OXYTOCIN/DOPAMINE RECEPTOR BIVALENT LIGANDS: A NEW STRATEGY TO TREAT NEUROPSYCHIATRIC AND NEURODEVELOPMENTAL DISORDERS

Marta Busnelli[1], Arianna Costanzo[2], Francesca Santini[3], Alessandro Gori[4], Bice Chini[1]

[1]CNR, Institute of Neuroscience, Milan - Italy, [2]Department of Pharmacological and Biomolecular Sciences- University of Milan, Milan - Italy, [3]Department of Medical Biotechnology and Translational Medicine, University of Milan, Milan - Italy, [4]Istituto di Chimica del Riconoscimento Molecolare, CNR, Milan - Italy

Introduction: Social behavior defects characterize many neurodevelopmental neuropsychiatric disorders, such as autism spectrum disorders and schizophrenia, and are difficult to treat. A pharmacological intervention with the neuropeptide oxytocin (OXT) and antipsychotics acting on the dopamine system, alone or in combination, were effective in some patients with schizophrenia and autism spectrum disorder to rescue social impairments and cognitive defects (Feifel et al., 2016; Gulliver et al., 2019; Andari et al., 2018). In the central nervous system, these two systems, the oxytocin and dopamine, cooperate to determine certain social and affiliative behaviours, such as pair bonding and sexual behaviours (Baskerville and Douglas, 2010). Moreover, the oxytocin (OXTR) and dopamine receptors (D2R) mRNA and binding sites exist in the same brain regions (Smeltzer et al., 2006; Quintana et al., 2019) and the receptors are in close proximity (Romero Fernandez et al., 2013).

Material and methods: In cells transfected with OXTR and D2R, using Bioluminescent Resonance Energy Transfer (BRET)-based methodology, we measured receptor-receptor interaction and downstream-signalling pathway activation. Moreover, we developed a novel fluorescent OXT-analog to map OXTR brain distribution and to determine where its expression overlaps with D2R.

Results: We found that OXTR physically interacts with D2R to form dimers or oligomers, and this interaction modulates receptor signaling. The stimulation of OXTR/D2R with dopamine and oxytocin does not influence dimer formation and potentiates Gi/o protein signaling. We are now developing bivalent ligands that target specifically OXTR/D2R heterodimers and we are characterizing the effects on receptor signaling and internalization. Moreover, we found that OXTR and D2R receptors are co-expressed in a number of brain regions relevant for social behaviors (i.e. hippocampus, amygdala).

Discussion and conclusion: Our studies are fundamental to indicate where OXTR/D2R dimers can be functional and to understand the signaling properties of OXTR/D2R dimers. The bivalent ligands generated can pave the way for the development of advanced therapies for neuropsychiatric and neurodevelopmental disorders.

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1. Feifel et al., A Review of Oxytocin's Effects on the Positive, Negative, and Cognitive Domains of Schizophrenia. 2016Biol. Psychiatry
2. Gulliver et al., Targeting the Oxytocin System: New Pharmacotherapeutic Approaches. 2019Trends Pharmacol. Sci.
3. Andari et al., A Precision Medicine Approach to Oxytocin Trials. 2018Current Topic Behav. Neurosci.
4. Baskerville and Douglas, Dopamine and oxytocin interactions underlying behaviors: potential contributions to behavioral disorders. 2010 CNS Neurosci. Ther.
5. Smeltzer et al., Dopamine, oxytocin, and vasopressin receptor binding in the medial prefrontal cortex of monogamous and promiscuous voles. 2006Neurosci. Letter
6. Quintana et al., Oxytocin pathway gene networks in the human brain. 2019Nat. Commun.
7. Romero Fernandez et al., Evidence for the existence of dopamine D2-oxytocin receptor heteromers in the ventral and dorsal striatum with facilitatory receptor-receptor interactions. 2013Mol. Psychiatry