Oxytocin-System

Subjects: Molecular Biology

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Definition

Oxytocin (OXT) is hypothalamic neuropeptide synthetized in the brain by magnocellular and parvo cellular neurons of the paraventricular, supraoptic and accessory nuclei of the hypothalamus. OXT acts in central and peripheral nervous system via G-protein-coupled receptors. The classical physiological functions of OXT are uterine contractions, the milk ejection reflex during lactation, penile erection and sexual arousal, but recent studies have demonstrated that OXT may has anti-inflammatory and anti-oxidant properties and regulates the immune and anti-inflammatory responses. In the pathogenesis of various neurodegenerative diseases, microglia are present in active form and release high levels of pro-inflammatory cytokines and chemokines, that are implicated in the process of neural injury. A promising treatment for neurodegenerative diseases involves new therapeutic approaches targeting activated microglia. Recent studies have reported that OXT exerts neuroprotective effects through inhibition of production of pro-inflammatory mediators, and in development of correct neural circuitry. The focus of this review is to attribute a new important role of OXT in neuroprotection through microglia-OXT interaction of immature and adult brain. In addition, we also analyzed the strategies that could enhance its delivery in the brain to amplificated its positive effects .

1. Introduction

Oxytocin (OXT) is expressed firstly as an inactive precursor by the *OXT* gene located on chromosome 20. After undergoing a series of post-translational hydrolysis, this inactive precursor is converted to an active OXT[1]. OXT is synthesized along with its carrier protein neurophysin I. OXT is put into vesicles and axonally carried into the nerve endings in the neurohypophysis, where it is either stored or released into the bloodstream[2][3].

OXT is also synthesized in various peripheral tissues such as placenta, uterus, corpus luteum, amnion, testis, thymus, pancreas and kidney[4].

2. Receptor

OXT binds to the oxytocin receptor (OXTR). The OXTR is a 389-amino acid belonging to the G-protein-coupled transmembrane receptor superfamily[5]. The human *OXTR* gene is located on chromosome 3 at locus 3p25.

The OXTR is bound by OXT, a neuropeptide composed of nine amino acids (Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly). The secondary structure of OTX is formed by a ring, with a disulphide connection between the first and sixth cysteine, and has a very short tail comprising three amino acids. Studies conducted in an in vitro analyzing homology model, a test of mutagenesis and pharmacological aspects[6][7][8][9][10] have shown that while the tail interacts with the OXTR regions exhibited in an extracellular space, the cyclic part reaches the deep part of a receptor’s transmembrane core, where it has an interaction with residues located in TMH5 and TMH6.

The site of oxytocin receptor mRNA in the brain offers a possibility to see the distribution of oxytocin binding[11], providing an accurate map of the anatomical geography of the oxytocin system in the brain.

Seminal animal researches using histochemical and immunohistochemical techniques have shown high concentrations of OXTR mRNA in the hypothalamus, ventral pallidum, amygdala, olfactory bulb and the dorsal vagal nucleus in rodents[12][13]. OXTR mRNA sites in rodent brains re well-known[14], but their anatomical distribution across the human brain is poorly understood.

A growing body of evidence suggests that changes in the epigenetic regulation of the oxytocin receptor gene gives the oxytocin system flexibility in response to various events, particularly in childhood. Indeed, a large number of recent studies have shown a single-nucleotide polymorphism association in oxytocin receptor genes and the social behavior and pathogenesis of psychiatric disorders[15].

Expression and binding of the OXTR in rat and mouse brains using radiolabeled ligand have been described previously[16]. Recently, a binding approach showed that commercially available radioligands can be used in combination with selective competitors to reveal specific distributions of both OXTR in postmortem human brain tissue. However, despite recent efforts, there are currently no in vivo neuroimaging agents for OXTR for PET imaging (Positron Emission Tomography), a technique that would be invaluable in research using humans and nonhuman primates)[17].

The activation of OXTR is associated with the activation of a number of various intracellular cascades of events that facilitate the OXT pathway[4]. OXTR is expressed within the peripheral organs and centrally in the brain[18]. Quintana et al. very recently identified the anatomical distribution of the oxytocin pathway of mRNA expression in the human brain in order to identify its functional importance and supposed gene interactions. They found that the oxytocin signaling system acts synergistically with dopaminergic and muscarinic acetylcholine signaling systems by exerting its complex effects on comprehension[19].

