Functional Selection of Adaptive Auditory Space Map by $GABA_A$-Mediated Inhibition

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The external nucleus of the inferior colliculus in the barn owl contains an auditory map of space that is based on the tuning of neurons for interaural differences in the timing of sound. In juvenile owls, this region of the brain can acquire alternative maps of interaural time difference as a result of abnormal experience. It has been found that, in an external nucleus that is expressing a learned, abnormal map, the circuitry underlying the normal map still exists but is functionally inactivated by inhibition mediated by γ-aminobutyric acid type A ($GABA_A$) receptors. This inactivation results from disproportionately strong inhibition of specific input channels to the network. Thus, experience-driven changes in patterns of inhibition, as well as adjustments in patterns of excitation, can contribute critically to adaptive plasticity in the central nervous system.

The external nucleus of the inferior colliculus in the barn owl contains an auditory map of space. In juvenile owls, alternative maps can be acquired as a result of abnormal experience. We found that, in the inferior colliculus that is expressing a learned, abnormal map, the circuitry underlying the normal map still exists but it is functionally inactivated by inhibition. The data show that input channel-specific adjustments in effectiveness of inhibition, as well as changes in excitation, contribute critically to adaptive plasticity in this network. These findings revealed that, in responding to individual life experience, the brain adjusts both excitation and inhibition cooperatively.

Experience can shape the functional properties of the brain, particularly during early life. The capacity of experience to adjust patterns of excitation in the central nervous system has been studied extensively (*1*). In contrast, the effects of experience on patterns of inhibition have not been documented and are not well understood (*2*). We found that, in the external nucleus of the inferior colliculus (ICX) of the barn owl, the patterns of inhibition were actively modified based on experience and this adjustment in the strength of inhibition is essential for the network to express fully the experience-dependent, functional plasticity: adjustments in patterns of inhibition can be critical in selecting the functional map that is expressed in this nucleus.

Neurons in the ICX of the barn owl are tuned sharply for interaural time differences (ITDs), and the value of ITD to which they are tuned varies topographically across the nucleus (*3, 4*), forming a map of auditory space (*5*). The space map is relayed to the optic tectum, where it is used to direct the animal's gaze to the locations of interesting auditory stimuli (*6*). Horizontally displacing prisms mounted in front of the eyes of a barn owl change the relationship between auditory spatial cues, such as ITDs, and the locations in the visual field that produce them. Because owls raised wearing prisms cannot compensate for the effects of the prisms by rotating their eyes in the orbits (*6*), they instead learn new associations between ITDs and the locations of sound sources in the optically displaced visual field. This learning is expressed as a shift in the map of ITD in the ICX (*3, 7*).

In prism-reared owls, ICX neurons have acquired strong responses to new, visually instructed values of ITD (learned responses) and have eliminated responses to inappropriate normal ITDs (normal responses). Acquisition of learned responses involves the potentiation and possibly the formation of excitatory connections (*8*). The basis for eliminating inappropriate normal responses, however, is not known. One hypothesis is that elimination of responses to inappropriate ITDs is accomplished through inhibition mediated by the A subtype of γ-aminobutyric acid ($GABA_A$) receptors. We tested this hypothesis by acutely blocking inhibition in the ICX of prism-reared owls with bicuculline methiodide, a selective antagonist of the $GABA_A$ receptor, to determine whether normal responses could be unmasked.

Iontophoresis of bicuculline into the ICX of normal owls resulted in a dramatic increase in the responsiveness of neurons to dichotically presented sounds (*9–11*), as shown for a representative site in Fig. 1A. Responses to ITDs within 40 μs of the best ITD (Fig. 1A, downward arrows) increased by about a factor of 3. The width of the tuning curve increased only slightly (width at half-maximum response, 34 μs without bicuculline and 44 μs with bicuculline) and the value of the best ITD remained unchanged. Additionally, the increase in response magnitude and the broadening of the tuning curve were symmetrical about the best ITD. As summarized by the data in Figs. 1B and 2, we consistently observed similar effects at all sites ($n = 30$) tested in two normal owls.

