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เคมีสื่อรัก
The Chemical of Love

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Introduction

Love is one of the most fascinating feelings that anyone has. Although each and everyone experiences love in many different ways, none of us can explain clearly what it is. In the past, love seems to have been the focus and subject of poets, artists and writers but now scientists seem to have joined the group. Up to now, scientists have shown that love is a complex phenomenon comprising trust, pleasure and reward activities involving the limbic part of the brain. In general in order for the nervous system to work, one or more chemicals is involved. So, would it be so hard to believe that Cupid's arrows might have some "special chemical" dipped in it? That "special chemical" might be what we now know as the hormone named oxytocin.

The role of oxytocin in paturition and the milk let down process of a mother has been studied in great detail. Oxytocin is the most potent chemical that causes the smooth muscle of the uterus to contract during the process of parturition or baby delivering. It is also used by obstetricians to induce the delivering process. Carbetocin, an oxytocin analog, is used to prevent or treat postpartum hemorrhage. Atosiban, an oxytocin antagonist, can inhibit premature uterine contractions in humans [1]. Moreover, oxytocin is also important in the milk ejection process, which was demonstrated in oxytocin deficient mice which were unable to lactate during the lactation period [2].

The lesser known but significant role in many animals may be oxytocin effect on such feelings as love, attraction, social bonding, fear and even trust which has

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sparked the interests of neuroscientists [3]. In addition, Oxytocin has been shown to act within the central nervous system to inhibit the tolerance to drugs such as morphine and heroin which further reduce the symptoms of drug withdrawal in mice and rats [4].

Structure and functions of oxytocin

Oxytocin is a short polypeptide hormone composed of 9 amino acids. The formula of oxytocin is $C_{43}H_{66}N_{12}O_{12}S_2$ with a molecular mass of 1007 daltons. The amino acid sequence of oxytocin is Cys Tyr Ile Gln Asn Cys Pro Leu Gly (NH_2). These cysteine residues at amino acid positions 1 and 6 form a disulfide bond with one another to create a cyclic six amino acid ring with 3 residues amidated tail. The synthesis site of oxytocin is in the magnocellular neurons of the hypothalamic paraventricular and supraoptic nuclei and is stored in the posterior pituitary in large, dense-core vesicles which is bound to neurophysin. The axon of these oxytocinergic neurons are found throughout the central nervous system. The additional synthesis sites of oxytocin are found in peripheral tissues such as the uterus, placenta, amnion, corpus luteum, testis, and heart [5]. A variety of stimuli such as suckling, parturition, or stress will induce the release of oxytocin from the posterior pituitary into the circulation.

Oxytocin has both peripheral and central actions in the body. The peripheral actions include uterine contraction, the milk let down process, orgasm in both sexes, ejaculation in males and the development of the heart of some rodents by promoting cardiomyocyte differentiation [6, 7]. Oxytocin can cause cervical dilation before birth and contraction of the uterus during labor. The uterus continues to contract from the stimulation of oxytocin during the first few weeks of lactation and help the clotting of the placental attachment site after birth. Nevertheless, a study of oxytocin receptor knockout mice found that the reproductive behavior and parturition are normal and have no cardiac insufficiencies [8].

During lactation, the sucking of the baby will stimulate the sensory receptor at the nipple which will relay the signals to hypothalamus. This will cause the posterior pituitary to release pulses of oxytocin in intermittent bursts into the circulation. Oxytocin in the circulation will bind to receptors at the mammary glands causing milk let down into collecting chambers from which the baby can suck out at the nipple.

Various parts of the brain and the spinal cord such as ventromedial, hypothalamus, septum, amygdala and brainstem have the receptors for oxytocin [9-11]. This indicates that oxytocin may have an effect on those parts of the central nervous system. However, the oxytocin released from oxytocinergic neurons in the brain into the

blood circulation is not the chemical that resulting in the central actions. The properties of the blood brain barrier will prevent any oxytocin from the circulation to re-enter the brain. Therefore, the oxytocin which acts on the brain cells themselves must be released directly from oxytocinergic neurons to the brain cells without passing through the blood circulation.