The OXT pathway is a multifaceted system associated with various biological functions. An increasing number of studies have reported the importance of the oxytocin system in the human development[20][21], modulation of pain processing[22] and feeding behaviors[23]. OXT has an important role in bird-related phenomena, and it is normally used clinically for the induction and increase of labor[12]. OXT is implicated in the contraction of smooth muscles during parturition and lactation. OXT is also involved in tolerance, cognition, adaptation and sexual and maternal behavior, as well as in the regulation of cardiovascular functions[24].

In addition, OXT was found in many areas of the brain and functions as a neurotransmitter that modulates a variety of social behaviors such as social cognition, nurturing and social bonding[25][26][27][28][29]. Further, OXT has been shown to have both antidiuretic and vasodilatory effects leading to an increased cerebral, coronary and renal blood flow[30][31][32].

References

1. M D Guillou; M Camier; C Clamagirand; Evidence for the presence of pro-oxytocin/neurophysin-converting enzyme in the human ovary. *Journal of Endocrinology* **1994**, *142*, 345-352, 10.1677/joe.0.1420345.
2. Brownstein, M.J.; Russell, J.T.; Gainer, H. Synthesis, transport, and release of posterior pituitary hormones. Science 1980, 207, 373–378.
3. Chatterjee, O.; Patil, K.; Sahu, A.; Gopalakrishnan, L.; Mol, P.; Advani, J.; Mukherjee, S.; Christopher, R.; Prasad, T.S. An overview of the oxytocin-oxytocin receptor signaling network. J. Cell Commun. Signal 2016, 10, 355–360.
4. Gerald Gimpl; Falk Fahrenholz; The oxytocin receptor system: structure, function, and regulation.. *Physiological Reviews* **2001**, *81*, 629-683, 10.1152/physrev.2001.81.2.629.
5. Sarah Arrowsmith; Susan Wray; Oxytocin: Its Mechanism of Action and Receptor Signalling in the Myometrium. *Journal of Neuroendocrinology* **2014**, *26*, 356-369, 10.1111/jne.12154.
6. Chini, B.; Mouillac, B.; Ala, Y.; Balestre, M.N.; Trumpp-Kallmeyer, S.; Hoflack, J.; Elands, J.; Hibert, M.; Manning, M.; Jard, S. Tyr115 is the key residue for determining agonist selectivity in the V1a vasopressin receptor. EMBO J. 1995, 14, 2176–2182.
7. Fanelli, F.; Barbier, P.; Zanchetta, D.; de Benedetti, P.G.; Chini, B. Activation mechanism of human oxytocin receptor: A combined study of experimental and computer-simulated mutagenesis. Mol. Pharmacol. 1999, 56, 214–225.
8. Favre, N.; Fanelli, F.; Missotten, M.; Nichols, A.; Wilson, J.; di Tiani, M.; Rommel, C.; Scheer, A. The DRY motif as a molecular switch of the human oxytocin receptor. Biochemistry 2005, 44, 9990–10008.