The identical procedure, carried out in the ICX of prism-reared owls (*12*), yielded significantly different results. The best ITDs measured before bicuculline application in the ICX of these owls were shifted from the predicted normal best ITD by 30 to 50 μs (*13*) toward either left ear or right ear leading ITDs depending on the direction of visual field displacement experienced by the owl. The effect of bicuculline iontophoresis at a representative site in a prism-reared owl is illustrated in Fig. 1C. Before bicuculline application, the site responded maximally to the learned range of ITDs and responded weakly (about one-third of the maximum response) to the normal range of ITDs. Bicuculline application caused a large, differential increase in the responses to normal ITDs so that normal responses became nearly as strong as learned responses. This differential unmasking of strong normal responses resulted in an asymmetrical broadening of the tuning curve: the 50% cutoff (Fig. 1C, dashed line) on the side toward normal ITDs shifted by 38 μs and the 50% cutoff on the opposite side did not change. Consequently, the width of the tuning curve increased dramatically (width at half-maximum response, 55 μs without bicuculline and 93 μs with bicuculline) and the value of the best ITD shifted back toward normal by 17 μs. As summarized by the data in Figs. 1D and 2, we observed similar effects at nearly all sites (26 of 28) that exhibited fully shifted ITD tuning.

For a given site, the increase in responses that resulted from blocking inhibition indicated the effectiveness of the inhibition that was activated by the respective ITD input channels to that site. Effectiveness of inhibition for a given ITD channel was quantified as the ratio of the magnitude of responses with inhibition blocked (during bicuculline iontophoresis) to the magnitude of responses with inhibition active (before and after bicuculline application) (note that this ratio cannot be derived from the population data in Fig. 1, B and D) (*14*). In normal owls, the effectiveness of inhibition was remarkably constant across ITDs for a given site as well as across all sites (Fig. 3A, open circles), which indicates that each ITD input channel to an ICX site activates about the same ratio of inhibition to excitation. This balance of inhibitory to excitatory activation presumably optimizes

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the response (gain) of the network while it maintains its functional stability (*15*).

In prism-reared owls, unlike normal owls, the effectiveness of inhibition in the ICX was highly ITD dependent (Fig. 3A, filled circles) (*14*). On average, the effectiveness of inhibition for learned ITDs was about the same as that observed in normal owls, which indicates that the newly functional connections that drove the learned responses activated inhibitory and excitatory circuitry in the normal ratio. In contrast, the average effectiveness of inhibition for the normal ITD input channel was nearly three times greater than that observed in normal owls (Fig. 3B, filled circles). This highly effective inhibition was responsible for suppression of an otherwise strong excitatory response to normal ITDs (Fig. 1, C and D). Thus, even though the ICX in prism-reared owls was expressing only a shifted map of ITD, it nevertheless retained the excitatory circuitry necessary to express a normal ITD map but was prevented from doing so by abnormally effective inhibition of normal responses.

We examined the effect of blocking inhibition in the ICX again in a subset of prism-reared owls ($n = 2$) that had the prisms removed, allowing ITD tuning to shift back toward normal (*16*). At sites ($n = 11$) where the return to normal ITD tuning was not yet complete (*17*), blocking inhibition resulted in a differentially large increase in the strength of responses to the previously learned range of ITDs and an asymmetrical broadening of the ITD tuning curve back toward the previously learned ITDs (Fig. 4A for a single site; Fig. 2, shaded triangles, for all sites). The effectiveness of inhibition for the learned ITD range was significantly greater (*18*) than that in normal owls ($P < 0.01$ for ITDs of 40, 50, and 60 μs; Fig. 3A, shaded triangles) (*14*). Thus, at these sites there was evidence that abnormally effective inhibition of inappropriate, previously learned responses plays a role in shifting ITD tuning curves back to normal after prism removal. In addition, the effectiveness of inhibition for the normal range of ITDs had decreased precipitously. Indeed, the effectiveness of inhibition dropped to slightly below that observed in normal owls ($P < 0.01$ for ITDs −10, 0, and +10 μs; Fig. 3A, shaded triangles), an effect that tended to amplify the responses of these sites to normal ITDs, thereby promoting their recovery of normal ITD tuning.

