

COMMENTARY ON: DIVERSITY OF OXYTOCIN NEURONS: BEYOND MAGNO- AND PARVOCELLULAR TYPES? FERDINAND ALTHAMMER AND VALERY GRINEVICH. *J NEUROENDOCRINOL* 2017;DOI: 10.1111/JNE.12549.

Suleima Jacob-Tomas and Masha Prager-Khoutorsky
McGill University, Montreal, QC, Canada, H3G1Y6
<http://masha-prager-khoutorsky.lab.mcgill.ca/>

In the recent issue of *Journal of Neuroendocrinology*, Ferdinand Althammer and Valery Grinevich review classical works as well as novel findings focusing on the understanding of the anatomical and functional properties of oxytocin (OT) neurons. In this comprehensive review, the authors present an updated overview of distinct morphological and electrophysiological properties and diverse projections of OT neurons, and highlight the implications of these novel findings for animal physiology and behavior (1). OT is a key neuropeptide involved in reproduction and social behavior including pregnancy, parturition, lactation, maternal behavior, sexual receptivity, and bonding (2). OT is synthesized in neurons located in several hypothalamic nuclei, including the paraventricular (PVN), supraoptic (SON), and accessory (AN) nuclei (3, 4). Early studies conducted in the 1980s classified two categories of OT cells: magnocellular (magnOT) and parvocellular (parvOT) neurons (5). MagnOT neurons are involved in milk ejection, uterine contractions, and fear response (1, 2), while parvOT neurons modulate autonomic system, including cardiovascular function, respiration, and pain perception (1, 6). Traditionally, magnOT neurons are believed to project to the posterior pituitary to release OT into the circulation, whereas parvOT are thought to project to hindbrain spinal cord areas (1).

The authors summarize accumulating evidence that challenges the conventional and over-simplified view of magnOT and parvOT neuron classification. Importantly, several pioneer studies described the presence of extrahypothalamic OT projections already in late 1970s (7-9), however, their functional significance remained unclear. Recent studies have significantly advanced the understanding of the oxytocinergic system by providing a comprehensive description of extrahypothalamic OT projections into many forebrain regions (10). Notably, in the seminal paper published in *Neuron* in 2012, the group of Grinevich demonstrated the functional significance of OT projections into the central amygdala in fear responses (10). This and later studies have confirmed that in addition to projections to the posterior pituitary, magnOT neurons also form collaterals and innervate over 50 forebrain regions including subcortical and cortical structures, as well as the hindbrain (e.g. amygdala and ventral tegmental area) (1, 10, 11). Likewise, new findings indicate that in addition to projecting to the hindbrain (e.g. dorsal vagal complex, nucleus *tractus solitarius*, and rostral ventrolateral medulla) and spinal cord structures, parvOT neurons project to the SON magnOT cells (to control activity-dependent secretion of OT into the circulation (6)) and possibly to additional forebrain areas (1). The parvOT neurons have also been shown to project to the ventral tegmental and *substantia nigra* to regulate dopamine system (12).

In addition to demonstrating anatomically- and connectivity-divergent populations of magnocellular and parvocellular OT neurons, new evidence suggests the existence of phenotypic differences within each category. Using a single-cell RNA-sequencing approach, a recent study has revealed at least four types of OT neurons having distinct genetic patterns (13).

These novel findings suggest that there are several genetically and anatomically distinct populations of OT neurons projecting to multiple brain areas. To increase our understanding of how different types of OT neurons mediate diverse reproductive and social behaviors, it is imperative to further characterize OT cell phenotypes based on genetic profiling, electrophysiological properties, and connectivity. Additional studies are necessary to further examine the complexity of OT neurons function and may undermine the simplistic view once believed of OT neurons.

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