9. Frantz, M.C.; Rodrigo, J.; Boudier, L.; Durroux, T.; Mouillac, B.; Hibert, M. Subtlety of the structure-affinity and structure efficacy relationships around a nonpeptide oxytocin receptor agonist. J. Med. Chem. 2010, 53, 1546–1562.
10. Busnelli, M.; Kleinau, G.; Muttenthaler, M.; Stoev, S.; Manning, M.; Bibic, L.; Howell, L.A.; McCormick, P.J.; Di Lascio, S.; Braida, D.; et al. Design and characterization of Superpotent bivalent ligands targeting oxytocin receptor dimers via a channel-like structure. J. Med. Chem. 2016, 59, 7152–7166.
11. Larry J. Young; Scott Muns; Zuoxin Wang; Thomas R. Insel; Changes in oxytocin receptor mRNA in rat brain during pregnancy and the effects of estrogen and interleukin-6.. *Journal of Neuroendocrinology* **1997**, *9*, 859-865, 10.1046/j.1365-2826.1997.00654.x.
12. Dogra, Y.; Suri, V.; Aggarwal, N.; Dogra, R.K. Induction of labor with oxytocin in pregnancy with low-risk heart disease: A randomized controlled trial. Turk. J. Obstet. Gynecol. 2019, 16, 213–218.
13. Adan, R.A.; Van Leeuwen, F.W.; Sonnemans, M.A.; Brouns, M.; Hoffman, G.; Verbalis, J.G.; Burbach, J.P. Rat oxytocin receptor in brain, pituitary, mammary gland, and uterus: Partial sequence and immunocytochemical localization. Endocrinology 1995, 136, 4022–4028.
14. T. R. Insel; L. E. Shapiro; Oxytocin receptor distribution reflects social organization in monogamous and polygamous voles.. *Proceedings of the National Academy of Sciences***1992**, *89*, 5981-5985, 10.1073/pnas.89.13.5981.
15. Krzysztof Maria Wilczyński; Andrzej Siwiec; Małgorzata Janas-Kozik; Systematic Review of Literature on Single-Nucleotide Polymorphisms Within the Oxytocin and Vasopressin Receptor Genes in the Development of Social Cognition Dysfunctions in Individuals Suffering From Autism Spectrum Disorder. *Frontiers in Psychology* **2019**, *10*, 380, 10.3389/fpsyt.2019.00380.
16. Benjamin Jurek; Inga D. Neumann; The Oxytocin Receptor: From Intracellular Signaling to Behavior. *Physiological Reviews* **2018**, *98*, 1805-1908, 10.1152/physrev.00031.2017.
17. Sara M. Freeman; Aaron L. Smith; Mark M. Goodman; Karen Bales; Selective localization of oxytocin receptors and vasopressin 1a receptors in the human brainstem. *Social Neuroscience* **2016**, *12*, 113-123, 10.1080/17470919.2016.1156570.
18. Yoshifumi Mizumoto; Tadashi Kimura; Richard Ivell; A genomic element within the third intron of the human oxytocin receptor gene may be involved in transcriptional suppression. *Molecular and Cellular Endocrinology* **1997**, *135*, 129-138, 10.1016/s0303-7207(97)00195-0.
19. Daniel S. Quintana; Jaroslav Rokicki; Dennis Van Der Meer; Dag Alnæs; Tobias Kaufmann; Aldo Córdova-Palomera; Ingrid Dieset; Ole A. Andreassen; Lars T. Westlye; Oxytocin pathway gene networks in the human brain. *Nature Communications* **2019**, *10*, 1-12, 10.1038/s41467-019-08503-8.
20. Miller, T.V.; Caldwell, H.K. Oxytocin during development: Possible organizational effects on behavior. Front. Endocrinol. 2015, 6, 76.
21. Johnson, Z.V.; Young, L.J. Oxytocin and vasopressin neural networks: Implications for social behavioral diversity and translational neuroscience. Neurosci. Biobehav. Rev. 2017, 76, 87–98.
22. Lincoln M. Tracy; Nellie Georgiou-Karistianis; Stephen J. Gibson; Melita Giummarra; Oxytocin and the modulation of pain experience: Implications for chronic pain management. *Neuroscience & Biobehavioral Reviews* **2015**, *55*, 53-67, 10.1016/j.neubiorev.2015.04.013.
23. Monica Leslie; Paulo Silva; Yannis Paloyelis; James Blevins; Janet Treasure; A systematic review and quantitative meta-analysis of the effects of oxytocin on feeding. *Journal of Neuroendocrinology* **2018**, *30*, e12584, 10.1111/jne.12584.
24. Tina Napso; Hannah E.J. Yong; Jorge Lopez-Tello; Amanda N. Sferruzzi-Perri; The Role of Placental Hormones in Mediating Maternal Adaptations to Support Pregnancy and Lactation. *Frontiers in Physiology* **2018**, *9*, e1091, 10.3389/fphys.2018.01091.
25. Page, K.; McCool, W.F.; Guidera, M. Examination of the pharmacology of oxytocin and clinical guidelines for use in labor. J. Midwifery Womens Health 2017, 62, 425–433.
26. Churchland, P.S.; Winkielman, P. Modulating social behavior with oxytocin: How does it work? What does it mean? Horm. Behav. 2012, 61, 392–399.
27. Zik, J.B.; Roberts, D.L. The many faces of oxytocin: Implications for psychiatry. Psychiatry Res. 2015, 226, 31–37.
28. Bordt, E.A.; Smith, C.J.; Demarest, T.G.; Bilbo, S.D.; Kingsbury, M.A. Mitochondria, Oxytocin, and Vasopressin: Unfolding the Inflammatory Protein Response. Neurotox. Res. 2018, 36, 239–256.
29. Walum, H.; Young, L.J. The neural mechanisms and circuitry of the pair bond. Nat. Rev. Neurosci. 2018, 19, 643–654.
30. Sapolsky, R.M. Doubled-Edged Swords in the Biology of Conflict. Front. Psychol. 2018, 9, 2625.
31. Ellis, J.A.; Brown, C.M.; Barger, B.; Carlson, N.S. Influence of Maternal Obesity on Labor Induction: A Systematic Review and Meta-Analysis. J. Midwifery Womens Health 2019, 64, 55–67.
32. Viteri, O.A.; Sibai, B.M. Challenges and Limitations of Clinical Trials on Labor Induction: A Review of the Literature. AJP Rep. 2018, 8, 4.

Keywords

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