For sites ($n = 37$) where ITD tuning had fully returned to normal after prism removal (*17*), iontophoresis of bicuculline resulted in a symmetrical increase in responsiveness on the two flanks of the tuning curves and a symmetrical broadening in ITD tuning [Fig. 4B for a single site; Fig. 2 (open triangles) for all sites]. The effectiveness of inhibition for previously learned ITDs was once again in the normal range (Fig. 3A, open triangles) (*14*). Thus, there was no evidence that the excitatory connections that had previously supported the learned responses remained functional (Fig. 3B). However, the effectiveness of inhibition for normal ITDs remained below the normal range ($P < 0.01$ for ITDs −10, 0, and +10 μs; Fig. 3A, open triangles).

The results reveal that one strategy used in the process of learning in the ICX was a parallel adjustment of input strengths to excitatory and inhibitory circuitry. The dramatic increase in excitatory strength for the learned ITD channels (Fig. 3B, filled circles), which was responsible for the acquisition of learned responses in prism-reared owls, must have been accompanied by an equally dramatic increase in input strength to inhibitory circuitry for these same ITD input channels in order to preserve the normal balance of inhibition to excitation, as was observed (Fig. 3A, filled circles). The converse argument applies to the loss of learned responses in owls after prism removal (Fig. 3, open triangles): a parallel decrease in excitatory and inhibitory drives for the learned ITD channel. This strategy enabled the network to acquire or eliminate strong, learned responses while maintaining normal functional stability and integrative properties (*15*).

The results also reveal that the process of learning in the ICX involves, in addition, a change in the balance of inhibition to excitation (effectiveness of inhibition) that is activated by a particular ITD channel. This second strategy was used during the learning process initially to help suppress inappropriate, learned responses (Fig. 3A, shaded triangles; Fig. 4A) and persistently to suppress inappropriate, normal responses that could not be completely eliminated by other mechanisms (Fig. 1, C and D; Fig. 3, filled circles).

In principle, the strategy of changing the effectiveness of inhibition could have been accomplished by a selective adjustment in input strength to excitatory circuitry alone. Indeed, the elimination of responses to normal ITDs in prism-reared owls appeared to involve a decrease in drive to excitatory circuitry, at least at some sites (*19*) (Fig. 3B).

