Alpha Cells Take Off First

Shigang He[1,*]
[1]State Key Laboratory of Brain and Cognitive Sciences, Institute of Biophysics, Chinese Academy of Sciences, 15 Da-tun Road, Beijing 100101, China
*Correspondence: shiganghe@moon.ibp.ac.cn
DOI 10.1016/j.neuron.2008.08.001

Using a transgenic mouse line in which GFP is expressed in a single population of retinal ganglion cells (RGCs), Huberman and colleagues report in this issue of *Neuron* that the axon terminals of RGCs exhibit an orderly pattern of distribution in the higher visual centers. This pattern undergoes a developmental refinement, and synchronous activity in early postnatal retina regulates columnar but not laminar formation.

It is textbook material that in cats and primates RGC axons from one eye travel to the lateral geniculate nucleus (LGN) and occupy specific layers termed the ocular dominance layers. The formation of ocular dominance layers undergoes an activity-dependent refinement when the initially exuberant and incorrectly placed branches of axon terminals are pruned. It is not clear how axon terminals of an entire population of RGCs distribute and to what degree axon terminals of different populations separate or overlap in higher visual centers. This knowledge is important for understanding how visual information extracted by each of about 15–20 types of RGCs in the retina (Masland, 2001) interacts in higher visual centers and how terminals of different types of RGCs compete and corroborate with each other to achieve their adult patterns. The major hurdle in tackling these questions is the lack of means to selectively and specifically label an entire population of RGCs.

Until recently, the only population of RGCs labeled was the RGCs that express melanopsin and function in non-image-forming aspects of vision (Hattar et al., 2002; Berson et al., 2002). Rapid development has emerged recently. A few months ago, a study reported the transgenic marking of a population of RGCs (Kim et al., 2008). The junctional adhesion molecule B (JAM-B) was shown to mark a class of OFF RGCs, previously classified as RG_{C6} on morphological bases in adult (Sun et al., 2002) and in early postnatal (Diao et al., 2004) mice. Functionally, these RGCs were shown to detect upward motion. In this issue of *Neuron*, Huberman and colleagues (Huberman et al., 2008) identified another type of RGC, previously classified as RG_{A2} (Sun et al., 2002; Diao et al., 2004) and physiologically identified as transient OFF α cells (Pang et al., 2003). More excitingly, this elegant study provided the first insight into the distribution of axon terminals of a complete population of RGCs in the higher visual centers and the developmental refinement processes of these terminals.

Huberman and colleagues screened a library of BAC transgenic mice with GFP expressed under the control of different promoters and found that, in the calretinin-EGFP mice, GFP was expressed in a population of regularly spaced neurons in the ganglion cell layer (GCL). The presence of an axon and degeneration after optic nerve transection confirmed that these cells are RGCs but not displaced amacrine cells also residing in the GCL. The large soma size and immunoreactivity to neurofilament indicate that the GFP-positive RGCs are likely α cells. Dendritic morphology revealed by microstaining with DiI further assured α cell identity. That the DiI-labeled dendrites stratify in the outer part of the inner plexiform layer, together with the subsequent electrophysiological recordings, showed the GFP cells are transient OFF αRGCs (tOFF-αRGCs). The regular spacing and complete tiling of dendritic fields suggested that every member of the population has been labeled. Therefore, in this mouse line, the population of tOFF-αRGCs was specifically and completely labeled.

Many interesting discoveries were made on this valuable preparation. Examining the projection of the tOFF-αRGCs axons indicated that they terminate only in the superior colliculus (SC) and the lateral geniculate nucleus (LGN), forming a highly stereotyped and specific map. Terminals of tOFF-αRGCs form clear stratification in the inner/medial part of the dLGN, despite no apparent cellular lamination observed in rodents. In the SC, axon terminals not only stratify but also form columnar structures. All axon terminals in the dLGN and SC originate from tOFF-αRGCs in the contralateral eye, because all GFP axons disappear if the contralateral eye is removed. So, what innervates columns alternating with the tOFF-αRGCs columns is an interesting question.

The innervation pattern of tOFF-αRGCs axon terminals in the SC undergoes a developmental refinement: axon terminals are initially less restricted in both lamination and column structure. The refinement is not due simply to the increase in SC thickness or to the reduction in number of tOFF-αRGCs. To further elucidate the mechanism, Huberman and colleagues used a mouse line deficient of nicotinic acetylcholine receptor β2 subunit, in which synchronous activities known as retinal waves (Meister et al., 1991; Bansal et al., 2000) were disrupted in early postnatal development. By crossing the nAChRβ2-deficient line with the calretinin-EGFP line, they can observe developmental changes of axon terminals of tOFF-αRGCs with disrupted synchronous activity in the early postnatal stage. They found that the columnar specification of this mouse line was severely disrupted, whereas the laminar specification in the SC and the LGN was normal, consistent with earlier findings that activity but not correlated activity is sufficient in instructing formation of lamination in the LGN (Huberman et al., 2003). In addition, even though the spontaneous activity returns to normal by P8 (Bansal et al., 2000), columnar structures were still

severely perturbed in the adult, indicating that there is a critical period for columnar specification during the first postnatal week and that correlated activity is required in this period for column formation.

