Oxytocin & well-being as promoters of affect regulation and homeostasis: a neuroscientific review

Ocitocina & bem-estar como promotores da regulação afetiva e da homeostase: uma revisão neurocientífica

Oxitocina y bienestar como promotores de la regulación del afecto y de la homeostasis: una revisión neurocientífica


Keywords: Oxytocin; Well-being; Translational Neuroscience.


Palabras clave: Oxitocina; Bem-estar; Neurociência Translacional.


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In 2014, the World Health Organization (WHO) declared that “mental health was a state of WB” (https://www.who.int/features/factfiles/mental_health/en/). The term WB has also been linked to other concepts such as quality of life (Salvador-Carulla, Lucas, Ayuso-Mateos & Miret, 2014), fitness (Netz, Wu, Becker, & Tennebaum, 2005), work (Litchfield, Cooper, Hancock, & Watt, 2016), pain (Gureje, Von Korff, Simon & Gater, 1998), psychiatry (Kinderman et al, 2015), and spirituality (Azarsa, Davoodl, Markani, Gahramanian, & Vargaei, 2015). Non-WB terms such as “anti-stress” (Uvnas-Moberg, & Petersson, 2005) and “non-noxious” (Uvnas-Moberg, Handlin, & Petersson, 2015) have also been used to define WB – that is, the concept is inferred from its opposite, and does not bear a definition of its own. Additionally, WB has been referred to as devoid of a physical, material dimension, and, in this case, is considered as a “psychological” phenomenon. Still other authors consider that physical WB is a component of psychological WB, agreeing that this concept has not yet been clearly defined (Netz et al, 2005).

How to articulate the release of OT with feelings of WB? What would be the specific characteristics of this type of WB? What semantics are used to refer to it? Answering these questions should be of great interest to the health scientist and has led to this review.

Around the 1980s, neuroscientific research started to acknowledge that neuropeptide OT was implicated in the generation of positive moods. The uncovering of neuroendocrine mechanisms revealed that this neuroendocrine primary-process system is typically aroused in the mother during the last months of pregnancy and delivery; and, after birth, both in the mother and the baby, generating pleasurable feelings of WB during their interaction (Panksepp, 1998). The baby usually relaxes upon receiving care, as OT promotes the release of endogenous opioids (Nelson & Panksepp, 1998). This state of pleasantness and relaxation counteracts many states of painful excitatory arousal, helping the baby to reach an affective, followed by a physiological, regulatory, state (and not the contrary). Mothers are also regulated through interaction with the baby (Schore, 2015).

The articulation of a neuroendocrine mechanism, a correspondent affective mood and a specific behavior results in a ‘whole’ brain-mind-body phenomenon (Panksepp & Biven, 2012). Accordingly, the authors of this review propose that OT & WB be considered as a brain-body-mind phenomenon that translates into a healthy, homeostatic balance; as such, a translational neuroscientific approach is suggested to investigate it.

Objectives: to identify in reviews and clinical trials (PICOS, phenomenological and neurobiological characteristics, as well as semantic equivalents, of WB linked to OT, as promoters of affect regulation and homeostasis, following PRISMA Guidelines (Liberati et al, 2009).

Methods

Study eligibility criteria: terms “OT” & “WB” and associated semantics were searched in reviews and clinical trials (PICOS), in human studies. Studies on labor, breastfeeding, post-partum, uterine hemorrhages, and animal models, were excluded.

Report eligibility criteria: searches in English language; in titles & abstracts, when available; on years---1980 to 2000 for early period of History of OT and 2014 to 2018 for present data.

Searches were made in reviews and clinical trials (PICOS), in PubMed, BVS Virtual (Medline, Lilacs) and SIBI-USP Portal de Busca Integrada electronic databases, and by handsearching books of reference and additional articles. The searches were run from February/2018 to August/2019. Eliana Nogueira-Vale and Nathália A. de Almeida made the initial electronic search; and Eliana Nogueira-Vale selected and read the articles and wrote the report; Marcelo da Costa Fernandes supervised the manuscript.

Example of electronic search

In BVS Virtual (Lilacs & Medline), an initial search was performed for “OT” AND “WB”, yielding 333 results.

Databases: BVS Virtual (MEDLINE n=333/ LILACS=0). Search on OT & WB.
Filters
Main subject: Oxytocin; Type of study: Qualitative Study on Systematic Reviews, Case-Control Studies; Limit: Humans; Idiom: English; Publication years: 2014-2018. Exclusion: postpartum haemorraghe; perinatal depression; maternal depression. Results: (2), with (1) selected:


Results
Study selection: See Table 1 for Flow Diagram.
Study characteristics: this is a qualitative research focused on screening information about situations and equivalent semantics of WB when associated to OT release.

