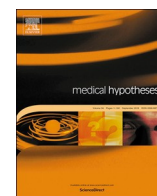




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Hypothesis: Oxytocin is a direct COVID-19 antiviral

A recent Correspondence proposed the neurohormone oxytocin as a defence for COVID-19 [1]. This is one of a handful of papers in the academic literature [2–4] providing patterns and mechanisms to support oxytocin as an intervention for COVID-19. We propose an additional arrow in the quiver of oxytocin's non-classical functions.

Our hypothesis is that oxytocin may have direct antiviral effects against SARS-CoV-2.

Dipeptidyl peptidase-4 (DPP4) protease inhibitors have been proposed as a treatment for Middle Eastern respiratory syndrome coronavirus and COVID-19 [5] and oxytocin happens to be a natural DPP4 inhibitor [6], therefore it is not unreasonable to propose that oxytocin could inhibit other proteases.

There are three papers that raise the possibility that oxytocin could be an antiviral against SARS-CoV-2 via other targets. The first two papers [7,8] identify oxytocin as one of the FDA drugs that could inhibit the SARS-CoV-2 main protease. The third paper [9] raises the possibility that oxytocin analogues, an oxytocin antagonist and a vasopressin analogue are inhibitors of the SARS-CoV-2 RNA-dependent RNA polymerase. We suggest that this raises the possibility that oxytocin, with its similar structure, could also be an inhibitor of some of these enzymes.

Future research is needed to confirm if oxytocin is a direct antiviral via inhibition of the SARS-CoV-2 main protease, other viral targets or if it inhibits transmembrane serine protease 2 (TMPRSS2) for instance.

Even if oxytocin does not have direct antiviral effects it still has sufficient mechanisms that could make it effective against COVID-19 such as immunomodulatory, cardioprotective, anti-diabetic and anabolic functions as well as psycho-social functions [10].

Increasing endogenous oxytocin could increase viral resistance and increase general health especially in vulnerable population groups. Oxytocin can be administered as an exogenous drug in multiple ways; however, oxytocin in solution requires consistent refrigeration. The more recent development of a dry inhaler makes oxytocin available to the whole world.

Therefore, if oxytocin is identified as a true antiviral it would make oxytocin the single most effective defence and treatment for COVID-19, helping us turn the tide in this global war and helping us stop the Second Wave that threatens to overwhelm us. Oxytocin may be the Achilles heel of a seemingly invulnerable enemy.

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2020.110329>.

References

- [1] Soumier A, Sirigu A. Oxytocin as a potential defence against Covid-19? *Med Hypotheses* 2020;140:109785.
- [2] Buemann B, Marazziti D, Uvnäs-Moberg K. Can intravenous oxytocin infusion counteract hyperinflammation in COVID-19 infected patients? *World J Biol Psychiatry* 2020;1–30.
- [3] Imami AS, O'Donovan SM, Creeden JF, Wu X, Eby H, McCullumsmith CB, et al. Oxytocin's anti-inflammatory and pro-immune functions in COVID-19: a transcriptomic signature based approach. *Physiol Genomics* 2020.
- [4] Diep PT, Buemann B, Uvnäs-Moberg K, Marazziti D. Oxytocin, a possible treatment for COVID-19? Everything to gain, nothing to lose. *Clin Neuropsychiatry* 2020;17:192–5.
- [5] Solerte SB, Di Sabatino A, Galli M, Fiorina P. Dipeptidyl peptidase-4 (DPP4) inhibition in COVID-19. *Acta Diabetol* 2020;6:1.
- [6] Chittepudi VCSR, Kalhotra P, Osorio-Gallardo T, Jiménez-Martínez C, Robles-de la Torre RR, Gallardo-Velazquez T, et al. New molecular insights into the inhibition of dipeptidyl peptidase-4 by natural cyclic peptide oxytocin. *Molecules* 2019;24(3887).
- [7] Pant S, Singh M, Ravichandiran V, Murty US, Srivastava HK. Peptide-like and small-molecule inhibitors against Covid-19. *J Biomol Struct Dyn* 2020;5:1–10.
- [8] Contini A. Virtual screening of an FDA approved drugs database on two COVID-19 coronavirus proteins. *ChemRxiv* 2020.
- [9] Ahmad J, Ikram S, Ahmad F, Rehman IU, Mushtaq M. SARS-CoV-2 RNA Dependent RNA Polymerase (RdRp)–A drug repurposing study. *Heliyon* 2020;6:e04502.
- [10] Kasabri V, Shawakri E, Akour A, Naffa R, Khawaja N, Al-Sarraf I, et al. Cross sectional correlates of Increased IL-18 but reduced fetuin-A and oxytocin with adiposity and blood indices in metabolic syndrome patients with or without diabetes. *Therap Advan Endocr Metab* 2018;329–38.

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