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REVIEW

Oxytocin: functions and activation

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ABSTRACT The objective of this review is to uncover the activity of oxytocin in various biological systems in the body related to reproductive functions. Oxytocin is a peptide hormone produced in the brain, storage, and secretion from the pituitary gland in most animals especially the mammals. Oxytocin was discovered at first time by Henry Dale in 1906. Whereas, its structure was discovered in 1952. Oxytocin has a wide variety of physiological functions such as milk removal, maternal behavior, cancer and sexual behavior in both type sex (male and female), for example, its play a role in excitation penile, ejaculation, accessory glands performance and the contractions of smooth muscles of the uterus and pelvic during mating and parturition, growth and development of the corpus luteum and progesterone level in blood. Also, oxytocin effect on some hormones such as prolactin and luteinizing hormone. Furthermore, there is a relationship between oxytocin and stress tolerance. So, understanding the effects of oxytocin on somebody's functions is important and necessary to provide information about body biological processes which control by this hormone.

KEYWORDS animal reproduction; hormone; milk removal; stress tolerance

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Ocitocina: funções e ativação

RESUMO O objetivo desta revisão é descobrir a atividade da ocitocina em vários sistemas biológicos do corpo relacionados às funções reprodutivas. A ocitocina é um hormônio peptídico produzido no cérebro, armazenamento e secreção da hipófise na maioria dos animais, especialmente nos mamíferos. A ocitocina foi descoberta pela primeira vez por Henry Dale em 1906. Considerando que sua estrutura foi descoberta em 1952. A ocitocina possui uma ampla variedade de funções fisiológicas, como remoção de leite, comportamento materno, câncer e comportamento sexual nos dois tipos de sexo (masculino e feminino) , por exemplo, desempenha um papel no desempenho da excitação peniana, ejaculação, glândulas acessórias e nas contrações dos músculos lisos do útero e pélvica durante o acasalamento e parto, crescimento e desenvolvimento do nível do corpo lúteo e progesterona no sangue. Além disso, o efeito da ocitocina em alguns hormônios como a prolactina e o hormônio luteinizante. Além disso, existe uma relação entre ocitocina e tolerância ao estresse. Portanto, é importante e necessário entender os efeitos da ocitocina nas funções de alguém para fornecer informações sobre os processos biológicos do corpo que controlam esse hormônio.

PALAVRAS-CHAVE: hormônio, remoção de leite, reprodução animal, tolerância ao estresse

Introduction

Oxytocin is a small peptide containing nine amino acids in its structure. However, the administration of oxytocin at the end time of the pregnancy period might stimulate the contractions of smooth muscle cells of the female (Borrow et al 2012). The other advantage of oxytocin is milk removal from the mammary gland through the lactation term (Lewis 2012; Hameed et al 2010). Studies have shown that oxytocin is liberated and worked in the genitals of males and females (Baribeau and Anagnostou 2015). Oxytocin has a role in regulating sexual behaviors by neuropeptide allusions of the

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nervous system, including both the brain and spinal cord accessories (Spetter and Hallschmid 2017). On the other hand, Chen and Sato (2017) reported that oxytocin has a positive role in normal behavior in farm animals.

Oxytocin is a neuronal hormone generated by neurons in the nucleus surrounding the ventricle and the supra-esoteric nucleus. The hubs of the neurons in the posterior pituitary finish from where oxytocin is released into the blood (Brown et al 2013). Oxytocin storage in axon terminals and neurosecretory granules placed in the posterior pituitary, and when there is a need to secrete oxytocin, the axons will release it into blood stem (Leng and Ludwig 2008; Stoop 2012). The oxytocin receptors are a part of the G protein pickup family and have seven transmembrane ranges (Cassoni 2001; Koehbach 2013).

The structure of oxytocin its biological function, It consists of nine amino acids, six of these amino acids are toroidal while the remaining three are caudal, which two cysteines (Cys1 and Cys6) in the primary sequence forming a ring that is necessary for binding to its molecular carrier, neurophysin (Gimpl and Fahrenholz 2001). Oxytocin may be formed by two major ways, one way is by the act of cysteine aminopeptidase and the second way is carried out by post proline endopeptidase, in the case of post proline endopeptidase (Martin and Carter 2013), cleavage happens between proline (Pro7) and leucine (Leu8), other main ways in which oxytocin is reduced in the body is by the action of enzymes such as carboxypeptidase, which cleaves amino acids from the carboxyl end (Figure 1). As well, Tsujimoto and Hattori (2005) reported that oxytocin has different forms (Figure 2). This short review aimed to give some pieces of information about oxytocin activity in different biological systems in the body related to the reproductive functions.

