Profile of maternal serum oxytocin in postpartum and non-pregnant rats

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Abstract

Oxytocin is primarly secreted in the brain as a neuromodulator that affects numerous neurophysiological and behavioral processes. It is also produced in the ovaries and uterus to stimulate delivery and lactation. Oxytocin mRNA is found in the endometrial epithelial cells of non-pregnant women during ovulation and menstruation. Until recently, there have been no data on scientific-level oxytocin in virgin female rats. This study aimed to compare the level of oxytocin in different physical biology between postpartum and non-pregnant experimental animals (virgin or had never given birth). This experimental study was conducted on 19 female white rats (*Rattus norvegicus*) allocated to two groups: T1 and T2. The ten rats in group T1 (nulliparous virgin) and the nine in group T2 (postpartum) were sacrificed on day two, except for group T1, which were sacrificed following vaginal delivery. Blood was collected intracardiacally, and serum oxytocin levels were evaluated using an ELISA assay. The T-test was used for statistical data analysis. The serum oxytocin level in the T2 group (628.06 ± 168.72 pg/mL) was significantly higher than in the T1 group (366.71 ± 185.03 pg/mL; $P < 0.05$). In conclusion, oxytocin levels were higher in postpartum animals than in virgin animals. Thus, oxytocin plays a greater role in female reproduction than in normal physiological condition.

Key words: *oxytocin; postpartum period; virgin; maternal health; medicine*

Introduction

Oxytocin (OT) is a hormone primarily synthesized by the nerve cell bodies of the paraventricular nucleus and produced by the hypothalamus gland. It affects the uterine smooth muscles and is responsible for stimulating contractions in the uterus during labor (Grazia et al., 2016; Prevost et al., 2014), and in other reproduction-related processes such as mating and lactation (Franke et al., 2018). In rats, oxytocin is important for initiation and maintenance of parturition (Scott and Brown, 2013). OT and OT receptors (OTR) are synthesized in the

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intrauterine tissues of rats and humans during late gestation (Fang et al., 2020). Oxytocin levels rise during pregnancy, pupbirth, and the early stages of labor, then decline by eight weeks postpartum (Prevost et al., 2014).

Labor consists of three stages and is related to the placenta's delivery. According to Uvnäs-Moberg et al. (2019), oxytocin levels double in the early stages of labor compared to prior to the start of labor. The oxytocin pulses are very short but very high in concentration. Oxytocin tends to rise and reach its peak (three beats per 10 minutes) before the infant's birth. It also responds to the Ferguson reflex, which stimulates uterine and myometrial contractions, causing the fetal head to touch the cervix and vaginal wall when the uterine contractions occur (Kumaresan et al., 1975; Husslein et al., 1983; Thornton et al., 1988; Fuchs et al., 1991; Uvnäs-Moberg et al., 2019).

Endometrial oxytocin influences the rate of uterine contractions. Receptor levels, receptor desensitization, and local oxytocin production determine oxytocin production. Neurohypophysis hormones induce the myometrium and myoepithelium to release oxytocin. During labor, oxytocin causes contractions in the myometrial smooth muscle of the uterus. As progesterone concentrations drop during labor, the increase in the ratio of estrogen to progesterone may activate the synthesis of oxytocin receptors. The posterior pituitary gland secretes oxytocin during labor, sending afferent fibers to the central nervous system (Bobak et al., 2005; Vrachnis et al., 2011). During pregnancy, estrogen enhances the activity of oxytocin by decreasing the membrane potential of smooth muscle cells, lowering the excitation threshold. The uterus becomes more responsive to oxytocin during the end of pregnancy due to an increase in estrogen levels and a reduction in the potential of the uterine smooth muscle cell membrane. Furthermore, the number of oxytocin receptors in the uterus rises, and their activation mobilizes cellular calcium by hydrolyzing polyphosphatidylinositol (Martin and Carter, 2013).