Results in individual studies:
Search on OT & WB in pioneering literature: because OT was notably well-conserved in mammals during evolution, findings on behavior and emotions of rodents in the 1990’s (early History of OT) already anticipated human data (Panksepp, 1998). Initial neuroscientific studies with animal models on OT started around the 1970s (Panksepp, 1998). Around 1987, in Sweden, a group of scientists started researching OT in humans. Pioneer Kirsten Uvnas-Moberg consistently studied OT and other peptides in animals and humans, and has an important role in associating OT & WB; however, scientific dissemination was difficult in the pre-internet era (see http://www.kerstinuvnasmoberg.com/). In parallel, in the USA, an early article on intranasal OT investigation with a sample of PTSD war veterans, was published (Pitman, Orr, Forgue, de Jong, & Claiborn, 1987), but research with humans only escalated after 2000. At the end of the 20th century, a significant database on OT research with animals had accumulated (Panksepp, 1998), and the implementation of electronic media fostered communication among scientists. In 1992 and 1997, two innovative collections on social influences of OT release in animals were published by The Annals of the New York Academy of Sciences [AAAS] on maternal, sexual and social behaviors (Pedersen & Caldwell, 1992), and affiliative behavior (Carter, Lederhendler, & Kirkpatrick, 1997). In 1998, the Oxford University Press published Jaak Panksepp’s work on Affective Neuroscience: the foundations of animal and human emotions, which extensively mapped discrete neural circuits in mammals, corresponding to basic affects (Panksepp, 1998). Also, an original issue of Psychoneuroendocrinology - Is there a neurobiology of love? was edited by neuroscientists Kirsten Uvnas-Moberg & C. Sue Carter. Attachment and other social behaviors
Emotion of warmth-liking: this category of emotion was identified as a system of opioidergic modulation activated during interpersonal and close relationships, creating a state of “physiological quiescence, less negative feelings and psychophysiological resilience” (Burgdorf, Rinn & Stemmler, 2016, p.1712). OT release has been frequently associated to µ opioids in similar situations (Nelson & Panksepp, 1998; Nummenmaa et al, 2016), but in that study, it was not cited. One of the authors argued that “more research on OT [concerning the subject] was needed” (e-correspondence between Nogueira-Vale and Stemmler, October, 29th, 2017).

Touch: considered one of the most powerful social stimuli, touch is fundamental for child development, attachment and the formation of human bonds (Carter, 2014), producing concomitant feelings of comfort, and behaviors of eye closure and cessation of stress vocalization in mammals; a role for OT release in human intimacy was anticipated in early literature (Panksepp, 1998). In attachment contexts, insistent physical closeness and contact with the mother is sought by young mammals, in a search for feelings of soothing and calmness (Carter, 1998; Uvnas-Moberg, 1998). In 1990, a special type of low-threshold, unmyelinated, mechanosensitive, tactile C-afferent fiber (CT-afferent) was identified (Vallbo, Olausson, & Wessberg 1990), innervating hairy, but not glabrous, human skin, and associated to social touch (Gentsch, Panagiotopoulou, & Fotopoulou, 2015). Some authors even consider that CT-afferent fibers constitute a specific neurobiological substrate for affect in affiliative behaviors and psychological WB (Walker & McGlone, 2013), in opposition to the discriminative properties of touch conducted by myelinated nerves (pressure/vibration, temperature, itch and pain) (McGlone, Wessberg, & Olausson, 2014). CT-afferents seem to best respond to gentle stroking touch, stimulating the release of OT (Behnia et al, 2014), endogenous opioids (Nummenmaa et al, 2016), and regulating serotonin (McGlone, Wessberg, & Olausson, 2014). Its effects translate into increased social motivation and reduced
reactivity to stressors, leading to feelings of comfort, softness, smoothness, and stress alleviation (Netz, Wu, Becker, & Tenenbaum, 2005; Ackerley et al., 2014). In romantic relationships, there is enhanced pleasantness when touch comes from the partner, although, some gender-specific variations were found in sexual behavior (Behnia et al., 2014; Ditzen et al., 2013): touch with partner and value of soft interpersonal touch seems to be facilitated by OT, and may contribute to enduring romantic bonds and monogamy (Kreuder et al., 2017). Touch changes social impressions; conversely, facial expression can also alter touch (Ellingsen et al., 2014). Other authors found that high-intensity (Turkeltaub, Yearwood, & Friedmann, 2014) or moderate intensity kinds of touch (Field, 2016) in opposition to soft touch, would be more effective in relieving stress and bringing relaxation. This apparent contradiction may be due to the social or non-social nature of touch: perhaps in social contexts a specific neural network might be in command for soft affective touch. Indeed, divergent neural processing for touch intensity and pleasantness were found in an fMRI study (Case et al., 2016).

