RESEARCH HIGHLIGHT

Illuminating brain development

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Intrinsically photosensitive retinal ganglion cells (ipRGCs) are light-sensing neurons in the retina that project to multiple retinorecipient brain regions. In a recent study by Hu et al., the authors show that light stimulation of melanopsin-expressing ipRGCs is required for the release of oxytocin in the brain to boost synaptogenesis and learning in adult mice.

The sun provides cell signaling ligands in the form of photons that regulate the timing of developmental events and behavior in animals. The retina plays an important role in this regulation because it contains a diverse array of neurons that detect light for both visual and non-visual physiology. Retinal light sensing is mediated by at least four types of photoreceptors: rods, cones, and two varieties of photosensitive retinal ganglion cells (RGCs) that express either melanopsin (OPN4) or neuropsin (OPN5). While rods and cones are responsible for image-forming vision, RGC photoreceptors function primarily in non-visual light sensing. OPN5 RGCs sense violet light for the regulation of a local circadian clock[1] as well as in vascular[2] and refractive development.[3]

The intrinsically photosensitive OPN4-expressing RGCs (ipRGCs) locally regulate retinal development,[4] but also project to distinct brain regions that regulate circadian photoentrainment,[5] the pupillary light reflex,[6] and mood.[7] ipRGCs can respond to light much earlier than rods and cones, which only become active after postnatal day 10 (P10) in the mouse. During the postnatal period, ipRGCs have already innervated many brain regions.[8] However, the biological function of many of these projections is unknown; similarly, the impact of light on brain development and its long-term effects on learning and cognition are unclear. The exciting study published by Hu et al.[9] uncovers one such pathway, in which melanopsin-expressing ipRGCs project to the supraoptic nucleus (SON) to regulate oxytocin release and synaptogenesis in a light-dependent manner (Fig. 1). These data suggest that this light sensing circuit fine-tunes brain development.

Synapses are the building blocks of neural circuits and the hubs for communication between neurons. By analyzing mice in which the *Opn4* gene was deleted, Hu et al. revealed that loss of melanopsin resulted in fewer synapses in multiple brain regions, including sensory cortices and hippocampus, the regions that function in learning and memory. These changes to synaptogenesis could be rescued by expressing melanopsin in *Opn4*-deficient ipRGCs, suggesting that OPN4-expressing ipRGCs are required for normal brain development. Interestingly, cortical synaptogenesis temporally coincides with ipRGC light responsiveness. Mice reared in the dark have synapse reductions similar to that observed in melanopsin-null mice, indicating that light sensing is required for cortical synaptogenesis.

The SON is a retinorecipient target of ipRGCs and is known to control oxytocin production. While canonical roles for oxytocin include social bonding and reproduction, it has also been implicated in synaptic plasticity during early development. Utilizing multiple viral labeling strategies, Hu et al. confirmed that melanopsin-expressing ipRGCs project to the SON, and that SON neurons form reciprocal connections with oxytocin neurons in the paraventricular nucleus (PVN). Furthermore, loss of melanopsin significantly reduced levels of oxytocin in the cerebrospinal fluid (CSF). The authors noted that oxytocin-null mice showed decreases in synaptogenesis similar to those observed in the melanopsin-null mice. Furthermore, synaptic defects were reversed by activating oxytocin neurons in melanopsin-null mice. Oxytocin neurons have complex projection patterns,[10] and whether these projections directly influence the observed changes in development and behavior has yet to be assessed.

ipRGCs are light sensitive but also integrate input from the rod and cone photoreceptors that become functional later in postnatal development. Surprisingly, Hu et al. found that melanopsin loss-of-function resulted in a synaptic deficiency by P9 but not later at P13 when rods and cones have become light sensitive. This suggests that rod and cone photoreceptors provide a compensatory mechanism for the observed synaptic defects.

Lastly, Hu et al. wanted to investigate whether alterations in synaptogenesis influenced behavior in adults. The learning ability of 2-month-old mice was tested using a sound discrimination task. Mice deficient in melanopsin during early development, but not in adulthood, were slower in completing the task. Similarly, activation of oxytocin neurons could rescue the learning deficits in melanopsin-null mice. The most interesting finding was that not only was light exposure required for cortical synaptogenesis but also for learning in adults, highlighting the significance of early light exposure for normal brain development and function.

Mechanisms underlying light-regulated physiological functions have profound implications for human health. Circadian desynchrony alters metabolism and mood, and disrupts neurotransmission and neuroplasticity. As Hu et al. have demonstrated, light is an important factor in brain development. Intriguingly, the risk of developing a variety of human diseases, including neurological conditions, is associated with birth season.[11] This association may be partially attributed to seasonal changes in light stimulation during crucial phases of development. Furthermore, given that people nowadays spend more time indoors, the intensity and spectral characteristics of interior lighting could be an important consideration. Thus, we are beginning to gain more insights into

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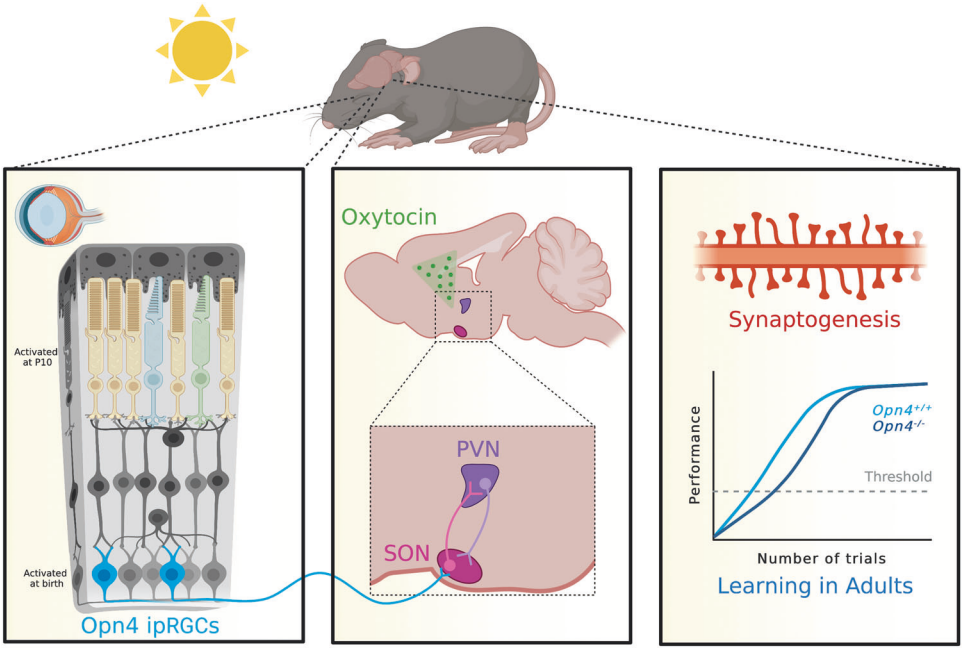

Fig. 1 The effect of melanopsin-expressing ipRGCs on brain development. Melanopsin-expressing ipRGCs are light-sensitive neurons in the retina that project to multiple regions of the brain. One such retinorecipient region is the SON, which forms a reciprocal circuit with the PVN, to release oxytocin. The release of oxytocin is required for normal synapse formation during development and impacts learning in adults. This figure was created with BioRender.

the importance of light stimulation in shaping human development and homeostasis. Future work assessing light sensing pathways in humans will be imperative for understanding their implications in human diseases.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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