LETTER TO THE EDITOR

OXYTOCIN, A POSSIBLE TREATMENT FOR COVID-19? EVERYTHING TO GAIN, NOTHING TO LOSE

Phuoc-Tan Diep, Benjamin Buemann, Kerstin Uvnäs-Moberg

Abstract

After comparing the morbidity patterns of COVID-19 infections, variations of oxytocin levels and some properties of the neurohormone oxytocin, the authors put forward their hypothesis that oxytocin might constitute a safe, inexpensive and readily available treatment for this disease.

Key words: COVID-19, pandemic, treatment, oxytocin, immune system, inflammation

Phuoc-Tan Diep[1], MBChB
Benjamin Buemann[2], PhD
Kerstin Uvnäs-Moberg[3], MD, PhD

[1] Histopathology Department, Royal Lancaster Infirmary, Ashton Road, Lancaster, Lancashire, UK, E-mail: ptdiep@doctors.org.uk
[2] E-mail: sigbuemann@gmail.com
[3] Department of Animal Environment and Health, Swedish University of Agricultural Sciences, Skara, Sweden. E-mail: k_uvnas_moberg@hotmail.com

OPEN ACCESS

Citation: Diep, P., Buemann, B., Uvnäs-Moberg, K., Marazziti, D., Carter, C.S. (2020). Letter to the editor. From the editor'desk. Commentary. *Clinical Neuropsychiatry*, *17*(3), 192-195.

doi.org/10.36131/CNEPUB20201703

Funding: None.

Competing interests: Phuoc-Tan Diep, Benjamin Buemann none. Kerstin Uvnäs-Moberg see the download page.

Corresponding author
Donatella Marazziti, M.D.
Adjunct Professor, Dipartimento di Medicina Clinica e Sperimentale, University of Pisa, and University Unicamillus, Rome, Scientific director of BRF Foundation Lucca, Italy
E-mail: dmarazzi@psico.med.unipi.it

Currently, there is no simple explanation for the differences in pattern of morbidity and mortality seen in COVID-19 infection between subgroups of the population and there is no safe effective treatment available. However, several clinical trials are underway investigating new treatments, for example, antiviral drugs.

Some of the risk factors for morbidity and death of COVID-19 – first emerging in China – have been shown to be consistent across different countries (Li et al., 2020).

1. Young people are less severely affected than the elderly people,
2. people showing metabolic risk factors are more severely affected than those without,
3. females are less severely affected than males,
4. pregnant women are not necessarily more vulnerable to the disease than non-pregnant women,
5. further African Americans are more at risk for serious disease than are other American groups.

Therefore, according to these parameters, the highest risk groups would be the elderly, the chronically ill, men and African Americans.

Indeed, the patterns of plasma oxytocin levels are the following:

1. Higher in the young than in the elderly (Elabd et al., 2014).
2. Higher in metabolically fit individuals compared to those demonstrating metabolic risk factors (Yuan et al., 2016).
3. Higher in women than in men (Marazziti et al., 2019).
4. Higher in pregnant women than in non-pregnant women (Prevost et al., 2014).
5. Race differences in oxytocin levels have been identified with lower levels in African Americans (Grewen, Light, Mechlin & Girdle, 2008).

The authors therefore hypothesize that higher levels of oxytocin might be associated with reduced morbidity and mortality in COVID-19 infection.

Oxytocin is a nonapeptide produced in the hypothalamus, acting as a neuropeptide in different brain areas and as a hormone and paracrine substance in peripheral organs. It was originally described as the hormone regulating labor and lactation, but has been shown to exert important behavioral and physiological functions including potent anti-stress and restorative effects (Uvnäs-Moberg, Handlin, Kendall-Tackett, Petersson, 2019).

It has colloquially been referred to as the "love hormone", given its role in social interaction and bonding (MacDonald & MacDonald, 2010).

If, indeed, variations in the oxytocin levels in part explain the difference in severity of the disease in the groups mentioned above, and in particular, if low levels of endogenous oxytocin are linked to severe disease there may be reason to suggest that administration of oxytocin could

Submitted April 10, 2020, accepted April 14, 2020

be used for the treatment of COVID-19 patients.

