Oxytocin, a Mediator of Anti-stress, Well-being, Social Interaction, Growth and Healing

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Abstract

The neuroendocrine and physiological systems related to pain and stress have long been subjected to study. More recently, the corresponding systems promoting anti-stress and restoration have also come into focus. It is not only important to investigate the mechanisms underlying disease but also to examine the physiological and psychological mechanisms which protect and heal the body and soul.

The nonapeptide oxytocin, originally known to stimulate labour and milk ejection, appears to play an important role in this regard. Oxytocin can induce anti-stress-like effects such as reduction of blood pressure and cortisol levels. It increases pain thresholds, exerts an anxiolytic-like effect and stimulates various types of positive social interaction. In addition, it promotes growth and healing.

Repeated exposure to oxytocin causes long-lasting effects by influencing the activity of other transmitter systems, a pattern which makes oxytocin potentially clinically relevant.

Oxytocin can be released by various types of non-noxious sensory stimulation, for example by touch and warmth. Ingestion of food triggers oxytocin release by activation of vagal afferents. Most likely, oxytocin can also be released by stimulation of other senses such as olfaction, as well as by certain types of sound and light. In addition, purely psychological mechanisms may trigger the release of oxytocin. This means that positive interaction involving touch and psychological support may be health-promoting. The social interaction of daily life, as well as a positive environment, continuously activate this system. In addition, various types of psychotherapy involving transfer of support, warmth and empathy are likely to induce similar effects, which thus contribute to the positive effects of these kinds of therapies.

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Oxytocin

Oxytocinergic neurons in the hypothalamic paraventricular (PVN) and the supraoptical nuclei (SON) reach the neurohypophysis whence oxytocin is released into the circulation. In addition, paraventricular oxytocinergic neurons project to several areas within the central nervous system (CNS), such as the olfactory bulb, the frontal cortex, the amygdala, the locus coeruleus (LC), the hippocampus, the periaqueductal grey (PAG), the raphe nuclei, the striatum, the vagal nuclei (DMX and NTS), and the spinal cord [1]. Different effect spectras are induced when oxytocin is released simultaneously in various areas of the brain. So far, only one oxytocin receptor has been demonstrated, the uterine type of oxytocin receptor, and this receptor has been found also in the CNS [2]. It is likely that there are other oxytocin receptors or subtypes since some fragments of the oxytocin molecule can induce different oxytocin-like effects. In further support of the existence of multiple oxytocin receptors, is the fact that some of the effects of oxytocin induced in the CNS are not possible to prevent by an oxytocin antagonist [3].

The oxytocinergic nervous system is equally developed in males and females, although it is under strong influence by the female steroid hormones [3, 4]. Estrogens stimulate synthesis and release of oxytocin and increases the number of oxytocin receptors in some areas of the brain [4, 5, 6]. For example, the estrogen β-receptor mediates oxytocin release, and recently it was shown that the estrogen induced increase in oxytocin receptors within the amygdala is mediated through the estrogen α-receptor [7, 8, 9]. Thus there is a strong connection between estrogens and oxytocin, which leads to sex differences with regard to some of the effects of oxytocin.

The enervation of the PVN is complex and the release of oxytocin is for example stimulated by acetylcholine [10], noradrenaline (α-1-adrenoreceptors) [11], dopamine (D2-D3 receptors) [12, 13], serotonin (5-HT1a receptors) [14], vasoactive intestinal polypeptide (VIP) [15] and cholecystokinin-8 (CCK-8) [16]. Interestingly, oxytocin itself stimulates its own release [17]. This kind of positive feed-back is unusual, and a possible explanation behind this effect might be an oxytocin-mediated reduction of GABAergic inhibition of the release of oxytocin [18]. Furthermore, oxytocin autoreceptors have been detected on some of the oxytocinergic neurons [19]. Strong stimuli of oxytocin release, for example exerted by suckling, parturition, and osmotic stimuli, induces a very specific firing pattern of the magnocellular neurons in both the PVN and the SON. The numbers of synapses increase and the glial coverage

Key words

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decreases so that both the somatic and the dendritic surfaces of the oxytocinergic neurons become juxtaposed which allows interaction and synchronisation of the neurons. In connection with these changes, all the neurons start to burst in synchrony, causing a pulsatile release of oxytocin into the circulation [20]. Whether these changes occur also in the parvocellular oxytocinergic neurons are not known.

