Psychoneuroendocrinology 96 (2018) 1–5

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Associations between traumatic stress symptoms, pain and bio-active components in burn wounds

N.E. Van Loey[a,b,*], H.W.C. Hofland[c], M. Vlig[d], E. Vandermeulen[e], T. Rose[e], R.H.J. Beelen[f], M.M.W. Ulrich[d,g]

[a] Behavioral Research, Association of Dutch Burn Centers, P.O. Box 1015, Beverwijk, Netherlands
[b] Clinical Psychology, Utrecht University, Utrecht, Netherlands
[c] Burn Center, Maasstad Hospital, Maasstadweg 21, 3079DZ Rotterdam, Netherlands
[d] Preclinical Research, Association of Dutch Burn Centers, P.O. Box 1015EA, Beverwijk, Netherlands
[e] Burn Center, Queen Astrid Military Hospital, Bruynstraat 1, 1120 Brussels, Brussels, Belgium
[f] Molecular Cell Biology and Immunology, VU University Medical Center, P.O. Box 7057, Amsterdam, Netherlands
[g] Plastic Reconstructive and Hand Surgery, VU University Medical Center, Amsterdam, Netherlands

ARTICLE INFO

Keywords:
Pain
Acute traumatic stress
Oxytocin
Cytokine
Burn wounds
Skin

ABSTRACT

Objective: Pain and traumatic stress symptoms often co-occur. Evidence suggests that the neuropeptide oxytocine and pro-inflammatory cytokines are associated with both stress and pain. The aim of this pilot study was to explore relations between self-reported pain and traumatic stress, oxytocin and three cytokines in burn wounds.
Methods: An observational study in three burn centres was performed. Patients were invited to participate in the study when deep dermal injury was suspected. Patients completed the Impact of Event Scale (IES), a self-report questionnaire assessing traumatic stress symptoms, and they rated their pain the day prior to surgery. During surgery, eschar (i.e., burned tissue) was collected and stored at −80 ° C until analysis. When the data collection was complete, oxytocin and cytokine levels were analysed.
Results: Eschar from 53 patients was collected. Pain and stress scores were available from 42 and 36 patients respectively. Spearman correlational analyses showed an association between lower oxytocin levels at wound site and a higher total IES score (r = −0.37) and pain (r = −0.32). Mann-Whitney U tests comparing groups scoring high or low on pain or stress confirmed these associations.
Conclusion: These analyses lend support to a hormonal pathway that may explain how psychological distress affects pain at skin level in patients with traumatic stress symptoms.

1. Introduction

Pain is a problem following burns, often complicated by anxiety and acute traumatic stress symptoms (Giannoni-Pastor et al., 2016; Summer et al., 2007). Psychological theories such as the mutual maintenance theory (Sharp and Harvey, 2001) propose that physiological, cognitive, behavioral and affective factors of pain and posttraumatic stress influence and maintain each other. According to the Neuromatrix theory (Melzack and Katz, 2013), a leading pain theory, pain is a multidimensional experience in which sensory and psychological inputs play an important role. These theories suggest that pain and psychological distress share biological components. Underlying bio-active components such as cytokines and neuropeptides such as oxytocin (OT) are associated with both pain and psychological distress (Boll et al., 2017; van Zuiden et al., 2011). Furthermore, OT has been found to act on the fear response (Koch et al., 2014; Olff et al., 2013) which plays a role in posttraumatic stress symptoms. But few studies investigated these components in the skin despite the knowledge that the skin can act as a neuro-endocrine organ (Arck et al., 2006).

In response to a (burn) injury, cytokines are released trying to re-establish homeostasis (Melzack and Katz, 2013) followed by neurohormones, e.g., glucocorticoids and catecholamines, released through the hypothalamic-pituitary-adrenal (HPA) axis, and neuropeptides such as OT. OT is released either peripherally from the pituitary, central from paraventricular neurons or in the skin were it can be expressed by dermal fibroblasts and keratinocytes (Deing et al., 2013; Landgraf and Neumann, 2004; Rash et al., 2014). The presence of neuropeptides in the skin is assumed to result from both local synthesis, blood transport

