Oxytocin Hormone synthesis and regulation in the Body

Oxytocin synthesis and function:

The hypothalamus plays an important role in the body by synthesizing and regulating hormones that modulate intercellular communication and body’s function. Hormones produced by the hypothalamus are organized in two groups based on their structure and function: (i) vasopressin group and (ii) oxytocin group (Gimpl and Fahrenholz, 2001). Remarkably, the amino acid sequence and structure of these hormones is very similar with the only difference being a pair of amino acid residues at the position two and eight. While oxytocin contains a tyrosine and leucine at position two and eight, respectively, vasopressin has phenylalanine and arginine at the same position. Furthermore, the genes that encode oxytocin and vasopressin are located in the same chromosome (chromosome 20 in humans) and at the same genomic region (or locus); however, they are transcribed in opposite directions. Given the similarities in amino acid and structure, it is hypothesize that oxytocin and vasopressin genes are paralogs (or genes originated from a single gene by duplication) that arose from duplication of the coding sequence followed by an inversion.

Oxytocin is nonapeptide (its structure contains nine amino acids) neurohormone that is synthesized by the magnocellular neurons located in the supraoptic (SON) and paraventricular nuclei (PVN) of the hypothalamus (Gimpl and Fahrenholz, 2001). Although oxytocin and other
nonapeptide hormones such as vasopressin are functional as small polypeptides, they are synthesized as inactive longer sequence form, called propeptides. In the case of oxytocin, prooxyphysin I is the propeptide that is hydrolyzed in smaller peptides, yielding oxytocin and neurophysin I, a small carrier proteins (page 134, book). The most important functions of neurophysysyns are to find, bind, translocate and store oxytocin in the secretory granules or vesicles before the second hormone is released in the bloodstream (Gimpl and Fahrenholz, 2001). The mature form of oxytocin and neurophysin I is transported inside vesicles to the terminal axon, from which they are released during a neural impulse.

Oxytocin physiological function is well known in females for its role during childbirth, where it stimulates smooth muscle contractions of the uterus. During lactation oxytocin is responsible for the contraction of the myoepithelial cells lining the ducts if the mammary glands to cause milk ejection (page 135, book). Oxytocin is also responsible, in both females and males, for the pleasurable sensation of rhythmic contractions of smooth muscles on the reproductive organs during an orgasm (page 135, book). It is also believe that oxytocin plays a role in human social behavior where increase the sense of trust. This function may be associated with the formation of bonds between the mother and the offspring (page 137, book).

**Oxytocin regulation:**

The expression of oxytocin in different tissues of the body in not well understood yet. However, it is known that Oxytocin production is stimulated during labor, breast feeding, and sexual intercourse to produce an orgasm (page 135, book). During the lactation, sucking of the
nipple stimulate oxytocin release (Hashimoto et al., 2012). At the time of parturition, estrogens seem to be important to increase the synthesis of prostaglandins and oxytocin receptors in the uterine myometrium, which facilitates the contraction of the uterus (page 353, book). Therefore, estrogen is considered an up-regulator of oxytocin. In parturition, mechanical stimulation of the vagina or uterus can release oxytocin in humans and induce a fetal ejection (page, 353, book). Other hormones such as estradiol increases the expression of oxytocin receptors, estrogen receptors and prostaglandins receptors, which all together seem to play an important role during luteolysis (corpus luteum destruction) in females (page 345, book).

Recent studies have shown what hormones are important to activate the release of oxytocin during childbirth. Progesterone is one of the hormones that is an important down-regulator of the oxytocin by inhibiting its activation using Gamma Amino Butyric Acid (GABA) inhibitory mechanism (Russell et al., 2003). GABA is known as the major inhibitory of neurotransmitter release in the central nervous system (CNS). However, as parturition arrive the levels of progesterone secretion decreases in the body; therefore, the inhibitory effect caused by GABA mechanism is also reduced (Russell et al., 2003). Once GABA is reduced, a central opioid mechanism is activated causing the excitation of oxytocin cells by the brain stem, followed by oxytocin release (Russell et al., 2003).

**Oxytocin metabolism:**

The structure of oxytocin nonapeptide is critical for its biological function. A disulfide bridge connects the two cystines (Cys1 and Cys 6) in the primary sequence forming a ring (Figure 1) that is necessary for binding to its molecular carrier, neurophysin I (Gimpl and
Fahrenholz, 2001). Upon triggering a specific physiological responds, oxytocin must be metabolized to prevent further activity. Oxytocin metabolism refers to the degradation of the structure of the hormone, which occurs through two major pathways. One way is by the action of cystine amino-peptidase and the second way is carried out by post-proline endopeptidase (Figure 1). Amino peptidase cleaves the tyrosine at position two, which opens the ring and destroys the conformational states which binds to neurophysin I hormone (Figure 1). In the case of post-proline endopeptidase, cleavage occurs between proline (Pro7) and leucine (Leu8), therefore, splitting the molecule in two inactive moieties (Figure 1). Other minor ways in which oxytocin is degraded in the body is by the action of enzymes such as carboxypeptidase, which cleaves amino acids from the carboxyl end, and other reducing enzymes that may disrupt the disulfide bridge present in oxytocin.