Opioids [21], GABA [22] and the c-terminal oxytocin fragment [own unpublished observation] inhibit the release of oxytocin.

**Acute effects of oxytocin**

Besides the classical endocrine effects on uterine contraction and milk ejection, oxytocin causes a wide spectrum of behavioural and physiological effects mediated through receptors within the brain. Maternal, sexual, social behaviours as well as the bonding between parent and infant and pair bonding among monogamous mammals are all stimulated by oxytocin [23, 24, 25, 26]. Administration of oxytocin can induce both anxiolytic-like effects and, in higher doses, sedative effects [27, 28]. The anxiolytic-like effect seems to be mediated within the amygdala, which is richly provided with oxytocin receptors [29]. The amygdala is also of great importance for social recognition, especially by olfactory stimuli. In support of this, oxytocin knockout mice have social amnesia, which can be restored when oxytocin is applied into the amygdala. [30, 31]. Both the anxiolytic-like effect and the effect on social recognition are important aspects of the ability of oxytocin to increase social interaction.

Oxytocin increases nociceptive thresholds through an enhancement of endogenous opioids. This effect has been linked to the PAG and the dorsal horn of the spinal cord [32, 33, 34]. Besides these effects, oxytocin induces several anti-stresses like effects; for example heart rate, blood pressure and the levels of stress hormones decrease and simultaneously the activity within the gastrointestinal tract and the endocrine pancreas increases. These effects of oxytocin are probably mediated through the hypothalamus and the vagal nuclei (DMX and NTS) [25, 35, 36, 37, 38]. However, oxytocin acts also directly in the pancreas and the adipose tissue, where it influences insulin and glucagon secretion and stimulates lipogenesis [36, 39, 40].

Systemic administration of oxytocin in rats induces an acute anti-inflammatory effect, and in vitro, oxytocin can induce antioxidative effects [41, 42]. Moreover, oxytocin stimulates proliferation of several cell types such as osteoblasts, pituitary cells and blastocysts [43, 44, 45].
Long-term effects of oxytocin

Oxytocin (1 mg/kg s.c. or 1 µg/kg i.c.v. indicating that the effects are mediated within the CNS) administered once a day for 5 days in rats decreases blood pressure for more than 1 week or as long as 3 weeks after the last oxytocin injection, in males and females, respectively (the more long-lasting effect in females is probably caused by the female steroid hormones [3, 46, 47]. Besides the reduction of blood pressure, this treatment increases nociceptive thresholds [48], decreases the levels of corticosterone (corresponding to cortisol in humans) [49], improves the ability to learn [50], and changes spontaneous motor activity, for more than 10 days after the last oxytocin injection [3, 50]. Oxytocin also acts as an antidepressant in animal models of depression [51]. In addition, oxytocin treatment increases the activity within the gastrointestinal tract and some slowly growing strains of female rats grow faster without an increase in food intake [52, 53]. Plasma levels of thyroid hormones are decreased compared to controls [54], while wound healing is increased and the levels of several growth hormones, such as insulin-like growth factor-I (IGF-1) and nerve growth factor (NGF), are increased [55, 56].

Oxytocin treatment during the neonatal period induces life-long effects of the same type as these described above. Thus, rat pups which are treated with oxytocin postnatally have lower blood pressure and corticosterone levels, increased nociceptive thresholds and increased weight in adulthood. These effects, in response to oxytocin, are even more pronounced when the animals have been exposed to prenatal stress [57, 58, 59]. The postnatal oxytocin treatment may also influence the offspring of the postnatally oxytocin treated rats, since female rats which have been treated with oxytocin postnatally have larger placentas and foetuses [60].