The high mortality of COVID-19 is due to an exorbitant inflammatory response, which may result in acute respiratory distress syndrome (ARDS) and multiorgan damage. It is therefore pivotal to bring this hyperinflammation under control. Different anti-inflammatory drugs may be deployed including glucocorticoids but in many cases the treatment is limited by their general immunesuppressive effects.

Also from this perspective it is interesting that oxytocin may exert potent anti-inflammatory effects in humans (Clodi et al., 2008) and may have a therapeutical potential against cardiovascular disease (Buemann & Uvnäs-Moberg, 2020). In contrast to glucocorticoids oxytocin may exert supportive (Stanić et al., 2016) and stimulatory (Macciò, Madeddu, Chessa, Panzone, Lissoni & Mantovani, 2010) impacts on lymphocytes.

Anti-inflammatory mechanisms may be involved in the organ protective properties of oxytocin as demonstrated in mice, where it has been shown to mitigate acute lung injury and multiorgan failure (Işeri, Sener, Saglam, Gedik, Ercan & Yegen, 2005). In addition, restorative effects of the peptide may add to this effect.

As far as implementation is concerned, it is easily available as exogenous oxytocin is administered every day in most hospitals worldwide to induce and enhance labor.

To implement the potential treatment of COVID-19 patients with oxytocin throughout the world would not take months, but just weeks or even days as soon as reliable data are available documenting positive effects of the peptide.

An additional and equally important aspect to be considered is that it is possible to increase endogenous oxytocin levels by behavioral modifications or interventions. This could be implemented immediately, even before using oxytocin as an exogenous drug (Marazziti et al., 2006).

If the administration of exogenous oxytocin would reduce progression and mortality of COVID-19 thousands of lives might be saved.

It should be noted that oxytocin is a natural hormone that is safe enough to be routinely administered in women in obstetric settings throughout the world. The risks of its use are small or negligible and the pharmacokinetics are well known (Uvnäs-Moberg et al., 2019).

There are many possible areas of research which could be used to confirm or refute this hypothesis: a. to assess oxytocin blood levels in COVID-19 patients with different levels of severity; b. and amongst at-risk groups; c. to carry out double blind placebo-controlled trials with oxytocin.

In conclusion, the authors believe that the variations in morbidity and mortality patterns observed in COVID-19 infection, are consistent with the proposal that lack of oxytocin might play a significant role in the expression of pathophysiology of COVID-19. There is sufficient experimental evidence that oxytocin possesses anti-inflammatory effects also in humans. In addition, it may stimulate the adaptive immune response and enhance restorative mechanisms which may accelerate the recovery of COVID-19 patients.

Oxytocin is a safe and inexpensive drug which is used and available in most hospitals. The authors suggest that it should be considered for clinical investigation for the treatment of COVID-19 by itself or in combination with other drugs.

(We have everything to gain and nothing to lose).

References

Buemann, B., & Uvnäs-Moberg, K. (2020). Oxytocin may have a therapeutical potential against cardiovascular disease. Possible pharmaceutical and behavioral approaches. *Medical hypotheses, 138*, 109597. https://doi.org/10.1016/j.mehy.2020.109597.

Clodi, M., Vila, G., Geyeregger, R., Riedl, M., Stulnig, T. M., Struck, J., Luger, T. A., & Luger, A. (2008). Oxytocin alleviates the neuroendocrine and cytokine response to bacterial endotoxin in healthy men. *American Journal of Physiology. Endocrinology and Metabolism, 295*(3), E686–E691. https://doi.org/10.1152/ajpendo.90263.2008.

Elabd, C., Cousin, W., Upadhyayula, P., Chen, R. Y., Chooljian, M. S., Li, J., Kung, S., Jiang, K. P., & Conboy, I. M. (2014). Oxytocin is an age-specific circulating hormone that is necessary for muscle maintenance and regeneration. *Nature Communications, 5*, 4082. https://doi.org/10.1038/ncomms5082.