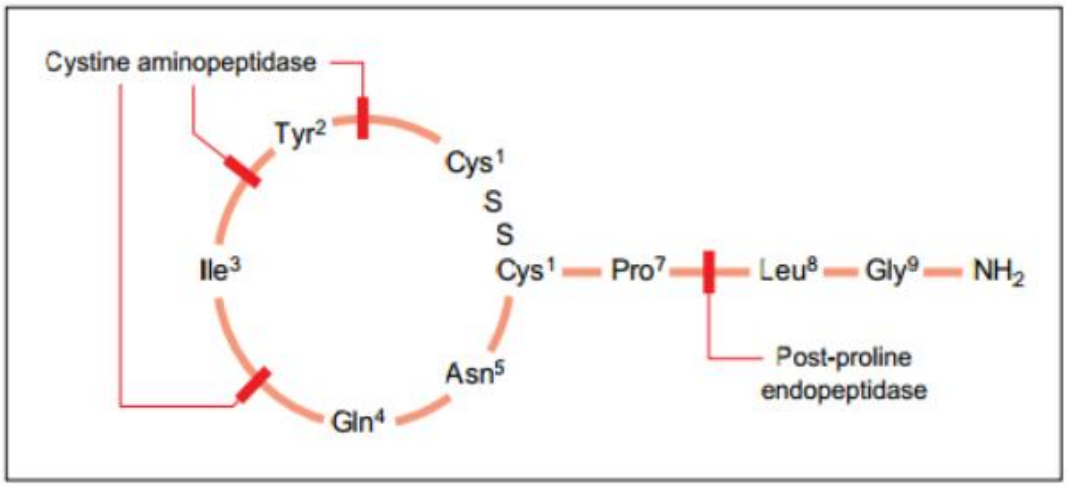

Figure 1 The structure of oxytocin.
Source: Mitchell et al (1998).

Functions and its effect on the body's organs

Uterus

Oxytocin has an important role in the uterine functions either during mating or calving such as rising the contraction of the smooth muscles of uterine or ovarian duct to carry both the sperm and ovum to the fertile area after mating action (Duzinski et al 2013). Also, it raises the contraction of the pelvic muscles when the calving process started (Jankoviæ et al 2001). Oxytocin when transport to uterine, it makes the myometrium more sensitive because of the large amount of momentum oxytocin receptors (Borrow et al 2012). Also, oxytocin is important for calving, for this point, the pituitary gland at this period will stimulate to release oxytocin. However, there are other sources to provide circulation with oxytocin, such as the uterus, which is considered as a major place to release oxytocin during the last stage of gestation (Kimura et al 2013). For example, in rats, the epithelial cells of the uterus can synthesize oxytocin

(Jarrett et al 2006). Furthermore, there is an indirect relationship between oxytocin and product of prostaglandins F2a (PGF2a) from endometrial cells (Veiga et al 2015).

According to the results of Seifi et al (2017) on Iranian Zel ewes, treated the animals with oxytocin at dosage 100 IU/head may cause cervical dilation, so, they suggested in their study that oxytocin injection could be important to improve the rates of pregnancy and lambing in sheep husbandry. In India, treated repeat breeder cattle with 4 ml of oxytocin during 4-5 hours after insemination improved the conception rate from 20 to 80 % as compared with untreated animals (Mahto et al 2008). Also, in Egypt, (Refaat and Hamdoun 2014) showed that treated ewes with 20 IU oxytocin increase the conception rate from 55.54 to 71 % as compared with ewes in the control group. While, in Pakistan, treated buffalo and cattle with oxytocin after parturition did not improve the productive and reproductive performances trails such as conception rate, retention of placenta, milk yield (Mustafa et al 2008).

In Ossimi ewes, a breed originated from the Giza Governorate of Egypt, Mohamed et al (2017) reported that oxytocin intramuscular injection before mating improving most of the reproductive trails of ewes such as estrus rate, non-return rate, lambing rate, on the other hand, it improves the proportion of twins by about 25% and also increases the size of the lambs by 8.67% as compared with the control group.