In summary, repeated administration of oxytocin induces an anti-stress like pattern through a decreased activity in the hypothalamo-pituitary-adrenal (HPA) axis and the sympathetic nervous system. Additionally, oxytocin induces calmness and increases nociceptive thresholds. Simultaneously, anabolism, healing and growth are promoted, for example through an increase in parasympathetic vagal nerve activity. By this way, energy is used for anabolism and growth instead of energy expenditure, which occurs, for instance, during motor activity.

Oxytocin interacts with other neurotransmitters

The long-lasting effects in response to oxytocin treatment is probably induced through secondary mechanisms, since oxytocin seems to change the activity in other transmitter
systems. The long-lasting increase in nociceptive thresholds appears to be related to an increased activity within the endogenous opioid system [48], and many of the anti-stress like effects seem to be induced through an increase in CNS α-2-adrenoreceptor function. When rats are pre-treated with oxytocin, only half as much of the α-2-adrenoreceptor agonist clonidine is required to reduce the firing of the noradrenergic LC neurons by 50% (measured by single-cell recording techniques) [61]. At the same time, the reduction of blood pressure and the sedative effect of clonidine are potentiated in oxytocin treated animals [3]. In rats treated with oxytocin, an increased number of α-2-adrenoreceptors have been demonstrated by autoradiography in for example the hypothalamus, the amygdala and the nucleus of the solitary tract [62].

As mentioned above, oxytocin decreases plasma corticosterone levels, and oxytocin influences HPA-axis activity through effects at several levels of the HPA-axis. For example, the amount of mineralocorticoid mRNA as well as the amount of glucocorticoid mRNA are changed in the hippocampus of oxytocin-treated rats [63]. A possible explanation to these central changes might be an increased activity of α-2-adrenoreceptors which in turn influences the HPA-axis at several levels. In addition, activation of α-2-adrenoreceptors decreases the activity of the sympathetic nervous system [64].

Oxytocin also induces changes in the function of the serotoninergic (5-HT) system. Rats treated with oxytocin have an increased synthesis of 5-HT in the frontal cortex as well as increased levels of 5-HT in the brain stem (own unpublished observation). Besides the mechanisms described above, oxytocin may induce long-lasting changes of the cholinergic transmission as well as other signalling mechanisms [37, 65, 66] (fig. 1). The duration of the long-term effects of oxytocin seems to be age dependent since rats treated with oxytocin postnatally have changed α-2-adrenoreceptor function in several brain areas as adults [67].
Non-noxious sensory stimulation releases oxytocin and induces oxytocin-like effects

Labour and lactation, or suckling, are followed by a release of oxytocin into the circulation and into the brain. Elevated levels of oxytocin have been found in the cerebrospinal fluid (CSF) and in more specific parts of the brain, such as the amygdala and the spinal cord. This means that oxytocin, in parallel to being released in the circulation, can be released in those parts of the brain that are reached by oxytocin containing nerves. Other types of sensory stimulation, such as sucking, food intake, warmth, touch, light pressure, massage-like stroking and sexual stimulation elevate oxytocin levels in the circulation as well as in the CSF [34, 68, 69, 70].

Feeding and sucking does not only give rise to oxytocin release but also to an anti-stress pattern which is similar to that caused by oxytocin. It has been shown that oxytocin is released after sucking, feeding, and after administration of the gastrointestinal hormone cholecystokinin (CCK). CCK induces oxytocin release via activation of vagal afferents; thereby some of the effects which follow after food intake may be secondary to the release of oxytocin [16].
Regarding touch, both thick A-β-fibres and a subpopulation of more slowly conducting C fibres, which are activated by low intensity stimulation, may be involved in the release of oxytocin. Activation of these fibres have been demonstrated to induce changes in the insular cortex, a part of the brain, which is related to emotions and interpretation of tactile stimuli [71, 72]. In addition, the front side of the chest, the abdomen and the urogenital organs are provided with a specific type of vagal innervation. These fibres do not enter the spinal cord, but project directly to the nodose ganglion and the NTS [73, 74]. The NTS is linked to the PVN via noradrenergic fibres which may mediate oxytocin release (fig. 2).

