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The role of the oxytocinergic system in pain physiology: new data and possible therapeutic strategies

M. Saveri (*), N. Stefenatto (**), V. Bonhomme (*), V. Geenen (***) and J.F. Brichant (*)

Summary : Pain is an essential subjective warning symptom that can transform into a disease when it becomes chronic and affects the patients' quality of life. The oxytocinergic system has long been known to play a physiological role in pain perception and its psychological aspects. Despite potential implications for pain treatment, the oxytocinergic system has not yet been therapeutically targeted in clinical practice. This narrative review explores the latest scientific findings on the subject, and discusses some of the unexplored leads for the clinical use of oxytocin in the domain of pain treatment.

Keywords : Oxytocin ; Pain ; Analgesia ; Placebo ; Central Nervous System.

The International Association for the Study of Pain defines pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (1). It is, however, important to differentiate acute pain from chronic pain. Acute pain acts as a warning sign, while chronic pain is a disease. For years, intense effort has been granted for the understanding and control of chronic pain, leading to therapeutic options that often have debatable long-term efficacy.

Recently, a growing interest has emerged for oxytocin (OT), a nonapeptide synthesized by specific hypothalamus nuclei and secreted by the posterior pituitary gland. Although OT is already known for its effect on the uterine muscular fibers during delivery (2), and for its role in milk-ejection during breastfeeding (3), recent studies have shown that it could have more properties, including some that may be of interest in the domain of algology.

This article aims at reviewing current knowledge on the analgesic properties of OT, and discussing the potential advantages it may have in clinical pain management. The first part briefly describes the main physiological mechanisms of pain. The currently known properties of OT are then reviewed, at the light of the most recent scientific data, and, finally, hypotheses regarding eventual clinical interest in the treatment of pain are discussed.

2. The physiopathology of pain

2.1 The perception of pain

This review focuses on pain and its perception, not on nociception. The latter is a physiological process involving the cutaneous, muscular and articular nociceptors, as well as the pathways transmitting the information they produce to the brain. Pain supposes the integration of this information by the brain, in a more complex framework, adding elements such as emotions, stress, or even cultural influence to end up with a subjective sensation.

2.1.1 Nociceptors

The nociceptors are relatively non-specialized receptors that can detect potentially damaging stimuli and transform them into nerve impulses (4). They can be found at any place that is sensitive to noxious stimulation. There are three main types of nociceptors: the mechanical and thermal nociceptors, which both involve Aδfiber axons, and poly-modal nociceptors, which involve C fibers (5).

2.1.2. Stimulus generation

The exact mechanism involved in the creation of nociceptive information is not known with precision. It appears that stimulus generation depends on numerous mediators secreted locally by injured tissues. Other substances like substance P and calcitonin gene-related peptide (CGRP) are released at the peripheral extremities of neurons emerging from the spinal ganglia. All those mediators create

Maximilien Saveri, M.D.; Nicolas Stefenatto; M.D.; Vincent Bonhomme, M.D., Ph.D.; GEENEN Vincent, M.D., Ph.D.; Jean François Brichant, M.D., Ph.D.

Department of (*) Anesthesia and ICM, CHU of Liege, 4000 Liege, Belgium; Student(**), University of Liège, 4000 Liège, Belgium; GIGA-I3 Center of (***) Immunoendocrinology, University of Liège, and Endocrinology, CHU of Liège, 4000 Liege, Belgium

Correspondence address :Maximilien Saveri,.Department of Anesthesia and ICM, CHU of Liege, 4000 Liege, Belgium. E-mail : Maximilien.saveri@student.ulg.ac.be

a 'peripheral soup', which activates the nociceptors, and induce peripheral sensitization.

2.1.3 Primary afferent fibers

There are several types of primary afferent fibers. They are listed in Table 1 (5) (6) (7).

2.1.4 Posterior horn of the spinal cord

Nociceptive fibers enter the spinal cord at the Lissauer tract, a white matter region that caps the dorsal horn. Inside it, the fibers cross the midline and go upward to the brain stem. (8).
Similarly to other places within the nervous system, neurons of the spinal cord are grouped in functional zones. They form flattened areas called 'Rexed laminae'. The posterior horn includes lamina I to V and the anterior horn the VI to IX. Laminae I and II receive information from thin myelinated fibers (Aδ) and non-myelinated fibers (C). Laminae III and IV only receive impulses from thick myelinated fibers (Aα and Aβ). Laminae V receives information from different types of fibers, allowing the management of various types of nerve impulses (6).
This organization of the posterior horn into laminae is also important for the projection towards the brainstem and the thalamus. The nervous pathway towards the main thalamic nuclei implicated in pain control comes from the laminae II, also known as 'substantia gelatinosa of Rolando' (SGR), which receives direct thin-diameter fiber terminations (7).

2.1.5. Ascending spinal tracts

Nociceptive information is carried by the anterolateral system, which, contains several distinct pathways: the spinothalamic tract, transporting information about the localization of pain toward the intralaminar and ventral posterior nuclei of the thalamus. A third neuron projects either to the somatosensory cortex (7) or to the periaqueductal gray matter (PAG) (9); and the spinoreticular tract, playing a role in the emotional side of pain. The last ascending tract is the spinomesencephalic tract (9).