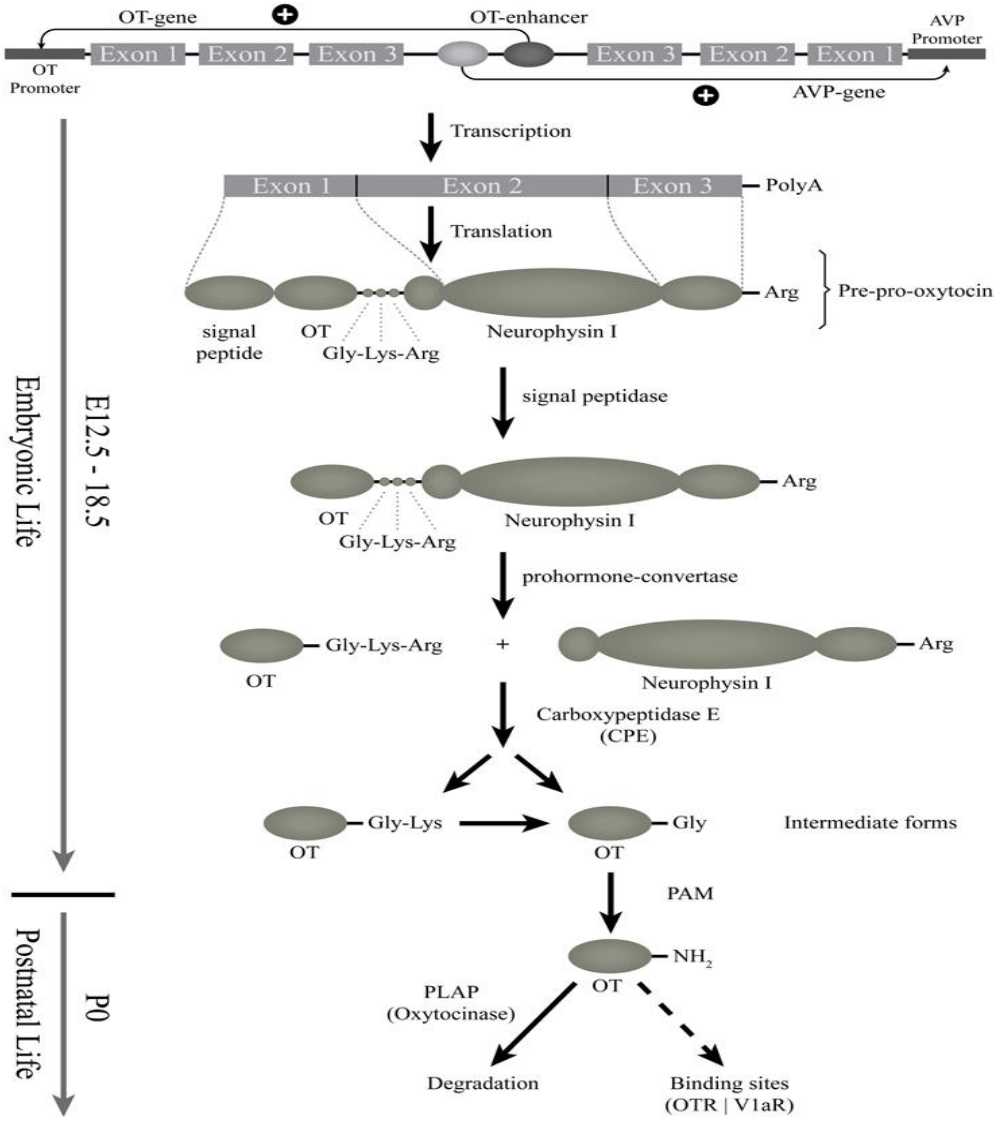

Figure 2 The different forms of oxytocin.
Source: Tsujimoto and Hattori (2005).

