in individuals with PWS.

Finally, in the longest duration pediatric OXT clinical trial in PWS to date, boys with PWS treated daily with OXT for a three month period showed significant improvements in social and eating behaviors compared to placebo (Damen et al., 2021). These effects were particularly pronounced in children with the paternal deletion vs the maternal uniparental disomy subtype of PWS. These genetic subtype findings were surprising, as maternal uniparental disomy of chromosome 15 has been more tightly linked to ASD (and its attendant social impairments) than has paternal deletion of 15q11-q13 (Veltman et al., 2005).

Additional work has been conducted examining the effect of OXT on feeding and social behaviors in infants with PWS using unblinded, differing dosing schedules (Tauber et al., 2017; Viaux-Savelon et al., 2016). Namely, escalated doses of OXT administration over a 7-day period normalized sucking, and improved swallowing, mother-infant interactions, and social skills, regardless of OXT dose. Long-term observational data implicated improvement on muscle tone and motor coordination, as OXT-treated infants were able to crawl as toddlers compared to untreated age-matched controls with PWS. However, long-term effects of this short-term OXT administration on feeding and social behaviors remain unclear. Furthermore, the study was not placebo-controlled and clinicians who rated behaviors were not blind to the intervention. Additional studies in infants with double-blind, randomized, placebo-controlled study designs investigating short- and long-terms effects are needed to more fully ascertain the therapeutic efficacy of OXT.

9.2. Carbetocin administration and behavioral functioning

The mixed findings from OXT treatment trials in PWS may speak to OXT's lack of specificity. Carbetocin is an analog of OXT and has

Table 4
Clinical pharmacological neuropeptide administration studies.

Article title	First author & publication year	Sample characteristics	Study design	Manipulation & outcome measures	Relevant findings
"Oxytocin may be useful to increase trust in others and decrease disruptive behaviours in patients with Prader-Willi syndrome: a randomised placebo-controlled trial in 24 patients"	Tauber et al. (2011)	Human adult study Age range: 18–44 y Median age: 28.5 y PWS: n = 24 Females:16 Males: 8	Double-blind, randomized, placebo-controlled	Manipulation: single intranasal dose of 24 IU OXT or placebo Outcomes: -Study specific behavioral measures -Sally-Anne Test -Reading the Mind in the Eyes Test	-Significant improvements were found in the two days following single intranasal dose of OXT on 3 items in the caregiver reported behavior grid: increase in trust, decrease in sadness tendencies, and a decrease in disruptive behaviors compared to placebo group -No improvement was found on validated social skills measures -Intranasal OXT was well tolerated without any adverse events
"A double-blind randomized controlled trial of oxytocin nasal spray in Prader Willi syndrome"	Einfeld et al. (2014)	Human adolescent and adult study Age range: 12–30 y Mean age: 17.8 y PWS: n = 30 Females: 10 Males: 20	Double-blind, randomized, placebo-controlled, cross-over	Manipulation: twice daily intranasal OXT or placebo (a washout period of 2 weeks before cross over to the alternative treatment) administration in the following doses for 8 weeks: -The first 11 PWS participants: 24 IU OXT (16 years and over) and 18 IU OXT (13–15 years) -Remaining 18 PWS participants: 40 IU OXT (16 years and over) and 32 IU OXT (13–15 years) Outcomes: -3 items on the Developmental Behavior Checklist (hyperphagia/pica, temper outbursts and weight)	-No significant improvement was found for any outcome measures or treatment groups -Significant increase in temper outbursts was found in the OXT group compared to the placebo group -The increase in temper outbursts was more significant in the high dose of OXT group than the overall group, but was not significant in the lower dose of OXT group -No side effects were reported
"Dyssynchrony and perinatal psychopathology impact of child disease on parents-child interactions, the paradigm of Prader Willi syndrom"	Viaux-Savelon et al. (2016) (Note: same study/population as Tauber et al., 2017 below)	Human infant study Age range: 0.8–5.7 m Mean age: 3.9 m PWS: n = 18 Females: 8 Males: 10	Unblinded dose escalation with 3 steps over 7 days	Manipulation: intranasal dose of 4 IU OXT every other day, daily, or twice daily for one week Outcomes: -Alarm Distress Baby Scale -Coding Interactive Behavior Scale	-Significant improvements on 4 out of the 8 Alarm Distress Baby Scale items: increase in eye contact, facial expression, general level of activity, and relationships were found after intranasal OXT treatment compared to baseline - Significant improvements on 4 out of 7 Coding Interactive Behavior Scale composites: increase in parental sensitivity, dyadic reciprocity, child social engagement and child state were found after intranasal OXT treatment compared to baseline -No adverse events were reported
"Promising effects of oxytocin on social and food-related behavior in young children with Prader-Willi syndrome: a randomized, double-blind, controlled crossover trial"	Kuppens et al. (2016)	Human child study Age range: 6–14 y Mean age: 9.3 y PWS: n = 25 Females: 11 Males: 14	Double-blind, randomized, placebo-controlled, cross-over	Manipulation: twice daily intranasal dose of 24–48 IU OXT or placebo for 4 weeks followed by no washout period to cross over to the alternative treatment for further 4 weeks Outcomes: -Food intake -Hyperphagia Questionnaire -Oxytocin Study Questionnaire (focused on changes in emotions, social, and eating behavior, as well as possible side effects)	-When all participants were included in the analysis, no significant effect of OXT was found on any outcome measures -When participants were divided into groups based on age (older vs. younger than 11 years), the younger participants showed significant improvements in social behavior, food-related behavior, anger, sadness, and conflicts during OXT treatment compared to placebo -Lower serum oxytocin levels after OXT treatment were associated with positive effects on social behavior in the younger children. This effect was not found in the older children. (Note: blood samples were not extracted). -No side effects or adverse events were reported
"Oxytocin treatment in children with Prader-Willi syndrome: A double-blind, placebo-controlled, crossover study"	Miller et al. (2017)	Human child study Age range: 5–11 y Mean age: 8.2 y PWS: n = 24 Females: 15 Males: 9	Double-blind, randomized, placebo-controlled, cross-over	Manipulation: daily intranasal dose of 16 IU OXT or placebo for 5 days followed by a minimum of 4-week washout period to cross over to the alternative treatment for further 5 days Outcomes: -Aberrant Behavior Checklist -Social Responsiveness Scale -Repetitive Behavior Scale-Revised -Hyperphagia Questionnaire -Clinical Global Impression Scale	- No significant improvements in any of the measures but trend towards significance was reported in all of the measures following intranasal OXT treatment -Intranasal OXT treatment was shown to be safe and well tolerated with a few adverse events (i.e., nasal irritation and irritability)

