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Binocular maps in *Xenopus* tectum: visual experience and the development of isthmotectal topography

Susan B. Udin

Department of Physiology and Biophysics, State University of New York, Buffalo, NY 14214, Tel: 716-829-3571, Fax: 716-829-3575

Susan B. Udin: sudin@buffalo.edu

Abstract

Xenopus frogs have a prominent binocular field that develops as a consequence of the migration of the eyes during the remodeling of the head during and after metamorphosis. In the optic tectum, a topographic representation of the ipsilateral eye develops during this same period. It is relayed indirectly, via the nucleus isthmi. In the early stages of binocular development, the topographic matching of the ipsilateral input and the retinotectal input from the contralateral eye is largely governed by chemical cues, but the ultimate determinant of the ipsilateral map is binocular visual input. Visual input is such a dominant factor that abnormal visual input resulting from unilateral eye rotation can induce isthmotectal axons to alter their trajectories dramatically, even shifting their terminal zones from one pole of the tectum to the other. This plasticity normally is high only during a 3–4 month critical period of late tadpole-early juvenile life, but the critical period can be extended indefinitely by dark-rearing.

NMDA receptors are involved in this process; plasticity can be blocked or promoted by chronic treatment with NMDA antagonists or agonists, respectively. Cholinergic nicotinic receptors on retinotectal axons are likely to play an essential role as well. Modifications in the polysialylation of NCAM are correlated with the state of plasticity. The circuitry underlying binocular plasticity is not yet fully understood but has proved not to be a simple convergence of ipsilateral and contralateral inputs onto the same targets.

Keywords

Xenopus; binocular; isthmi; tectum; nicotinic

INTRODUCTION

The *Xenopus* tectum has produced a wealth of information about the development of the retinotectal projection from the contralateral eye (Ruthazer and Cline, 2004; Richards et al., 2010), but there are also fascinating lessons to be learned from other tectal inputs: the tectum also receives input from the ipsilateral eye via the nucleus isthmi, and this isthmotectal input develops in dramatically different ways from the retinotectal (contralateral eye) input. As this review will explain, the ipsilateral map develops at a significantly later stage; the axons that bring in this binocular information show distinctly different patterns of growth; and the formation of orderly connections by these axons is overwhelmingly controlled by binocular visual input during a critical period of development starting at the end of metamorphosis. We will examine mechanisms by which correlated input from the two eyes brings the ipsilateral eye's input into register with that from the contralateral eye.

The challenge of binocularity

A cursory examination of an adult *Xenopus* frog reveals that the eyes are positioned on the top of the head, producing large binocular overlap (Fig. 1A, bottom). Within the brain, electrophysiological methods reveal correspondingly large binocular visual inputs encompassing almost all of the tectum (Fig. 1B, bottom). However, *Xenopus* do not begin life with this large binocular overlap or large tectal binocular map. Like typical tadpoles, larval *Xenopus* have eyes on the sides of the head, facing laterally, and there is minimal binocular overlap (Fig. 1A, top) (Grant and Keating, 1986b).

As *Xenopus* develop, their heads undergo remodeling that gradually brings the eyes to a dorsofrontal position (Fig. 1A). This process begins at the last stages of metamorphosis and continues for a few months during postmetamorphic life. During this period of change from monocular to binocular vision, there is a similar transformation occurring within the tectum; as the eyes begin to shift, a small region at the front of the tectum, where receptive fields within the new region of binocular overlap are represented, begins to respond to the ipsilateral eye as well as the contralateral eye. As binocular overlap increases, this tectal binocular zone increases from 11% to 77% of the tectal surface (Fig. 1B) (Grant and Keating, 1989a). Throughout the period of increase of binocular vision, the map from the ipsilateral eye not only increases in size but it also stays in topographic register with the map from the contralateral eye (Grant and Keating, 1989a). As described below, this process involves substantial remodeling of axonal arbors (Udin, 1989); and the maintenance of matching of the two eyes' maps requires binocular vision (Grant and Keating, 1989b) and the mediation of NMDA receptors (Scherer and Udin, 1989).