Corpus luteum

Oxytocin is essential for the final growth of corpus luteum during the luteal stage (Roshangar et al 2009; Brozos et al 2012). In all animals, oxytocin is syntheses by big luteal cells. In general, oxytocin controls the function of the corpus luteum, but this control varies among animals according to age and nutrition as well as the development of the corpus luteum itself. The relationship between oxytocin and prostaglandin in regulation the corpus luteum can be explained as follows: the layers of the uterus, especially, the endometrium produce prostaglandin at mid-luteal phase, in the same time, in the ovary, prostaglandin catalyzes the liberation of oxytocin via luteal cells (Gimpl and Fahrenholz 2001). So, the positive feedback endometrial prostaglandin catalyzed, and oxytocin catalyzed by the corpus luteum provides the best conditions for corpus luteum development (Wiltbank and Ottobre 2003). On the other hand, some experiments suggested that treatment with oxytocin is requisite for the expression of a sexual attitude, especially in female rats (Miller and Caldwell 2015). Moreover, Brozos et al (2012) showed that oxytocin infusion in Holstein Friesian cows effected significantly on progesterone level in the females, those behavioral impacts of oxytocin management did not present at once, they appear only after 72h of infusion as compared with prolactin treatment.

Male reproductive tract

Many studies on several animals presented that oxytocin sports a function in the reproductive male genitalia by transporting the sperm throughout the epididymis or sharing in the synthesis of steroid hormone (Zhang et al 2017; Sailer et al 2019). It showed that both oxytocin and its receptors are existing in the prostate, testicles, and epididymis, of many animals (Studdard et al 2002; Thackare et al 2006).

Oxytocin increases the contraction of epithelium tissues, which surround the testicular tubes that led to increase in the movement of the sperm in the epididymis of the testis (Whittington et al 2001). As well, oxytocin has a role in elevating the performance of the prostate gland by stimulating the contractile activity of prostatic tissue and increase the prostate secretions during the ejaculation (Liu et al 2019).

The first information about the link between oxytocin hormone and the sexual behavior in mammalian was observed in 1992 by (Carter 1992). At the present time, there is a certain fact that a correlative relationship between oxytocin and the sexual manner in both female and male has been detected (Veening et al 2015), oxytocin may lead to an opener`s role in regulating the activation of the reproductive system and the social-sexual behaviors in mammals (Anacker and Beery 2013). Many studies showed that oxytocin rise in the blood when mating activity is higher and the expression of sexuality in maximum degrees. (Borrow et al 2012; Veening et al 2015).

In several species, the activity of oxytocin increase is associated with ejaculation in males when peripherally stimulating smooth muscle cells are beginning in contraction, and, it may release as a reflect active on the central nervous system to present the sexual behavior (Gimpl and Fahrenholz 2001). For example, the concentration of oxytocin was increased in Leydig cells of the rat testes which its basically a source of the testosterone hormone (Ghasemnezhad et al 2015) as compared with other locations in the male reproductive tract. It was presented that oxytocin is catalyzed sexual manner via rising the synthesis action in the cell frames of oxytocinergic nervous converting to extra-hypothalamic brain areas (Gordon et al 2011). The data of Liu et al (2019) indicted that oxytocin is particularly regulating the transmission of sperm from the epididymis by elevating its level in peripheral circulation, which may cause a significant increase in sperm conveyance that takes place through ejaculation. In mice, Anjum et al (2017) found that oxytocin treatment caused morale changes in the spermatogenic and steroidogenic efficacy by raising expression of oxytocin receptors in the testicles before the Puberty in mice, also, treated mice with oxytocin raised the germ cells as a result to increase the number of spermatocytes, It was observed that pre-puberty mice treated with a higher dose of oxytocin had a higher concentration of testosterone. Furthermore, El-Badry et al (2013) suggested that injection oxytocin before semen collection in rams may be beneficial leading to the increase in the semen ejaculation and increase in the total number sperm in frozen semen, Also, repeated injection of oxytocin did not cause any side effect on the fineness of semen in all cases, whether fresh or frozen, add to the action of antioxidants or sperm plasma and testosterone grade in the rams.

The relationship between oxytocin and some hormones

Oxytocin may control the function of the anterior pituitary gland that has been offered by observing that several neurons perform to oxytocin were dropping their axons across the medial appearance (Yin and Gore 2010). On the other hands, the oxytocin has been freed in the gate of vessels, its concentration is often basal, and greater than what is found in the peripheral circulation (Gonzalez-Iglesias et al 2014). The expression of an oxytocin receptor gene (OTR) in the rat was evinced in anterior pituitary cells, fundamentally in lactotrophs where there is a significant increase in oxytocin receptors (OTR mRNA) is most apparent in the later stages of pregnancy after estrogen injection (Zheng et al 2013).