2.1.6. Afferent supraspinal terminations

Thalamus is the focal point of somatosensory information. It includes two nuclear functional groups: the posterior and the lateral one. The latter receives information from the spinothalamic tract. Studies have shown that inhibitory interactions between the ventral posterolateral (VPL) and ventral posteromedial (VPM) allow modulating the propagation of pain towards the brain (6). The posterior nuclear functional group creates connections with the insula and the cingular cortex, and takes part in the cognitive and emotional aspect of pain (6).

Table 1
Table of the different types of somatosensory afferent fibers.

Type of fibers	Level of myelination	Axon's diameter	Conduction velocity	Function
Aα	High	Very large: 13 to 20 µm	Very fast: 80 to 120 m/s	Proprioception.
Aβ	High	Large: 6 to 12 µm	Fast: 35 to 70 m/s	Epicritic (touch)
Aδ	Poor	Small: 1 to 5 µm	Slow: 5 to 30 m/s	Primary pain: fast and well-localized pain
C	None	Very small: 0.2 to 1.5 µm	Very slow: 0.5 to 2 m/s	Secondary pain: higher latency, slower and badly localized pain

2.2. The modulation of pain

2.2.1. Descending tracts

Acute and chronic pain is modulated by descending tracts emerging from different parts of the brain. Controls emerging from the same area can inhibit or facilitate the transfer of nociceptive information (10). They project onto the dorsal horn of the spinal cord. (11). They can be tonic or, more often, modulate the balance between inhibition and facilitation. They constitute an efferent arm of the effect of behavior, as well as emotional and pathological states on pain perception (10).
The PAG plays a key role in the endogenous control of pain. It receives nerve impulses from the frontal and insular cortex, the hypothalamus and the amygdala (7). The periaqueductal gray, parabrachial nucleus and the solitary tractus nucleus communicate with the rostral ventromedial medulla which projects directly to the dorsal horn of the spinal cord. The involved neurotransmission system is noradrenergic and serotonergic. The periaqueductal gray and the rostral ventromedial medulla contains high concentrations of opioid receptors, being one of the effectors of the analgesic effect of opioids (9).

2.2.2. Endogenous opioids

Analgesic medications typically act through a modulation of neurotransmission within the ascending and descending nociception pathways. The endogenous opioid system is an interesting target for the development of analgesic medications. It participates in the descending modulation of pain perception (7).

3. Oxytocin

3.1. Neuro-anatomical bases

Oxytocin is a nonapeptide hormone that is primarily synthesized by the magnocellular and parvocellular neurosecretory cells of the paraventricular (PVN) and supraoptic nuclei (SON) of the hypothalamus. It is released into the peripheral circulation by the posterior pituitary gland. Oxytocin acts both as a hormone through its peripheral effects, and as a neurotransmitter through its central action (7). Table 2 shows two oxytocinergic neurons type. Magnocellular neurosecretory cells are located in the SON and PVN, whereas the parvocellular cells are found only in the PVN. Some of them project to the forebrain, including the accumbens nucleus and the central nucleus of the amygdala, thus exhibiting a central action (12).

Parvocellular cells have mainly a peripheral effect through their hormonal secretion at the level of the posterior pituitary gland. More recently, it has been shown that parvocellular-released OT plays a critical role in modulating breathing, the cardiovascular system, social behavior, and nociception. However, the place of the parvocellular and magnocellular cells within the oxytocinergic system remains unclear (12).

Table 2
Known oxytocinergic neurons of the thalamus.

Neurosecretory cell	Localization	Projection	Fonction
Magnocellular	Supraoptic and paraventricular nuclei	Forebrain	Released OT into the systemic blood flow
Parvocellular	Paraventricular nucleus	Nuclei in the brainstem and spinal cord	Not yet understood, probably in the generation of nociveption

3.2. Oxytocin receptor

The OT receptor (OTR) is a rhodopsin-type member of the G protein-coupled receptors family, characterized by a structure containing seven transmembrane helices. It has three potential N-glycosylation sites in its extracellular NH2-terminal domain (13).

As expected, the main agonist of the receptors is OT; however, it shows a weak ligand selectivity profile. For instance, arginine vasopressin (AVP) acts as a partial agonist. It requires a concentration multiplied by 100 in order to elicit the same level of response. Moreover, the binding of OT to its receptors is modulated by several hormones, notably gonadal steroids like testosterone and estrogens. In the brain, estrogens exert only a modest influence on the synthesis of OT, but they have a pronounced effect on the regulation of OTR. These hormones increase the affinity of OT toward its receptor. Furthermore, it has been shown, in vitro, that OTR expression could be raised by activating either the protein kinase A (PKA) or protein kinase C (PKC). Like most other G protein–coupled receptors (GPCRs), the OTR can be active without need of binding any agonist. Similarly, OTR may undergo rapid homologous desensitization following persistent agonist stimulation (13).

OTR is mainly expressed by myoepithelial cells of the mammary glands, the myometrium and the endometrium of non-pregnant women. In the central nervous system, the expression of the receptors is uneven. Study on primate models showed that OTRs are localized both on hypothalamic neurons and astrocytes. For the regional distribution, however, their locations vary depending on the species and have yet to be precisely described in humans. This expression disparity has raised the question of possible subtypes of the receptors. Such subtypes have been suggested to explain the evidenced differences in pharmacological profiles or immuno-reactivity patterns. So far, studies failed to issue any evidence to the benefit of this theory (13).