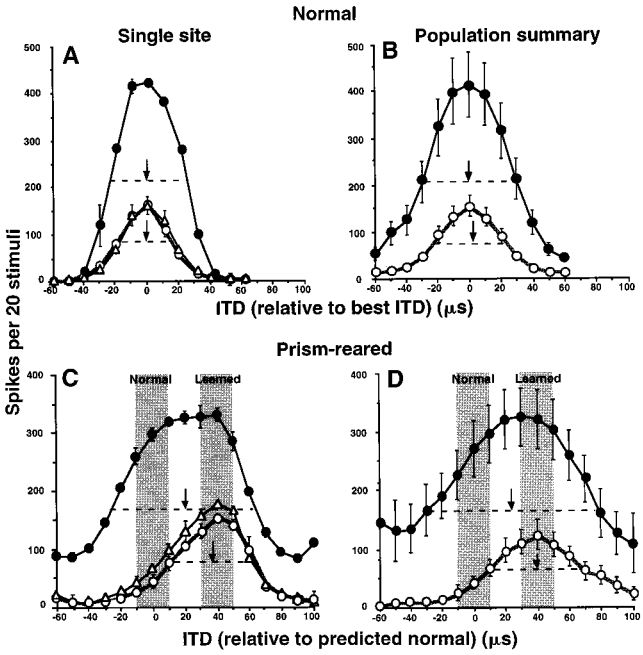

Fig. 1. Effect of blocking $GABA_A$-mediated inhibition on the ITD tuning of ICX units in normal and prism-reared owls. (**A** and **C**) Unit responses before (open circles), during (filled circles), and after (open triangles) iontophoretic application of bicuculline for single sites (*11*). (**B** and **D**) Averaged responses for all sites. ITD values are plotted in microseconds relative to the best ITD for normal owls and relative to the predicted normal best ITD (*13*) for prism-reared owls. Dashed line inside each tuning curve represents the range of ITDs that evoked >50% of the maximum response; downward arrow indicates the midpoint of this range (the best ITD). Error bars in all turning curves indicate the standard error for each data point. (A) Single site in a normal owl. Each point represents the number of spikes to 20 stimulus repetitions averaged across five series of stimuli. We used a two-tailed *t* test to compare the increases in responses to ITDs 40 ± 10 μs away in each direction from the best ITD (Fig. 2A). For this site, the increases on the two flanks were not significantly different (29 ± 45 SD versus 34 ± 26 SD spikes per 20 stimuli, $P = 0.90$). (B) Population tuning curve representing data from all ICX sites ($n = 30$) in two normal owls. Each point represents the mean across all sites of the average response to 20 stimulus repetitions. The increases in responsiveness on the two flanks of the tuning curve (40 ±10 μs away from the best ITD) were not significantly different (113 ± 40 SD versus 102 ± 34 SD spikes per 20 stimuli, $P = 0.80$). (C) Single site in a prism-reared owl, presented as in (A). Shaded vertical bars denote the predicted normal ITDs (0 ± 10 μs of the predicted normal best ITD) and the learned ITDs (40 ± 10 μs away from the predicted normal best ITD) (*13*). The increases in responses to ITDs 40 ± 10 μs away in each direction from the best ITD (measured before bicuculline application) were significantly different from each other (240 ± 12 SD versus 76 ± 10 SD spikes per 20 stimuli, $P < 0.0001$). (D) Population tuning curve representing data from all ICX sites ($n = 28$) in six prism-reared owls with fully shifted maps of ITD, presented as in (B). The increases in responsiveness on the two flanks of the tuning curve (40 ± 10 μs away from the best ITD measured before bicuculline application) were significantly different (219 ± 16 SD versus 116 ± 36 SD spikes per 20 stimuli, $P < 0.01$).

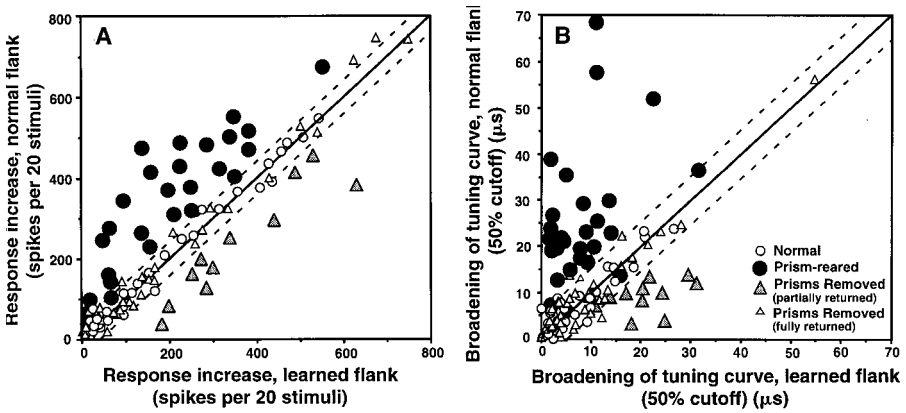

Fig. 2. Comparison of effects of blocking $GABA_A$-mediated inhibition on the ITD tuning of neurons in the ICX of normal owls (open circles), prism-reared owls with fully shifted ITD maps (filled circles), and prism-removed owls before (shaded triangles) or after (open triangles) the ITD map fully returned to normal. (**A**) Symmetry of response increase on normal and learned flanks of the tuning curves. The learned flank is the side of the tuning curve in the direction of the adaptive shift in ITD tuning; the normal flank is the opposite side of the tuning curve. For normal owls, the left-ear leading flank served arbitrarily as the normal flank and the right-ear leading flank served as the learned flank. Response increase is based on the average response to 20 repetitions of sounds with ITD values 40 ± 10 μs away in each direction from the best ITD measured before application of bicuculline. Diagonal solid line indicates a symmetrical response increase on the two flanks of the tuning curve; dashed lines indicate the mean ± 2SD of the difference between response increases on the two flanks of the tuning curves for all ICX sites in normal owls. (**B**) Symmetry of tuning curve broadening on normal and learned flanks of the tuning curves. Broadening of tuning curves was measured as the outward shifts of the 50% cutoffs on the normal and learned flanks, as defined in (A). Diagonal solid line indicates a symmetrical broadening of the tuning curve; dashed lines indicate the mean ± 2SD of the difference between ITD shifts in 50% cutoffs on the two flanks of the tuning curves for all ICX sites in normal owls.