This study signifies the dawn of a new era—one can imagine that in the near future different populations of RGCs labeled with XFPs will allow visual neuroscientists to discern, in a single preparation, the relationship of axon terminals of different types of RGCs in the SC, LGN, or other visual centers, therefore revealing convergence of information coded by different channels from the retina. Furthermore, it will be possible to visualize developmental interactions between terminals of different populations of RGCs to establish maps in higher visual centers. Molecular mechanisms found to regulate map formation (Luo and Flanagan, 2007) can now be tested in these preparations at the global rather than individual level.

REFERENCES

Bansal, A., Singer, J.H., Hwang, B.J., Xu, W., Beaudet, A., and Feller, M.B. (2000). J. Neurosci. *20*, 7672–7681.

Berson, D.M., Dunn, F.A., and Takao, M. (2002). Science *295*, 1070–1073.

Diao, L., Sun, W., Deng, Q., and He, S. (2004). J. Neurobiol. *61*, 236–249.

Hattar, S., Liao, H.W., Takao, M., Berson, D.M., and Yau, K.W. (2002). Science *295*, 1065–1070.

Huberman, A.D., Wang, G.Y., Liets, L.C., Collins, O.A., Chapman, B., and Chalupa, L.M. (2003). Science *300*, 994–998.

Huberman, A.D., Manu, M., Koch, S.M., Susman, M.W., Lutz, A.B., Ullian, E.M., Baccus, S.A., and Barres, B.A. (2008). Neuron *59*, this issue, 425–438.

Kim, I.J., Zhang, Y., Yamagata, M., Meister, M., and Sanes, J.R. (2008). Nature *452*, 478–482.

Luo, L., and Flanagan, J.G. (2007). Neuron *56*, 284–299.

Masland, R.H. (2001). Nat. Neurosci. *49*, 877–886.

Meister, M., Wong, R.O., Baylor, D.A., and Shatz, C.J. (1991). Science *252*, 939–943.

Pang, J.J., Gao, F., and Wu, S.M. (2003). J. Neurosci. *23*, 6063–6073.

Sun, W., Li, N., and He, S. (2002). J. Comp. Neurol. *451*, 115–126.

Confused about NMDA and Addiction? Targeted Knockouts Provide Answers and New Questions

David B. Carr[1] and Peter W. Kalivas[1,*]
[1]Department of Neurosciences, Medical University of South Carolina, Charleston, Charleston, SC 29425, USA
*Correspondence: kalivasp@musc.edu
DOI 10.1016/j.neuron.2008.07.025

NMDA-dependent plasticity in VTA dopamine neurons has been hypothesized to be an important first step in the development of long-term changes in the brain reward circuitry that underlie addiction. Two papers from Zweifel et al. and Engblom et al. in this issue of *Neuron* raise new questions concerning the role of NMDA receptors within VTA dopamine neurons in mediating the behavioral effects of drugs of abuse.

Many theories on the development of addiction to drugs of abuse suggest that repeated exposure to these substances co-opts and overpowers the neural circuitry utilized by natural rewards to motivate behavior. By their association with the behavioral effects of the drug, stimuli in the environment become strongly associated with the drug's reinforcing properties. The development of these learned drug associations is thought to contribute to the progression from casual drug use to compulsive drug relapse. Supporting this view is a large body of evidence showing that drugs of abuse can alter learning-related synaptic plasticity mechanisms within the brain's reward processing circuitry. One key area for the development and expression of behaviors associated with drug addiction is the ventral tegmental area (VTA). The VTA contains the dopamine (DA)-containing neurons that project to reward-associated areas of the brain such as the prefrontal cortex and nucleus accumbens. Stimulation of glutamate receptors within the VTA appears to be a critical first step in the development of drug-induced behaviors in experimental animals thought to model the development of compulsive drug seeking, such as conditioned place preference (CPP—a preference for environments associated with the drug) and locomotor sensitization (the progressive increase in the locomotor effects of psychostimulant drugs such as cocaine or amphetamine). Correspondingly, most previous studies reveal that injections of NMDA receptor antagonists directly into the VTA block the development of these addiction-related behaviors.

The cellular mechanisms whereby NMDA receptor stimulation in the VTA is necessary to develop CPP or sensitization was first provided in a series of papers by Bonci and colleagues (Borgland et al., 2004; Ungless et al., 2001). These authors reported that a single injection of cocaine or other addictive drugs increases the strength of glutamatergic synapses on VTA DA neurons. Similar to the strengthening of glutamate synapses in the hippocampus by long-term potentiation (LTP), this increase in synaptic strength was produced by the addition of new AMPA