Targeting the oxytocin system: novel therapeutic agents for neurodevelopmental diseases and neuropsychiatric disorders

Defects in social behaviours, such as interpersonal communication, emotion recognition and empathy, are a characteristic symptom of a range of neuropsychiatric disorders. These symptoms are often intractable and profoundly affect the patient’s quality of life. The hypothalamic neurohormone oxytocin (OT) has emerged as a key regulator of diverse social behaviours across species, and thus it has been proposed as a potential therapeutic intervention to improve social dysfunction in various neuropsychiatric disorders, such as stress, anxiety disorders, social phobia, postpartum depression, bipolar disorder, autism spectrum disorder (ASD), and schizophrenia. OT administration has been found to efficaciously reverse social deficits in many animal models of neuropsychiatric diseases, whereas clinical trials investigating peripheral OT administration in patients with schizophrenia and ASD and healthy cohorts reported inconclusive or divergent results1,2. The interpretation of these studies, however, is complicated by the small patient cohorts analyzed, the heterogeneous behavioural readouts, the large variations in dosing regimens and by the limited understanding of the complex neurobiology underpinning OT signalling in the brain.

The oxytocin receptors (OTRs), that can be expressed on the cell surface as monomers, homodimers or heterodimers, transduce the OT signal intracellularly via the activation of different G proteins subtypes and downstream effectors.

The main goals of our research are to understand the various signaling mechanisms mediating oxytocin receptor-induced cell responses in the brain and to develop novel OTR active molecules with increased therapeutic efficacy and no undesirable effects. Introducing subtle modifications in the OT aminoacidic sequence, we have obtained three ligands able to activate specific G-protein subtype pathways associated with the OTR3,4. Two synthetic ligands, Atosiban and DNalOVT, specifically activate Gαi1 and Gαi3, respectively, but don’t induce β-arrestin recruitment. The long-acting OT analog Carbetocin selectively engages the Gαq-signalling pathway, and promotes receptor internalization through a still uncharacterized β-arrestin-independent pathway. These functionally selective ligands for the OTR could be used to explore the cellular and behavioral effects of OTR-mediated Gαi/o and Gαq signaling and may have a range of therapeutic applications. As an example, the use of Atosiban recently helped us to identify a new population of oxytocinergic neurons involved in pain signalling, and contributed to clarify the role of OTR/Gαi in the CNS5.

We also generated a new class of oxytocin bivalent ligands, where two oxytocin-derived agonists were joined by a flexible carbonylic spacer. These pioneering ligands, specifically targeting OTR homodimers, behave as OTR superagonists activating, in functional cell assays, the OTR/Gαq signalling pathway at a concentration that is 1,000 times less than that required by their monovalent counterparts. Moreover, their administration boosts social interactions in a mice model characterized by social defects and also in zebrafish6.

We are now investigating the interactions between OTRs and other GPCRs important for neuropsychiatric dysorders, i.e. dopamine receptors, and we are generating bivalent ligands able to specifically target OTR heterodimers.

Our newly developed OT-analogs can help not only to define how the specific cellular responses and behavioral effects are generated, but to pave the way for the development of advanced therapies for social dysfunction in neuropsychiatric and neurodevelopmental disorders.

References:
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2 Andari E et al., A Precision Medicine Approach to Oxytocin Trials. Curr Top Behav Neurosci. 2018

Keywords: oxytocin analogues, neuropsychiatric disease, neurodevelopmental disorders

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