* Corresponding author at: Behavioral Research, Association of Dutch Burn Centers, P.O. Box 1015, Beverwijk, Netherlands.
E-mail addresses: nvanloey@burns.nl (N.E. Van Loey), HoflandH@Maasstadziekenhuis.nl (H.W.C. Hofland), mvlig@burns.nl (M. Vlig), Els.vandermeulen@mil.be (E. Vandermeulen), Thomas.Rose@mil.be (T. Rose), RJH.Beelen@vumc.nl (R.H.J. Beelen), mulrich@burns.nl (M.M.W. Ulrich).

https://doi.org/10.1016/j.psyneuen.2018.05.037
Received 3 April 2018; Received in revised form 29 May 2018; Accepted 29 May 2018

and release from nerve endings and immune cells (Slominski et al., 2015). As such it can bi-directionally communicate with the central system (Zmijewski and Slominski, 2011). There is ample evidence that OT plays a neuromodulatory role in (traumatic) stress and anxiety (Boll et al., 2017; de Kloet et al., 2005; Koch et al., 2014; Landgraf and Neumann, 2004; Neumann and Landgraf, 2012; Olff et al., 2013) and that emotional and environmental stressors can activate the skin stress response (Slominski et al., 2013).

Both OT and cytokines are related to pain. Most studies support analgesic effects of central administration of OT exerting a decreased sensitivity to noxious stimuli, be it that animal studies show more consistent findings compared to human studies (Boll et al., 2017; Rash et al., 2014). Recently, a study found evidence for analgesic effects after subcutaneous injection of OT (Gonzalez-Hernandez et al., 2017). Where OT seems to reduce pain, higher levels of pro-inflammatory cytokines were found associated with hyperalgesia: a study in rats receiving burns revealed that hyperalgesia was related to higher levels of the pro-inflammatory cytokine IL-6 in the skin (Summer et al., 2008). Another study has documented a role of inflammatory cytokines in the (neuropathic) pain process in which proinflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor α (TNFα) which are released by activated macrophages in wounds, showed to increase pain (Inoue, 2006).

Despite the plethora of studies on the associations between pain, stress, OT and pro-inflammatory cytokines there is a paucity of studies investigating its possible inter-relatedness in the skin. The aim of the current pilot study was to explore a relationship between self-reported pain and acute traumatic stress symptoms and bio-active components such as OT and pro-inflammatory cytokines measured in burned tissue (eschar) from patients with deep dermal or fullthickness burns. We hypothesize that these bio-active components are involved in a cross-talk interaction and that lower levels of OT and higher levels of cytokines in burn wounds are correlated with higher pain and traumatic stress scores.

2. Material and method

2.1. Participants

Participants were recruited at two Dutch and one Belgian burn centre between October 2011 and October 2012. Participants were included in the study if they were assumed to need skin grafting, were aged 18 years or older, and were Dutch or French-speaking. Individuals were excluded from the study if they had self-inflicted burns or a cognitive impairment that prevented reliable traumatic stress and pain estimates.

2.2. Procedure

The study featured a prospective design. Eligible patients were invited to participate into the study by a local researcher during the period of hospitalisation. All patients gave written informed consent after oral and written information about the study was provided. The researcher collected eschar during surgery and provided a questionnaire to the patient during the first week of admission to the hospital. Patients requiring mechanical ventilation were included in the study after they regained consciousness. Pain scores were assessed the day before surgery. The study was conducted according to the Helsinki Declaration and two institutional review boards in the Netherlands and Belgium boards approved the study.

2.3. Measures

Socio-demographics and burn characteristics such as age, gender, Total Body Surface Area (TBSA) burned, number of surgical procedures were recorded from the medical file. TBSA burned is the estimated percentage affected body area covered by partial and deep dermal injury.

The Impact of Event Scale (IES; Horowitz 1976) was used to assess acute traumatic stress symptoms related to the burn event. The Dutch validated scale was used in this study (Brom and Kleber, 1985). Fifteen items assess symptoms of intrusion and avoidance which are core symptoms of posttraumatic stress disorder, scored on a 4-point scale (0-1-3-5). Clinically significant symptoms were defined according to a cut-off of 26 (e.g., Bakker et al., 2013).

