

# Chronic melatonin and binocular plasticity in *Xenopus* frogs

Susan B. Udin \*

*Department of Physiology and Biophysics, State University of New York at Buffalo, Buffalo, NY 14214, USA*

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## Abstract

The topographic binocular maps in the optic tectum of *Xenopus* frogs are notable both for their dramatic plasticity during development and for the high expression of melatonin receptors in the circuitry contributing to those binocular maps. The goal of this study was to determine whether melatonin contributes to the control of binocular tectal plasticity. During development, rotation of one eye leads to compensatory rewiring of ipsilateral maps. The effect of 3–4 months of chronic 20 or 200 nM melatonin on this rewiring was tested by electrophysiological mapping. No decrease in plasticity was observed. In adult *Xenopus*, rotation of one eye normally does not lead to rewiring of the ipsilateral projection, although adults can exhibit plasticity if they have been dark-reared or have been treated as adults with NMDA. We tested whether exposure to 20–200 nM melatonin during and after the normal critical period would similarly extend plasticity. Eye rotation in adults that had been treated with melatonin did not demonstrate retained plasticity. These results show that melatonin does not reduce the normally high plasticity characteristic of young *Xenopus* nor does it increase the normally low plasticity of adult *Xenopus*.

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## 1. Introduction

Many aspects of neural development are marked by critical periods during which activity can influence the stability of connections among neurons. High plasticity is normally found during early life, with diminished capacities for reorganization in response to altered input in later life. Such transitions generally are correlated with changes in NMDA and/or GABA receptor activity but also can be affected by neuromodulators, particularly those that alter protein kinase A activity [reviewed in Hensch (2004)]. One such modulator is melatonin, which typically causes a reduction in protein kinase A activity and which plays a role in seasonal changes in forebrain nuclei associated with song learning and production in starlings (Bentley et al., 1999).

Another system in which it seemed plausible that melatonin might modulate plasticity is the optic tectum of *Xenopus laevis*, which contains high amounts of melatonin receptors and which displays marked visually dependent plasticity during development. Each lobe of the tectum receives binocular input, with direct input from one eye and indirect input from the other eye, relayed via the nucleus isthmi. (See Fig. 1A.) In normal adults, these two projections cover most of the tectum and are in topographic register. However, in tadpoles and juvenile frogs, the situation is quite different. Initially, there is little binocularity, because the animal's eyes face laterally. Over the next 3 months, the eyes shift dorsally and the binocular field expands to 160° (Grant and Keating, 1986b). During this critical period, the proportion of the tectum with binocular input similarly expands, starting from a very small zone that receives both contralateral and ipsilateral eye input, and eventually occupies about 90% of the tectum (Grant and Keating, 1986a). As the

\* Fax: +1 716 829 3575.

E-mail address: [sudin@buffalo.edu](mailto:sudin@buffalo.edu).

