Developmental specification and adult cellular plasticity of oxytocin and vasopressin systems

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ABSTRACT

The neuromodulators oxytocin (OXT) and arginine vasopressin (AVP) are closely related neuropeptidergic peptides that play critical roles in regulating complex animal behaviors and homeostatic functions. Both neuropeptides are mainly synthesized in specific hypothalamic nuclei, such as the paraventricular and supraoptic nuclei (PVN and SON), among others. Our previous work (Madrigal & Jurado, 2021) revealed that distinct OXT and AVP nuclei are developed independently and most of them show a significant number of neurons co-expressing OXT and AVP during early postnatal stages (PND). Coincident population, of OXT and AVP+ neurons drastically decline in the adult brain suggesting cellular plasticity is developmentally regulated. Using brain clearing techniques (DISCO®) and 3D imaging, we analyzed whether OXT and AVP systems also exhibit plastic properties in the adult brain. Our results indicate that certain nuclei undergo cellular plasticity in a sex and motherhood-dependent manner obtaining the most prominent phenotype in the periventricular nucleus (PeVN) (sex-dependent), and the SON and retrochiasmatic area (RCH) in which OXT and AVP plasticity is mainly motherhood-dependent. Furthermore, sexual experience induces an increase of tyrosine hydroxylase (TH) expression levels in a subpopulation of OXT and AVP neurons in the RCH. Our findings provide new information to understand the specification of neuropeptidergic systems during development and their plastic properties upon critical life events in the adult animal.

RESULTS I

Characterization of OXT and AVP neurons in their specific nuclei

RESULTS II

Partitioning-dependent plasticity of OXT & AVP systems

We wondered whether vital experiences such as sexual encounters and parturition were able to elicit changes in cell identity in the adult brain. Our preliminary data show dynamic changes in distinct OXT and AVP populations between virgin and mothers. On the one hand, the percentage of OXT+ neurons appears increased in parturition females in the PeVN, whereas the percentage of AVP+ or the mixed population (OXT+AVP+) cells are decreased. Furthermore, AVP+ cell population is increased in female after parturition in the PeVN. In the mixed population is decreased. These results indicate a dynamic neuroplastic expression in response to vital experiences such as sexual encounters and gestation. Next experiments will explore the expression of AVP+ and OXT+ neurons during pregnancy to identify the time point at which changes first appear.

RESULTS III

Partitioning increases TH expression in a subpopulation of OXT and AVP cells

Given the importance of dopaminergic signaling for maternal care, we explored the expression of tyrosine hydroxylase (TH) expressing cells (rabbit anti-TH; Merck, AR152). TH immunohistochemistry revealed a large number of positive cells in almost all hypothalamic nuclei of both virgin females and mothers (except in SCH, SON). Interestingly, TH expression did not colocalize with OXT or AVP in most of the nuclei, except for the RCH where most TH cells were also TH-OXT co-expressing. Consequently, parturition did not increase the expression or the distribution of the TH-OXT population. Furthermore, the increase in the TH-OXT population appears in parallel with a significant reduction of OXT+AVP cells suggesting that the identity of OXT and AVP neurons undergoes a region-specific regulation in response to sexual experience and parturition, which highlights the dynamic nature of these systems in the mature brain.

CONCLUSIONS AND HYPOTHESIS

1. 3D brain reconstructions indicate that certain OXT-AVP nuclei undergo cellular plasticity in a sex-dependent manner in specific hypothalamic nuclei such as AN and PeVN, and periventricular areas like the BNST.

2. DISCO® and 3D imaging have exposed a motherhood-dependent cellular plasticity of the OXT and AVP systems in the hypothalamus. Furthermore, OXT and AVP+ neurons in the retrochiasmatic area (RCH).

FUTURE DIRECTIONS

Since the natural development of the OXT and AVP systems has been established (Madrigal & Jurado, 2021), future studies will explore the plastic properties of the oxytocinergic and vasopressinergic circuits in the adult brain in response to vital life events such as sexual experience and aging. Furthermore, we aim to analyze these plastic properties under pathological conditions by employing a Mice KO mice, a mouse model of Ret’s syndrome which have been shown to exhibit severe social deficits (Martinez-Rodriguez et al., 2019, 2020). This work is being carried out in collaboration with Dr. Carmen Agustín and Enrique Lainz’s laboratory at University of Valencia. We expect this analysis will reveal disruptions in the formation and plasticity of the OXT and AVP systems in the adult and developing brain of this animal model that may underlie some of their cognitive and social deficits. Moreover, this basic knowledge may allow designing novel strategies to palliate this and other neurodevelopmental disorders characterized by impairments in social behavior.

METHODS

Brain clearing (DISCO®) and 3D brain reconstruction imaging

The main technique used in this work is the 3D imaging of solvent-cleared organ protocol (DISCO® - Fig. A). We analyzed OXT and AVP positive neurons with specific primary antibodies (rabbit anti-Vasopressin, Millipore PC2345L; mouse anti-Oxytocin; NIH Cambridge, a gift from Dr. Howard Gainer (NIH).