We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Molecular Aspects and Structure Activity Relationship of Oxytocin Agonists and Antagonist's Role in Health

Veera C.S.R. Chittepu, Poonam Kalhotra, Tzayhri Gallardo Velazquez and Guillermo Osorio Revilla

Abstract

Oxytocin (OT) and Oxytocin receptor signaling mechanism had emerged as a pathway for treatment of metabolic disorders like obesity, and diabetes. Both agonists and antagonists activity of the oxytocin receptor has beneficial aspects. This chapter will outline the receptor agonists and antagonist's activity as a function of the features: hydrophobic regions, activity shapes, and positive and negative electrostatics. Also, their phenotype characteristics in various diseases like diabetes, obesity, cardiovascular and immune related diseases will be outlined. Finally, therapeutic development strategies for using various nanomaterials, and other biomaterials, as well as those in present use will be discussed.

Keywords: oxytocin, agonists and antagonists, drug delivery, nanomaterials, biomaterials, diabetes, obesity, regenerative medicine

1. Introduction

Oxytocin (OT) was the first hormone to have its composition determined and was synthesized in a biologically active manner [1]. OT is a major neuropeptide, and its roles involve control of neuroendocrine reflexes [2], the development of particular social and bonding habits [3], and the reproductive and maternal functions [4]. Cyclic nonapeptide OT and its structurally related peptides facilitate reproduction in many vertebrates.

In earlier years, OT was believed to be restricted to stimulate uterine contractions during childbirth [5] and milking (lactation) but the fact that OT is found in both men and women in the brain and plasma indicates there are other significant roles.

Most of the OT like peptides are nonapeptides and have a disulfide bridge between cysteine residues 1 and 6. The residue Lysine at position 3 and arginine or lysine at position 8 are responsible for biological activity of oxytocin peptide, that is, to activate oxytocin receptor [1]. Generally, the nonapeptides are classified as vasopressins and OT families, and are based on the presence of basic amino acid at position 8 and neutral amino acids. **Figure 1** shows the phylogenetic tree corresponding to oxytocin like peptides, retrieved from Uniprot webpage [6].

The oxytocin gene is located on chromosome 3p25 and comprises 3 introns and 4 exons and belongs to the G protein-coupled receptor (GPCR) superfamily. Oxytocin binds to receptors that activate intracellular signaling pathways, triggering the activation of proteins. **Figure 2** was developed by the authors to show in a schematic way, the oxytocin-oxytocin receptor (OT-OTR) signaling pathway in the body. Upon binding OT to OTR, Gq/phospholipase C (PLC)/inositol

Figure 1. Phylogenetic tree of oxytocin like peptides. Oxytocin like peptides are denoted using their Uniprot ID (Uniprot webpage [6]).

Figure 2. Molecular features of oxytocin receptor modulators calculated using forge tool. Oxytocin receptor linked signaling pathways resulting in cell phenotype. OT: Oxytocin, OTR: Oxytocin receptor, PLC: Phospholipase, PIP2: Phosphatidylinositol 4,5-bisphosphate, InsP3: Inositol 1,4,5- triphosphate, DAG: Diacylglycerol, PKC: Protein kinases type C, MLC: Myosin light-chain, MAPK: Mitogen-activated protein kinase, cPLA2: Cytosolic phospholipase A2, ROK: RhoA associated protein kinase.

1,4,5-triphosphate (InsP3) pathway dominates the phosphatidylinositol 4,5-bisphosphate (PIP2) hydrolysis and this results in InsP3 and diacylglycerol (DAG) (DAG). InsP3 releases Ca^{2+} ions from the intracellular sarcoplasmic reticulum stores, but the DAG further activates protein kinases which phosphorylate other proteins. Mammary epithelial cells and milk ejection is caused by Ca^{2+} ions. Activation of MAPK cascade is triggered by OTR and PKC resulting in increased expression of cPLA2 activity, which eventually results in development of prostaglandins. The profusion of prostaglandins development often causes muscle contractions. OTR activation elicits phosphorylation of calcineurin. All these signaling pathways result in many cellular effects such as cell formation, cell differentiation, and motility.

Transmembrane domains 3,4, and 6 of oxytocin receptor forms the docking site to oxytocin peptide cyclic part, and other c terminal domain of oxytocin interacts closely with domain 2 and domain 3 in the extracellular space of the oxytocin receptor. The key OTR residues R34, F103, D85, F284, and Y209, play a role in selectivity of oxytocin peptide. Based on the activity of oxytocin receptor, the oxytocin analogues were classified as agonists and antagonists.

