# Pain and the endogenous antinociceptive neuronal system: physiologic role of oxytocin

Dor e sistema neuronal antinociceptível endógeno: papel fisiológico da ocitocina

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#### ABSTRACT

The unpleasant pain sensation is a sub-modality of somatic sensation that exerts fundamental warning and protective functions. Pain is the more frequent complain in a neurological outpatient clinic. In a series of 200 consecutive patients in a neurological outpatient clinic, 51% of them complained of some type of pain, the more frequents were headache and carpal tunnel syndrome. The role of oxytocin in pain regulation was reviewed. It seems that oxytocin may play a major role in the mechanism of pain regulation, particularly through the endogenous antinociceptive neuronal system.

Keywords: Pain; Headache; Oxytocin; Carpal tunnel syndrome

### RESUMO

A sensação desagradável de dor é uma modalidade sensitivosomática que serve como alarme e exerce funções de proteção. A dor foi a queixa mais frequente em um ambulatório neurológico. Em uma série de 200 pacientes consecutivos em um ambulatório de neurologia, 51% deles se queixaram de algum tipo de dor, mais frequentemente cefaleia e síndrome do túnel do carpo. O papel da ocitocina na regulação da dor foi revisado. Parece que a oxitocina pode desempenhar uma função importante no mecanismo de regulação da dor, particularmente através do sistema neuronal antinociceptivo.

**Palavras-chave:** Dor; Cefaleia; Ocitocina; Síndrome do túnel do carpo

### INTRODUCTION

The unpleasant pain sensation (pricking, aching, burning, stinging, or soreness) is a sub-modality of somatic sensation that exerts fundamental warning and protective functions.

Under physiologic conditions, pain sensation are mediated by two primary afferent neurons: 1) the smalldiameter nonmyelinated C-fibers and 2) thinly myelinated  $A\delta$ -fibers, both referred to as nociceptors. Nociceptors respond to mechanical, thermal, and chemical forms of energy. Polymodal nociceptors are activated by thermal, chemical and high-intensity mechanical stimuli. The  $A\delta$ fibers are glutamatergic neurons that transmitter the fast sharp pain (5-30 m/s). The C-fibers transmitter the slow dull pain. Substance P is released from C fibers, and may enhance and prolong the actions of glutamate.<sup>(1)</sup>

In human, rapid immersion of a finger in a hot water bath (57° C) causes at onset a stinging pain after a time interval of 0.84 s on average. This is followed by a second wave of a burning pain after 2.1 s. The latency between the two forms of pain waves decrease as the stimulus moves up the limbs toward the trunk, and at the trunk level it is not feasible to obtain a double pain sequence. This double pain experience is triggered by fast rising stimulus (electric shock, pinprick, or heating pulse). Interestingly, opioid substances appear to affect the second pain component more than the first one.<sup>(2,3)</sup> On the other hand, the first pain is differentially blocked by compression-ischemia.<sup>(1)</sup>

# FREQUENCY OF PAIN COMPLAINS IN CLINICAL PRACTICES

Pain is the more frequent complain in a neurological outpatient clinic. Table 1 illustrates the principal diagnoses identified in a series of 200 consecutive patients in a neurological outpatient clinic of one of the authors (MMV, Hospital Santa Helena, 1993).

Table 1 - Principal diagnoses identified in a series of 200   consecutive patients		
Diagnosis	n	%
Pain		
Headache	77	38.5
Carpal tunnel syndrome	13	6.5
Disc hernia or back pain	10	5.0
Trigeminal neuralgia	2	1.0
All	102	51.0
Epileptic seizure	30	15.0
Stroke	25	12.5
Head trauma	12	6.0
Psychiatric conditions	13	5.5
Vertigo	11	5.5
Sincope	7	3.5
Bell´s palsy	4	2.0
Myelophaty	4	2.0
Other	12	6.0