3.3. Peripheral effects of oxytocin

3.3.1. Potential modulation of inflammation

Oxytocin has also an effect on the inflammatory cascade. Oxytocin reduces the production of cytokines and NF-ϰB. (14). It has been demonstrated to promote the transduction of the signal coding for a protein kinase that is responsible for the positive

regulation of the cyclo-oxygenase 2 synthesis (15). Ongoing research looks at its anti-inflammatory properties in other patients than the pregnant woman, and in patients with some cardiac and bowel diseases (16) (17).

3.3.2. Other effects

Oxytocin have effects on lactation (18) (19), and on the uterus (18) (3). It also participates to wound healing, and in the differentiation of cardiomyocytes. These effects are beyond the scope of this article (7).

3.4. Oxytocin effects on pain

Several studies on a potential effect of OT administration on pain have already been published. They are summarized in Table 3, and commented hereafter.

3.4.1. Animal models

Oxytocin is simultaneously a hormone and a neurotransmitter engaged in several physiological processes. In animals, both central and peripheral OT administration, and the endogenous stimulation of the nuclei responsible for the release of OT, are responsible for increased pain tolerance and decreased perception of acute pain. These effects are blocked by the administration of a selective OTR antagonist (20). A high tolerance to pain is associated with higher OT plasma concentrations (15).

3.4.2. Central effect of oxytocin

In the central nervous system, and similarly to cortisol and estrogen, OT is involved in the coordination of behavior and stress response (7). Oxytocin works as a neurotransmitter in the hippocampus, amygdala,

Table 3
Published studies on pain modulation after oxytocin administration.

Source	Study type	Participants	Pain evaluation and type of pain	Main findings
Rash et al., 2014	- Double-blind - Placebo-controlled - Crossover	- Humans - Both genders - 40 participants	- Acute thermal pain (cold). - Pain assessed by visual analogue scales and the SF-MPQ-2.	- Oxytocin administration reduces acute pain sensitivity. - Lower pain unpleasantness, lower pain intensity and higher pain threshold. - Oxytocin administration reduces acute pain sensitivity.
Zunhammer et al., 2015	- Double-blind - Placebo-controlled - Cross over	- Humans - Male - 18-50 years - 36 participants	- Acute thermal pain (heat). - Pain and pain unpleasantness assessed by visual analogue scales. - Functional magnetic resonance imaging to assess changes in the whole brain activity as well as in the amygdala.	- Modest effect of OT on heat intensity ratings. - Small but significant decline of bilateral amygdala activity. - None effect was proportional to temperature, and OT affects the intensity of heat, not its unpleasantness. An anti-nociceptive effect of OT could not be demonstrated.
Futagomi et al., 2016	- Randomized - Placebo-controlled	- Adult rats - Both genders - 40 participants	- Electric choc. - Pain was assessed by the movement of the rats after stimulation.	- Rats who received placebo were able to withstand higher intensities of electric shocks on their tail before moving than rats having received OTR antagonists intra-cerebrally.
Paloyelis et al., 2016	- Double-blind - Placebo-controlled - Crossover	- Humans - Male - 13 participants	- Acute thermal pain (heat). - Pain was assessed by visual analogue scales.	- Patients who receive intranasal OT are more tolerant to laser-induced finger pain. - Patients who receive intranasal OT show changes in cortical activity.
Zunhammer et al., 2016	- Randomized - Double-blind - Placebo-control - Crossover	- Humans - Male - Right-handed - 18-50 years old - 36 participants	- Acute thermal pain (heat) while being shown emotional pictures (positive, neutral, negative). - Pain and pain unpleasantness were assessed by VASs. - Functional magnetic resonance imaging was performed at the same time.	- The positive emotional context decreases the perception of pain, while the negative emotional context increases it. - Oxytocin significantly strengthened both effects. - No direct analgesic effect of OT was evidenced.
Kessner et al., 2013	- Double-blind - Placebo-controlled	- Humans - Male - 20-38 years - 80 participants (5 excluded for technical failure)	- Acute thermal pain (heat) after application of a placebo ointment on one arm and a control on the other one. - Pain was assessed by visual analogue scales.	- Pain was reduced for the arm receiving the placebo ointment as compared to the control arm in both groups. - The placebo analgesic response was significantly higher in the OT group as compared to the saline group, although indicators of analgesia were identical for both groups.

hypothalamus and nucleus accumbens. In the amygdala, the peptide participates in the response to threats, stress, anxiety and nociceptive influx. Stress and anxiety are known to modulate the perception of pain (7).