Grewen, K. M., Light, K. C., Mechlin, B., & Girdler, S. S. (2008). Ethnicity is associated with alterations in oxytocin relationships to pain sensitivity in women. *Ethnicity & Health, 13*(3), 219–241. https://doi.org/10.1080/13557850701837310.

Işeri, S. O., Sener, G., Saglam, B., Gedik, N., Ercan, F., & Yegen, B. C. (2005). Oxytocin protects against sepsis-induced multiple organ damage: role of neutrophils. *The Journal of Surgical Research, 126(1)*, 73–81. https://doi.org/10.1016/j.jss.2005.01.021.

Li, L.Q., Huang, T., Wang, Y.Q., Wang, Z.P., Liang, Y., Huang, T.B., Zhang, H.Y., Sun, W., & Wang, Y. (2020). COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *Journal of Medical Virology 12*. doi: 10.1002/jmv.25757

Macciò, A., Madeddu, C., Chessa, P., Panzone, F., Lissoni, P., Mantovani, G. (2010). Oxytocin both increases proliferative response of peripheral blood lymphomonocytes to phytohemagglutinin and reverses immunosuppressive estrogen activity. *In Vivo (Athens, Greece), 24*(2), 157-163.

MacDonald, K., & MacDonald, T. M. (2010). The peptide that binds: a systematic review of oxytocin and its prosocial effects in humans. *Harvard Review of Psychiatry, 18*(1), 1-21.

Marazziti, D., Bani, A., Casamassima, F., Catena, M., Consoli, G., Gesi, C., Iovieno, N., Massei, G. J., Muti, M., Ravani, L., Romano, A., Roncaglia, I., Scarpellini, P. (2006). Oxytocin: an old hormone for new avenues. *Clinical Neuropsychiatry, 3*(5), 302-321.

Marazziti, D., Baroni, S., Mucci, F., Piccinni, A., Moroni, I., Giannaccini, G., Carmassi, C., Massimetti, E., & Dell'Osso, L. (2019). Sex-Related Differences in Plasma Oxytocin Levels in Humans. *Clinical Practice and Epidemiology in Mental Health*, *15*, 58–63. https://doi.org/10.2174/1745017901915010058).

Prevost, M., Zelkowitz, P., Tulandi, T., Hayton, B., Feeley, N., Carter, C. S., Joseph, L., Pournajafi-Nazarloo, H., Yong Ping, E., Abenhaim, H., & Gold, I. (2014). Oxytocin in pregnancy and the postpartum: relations to labor and its management. *Frontiers in Public Health*, 2, 1. https://doi.org/10.3389/fpubh.2014.00001.

Stanić, D., Plećaš-Solarović, B., Petrović, J., Bogavac-Stanojević, N., Sopić, M., Kotur-Stevuljević, J., Ignjatović, S., Pešić, V. (2016). Hydrogen peroxide-induced oxidative damage in peripheral blood lymphocytes from rats chronically treated with corticosterone: the protective effect of oxytocin treatment. *Chem Biol Interact*, 256, 134-141.

Uvnäs Moberg, K., Handlin, L., Kendall-Tackett, K., Petersson, M. (2019). Oxytocin is a principal hormone that exerts part of its effects by active fragments. *Med Hypotheses,* 133:109394.

Yuan, G., Qian, W., Pan, R., Jia, J., Jiang, D., Yang, Q., Wang, S., Liu, Y., Yu, S., Hu, H., Sun, W., Ye, J., Mao, C., Zhuang, R., Zhou, L. (2016). Reduced circulating oxytocin and High-Molecular-Weight adiponectin are risk factors for metabolic syndrome. *Endocr J, 63*(7), 655-62.