Overall pain in rest (background pain) was assessed using an 11-point graphic numerical rating scale ranging from 0 ‘no pain’ to 10 ‘the worst pain one can think of’ one or two days before surgery. All affected body areas were rated. A mean score was calculated if more than one pain score was provided.

Burn eschar was collected during surgery and stored at −80 °C until further use. Eschar is the unviable tissue resulting from deep dermal burned skin. It was transferred into cryovials which contained a stainless steel bead (Qiagen, Venlo, The Netherlands) and Lysis Buffer with Protease Inhibitor Cocktail (EMD Millipore, Billerica, USA). Biopsies were lysed using a TissueLyzer (Qiagen) for 5 min at 50 Hz. Aliquots of the supernatant were stored at −80 °C until further analysis was performed.

The magnetic bead panel Milliplex MAP kit (EMD Millipore, Billerica, USA) were used to analyse three cytokines (IL-1b, IL-6, TNF-alpha) and the neuropeptide oxytocin. The total amount of protein was determined using the colorimetric BCA total protein assay (PIERCE, Rockford, USA) according to the manufacturer instructions. Total protein levels were measured using the Nanodrop Spectrophotometer (Thermo Scientific, Wilmington, USA).

Neuropeptides were extracted from the tissues lysates using acetonitrile. 250 µl Tissue lysate was incubated with 375 µl acetonitrile for 10 min. After centrifugation, the supernatant was dried overnight using a Speed-Vac (Savant, Thermo Fisher Scientific, Breda, The Netherlands). Samples were then re-suspended in Assay buffer provided with the kit. Both cytokine samples and neuropeptide samples were aliquoted and either stored at −80 °C or used immediately for cytokine and neuropeptide analysis according to the manufacturer instructions (EMD Millipore).

The cytokine and neuropeptide levels were measured using Bio-Plex 200 (Bio-Rad, Hercules, USA) and data were analyzed using Bio-Plex manager software (Bio-Rad). The Milliplex MAP kits were measured using Bio-Plex 200 (Bio-Rad, Hercules, USA) and data were analyzed using Bio-Plex manager software (Bio-Rad). Cytokine and neuropeptide levels measured were divided by total protein levels of the samples and expressed as pg/mg protein.

2.4. Statistical analyses

Spearman correlations between pain, traumatic stress, cytokines and OT were calculated. Non-parametric tests, i.e., Mann-Whitney U tests, were used to investigate differences between groups of patients scoring low versus high on pain and traumatic stress. A cutoff point of 4 for pain and a cutoff point of 26 for clinically relevant stress levels were previously determined (de Jong et al., 2015) or commonly used (Bakker et al., 2013; Egberts et al., 2017) to indicate low pain and stress scores. Analyses were performed using SPSS 24.

3. Results

3.1. Participants

Sixty patients provided written informed consent. Eschar from 52 participants was collected. Of these, 10, 19 and 23 participants respectively were admitted to the burn centres in Beverwijk, Brussels and Rotterdam. Participants were predominantly male (n = 34; 65%), they were on average 47 years old (SD = 18). Burn severity in terms of total

Table 1
Spearman's rho correlations, Mean, Median, SD, and Minimum and Maximum scores of the study variables.

	IL-1β	IL-6	TNF-α	OT	Pain	stress
IL-1β	1					
IL-6	0.03	1				
TNF-α	0.28	0.29[a]	1			
OT	−0.08	0.10	0.20	1		
Pain	0.30	0.23	−0.01	−0.32[a]	1	
Stress	−0.26	0.21	−0.05	−0.37[a]	0.36	1
Mean	0.75	0.83	0.10	0.16	3.8	20.8
Median	0.19	0.49	0.05	0.14	3.5	15.5
SD	1.43	0.88	0.13	0.13	2.3	17.6
Min	0.003	0.003	0.002	0.020	0	0
Max	8.22	4.34	0.62	0.53	10	49

[a] Correlation is significant at the 0.05 level (2-tailed).

body surface area (TBSA) burned was 13.9 percent on average (SD = 15.8). Thirty-two patients (62%) received one skin graft procedure wheras 20 patients (38%) underwent two or more skin graft procedures. Eschar was collected 2 to 33 days after the burn event, on average 12.5 days post burn (SD = 7.9). Of the 52 participants, 36 and 42 completed the IES and provided pain scores respectively.

