



## Review Article

# Oxytocin and the role of “regulator of emotions”: Definition, neurobiochemical and clinical contexts, practical applications and contraindications

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## Abstract

In the field of neuroscience applied to emotions and affects, some hormones have been studied for their relational and social activation capacity. Among these, the peptide hormone called oxytocin, long known for the induction of birth contractions and other physiological functions, is involved in attachment, confidence and reduction of anxiety, facilitating the stability of emotional relationships and therefore loyalty and love. Therapeutic uses are then proposed for synthetic oxytocin for eating disorders, substance addictions and even autism. In the following review, the primary experimental evidence and the possible side effects are proposed again, orienting the study on more detailed specific investigations.

## Introduction

The neurosciences applied to emotional and affective processes consider the emotion as an affective psychic state which consists in the reaction opposed by the organism to perceptions or representations that disturb its balance, a phenomenon incorporated in the neurobiological structures that establish consciousness [1], on the basis of complex sub-cortical systems linked to motivational processes (which imply automatic responses) and to cortical mechanisms responsible for controlling behaviour [2]. These processes, as we know today, are mediated and conveyed by specific hormones; in the case of emotions, the main one is undoubtedly oxytocin [3].

Oxytocin is a peptide hormone composed of nine aminoacids (Cysteine-tyrosine-isoleucine-glutamine-asparagine-cysteine-proline-leucine-glycine-amide: Cis-Tir-Ileu-Glu (NH<sub>2</sub>) -Asp (NH<sub>2</sub>) -Cis-Pro- Leu-Gli (NH<sub>2</sub>), in summary,

CYIQNCPLG-NH<sub>2</sub>), is part of the same family as vasopressin and is produced by hypothalamic nuclei above (mainly) and paraventricular (in smaller quantities) and secreted in neurohypophysis, present in all mammals, in based on the activation of the gene defined precisely OXT. In addition to being synthesized by pituitary neuroendocrine cells, the peptide is present in various types of brain neurons that use it as a transmitter [4].

Sir Henry Hallet Dale, Nobel Prize winner for studies on acetylcholine and author of brilliant research on histamine, was the first to discover the effectiveness of oxytocin in inducing birth contractions: in fact, this hormone has a specific role in women, as it stimulates maternal behaviour and facilitates intimate bonding with the child (even non-biological), induces sexual arousal, reduces blood pressure and the rate of cortisol. Always this hormone also starts the reflex that makes the milk flow from the mother's breast during feeding and acts on the



brain, where there are specific receptors for this molecule. Men also have oxytocin on average in the same amount as women, but they have more estrogens which enhance their effectiveness while testosterone, in the male, counteracts the effect. The first researcher who first isolated and synthesized oxytocin was Vincent du Vigneaud, in 1953, also a Nobel laureate [5,6].

Oxytocin is an antagonist of acetylcholine [4], and the correct release into the body produces the following psycho-bio-behavioural effects:

1. Stimulates prolactin and the release of dopamine (in mesencephalic systems, which determine the reinforcement associated with pleasant experiences) during orgasm, which is thus more intense and deep [4].
2. Facilitates social perception, increasing the attractiveness and reliability of faces [7,8,29]. The role of oxytocin and vasopressin for the control of social and cognitive behaviour disorders (in an animal model) has been demonstrated. Oxytocin and vasopressin show a high capacity to positively influence sociality defects and cognitive flexibility, in individuals with the fully developed nervous system [44]. Further research has finally shown the direct correlation between; oxytocin and autism, and how this hormone is able to facilitate patients in improving their relational and social abilities, since already since 1998, it was known that autistic patients have a lower amount of oxytocin (mean). [13-20,45-48].
3. Increases the willingness to share emotions [9]. Receiving trust from a stranger in the form of money or other reinforcement makes us more satisfied and more confident in others: this corresponds to an increase in oxytocin in the blood, although it is not clear whether this is a cause or a consequence. Faced with the vision of advertising campaigns on the dangers of smoking, alcohol, reckless driving and global warming, the intake of oxytocin increases the sense of concern for others and leads to donate more money for a good cause. Oxytocin, therefore, leads to being more generous [10] and, in some ways, more empathetic [11]. In this sense, several studies have confirmed that the use of the exogenous oxytocin in psychiatric patients with mood disorders, psychotic subjects and autistic people compares their social performances, mitigating the symptoms [57,58], also if the use in psychopharmacology is still present a whole series of complications related to the pressure and cardio-vascular system, to be taken into consideration [59].
4. Contributes to maintaining fidelity and the ability to create bonds between animals and between human beings [21]. Love, like other emotions, in fact, is mediated by different molecules that perform the function of messengers; not surprisingly, the identification of a potentially loving partner does not seem to be entirely random, but is conditioned by dopamine, vasopressin