FROM THE EDITOR'DESK

Donatella Marazziti

Donatella Marazziti, MD: Adjunct Professor, Dipartimento di Medicina Clinica e Sperimentale, University of Pisa, and University Unicamillus, Rome, Scientific director of BRF Foundation Lucca, Italy, e-mail address: dmarazzi@psico.med.unipi.it, ORCID: 0000-0002-4021-5829

I read with interest the letter to the editor entitled "Oxytocin, a possible treatment for COVID-19? Everything to gain, nothing to lose" written by Drs. Phuoc-Tan Diep, Benjamin Buemann and Kerstin Uvnäs-Moberg and decided to accept it for publication in my journal after the positive comments of rewievers and myself.

With no doubt, the COVID-19 pandemic is a tragic event involving and scrambling everybody worldwide for its high morbidity and mortality provoking negative consequences at both societal and individual level (Marazziti, 2020).

Unfortunately, there are still no specific therapeutic strategies for COVID-19, being massive vaccination the only effective treatment to curb and possibly stop its diffusion. As a result the treatment of COVID-19 patients is mainly empirical and, therefore, symptomatic, or derived from previous experiences with other coronavirus, such as that of SARS, or simply experimental. In the meanwhile, it is essential to develop novel and effective treatments. The nonapeptide oxytocin seems to exert multiple activities that would indicate that it might be a good candidate as an effective treatment for COVID-19 infection.

The possible usefulness of oxytocin infusion was already proposed for COVID-19 patients (Buemann, Marazziti and Uvnäs-Moberg, paper submitted). Indeed, there is a consistent literature highlighting the anti-inflammatory properties of oxytocin exerted through multiple mechanisms involving inhibition of pro-inflammatory cytokines and the macrophage-mediated pro-inflammatory cascade, as well as decrease of oxidative stress exposure (Clodi et al., 2008; Li Wang, Wang & Wang, 2016; Garrido-Urbani et al., 2018). It is also worth noting that oxytocin is of great importance in regulating immune system that links social behavior and experiences with the capacity to heal when facing a stress or trauma especially in the central nervous system (CNS). For these reason, oxytocin administration might be relevant to potentiate impaired immune processes due to isolated COVID-19 patients that show also CNS damage. In addition, isolation due to hospitalization and even to quarantine or forced loneliness may impair the engagement of the most evolved mammalian autonomic nervous system at the basis of our social behavior mainly regulated by oxytocin, with further detrimental consequences in the immune system (Carter, 2017).

In conclusion, I would like to mention that, in the review process of this letter, I involved great experts in the oxytocin field that all approved its fast publication. I must confess that I was moved and even happy to note the easiness of scientific collaboration amongst international colleagues. Their behaviour was altruistic and so far away from the short-sightedness of too many goverments that are still unable to cooperate to fight the common threat represented by the current pandemic.

Our shared comment is that we cannot wait too long: the pandemic requires urgent medical countermeasures and targeted weapons. Therefore, we strongly invite governative medical agencies to implement clinical trials with oxytocin in COVID-19 patients.

References

Buemann, B., Marazziti, D., Uvnäs-Moberg, K. (2020). Can intravenous oxytocin infusion counteract hyperinflammation in COVID-19 infected patients? (submitted)

Carter, C. S. (2017). The oxytocin-vasopressin pathways in the context of love and fear. *Frontiers in Endocrinology, 22*;8:356. doi: 10.3389/fendo.2017.00356. eCollection 2017.

Clodi, M., Vila, G., Geyeregger, R, Riedl, M., Stulnig, T.M., Struck, J., Luger, T.A., & Luger, A. (2008). Oxytocin alleviates the neuroendocrine and cytokine response to bacterial endotoxin in healthy men. *American Journal of Physiology & Endocrinology & Metabolism*, *295*(3):E686-691. doi: 10.1152/ajpendo.90263.2008

Garrido-Urbani, S., Deblon, N., Poher, A.L., Caillon, A., Ropraz, P., Rohner-Jeanrenaud, F., & Altirriba, J. (2018). Inhibitory role of oxytocin on TNFα expression assessed in vitro and in vivo. *Diabetes & Metabolism*, *44*(3):292-295. doi: 10.1016/**j**.diabet.2017.10.004

Li, T., P. Wang, S. C. Wang and Y. F. Wang (2016). Approaches mediating oxytocin regulation of the immune system. *Frontiers in Immunology,* 89. 1291-1304. doi.org/10.3389/fimmu.2016.006

Marazziti, D. (2020). The COVID-19 outbreak: the latest challenge to psychological and psychiatric intervention. *Clinical Neuropsychiatry*, *17*(2), 39-40.