(*continued on next page*)

Table 4 (*continued*)

Article title	First author & publication year	Sample characteristics	Study design	Manipulation & outcome measures	Relevant findings
"The use of oxytocin to improve feeding and social skills in infants with Prader–Willi syndrome"	Tauber et al. (2017) (Note: same study/ population as Viaux-Savelon et al., 2016 above)	Human infant study Age range: 0.8–5.7 m Mean age: 3.9 m PWS: n = 18 Females: 8 Males: 10	Unblinded dose escalation with 3 steps over 7 days	Manipulation: intranasal dose of 4 IU OXT every other day, daily, or twice daily for one week Outcomes: -Neonatal Oral-Motor Assessment Scale -Clinical Global Impression -Alarm Distress Baby Scale - Coding Interactive Behavior Scale	-Significant improvements in sucking, swallowing, Clinical Global Impression scores, social withdrawal behavior and mother-infant interactions were reported following intranasal OXT treatment compared to baseline - Intranasal OXT was well tolerated without any adverse events
"Intranasal carbetocin reduces hyperphagia in individuals with Prader-Willi syndrome"	Dykens et al. (2018)	Human adolescent study Age range: 10–18 y Mean age: 13.7 y PWS: n = 37 Females: 23 Males: 14	Double-blind, randomized, placebo-controlled parallel trial between Subjects	Manipulation: thrice daily intranasal dose of 9.6 mg carbetocin or placebo for two weeks Outcomes: -Hyperphagia in PWS Questionnaire-Responsiveness -Children's Yale-Brown Obsessive- Compulsive Scale -Clinical Global Impression-Improvement Scale -Reiss Profile food domain	-Significant improvements in hyperphagic symptoms, food-related behaviors and emotions, compulsivity, and overall functioning were found following intranasal carbetocin treatment compared to placebo -Intranasal carbetocin was well tolerated
"Oxytocin in young children with Prader-Willi syndrome: Results of a randomized, double-blind, placebo-controlled, crossover trial investigating 3 months of oxytocin"	Damen et al. (2021)	Human child study Age range: 3–11 y Mean age: 7.5 y PWS: n = 26 Females: 13 Males: 13	Double-blind, randomized, placebo-controlled, cross-over	Manipulation: twice daily intranasal dose of 16–40 IU OXT or placebo for 3 months followed by a 1-month washout period to cross over to the alternative treatment for further 3 months Outcomes: -Oxytocin Study Questionnaire (focused on changes in emotions, social, and eating behavior, as well as possible side effects) -Hyperphagia Questionnaire -Repetitive Behavior Scale-Revised -Social Responsiveness Scale	-No significant improvement in hyperphagia or social behavior was found following OXT treatment in the total group -Oxytocin Study Questionnaire scores improved significantly only in boys but not in girls following OXT treatment compared to placebo -Significant improvements in hyperphagia and social behavior were found in children with PWS who had paternal deletion on chromosome 15 -Intranasal OXT was well tolerated without significant side effects
"Intranasal oxytocin versus placebo for hyperphagia and repetitive behaviors in children with Prader-Willi Syndrome: A randomized controlled pilot trial"	Hollander et al. (2021)	Human child and adolescent study Age range: 5–18 y Mean age: 8.87 y PWS: n = 23 Females: n = 5 Males: n = 18	Double-blind, randomized, placebo-controlled parallel trial	Manipulation: daily intranasal dose of 16 IU OXT or placebo for 8 weeks Outcomes: -Hyperphagia Questionnaire -Repetitive Behavior Scale-Revised -World Health Organization Quality of Life Scale-BREF -Caregiver Strain Questionnaire	-No significant improvement in hyperphagia or repetitive behaviors was found following OXT treatment but there were significant reductions in these domains in the placebo group -Intranasal OXT was well tolerated with only one adverse event (i.e., nocturia)