The effect of OT on the amygdala provokes an inhibition of the hypothalamic-pituitary-adrenal axis. This axis controls the production of cortisol, referred to as the 'stress hormone'. The subsequent decrease in cortisol reduces the influence of anxiety on nociception, although the involved pathways are still unclear (7). Noteworthy, there is substantial interaction between the regions of the

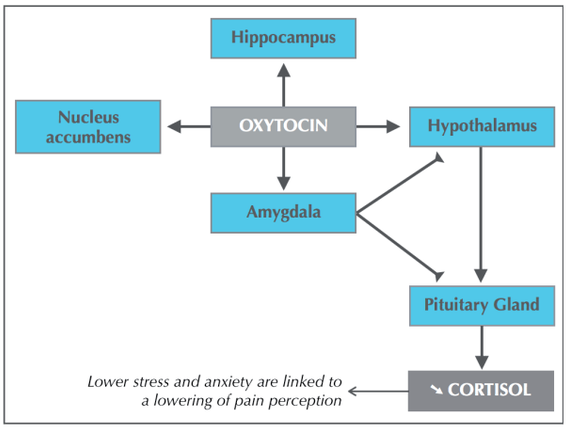

Fig. 1. — Central effect of OT.

brain controlling autonomic functions, and those responsible for managing nociception (21). Those two regions happen to be highly connected (7). Figure 1 outlines the central actions of OT.

3.4.3. Possible biological mechanisms of the oxytocin analgesic effect

3.4.3.1. Endogenous opioid system

In animal models, the OT analgesic effect has been linked to its interaction with the endogenous opioid system. Indeed, the administration of antagonists of the k-opioid and μ-opioid receptors partially blocks the OT analgesic effect (20).

The opioid system, located in the periaqueductal gray, activates a series of descending control pathways that prevents the spinal transmission of pain information. It is thought that OT stimulates the release of endogenous opioids. Indeed, the administration of the peptide in the periaqueductal gray provides anti-nociception, which can then be revoked by the administration of an opioid antagonist (20).

However, the mechanism of action of OT on the opioid system remains unclear. A possibility is that this effect is mediated by a specific neurotransmitter, the arginine vasopressin (AVP). Similarly to OT, AVP is synthesized in the magnocellular neurosecretory cells of the paraventricular and supraoptic nuclei of the hypothalamus. Both molecules are sent to the posterior lobe of the pituitary gland to be secreted into the bloodstream. AVP can also be secreted by PVN neurons that project to the periaqueductal gray (22).

3.4.3.2. Direct oxytocinergic projection on the posterior horn

The stimulation of the PVN, as well as OT administration activates presynaptic receptors located superficially in the dorsal horn. This effect in turn stimulates GABAergic interneurons. The latter are inhibitory neurons that block, at a presynaptic level, the nerve impulses from Aδ and C fibers to the WDR neuron of lamina I and II (20).

In addition, PVN stimulation reduces the extent of WDR neuronal response facilitation by the afferent Aδ and C fibers. This mechanism could also work at the post-synaptic level, by modulating the responses of postsynaptic neuronal projections of the posterior spinal column to a nociceptive influx (20).

3.4.3.3. Biopsychosocial model of pain

The biopsychosocial model of pain is an attempt to explain pain in a more accurate way, considering non-biological parameters. It was proposed in 1977 by Engel. In addition to neurophysiological elements, this model takes account of behavior and its influences. Oxytocin is a key factor in the coordination of behavior (20).

The Impact of Attention

Attention is a cognitive process that enhances the perception of useful stimuli, and diminishes the perception of non-useful ones. Focusing one's attention on a painful stimulus increases the sensation of pain, while focusing on something else helps decrease it (7).

The Placebo Effect

The placebo effect is a well-known and yet badly understood process affecting all medical disciplines. Its impact varies and depends on the patient confidence in the information he or she has been given, but, more importantly, is affected by the trust in the truthfulness of the information. Oxytocin being a key factor in the processes of trust, it is not surprising that studies have been able to establish that intranasal OT administration increases the placebo effect (23).