3.2. Cytokine and OT levels, pain and traumatic stress

The total level of the cytokines and OT was determined and divided by the total amount of protein. Table 1 presents the mean, SD, minimum and maximum levels in pg-mg for the respective cytokines and OT and, self-reported pain and traumatic stress symptoms levels. Seventeen (40%) scored their pain higher than 4. Sixteen (44%) scored traumatic stress symptoms in the clinical range (scores > 26), indicating clinically relevant traumatic stress symptoms.

3.3. Spearman correlations

Table 1 presents Spearman correlations between pain and stress scores, cytokines and OT as measured in eschar. Higher levels of IL-6 and IL-1β (p = .06) were positively correlated with higher TNF-α. OT was not correlated with any of the cytokines, but showed to be negatively related to pain and traumatic stress scores indicating that patients scoring high on pain or traumatic stress had lower levels of OT in their wound. As expected pain and traumatic stress were positively correlated but the strength of the correlations was modest (rho = 0.36, p = .06)

3.4. Testing groups scoring high versus low on pain and traumatic stress

When using cutoff scores for pain (> 4) and traumatic stress (> 26), Mann-Whitney U tests indicated that patients rating their pain higher than 4, had lower OT levels (p = .032) and patients scoring within the clinical range of traumatic stress had lower levels of OT (p = .020) in their wound (Table 2).

Fig. 1 shows the distribution of OT levels in those scoring low on both pain and traumatic stress and the group scoring high on pain and/or traumatic stress. It illustrates that only in patients scoring low on both pain and traumatic stress, the range of OT was larger. The other group showed to have lower OT-levels on average. The difference was significantly different (Mann-Whitney U = 37, p = .018).

4. Discussion

In this study the connection between pro-inflammatory cytokines and OT wound levels was examined in relation to self-reported pain and acute traumatic stress symptoms. As hypothesized, the results indicated that lower OT-levels in the wound were associated with higher acute traumatic stress levels and higher pain scores. A comparison between groups scoring low on both pain and traumatic stress and high on pain or traumatic stress confirmed a relationship between pain, stress and OT-levels in the wound.

Table 2
Mann-Whitney U tests to indicate differences between patients scoring low and high for pain or stress.

Bio-active component	Pain (N)	Mann-Whitney U	p-value
IL-1β	0 = pain score ≤ 4 (n = 20) 1 = pain score > 4 (n = 14)	109	.278
IL-6	0 = pain score ≤ 4 (n = 24) 1 = pain score > 4 (n = 15)	125	.112
TNF-α	0 = pain score ≤ 4 (n = 24) 1 = pain score > 4 (n = 14)	145	.486
OT	0 = pain score ≤ 4 (n = 21) 1 = pain score > 4 (n = 16)	98	.032
	Stress (N)		
IL-1β	0 = Stress score ≤ 26 (n = 17) 1 = Stress score > 26 (n = 12)	70	.156
IL-6	0 = Stress score ≤ 26 (n = 19) 1 = Stress score > 26 (n = 14)	114	.489
TNF-α	0 = Stress score ≤ 26 (n = 18) 1 = Stress score > 26 (n = 14)	113	.621
OT	0 = Stress score ≤ 26 (n = 18) 1 = Stress score > 26 (n = 13)	59	.020

The negative correlation between OT levels and self-reported pain and traumatic stress symptoms concurs with prior animal studies and experimental studies in humans that identified such a relationship in blood with pain and psychological distress (Bizik et al., 2012; Gouin and Kiecolt-Glaser, 2012; Rash et al., 2014). Nevertheless, our findings provide a preliminary indication that higher levels of traumatic stress symptoms can also influence OT-levels in the wound. The finding that psychological distress can have a negative impact at skin level is well established. A meta-analysis showed an estimated correlation of -0.42 between stress and wound healing indicating that more stress was associated with slower wound healing (Walburn et al., 2009). In the burns literature, it was reported that those with pre-existing or postburn high distress showed slower wound healing (Wisely et al., 2010). Higher oxytocin (OT) plasma level, in contrast, can exert a positive effect of wound healing (Gouin and Kiecolt-Glaser, 2012). It is assumed that the release of pro-inflammatory cytokines in the initial inflammatory phase involved in the repair process of wounds, plays a key role in subsequent phases of wound healing. In reponse to psychological stress a decrease in some cytokines (e.g., IL-1, IL-8 and TNFα) was reported (Gouin and Kiecolt-Glaser, 2012). But correlations between traumatic stress and higher serum IL-6, in persons with depression, are also reported (Bob et al., 2010). Studies that investigate both serum and wound levels are indicated.