IU, international units; OXT, oxytocin; PWS, Prader-Willi syndrome

receptor-selectivity for OXT receptors over AVP receptors which may overcome potential unfavorable effects of OXT at higher doses. A recent double-blind, randomized, placebo-controlled study examined the therapeutic benefit of carbetocin in adolescents with PWS (Dykens et al., 2018). Three times daily carbetocin administration for 14 days reduced hyperphagia and obsessive-compulsive behaviors as well as improved overall behavioral symptoms. A larger multi-center, double-blind, randomized, placebo-controlled phase 3 study has also evaluated the efficacy, safety, and tolerability of intranasal carbetocin in participants with PWS (https://clinicaltrials.gov/ct2/show/NCT03649477). Numeric trends toward improvement in Children's Yale-Brown Obsessive--Compulsive Scale (CY-BOCS) and PWS Anxiety and Distress Questionnaire (PADQ) scores were observed in each dose arm, but did not reach statistical significance versus placebo. Unfortunately, this study was terminated early due to the global SARS-CoV-2 pandemic, and no additional data are currently available. During this studyTauber et and adolescents with PWS (https://www.levotx.com/news/care-pws_top-line_results/). These data indicate that longer studies to confirm safety and efficacy of carbetocin in individuTauber et als with PWS across all ages are warranted.

10. Summary and implications

The goal of the present effort was to review the extant literature on OXT and AVP signaling and neuropeptide administration in animal models and in individuals with PWS. Across both preclinical and clinical studies, pronounced and wide-ranging dysfunction in OXT and/or AVP signaling pathways was evident, impacting cellular production, neural transmission, and/or receptor availability (Fig. 1; Tables 1 and 3). The majority of preclinical research to date has been conducted in a single PWS animal model involving a single gene, *Magel2*; perhaps this is why the preclinical PWS "story" is fairly straightforward at present: *Magel2* mutant mice exhibit pronounced central neuropeptide signaling disruption that likely arises from a prohormone processing defect early in life, and which in all likelihood persists into adulthood. In PWS patients, although neuropeptide dysregulation is robustly evident, the directionality and severity of this dysfunction is not consistent across studies, likely due, at least in part, to differences in subjects' age, sex, and PWS genetic subtype, as well as the type of biological specimen collected and the biological measurement techniques employed.

Preclinically, OXT (Meziane et al., 2015) and AVP (Borie et al., 2021) administration were each shown to reverse behavioral deficits in a PWS

