Neuropeptide Signaling Networks and Brain Circuit Plasticity

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Cynthia K McClard[1,2] and Benjamin R Arenkiel[2,3,4,5]

[1]Medical Scientist Training Program, Baylor College of Medicine, Houston, TX, USA. [2]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA. [3]Graduate Program in Developmental Biology, Baylor College of Medicine, Houston, TX, USA. [4]Jan and Dan Duncan Neurological Research Institute, Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA. [5]Department of Neuroscience, Baylor College of Medicine, Houston, TX, USA.

ABSTRACT: The brain is a remarkable network of circuits dedicated to sensory integration, perception, and response. The computational power of the brain is estimated to dwarf that of most modern supercomputers, but perhaps its most fascinating capability is to structurally refine itself in response to experience. In the language of computers, the brain is loaded with programs that encode when and how to alter its own hardware. This programmed "plasticity" is a critical mechanism by which the brain shapes behavior to adapt to changing environments. The expansive array of molecular commands that help execute this programming is beginning to emerge. Notably, several neuropeptide transmitters, previously best characterized for their roles in hypothalamic endocrine regulation, have increasingly been recognized for mediating activity-dependent refinement of local brain circuits. Here, we discuss recent discoveries that reveal how local signaling by corticotropin-releasing hormone reshapes mouse olfactory bulb circuits in response to activity and further explore how other local neuropeptide networks may function toward similar ends.

KEYWORDS: Neuropeptide, CRH, CRHR1, activity-dependent, plasticity

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CORRESPONDING AUTHOR: Benjamin R Arenkiel, Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX 77030, USA.
Email: arenkiel@bcm.edu

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Introduction

"Intelligent" computer programs in the modern age strive to learn from experience, but this magnificent feat is routinely performed by the most complex and mysterious of all computing devices: the brain. The brain is a labyrinth of specialized circuits that gather information from the environment to generate appropriate behavioral and physiological responses. One of the brain's most remarkable capacities is the ability to perceive new information about a changing world and to fine-tune itself for adaptation. A long and rich history of experiments has established that such adaptation to experience occurs by physically reshaping the synapses and branches of interconnected neurons. But rewiring circuits is a precarious task, unless it is invoked and executed with precision. Indeed, brain circuit remodeling by the hands of experience is localized not just to selectively activated circuits, but to specific microdomains within those circuits. This suggests that elements deep within the brain's architecture tightly regulate the brain's capacity to remodel itself. Only sophisticated circuit schematics and molecular syntax could specify how the brain can accomplish such exacting changes to its wiring diagram.

Programming Power in the Language of Neuropeptides

Of all languages available for programming such remarkable capabilities, signaling by secreted neuropeptides provides perhaps the most diverse and flexible means of molecular communication. It is estimated that up to hundreds of genes in the human genome encode neuropeptide precursors,[1,2] and that many more encode G protein–coupled receptors (GPCRs),[3] which serve as the most common receptor types for neuropeptide ligands. Interestingly, others have demonstrated in the mouse model that the most of the GPCRs that bind neuropeptide ligands are expressed in the brain.[3] This implies the importance of GPCR signaling for normal brain function. Together, the variety and promiscuity of neuropeptides for GPCR targets, and the inherent modularity of intracellular GPCR signaling,[4] render it likely that neuropeptide signaling networks execute highly refined roles in both neural computation and plasticity.

Since their recognition as a distinct subset of signaling molecules in the 1960s to 1970s,[5,6] neuropeptides have been associated with a wide range of brain functions,[1,4] from mediating global behaviors to modulating synapse firing.[7] Neuropeptide-secreting neurons have best been characterized in the hypothalamus, with one of their major known functions being endocrine regulation of organism-wide homeostasis. Interestingly, neurons that express neuropeptides are also widely distributed throughout brain tissue, with lesser known effects.

One example of a neuropeptide historically characterized for its role in the hypothalamus is corticotropin-releasing hormone (CRH). Via the hypothalamus-pituitary-adrenal axis, CRH secretion is induced following novel or challenging

stimuli and coordinates physiological stress responses across multiple organ systems. The CRH signaling thus serves as a powerful mechanism that can directly influence an organism's behavioral adaptations to changing environments. Interestingly, CRH is also expressed by neurons in several other brain areas, together with its cognate receptors CRHR1 (CRH receptor 1) or CRHR2.[8,9] This spatial pairing of CRH-secreting and receptor-expressing cells within specialized regions suggests a role for local CRH signaling in circuit-specific regulation. Notably, local CRH expression has been linked to novel environmental input[10] and to dendritic remodeling.[11] Local CRH signaling thereby offers a molecular route for physiological experience to reshape brain circuits and mediate specific circuit outputs. Wiring diagrams that include local CRH-CRHR1 signaling loops could therefore endow brain circuits with a potent mechanism for activity-dependent self-modulation.

Local CRH Signaling: An Element Encoding Activity-Dependent Remodeling

Insights into the roles for local CRH signaling in experience-dependent plasticity have largely derived from work in animal models, with particular attention to its function in the hippocampus and olfactory bulb (OB) in rodents. The mouse OB features multiple forms of experience-dependent circuit plasticity that persist into adulthood, including ongoing neurogenesis and the continued synaptic integration and dendritic refinement of adult-born neurons. This remarkable capacity of the OB to restructure itself throughout life in part arises from its anatomical organization, circuit architecture, and the unique cell types embedded within.