No statistically significant correlations between the cytokines and pain or stress were found in this study. Only a trend towards higher IL-6 to be associated with pain was found in this study (p = .11). Possibly, this was due to limited statistical power associated with small sample sizes. A sample size of at least 30 subjects in each group would be needed (posteriori sample size calculation for the Mann-Whitney test based on this study using an effect size of 0.50). Nevertheless, the trend supports earlier results where hyperalgesia was reported in rats with higher IL-6 in the burn wound (Summer et al., 2008). Levels of IL-1β and TNF-α were not related to pain as was also reported in the animal

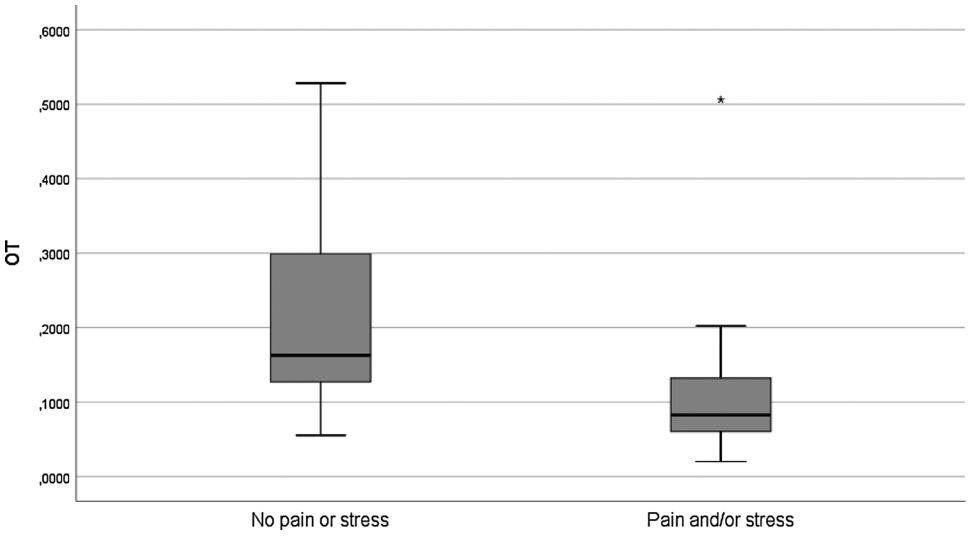

Fig. 1. Distribution of OT levels in patients scoring low on pain and stress versus patients scoring high on pain or stress.
Footnote: N (no pain or stress) = 12: This group of patients scores below the cut-off score for pain and stress; N (Pain and/or stress) = 17: This group of patients scores above the cut-off score for pain and/or stress. Mann-Whitney U test indicates a statistically significant effect (U = 37, p = .018).

study (Summer et al., 2008). Summer et al argued that the lack of a statistically significant association between hyperalgesia and IL-1 β could have been due to a power problem in their study. This may also be the case in the current study. This study did not reveal an association between OT and the cytokines. This contrasts a prior study that reported that OT-depleted keratinocytes were able to increase the release of for example IL-6 in vitro (Deing et al., 2013). More research in larger samples is needed to establish such a relationship.