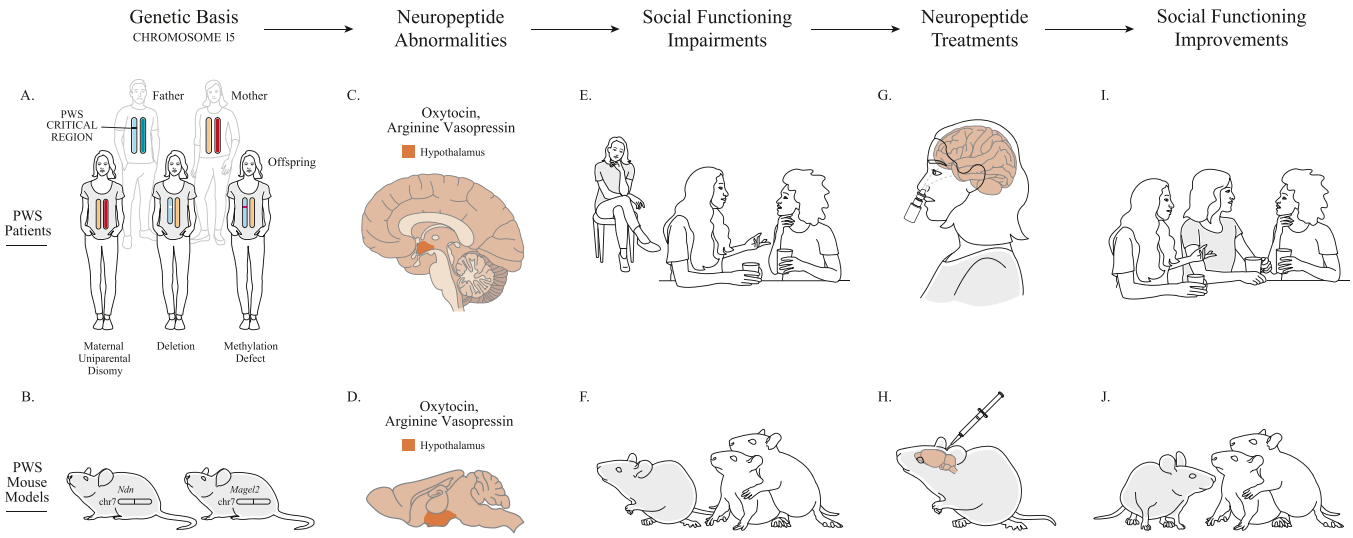

Fig. 1. Hypothalamic neuropeptides and social functioning in Prader-Willi syndrome (PWS). A. PWS is caused by genetic changes within the PWS critical region on chromosome 15 (15q11-q13). The top section of panel A represents an unaffected father (with the PWS critical region indicated on chromosome 15) and an unaffected mother. The bottom section of panel A depicts the specific changes to chromosome 15 that cause PWS in offspring (shaded in gray): maternal uniparental disomy of chromosome 15 (i.e., both copies of chromosome 15 are inherited from the mother), paternal deletion of 15q11-q13, or an imprinting (methylation) defect of paternal 15q11-q13. B. Mice carrying targeted gene mutations of PWS (shaded in gray) in *Ndn* and *Magel2* on chromosome 7 (chr7) recapitulate many core characteristics of PWS. C. and D. Prohormone convertase deficiency (not pictured) is hypothesized to alter precursor processing of the hypothalamic neuropeptides, oxytocin and arginine vasopressin, in both PWS patients and mouse models of PWS. E. and F. The resulting neuropeptide signaling abnormalities, in turn, are associated with social functioning deficits in both PWS patients and mouse models. G. and I. Intranasal oxytocin or carbetocin (an oxytocin analogue) treatment improves social functioning in at least some individuals with PWS. H. and J. Oxytocin or arginine vasopressin administration improves social functioning in mouse models of PWS. (The effect of arginine vasopressin administration on social functioning has not been tested in PWS patients.).

mouse model (Fig. 1; Table 2). Although far more pharmacological research has been conducted in people with PWS than in mouse models, clinical trial outcomes have been highly variable, and likely impacted by subjects' age, sex, and PWS genetic subtype, as well as by the study design, drug dose, treatment length, and power to detect meaningful effects. Nevertheless, despite this study-to-study variability, several OXT clinical trials reported promising efficacy on behavioral endpoints, particularly in patients at younger ages, and particularly in males (Fig. 1; Table 4).