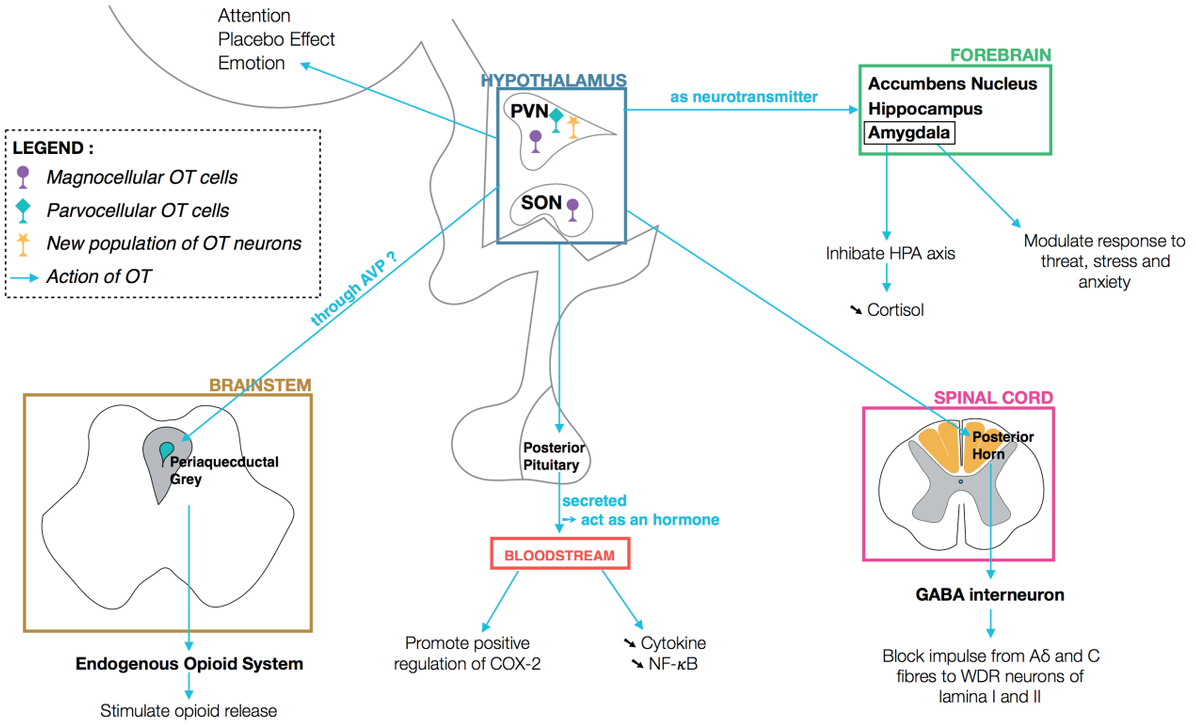

Fig. 2. — The effects of oxytocin on pain.

The Impact of Emotions

As mentioned above, OT has an anxiolytic effect while anxiety plays a role in pain perception (24).

The Impact of a Strong Social Support

Studies have shown that a strong social support reduces pain after surgery or labor. This could be linked to the effect of OT on contentment, calmness, and security (7) (Fig.2).

3.4.4. Potential use of synthetic agonist of oxytocin receptor in place of oxytocin

In 2011, De Bonis et al. preformed a prospective controlled clinical trial to compare the effectiveness of OT and carbetocin, a synthetic agonist of OTR, in reducing post-partum hemorrhage after a cesarean section in 110 women. The authors decided to also take account of the abdominal pain and use of analgesic medications after the procedure. Their results showed that women treated with carbetocin showed a lower level of abdominal pain and a decreased use of paracetamol during the post-operative period. In their publication, the authors postulate that this reduction may be due to a lower amount of medication received, and hence to different characteristics of the uterine contractions with carbetocin. Yet, it cannot be ruled out that a synthetic agonist of OTR such as carbetocin is actually amplifying the oxytocinergic effect on pain (25).

4. Newest research and what they bring to the understanding of the role of OT in the physiology of pain

A craze for studying the relationship between the OT system and analgesia has emerged recently. The idea is to find additional pharmacological means to control pain, and prevent it from becoming chronic.

4.1. Evolution of the physiological model

4.1.1. Highlighting the existence of an oxytocin analgesic activity

Studies increasingly seek to document a link between the OT system and analgesia. Up to now, the assessment of pain relied on subjective scales or on the variation of hormonal levels such as the cortisol plasma concentration.

Oxytocin could likely reduce the pain threshold. Rats that received a placebo can withstand higher intensities of electric shocks on their tail before moving than rats having received OTR antagonists intra-cerebrally (26).

Patients who receive intranasal OT are more tolerant to laser-induced finger pain, which is specifically mediated by afferent Aδ and C fibers. Furthermore, changes in electrophysiological patterns suggesting a change in cortical activity can be demonstrated in patients who received OT, while no change is

detected in placebo-treated patients. These results suggest that OT modulates the neural processes responsible for painful perception (27).

In another study, Rash et al. designed a placebo-controlled, double-blind, within-participant crossover investigation studying the effect of synthetic intranasal OT on acute pain sensitivity. Forty healthy participants, male and female, were asked to immerge one of their hands into cold 2C° water and to evaluate the threshold and intensity of the pain, as well as the unpleasantness. The patients were also asked to complete the "Short-form McGill Pain Questionnaire 2" which assesses neuropathic and non-neuropathic pain. One group was given 40 UI of intranasal OT, while the other was given placebo (28). The results showed a decrease in pain intensity and pain unpleasantness, an increase in pain threshold for the OT group, as compared to the placebo group. The pain as assessed by the Short-Form McGill Pain Questionnaire-2 was also significantly lower (28), but the difference between the two groups was small. Of note, this study has a few limitations that do not permit a generalized use to a wider population.

It is also worth noting that the main effect of intranasal OT in the Rash et al. study was on the descriptors of the neuropathic subscale of the Short-Form McGill Pain Questionnaire-2 (28).

Zunhammer et al. investigated how intranasal OT effects pain perception using a randomized, placebo-controlled, double-blind, crossover trial. With the help of 36 healthy male volunteers aged 18 to 50 years, the team determined a thermal threshold of each participant 40 minutes after they self-administered an intranasal spray containing either OT or placebo. Thereafter, a 14 successive seconds thermal stimulation was applied while participants were undergoing functional magnetic resonance imaging. After each stimulation, the participants were asked to rate pain and unpleasantness using visual analogue scales. Functional magnetic resonance imaging analysis was set to assess changes in whole brain activity, as well as in the amygdala (29). This trial showed a compelling although modest effect of OT on heat intensity ratings ($p = 0.046$). This action was linked with a small but significant decline in bilateral amygdala activity. It was not possible to prove any effect of OT on the rest of the brain, and it is worth noting that neither effect was proportional to temperature, leading the authors to the conclusion that an anti-nociceptive effect of OT could not be demonstrated. Indeed, OT affected the intensity of perceived heat, not its unpleasantness (29)

4.1.3. Discovery of a new population of oxytocin neurons

Recently, Eliava et al. have described the existence of a new population of approximately 30 parvocellular neurons in the PVN of the hypothalamus in animal models. These cells project onto both hypothalamic SON and the deep layers of the spinal cord (12).