This study has limitations that merit note. First, the sample size was small while the variation in the variables of interest was substantial. Wide variations in plasma cytokine levels in patients with burns, i.e., fluctuations over time within patiens as well as fluctuations between patients, have been reported earlier and may stem from the high inflammatory response associated with burn injuries (Finnerty et al., 2008). Moreover, the small sample size prevented the investigation of OT and cytokines in one model. Bi-directional influences, controlled for other associations, could therefore not be investigated. This may be relevant because OT expression is regulated by different cytokines at skin level (Deing et al., 2013). Centrally, OT also interacts with endogenous opioids (Carter, 2014; Meguro et al., 2018; Xin et al., 2017) and has been found to interplay with the structurally similar neuropeptide vasopressin (Neumann and Landgraf, 2012) but it is unclear to what extent similar interactions apply to the skin level. Replication of this study in a larger sample that allows analysis in one model is therefore warranted. Second, the collection of plasma blood samples was scheduled based on blood samples taken during clinical routine. Unfortunately, routine blood sampling provided insufficient samples. Future research should include venapunction for reseach purposes to investigate possible associations with blood plasma levels.

Although more research is warranted, this study may provide an explanation as to why individuals suffering from high traumatic stress report higher pain levels. Recent studies suggest that it is posttraumatic stress that influences (chronic) pain and not the other way around (Brown et al., 2014; Jenewein et al., 2009; Van Loey et al., 2018). A recent study showed that OT receptors in nociceptive terminals can inhibit nociceptive input (Gonzalez-Hernandez et al., 2017) suggesting avenues for pain improvement at skin level. However, positive social interactions have also been found to produce higher plasma OT and resulted in faster wound healing (Gouin and Kiecolt-Glaser, 2012; Vitalo et al., 2009). Particularly in a patient population that is isolated because of infection risk, experiments increasing positive social interactions may be worth trying to increase endogenous production of OT. Also, early psychological interventions that modulate the stress response may excert beneficial effects on pain. And last, recent evidence showed that OT can enhance μ opioid receptor signalling in vitro (Meguro et al., 2018). As such this neuropeptide warrants further attention in burn research as opioids are still the mainstream analgesics used in burn care (Richardson and Mustard, 2009). Such research can have important clinical implications.

5. Conclusions

This study suggests a connection between self-reported psychological stress and pain in connection with OT. Although replication of this study is a prerequisite, it may provide a possible explanation how traumatic stress and pain are inter-related and how it can have a measureable influence on neuropeptides directly at the wound site. OT may be a promising neuropeptide that may help patients with burns in controlling their pain through its pain-reducing, anxiolytic, and stress-controlling characteristics.

Author contributions

NVL and MU participated in the writing process and interpreted the statistical analyses; MV analysed the biological material, revised the article and approved the final version; HH, TR and EV contributed to data collection, revised the article and approved the final version; NVL, MU and RB contributed to conception and design of the study. NVL takes responsibility for the integrity of the work as a whole from inception to published article.

Conflict of interest

The authors have no conflict of interest.

Acknowledgement

The study was financially supported by the Dutch Burns Foundation, pilot study grant number 10.01.

References

Arck, P.C., Slominski, A., Theoharides, T.C., Peters, E.M., Paus, R., 2006. Neuroimmunology of stress: skin takes center stage. J. Invest. Dermatol. 126, 1697–1704. http://dx.doi.org/10.1038/sj.jid.5700104.
Bakker, A., Van der Heijden, P.G., Van Son, M.J., Van Loey, N.E., 2013. Course of traumatic stress reactions in couples after a burn event to their young child. Health Psychol. 32, 1076–1083. http://dx.doi.org/10.1037/a0033983.
Bizik, G., Bob, P., Pavlat, J., et al., 2012. P-473 - oxytocin reflects levels of trauma-related and dissociative symptoms in patients with severe depression. Eur. Psychiatry 27 (Suppl.1). http://dx.doi.org/10.1016/S0924-9338(12)74640-0.
Bob, P., Raboch, J., Maes, M., et al., 2010. Depression, traumatic stress and interleukin-6.

