

Using iLINCS to mine for Oxytocin signature to find new drug candidates or molecular pathways that can be used for future treatment for autism

Gabby (Chris) Vento^{1*}, Elissar Andari²

¹College of Medicine and Life Sciences, 3000 Arlington Avenue, The University of Toledo, Toledo OH 43615

²Assistant Professor, Department of Neurosciences and Psychiatry, 3000 Arlington Avenue, The University of Toledo, Toledo OH 43615

Email: christopher.vento@rockets.utoledo.edu

Received 12/4/2024

Accepted: 12/18/2024

Published 10/15/2025

Introduction: There are currently no pharmacological treatments available to treat social affective symptoms in Autism. It has been proposed that the social-bonding hormone oxytocin could be administered to promote social affective ability in those with ASD 1–3. The problem with simply administering Oxytocin as a neuropeptide is that its half-life is only around three minutes, thus greatly limiting its clinical usefulness 2. Identifying molecular pathways of oxytocin and mechanisms of action (MOA) of targets that are similar to oxytocin's action, using transcriptomics available datasets, can be promising in identifying genes and pathways that could be further investigated in future translational autism research.

Methods: Three RNA-SEQ studies were identified on the NCBI database that examined Oxytocin exposure to nerve cells in these data sets: GSE210528, GSE24666, and GSE199427, with the first two studies from rat tissue samples and the last one from human stem cells in a laboratory setting 4–6. The data was analyzed with the Library of Integrated Network-Based Cellular Signatures – or iLINCS, to find molecular pathways of oxytocin and mechanisms of action of genes that have similar transcriptomics signature to oxytocin.

Results: Oxytocin had a significant effect on neural activity and signaling pathways, including enrichment of MAPK signaling. Oxytocin exposure led to positive regulation of protein phosphorylation and to Phosphatase Binding. Among the top concordant mechanisms of actions were shown to be HDAC Inhibitor, NF-κB Pathway Inhibitor, Dopamine Receptor and Serotonin Receptor Antagonist.

Conclusion: This analysis indicates that Oxytocin does enrich molecular pathways, and has similar mechanisms of action to genes, that are directly involved in autism psychopathology. A combination of oxytocin and SSRIs or anti-inflammatory markers can be further investigated in laboratory settings under control conditions to better understand its mechanisms in the context of autism research.

Keywords: Autism, ASD, Aspergers, Oxytocin, Psychoneuroendocrinology

References

1. Andari E, Duhamel JR, Zalla T, Herbrecht E, Leboyer M, Sirigu A. *Promoting social behavior with oxytocin in high-functioning autism spectrum disorders*. Proc Natl Acad Sci U S A, 2010. 107(9): pp. 4389-4394. doi:10.1073/pnas.0910249107
2. Guastella AJ, Hickie IB. *Oxytocin Treatment, Circuitry, and Autism: A Critical Review of the Literature Placing Oxytocin Into the Autism Context*. Biol Psychiatry, 2016. **79**(3):234-242. doi:10.1016/j.biopsych.2015.06.028
3. Young LJ, Wang Z. *The neurobiology of pair bonding*. Nat Neurosci, 2004. **7**(10): pp. 1048-1054. doi:10.1038/nn1327
4. Janz, P., Knoflach, F., Bleicher, K., Belli, S., Biemans, B., Schnider, P., Ebeling, M., Grundschober, C., & Benekareddy, M. *Selective oxytocin receptor activation prevents prefrontal circuit dysfunction and social behavioral alterations in response to chronic prefrontal cortex activation in male rats*. Front Cell Neurosci, 2023. **17**: p. 1286552. doi:10.3389/fncel.2023.1286552
5. Nishimura H, Yoshimura M, Shimizu M, Sanada K, Sonoda S, Nishimura K, Baba K, Ikeda N, Motojima Y, Maruyama T, Nonaka Y, Baba R, Onaka T, Horishita T, Morimoto H, Yoshida Y, Kawasaki M, Sakai A, Muratani M, Conway-Campbell B, Lightman S, Ueta Y. *Endogenous oxytocin exerts anti-nociceptive and anti-inflammatory effects in rats*. Commun Biol, 2022. **5**(1): p.907. doi:10.1038/s42003-022-03879-8
6. Wasserman, A. H., Huang, A. R., Lewis-Israeli, Y. R., Dooley, M. D., Mitchell, A. L., Venkatesan, M., & Aguirre, A. *Oxytocin promotes epicardial cell activation and heart regeneration after cardiac injury*. Front Cell Dev Biol, 2022. **10**: p.985298. doi:10.3389/fcell.2022.985298
7. Xie, Z., Kropiwnicki, E., Wojciechowicz, M. L., Jagodnik, K. M., Shu, I., Bailey, A., Clarke, D. J. B., Jeon, M., Evangelista, J. E., V Kuleshov, M., Lachmann, A., Parigi, A. A., Sanchez, J. M., Jenkins, S. L., & Ma'ayan, A. *Getting Started with LINCS Datasets and Tools*. Curr Protoc, 2022. **2**(7): p. e487. doi:10.1002/cpz1.487