The ipsilateral pathway

Information from the ipsilateral eye does not reach the tectum directly (Gruberg and Udin, 1978; Udin and Keating, 1981). Instead, there is an indirect route. As Fig. 2A shows, for ipsilateral eye input to reach the left lobe, the left eye first sends retinotectal input to the right lobe. From there, tectal cells send a topographic projection to the right nucleus isthmi, a structure lying near the border between the midbrain and hindbrain. The right nucleus isthmi in turn sends a topographic projection via the optic chiasm and post-optic commissure to the left tectal lobe. A corresponding pathway brings ipsilateral input from the right eye to the right tectal lobe. (A homologous crossed pathway is also found in mammals as the parabigeminal projection (Graybiel, 1978) but is absent in fishes, reptiles, and birds.) The axons terminate as two laminae in the superficial layers of the tectum, where they intermingle with the upper and lower tiers of the retinotectal axons (Gruberg and Udin, 1978) (See Fig. 2B). The responses of the ipsilateral axons to visual stimuli are very similar to those of the retinotectal axons in the same laminae, although the receptive fields are somewhat larger and the tendency to habituation is greater (Gaze and Keating, 1970; Gruberg and Lettvin, 1980).

Early development of the isthmotectal projection

Despite the fact that the migration of the eyes does not begin until quite late in tadpole development (Nieuwkoop and Faber stage 60), isthmoc axons reach the tectum several weeks earlier, by stage 52 (Nieuwkoop and Faber, 1967; Udin and Fisher, 1985). Although the retinotectal projection is subserving an almost completely monocular field, the isthmotectal axons nevertheless grow from the rostral to the caudal end of the tectum (Fig. 3A, left). In this respect, their behavior is quite reminiscent of mammalian retinocollicular axons, which also enter the colliculus and initially extend a rostrocaudal process across the full length of the structure. The isthmotectal axons extend short branches throughout their length and make morphologically-identifiable synapses (Udin et al., 1992).

Starting at stage 60, isthmotectal axons with nasosuperior receptive fields begin to arborize at the front margin of the tectum. (For example, see the right-most axon in of the Stage 60-66 axons in Fig. 3A.) This tectal location is where the retinotectal map contains the nasosuperior portion of the visual field. This is the only binocular zone at this age (Grant and Keating, 1986a; Udin, 1989). Therefore, the ipsilateral (isthmotectal) and contralateral (retinotectal) projections match in the binocular zone. Most of the other isthmotectal axons still have receptive fields in the monocular zone and remain poorly arborized. (See Fig. 3, St. 60-66, middle axons.)

In contrast to the mammalian retinocollicular axons, however, a *Xenopus* isthmotectal axon does not have the simple task of arborizing in a fixed terminal zone. Its challenge is that it must shift its terminal zone rostrocaudally as the binocular zone expands and as the retinotectal axons themselves slowly shift due to the continuing growth of the retina (Grant and Keating, 1986b). The two eyes are situated such that the small zone of overlap in their visual fields comes from the temporoventral sectors of the two retinas (nasosuperior visual field). At stage 60, the contralateral eye's temporoventral ganglion cells project to the rostral tectum, and it is to this location that the an isthmoc cell with a nasosuperior visual receptive field will project at this stage. But then the eyes begin to shift position from lateral to dorsomedial; in effect, the animal is becoming cross-eyed, so those two sets of axons no longer have matching receptive fields. In response, the original isthmotectal axon shifts caudally, and a different set of isthmotectal axons arborizes in its old terminal zone (Grant and Keating, 1986a; Udin, 1989). Over the course of about 3 months, the entire population gradually takes its place in the array and forms mature arbors. (See Fig. 3A, Adult.)

The retinotectal system is already quite mature in terms of the extent and linearity of the map and the sizes of the multi-unit receptive fields by the end of metamorphosis (Gaze et al, 1974), and the growth of the ventral retina contributes only minimally during this process (Grant and Keating, 1986b). Thus, the map of the contralateral eye is available as the template for the ipsilateral input. Indeed, during the period of head remodeling and expansion of the binocular field, the ipsilateral map expands and maintains good registration with the contralateral map. One might suppose that binocular visual cues would be the only factor guiding this phenomenon, but surprisingly, the early stages of progressive expansion and shifting of the early isthmotectal map can occur in the absence of visual input. One major piece of evidence indicating that non-visual cues convey topographic cues is that dark-reared *Xenopus* initially display almost normal maps (Grant and Keating, 1989b). Only with time does the requirement for visual activity become apparent, as the ipsilateral axons show increasing topographic errors, particularly along the rostrocaudal tectal axis (Grant and Keating, 1989b).