and oxytocin: these substances and the brain-target areas would be activated during the monitoring of the possible partners, conditioning their choice [22]. It has been shown that oxytocin facilitates love bonds in men by making its partners more attractive than other women [23]. Analyzing the active brain areas of people in love, we have seen that the two particularly active areas are the caudate nucleus (the area that allows concentrating energy to obtain a reward) and the segmental ventral nucleus (where dopamine is produced and diffused in the other areas of the brain). According to some studies, romantic love is a drive comparable to hunger and thirst [24], but the effect is differentiated according to the prevalent hormone: sexual desire is correlated mainly with the production of estrogens and endorphins; romantic love with that of dopamine, norepinephrine and serotonin; attachment, on the other hand, with an increase in oxytocin and vasopressin [25]. You can, therefore, have a strong attachment to someone and at the same time feel romantic love for another person, and be sexually attracted to a third party [26]. The level of oxytocin is, in fact, significantly related to the reduction of anxiety-related to attachment in intimate relationships [27]. It is highly probable that those who produce more oxytocin in the specific area of the brain are able to create more stable bonds. Oxytocin is capable of limiting, or even nullifying, the male propensity to betrayal and increasing that of monogamy. It has been discovered that men engaged in a stable relationship, who maintain distances towards another woman more often despite being considered very attractive, register high levels of this hormone: it is confirmed that oxytocin is involved in the formation of social relationships, especially sentimental and family ones [28].

5. Is connected with depressive disorders [31] and with separation anxiety, as this hormone interacts with the activity of the amygdala (which plays a central role in anxious emotions) [29,30]. Furthermore, by interfering with the neuroendocrine functions, it necessarily interacts with the sex hormones, conditioning their performance (as in the case of premature ejaculation) [33,34] and with hormones linked to substance-dependent disorders (such as alcoholic beverages) [40,41] and food (anorexia, bulimia, obesity) [35,43]. A study conducted at the Harvard Medical School in Boston showed that oxytocin, administered in the form of a nasal spray, reduces a person's caloric intake, the amount of food ingested, especially fatty foods, and could, therefore, become an excellent antiobesity tool. In reality, the mechanism of action of the hormone, which does not seem to act on the perceived sense of satiety, is not clear; and it also created some side effects such as dizziness, drowsiness, nasal irritation and abdominal pain even though none of them was considered serious [38]. Another research revealed the positive emotional responses of some girls suffering from anorexia who had been given oxytocin through a spray. These girls would have shown, after the treatment, a more



favourable attitude towards food and improvements in the expressive features of the face, with modification of emotional processes such as fear, anger and worry [39].

6. Protects the nervous and immune system of the fetus [32].
7. A methylation analysis limited to CpG (miRNA) sites associated with microRNA revealed that the MIR4456 gene is presumably involved in the main neuronal molecular mechanisms of hypersexuality, significantly influencing the plasma oxytocin value. This indicates the likely connection between hypersexuality and high oxytocin levels, following a gene mutation [56].