Until now, the established 'dogma' was an absence of communication between the two types of oxytocinergic neurons, namely the parvocellular and magnocellular neurons. If confirmed, the discovery made by Elivia and colleagues would establish that a group of neurons connecting both types exists, and that these neurons are oxytocinergic (12).

The axons of this new population seem to extend to the deep layers of the spinal cord, and are connected with neurons expressing neurokinin receptors (NK1R) and OTR. Those are described as Wide Dynamic Range (WDR) neurons, which are activated by nociceptive influxes. The administration of capsaicin on the skin increases c-Fos expression in those neurons, a marker of neuronal activity. The release of OT by this new population of neurons would inhibit the WDR neurons, and therefore the downstream transmission of the nociceptive influx (12).

Consequently, OT modulates the nociceptive influx through two routes. One way is direct, fast, and allows the inhibition of WDR neurons in the spinal cord. The second is indirect, slower, and provokes the release of OT by SON neurons in the blood stream (12). The inhibition of the newly described population has no impact on the transmission of thermal and mechanical information (12).

Interestingly, the newly described population is a very restricted one, counting only about thirty neurons. In animal models, its activation modulates the inflammatory pain only, and has no impact on neuropathic pain. Such properties could be used in the development of future analgesic medications (12).

4.2. Evolution of the biopsychosial model

4.2.1 Oxytocin-related modulation of pain in relation with emotional changes

Intra-nasal OT administration modifies the impact of the emotional background on pain. In a randomized double-blind placebo-controlled crossover study, subjects were given intranasal OT or placebo. Thereafter, they underwent functional magnetic resonance imaging while being shown

several pictures from the International Affective Picture System (IAPS). The IAPS is a set of standardized, normative emotional stimuli for experimental investigations. Each group was submitted to heat stimuli (non-noxious, 44.7°C and noxious, 47.1°C) and emotional pictures viewing (positive, neutral, negative). Baseline temperature (35.0°C) and scrambled picture conditions were assessed as additional control conditions.

After a 3 to 6 seconds of rest, the participants were asked to evaluate the perceived 'intensity' and 'unpleasantness' on two consecutive visual analogue scales, with the following endpoints: 'no stimulus perceived'/'not unpleasant' and 'maximally intense'/'maximally unpleasant', respectively. The control group and OT group were then inverted after a washout period of at least 7 days to minimize the risk of carry-over effects.

The results of this study show that, for both medication conditions, the positive emotional context decreases the perception of pain, while the negative emotional context increases it. However, in both case, OT significantly strengthens those effects. Unfortunately, no between-group connectivity differences were objectified by functional neuroimaging, and no direct analgesic effect of OT was shown. The authors suggest this may be because noxious stimuli were assessed after performing functional imaging, thus after a longer interval than in other studies (30).

4.2.2 Placebo effect on pain: action of oxytocin

The placebo response is best depicted as a complex psycho-neurobiological process. It hinges on several central and peripheral physiological mechanisms modulating pain perception, clinical symptoms, and largely modifies the response to active analgesic medications (31).

Receiving a placebo activates several brain areas, including the anterior rostral cingulate, the dorsal lateral prefrontal cortex, the orbital frontal cortex, the insula, the nucleus accumbens, the tonsils, the medial thalamus, and the periaqueductal gray matter. This occurs through a change in dopaminergic and opioid neurotransmission. These processes are less active in patients suffering from chronic pain (31).

It has been shown that the implementation of emotional and cognitive processes during the administration of an otherwise inactive product is able, through its placebo effect, to modulate several physiological processes, although with large inter-individual variability. Factors influencing this variability are of genetic, anatomical and neuropsychological nature (32).

Beyond its role in pain perception, the placebo effect also affects the response to stress, changes autonomic and endocrine functions, and mood or cognitive processes (32). Oxytocin increases the placebo effect on pain perception through a different mechanism than the one involved in its analgesic effect. In addition to decreasing the nociceptive influx of information, OT decreases its cognitive perception (33). Though, the involved mechanisms are still poorly understood. An attractive hypothesis is that OT favors the trust effect (33).

Further research is warranted in this field, the main difficulty being to design studies that respect ethics, and that lead to conclusions being usable in clinical practice.

5. Conclusion

Even though pain is a frequent and feared symptom, many dark areas remain in the understanding of its physiology. The major impact of pain on patients' quality of life, particularly in chronic pain, oncological pain, or more complex pain syndromes like fibromyalgia, justifies continued research on new pharmacological tools to reinforce the current therapeutic arsenal.

Among novel therapeutic roads, OT is a promising one since several studies have evidenced its significant analgesic effect. However, despite scientific infatuation and growing number of published studies, no consensus on the exact mechanism of OT has been reached yet. Its mode of action is more than probably multimodal.

Among the action of OT on pain, inhibition of the nerve impulse is the most studied. We know that OT-producing neurons in the hypothalamus have projections in several areas of the central nervous system. They have an inhibitory action on the spinal cord, act on distinct part of the forebrain and even release neuro-hypophyseal OT as a hormone in the peripheral blood stream. OT is as much a neurotransmitter as a hormone. OT modulates the cognitive perception of pain and modulates the cortisol plasma level. It also influences trust, and the placebo effect.