The switch from non-visual to visual determinants can be demonstrated even more dramatically by rearing the animals with abnormal binocular visual input. This can be achieved by rotating one eye surgically, for example by rotating the right eye 180° around the optic axis. This simple operation is performed by detaching the extraocular muscles and does not involve cutting the optic nerve. The visuotopic map from the rotated eye is, of course, rotated 180°, just as the image on a monitor from a video camera would be if one were to turn the camera 180°. If the map from the unrotated eye did not compensate, the two eyes' maps would thus be completely discordant. At first, this is the case. The isthmotectal axons grow into the tectum and form an essentially normal map that retains its original polarity and internal organization for the first few weeks (Grant and Keating, 1992). (See Fig. 3B.) Gradually, however, the axons shift their trajectories and find new terminal zones such that the ipsilateral map comes into congruence with the rotated retinotectal map (Grant and Keating, 1992). (See Fig. 3C, D.)

An examination of the axons during the transition period after eye rotation reveals that not only do they initially grow toward their normal terminal zones, but despite the mismatched receptive fields, they form quite elaborate arbors (Guo and Udin, 2000). (See Fig. 3C.) It appears that only after forming connections do the axons “detect” the mismatch of activity resulting from the eye rotation. The axons ultimately extend branches away from the main arbor, often taking highly abnormal medial, lateral or even rostral trajectories. After a prolonged period that may last 2-3 months, the axons reach new sites where their visual receptive fields match those from the other eye, and new arbors form (Grant and Keating, 1992; Guo and Udin, 2000). (See Fig. 3C.) The arbors can transiently maintain two arbors -- original ones that conform to the non-visual cues and new ones that conform to the binocular visual cues. Eventually, the original branches are retracted (Guo and Udin, 2000) (but see (Brickley et al., 1994, who observed that some of the original connections persisted and could be unmasked by acute removal of the retinotectal projection). (See Fig. 3D.)

The critical period

The ability of the axons to shift their locations in response to normal or abnormal changes in visual input diminishes with age. The axons can remap after any degree of eye rotation if the manipulation is performed prior to the onset of binocularity, but the degree of rotation for which they can compensate becomes smaller and smaller if surgery is done at progressively later ages (Keating and Grant, 1992). By about 3–4 months post-metamorphosis, the axons do not remap at all after eye rotation (Keating and Grant, 1992). As described above, this change in plasticity during the critical period is not marked by dramatic changes in the retinotectal map, (Grant and Keating, 1986b), but, as noted below, the neurochemistry of the tectum does change, and spontaneous EPSC frequency in the superficial layers is about twice as high at the time of metamorphosis as it is after the critical period (Titmus et al., 1999).

The critical period can be extended indefinitely if the animals are reared in the dark beginning as tadpoles (Grant et al., 1992). Although the isthmotectal axons fail to develop normally in the dark, they will establish a normal map when the animals are brought into normal lighting conditions (Keating et al., 1992) and they will show full plasticity in response to eye rotation (Grant et al., 1992).

Cell death

Could selective cell death of isthmotectal axons underlie the changes in connections that are observed during normal remapping of the ipsilateral projection or of the remapping that occurs after eye rotation? Two observations make this explanation highly unlikely. First, the anatomical rearrangements of the axon trajectories and terminal zones can fully explain the maps of normal and eye-rotated tecta (Udin and Keating, 1981; Guo and Udin, 2000). Second, the period of cell death in the nucleus isthmi is completed before the end of metamorphosis, prior to the time of reorganization of the isthmotectal projection, and is not altered by eye rotation (Udin and Fisher, 1985).

NMDA receptors

As in many systems involving plasticity, including the larval *Xenopus* retinotectal projection (Ewald et al., 2008; Yashiro and Philpot, 2008), N-methyl-D-aspartate (NMDA) receptors play a pivotal role in *Xenopus* binocular reorganization. Plasticity can be blocked during the critical period by slow-release application of the NMDA receptor antagonist 2-amino-5-phosphonopentanoic acid (AP5): after early eye rotation, the ipsilateral maps transmitted by the isthmotectal axons remain out of alignment with the contralateral retinotectal maps. As Fig. 4 shows, electrophysiological mapping of the receptive field centers of the retinotectal and isthmotectal axons at individual tectal sites shows much larger angular differences in

animals with chronic AP5 compared to the rather small disparities in controls (Scherer and Udin, 1989). (See Fig. 4.)