J. Affect. Disord. 120, 231–234. http://dx.doi.org/10.1016/j.jad.2009.03.017.
Boll, S., Almeida de Minas, A.C., Raftogianni, A., Herpertz, S.C., Grinevich, V., 2017. Oxytocin and pain perception: from animal models to human research. Neuroscience. http://dx.doi.org/10.1016/j.neuroscience.2017.09.041.
Brom, D., Kleber, R.J., 1985. De Schok Verwerkings Lijst [The Impact of Event Scale]. Ned. Tijdschr. Psychol. 40, 164–168.
Brown, E.A., Kenardy, J.A., Dow, B.L., 2014. PTSD perpetuates pain in children with traumatic brain injury. J. Pediatr. Psychol. 39, 512–520. http://dx.doi.org/10.1093/jpepsy/jsu014.
Carter, C.S., 2014. Oxytocin pathways and the evolution of human behavior. Annu. Rev. Psychol. (65), 17–39. http://dx.doi.org/10.1146/annurev-psych-010213-115110.
de Jong, A.E., Bremer, M., Hofland, H.W., Schuurmans, M.J., Middelkoop, E., van Loey, N.E., 2015. The visual analogue thermometer and the graphic numeric rating scale: a comparison of self-report instruments for pain measurement in adults with burns. Burns 41, 333–340. http://dx.doi.org/10.1016/j.burns.2014.07.002.
de Kloet, E.R., Joels, M., Holsboer, F., 2005. Stress and the brain: from adaptation to disease. Nat. Rev. Neurosci. 6, 463–475. http://dx.doi.org/10.1038/nrn1683.
Deing, V., Roggenkamp, D., Kuhnl, J., et al., 2013. Oxytocin modulates proliferation and stress responses of human skin cells: implications for atopic dermatitis. Exp. Dermatol. 22, 399–405. http://dx.doi.org/10.1111/exd.12155.
Egberts, M.R., van de Schoot, R., Geenen, R., Van Loey, N.E., 2017. Parents' posttraumatic stress after burns in their school-aged child: a prospective study. Health Psychol. 36, 419–428. http://dx.doi.org/10.1037/hea0000448.
Finnerty, C.C., Jeschke, M.G., Herndon, D.N., et al., 2008. Temporal cytokine profiles in severely burned patients: a comparison of adults and children. Mol. Med. 14, 553–560. http://dx.doi.org/10.2119/2007-00132.Finnerty.
Giannoni-Pastor, A., Eiroa-Orosa, F.J., Fidel Kinori, S.G., Arguello, J.M., Casas, M., 2016. Prevalence and predictors of posttraumatic stress symptomatology among burn survivors: a systematic review and meta-analysis. J. Burn Care Res. 37, e79–e89. http://dx.doi.org/10.1097/BCR.0000000000000226.
Gonzalez-Hernandez, A., Manzano-Garcia, A., Martinez-Lorenzana, G., et al., 2017. Peripheral oxytocin receptors inhibit the nociceptive input signal to spinal dorsal horn wide-dynamic-range neurons. Pain 1 (58), 2117–2128. http://dx.doi.org/10.1097/j.pain.0000000000001024.
Gouin, J.P., Kiecolt-Glaser, J.K., 2012. The impact of psychological stress on wound healing: methods and mechanisms. Crit. Care Nurs. Clin. North. Am. 24, 201–213. http://dx.doi.org/10.1016/j.ccell.2012.03.006.
Inoue, K., 2006. The function of microglia through purinergic receptors: neuropathic pain and cytokine release. Pharmacol. Ther. 1 (09), 210–226.
Jenewein, J., Moergeli, H., Wittmann, L., Buchi, S., Kraemer, B., Schnyder, U., 2009. Development of chronic pain following severe accidental injury. Results of a 3-year follow-up study. J. Psychosom. Res. 66, 119–126.
Koch, S.B., van Zuiden, M., Nawijn, L., Frijling, J.L., Veltman, D.J., Olff, M., 2014. Intranasal oxytocin as strategy for medication-enhanced psychotherapy of PTSD: salience processing and fear inhibition processes. Psychoneuroendocrinology 40, 242–256. http://dx.doi.org/10.1016/j.psyneuen.2013.11.018.
Landgraf, R., Neumann, I.D., 2004. Vasopressin and oxytocin release within the brain: a dynamic concept of multiple and variable modes of neuropeptide communication. Front. Neuroendocrinol. 25, 150–176. http://dx.doi.org/10.1016/j.yfrne.2004.05.001.