The release of oxytocin enhances actin and myosin bonds at the cellular level, resulting in greater uterine contractions and enhanced uterine involution. Ca^{2+}-dependent and independent pathways are utilized by oxytocin to promote uterine contractions. The Rho kinase pathway mediates the independent Ca^{2+} pathway. The pituitary gland's production of oxytocin intensifies and regulates uterine contractions, constricts blood vessels, and aids in hemostasis. The contraction and relaxation of the uterine muscles lower the uterus' blood supply. The release of oxytocin that causes uterine contractions, an increase in the ratio of estrogen to progesterone, the activation of the Ferguson reflex at the cervix, and the stretching of the puborectalis muscles as the fetus emerges the vaginal wall is overstretched during the process of fetal expulsion. The *lamina propria*, which composes the vaginal wall, consists primarily of collagen fibers and elastin and contains dense plexuses of tiny blood vessels, lymphatic vessels, and maximum stretched nerves. Stretching the vaginal wall during labor helps to decrease placental implantation scars and bleeding (Tahara et al, 2002; Bobak et al., 2005; Dietz et al., 2016; Abdool et al., 2018).

Oxytocin also can be released from the posterior pituitary into the bloodstream under various circumstances, including hypoglycemia and psychological stress (Prevost et al., 2014). As a neuromodulator, oxytocin influences di-

verse neurophysiological and behavioral processes, such as anxiety, aggression, and stress response to external stimuli (Boose et al., 2018), sexuality, and the environment (Prevost et al., 2014).

There are already studies on oxytocin receptors in the reproductive system of pregnant rats, though research on non-pregnant rats is relatively uncommon. Outside pregnancy, oxytocin receptors in the uterus and ovaries have also been identified (Lippert et al., 2023). Oxytocin plays a role in sperm transport and menstruation in the pregnant and non-pregnant uterus (Alotaibi, 2017). During labor, mRNA for the oxytocin receptor is increased in pregnant rats. Nonetheless, it remains low in non-pregnant, unextended horns despite exposure to the same systemic endocrine milieu as the pregnant horn (Parry et al., 2020). Oxytocin receptors are highly expressed in the brainstem, limbic region (amygdala and septum), and hypothalamus (Douglas et al., 2007). The amygdala is the brain area responsible for regulating calorie intake, stress, and behavior (Li et al., 2015). This study aims to compare the oxytocin reproduction level in postpartum (at least one prior reproductive experience) and virgin (no previous reproductive experience) rats, since the dominant role of oxytocin in reproduction or normal physiology is well known.

Materials and methods

This experimental study was conducted on 19 female white rats *(Rattus norvegicus)* allocated to two groups: T1 and T2. The ten rats in Group T1 (virgins that had never given birth) were sacrificed on day two, and the nine rats in Group T2 (postpartum) were sacrificed on the second day after vaginal delivery.

Mating and postpartum female rats

Female rats were injected with pregnant mare serum gonadotropin (PMSG) to synchronize the heat cycle and human chorionic gonadotropin (HCG) for superovulation. After 48 hours, 10 IU PMSG and 10 IU HCG were administered intraperitoneally. After HCG injection, the female mice were monomated with male rats. After 17 hours, female rats were identified by examining the vaginal plug. The vaginal plug consisted of coagulated gelatin that blocked the spermatozoa from spilling out. If a vaginal plug was present, it was assumed that copulation had occurred and was regarded as day zero of pregnancy. The pregnancy lasted 21 days. Blood sampling was collected on the 23rd day (Setyaningrum et al., 2018).

Serum sampling

Surgical procedures were performed on experimental animals under general anesthesia using ketamine and xylazine. Following decontamination with 70% alcohol, an incision from the abdomen to the chest wall was performed until the heart was exposed. Using a 3 mL disposable syringe with a 2 mL, 26 G needle, intracardiac blood samples were obtained and deposited in a 1.5 mL Eppendorf tube with a maximum capacity of 1 mL. The blood was left for approximately two hours with the tube tilted until two distinct layers formed: blood (red) in the bottom layer and serum (clear) in the top layer. The serum was centrifuged at 3000 rpm for 10 minutes. Oxytocin levels in the serum were measured using an ELISA assay (Negabi et al., 2022).

Measurement of the oxytocin levels using ELISA assay

The oxytocin levels were measured using an Oxytocin ELISA kit (ab133050).

The collected serum samples were centrifuged at a speed of 2000-3000 rpm for 20 minutes, and supernatants were taken from the samples. The reagents were incubated at room temperature before use. Wells coated with anti-oxytocin antibodies were used. OD was measured for each well using a microplate reader at a wavelength of 405 nm, a maximum of 30 minutes after adding the stop solution (Budiono et al., 2022). The oxytocin levels were calculated using a regression equation of the standard solution.

