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.

Keywords: COVID-19, pandemic, treatment, oxytocin, immune system, inflammation

Phuoc-Tan Diep¹, MBChB

Benjamin Buemann², PhD Kerstin Uvnäs-Moberg³, MD, PhD

Keistili Uvilas-Mobelg , MD, FID

¹Histopathology Department, Royal Lancaster Infirmary, Ashton Road, Lancaster, Lancashire, UK, E-mail: ptdiep@doctors.org.uk

²E-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



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

© 2020 Giovanni Fioriti Editore s.r.l. This is an open access article. Distribution and reproduction are permitted in any medium, provided the original author(s) and source are credited.

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 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 antiinflammatory 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. *Me*-*dical 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/10.2174/1745017 901915010058).
- 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.