The results of the central actions of oxytocin include, for example, sexual arousal in rats, pair bonding in prairie voles, maternal behavior, stress and fear reduction and trust increase [3, 5, 7, 12]. In addition, oxytocin was found to inhibit the tolerance of some addictive drugs such as cocaine, alcohol and can reduce withdrawal symptoms in animal studies [4].

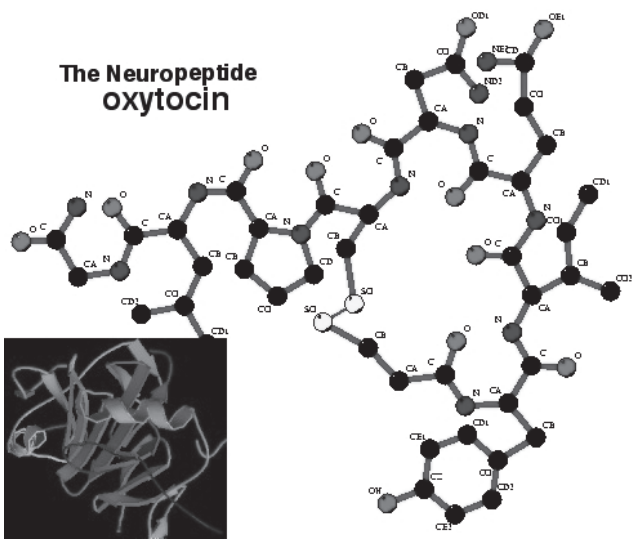

Figure 1 Structure of oxytocin [13]

Oxytocin receptors

One of the reasons that the classic concept of oxytocin action has been extended is because of the discovery of new sites of expression of the gene encoding the oxytocin receptor (OT). These new sites include the brain pituitary, kidney, ovary, testis, thymus, heart, vascular endothelium, osteoclasts, myoblasts, pancreatic islet cells, myenteric ganglia in proximal and distal gut, submucosal ganglia in ileum and colon, adipocytes and several types of cancer cells. All these receptors are functional and can induce various intracellular signaling pathways in response to oxytocin application [5, 14-16].

Oxytocin receptors belong to the class I family of G protein-coupled receptors

(GPCR) which contain seven transmembrane domains. The conserve (-helices residues may be involved in a mechanism for activation and signal transduction to the G-protein. Oxytocin receptors together with 3 subtypes of vasopressin receptor, V_{1a}, V_{1b} and V_2 are structurally closely related receptors. The first 3 types of receptors (Oxytocin, V_{1a}, V_{1b}) are coupled to $G_{q/11}$ α class and activate phospholipase C in response to agonist binding but the last type (V_2) activates adenylyl cyclase via coupling to G_s [13]. It is believed that the important parts for receptor activation are Asp in transmembrane domain 2 (Asp-85) and a tripeptide (E/D RY) at the interface of transmembrane 2 and the first intracellular loop. The mutation of the tripeptide motif DRY results in an either inactive or a constitutively active oxytocin receptor [17].

Studies involving site-directed mutagenesis, photoaffinity labeling and molecular modeling indicate that the cyclic part of the oxytocin molecule is in the upper one-third of the receptor binding pocket and interacts with transmembrane domains 3, 4 and 6. On the other hand, the linear C-terminal part of the oxytocin molecule remains closer to the surface and interacts with transmembrane domains 2 and 3, in addition to the first extracellular loop (Fig. 2) [13]. All four intracellular domains of oxytocin receptor are involved in coupling to the $G_{q/11}$ α class. The activation process induced by agonist binding involves the opening of a solvent-exposed site formed by the second intracellular loop, the cytosolic extension of transmembrane domain 5 and the third intracellular loop [18]. The C-terminal part of the third intracellular loop of the receptor is important in G-protein coupling especially lysine residue (K270 in Fig. 2). It is involved in receptor signaling and receptor internalization [13].