Skin-to-skin contact: skin-to-skin contact with the mother is usually the first one in a newborn’s life, and has a primal, ontological role (Nelson & Panksepp, 1998; Carter, in: Uvnas-Moberg & Carter, 1998; Porges, 2011). Together with warmth, stroking and massage-like movements of the hand of the mother, it seems to lead to an increase in exchange of glances, smiling and vocalizations, generating feelings of calmness and WB in the baby, improving the quality of later social and affective bonds of the baby (Uvnas-Moberg & Carter, 1998; Uvnas-Moberg & Petersson, 2005). In fact, skin-to-skin contact seems to be critical for development (Rilling, 2013), being linked to CT afferents in maternal, affiliative, sexual, and other social contacts, bringing feelings of pleasantness (Kreuder et al., 2015) and influencing social contact; gentle skin-to-skin touch was found to bring acute effects on social evaluation of others (Ellingsen et al., 2014).

Touch and mobile technology: an original article inquired whether contact by means of mobile technology could help in the development of empathy, likely to be related to OT & WB (Konrath et al., 2015). Would mobile technology lead to a more non-social, elated kind of WB, through the eventual activation of the reward system by key-pressing on cell phones, tablets, keyboards, etc.? Visual stimuli

Eye contact: during development of human attachment, eye-gaze together with touch, constitutes one of the first and most important kinds of social contacts between baby and mother, coinciding with an increase in OT release (Carter, Lederhendler, & Kirkpatrick, 1997); intranasal OT was also reported to enhance eye-contact in autistic, as well as in normal people (Quattrocchi & Friston, 2014).

Pleasant mental images: the reminiscence of positive memories is associated to OT release, and seems to attenuate acute stress responses, contributing to emotion regulation (Speer & Delgado, 2017); this elicit positive affect more than positive pictures; OT release, on the other side, can enhance retrieval of positive social memories, attenuating stress feelings (Wudarczyk, Earp, Guastella, & Savulescu, 2013; Kirsch, 2015).

Face memory/recognition: the human brain was programmed during evolution to preferentially identify and recognize human faces among other visual stimuli (Porges, 2011). OT release improves emotion recognition in faces, the encoding of positive social memories in humans, and recognition of familiar faces identity (Guastella, Mitchell, & Mathews, 2008).

Auditory stimuli:

Music-listening: Frisson, chills and goosebumps were observed in situations of music-listening (Colver & El-Alayli, 2015). Would this kind of phenomenon also occur in the appreciation of other aesthetic stimuli? Decreases in blood pressure and heart rate were also observed in coronary male patients, but not in normal men, during music listening; it reduced stress, anxiety and depression, as well as enhanced life satisfaction, optimism, hope and meaning in life, more intense in coronary male patients than in healthy man (Gupta & Gupta, 2015). Conversely, unpleasant
music seemed to increase anxiety when listened during stress exposure (Jezova et al, 2013).

Music-singing: a recent study relates an improvement in the mood, and a significant immunological increase, but an apparently contradictory finding on decreases in OT and β-endorphin, in cancer patients after music singing. The hypothesis for that unexpected result was that the decrease represented “a generalized down-regulation of stress response, which may have over-ridden any social bonding or happiness-associated increase” (Fancourt et al, 2016, p.9). However, another study found that OT concentrations increased significantly both in singers after a singing lesson (Grape, Sandgren, Hansson, Ericson, & Theorell, 2003).

Sounds of infant distress: Adult humans react to sounds and visual cues of infant vulnerability and stress by exhibiting brain amygdala activation (Marsh, 2016). This might be due to the survival value of this kind of alert concerning helpless children.

Shade in nature

An original study found that there was an ideal range of tree shade, promoted by the density of tree canopy, in the recovery from an experimental stress situation in men, but not in women. Density of tree cover showed a dose-response curve in the form of an inverted U, assessed by salivary cortisol levels and Trier Social Stress Test. It was also suggested that contact with nature brings WB and health (Jiang, Chang, & Sullivan, 2014).