2. OTR agonists and antagonists

Receptor binding and functional studies were generally used to identify oxytocin receptor agonists and antagonist activity. There are more than thousand compounds in literature as OTR agonists and antagonists, and this section was focused to demonstrate the applicability of molecular shape features as tool to develop agonists and antagonists. For this reason, peptide agonist and antagonist molecular shapes features are compared with oxytocin.

Substitution of hydroxyl group at position 1 and threonine at position 4 of original oxytocin peptide (peptide 1, **Figure 3**) revealed highest affinity to oxytocin receptor (OTR), with value of K_i 0.31 nM and served as oxytocin agonist and as a possible treatment of autism [7], and for the treatment of postpartum hemorrhage [8].

Figure 3.
Molecular features of oxytocin receptor modulators calculated using forge tool.

Peptide atosiban (peptide 2, **Figure 3**) revealed affinity to oxytocin receptor with a value of K_i 76 nM, and it is used in clinical as oxytocin antagonist [9]. Newly developed Cresset XED force field provided by software Forge [10] was utilized to understand the key features of oxytocin, agonist and antagonist of oxytocin receptor.

Figure 3 was developed by the authors using Forge tool for oxytocin, agonist and antagonist of OTR, and features were visualized using Forge visualization software to show the comparison of features: red color (positive electrostatics), blue color (negative electrostatics), and gold color (hydrophobic shapes).

The molecular features shown in **Figure 3** are the result of activities and clearly reveal agonist and antagonist function on the oxytocin receptor. Visual examination either manually or using imaging algorithms of all the fields, reveals the presence of positive electrostatic feature in definite coordinates, and size and shape are responsible for agonist and antagonist activity of OTR. Increased electronegative regions favor agonist activity, and similarly, hydrophobic shape features are distinct for agonist and antagonist activity of OTR. The features mentioned in this study, indeed can be utilized by various investigators to discover, develop, and optimize agonist and antagonists of OTR. It is well possible to screen various libraries and chose the molecules of interest.

3. Phenotype characteristics in various diseases

Oxytocin receptor agonists and antagonists has potential benefits in health care, especially in treating diabetes, obesity, cardiovascular, and immune related disorders. It is well known that diabetes is considered one of the major causes of mortality and a metabolic disorder. Incidence of diabetes mellitus will increases over coming decades and is generally considered that affect many organs [11]. Many researchers has demonstrated beneficial effect of oxytocin, as endogenous factor, with significant changes in insulin sensitivity [12], lipidomic [13], and glucose metabolism [14]. Oxytocin stimulates glucose uptake [14, 15], and glucagon secretion [16] in pancreatic islets which is directly implicated in improvement and involvement of pathophysiology of diabetes.

Apart from diabetes, another major problem most of countries are concerned about is obesity, both in Mexico and worldwide [17, 18]. Oxytocin is well known for its effects in control of the energy balance [19]. It's well proven that oxytocin administration reduces body weight [20], food intake [21], and glucose tolerance was observed with administration of oxytocin [22]. In addition, oxytocin administration induces a marker of neuronal activation that is known as Fos [23], that is linked to control meal size, regulation of intake of food and indeed bodyweight.

Another class of disease is cardiovascular disease, where 13% of deaths are due to this, specifically due to blood pressure, followed by tobacco, diabetes, and lack of exercise [24]. Cardiovascular diseases involve generally blood vessels or heart [25]. Oxytocin receptor decreases blood pressure [26] and lowers brain natriuretic peptide [27]. Oxytocin was also proven to facilitate the recovery of cardiovascular system (CVS) [28] from injuries [29] and decrease progression of atherosclerosis. Key pathways involved in cardiovascular protection upon treatment with oxytocin act by suppressing the increasing production of cytokines, apoptotic pathways are activated through the involvement of multiple signaling pathways [29].

Oxytocin is also involved in immune related health problem; oxytocin was proven to trigger thymocyte proliferation [30], inducing immune tolerance, which is generally observed in thymus which is a primary tissue responsible for [31]. The nonapeptide oxytocin interacts with neurohypophysial peptide receptors expressed by pre-T cells and induces phosphorylation of focal adhesion kinase [32]. Generally,

oxytocin production decreases with age, which is linked to thymic involution. Oxytocin also has antiviral activity and it has been reported its possible used to treat CoVID-19 through DPP-inhibition mechanism of action [33, 34].

4. Nano, micro and macro materials for delivery of agonists and antagonists

Up today, oxytocin receptor agonists and antagonists formulations including nano, micro and macro materials are not available in the market. Existing oxytocin receptor agonists and antagonists possess drawbacks like lack of efficacy, no improvement in neonatal outcomes, low stability, short half-life in-vivo, and low bioavailability.