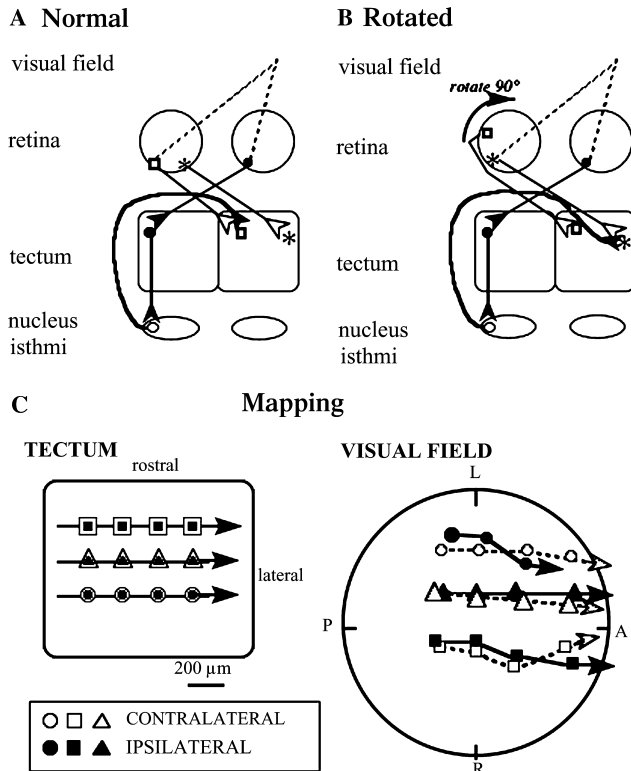


Fig. 1. (A) Schematic diagram of binocular input to one locus on the right tectal lobe. Visual input via the left eye is relayed directly by retinotectal axons (thin lines), and input from the right eye is carried indirectly by isthmotectal axons (thick line). Input from each position in the binocular visual field activates a single locus on each tectal lobe via these two pathways. In this diagram, the inputs converge at a medial site shown by the square. Similar circuitry underlies binocular inputs to approximately 90% of the tectal area. Mirror-image circuitry brings binocular input to the left tectal lobe (not shown). (B) After 90° rotation of the left eye, stimulation at a given visual field locus now activates different ganglion cells. The visual input (dashed line) now activates the cell in the left eye (asterisk) that projects to a lateral position in the tectum (asterisk). The isthmotectal axons that receive input from the other eye shift their connections to restore topographic matching with the retinotectal axons. (C) Relationship between positions in the right lobe of the tectum and the visual field as seen by the left eye (open symbols) and the right eye (filled symbols). Electrode penetrations are made at the sites indicated in the tectum while the visual stimuli are presented on a hemisphere, indicated by the circle on the right. For each tectal site, the receptive field of the left-eye input is mapped with the right eye occluded, and vice versa.

eyes shift towards each other in the head, the maturation process keeps their maps in register, so each position in the binocular zone of the tectum receives input corresponding to one position in the visual field from the contralateral eye and input corresponding to the same visual location from the ipsilateral eye (Grant and Keating, 1989).

This process depends upon visual input, the instructive role of which is demonstrated by the results of experiments with early eye rotation. If one eye is rotated in the tadpole, the ipsilateral map gradually becomes rewired so that the ipsilateral map matches the contra-

lateral map, despite the abnormal eye position (Gaze et al., 1970). (See Fig. 1B.) The plasticity diminishes markedly with age, and eye rotation in adults leads to no apparent reorganization in the 3-month period that suffices for reorganization in juvenile animals (Keating and Grant, 1992). However, if the frogs are dark-reared starting as tadpoles, then plasticity is maintained indefinitely: such animals retain plasticity for at least 3 years (Grant et al., 1992). Plasticity also can be altered by chronic treatment with agonists or antagonists of NMDA receptors; blocking those receptors during the critical period eliminates plasticity, whereas application of NMDA itself during the critical period accelerates plasticity (Bandarchi et al., 1994) and NMDA application in adults restores plasticity (Scherer and Udin, 1989; Udin and Scherer, 1990).

For four reasons, we were prompted to test whether chronic treatment with melatonin might either decrease critical period plasticity or increase adult plasticity. First, the retina, tectum, and nucleus isthmi in *Xenopus* express high amounts of melatonin receptors (Mazzucchelli et al., 1996; Wiechmann et al., 1999). Second, melatonin has modulatory effects on retinotectal axons, tectal cells, and many isthmic cells (Prada and Udin, 2003; Prada et al., 2004) (Lima and Udin, unpublished observations). Third, the likelihood that dark-rearing leads to abnormal patterns of melatonin secretion as well as prolonging plasticity suggested that melatonin might affect maturation or function of the tectum. Fourth, our previous studies have demonstrated that tectal plasticity is modifiable by chronic pharmacological manipulations (Bandarchi et al., 1994; Scherer and Udin, 1989; Udin and Scherer, 1990). We therefore tested whether chronic treatment with melatonin, starting at tadpole stages, would alter plasticity.

## 2. Methods

### 2.1. Chemicals

All chemicals were purchased from Sigma–Aldrich (St. Louis, MO).

### 2.2. Eye rotation and rearing conditions

For pre-critical period eye rotation, stage 55–57 (Nieuwkoop and Faber, 1967) tadpoles were anesthetized by immersion in 1:3500 tricaine methanesulfonate in 10% Holtfreter's solution. The skin overlying the left eye was teased apart and the extraocular muscles were pinched apart. The eye was then rotated 90° clockwise. The tadpoles were maintained under 24-h light in 20, 40, or 200 nM melatonin in aerated 10% Holtfreter's solution; control solutions contained no melatonin. After metamorphosis, aged tap water was substituted for

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