### OXYTOCIN

In 1982, Berkowitz and Sherman<sup>(4)</sup> reported that peripheral injection of oxytocin (OT) does not have any analgesic effects. On the other hand, Caldwell et al.<sup>(5)</sup> demonstrated that intracisternal injection of OT in mice induced analgesia. Kordower and Bodnar<sup>(6)</sup> showed in rats that injection of OT into the lateral ventricle also caused analgesia. Besides, OT levels in plasma and cerebrospinal fluid (CSF) increased after 30-min exposition to different non-noxious sensory stimulation, which were concomitant with the development of analgesia.<sup>(7)</sup> The OT antagonist 1-deamino-2-D-Tyr-(OEt)-4-Thr-8-Ornoxytocin (1 mg kg<sup>-1</sup>) reversed the prolongation of the latency observed in the TFT after exposition to such stimuli. The OT-ANT treatment by itself did not change significantly the latency, although it reduced the analgesia induced by OT (1 mg  $kg^{-1}$ ).

On the contrary, Xu and Wiesenfeld<sup>(8)</sup> interpreted the increase in the latency response in the hot-plate test in rats as a result of sedative and vasoconstrictive effects of OT, rather that an analgesic phenomenon. Additionally, they also reported that OT-ANT (1 mg/kg, i.p.) did not influence response latency to heat pain sensitivity in rats.

Yang<sup>(9)</sup> investigated the actions of OT on the analgesia in both rat and human being. In humans, acute and chronic low back pain causes significant change of OT concentration within CSF and plasma. Oxytocin administration alleviated low back pain. In rats, OT had a dose-related analgesic effect. The use of the OT-ANT [d(CH2)5, Tyr(Me)2, Orn8]-vasotocin and naloxone both reversed the analgesia induced by OT. Oxytocin also increased the levels of endogenous opioide peptides (EOP) (endorphin, encephalin, and dynorphin) in the spinal cord, whereas OT-ANT caused a decline.

As clinical use, OT, vasopressin and somatostatin were injected into the cerebral ventricle of a ill cancer patient a diffuse mesothelioma suffering intractable continuous and incapacitating thoracic pain. Oxytocin induced a strong analgesia (by 88%) lasting 77 minutes. Somatostatin-14 reduced pain by 90% for 48 min and arginine vasopressin reduced pain by 95% for 75 min.<sup>(10)</sup>

Furthermore, acupuncture caused changes in OT content in many regions of rat brain, suggesting that OT might modulate acupuncture-induced analgesia.<sup>(11)</sup>

Liu<sup>(12)</sup> studied the effects of intracerebroventricular (icv) injections of OT, naloxone, or CCK-8 on electroacupuncture (EA) analgesia in rats. They concluded that the role of OT in EA was not entirely dependent upon the EOP.

Song and coworkers<sup>(13)</sup> studied the possible involvement of EOP on OT analgesic actions, by using icv injection of anti-opioid peptide sera in rats which OT induced an increase of EA analgesia. Injection of antibeta-endorphin serum alone attenuated EA analgesia. Although, the same antiserum treatment, prior to intraventricular injection of OT, could not block the enhancement of EA analgesia by OT. The antidynorphin A1-13 serum alone could also reduce the EA analgesia and when the antiserum was given prior to injection of OT a potentiation of the EA analgesia induced by OT was found. No effect was observed with the administration of either anti-methionine enkephalin serum or the anti-leucine enkephalin. They concluded that the enhancement of EA analgesia by OT does not depend upon the brain EOP. In a review Richard and colleagues<sup>(14)</sup> concluded that "in no case does OT-induced analgesia appear to be opiate dependent". Interestingly, they also described that fragment of the OT molecule, oxytocin-,<sup>(7-9)</sup> can under certain circumstances act as an opioid antagonist.