Unfortunately, one of the obstacles on the road to a clinical use of OT is its peptide nature. A peptide oral intake exposes the peptide to digestion, and absence of absorption, and thus loss of function by denaturation. The intranasal administration could be a solution. However, this brings new concern such as the control of the given amount, and would still generate difficulties in passing through the blood-brain barrier. It might be wise to consider

a specific galenic formulation. Such a compound could be useful for research as well as clinical use in humans. Such research exists, notably in the context of oncological diseases. Currently, it seems that the solution might come from the use of nanoparticles or nanogel, liposome vehicles, intra-thecal injection through the cribriform plate, delivery by a modified cellular agent or a modification of the target molecule (34). Obviously intravenous infusion and intramuscular injection are always an option. However, this mode of administration brings many disadvantages and constraints to patients. It also makes their use as chronic treatments impractical.

All those advances in the understanding of the multimodal action of OT offer new therapeutic possibilities. One could also reside in the modulation of the activity of the newly discovered population of oxytocinergic neurons. This might allow promoting the inhibitory effect of OT on inflammatory pain. Oxytocin could also be used to potentiate the analgesic medications already in use by the patient, to increase or maintain their efficacy while using lower doses.

Finally, one of the remaining essential objectives of future research is to define the target population who would benefit from oxytocin treatment. In this respect, several points are to be kept in mind. First, it is clear that OT will not be effective at relieving all types of pain. It would therefore be helpful to investigate its efficacy in treating neuropathic, inflammatory, and other types of pain separately. Second, the vast majority of already published studies were performed in healthy volunteers being exposed to acute pain. Chronic pain has been poorly studied in that respect so far. Third, the effect of OT is altered by the emotional context and the mood of participants, and by seemingly intrinsic characteristics of patients such as a pro-social or selfish behavior. It would be beneficial to include such variables in forthcoming trials. For example, it would be interesting to assess the role of OT in the perception of pain in anxious or depressed subjects, insofar as those features are common in patients suffering from chronic pain.

References

1. Loeser J. D., Treede R. D., *The Kyoto protocol of IASP basic pain terminology*, Pain, **137**; 473-77, 2008.
2. Szukiewicz D., Bilska, A., Mittal T. K., Stangret A., Wejman, J., Szewczyk G., Pylzak M,. Zamlynski J., *Myometrial contractility influences oxytocin receptor (OXTR) expression in term trophoblast cells obtained from the maternal surface of the human placenta*, BMC Pregnancy and Childbirth, **15**, 1220, 2015.
3. Demirel G., Guler H., *The Effect of Uterine and Nipple Stimulation on Induction With Oxytocin and the Labor Process*, Worldviews Evid Based Nurs., **12** (5), 273–80, 2005.
4. Basbaum A. I., Jessel, T. M., *The perception of pain*, Principles of Neuroscience, 4th ed., 472-491, New York, McGraw-Hill, 2000.
5. Purves D., Augustine G. J., Fitzpatrick W. C., Hall W. C., LaMantia A.-S., McNamara J.O., White, L. E., *The Somatic Sensory System*, Neuroscience, 4th ed., 207-30, Sunderland, Sinauer Associates, 2008.
6. .Almeida T. F., Roizenblatt S., Tufik S., *Afferent pain pathways: a neuroanatomical review*, Brain Res., **1000** (1-2), 40-56, 2004.
7. Tracy L. M., Georgiou-Karistianis N., Gibson, S. J., Giummarra M. J., *Oxytocin and the modulation of pain experience : Implications for chronic pain management*, Neurosci Biobehav Rev., **0** , 54-67, 2015.
8. Martin J. H., *Somatic Sensation: Spinal Systems for Pain, Temperature, and Itch*, Neuroanatomy : text and atlas, 4th ed., 107-26, New York, McGraw-Hill, 2012.
9. Reddi D., Curran N., Stephens R., *An introduction to pain pathways and mechanisms*, Br J Hosp Med., **74** (Suppl 12), 188-91, 2013.
10. Heinricher M. M., Tavares I., Leith J. L., Lumb B. M., *Descending control of nociception: specificity, recruitment and plasticity*, Brain Res Rev., **60** (1), 214-25, 2009.
11. Know M., Altin M., Duenas H., Alev L., *The role of descending inhibitory pathways on chronic pain modulation and clinical implications*, Pain Practice, **14** (7), 656-67, 2014.
12. Eliava M., Melchior M., Knobloch-Bollmann H. K., Wahis J., da Silva Gouveia M., Tang Y., Ciobanu A. C., Triana del Rio R., Roth L. C., Althammer F., Chavant V., Goumon Y., Gruber T., Petit-Demouliere N., Busnelli M., Chini B., Tan L. L., Mitre M., Froemke R. C., Chao M. V., Giese G., Sprengel R., Kuner R., Poisbeau P., Seeburg P. H., Stoop R., Charlet A., Grinevich V., *A New Population of Parvocellular Oxytocin Neurons Controlling Magnocellular Neuron Activity and Inflammatory Pain Processing* , Neuron , **89** (6) , 1291-1304 , 2016.
13. Gimpl G., Fahrenholz F., *The Oxytocin Receptor System: Structure, Function, and Regulation*, Physiol Rev., **81** (2), 629-83, 2001.
14. Kim S. H., MacIntyre D. A., Hanyaloglu A. C., Blanks A. M., Thornton S., Bennett S. R., Terzidou V., *The oxytocin receptor antagonist, Atosiban, activates pro-inflammatory pathways in human amnion via G(α) signalling* , Mol Ceil Endocrinol , **420**, 11-23, 2016.
15. Terzidou V., Blanks A. M., Kim S. H., Thornton S., Bernett P. R., *Labor and Inflammation Increase the Expression of Oxytocin Receptor in Human Amnion*, Biol reprod., **84** (3), 546-552, 2011.
16. Chen D., Zhao J., Wang H., An N., Zhou Y., Fan J., Luo J., Su W., Liu C., Li J., *Oxytocin evokes a pulsatile PGE2 release from ileum mucosa and is required for repair of intestinal epithelium after injury*, Sci Rep , **5**, 11731, 2015.
17. Jankowski M., Bissonauth V., Gao L., Gangal M., Wang D., Danalache B., Wang Y., Stoyanova E., Cloutier G., Blaise, G., *Anti-inflammatory effect of oxytocin in rat myocardial infarction*, Basic Res Cardiol, **105** (2), 205-18, 2010.
18. Barman S., Barrett K., Boitano S., Brooks H., *Hypothalamic Regulation of Hormonal Functions*, Ganong's Review of Medical Physiology, 23rd ed., 289-300, New York, Mc Graw Hill, 2009.
19. Crowley W. R., *Neuroendocrine Regulation of Lactation and Milk Production*, Compr Physiol, **5** (1), 225-91, 2015.
20. Rash J. A., Aguirre-Camacho A., Campbell, T. S., *Oxytocin and Pain : A Systematic Review and Synthesis of Findings*, Clin J Pain, **30** (5), 453–62, 2014.
21. Benarroch E. E., *Pain-autonomic interactions*, Neurol Sci,