Other categories frequently associated with OT & WB

OT & WB and Trust

Trust has been associated to the release of OT & WB along OT history (Pitman, Orr, Forgue, de Jong, & Claiborn, 1987; Kosfeld,...Fehr, 2005). In 2013, however, McCullough casted doubt on OT and trust databank (Michael, McCullough, Churchland & Mendez, 2013); subsequently, in 2015, a critical review also failed to confirm robust evidence in cumulative data, and authors made suggestions to improve rigor in trust research (Nave, Camerer, & McCullough, 2015).

OT & WB and Psychiatry

Considering that many psychiatric diseases bring about negative and unpleasant feelings, biological psychiatry has shown an interest in intranasal OT effects (MacDonald & Feifel, in: Shalev & Ebstein (Eds.), 2015). Nonetheless, clinical trials are still incipient, with highlights in the areas of autism (Scheele et al, 2014; Young & Barrett, 2015); schizophrenia (Fischer-Shofty et al, 2013); depression (Gorgen, Joormann, Hiller, & Witthoof, 2016); anxiety (Neumann & Slattery, 2016); and PTSD (Sack et al, 2017). However, sample sizes are frequently modest for statistical validation purposes.

OT & WB and variations for age, gender, context and individual profile

As with other hormones, OT release in humans seems to decline with age (Elabd et al, 2014). The existence of genetic, neural and sociocognitive processes related to OT release, as well as individual differences in socioemotional processes associated with the OT receptor gene, together with social isolation, may represent a potential risk for depression, social stress, and anxiety in the eldest (Ebner, Maura, Macdonald, Westberg, & Fischer H, 2013; Emney et al, 2014). Besides variation on the production of OT with age, variations were also found for gender (Behnia et al, 2014); personality profile (Kelly & Goodson, 2014), social context (Schladt et al, 2017) and interindividuality (Olif et al, 2013) in response to OT administration.

OT & WB and Familiarity

In early OT research, it was demonstrated that OT mediated conditioned place (Liberzon, Trujillo, Akil, & Young, 1997) and smell preference (Kojima & Alberts, 2011) in rats. Familiarity is a condition often linked to OT & WB, as it has an important survival value (De Dreu, Greer, Van Cleef, Shalvi, & Handgraaf, 2011). It should also be considered the fact that OT is mainly a prosocial and affiliative hormone, having a pivotal importance in attachment processes (Swain et al, 2014), and has shown to be adaptive in situations associated to OT & WB such as: partner’s touch (Bennia et al, 2014), face-memory and prosocial cooperation (Kirsch, 2015), altruism among family, but not other people (Marsh, 2016), caring for ageing people (Ebner et al, 2013), and even promoting dishonesty in behalf of one’s group (Shalvi &
De Dreu, 2014). The neurobiological common
ground for these different situations of familiarity is
probably linked to vagal activation, which occurs
in situations of proximity without fear, inhibiting
visceral activation (Porges, 2011), and contributing
to affective regulation (Schore, 2015).

Synthesis of results
The main variables associated to OT & WB
found in this review refer to social situations,
sensorial stimuli, and trust. Variations according
to gender, age, familiarity, individual profile and
context were found for the studied variables.

Discussion
Summary of evidence
Many semantic categories for WB found in
animal pioneering research are applicable to
human beings, especially those concerning
attachment variables. It should be considered
that recent developments in neuroscience
have allowed for more comprehensive data on
humans. Among screened studies, most salient
variables associated to WB were: sensorial stimuli,
feelings of trust, companionship, and heterosexual
couples. Psychiatric studies emphasized the lack
of WB in psychiatric disorders. More studies on OT
& WB in psychiatry, with more scientific power, are
needed. Among screened emotional stimuli likely
to be associated to WB, there were mentioned
tactile, auditory & visual stimuli, and shade/
luminosity. In spite of prior acceptance of OT & WB
associated to trust, recent critical reviews found
inconclusive results, suggesting new strategies
for research. When selecting samples, attention
should be given to variations in gender, individual
profile, age, contexts and familiarity.

Limitations
This research was limited for being partly
performed by a single reviewer. Another limitation
refers to the small temporal span of the research.
Considering that central OT discoveries date from
the 1980’s, and the advent of intranasal OT dates
from 2000, a more exhaustive research would be
advisable. The subjects selected by the authors
for this discussion may have left other relevant
points aside.