Figure 2: A schematic illustration of the projection of vagal afferents to the nucleus of the solitary tract (NTS) and from thereon to the paraventricular nucleus (PVN) from which oxytocin is released in response to stimulation of these sensory nerves.
When we discuss the effects of touch below, it is not the experience of the cortically registered sensation of touch which is in focus, but rather the effects of touch on emotions and the autonomic nervous system residing in deeper limbic areas of the brain. In support of this, non-noxious sensory stimulation such as touch or low intensity electrical stimulation of somatosensory afferents in anaesthetized rats gives rise to a physiological anti-stress pattern which is similar to that induced by suckling and breastfeeding [75-83]. If conscious rats, males or females, are stroked on the front side (40/min) oxytocin levels rise and an oxytocin-like effect spectrum is induced. Pulse and blood pressure decrease, the levels of gastrointestinal hormones increase, nociceptive thresholds increase and the animals get calmer. Oxytocin antagonists antagonise some of these effects, for example the effect on nociceptive thresholds [84, 85, 86]. Repeated treatment with this kind of massage-like stroking does, like repeated treatment with oxytocin, give rise to long-lasting effects of the same type as those induced by acute stimuli. The animals also increase more in weight, in particular if they have been stressed. They become more interactive and their ability to learn is ameliorated (in a test for conditioned avoidance) [Lund et al. to be published]. Obviously, the animals treated with the massage-like stroking exhibit an effect pattern which is similar to that induced by oxytocin injections. This similarity together with the fact that oxytocin is released by the treatment and that oxytocin antagonists block several of the massage induced effects, for example the increased nociceptive thresholds, indicate that oxytocin is an important mediator of the effects induced by massage-like stroking. It is possible that repeated release of endogenous oxytocin gives rise to effects that are similar to those induced by repeated administration of exogenous oxytocin, for example secondary changes in the activity of other transmitter systems such as an increased activity in the \( \alpha-2 \)-adrenoreceptor function.

Addition of extra sensory stimulation in the neonatal period is followed by a more rapid growth and also to the fact that the animals become calmer and have a reduced activity within the HPA-axis as adults. In addition, their blood pressure is lower. This treatment has been shown to be followed by an increased activity in \( \alpha-2 \)-adrenoreceptor function in adult rats [67, 87, 88, 89]. It is possible that some of these postnatal effects are in part indirectly mediated by oxytocin release.

Oxytocin release can also be induced by odours, sound and light. Oxytocin treated animals release an odour which elevates nociceptive thresholds and counteracts stress in animals kept in the same cage. In addition, endogenous oxytocin is released in the animals reached by the olfactory stimuli. The olfactorily induced effects can be antagonized by an oxytocin antagonist and also by local anaesthesia of the nasal mucosa. This data indicate that the
effects are mediated by oxytocin also in the recipient animals [90, 91]. An odour with calming properties which induces social behaviour has been isolated from lactating dogs [92]. Another important fact is that oxytocin release can be conditioned to other stimuli such as sound, odours and people [93]. Even thoughts, associations and memories can, most likely, induce a release of oxytocin.

**Oxytocin, closeness and breastfeeding**

Newborn babies are placed skin to skin on their mothers’ chest immediately after birth. If the babies’ spontaneous activity is not interfered with, they start to breastfeed within one to two hours [94]. Before suckling, they massage their mothers’ breasts with their hands. The mothers’ oxytocin levels exhibit a pulsatile pattern during this period. It is possible that the children’s own motor activity lies behind these oxytocin pulses since the amount of massage-like movements performed by the newborn as well as the rate of sucking relate to the amount of maternal oxytocin pulses [95]. Oxytocin released into the blood stimulates ejection of milk but it also dilates the cutaneous blood vessels on the chest whereby the mother may transfer warmth to the infant [96]. It is likely that in parallel to the release of oxytocin into the circulation there is also a release of oxytocin into the CNS of the mother, as previously demonstrated in animals, and that this oxytocin contributes to increased maternal interaction and bonding to the infant and also to her own well-being.