COMMENTARY

OXYTOCIN, LOVE AND THE COVID-19 CRISIS

C. Sue Carter

C. Sue Carter, PhD: The Kinsey Institute, 150 S. Woodlawn Ave. Indiana University, Bloomington, IN 47405 USA
E-mail: suecarterporges@gmail.com

As brilliantly described by Dr. Phuoc-Tan Diep et al. (Diep, Buemann, Uvnäs-Moberg, 2020) in "Oxytocin, a possible treatment for COVID-19? Everything to gain, nothing to lose," it very plausible that the presence (or absence) of oxytocin could help explain the patterns of vulnerability seen in the COVID-19 epidemic. This is wonderful news for those who survive and suggests that oxytocin might be used as a treatment for COVID-19 patients who are suffering from what appears to be an over-reactive immune response to this virus (Buemann, Marazziti,Uvnäs-Moberg, submitted).

Epidemiological research has long supported the therapeutic power of social support and "love." There is strong evidence that the physiological benefits of human social attachment include the actions of the mammalian peptide hormone known as oxytocin (Carter, 2017). Oxytocin is now applied in roughly half of all hospital births to induce or facilitate labor. It affects tissues throughout the body including brain, autonomic nervous system and immune system helping to deliver babies, milk and affection.

Evidence for the healing power of oxytocin is impressive, possibly due directly to the capacity of oxytocin to overcome inflammation, and thus suggesting a way to reduce damage from COVID-19. In addition, oxytocin appears to help normalize the functions of the brain, autonomic nervous system, immune system and mitochondria, and might help reduce the fatigue and other post infection consequences of this virus (Bordt, Smith, Demarest, Bilbo & Kingsbury, 2019).

Under ideal circumstances preclinical studies would be done, first testing the effects of oxytocin against the COVID-19 virus. However, these are not ideal circumstances, and this approach would be too slow to help the hundreds of thousands suffering from this infection. Even in the absence of such studies there is strong evidence that oxytocin could be added immediately to the battery of molecules being tested as **acute** treatments for COVID-19.

It will be very important to future understanding of viral illness in general to know more about the endogenous levels of oxytocin and its receptors in individuals who are asymptomatic or who are exposed do not become infected. For example, does oxytocin really explain why women are less vulnerable to COVID-19?

Oxytocin is globally available, inexpensive and, especially when given acutely and in nonpregnant adults is safe with few known side effects. Although oxytocin is considered a nontoxic molecule, the route of administration (intravenous or intranasal), dose and duration of treatment matters. However, in excessive amounts oxytocin may act on receptors for other systems, such as vasopressin, that are actually "proinflammatory" (Carter, 2017). It is critical that this work be done in the context of data collection and be conducted as controlled clinical trials.

References

Buemann, B., Marazziti, D.,Uvnäs-Moberg, K. (2020) Can intravenous oxytocin infusion counteract hyperinflammation in COVID-19 infected patients? (submitted)

Bordt, E. A., Smith, C. J., Demarest, T. G., Bilbo, S. D. & M. A. Kingsbury (2019). Mitochondria, Oxytocin, and Vasopressin: Unfolding the Inflammatory Protein Response. *Neurotox Res, 36*(2), 239-256

Carter, C. S. (2017). The oxytocin-vasopressin pathways in the context of love and fear. *Front. in Endocrinology, 22*(8), 356. doi: 10.3389/fendo.2017.00356. eCollection 2017.

Diep, P., Buemann, B., Uvnäs-Moberg, K. (2020). Oxytocin, a possible treatment for COVID-19? Everything to gain, nothing to lose. *Clinical Neuropsychiatry, 17*(3) Epub ahead of print. doi.org/10.36131/cnepub20201703