Urnäs-Moberg and coworkers<sup>(15)</sup> postulated that low doses of ethanol could cause anti-nociceptive effects via an oxytocinergic mechanism. Administration of ethanol also stimulated the elevation in plasma OT levels and the use of OT-ANT reduced the increased pain threshold produced by ethanol. However, Urnäs-Moberg and colleagues<sup>(15)</sup> made a statement that "opioid mechanisms do not seem to be involved in the oxytocin induced effects on pain threshold, since the effects are not blocked by naloxone (Lundeberg, personal communication)." The results of the mentioned experiment was not published neither the doses or the study design, as far as we know. Looking back the results published by Urnäs-Moberg and colleagues,<sup>(16)</sup> the latency in the tail flick test in the presence of OT-ANT was higher with OT, suggesting some degree of analgesia exerted by OT throw some other receptor subtype not blocked by the OT-ANT used.

Lundeberg and colleagues<sup>(17)</sup> suggested a central action of OT since after intrathecal injection of this neuropeptide (1  $\mu$ g kg<sup>-1</sup>) induced a delay in the reaction time in the paw pressure test.

Parturition and vaginal dilatation both cause enhancement in plasma OT concentration and increase of the pain threshold, and since during the labour is of paramount importance the action of OT over the uterus, provoking increment in muscle contraction, an event which would trigger pain sensation, it would be logical that the same peptide would exert a dual physiological function: analgesia and uterus contraction during labor.<sup>(18)</sup>

Under physiologic conditions OT is released from nerve terminals of the neurophypophisis and median eminence into the blood, into the cerebrospinal fluid (CSF) or into specific regions of the CNS. The half-life of plasma OT is 1-2 min. At CSF OT is present with concentrations raging from 10 to 50 fmol/ml, which half-life is 28 min. At a physiologic level the OT present in the sytemic blood does not penetrete into the CSF or into the brain. The OT perikarya are presented largely in the magnocellular nuclei, although fibers are widely distributed in CNS (dorso medial hypothalamic nucleus, thalamic nuclei, limbic system, mesencefalic central nucleus, substancia nigra, locus coeruleus, raphe nucleus, nucleus of the solitary tract, dorsal motor nucleus of the vagus nerve, and at the spinal cord ending particularly in layers I, II, and X of the gray matter). In guinea pigs only 2%-3% of the ip administrated OT were detected in brain. Hence, the necessity of high doses of OT, if injected systemically, to induce analgesia, in the case of considering a central site of action.<sup>(19)</sup> It was reported that the neurohypophyseal hormones or their fragments are transported under normal conditions from blood to brain.

Lesions of the PVN had no effect on nociception. In the spinal cord the OT fibers may originate from PVN and C-fibers of the dorsal root ganglia.

Modification of the response latencies to the jump test (hot plate) and TFT at different temperatures were encountered with OT anti-serum icv injections: no changes at high temperatures, decrease in the latencies at moderate temperature, and increase the latencies at low temperature (analgesia). Similar results were observed with other antisera, such as against vasopressin, met-enkephalin, and beta-endorphin. Naloxone does not cause pain, but may enhance the perception of pain.<sup>(20)</sup>

Thermal nociceptores are activated by extreme temperatures (>45° C or <5° C). The mechano- and heat-responsive C-fibers present heat thresholds raging from 40° and 50° C in the glabrous and hairy skin of mammals.<sup>1</sup> In human heat pain thresholds range from 41° to 49° C.<sup>(21)</sup>

In addition, chronic treatment with OT had no effect on analgesia.  $\ensuremath{^{(22)}}$ 

Analgesia may be caused by different type of stress,<sup>(23)</sup> in some of them the analgesia is mediated by EOP,<sup>(24)</sup> other are unaffected by previous opioid receptor blockade or through a nonopioid mechanism.

Recent evidence from our Laboratory suggests that OT leads to an analgesic state, an effect that was abolished with the blockade of opioid receptor by naloxone, in mice. This indicated that OT might cause analgesia throw the involvement of EOP.<sup>(25)</sup>

Administration of OT (icv) or antioxytocin serum in rats modified the pain threshold to electroacupuncture analgesia, evaluated by potassium iontophoresis induced tail flick. The OT when injected icv elevated both the pain threshold and electroacupuncture analgesia. On contrary, the antiserum reduced the analgesia induced by electroacupuncture.<sup>(26)</sup>