Many researchers had started to utilize alternative approaches to address mentioned drawbacks, and among these, encapsulations for slow and steady oxytocin release are under investigation. Most of them are polymeric carriers, and liposome-based technologies.

Among the polymeric carriers for oxytocin, solvent displacement method was utilized to synthesize poloxamer hydrogel scaffold, to encapsulate oxytocin in hydrogel graft constituted of poly(D, L-lactide-co-glycolide) (PLGA), β -tricalcium phosphate, and hydroxyapatite (CP). This method yielded 89.5% encapsulation efficiency, slowly release encapsulated oxytocin, and finally yielded significant regeneration of bone loss in rat calvaria [35].

Another nanomaterial application was based on Bovine Serum Albumin (BSA) based nanocomposites. It is a two-step process to synthesize nanocomposites, nanoprecipitation followed by lyophilization. Transferrin (Tf) and Rabies Virus Glycoprotein (RVG) was conjugated to synthesized oxytocin-BSA nanoparticles for successful delivery of oxytocin across blood brain barrier (BBB). This composite was delivered intranasally, and an improvement in oxytocin bioavailability was observed. Delivery of oxytocin using nanocomposites led to greater pro-social effects in comparison to oxytocin alone within 3 days of intranasal administration. This delivery system definitely benefits social-deficit disorders and indeed enhance the brain delivery peptides [36].

Another important nanocarrier utilized in successful delivery oxytocin receptor agonists and antagonists is liposomal drug delivery systems. In specific, antibody-based liposomes were applied where PEGylated liposomes were conjugated with atosiban (ATO-Lipo, OTR antagonist) or anti-OTR monoclonal antibodies (OTR-Lipo) using the technology of dried lipid film hydration. This method increased intracellular internalization, and revealed that the cellular uptake is dependent on caveolin-mediated mechanisms, with no cellular toxicity observed. Antibody-conjugated liposomes gave way to improved treatment for obstetric complications [37].

5. Future perspectives

Since the therapeutic effects of agonists and antagonists are growing, more studies will be needed to protect them against biodegradation, to increase intestinal absorption particularly with use of technologies, such as enhancer absorption (cyclodextrines), surfactants, cell penetration peptide, chemistry modifications, nano, micro and macromaterials.

Besides improving drug delivery methods, additional cell-based experiments are required to understand the role of oxytocin such as the use of fluorescent tags

(HaloTag) to monitor new functions for agonists or antagonists, the use of imaging techniques to classify and develop imaging biomarkers is needed to explore the ability of oxytocin receptor agonists or antagonists across tissues, cell-host interactions. In addition, the molecular features described in this study can be used to discover new and novel oxytocin receptor agonists and antagonists.

6. Conclusion

Molecular shape features of oxytocin receptor agonist and antagonist activity as a function of positive and negative electrostatic, and hydrophobic shapes features were developed and detailed. Also, liposome and polymeric based strategies in improving most of the drawbacks associated with oxytocin delivery were discussed. More studies are needed towards the application of diverse nanomaterials to deliver neuropeptides and improve their efficacy. Some of the tools proposed in this chapter can guide the future research in improving the delivery strategies of oxytocin receptor agonists and antagonists.

It has to be remembered that, technologies need to be developed for each route of administration, maintain stability, and steady state release of encapsulated active ingredients.

Acknowledgements

All authors would like to thank for the support provided by Consejo Nacional de Ciencia y Tecnología (CONACYT), Escuela Nacional de Ciencias de Biológicas (ENCB) and Instituto Politécnico Nacional (IPN).

Conflict of interest

The authors declare no conflict of interest.

IntechOpen

IntechOpen

Author details

Veera C.S.R. Chittepu¹, Poonam Kalhotra², Tzayhri Gallardo Velazquez²
and Guillermo Osorio Revilla^{1*}

¹ Departamento de Ingeniería Bioquímica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Av. Wilfrido Massieu S/N, Col. Unidad Profesional Adolfo López Mateos, Zacatenco, Ciudad de México, CP, Mexico

² Departamento de Biofísica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Prolongación de Carpio y Plan de Ayala S/N, Col. Santo Tomás, Ciudad de México, CP, México