Statistical analysis

Data were analyzed using SPSS 24.0 software. The normality of data was assessed using the Kolmogorov–Smirnov test. Parametric inter-variable data were verified using the independent T-test to compare the two groups. The Mann-Whitney test is used as an alternative to a T-test when the data are not normally distributed. A value of $P < 0.05$ was considered statistically significant.

Ethical approval

Ethics approval of this research was granted by the Committee of Ethics in the Health Research Faculty of Veterinary Medicine, Universitas Airlangga Surabaya with certificate number: 2.KE.116.12.2020. All research work was completed at this institute.

Results

Measurement of oxytocin levels

The data showed that they were not normally distributed, so analysis was continued using the non-parametric Mann-Whitney test. The Mann-Whitney tests showed that the T2 group (628.06 ± 168.721 pg/mL) had significantly greater serum oxytocin levels than the T1 group (366.711 ± 185.026 pg/mL; $P = 0.005$) (Table 1).

Discussion

The mother's body produces oxytocin during childbirth. Oxytocin is primarily produced by the placenta, and its levels increase during the third trimester of pregnancy as the sudden decline in metabolism approaches the phase of placental detachment. The placenta's detachment encourages the hypothalamus to produce oxytocin. However, if it mixes with other chemical substances, it can expand its biological function. The axons of neurons with cell bodies in the supraoptic and paraventricular nuclei secrete oxytocin. Oxytocin then attaches to the transport proteins neurophysins I and II (Martin and Carter, 2013; Uvnäs-Moberg, 2014).

In this study, the postpartum group had significantly higher oxytocin levels

Table 1. Result of the Mann-Whitney Test for Oxytocin Levels

Group	Level of Oxytocin					
	N	Mean	Standard Deviation	Minimum	Maximum	*P*
T1	9	366.711	185.03	95.88	617.75	0.005*
T2	10	628.06	168.72	401.50	864,00	

(*) Significant at P=0.005; α<0,05

(T1 group: female rats virgin; T2 group: postpartum female rats)

than the virgin group. This phenomenon is probably oxytocin related to social control and facilitates improving their relationships. This finding is in line with Prevost et al. (2014) who showed that plasma oxytocin levels were higher in lactating women compared to non-breastfeeding women. First-time pregnant women have higher oxytocin levels than women who have already had one or more children. Maternal oxytocin levels were also found to be higher in spontaneous labor than during cesarean section (Achie et al., 2016).

Moreover, oxytocin influences numerous reproductive systems, including the mammary glands, ovaries, brain, and uterus, as seen in the increased expression of oxytocin binding sites in the uterus of mice, humans, rabbits, and cows. This rise was also observed in the mRNA expression of estrogen receptors in cattle, mice, humans, and goats. In addition to estrogen receptor messenger RNA (mRNA), this oxytocin receptor (OTR) is known to play a crucial part in the dynamic alterations of the estrous cycle. During the pre-estrus period in the rat uterus, an increase in OTR mRNA and a decrease in estrogen receptor mRNA was observed (Murata et al., 2003, 2014).

Oxytocin is released naturally. The release of oxytocin can be stimulated by placing the infant on the mother's stomach to encourage breastfeeding. According to Marilynn (2001), nipple stimulation during breastfeeding enhances the production of oxytocin from the pituitary, increases myometrial contractions, and decreases blood loss. According to Palmer (2000), a newborn should be breastfed immediately upon birth. This speeds up placental expulsion and oxytocin release, decreasing the risk of postpartum hemorrhage. Every time a woman breastfeeds, she secretes oxytocin, which urges her to place the nipple into the baby's mouth. This aids the uterus in returning to its usual size. Carter (2014) stated that oxytocin influences the behavior and neurobiology of mammals. Oxytocin has long-lasting effects on the neocortex and behavior of breastfeeding mothers in postnatal mammals. Lactation boosts the size of the mother's brain indirectly. In addition, oxytocin-controlled breastfeeding can inhibit ovarian function, which prevents ovulation and leads to amenorrhea. (Marilynn, 2001; Niswender et al., 2007; Rakic, 2009; Yunita, 2010; Somel et al., 2013; Carter, 2014).