Prolactin

Prolactin regulates milk induction in the mammary gland through lactation. As known, the lactation stage inhibits fertilization. Numerous studies have indicated that high blood prolactin concentration (hyperprolactinemia) was closely associated with infertility in both females and males, on the other hand, has an important role in the reproductive process as well as being a stress hormone in both females and males. It is produced largely in response to different stress conditions. However, It's the job of regulating stress is unknown (Grattan 2015).

There is an overlap in the action of the oxytocin and prolactin as the prolactin works on the synthesis of milk, whereas, oxytocin acts on its secretion. Although prolactin inhibits oxytocin neurons, this can be irreversible during lactation, therefore, in increase the expression of oxytocin. So, the prolactin curb of oxytocin neurons has been missing in lactation that might already a synchronous rise of prolactin excretion of the pituitary gland and stimulate of oxytocin neurons for the completion and transmission of the milk to the newborns. (Tabak et al 2010; Augustine et al 2017). Nonetheless, the role of oxytocin as a release agent for prolactin is unknown, Nonetheless, some studies have indicated that oxytocin contributes to prolactin secretion (Denef 2008).

Luteinizing hormone

The output of luteinizing hormone in the period before estrus important to successful ovulation. A few years ago, some studies suggested that oxytocin controls the secretion of luteinizing hormone wave, in the pre-estrus period, oxytocin is the highest in the blood and peripheral plasma (Gimpl and Fahrenholz 2001). Some studies on different animals have indicated an increase in luteinizing hormone in response to oxytocin treatment, the effect of oxytocin was stimulated by estrogens and inhibited by progesterone (Gimpl and Fahrenholz 2001). On the other hand, studies have shown that there is a direct effect of oxytocin on luteinizing hormone excretion as well as an indirect impact via Initialize autotrophs to Gonadotropin-releasing hormone (Yan et al 2014).

Oxytocin and its role in the removal of milk

Most newly born mammals need enough milk from their mothers, one of the classical functions of oxytocin is milk expulsion from the mammary gland, the process of absorption of the nipple leads to the stimulation of the mammary glands (Gimpl and Fahrenholz 2001). As known, the receptors of oxytocin are found in both the brain and peripheral tissues such as udder, this will help to regulate the physiological and behavioral processes to secret the milk. Through the lactation stage, breastfeeding motivation the liberation of oxytocin in peripheral blood, which activates the milk ejection, at itself moment, oxytocin helps the mother to present their expression maternal manner (Landgraf and Neumann 2004). Furthermore, during lactation stage, the stimulation of receptors that site in nipple becomes more sensitive and give sensory pulsations (nerve impulse) that have been transported to the spinal cord from the tits, it is then transferred to the secretive oxytocinergic neurons at the hypothalamus, oxytocin is released from the mother after lactation by the posterior lobe of the pituitary gland, milk secretion requires the reduction of myoepithelial cells from the mammary gland (Gimpl and Fahrenholz 2001). However, the mechanism of milk secretion show in Figure 3.

Before parturition, the secretion of oxytocin will be necessary to continue to milk removal and also to both alveolar proliferation and mammary gland assignment. Alveolar consistency and mammary epithelial cells are affected

by the levels of oxytocin in the blood. Constantly towering oxytocin intensification like those through natural milking is also important for full milk sweep in dairy cows (Tancin and Bruckmaier 2001).