*Address all correspondence to: osorgi@gmail.com

IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] Gimpl G, Fahrenholz F (2001) The oxytocin receptor system: Structure, function, and regulation. *Physiol Rev.* <https://doi.org/10.1152/physrev.2001.81.2.629>
- [2] Bisset GW, Chowdrey HS (1988) CONTROL OF RELEASE OF VASOPRESSIN BY NEUROENDOCRINE REFLEXES. *Q J Exp Physiol.* <https://doi.org/10.1113/expphysiol.1988.sp003223>
- [3] Lim MM, Young LJ (2006) Neuropeptidergic regulation of affiliative behavior and social bonding in animals. *Horm Behav.* <https://doi.org/10.1016/j.yhbeh.2006.06.028>
- [4] Burbach JPH, Young LJ, Russell JA (2006) Oxytocin: Synthesis, secretion, and reproductive functions. *Knobil Neill's Physiol Reprod.* <https://doi.org/10.1016/B978-012515400-0/50063-4>
- [5] Khajehei M (2017) Labour and beyond: The roles of synthetic and endogenous oxytocin in transition to motherhood. *Br J Midwifery.* <https://doi.org/10.12968/bjom.2017.25.4.230>
- [6] Bateman A, Martin MJ, O'Donovan C, et al (2017) UniProt: The universal protein knowledgebase. *Nucleic Acids Res.* <https://doi.org/10.1093/nar/gkw1099>
- [7] Hollander E, Bartz J, Chaplin W, Phillips A, Sumner J, Soorya L, Anagnostou E, Wasserman S (2007) Oxytocin Increases Retention of Social Cognition in Autism. *Biol Psychiatry.* <https://doi.org/10.1016/j.biopsych.2006.05.030>
- [8] Su LL, Chong YS, Samuel M (2007) Oxytocin agonists for preventing postpartum haemorrhage. *Cochrane Database Syst Rev.* <https://doi.org/10.1002/14651858.CD005457.pub2>
- [9] Manning M, Cheng LL, Stoev S, Ching Wo N, Chan WY, Szeto HH, Durroux T, Mouillac B, Barberis C (2005) Design of peptide oxytocin antagonists with strikingly higher affinities and selectivities for the human oxytocin receptor than atosiban. *J Pept Sci.* <https://doi.org/10.1002/psc.667>
- [10] Kalhotra P, Chittepu V, Osorio-Revilla G, Gallardo-Velázquez T (2018) Structure–Activity Relationship and Molecular Docking of Natural Product Library Reveal Chrysin as a Novel Dipeptidyl Peptidase-4 (DPP-4) Inhibitor: An Integrated In Silico and In Vitro Study. *Molecules* 23:1368
- [11] Dabelea D, Bell RA, D'Agostino RB, et al (2007) Incidence of diabetes in youth in the United States. *J Am Med Assoc.* <https://doi.org/10.1001/jama.297.24.2716>
- [12] Zhang H, Wu C, Chen Q, Chen X, Xu Z, Wu J, Cai D (2013) Treatment of Obesity and Diabetes Using Oxytocin or Analogs in Patients and Mouse Models. *PLoS One.* <https://doi.org/10.1371/journal.pone.0061477>
- [13] Elabd SK, Sabry I, Mohasseb M, Algendy A (2014) Oxytocin as a novel therapeutic option for type I diabetes and diabetic osteopathy. *Endocr Regul.* https://doi.org/10.4149/endo_2014_02_87
- [14] Gutkowska J, Jankowski M (2012) Oxytocin Revisited: Its Role in Cardiovascular Regulation. *J Neuroendocrinol.* <https://doi.org/10.1111/j.1365-2826.2011.02235.x>
- [15] Florian M, Jankowski M, Gutkowska J (2010) Oxytocin increases glucose uptake in neonatal rat cardiomyocytes. *Endocrinology.* <https://doi.org/10.1210/en.2009-0624>
- [16] Vilhardt H, Krarup T, Holst JJ, Bie P (1986) The mechanism of the effect of

oxytocin on plasma concentrations of glucose, insulin and glucagon in conscious dogs. *J Endocrinol.* <https://doi.org/10.1677/joe.0.1080293>

[17] Haua-Navarro K (2016) Overweight and obesity. *Gac Med Mex.* <https://doi.org/10.4324/9781003139157-7>

[18] World Health Organization (2011) Fact Sheet Obesity and overweight. World Heal. Organ.

