Review Article

J Mucopolysacch Rare Dis 2021;5(1):39-41
https://doi.org/10.19125/jmrd.2021.5.1.39
pISSN 2465-8936 · eISSN 2465-9452

JMRD
Journal of Mucopolysaccharidosis and Rare Diseases

A Brief Review of Preclinical Researches and Clinical Trials of Oxytocin on Behavior-Related Phenotypes in Prader-Willi Syndrome

Jiyeon Kim

Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Prader-Willi syndrome (PWS) is a rare genetic neurodevelopmental disorder of hyperphagia leading to severe obesity, intellectual deficits, compulsivity, and other behavioral problems. PWS is caused by the inactivation of contiguous genes on chromosome 15q11-q13, which complicates the development of targeted, effective therapeutics. Various preclinical studies have been conducted by developing mouse models that exhibit phenotypes similar to PWS. Oxytocin deficiency in PWS is associated with hyperphagia with impaired satiety and, food-seeking and behavior disorders. Here, we summarize the oxytocin study of ingestion behavior tested in the PWS mouse model and published data from clinical trials that have evaluated treatment effectiveness on ingestion behavior and social dysfunction in patients with PWS.

Keywords: Prader-Willi syndrome, Oxytocin

Introduction

Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder causing endocrine, musculoskeletal, and neurological dysfunction. PWS, one of the best-studied neurodevelopmental diseases, is characterized mainly by developmental disability, hyperphagia, and behavioral problems. It is caused by the inactivation of contiguous genes on chromosome 15q11-q13[1]. The extremely well-conserved synteny between the human and the murine regions helped to generate PWS mouse models. These animal models guide clinical trial priorities or provide information about the efficacy of a compound within the context of a specific disease[1,2].

The neuropeptide oxytocin (OT) produced by the hypothalamus and released by the posterior pituitary has emerged as a key regulator of diverse social behaviors and a potential therapeutic target for improving social dysfunction[3]. PWS is associated with a marked deficiency in oxytocin- containing neurons in the hypothalamic paraventricular nucleus. PWS features, including hyperphagia and social dysfunction, are reportedly related to the consequent hypothalamic hyposecretion of oxytocin.

Here, we briefly summarize the preclinical studies measuring the behavior-related effect of therapeutics on PWS animal models and clinical trials of oxytocin on PWS patients.

Oxytocin in Prader-Willi Syndrome

PWS patients typically have fewer oxytocin-producing neurons in the hypothalamic periventricular nucleus and a smaller-than-average ventricular peripheral nucleus[4]. Oxytocin is an endogenous neuropeptide hormone produced in the hypothalamus and released from the posterior pituitary gland that plays an important role in childbirth, food intake, body weight, and social bonding, all of which have a serious impact on patients with PWS. Most people with PWS suffer from hyperphagia with impaired satiety and food-seeking, which poses a serious risk of obesity and associated metabolic diseases in children. They also show significant social cognitive dysfunction, including symptoms of

Received May 24, 2021; **Revised** June 9, 2021; **Accepted** June 14, 2021
Correspondence to: Jiyeon Kim
Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
Tel: +82-2-3410-3537, Fax: +82-2-3410-0043, E-mail: kim.jiyeon48@gmail.com

Autism Spectrum Disorder (ASD), which has a significant impact on their family and surrounding environments. It is difficult to treat abnormal ingestive behaviors and social dysfunction in patients with PWS due to their intellectual disability, anxiety, and endocrine dysfunction. Until recently, the pharmacological treatment for PWS was limited to symptomatic treatments, such as hormone replacement or psychiatric drugs, or behavioral or physical therapy. Several therapeutics have been tested for their effect on PWS phenotypes, including hyperphagia and social-behavioral problems. Oxytocin is one of the most promising targets.

Preclinical Researches of Oxytocin in PWS

Several types of pharmacological compounds have been tested in PWS mouse models to modify behavior-related phenotypes. Initially, many types of gene-targeted mice were developed to investigate the mechanisms of gene regulation and gene function associated with PWS phenotypes. Among these, two mouse models lacking the neccdin and Magel2 genes located in the PWS critical region reportedly had an oxytocin deficiency similar to that of PWS patients[5,6]. Several studies have reported the effect of therapeutic intervention in Magel2 mutant mice. The administration of oxytocin, immediately after birth, improves survival and helps with ingestive problems and social dysfunction in Magel2 knockout mice[5-7]. In a follow-up study, Magel-2 mutant mice who received oxytocin injections immediately after birth did not have social and learning deficits as adult[2,6,7]. These findings suggest that there is a problem with oxytocin function in PWS, and that oxytocin administration may have a positive effect on PWS phenotype.