The opposite effect can be achieved by application of NMDA to the tectum. As described above, after eye rotation, electrophysiological mapping reveals a lag period of about 4 weeks before the ipsilateral map is reorganized. NMDA accelerates this process (Bandarchi et al., 1994). (See Fig. 4.) Even more dramatically, plasticity can be reinduced in adults by application of NMDA, so that eye rotation leads to ipsilateral map reorganization at ages when it normally does not occur (Udin and Scherer, 1990). (See Fig. 4.)

These results suggest that the NMDA receptors and/or the mechanisms coupled to NMDA receptors change as the frogs move through the critical period. Unpublished preliminary data (Susan Udin and Raquel Lima) indicate that NR2B receptors, which are generally associated with the immature brain and high plasticity (Quinlan et al., 1999), are indeed present at higher levels in the critical period tectum than in the adult tectum. Similarly, NR2D receptors, which have properties such as long open times and weak magnesium block (Monyer et al., 1994) that suit them to promotion of plasticity, are also more prevalent during the critical period (Udin and Lima, unpublished observations). The degree to which the NR2D receptors are part of heterotrimers with NR2A or NR2B subunits in *Xenopus*, as they are in the mammalian superior colliculus (Dunah et al., 1998), has not yet been determined.

The circuitry

We have demonstrated that NMDA receptors play a pivotal role in binocular plasticity, but where are they located in the circuitry that leads from activity to structural reorganization? Extensive evidence indicates that retinotectal axons and some tectal cells are glutamatergic but that isthmotectal axons are cholinergic (Ricciuti and Gruberg, 1985; Wu et al., 1996). It would be relatively simple to understand how a Hebbian mechanism could work in the binocular system if both the isthmotectal and retinotectal axons synapsed upon the same tectal cells' dendrites. Isthmotectal and retinotectal axons terminate in close proximity to each other (Fig. 2B) (Udin et al., 1990), so such an arrangement initially seemed plausible. In that case, when both sets of inputs fired in a correlated manner, LTP would occur and the active inputs would become stabilized. In reality, however, the situation does not appear to be so simple. Electron microscopy has revealed no convergence of retinotectal and isthmotectal synapses onto the same dendrite within the same section or nearby sections (Rybicka and Udin, 2005). Similarly, neither set of axons makes morphologically identifiable axo-axonic synapses onto the other (Rybicka and Udin, 2005).

How, then, does the activity of retinotectal axons influence the isthmotectal axons? One possibility is that the retinotectal axons terminate on tectal cells, which in turn converge on the cells with isthmotectal input. Thus, there simply would be one interneuron interposed in the circuit. A difficulty with this proposal is that 90% of the connections that converge onto isthmo-recipient tectal cells are GABA-positive (Rybicka and Udin, 2005). Therefore, those connections would not excite the target cell but would inhibit it. The remaining 10% of excitatory connections may hold the key, or there may be multisynaptic connections that would lead to disinhibition of dendrites when both retinotectal and isthmotectal axons are active.

A possibility that we favor involves "paracrine volume transmission" (Descarries et al., 1997; Lester, 2004), with the release of acetylcholine by isthmotectal axons producing excitation of presynaptic nicotinic receptors on nearby retinotectal axons (Sargent et al., 1989; Edwards and Cline, 1999; Titmus et al., 1999; Dudkin and Gruberg, 2003). As Fig. 5 shows, when isthmotectal and retinotectal axon terminals are correctly located and an

appropriate visual stimulus occurs, the retinotectal axon will begin to fire, releasing glutamate. Then, after a delay of 10–15 msec due to the extra stages involved in the ipsilateral pathway (Scherer and Udin, 1991), the isthmotectal axon will begin to fire, releasing acetylcholine. The acetylcholine will depolarize the retinotectal terminals and thereby augment retinotectal glutamate release. This additional glutamate release should promote additional opening of NMDA receptors and consequent release of BDNF or some other trophic substance, which in turn would stabilize the nearby isthmotectal axon terminals (Alsina et al., 2001; Cohen-Cory et al., 2010). In contrast, if the isthmotectal arbor's receptive field is misplaced relative to the retinotectal map, then the cholinergic boost will not occur. The lower level of glutamate may lead to release of a different substance which could have destabilizing effect on the isthmotectal axons.