27 (Suppl 2), 130-3, 2006.
22. Meyer-Lindenberg A., Domes G., Kirsch P., Heinrichs M., *Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine*, Nat Rev Neurosci, **12** (9), 524-38, 2011.
23. Keefe F. J., Lumley M., Anderson T., Lynch T., Carson K. L., *Pain and emotion: New research directions*, J Clin Psychol, **57** (4), 587-607, 2001.
24. Crock L. W., Kolber B. J., Morgan C. D., Sadler K. E., Vogt S. K., Bruchas M. R., Gereau R.W., *Central Amygdala Metabotropic Glutamate Receptor 5 in the Modulation of Visceral Pain*, J Neurosci, **32** (41), 14217-26, 2012.
25. De Bonis M., Torricelli M., Leoni L., Berti P., Ciani V., Puzzutiello R., Severi F. M., Petraglia F., *Carbetocin versus oxytocin after caesarean section: similar efficacy but reduced pain perception in women with high risk of postpartum haemorrhage*, J Matern Fetal Neonatal Med., **25** (6), 732-5, Jun 2012.
26. Futagamia H., Sakumab Y., Kondo Y., *Oxytocin mediates copulation-induced hypoalgesia of male rats*, Neurosci Leti, **618**, 122-6, 2016.
27. Paloyelis,Y., Krah C., Maltezos S., Williams S. C., Howard M. A., Fotopoulou A., *The Analgesic Effect of Oxytocin in Humans: A Double-Blind, Placebo- Controlled Cross-Over Study Using Laser-Evoked Potentials*, J Neuroendocrinol, **28** (4), 2016.
28. Rash J. A., Campbell T. S., *The Effect of Intranasal Oxytocin Administration on Acute Cold Pressor Pain: A Placebo-Controlled, Double-Blind, Within-Participants Crossover Investigation*, Psychosom Med., **76** (6), 422-9, Jul-Aug 2014.
29. Zunhammer M., Geis S., Busch V., Greenlee M. W., Eichhammer P., *Effects of Intranasal Oxytocin on Thermal Pain in Healthy Men: A Randomized Functional Magnetic Resonance Imaging Study*, Psychosom Med., **77** (2), 156-66, Feb-Mar 2015.
30. Zunhammer M., Geis S., Busch V., Eichhammer P., Greenlee M. W., *Pain modulation by intranasal oxytocin and emotional picture viewing — a randomized double-blind fMRI study*, Sci rep, **6**, 31606, 2016.
31. Colloca L., Klinger R., Flor H., Bingel U., *Placebo analgesia: Psychological and neurobiological mechanisms*, Pain, **154** (4), 511-14, 2013.
32. Zubieta J.-K., Stohler C. S., *Neurobiological Mechanisms of Placebo Responses*, Ann N Y Acad Sci., **1156**, 198-210, 2009.
33. Kessner S., Sprenger C., Wrobel N., Wiech K., Bingel U., *Effect of Oxytocin on Placebo Analgesia: A Randomized Study*, Jam a, **310** (16), 1733-735, 2013.
34. Yi X., Manickam D. S., Brynskikh A., Kabanov, A. V., *Agile Delivery of Protein Therapeutics to CNS*, J Control Release, **28**, 637–63, 2014.
35. Colloca L., Klinger R., Flor H., Bingel U., *Placebo analgesia: Psychological and neurobiological mechanisms*, Pain, **154** (4), 511-14, 2013.