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Review

A reassessment of the role of activity in the formation of eye-specific retinogeniculate projections

Leo M. Chalupa

Department of Ophthalmology and Vision Science, School of Medicine and Neurobiology, Physiology and Behavior, College of Biological Sciences, University of California, Davis, CA 95616, USA

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ABSTRACT

In all mammalian species the projections from the two eyes to the dorsal lateral geniculate nucleus of the thalamus terminate in separate layers or territories. This mature projection pattern is refined early in development from an initial state where the inputs of the two eyes are overlapping. Here I discuss the results of studies showing that the formation of segregated eye-specific retinogeniculate projections involves activity-mediated binocular competition. I conclude that while retinal activity undoubtedly is involved in this process, the results of recent studies cast doubt on the prevalent notion that retinal waves of activity play an instructional role in the formation of segregated retinal projections.

Contents

1. Introduction

Based on the stationary images Ramon y Cajal observed under his microscope, he was able to deduce a number of astonishing facts about the development and plasticity of neurons. Mostly everyone is familiar with his proposal that extension of developing axons occurs by means of growth cones sensing chemicals that signal their direction of growth. Today the discovery of these signals, and the means by which they regulate axonal growth and direction, is a major theme in molecular neuroscience. Perhaps less well known is the fact that Cajal also proposed the notion that early neuronal connections are exuberant and that “exercise or use” promoted the formation of certain connections while disuse resulted in the loss of others (DeFilipe, 2006). Knowledge of neuronal physiology was primitive at the time, but Cajal’s

E-mail address: lmchalupa@ucdavis.edu.

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proposal clearly presupposes that the activity of neurons is involved in the refinement of early exuberant connections. One hundred years after Cajal was awarded the Nobel Prize for Physiology and Medicine the fact that neuronal activity plays a role in the development of the nervous system has been unequivocally demonstrated by numerous studies at virtually every level of the nervous system. What is still debated, however, is what features of neuronal activity regulate which aspects of development, as well as the mechanisms by which such activity strengthens and weakens specific connections between neurons.

For many decades the visual system, and in particular, the connections between the two eyes and the visual centers of the brain, have served as a model for studies dealing with neuronal development and plasticity. Here I provide an overview of the literature dealing with the role of activity in the formation of segregated left and right eye inputs to the dorsal lateral geniculate nucleus. Until recently, the paramount role of neuronal activity in this developmental process seemed to be firmly established. But now, several studies have raised questions about the main tenets of this widely accepted premise.

This essay will be divided into four parts. First, I will provide some relevant background information on the organization and development of projections from the two eyes to the dorsal lateral geniculate nucleus (dlgn). Next I will summarize the results of some of the studies that support the notion that one particular type of activity, aptly described as retinal waves, plays an instructional role in the formation of segregated eye-specific retinal-dlgn projections. I will then discuss the results of studies that question this prevalent viewpoint, and also consider future research directions that could reconcile some of the seemingly diverse findings in this field. Readers are directed elsewhere for fuller accounts of this topic (Chalupa and Huberman, 2004; Huberman and Chapman, 2006).

2. Relevant features of developing retinogeniculate projections

Retinal ganglion cells from both eyes project to the dlgn in all mammalian species, and the territory innervated by the crossed retinal input is segregated from that of the uncrossed retinal input. Such segregation of retinogeniculate projections, which is a hallmark of the visual system of adult animals, is established during early development from an initial pattern where the inputs of the two eyes are overlapped. This progression from overlapping to segregated retinogeniculate projections was first described about 30 years ago in the fetal monkey by Rakic (1976), and since that time it has been observed in many other species (Chalupa and Dreher, 1991). The timing of this event differs in different species; in some animals, such as cat and monkey it occurs *in utero*, while in others, such as ferret and mouse, it takes place during postnatal life. There also appear to be species differences with respect to the cellular events underlying the gradual refinement of initially exuberant retinal inputs. For instance, in the cat, there is evidence that retraction of initially widespread terminal arbors (Sretavan and Shatz, 1986a,b) as well as the loss of inappropriately projecting retinal ganglion cells (Williams et al., 1983; Chalupa et al., 1984) is responsible for this process. By contrast, in the fetal monkey retinogeniculate terminals show no evidence of early exuberance (Snider et al., 1999), and ganglion cell loss is thought to be solely responsible for the shift from the overlapped to the segregated state.

This brief description of the sequence of events leading to the formation of the mature retinogeniculate pathway raises two related questions: why are retinal projections initially overlapping and what causes the inputs from the left and right eye to become segregated? The former can only be addressed meaningfully when an answer to the latter question becomes apparent.

3. Role of activity in formation of segregated retinogeniculate projections

The seminal studies of Wiesel and Hubel on the development of ocular dominance columns demonstrated in a dramatic fashion that balanced visual stimulation of the two eyes is required for this feature of the visual cortex to form normally (Wiesel, 1982). Their model of activity-based binocular competition appeared to follow Hebb's (1949) postulate whereby cells that fire together wire together. It seemed logical to extend this powerful concept to the development of segregated retinogeniculate projections. The fact that binocular competition plays a role at this level of the visual system was demonstrated by the finding that removal of an eye in a developing animal, at a time when retinal projections from the two eye were overlapping, resulted in the maintenance of a widespread projection from the remaining eye (rat: Lund et al., 1973; macaque: Rakic, 1981; cat: Chalupa and Williams, 1984; ferret: Guillery et al., 1985). Shatz and Stryker (1988) obtained the first evidence that this binocular competition is based on neuronal activity. They showed that infusion of tetrodotoxin (TTX), the sodium voltage-gated channel blocker that abolishes action potentials, into the region of the optic tract of a fetal cat prevented the formation of eye-specific retinogeniculate projections. This was found to reflect an abnormal increase in the size of individual retinogeniculate arbors in the TTX-treated animals (Sretavan et al., 1988).

The next crucial piece of this story was provided by heroic studies from Lamberto Maffei's laboratory in Pisa. These investigators made extracellular recordings from retinal ganglion cells of embryonic rats and discovered that ganglion cells periodically discharge spontaneous action potentials (Galli and Maffei, 1988); moreover the firing patterns of neighboring cells (recorded by one microelectrode) were found to be correlated (Maffei and Galli-Resta, 1990). This work was followed by multi-electrode recordings in Denis Baylor's laboratory at Stanford, using an isolated retinal preparation obtained from developing ferrets. Such recordings revealed in greater detail the spatial–temporal pattern of spontaneous retinal discharges (Meister et al., 1991). It has now been shown in a number of species that the developing retina is characterized by periodic waves of activity whereby closely positioned ganglion cells fire in synchrony (Wong, 1999). Such