Meguro, Y., Miyano, K., Hirayama, S., et al., 2018. Neuropeptide oxytocin enhances mu opioid receptor signaling as a positive allosteric modulator. J. Pharmacol. Sci. http://dx.doi.org/10.1016/j.jphs.2018.04.002.
Melzack, R., Katz, J., 2013. Pain. Wiley Interdiscip. Rev. Cogn. Sci. 4, 1–15. http://dx.doi.org/10.1002/wcs.1201.
Neumann, I.D., Landgraf, R., 2012. Balance of brain oxytocin and vasopressin: implications for anxiety, depression, and social behaviors. Trends Neurosci. 35, 649–659. http://dx.doi.org/10.1016/j.tins.2012.08.004.
Olff, M., Frijling, J.L., Kubzansky, L.D., et al., 2013. The role of oxytocin in social bonding, stress regulation and mental health: an update on the moderating effects of context and interindividual differences. Psychoneuroendocrinology 38, 1883–1894. http://dx.doi.org/10.1016/j.psyneuen.2013.06.019.
Rash, J.A., Aguirre-Camacho, A., Campbell, T.S., 2014. Oxytocin and pain: a systematic review and synthesis of findings. Clin. J. Pain 30, 453–462. http://dx.doi.org/10.1097/AJP.0b013e31829f57df.
Richardson, P., Mustard, L., 2009. The management of pain in the burns unit. Burns 35, 921–936. http://dx.doi.org/10.1016/j.burns.2009.03.003.
Sharp, T.J., Harvey, A.G., 2001. Chronic pain and posttraumatic stress disorder: mutual maintenance? Clin. Psychol. Rev. 21, 857–877.
Slominski, A.T., Zmijewski, M.A., Zbytek, B., Tobin, D.J., Theoharides, T.C., Rivier, J., 2013. Key role of CRF in the skin stress response system. Endocr. Rev. 34, 827–884. http://dx.doi.org/10.1210/er.2012-1092.
Slominski, A.T., Manna, P.R., Tuckey, R.C., 2015. On the role of skin in the regulation of local and systemic steroidogenic activities. Steroids 103, 72–88. http://dx.doi.org/10.1016/j.steroids.2015.04.006.
Summer, G.J., Puntillo, K.A., Miaskowski, C., Green, P.G., Levine, J.D., 2007. Burn injury pain: the continuing challenge. J. Pain 8, 533–548.
Summer, G.J., Romero-Sandoval, E.A., Bogen, O., Dina, O.A., Khasar, S.G., Levine, J.D., 2008. Proinflammatory cytokines mediating burn-injury pain. Pain 135, 98–107.
Van Loey, N.E., Klein-Konig, I., de Jong, A.E.E., Hofland, H.W.C., Vandermeulen, E., Engelhard, I.M., 2018. Catastrophizing, pain and traumatic stress symptoms following burns: a prospective study. Eur J. Pain. http://dx.doi.org/10.1002/ejp.1203.
van Zuiden, M., Heijnen, C.J., van de Schoot, R., et al., 2011. Cytokine production by leukocytes of military personnel with depressive symptoms after deployment to a combat-zone: a prospective, longitudinal study. PLoS One 6, e29142. http://dx.doi.org/10.1371/journal.pone.0029142.
Vitalo, A., Fricchione, J., Casali, M., et al., 2009. Nest making and oxytocin comparably promote wound healing in isolation reared rats. PLoS One 4, e5523. http://dx.doi.org/10.1371/journal.pone.0005523.
Walburn, J., Vedhara, K., Hankins, M., Rixon, L., Weinman, J., 2009. Psychological stress and wound healing in humans: a systematic review and meta-analysis. J. Psychosom. Res. 67, 253–271. http://dx.doi.org/10.1016/j.jpsychores.2009.04.002.
Wisely, J.A., Wilson, E., Duncan, R.T., Tarrier, N., 2010. Pre-existing psychiatric disorders, psychological reactions to stress and the recovery of burn survivors. Burns 36, 183–191.
Xin, Q., Bai, B., Liu, W., 2017. The analgesic effects of oxytocin in the peripheral and central nervous system. Neurochem. Int. 103, 57–64. http://dx.doi.org/10.1016/j.neuint.2016.12.021.
Zmijewski, M.A., Slominski, A.T., 2011. Neuroendocrinology of the skin: an overview and selective analysis. Dermatoendocrinology 3, 3–10. http://dx.doi.org/10.4161/derm.3.1.14617.