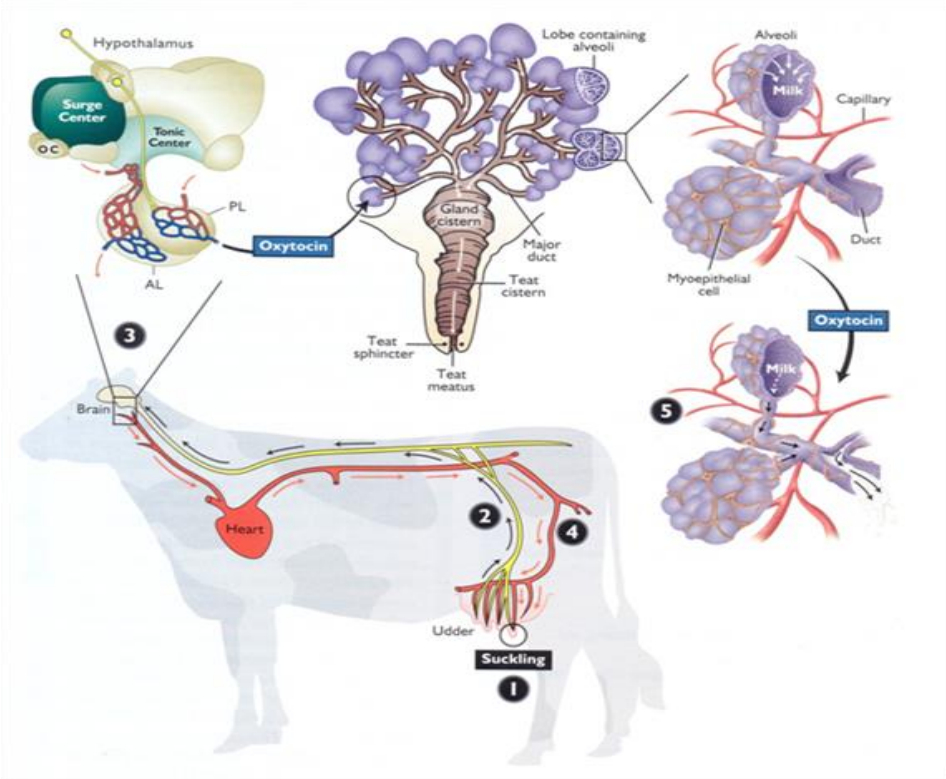

Figura 3 The mechanism of milk secretion.
Source: Husvéth (2011).

In mammals, oxytocin receptors are a protein with a molecular weight of 65 kDa (Gimpl and Fahrenholz 2001). Some studies have indicated that oxytocin receptors increase in the mammary gland during the first day of pregnancy and lactation (Knobil 2006). Also, Breton et al (2001) found a considerable rise in oxytocin binding sites in the mammary tissues.

Data of Taein et al (2001) indicated that oxytocin excretion has been blocked in dairy cows (twelve Brown Swiss cows) at the beginning of breastfeeding with the propensity of the tardy rise through the top minutes of breastfeeding (breastfeeding continued around 10 min), with the exception of two cows, they showed a rise in oxytocin shot at the top moment of breastfeeding. The shot of oxytocin in restraint to fourth breastfeeding increased dramatically once breastfeeding began. Some experiments did not find the impact of oxytocin on milk yield and milk release such as the study done by, Raghum et al (2014) in buffaloes, Morgan et al (2000) in ewes, those experiments recorded that oxytocin administration caused a little increase in milk yield and this amount elevated when females removal their milk by machine as compared with hand milking. Intramuscular oxytocin injection of (50 IU) caused a rise in oxytocin blood concentration and more active myoepithelial and alveolar contraction. Furthermore, it caused a poor improvement in the milk yield of Brown Swiss dairy cows (Macuhova et al 2004).

In Iraq, Alkass and Merkhan (2012) showed that treated the Karadi ewes with oxytocin at a dose rate of 10 IU intramuscularly effected significantly on milk yield, but not on the composition of milk, and they suggested that this dose will stimulate milk release.

Studies showed that injection of oxytocin (10 IU) intramuscular as an attempt to ameliorate the milk ejection in dairy cows has a predatory impact on index of behavior, stress and the authors approached that favorable motivate should be used to catalyze milk deportation with an eschewal of oxytocin routine treatment (Lammoglia et al 2016).

It has been shown in Sahiwal dairy cows that oxytocin has considerable effects on some milk minerals like Na, Cl and Cu, respectively, were higher (19.74, 9.39 and 146.89%), while K and lactose decreased by 10.06 and 0.39%, respectively (Hameed et al 2016), while, Akhtar et al (2012) showed that milk production improved by oxytocin injection in Buffalo.

The role of oxytocin on stress tolerance

Oxytocin has anti-stress impact by an effect on the hypothalamus-adrenal axis, this hormone is necessary for excretion the adrenal cortical tropic hormone (ACTH) under stress conditions such as in Holstein's calves extenuated cortisol excretion (Yayou et al 2008). On the other hand, Chen and Sato (2017) reported that the oxytocin is the main index for better welfare, rise enjoyment, put down the stress, and activating its own emission. Oxytocin release is related to favorable natural manner performance and fertility, like brushing, which can moreover precipitation oxytocin excretion, should give more alertness to the methods to get better administration practices to stimulate oxytocin, this leads to improve the rest and stress toleration of the animals, and not just focus on how to control stress in farm animals.

Final Considerations

Oxytocin has a very important role in the different biological systems of the body of the organism, especially the sexual functions of both sexes (female and male).

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