After binding to oxytocin receptors which are coupled to the $G_{q/11}$ α class, the stimulated GTP binding proteins will then activate the phospholipase C leading to the generation of inositol trisphosphate and 1,2-diacylglycerol. Inositol trisphosphate triggers the increase of intracellular Ca^{2+} by releasing them from intracellular stores, while diacylglycerol stimulates protein kinase C, which phosphorylates unidentified target proteins which also result in an increase of intracellular Ca^{2+}. This stimulation of phospholipase C is inhibited by cAMP. The third signaling pathway is the stimulation of nitric oxide production. This pathway involves protein kinase C and Ca^{2+}-calmodulin complexes which activate neuronal and endothelial isoforms of nitric oxide synthase. Nitric oxide activates the soluble guanylate cyclase to produce cGMP. In addition, the oxytocin-induced intracellular Ca^{2+} increase is greater in the presence of extracellular Ca^{2+}. This suggests that oxytocin has effects on calcium influx through voltage gated or ligand-gated channels [5, 13].

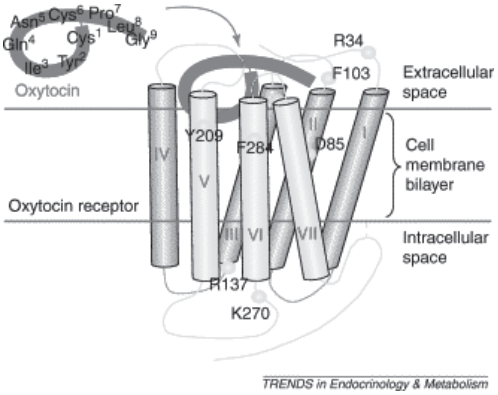

Figure 2 Schematic model of the structure of the Oxytocin receptor and its interaction with the ligand. [14]

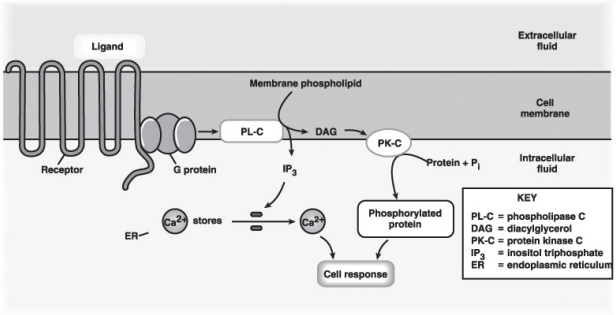

Figure 3 Second messenger system of oxytocin follows the phospholipase C system. [19]

Neurobiology of love

Romantic love is associated with specific physiology, psychology and behaviors which include emotional responses such as euphoria, intense focused attention and obsessive thinking of an individual, craving for emotional union with the love one and even an increase in energy; all of these suggest that reward and motivation systems i.e. the limbic system in the brain may be involved. It was found that the viewing of loved ones activated the left ventral tegmental area of the brain and that the left insula-putamen-globus pallidus activation correlated with trait affects intensity which suggests that romantic love uses the subcortical reward and motivation system of the brain. These areas of the brain involve oxytocin, vasopressin, dopamine and serotonergic signaling [20-22].