The concentration of OT in CSF of dog with spinal cord compression was higher than what found in control dogs, suggesting that during painful conditions OT is released into CSF or other CNS sites to attenuate the animal unpleasant, hurtful situation.<sup>(27)</sup>

In humans, intrathecal injection of oxytocin is effective in treating low back pain for up to 5 hours.<sup>(28)</sup> Interestedly, it was described an enhanced hind paw withdrawal latency in response to nociceptive heat after OT subcutaneous administration in rat, an effect also found in the untreated cage mates of an OT-treated animal. This analgesic action of OT was canceled in OT-ANT-injected cage mates. Suggesting that cage mates develop anti-nociception mediated via olfactory tract, which is induced throw, an oxytocinergic mechanism.<sup>(29)</sup>

### HEADACHE AND OXYTOCIN

Phillips and colleagues<sup>(30)</sup> reported that acute migraine headache attack can be relieved by intravenous oxytocin. On the other hand, a few authors reported that there is a lactational headache in the literature attributed to OT surges in association with the milk-ejection reflex.<sup>(31,32)</sup> A case of a 26-year-old woman suffering from brief attacks of headache that happened on every occasion of nursing was reported by Askmark and Lundberg.<sup>(32)</sup> However, a case was described when the apparent headache trigger was breast overfulness, and not the oxytocin surge, occurring when the infant was sleeping through the night or after a missed, delayed, or partial feed. In this case, interestingly, the headaches were alleviated by putting the baby to the breast (activation of the milk-ejection reflex).<sup>(33)</sup>

## CONCLUSION

In conclusion, pain is a frequent complain observed in a neurological outpatient clinic. In this report, 51% of the patients complained of some type of pain, the more frequents were headache and carpal tunnel syndrome. Oxytocin plays a major role in the mechanism of pain regulation, particularly through the endogenous antinociceptive neuronal system.

### REFERENCES

- Handwerker HO, Kobal G. Psychophysiology of experimentally induced pain. Physiol. Rev. 1993;73(3):639-71.
- Price DD, McHaffie JG. Effects of heterotopic conditioning stimuli on first and second pain: a psychophysical evaluation in human. Pain. 1988; 34(3):245-252. Comment in: Pain. 1989;38(2): 231-4.
- Price DD, Von der Gruen A, Miller J, Rafii A, Price C. A psychophysical analysis of morphine analgesia. Pain 1985;22(3): 261-9.