The natural production of this hormone increases with the tactile stimulation of breasts and nipples (the same reaction as breastfeeding), as well as the clitoris; it also increases in the presence of a sincere and reciprocal embrace not inferior in duration to twenty seconds, interacting with other hormones released in this communicative context that favour the production of haemoglobin, the activation of the immune system, the release of dopamine and the consequent decrease of cortisol, thus generating a systemic well-being [37]. It is not surprising, in fact, that in the cultural systems where the importance of personal space and the limits of subjective boundaries prevail, as in the United Kingdom or Scandinavian countries, in favor of a legal regulation more oriented to minimize physical contacts, especially in schools, the rate of anxious and depressive psychopathologies is considerably higher than the world average, as are the neurotic psychopathologies in general. A system that codes this hypothesis generates in itself a dysfunctional relationship mechanism that then translates into a real socially accepted self-injurious behavior (maintaining a rigid and inflexible attitude during working hours, to then exaggerate with the use of alcohol and drugs in the late afternoon, evening and night). Based on this awareness, recently, in the Scandinavian countries, they are introducing into the school system practices related to physical contact and hugs, precisely to increase the sensitivity of students and become familiar with the development of empathy [36].

However, oxytocin is a simple molecule, and therefore it can also be chemically synthesized, taking the name of Pitocin or Syntocinon. However, the difference between natural and synthetic is substantial. Natural has a double effect, as it enters the bloodstream and reaches peripheral organs, while at the central level it acts on social behaviour; the synthetic one, on the other hand, has an effect mainly linked to peripheral phenomena, as it enters the circulation through the intravenous route and finds it difficult to reach the brain cells due to the blood-brain barrier that protects the brain against foreign substances released into the blood. Again, natural oxytocin is released by pulsation, and the more intense the pulse, the more oxytocin is effective; synthetic oxytocin, on the other hand, is continuously administered intravenously, is less effective and much higher dosages are required to activate receptors. At the moment, the only use approved by the national health system for oxytocin is that related to childbirth, with intravenous

administration. Oxytocin is also used to alleviate pain both acute (such as headache) and chronic pain, such as gastritis and arthritis, as it is able to raise the levels of beta-endorphin which reduces the sensation of pain. Formulations have also been studied to administer oxytocin intranasally, in order to facilitate more direct access to brain circuits, based on the research of Paul Zak. These formulations are only available for experimental studies and have not been approved for clinical use. However, products of the uncertain formulation are available on the market, which can be purchased via the internet, but not checked and experimentally and with uncertain consequences regarding the effectiveness and duration of the action [3,42].

Oxytocin, however, at very high levels, becomes toxic and can induce aggressive behaviours, stimulating an exponential increase in alert levels, causing anxiety, fear and physical pain [49]. Indeed, after a negative social experience, oxytocin circulating, interacting with the amygdala, triggers reactions of anxiety and fear in the face of the repetition of the stressful situation [50]. Therefore, contrary to what happens for positive and comforting experiences, the hormone in high quantity after the experience of stressful or adverse situations intensifies the memory, increasing the sensitivity towards the negative feelings that can arise when the situation recurs or a similar one. Other possible contraindications detected during an excessive presence of oxytocin in the organism concern: envious and rancorous behaviors, as shown by a research by the University of Haifa [51]; learning and memory deficits [52]; immoral behavior and against social laws [53]; prejudicial conduct towards a subject or a group [54]; hypersexual behaviour, inhibition and frenetic sex addiction [55].

In conclusion, it is clear that psychological relationships involve such complexity that they do not allow simplified explanations and reduced to a linear causality, without taking into account the many factors. It is naive and anti-scientific to assume that the substance that 'facilitates life' can be found in a neuropeptide such as oxytocin: a cure-all for psychological well-being, with a dose that can relieve pain, you can increase confidence, sexual problems and marital crises can be solved after treason; and with appropriate administrations, improve social relationships in autism or in other pathologies. It is therefore essential to continue research in this field to better understand all the possible clinical implications.

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