Neuro-endocrinology

42

BRIEFINGS

The Neurohypophysis – Fishing for New Insights

SUMMARY

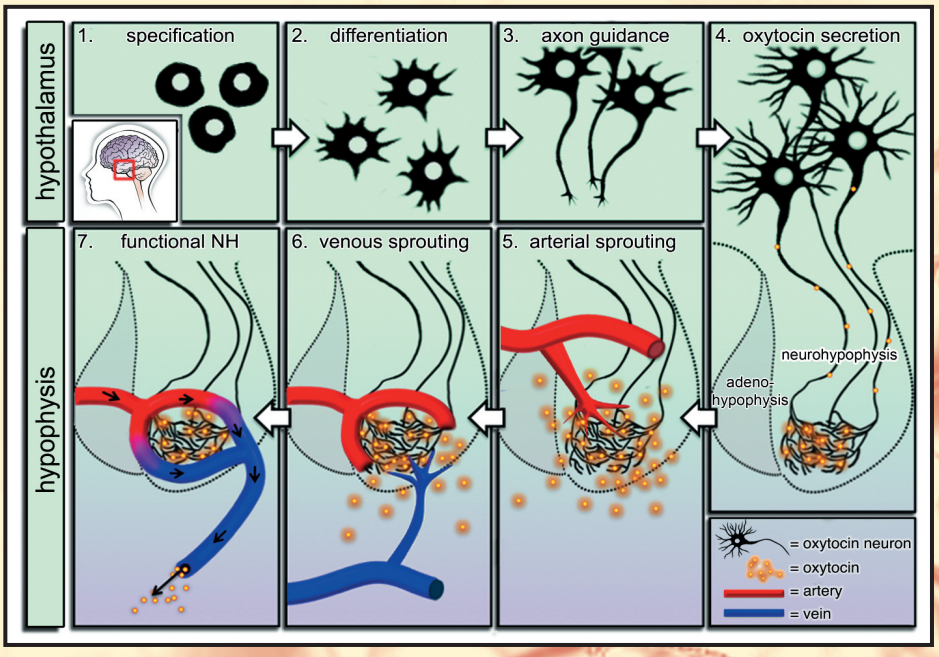
The neurohypophysis is a neuro-vascular interface through which the brain regulates peripheral organs in order to maintain homeostasis. The emergence of new genetic and imaging tools has begun to yield new insights into the molecular mechanisms underlying its formation. In a recent study, researchers discovered that in embryonic zebrafish, oxytocin secreted from hypophyseal axons serves as a local angiogenic cue that pulls in nearby blood vessels.

The hypothalamo-neurohypophyseal system (HNS) consists of neuronal cell bodies residing in the supraoptic and paraventricular nuclei of the hypothalamus. These neurons produce the peptides oxytocin and vasopressin, which are packaged into vesicles that are transported along axons that terminate in the neurohypophysis. In response to stimulation, the vesicles release their contents onto a matrix of fenestrated (i.e., permeable) capillaries, through which they enter the blood to exert their well-known effects on water balance and reproduction.

A rendezvous

Over a century of research has elucidated the structure of the neurohypophysis in much detail. At its essence, it is an interface between two discrete biological components: axons of neurons from the CNS and peripheral blood vessels. A third component, glial pituicytes, facilitates this interface. Each of the system's building blocks descends from a distinct lineage during embryonic development, but somehow they all reach the same point and interact with one another to form the neurohypophysis. The precise cellular events that underlie this process have remained largely unknown because the developmental dynamics of this complex 3-D structure cannot be readily deduced from fixed histological sections. This limitation has been recently addressed using advanced live imaging and molecular genetic tools and the establishment of the zebrafish as a model system for studying development of the vertebrate brain.

During embryonic development, hypothalamic neurons are born from progenitor cells that progressively acquire neuronal properties following exposure to gradients of



Neuronal precursors in the hypothalamus respond to external and internal signals that promote specification (1). They differentiate into oxytocin neurons (2) and their axons extend into the neurohypophysis (3). Oxytocin is produced in neuronal cell bodies, trafficked to the axon terminals and secreted into the neurohypophysis (4). Oxytocin acts as an angiogenic factor, pulling vascular sprouts from nearby arteries (5) then veins (6). When the mature hypophyseal vasculature forms, blood flows through the neurohypophysis and carries oxytocin to the periphery.

secreted molecular cues. These cues activate specific neuronal transcriptional programs that drive oxytocin and vasopressin cell identities. During HNS differentiation, elongating axons traverse long distances to reach their target by extending towards attractant molecular cues and away from repulsive cues secreted along the way.

Unlike neurons, blood vessels are not born in the brain, but rather extend into it via angiogenesis, a process by which new vessels form by sprouting and extending from existing vessels. As with axons, vascular sprouts grow towards sources of secreted trophic molecules. In this manner, the hypophyseal capillary network originates from the major arteries and veins of the head. It is known that the passage of neurohypophyseal hormones from nerve termini into the blood is facilitated by the permeable nature of the fenestrated hypophyseal capillaries, but it remains unclear what controls fenestration of these vessels.

Finding the way

How, then, do the axons and blood vessels interact with one another to form the functional neurohypophysis? This question has remained largely unanswered, but our growing understanding of axon guidance and vascular patterning can help us to speculate on likely strategies. One possibility is that a trophic biochemical cue is secreted from the neurohypophyseal anlage itself (perhaps by pituicytes), and simultaneously pulls in both axons from hypothalamic neurons and nearby vascular sprouts. This idea gains credence from evidence that axonal growth cones respond to known angiogenic factors just as vascular sprouts grow towards known axon guidance cues. Another possibility is that one component pulls in the other- i.e., nascent hypophyseal vessels release an attractant molecule for growing axons from hypothalamic neurons or axon terminals secrete an angiogenic factor that attracts nearby vascular sprouts. A recent report helped answer this question by demonstrating that in zebrafish embryos, oxytocin acts as an angiogenic cue for nearby vascular sprouts, drawing them towards the axon terminals where they go on to form the hypophyseal arteries and veins (Fig. 1). This finding emphasizes a clear hierarchy in the design of the neurohypophyseal interface. In a way, oxytocin actively builds the vascular platform required for its own release into the periphery.

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Rebuilding the broken

Severing the axons of the HNS tract in rats causes nerves terminals to regenerate in an ectopic location, which in turn shows increased angiogenesis, and thus the neurohypophysis is functionally re-established in a new, ectopic location. Amazingly, this feat of regeneration has since been found to occur in human patients whose pituitary had been surgically removed. Using live imaging of regenerating axons and vessels in the zebrafish model, it may soon be possible to understand the molecular mechanism driving this remarkable regenerative process, potentially leading to clinically significant insights into CNS regeneration.

Quo Vadis

For over a century, the quest to understand the neurohypophyseal interface has provided us with many insights into the nature of neurosecretion and neurovascular interaction. Still more intriguing questions await answers, some of which may soon be provided through a variety of powerful new genetic tools and imaging methods. How do the axons of oxytocin and vasopressin neurons find their way to the neurohypophysis? What role, if any, do pituicytes play in this axon guidance event? What regulates fenestration of the hypophyseal capillaries and when do they become permeable to neuropeptides? No doubt the century-old story of the neurohypophysis still has some surprising plot twists to deliver.

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