11. Limitations and directions for future research

Findings from the studies reviewed here point to numerous avenues for future research. First, although multiple mouse models lacking single genes in the PWS locus have been developed (Kummerfeld et al., 2021), the vast majority of research has focused on eating behavior (a topic discussed in detail elsewhere (Griggs et al., 2015) and one beyond the scope of this social behavior focused review). The work that has been conducted on neuropeptide dysregulation and social impairment in PWS has been restricted nearly exclusively to a single genetic model (i.e., *Magel2*). Social behavior-focused research using existing mouse genetic models can thus readily be conducted to gain a more nuanced understanding of the unique contribution of each PWS-associated gene to neuropeptide dysregulation and its role(s) in social impairment. Second, these mouse models can also be deployed to gain a better mechanistic understanding of the therapeutic actions of OXT and AVP on social behavior, and the PWS phenotype more generally, as specific receptor targets for each of these medications remain poorly understood in humans (Rae et al., 2022). Third, although preclinical research efforts have established a credible link between neuropeptide dysregulation and social impairment in PWS, mechanistic research is still needed to better understand the relationship between prohormone convertases and OXT and AVP signaling, particularly given the large role prohormone processing deficits may play in other neuroendocrine features of PWS (Burnett et al., 2017). Fourth, it is likely that neuropeptide dysregulation differs across the PWS population as a whole. This possibility points to the importance of systematically measuring OXT and AVP concentrations in individuals with PWS compared to matched controls, using gold-standard neuropeptide measurement techniques (Tabak et al., 2022), to better understand how and to what extent neuropeptide signaling may be disrupted in this clinical population. Moreover, it is also imperative to determine whether individual differences in neuropeptide levels relate to social symptom severity, and how certain factors, such as age, sex, and PWS genetic subtype may impact OXT and AVP concentrations. Fifth, once this biological information is better synthesized, researchers will be poised to conduct biologically informed (and possibly biomarker stratified) precision treatment trials to better and more rigorously test OXT's therapeutic potential in PWS. A similar precision medicine approach has already been applied to individuals with idiopathic ASD (Parker et al., 2017) and to fragile-X syndrome patients (Hall et al., 2012), the latter who as a population have been hypothesized to have OXT signaling deficits (Francis et al., 2014). Sixth, a precision medicine approach to studying and treating PWS would also increase the power to detect effects of OXT or AVP administration in the small study samples which are common in rare disease research efforts. Indeed, the low population prevalence of PWS typically limits the ability of single sites to recruit large study samples, and standard research funding caps limit the number of multi-site projects which can support large-scale recruitment efforts. Cross-over trial designs enable a repeated measures approach to statistical analysis, and, in theory, can be useful for testing medications in smaller study samples. However, cross-over designs are vulnerable to learning effects across treatment arms when a participant is repeatedly exposed to test stimuli (which is particularly problematic if these stimuli are used to evaluate treatment efficacy). Cross-over designs are also vulnerable to carry-over effects that can occur when active treatment is administered prior to placebo. Standard placebo-controlled parallel designs guard against these concerns, but typically require larger study samples. One potential way to mitigate these concerns is to employ Sequential Parallel Comparison Design (SPCD) (Doros et al., 2013; Tamura and Huang, 2007) in

PWS medication trials. SPCD is an innovative and statistically powerful approach to double-blind randomized placebo-controlled trial design. SPCD enhances signal detection by minimizing the effect of placebo responses and can be used successfully in the context of smaller study samples. Seventh, carefully designed research studies are also needed to ascertain when during development OXT treatment is most beneficial, and whether there is a "critical period" for its administration (DeMayo et al., 2019). Eighth, it is also crucial to determine whether OXT treatment is most efficacious when administered intermittently in the context of social skills training (which would be the case if its primary mechanism of action is to increase social salience) (Ford and Young, 2022; Peled-Avron et al., 2020) or whether OXT treatment is most effective as a "replacement" strategy for a neuroendocrine deficiency, not unlike other hypothalamic-pituitary hormones in PWS which require routine, standard-of-care replacement therapy (Tauber and Diene, 2021). Finally, the safety and efficacy of AVP treatment for social impairments in individuals with PWS warrants investigation, particularly in light of the fact that AVP appears to be deficient in at least some PWS patients, and AVP has been shown to "rescue" social functioning in *Magel2*-deficient mice with impaired AVP signaling (Borie et al., 2021). However, as with OXT, there is a need to develop a therapy with appropriate receptor specificity, and demonstrated target engagement in this patient population.

12. Conclusion

Compelling evidence from both animal models and individuals with PWS implicates pronounced dysregulation of brain OXT and AVP signaling pathways and subsequent effects on social behavior. Preclinical research has begun to forge links between neuropeptide dysregulation and social functional deficits, although the process by which this dysregulation occurs in PWS awaits mechanistic investigation. Clinical research to date points to similar links, but further research is still needed to better and systematically characterize how OXT and AVP biology relate to social impairment and how this dysregulation may be affected by other factors, such as age, sex, and genetic subtype in individuals with PWS. Nevertheless, the preponderance of biological evidence, and accumulating clinical trial results, suggest that these neuropeptide pathways may provide promising targets for therapeutic intervention in a patient population that currently lacks a pharmacological strategy for its debilitating social behavior symptoms.

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