Clinical Trials on Oxytocin and Behavior-related PWS Phenotypes

Many clinical studies have been conducted on various pharmacological compounds to treat PWS symptoms. Preclinical studies can provide valuable information about how animals respond to potential treatments in vivo. Animal testing can accelerate clinical practice adaptations. To date, five clinical trials have been reported on oxytocin administered as an intranasal spray in PWS patients[8]. In most of the clinical studies, oxytocin or an oxytocin analogue (intranasal carbetocin, FE992097) was tested in PWS patients to confirm their positive effects on both hyperphagia and social dysfunction[9-14]. Of these, four trials were randomized controlled studies in children and adolescents with PWS. These demonstrated that oxytocin has a beneficial effect with few side effects on PWS patients. However, the research has limitations, such as the lack of a control group and the use of non-verified psychometric assessments.

Oxytocin in higher doses can worsen social behavior. The effectiveness of long-term oxytocin administration remains unknown, warranting further study. Intranasal oxytocin administration reduces the body-weight of obese PWS and non-PWS patients, and a single administration improves emotional awareness in healthy autistic adults and reduces repetitive behavior in ASD patients. A recent clinical trial for intranasal carbetocin(LV-101), an oxytocin analogue, reported promising results[14]. A Phase 3, randomized, double-blind study measured the outcome of changes in parent or caregiver-rated hyperphagia, obsessive-compulsive symptoms, and Clinical Global Impressions Scale score after administration of intranasal carbetocin or placebo three times daily for 14 days. Intranasal carbetocin was well tolerated and improved hyperphagia and behavioral symptoms of PWS.

Conclusion

This short review reports the positive effects of oxytocin on PWS symptoms and highlights some limitations of clinical trials. Many preclinical and clinical studies indicate that administration of oxytocin in PWS patients may have a positive impact on their social limitations. Increased investment in and facilitating conduction of preclinical animal models studies accelerates new PWS treatments. Many experts are currently working to introduce oxytocin and other compounds into PWS therapy for more effective and beneficial interventions.

References

1. Kalsner L, Chamberlain SJ. Prader-Willi, Angelman, and 15q11-q13 Duplication Syndromes. Pediatr. Clin. North Am 2015;62:587-606.
2. Carias KV, Wevrick R. Preclinical Testing in Translational Animal Models of Prader-Willi Syndrome: Overview and Gap Analysis. Mol Ther Methods Clin Dev 2019;13:344-58.
3. Kendrick KM, et al. Overview of human oxytocin research. Curr Top Behav Neurosci 2018;35:321-48.
4. Swaab DF, Purba JS, Hofman MA. Alterations in the hypothalamic paraventricular nucleus and its oxytocin neurons (putative satiety cells) in PraderWilli syndrome: a study of five cases. J Clin Endocrinol Metab 1995; 80:573-9.
5. Muscatelli F, Abrous DN, Massacrier A, et al. Disruption of the mouse Necdin gene results in hypothalamic and be-

havioral alterations reminiscent of the human Prader-Willi syndrome. Hum Mol Gen 2000;9:3101-10.
6. Schaller F, Watrin F, Sturny R, et al. A single postnatal injection of oxytocin rescues the lethal feeding behaviour in mouse newborns deficient for the imprinted Magel2 gene. Hum Mol Gen 2010;19:4895-905.
7. Meziane H, Schaller F, Bauer S, et al. 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. Biol Psychiatry 2015; 78:85-94.
8. Rice LJ, Einfeld SL, Hu N, Carter CS. A review of clinical trials of oxytocin in Prader-Willi syndrome. Curr Opin Psychiatry 2018;31:123-7.
9. Tauber M, Mantoulan C, Copet P, et al. 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. Orphanet J Rare Dis 2011;6:47.
10. Einfeld SL, Smith E, McGregor IS, et al. A double-blind randomized controlled trial of oxytocin nasal spray in Prader Willi syndrome. Am J Med Genet A 2014;164A:2232-9.
11. Kuppens RJ, Donze SH, Hokkens-Koelega ACS. Promising effects of oxytocin on social and food-related beahvior in young children with Prader-Willi syndrome: a randomized, double-blind, controlled crossover trial. Clin Endocrinol 2016;85:979-87.
12. Miller JL, Tamura R, Butler MG, et al. Oxytocin treatment in children with Prader-Willi syndrome: a double-blind, placebo-controlled, crossover study. Am J Med Genet A 2017;173:1243-50.
13. Tauber M, Boulanouar K, Diene G, et al. The use of oxytocin to improve feeding and social skills in infants with Prader-Willi syndrome. Pediatrics 2017;139:e20162976.
14. Dykens EM, Miller J, Angulo M, Roof E, Reidy M, Hatoum HT, et al. Intranasal carbetocin reduces hyperphagia in individuals with Prader-Willi syndrome. JCI Insight 2018;3:e98333.