[19] Zhang G, Bai H, Zhang H, Dean C, Wu Q, Li J, Guariglia S, Meng Q, Cai D (2011) Neuropeptide Exocytosis Involving Synaptotagmin-4 and Oxytocin in Hypothalamic Programming of Body Weight and Energy Balance. *Neuron.* <https://doi.org/10.1016/j.neuron.2010.12.036>

[20] Blevins JE, Baskin DG (2015) Translational and therapeutic potential of oxytocin as an anti-obesity strategy: Insights from rodents, nonhuman primates and humans. *Physiol Behav.* <https://doi.org/10.1016/j.physbeh.2015.05.023>

[21] Ott V, Finlayson G, Lehnert H, Heitmann B, Heinrichs M, Born J, Hallschmid M (2013) Oxytocin reduces reward-driven food intake in humans. *Diabetes.* <https://doi.org/10.2337/db13-0663>

[22] Olson BR, Drutarosky MD, Chow MS, Hruby VJ, Stricker EM, Verbalis JG (1991) Oxytocin and an oxytocin agonist administered centrally decrease food intake in rats. *Peptides.* [https://doi.org/10.1016/0196-9781\(91\)90176-P](https://doi.org/10.1016/0196-9781(91)90176-P)

[23] Seeley RJ, Yagaloff KA, Fisher SL, Burn P, Thiele TE, Van Dijk G, Baskin DG, Schwartz MW (1997) Melanocortin receptors in leptin effects. *Nature.* <https://doi.org/10.1038/37016>

[24] Mendis S, Puska P, Norrving B (2011) Global atlas on cardiovascular

disease prevention and control. World Heal. Organ.

[25] Mackay, Judith, Mensah GA (2004) Types of Cardiovascular Diseases. *Atlas Hear. Dis. Stroke*

[26] Japundzic-Zigon N (2013) Vasopressin and Oxytocin in Control of the Cardiovascular System. *Curr Neuroparmacol.* <https://doi.org/10.2174/1570159x11311020008>

[27] Gutkowska J, Jankowski M, Lambert C, Mukaddam-Daher S, Zingg HH, McCann SM (1997) Oxytocin releases atrial natriuretic peptide by combining with oxytocin receptors in the heart. *Proc Natl Acad Sci U S A.* <https://doi.org/10.1073/pnas.94.21.11704>

[28] Petersson M (2002) Cardiovascular effects of oxytocin. *Prog Brain Res.* [https://doi.org/10.1016/S0079-6123\(02\)39024-1](https://doi.org/10.1016/S0079-6123(02)39024-1)

[29] Wang P, Wang SC, Yang H, et al (2019) Therapeutic potential of oxytocin in atherosclerotic cardiovascular disease: Mechanisms and signaling pathways. *Front Neurosci.* <https://doi.org/10.3389/fnins.2019.00454>

[30] Geenen V, Legros JJ, Franchimont P, Baudrihay M, Defresne MP, Boniver J (1986) The neuroendocrine thymus: Coexistence of oxytocin and neurophysin in the human thymus. *Science* (80-). <https://doi.org/10.1126/science.3961493>

[31] Nikolich-Žugich J, Slifka MK, Messaoudi I (2004) The many important facets of T-cell repertoire diversity. *Nat Rev Immunol.* <https://doi.org/10.1038/nri1292>

[32] Martens H, Kecha O, Charlet-Renard C, Defresne MP, Geenen V (1998) Neurohypophysial peptides stimulate the phosphorylation of pre-T

cell focal adhesion kinases.
Neuroendocrinology. <https://doi.org/10.1159/000054324>

[33] Diep P-T, Talash K, Kasabri V (2020) Hypothesis: Oxytocin is a direct COVID-19 antiviral. *Med Hypotheses* 145:110329

[34] Chittepu VCSR, Kalhotra P, Osorio-Gallardo T, Jiménez-Martínez C, Robles-de la Torre RR, Gallardo-Velazquez T, Osorio-Revilla G (2019) New Molecular Insights into the Inhibition of Dipeptidyl Peptidase-4 by Natural Cyclic Peptide Oxytocin. *Molecules* 24:3887

[35] Akay AS, Arısan V, Cevher E, Sessevmez M, Cam B (2020) Oxytocin-loaded sustained-release hydrogel graft provides accelerated bone formation: An experimental rat study. *J Orthop Res*. <https://doi.org/10.1002/jor.24607>

[36] Oppong-Damoah A, Zaman RU, D'Souza MJ, Murnane KS (2019) Nanoparticle encapsulation increases the brain penetrance and duration of action of intranasal oxytocin. *Horm Behav*. <https://doi.org/10.1016/j.yhbeh.2018.12.011>

[37] Hua S, Vaughan B (2019) In vitro comparison of liposomal drug delivery systems targeting the oxytocin receptor: A potential novel treatment for obstetric complications. *Int J Nanomedicine*. <https://doi.org/10.2147/IJN.S198116>