Conclusions
Feelings, emotions and sensations of WB found
in this research were mainly related to sensorial
and social stimuli, or a blend of the two of them.
For better results, a more exhaustive data retrieval
would be desirable. The best methodological
approach for this kind of study would be a
translational research. The retrieved semantic
categories for WB could be of use in favor of the
construction of a scale, associating OT & WB.

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Disclosures
The authors have no conflict of interests to
declare.

References
C-Tactile Afferents Are Tuned to the Temperature of
a Skin-Stroking Caress. *The Journal of Neuroscience,*
Azarsa, T., Davoodi, A., Markani, A. K., Gahramanian,
toward spiritual care and its relationship with spiritual
care competence among critical care nurses. *Journal of
Behnia, B., Heinrichs, M., Bergmann, W., Jung, S., Ger-
effects of intranasal oxytocin on sexual experiences
and partner interactions in couples. *Hormonal Behavior,
Burgdorf, C., Rinn, C., & Stemmler, G. (2016). Effects of
personality on the opioidergic modulation of the emo-
tion warmth-liking. *Journal of Comparative Neurology,
524*(8):1712–26. 10.1002/cne.23847


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Table 1 – PRISMA 2009 Flow Diagram (1): Oxytocin & Well-being – Systematic Review

### Table 2 – Semantic equivalents and Categories of WB retrieved in this review

<table>
<thead>
<tr>
<th>Source</th>
<th>Semantic Equivalents &amp; Categories for Emotions/feelings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panksepp, 1998</td>
<td>Comfort, flirtatiousness, friendship, peaceful coexistence, playfulness, positive erotic feelings, positive social memories, sense of ease, orgasm, security, sedation, sexual pleasure, sleep, yawning</td>
</tr>
<tr>
<td>Uvnas-Moberg &amp; Petersson, 2005</td>
<td>Anti-stress, calm, calmness, homeostasis, relaxation</td>
</tr>
<tr>
<td>Porges, 2012, Schore, 2015</td>
<td>Affect regulation</td>
</tr>
<tr>
<td>Colver &amp; El-Alayli, 2015</td>
<td>Frisson, chills and goose-bumps</td>
</tr>
<tr>
<td>Gupta &amp; Gupta, 2015</td>
<td>Reduction of stress, depression, anxiety; enhanced life satisfaction, optimism, hope and meaning in life</td>
</tr>
<tr>
<td>Burgdorf, Rinn &amp; Stemmler, 2016</td>
<td>Quiescence, resilience</td>
</tr>
</tbody>
</table>

### Table 3 – Summary of skin stimuli categories and semantic equivalents for WB

<table>
<thead>
<tr>
<th>Source</th>
<th>Categories of variables for touch</th>
<th>Semantic Equivalents for Emotions/feelings</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Burgdorf, Rinn &amp; Stemmler, 2016.</td>
<td>Emotion of warmth-liking</td>
<td>Physiological quiescence, less negative feelings and psychophysiological resilience</td>
</tr>
<tr>
<td>- Panksepp, 1998</td>
<td>Soft touch</td>
<td>Comfort, soothing and calmness</td>
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<td>- Uvnas-Moberg, 1998</td>
<td></td>
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<td>- Carter, 2014</td>
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<tr>
<td>Nummenmaa et al. 2016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Vallbo, Olausson, &amp; Wessberg 1990</td>
<td>CT-afferents</td>
<td>Comfort, softness, smoothness, and stress alleviation</td>
</tr>
<tr>
<td>- Netz, Wu, Becker, &amp; Tenenbaum, 2005</td>
<td></td>
<td>Affect in affiliative behaviors, well-being</td>
</tr>
<tr>
<td>- Walker &amp; McGlone, 2013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Behnia et al. 2014</td>
<td>Romantic relationships</td>
<td>Pleasantness</td>
</tr>
<tr>
<td>- Ditzen et al. 2013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Turkeltaub, Yearwood, &amp; Friedmann, 2014</td>
<td>Touch of high-intensity or moderate intensity</td>
<td>Relieve stress &amp; bring relaxation</td>
</tr>
<tr>
<td>- Field in: Olausson, Wessberg, Morrison, &amp; McGlone (Eds.), 2016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Uvnas-Moberg &amp; Carter, 1998; Uvnas-Moberg &amp; Petersson, 2005</td>
<td>Skin-to-skin contact</td>
<td>Calmness and WB; affective-emotional pleasantness</td>
</tr>
<tr>
<td>- Kreuder et al. 2015</td>
<td></td>
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</tbody>
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