In this study, oxytocin was also observed in experimental animals that showed virgin rats have lower levels than postpartum rats. Leake et al. (1981) first reported that oxytocin concentrations were found in the plasma of non-pregnant women (1.4 ± 0.2 μU/mL). Steinwall et al. (2004) explained that oxytocin also plays an important role in the reproductive conditions of non-pregnant women. This is supported by the discovery of abundant oxytocin mRNA in the endometrial glandular cells of non-pregnant women, most of which play a role in ovulation and menstruation (Leake et al., 1981; Steinwall et al., 2004). In non-pregnant females, oxytocin is also abundant in the thymus, fat cells, osteoblasts, adrenal glands, and stomach (contributing to the motility of these tissues) (Gimpl and Fahrenholz, 2001). A human uterus that is not pregnant resembles a pregnant uterus in that it possesses a high-affinity though inactive binding site for oxytocin. However, the non-pregnant uterus has is a functioning second-class binding site with lesser affinity and greater capacity for oxytocin (Fuchs et al., 1985). Depressive

symptoms are closely linked to reduced plasma oxytocin levels (Negabi et al., 2022). In the non-pregnant uterus, uterine oxytocin receptor (OTR) expression fluctuates throughout the menstrual cycle, where OTR is higher in the late-luteal and menstrual phases than in the follicular phase. Estrogen may play a role in OTR expression in the non-pregnant uterus (Alotaibi, 2017).

Oxytocin is also related to vasopressin hormone function in non-pregnant and pregnant women. Plasma vasopressin levels in non-pregnant women increase with myometrial activity and reduced uterine blood flow during dysmenorrhea. Through the vasopressin V1a and oxytocin receptors, vasopressin stimulates smooth muscle activity in the myometrium and uterine arteries. These receptors play an important function in both non-pregnant and pregnant females (Akerlund, 2004; Gainer, 2012; Grippo et al., 2012; Stevenson and Caldwell, 2012). The research results related to oxytocin levels in virgin rats can be used as a theoretical basis to illustrate the role of oxytocin in normal physiological aspects, even though it tends to play a more significant role in reproductive elements, especially postpartum. In conclusion, the oxytocin levels in postpartum experimental animals were higher than in those that had never given birth, and therefore oxytocin plays a more significant role in reproductive conditions than in normal physiology.

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Profil oksitocina u serumu u ženki štakora nakon okota i ženki štakora koje nisu skotne

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Oksitocin se, prije svega izlučuje u mozgu kao neuromodulator koji utječe na brojne neurofiziološke i bihevioralne procese. Isto tako proizvodi se i u jajnicima i maternici da bi se potaknuo porođaj i laktacija. mRNK oksitocina se tijekom ovulacije i menstruacije se može pronaći i u endometrijskim epitelnim stanicama žena koje nisu trudne. Do nedavno nije bilo podataka o znanstvenoj razini oksitocina u djevica. Cilj je ove studije bio usporediti razinu oksitocina u fizički različitoj biologiji između ženki eksperimentalnih životinja nakon porođaja i onih koje nisu skotne (koje se nisu prethodno parile ili nikada nisu kotile). Ovo eksperimentalno istraživanje provedeno je na 19 ženki bijelog štakora (*Rattus norvegicus*) podijeljenih u dvije skupine: T1 i T2. Deset ženki u skupini T1 (nikada nisu kotile, nikada se nisu parile) i devet u skupini T2 (nakon okota) žrtvovano je na dan dva, osim skupine T1 koja je žrtvovana nakon vaginalnog porođaja. Krv je uzorkovana intrakardijalno te su procijenjene razine oksitocina u serumu pomoću ELISA testa. T-test je rabljen za analizu statističkih podataka. Razina oksitocina u serumu u T2 skupini (628,06 ± 168,72 pg/mL) bila je značajno veća od one u T1 skupini (366,71 ± 185,03 pg/mL; $P < 0,05$). Zaključno, razine oksitocina u životinja nakon okota bile su veće od razina oksitocina u ženki koje se nikada nisu kotile. Nakon naših istraživanja zaključak je da oksitocin ima veću ulogu u reprodukciji ženki nego u fiziološkom stanju.

Ključne riječi: *oksitocin, razdoblje nakon okota, zdravlje majki*