The attachment formed between sexual partners is caused by the release of oxytocin during sexual intercourse. As a result, one becomes attached to that particular partner which leads to monogamy practiced in humans and other species such as prairie voles *(Microtus ochrogaster)*. Prairie voles are excellent experimental animals for studying monogamy and social bondings effects of oxytocin due to their monogamous

behavior while other vole species, for example, montane vole *(Microtus pennsylvanicus)*, display promiscuous behavior and low levels of social affiliation. Eventhough the brain of voles and human are not identical, it may still help us understand the importance of oxytocin in the formation of social bonding. Prairie voles, like humans, form life-long monogamous relationships. Both parents also help care for the offsprings. Prairie voles have higher densities of oxytocin receptors in the nucleus accumbens and caudate putamen than do nonmonogamous montane voles. Several studies found oxytocin receptors in the prefrontal cortex and that when the release of oxytocin was blocked, mating pairs no longer formed lasting bonds. In addition, females voles are more sensitive to oxytocin and the oxytocin receptors are more dense in the brain while males are more sensitive to vasopressin. Therefore, administering of oxytocin exogenously can induce pair bonding in both sexes while administering of oxytocin receptor antagonists into the brain may alter pair bond formation in female praire voles [10, 22].

Oxytocin is well known to facilitate interactions between mothers and infants such as the lactating and licking behavior in many species. It was found that female rats that received more maternal care as infants have a higher number of oxytocin receptors in preoptic area, lateral septum and stria terminalis but receiving oxytocin receptor antagonist reduces such behaviors and may cause mothers to abandon their offspring. In addition, virgin female rats that had oxytocin administered to them exhibited mother-like behavior such as cuddling and caring for babies [23]. Direct paternal care can be found in some species; for example, prairie voles, Mongolian gerbils and Djungarain hamsters. Paternal behavior includes all aspects of maternal behavior except lactation. Several hormone such as glucocorticoids, prolactin, oxytocin and vasopressin may be involved in these behaviors. Oxytocin are involved in affiliative behaviors such as pair bonding and inhibit behaviors such as infanticide and thus result in priming and/or facilitating social attractions with offspring [24].

Parental and romantic love share a common evolutionary purpose to maintain the species. Bartels and Zeki found that romantic and maternal love in humans involves an overlapping area of the brain such as the striatum and ventral tegmental area [25]. These regions are known to have a high density of oxytocin receptors suggesting that oxytocin plays a role in both kinds of love. Furthermore, they also show that both kinds of love involve the reward system of the brain and deactivate the negative emotion circuits.

Eventhough we are not close to understanding the neural basis of love, the research thus far has shown that the neural mechanisms of love deeply involve the part

of the brain associated with the rewarding system and the chemical oxytocin in animals and human. Therefore, it might not be too bold to conclude that oxytocin, the chemical of love, is essential for happiness and is an instrument of evolution to procreate and maintain the species.

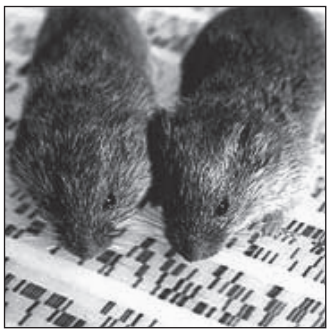

Figure 4 Prairie voles [26]

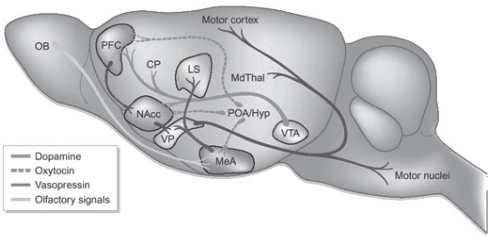

Figure 5 Sagittal view of a prairie vole brain illustrating a proposed neural circuit model for pair bonding.

The figure shows prefrontal cortex (PFC), nucleus accumbens (NAcc), olfactory bulb (OB), the medial nucleus of the amygdala (MeA), mediodorsal thalamus (MdThal), ventral pallidum (VP). Mating activates the ventral tegmental area (VTA), resulting in increased dopamine activity in the PFC and NAcc. Oxytocin acts in the MeA, to facilitate olfactory learning and memory. Mating also stimulates increased extracellular concentrations of oxytocin in the PFC and NAcc of females, and of vasopressin in the of males [20].

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