The physiological relaxation is expressed by decreased levels of cortisol and blood pressure and an increased activity of the gastrointestinal tract [80, 97, 98]. The mothers’ well-being is reinforced by the feeling of warmth caused by the dilatation of cutaneous blood vessels.

The closeness is of course reciprocal. The infant is also influenced by the contact with the mother and the warmth stimulates the interaction with the mother which is expressed by the spontaneous breastfeeding behaviour [94]. The infant also becomes calmer and it does not scream as long as it is kept skin to skin on its mother’s chest [99]. The physiological relaxation is followed by an increased peripheral circulation and thereby the feet of the infant become warm. The fine-tuned interplay between mother and infant is revealed by a relation between the maternal skin temperature and the increase of temperature in the feet of the infant. The warmer the mother is the warmer are the feet of the infant [100].

The release of oxytocin has not been studied in the newborn, but since the levels of the hormone cortisol decrease and since the levels of the gastrointestinal hormone CCK increase (effects which may be secondary to an increased release of oxytocin in the hypothalamus and
the DMX) in premature infants which have been allowed to have ventral skin contact (kangaroo care) it might be assumed that oxytocin release is stimulated [101, 102]. The infants sucking during breastfeeding, reinforces the effects induced by touch [80, 98, 103]. Even stimulation of other senses (vision, sound and odours, and also eye contact – an indirect touch between mother and infant) play an important role for these reciprocal effects.

Figure 3: The ventral side is of importance in close relationships. The vagal nerve afferents originating in this area are activated by touch and closeness and may be of importance for the psychophysiological reactions triggered by ventral closeness.

Long-term effects by closeness and breastfeeding

Skin to skin contact between the newborn baby and the mother and breastfeeding immediately after birth are not only followed by immediate changes as described above but also by more long-lasting effects. The bonding between mother and infant may be reinforced by this treatment as expressed by a more frequent interaction between mothers and infants four days after birth and also to a reduced occurrence of abandonment of the babies. In addition, some studies show that milk production is ameliorated and the time for breastfeeding prolonged [104-109].
Breastfeeding women, after a period of breastfeeding, become calmer and more socially interactive as measured by the Karolinska Scale of Personality (an inventory measuring personality traits) [110-113]. In addition, their blood pressure is lower, and the cortisol release induced by physical activity reduced [114, 115]. Moreover, the vagal control of the levels of gastrointestinal hormones is changed in a way which is consistent with optimal digestion and storing of nutrients [116]. The idea that oxytocin contributes to the psychological changes during breastfeeding is supported by the fact that the number of oxytocin pulses in connection with the breastfeeding session is related not only to the amount of milk which is received by the infant during breastfeeding but also to the mothers level of calm and interest in social interaction. Even the prolactin levels in these mothers correlate to maternal levels of calm and relaxation [110, 111].

There is further experimental data supporting the notion that oxytocin may be of physiological importance during the neonatal period. Women who have been delivered by Caesarean section have, on the average, fewer pulses of oxytocin in connection with breastfeeding measured 2-3 days after birth, compared to those delivered vaginally (fig. 3). Nor are they as calm and socially interactive as the mothers having had a vaginal delivery. Obviously, the development of the breastfeeding related oxytocin pattern and the behavioural adaptation is delayed by Caesarean section. It is not possible to decide whether these effects are due to a reduction of labour related oxytocin release or to a delayed skin to skin contact between mother and infant [111, 117]. Alternatively, pain or stress in connection with the surgical intervention may have antagonised oxytocin release and oxytocin induced effects in the newly delivered mother. Anyway, it seems as if reduced exposure to oxytocin during this critical period delays the development of the psychophysiological adaptation taking part in connection with birth, in particular in primiparous. In a longer time perspective this may be related to problems with breastfeeding and reduced interaction between mother and child. Also other pain relieving interventions in connection with labour as for example epidural anaesthesias reduce the release of oxytocin and may therefore influence the developing mother infant interaction [118].
Figure 4: Oxytocin levels in response to breastfeeding 2 days after birth. The upper panel shows the flat oxytocin pattern in a woman having had an emergency caesarean section. The lower panels show the pulsatile oxytocin pattern in two women having had a vaginal delivery. (from Nissen et al. 1996 [117]).