The mouse OB circuit displays both laminar and columnar organization. Odor signaling is carried into the bulb via olfactory sensory neuron axons, which synapse with the terminal apical branches of mitral/tufted (M/T) cell dendrites in glomeruli. From the glomeruli, signaling then moves deeper into the bulb along M/T cell apical dendrites, which transverse the external plexiform layer (EPL). Interwoven in the EPL are interneurons that contribute to feed-forward signal processing and impart inhibition onto M/T cell activity. Deep to the EPL, mitral cell soma and their lateral dendrites maintain a clustered configuration. The deepest layer of the bulb, the granule cell layer (GCL) harbors granule cell interneurons, which provide additional input onto mitral cell signaling and further shape odor information before it is sent to higher brain areas. Notably, when newborn neurons are activated by experience during circuit integration, they predominantly take residence within the GCL. Mature granule cells provide inhibitory input onto lateral dendrites of M/T cells via dendrodendritic connections. Similar to M/T cells, granule cells appear to cluster with sister cells, together shaping odor-specific signals. Thus, spanning concentric layers of the bulb are columns of functionally connected units of excitatory cells and inhibitory interneurons that together form an operational "neighborhood" tuned to given odors.

Local CRH signaling networks in the OB comprise CRH-secreting interneurons in the EPL and CRHR1-expressing granule neurons in the GCL. The CRH-secreting interneurons are reciprocally connected to mitral cells[12] and can be induced by circuit activity to secrete CRH ligand[13] onto nearby CRHR1-expressing granule cells. This signaling has been found to be important for the survival and integration of newborn neurons.[13] Moreover, CRHR1 activation in granule cells initiates expression of regulatory genes, such as POU6f1, that promote dendritic outgrowth and new excitatory synapses onto granule cells.[14] Enhanced inhibitory input by newborn granule cells is hypothesized to provide an optimal signal-to-noise ratio during odor processing. Thus, in the mouse OB, CRH signaling molecularly links circuit activation to remodeling, which facilitates adaptive circuit function.

Interestingly, the reciprocal connectivity of CRH interneurons with mitral cell cohorts implies that local CRH signaling, and its associated circuit remodeling capacity, can be induced in an odor-specific manner. Indeed, odor association learning alters the synaptic connectivity[12] and odor response domains[15] of new granule cells to trained odors. These changes are not observed in OBs of mice where general circuit activity is present, but learned odor associations are never established.[12] Local signaling by CRH thus offers a mechanism by which experience reshapes the olfactory circuit with exquisite specificity.

Learning Odor Signatures of a Familiar Mouse: New Roles for Oxytocin and Vasopressin in Olfactory Plasticity?

Much attention has been given to 2 other neuropeptides involved in mediating social olfactory behavior: oxytocin and vasopressin.[16] Similar to CRH, both oxytocin and vasopressin have classically been studied for roles in long-range hypothalamic signaling but have been increasingly recognized for local effects in brain circuits, including regulating dendritic plasticity.[17] In contrast to CRH, no local source of oxytocin has yet been identified in the bulb. However, the structurally similar neuropeptide vasopressin, with known receptor cross-reactivity, is expressed in local cell types of the rodent OB.[18] Intriguingly, the receptors for both oxytocin (OXTR [oxytocin receptor]) and vasopressin (AVPR1b [arginine vasopressin receptor 1b]) are robustly expressed in the OB,[19] suggesting that signaling through these peptide networks may partially rely on long-range diffusion, volume transmission, or systemic signaling from the hypothalamus. It has been hypothesized that experiences such as mating, parturition, and pup rearing activate secretion from the hypothalamus, which then may directly influence olfactory guided social recognition and/or bonding behaviors.[16]

When oxytocin signaling pathways are disrupted via genetic knockout of OXTR[20] or AVPR1b,[21,22] mice display defective social recognition and memory. Interestingly, both OXTR and AVPR1b knockout mice have normal odor sensitivity and discrimination[21,22] and display generally normal social interactions,[20] indicating that primary defects may include aspects of learning and/or memory. By contrast, rescue experiments have shown that infusion of oxytocin or vasopressin into wild-type rat

OBs improves social memory.[23] Given that both hormones have been implicated in physical remodeling of brain circuits,[17] we entertain the hypothesis that oxytocin and/or vasopressin signaling in the bulb is required for newborn neuron circuit refinement in response to novel learned and/or socially significant odor stimuli. This would be promising ground for future inquiry.

Conclusions

A major challenge for encoding experience-dependent remodeling into a biological circuit lies in the mandate for action linked to a probabilistic phenomenon. One of the most flexible means of communication within and across brain circuits includes signaling by neuropeptides and their cognate GPCRs. Over the past 4 decades, great strides have been made toward understanding how peptide signaling alters synaptic dynamics,[24] offering insight into how such mechanisms might transcend static wiring diagrams to create new functional brain circuits.[25] A growing body of evidence indicates that peptide signaling may also convey circuit-shaping effects of experience in local neuronal networks, by influencing the cellular and synaptic integration of new neurons.[11,13,14,26] We hypothesize that CRH, OXT, and AVP are just a few examples of a larger paradigm of neuropeptide programming for the brain—a prototype mechanism of circuit "intelligence" that resolves the need to modify circuit output with dynamic changes to physiological conditions. Regulatory programs that control such circuit restructuring programs are of great future interest and are certain to be as diverse as the neuropeptides themselves.

Author Contributions

CKM and BRA wrote the commentary.

ORCID iD

Benjamin R Arenkiel https://orcid.org/0000-0001-9047-2420

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