![Image](image.png)

**Figure 1. The structure and degradation/inactivation target site of the oxytocin nonapeptide.**

The complete nine amino acid residues sequence and its tertiary structure is shown. Cys1 and Cys6 form a disulfide bridge between their side chains that circulazises the polypeptide sequence between these two residues. Cystine aminopeptidase catalyzes the cleavage of peptide bond between Cys1-Tyr2 and Tyr2-Ile3, and thus breaking the functional ring. Post-proline endopeptidase, on the other hand, targets the peptide bond between Pro7 and Leu8,
breaking the polypeptide in two smaller inactive moieties. (Figure adapted from Mitchell et al., 1998)

**Oxytocin receptor:**

The oxytocin receptor (OTR) is encoded by a single gene located in the chromosome 25. The gene of the OTR contains 3 introns and 4 exons. The human OTR mRNA is transcribed in two forms, a 4.4-long kb transcript found in the ovary and a 3.6 kb transcript in the breast (Gimpl and Fahrenholz, 2001). This isomers results from alternative splicing of the OTR gene, in which some exons may be included or excluded from the final mRNA product during transcription. The encoded OTR product is a 389 amino acid polypeptide which contains seven transmembrane domains. The receptor belongs to the rhodopsin type class I G protein coupled receptor (GPCR) superfamily (Gimpl and Fahrenholz, 2001). The name of G protein is derived from the ability of G proteins to bind and hydrolyzed the nucleotide guanosine triphosphate (GTP). G proteins are known for their actions as bioregulators that use second messenger in the cytosol, which carry the bioregulator inside the target cell (page 53, book). The GPCR once activated interact with others G proteins such as Gs protein, Gi protein or Gq protein. The interaction between these G proteins causes the activation of different second messenger such as cAMP for the Gs protein and inhibition of the cAMP for the Gi protein (page 55, book). In contrast with other hormones the GPCR in the OTR interacts the Gq protein, which activates the complex phospholipase (PLC), and then hydrolyses its substrate to give rise to two important second messenger molecules, inositol triphosphate (InsP3) and 1, 2 diacyl-glycerol (DAG) (pag 55, book). InsP3 triggers Ca^{2+} influx release from intracellular stores, which bind to the calmodulin forming the complex Ca^{2+}-calmodulin that later will activate the myosin light chain
(MLC) kinase resulting in a contraction of the myometrial cell. DAG activates protein kinases that produce a cascade of events that will also stimulate myometrial contraction.

**Oxytocin receptor regulation (refers to image 3-13, page 57, book):**

The OTR is activated when its bioregulator (oxytocin) binds to it. Then the target cell is stimulated to produce the second messenger in a cytoplasmic cascade of events that results in contraction of the target cell as mentioned before. In order to eliminate the action produced in the target cell, oxytocin has to be removed from its receptor and the second messenger has to be inactivated (pag 56, book). The mechanism that regulates the OTR is the following. Once the OTR is activated, the occupied receptor will migrate with its ligand to a special zone or pits (containing proteins such as clathrin, caveolin, or dynamyn) in the cell membrane where there are engulfed in vesicles called endosomes (part of the phagosomes). Endosomes, vesicles formed during endocytosis, consist of a small sphere membranes that have ligand-biding sites attach to their lumen. Internal proteins such as Rab proteins are in charge in the translocation and distribution of the endosomes in the cytoplasm. Rab proteins also bring other hydrolytic enzymes that fuse with the endosomes to form endolysosomes (refer to image 3-13, page 57, book). The hydrolytic enzymes present in the endolysosomes catalyzed the degradation of the receptor and the ligand. In other cases the endosomes may be directed back to the cell membrane to recycle the receptor without the ligand in the cell surface (refer to image 3-13, page 57, book). This phenomenon of internalization explains the down-regulation of the receptor protein. Down-regulation in this case refers to the reduction in the number of receptors that are present on the surface of the cell, which results in decreasing the sensitivity
of the target cell for oxytocin. Up regulation of the receptor may be induced by the formation of the ligand-receptor complex, which triggers transcription up regulation and synthesis of new proteins.

Although it is assumed that steroid hormones may influence the number of OTR, the entire mechanism of action is very complex and not well understood yet. The interaction between the receptor and the G protein seem to be regulated first, by phosphorylation of the receptor, which inhibits G protein activation, and second by the binding of proteins called arrestins that avoid G protein activation and promote the receptor internalization (Vrachnis N., et al., 2011)
References:


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