Oxytocin release in other types of relations and therapeutic situations

The psychophysiological effects, described above, which occur in response to closeness between mother and infant can be regarded as a model for a reaction pattern which is triggered in many different types of contacts and relations among humans of different ages and sexes. Sexual activity, in particular, is connected to a very powerful release of oxytocin in both sexes [119]. Despite the differences, basically, the same psychophysiological system, including calm, social interaction, relaxation, and stimulation of restoration processes is induced by many kinds of social contacts. These effects induced are of course health promoting and may be one of the reasons why people with good social relations have a better health [120, 121, 122].
It is well-known that the fight-flight pattern can be triggered by threatening situations. External as well as internal situations which by a certain individual are experienced as dangerous or uncontrollable give rise to stress responses via activation of the amygdala/hippocampus region. The activity within the LC is increased as well as the release of CRF in the hypothalamus leading to stimulation of the HPA-axis and the sympathetic nervous system [123, 124]. By analogy, it is likely that a psychophysiological pattern related to calm and relaxation can be triggered by purely psychological mechanisms for example by a calm, supportive and warm surrounding. It remains to be established if oxytocin is involved in such responses of antistress nature. The fact that oxytocin release can be induced in response to sensory stimuli as well as by thoughts and associations support this assumption.

A doula is a woman who touches, holds and supports a woman in labour, physically and mentally. With this type of support it has been shown that women give birth more quickly and that the need for Caesarean section and pain relief is significantly reduced. The experience of labour becomes more positive. Recently some well documented articles have been published which show that the presence of a doula also gives rise to beneficial long-term effects. Two months after birth, mothers who have been helped by a doula during labour, have been shown to have a better relation to their children and also to their partners, when compared to those who did not have this type of support. In addition, they are less depressed [125, 126, 127]. It is possible that it is the combination of physical touch and emotional support given by the doula which lies behind these effects. Perhaps, the doula changes the activity in different neurotransmitter systems in the brain in a way similar to those induced by repeated oxytocin administration in animal experiments. It is possible that such neurochemical changes lie behind the stimulation of social interaction and decreased levels of mental and physiological stress observed in the mother that have been supported by a doula.

It is important to note that the openness to impressions of all kinds is very high during birth, when oxytocin levels are high. Therefore a loving and caring treatment may influence the individual in a deep going and long-lasting way just as a difficult and extremely painful labour can be traumatizing for the mother and induce a posttraumatic stress syndrome.

A combination of touch and a positive supportive psychological support may have even more favourable anti-stress effects than either treatment alone. If an individual is very anxious and afraid it may be difficult to reach this person by psychological mechanisms. Touch may sometimes work better, since somatosensory stimulation activates the release of oxytocin from PVN via a direct mechanism which cannot easily be blocked by anxiety.
It is possible that openness to the positive effects of supportive treatments may be induced by a combination of physical and mental support in people of all ages and sexes. Such a combined treatment is, and should perhaps be used more often, in many therapeutically situations, involving psychological and somatic treatments.

The fact that oxytocin levels are decreased in patients with depression, stress-related disorders, anxiety and chronic pain support the idea that stimulation of oxytocin release may have health promoting properties [128-133]. Interestingly, some of the pharmacological drugs used to treat these disorders may involve oxytocinergic mechanisms. Thus oxytocin release is triggered by 5HT1a-receptors and oxytocin levels even increase in response to the administration of SSRI in animal experiments [134,135]. These data indicate that oxytocin is a common mediator of several pharmacological, physiological and psychological treatments.

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