- Caldwell JD, Mason GA, Stanley DA, Jerdack G, Hruby VJ, Hill P, et al. Effects of nonapeptide antagonist on oxytocin and argininevasopressin-induced analgesia in mice. Regul Pept. 1987;18(3-4):233-4.
- Kordower JH, Bodnar RJ. Vasopressin analgesia: specificity of action and non-opioid effects. Peptides. 1984;5(4):747-56.
- Uvnäs-Moberg K, Bruzelius G, Alster P, Lundeberg T. The antinociceptive effect of non-noxious sensory stimulation is mediated partly through oxytocinergic mechanisms. Acta Physiol Scand. 1993;149(2):199-204.
- 8. Xu XJ, Wiesenfeld HZ. Is systemically administered oxytocin an analgesic in rats? Pain. 1994;57(2):193-6.
- Yang J. Intrathecal administration of oxytocin induces analgesia in low back pain involving the endogenous opiate peptide system. Spine. 1994;19(8):867-71.
- Madrazo I, Franco-Bourland RE, León-Meza VM, Mena I. Intraventricular somatostatin-14, arginine vasopressin, and oxytocin: analgesic effect in a patient with intractable cancer pain. Appl Neurophysiol. 1987;50(1-6):427-31.
- Jun Y. [Effect of acupuncture on the contents of vasopressin and oxytocin in the rat]. Zhen Ci Yan Jiu. 1992;17(3):217-20
- Liu W, Song C, Wang C, Lin B. [Effect of oxytocin and cholecystokinin octapeptide (CCK-8) on electroacupuncture (EA) analgesia]. Zhen Ci Yan Jiu. 1992;17(2):136-8
- Song CY, Liu WY, Gu XY, Lin BC. Effect of anti-opioid peptide sera on oxytocin-induced enhancement of electroacupuncture analgesia. Sheng Li Xue Bao. 1993;45(3):231-6
- Richard P, Moos F, Freund-Mercier MJ. Central effects of oxytocin. Phisiol Rev. 1991;71(2):331-70.
- Uvnäs-Moberg K, Lundeberg T, Bruzelius G, Alster P. Low doses of ethanol may induce anti-nociceptive effects via an oxytocinergic mechanism. Acta Physiol Scand. 1993;149(1):117-8.
- Uvnäs-Moberg K, Bruzelius G, Alster P, Bileviciute I, Lunderberg T. Oxytocin increases and a specific oxytocin antagonist decreases pain threshold in male rats. Acta Physiol Scand. 1992; 144(4):487-8.
- Lundeberg T, Meister B, Björkstrand E, Uvnäs-Moberg K. Oxytocin reverses galanin-induced hyperalgesia in rats. Brain Res. 1993;608(2):181-5.
- Crowley WR, Rodriguez-Sierra JF, Komisaruk BR. Analgesia induced by vaginal stimulation in rats is apparently independent of a morphinesensitive process. Psychopharmacology. 1977; 54(3):223-5.
- Robinson IC. Neurohypophysial peptides in cerebrospinal fluid. Prog Brain Res. 1983;60:129-45.
- Buchsbaum MS, Davis GC, Naber D, Pickar D. Pain enhances naloxone-induced hyperalgesia in humans as assessed by somatosensory evoked potentials. Psychopharmacology. 1983; 79(2-3):99-103.
- LaMotte RH, Campbell JN. Comparison of responses of warm and nociceptive C-fiber afferents in monkey with human judgements of thermal pain. J Neurophysiol. 1978;41(2):509-28.
- Witt DM, Winslow JT, Insel TR. Enhanced social interactions in rats following chronic, centrally infused oxytocin. Pharmacol Biochem Behav. 1992;43(3):855-61.

- 23. Amit Z, Galina ZH. Stress-induced analgesia: Adaptive pain suppression. Physiol Rev. 1986;66(4):1091-120.
- Valença MM, Dias MH, Araújo AMB, Lins Filho RL, Valença LPAA. Analgesia and immobilization and surgical stresses. An Fac Med UFPE. 1999;44(2):97-101
- 25. Lins Filho RLM. Ocitocina e sistema opióide endógeno: evidência de uma ação analgésica em condições fisiológicas ou durante analgesia induzida pelo estresse de imobilização. Dissertação de Mestrado, Universidade Federal de Pernambuco, 2001.
- Song CY, Liu WY, Yang J, Lin BC, Zhu HN. [The role of central oxytocin in electroacupuncture analgesia]. Sheng Li Xue Bao. 1990;42(2):169-74.
- 27. Brown DC, Perkowski S. Oxytocin content of the cerebrospinal fluid of dogs and its relationship to pain induced by spinal cord compression. Vet Surg. 1998;27(6):607-11.
- Yang J. Intrathecal administration of oxytocin induces analgesia in low back pain involving the endogenous opiate peptide system. Spine (Phila Pa 1976). 1994;19(8):867-71.
- Agren G, Uvnas-Moberg K, Lundeberg T.Olfactory cues from an oxytocin-injected male rat can induce anti-nociception in its cagemates. Neuroreport. 1997;8(14):3073-6.
- Phillips WJ, Ostrovsky O, Galli RL, Dickey S. Relief of acute migraine headache with intravenous oxytocin: report of two cases. J Pain Palliat Care Pharmacother. 2006;20(3):25-8.
- 31. Prieto Peres MF, Valença MM. Headache endocrinological aspects. Handb Clin Neurol. 2010;97:717-37.
- 32. Askmark H, Lundberg PO. Lactation headache a new form of headache? Cephalalgia. 1989;9(2):119-22.
- Thorley V. Lactational headache: a lactation consultant's diary. J Hum Lact. 1997;13(1):51-3.

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