Isthmotectal axons also make conventional synapses onto tectal cells and perhaps presynaptic terminals of tectal cells, and these synapses are muscarinic (Butt et al., 2001; Baginskaskas and Kuras, 2011); the role of this system is currently under study.

Control of arbor size and branch number

Although binocular visual cues are the ultimate determinant of the location of isthmotectal arbors, they are not necessarily the determinant of arbor size. The observation that dark-rearing leads to disorganized ipsilateral maps, often with small spike size (Grant and Keating, 1989b), prompted a study of the morphology of the isthmotectal axons to determine whether the absence of binocular correlated activity would lead to a failure of normal pruning of the arbors. Surprisingly, the isthmotectal arbors' rostrocaudal and mediolateral dimensions turned out to be normal, although they did have fewer than half the normal number of branches (Fig. 3A, right) (Udin, 2008). Could chemical cues such as ephrins be the factor that governed these arbor dimensions? This explanation seems unlikely because the typical isthmotectal arbor in a dark-reared *Xenopus* is not located in the correct tectal location (Grant and Keating, 1989b) and should thus not be subject to the chemical cues that it would experience under normal rearing conditions. A more likely mechanism may stem from spontaneous activity; the *Xenopus* retina is active in the dark, and prolonged dark-rearing is expected to trigger homeostatic increases in excitatory process within the tectum (Turrigiano, 2008; Dunfield and Haas, 2009). These alterations may allow isthmotectal axons to activate local tectal modules that in turn would feed back to stabilize branches within the area of the module.

PSA-NCAM (Polysialic Acid-Neural Cell Adhesion Molecule)

NCAM is a widely-expressed adhesion molecule that is involved in modulating growth and stabilization of axons and in their synaptic function, and the influence of NCAM is strongly modified by the degree to which it is polysialylated in response to stimuli such as NMDA receptor activation (Muller et al., 1996; Dityatev et al., 2004; Vaithianathan et al., 2004; Kochlamazashvili et al., 2010). In *Xenopus*, we have found a strong correlation between isthmotectal plasticity and the presence of PSA-NCAM (Williams et al., 1996). Antibodies to PSA reveal its presence in the superficial layers of the tectum and show intriguing changes in polysialylation during development. PSA is high in tadpoles, but drops transiently during the early part of the critical period when isthmotectal axons arborize independently of visual input; the levels rise again in the latter part of the critical period when arborization depends upon visual input. The PSA levels are low in the remainder of post-metamorphic life. However, two conditions can cause expression of high PSA levels in adults: dark-rearing and NMDA treatment, both of which also bring about adult binocular plasticity (Williams et al., 1996). Thus, the conditions that promote plasticity also are associated with expression of PSA-NCAM. The fact that addition of NMDA reinduces PSA

in adults indicates that PSA is downstream from NMDA in the chain of factors involved in *Xenopus* binocular plasticity (Williams et al., 1996; Dityatev et al., 2004).

Future directions

Many issues remain to be explored in this system. The development of methods to image growing isthmotectal axons *in vivo* will reveal the dynamics of the axons in response to different patterns of correlated and uncorrelated visual input and as well as the specific contributions of different neurotransmitter systems. Among these transmitter systems are, of course, NMDA receptors, but GABA receptors also will merit study in the context of *Xenopus* binocular plasticity. GABA receptors promise to hold some surprises, because not only are GABAergic cells a major population among tectal cells (Antal, 1991; Rybicka and Udin, 1994), but also the tectum contains a large population of ill-understood GABAergic dendrodendritic synapses (Székely et al., 1973) and depolarizing GABA_A retinotectal presynaptic receptors (Nistri and Sivilotti, 1985; Prada and Udin, 2005). Another question is the possible role of the isthmic axons' muscarinic synapses (Butt et al., 2001). All of these aspects of the circuitry will help to complete the picture of binocular development as well as of tectal structure and function overall.

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Figure 1.

A. Photographs of *Xenopus laevis* at 3 developmental stages, prior to eye migration (top), at the end of metamorphosis (middle), and in adult (bottom). Scale bar: 1 mm for top 2 images, 2 mm for bottom. B. Drawings of dorsal views of optic tectum showing proportion occupied by binocular zone of the retinotectal map, based on the data of Grant and Keating (1986a).

Figure 2.

A. Schematic view of the circuitry underlying binocular input to the left lobe of the optic tectum. Input reaches the left lobe directly from the right eye via the topographic retinotectal projection. That projection is represented here by two axons, relaying input from two ganglion cells, one (gray cell) with receptive field at position A and the other (stippled cell) at position B. Input from the left eye reaches the left lobe by an indirect pathway, illustrated by the connections that begin with ganglion cell b in the left eye. This cell has its receptive field at visual field B, the same as the receptive field of right eye cell B. Cell b projects to tectal cell b. The right lobe of the tectum projects topographically to the right nucleus isthmi (cell b), which in turn projects to the left tectal lobe. Under normal conditions, isthmoc cell b terminates at the same site as retinotectal axon B. B. Comparison of distribution of retinotectal (left) and isthmotectal (right) axons in sagittal sections of the superficial layers of the tectum. Retinotectal axons were labeled by horseradish peroxidase application to the optic nerve, and isthmotectal axons were labeled in a different animal by horseradish peroxidase injection into the nucleus isthmi opposite to the tectal lobe shown in the figure. Scale bar: 100 μ m.

Figure 3.

A. Camera lucida drawings and one photograph (left-hand Adult axon) of horseradish peroxidase-filled isthmotectal axons in flat-mounted tecta. Rostral is up in figure (Udin, 1989; Udin, 2008). Scale bar: 100 μ m. B. Plasticity after rotation of one eye in a *Xenopus* tadpole. Left side: schematic of visual fields and example isthmotectal axon. Right side: camera lucida drawings of axons from corresponding stages. During the first few weeks after an eye rotation, the isthmotectal axons initially take approximately normal trajectories and arborize at sites that would be appropriate along the mediolateral tectal axis and often correct along the rostrocaudal axis as well. However, because of the rotation of the eye (right eye, in this example), this growth behavior brings the axons to regions of the tectum that now have retinotectal input with different receptive fields. Thus, in this example, isthmotectal axon b now terminates at a site with a retinotectal axon that fires when there is a visual stimulus at field A. C. After another 1–2 months, the axons have begun to correct the topographic mismatch. Axons can have two distinct arbors, one at the original location and the other at a location where the isthmotectal axon's visual field matches that of the retinotectal axon (b and B, respectively). D. The original arbor tends to be retracted as the new one is consolidated. Scale bar: 100 μ m. Drawings in B–D taken from Guo and Udin (2000).

Figure 4.

Summary of normal refinement of matching of ipsilateral and contralateral maps and of changes induced by nicotinic ligands. Data were obtained by electrophysiological mapping of receptive field locations of ipsilateral and contralateral eye inputs at multiple sites in tecta in 5–14 frogs. The angular distance between the receptive field centers was calculated for each location and an average was computed for each animal. Each column shows the average for all animals per condition or stage. Black bars: normal animals. Results show that the angular difference between the two maps decreases with age. White bars: eye rotation as tadpole or adult (arrow). Results show that there is a large discrepancy at 1 month that is reduced to almost normal levels by 3 months. In contrast, eye rotation in adults leads to minimal compensation. The bar masks the fact that over time after adult eye rotation, many positions fail to respond to ipsilateral eye stimulation and thus lead to relatively mild discrepancy of the maps. Bar with horizontal hatching: Blocking NMDA receptors during the critical period with AP5 prevents reorganization of the ipsilateral map after eye rotation. Stippled bar: Application of NMDA after adult eye rotation permits a high degree of compensation for eye rotation. Error bars show standard deviations.

Figure 5.

Model of retinotectal-isthmotectal interaction. A. Retinotectal and isthmotectal axons terminate on different tectal cells. The low level of excitation of the cell that receives retinotectal input is indicated by the small stippling. Retinotectal cells have nicotinic acetylcholine receptors on their terminals. B. When a visual stimulus appears that activates the retinotectal axon, it releases glutamate, and cell #1 becomes more depolarized (larger stippling). C. After a delay of 10 msec, the visual stimulus activates the isthmotectal axon. It releases acetylcholine (gray cloud). Some of the ACh reaches the receptors on the retinotectal axons. D. The activation of the ACh receptors causes the retinotectal axons to release more glutamate. Cell #1 now is sufficiently excited (large stippling) and NMDA receptor channels open. E. Cell #1 releases a retrograde messenger that can stabilize the isthmotectal axon.