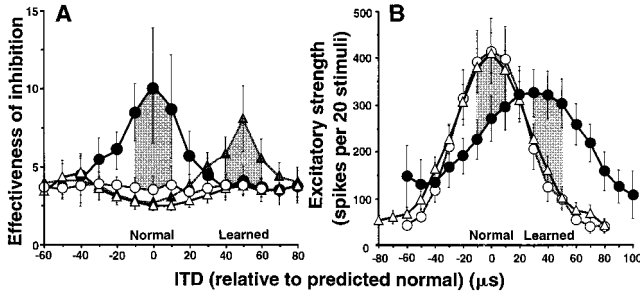

Fig. 3. ITD channel-specific adaptive changes in the effectiveness of inhibition and strength of excitation. Data are plotted as a function of ITD relative to the predicted normal best ITD for each site (*13*). Shaded vertical bars indicate experience-induced changes for normal and learned ranges of ITDs. Error bars in all curves indicate the standard error for each data point. (**A**) ITD dependence of effectiveness of inhibition (defined in text) (*14*). Values were calculated for individual sites and then averaged across all sites measured from normal owls (open circles, 30 sites), prism-reared owls with fully shifted ITD maps (filled circles, 28 sites), and prism-removed owls before (shaded triangles, 11 sites) or after (open triangles, 37 sites) the ITD map fully returned to normal (*14, 17*). (**B**) Population excitatory tuning curves measured with local inhibition blocked (during bicuculline iontophoresis). The excitatory tuning curves for normal owls (open circles) and for prism-reared owls (filled circles) are replotted from Fig. 1, B and D, respectively. The curve for prism-removed owls with fully returned ITD tuning is shown as open triangles. Each point represents the mean across all sites of the average responses to 20 stimulus repetitions.

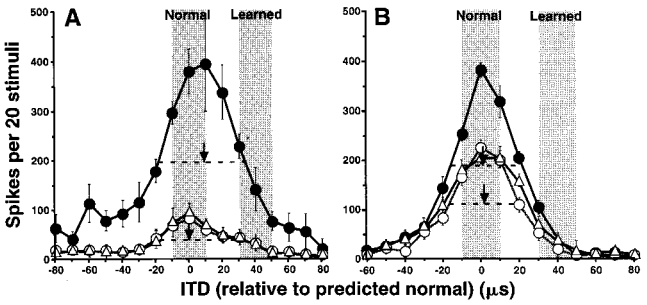

Fig. 4. Effect of blocking local $GABA_A$-mediated inhibition on ITD tuning curves in prism-removed owls. Data are plotted as described in Fig. 1C. (**A**) Data from a site with ITD tuning that had not fully returned to normal (*17*). (**B**) Data from a site with ITD tuning that had returned to normal.

However, this apparent decrease in excitatory drive is unlikely to account entirely for the elimination of normal responses, because the decrease, if it occurred at all, was small and the increase in inhibitory effectiveness was large (Fig. 3A). Therefore, this explanation of the data requires a highly nonlinear relationship between excitatory drive and the effectiveness of inhibition in determining neuronal responses.

A more likely explanation for the ITD-specific increases in the effectiveness of inhibition is that they resulted, at least in part, from adaptive adjustments in input strength to inhibitory circuitry. Independently of any adjustment in input strength to excitatory circuitry, such channel-specific plasticity of inhibitory strength could have selectively suppressed inappropriate responses to normal ITDs in prism-reared owls with shifted ITD maps as well as inappropriate responses to previously learned ITDs in owls with ITD maps that were shifting back to normal (Fig. 3A).

These data demonstrate that the strength of input to inhibitory circuits is adaptively adjusted during auditory learning in the ICX. In this network of neurons, ITD channel-specific adjustment of inhibition plays an essential role in shaping the representation of auditory space based on experience. Recently, a similarly essential role for GABAergic inhibition in activity-dependent changes of ocular dominance in visual cortex and rapid reorganization of cortical somatosensory maps has been demonstrated (*2, 20*). In the ICX of prism-reared owls, excitatory connections supporting two alternative ITD maps can coexist and, when they do, the functional selection of the behaviorally appropriate map is accomplished by $GABA_A$-mediated inhibition of the inappropriate map.

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9. Neurophysiology: We prepared the owls for repeated neurophysiological recording sessions as described (*3*). We discontinued anesthesia (1.5% halothane in a 55:45 mixture of oxygen and nitrous oxide) after the owl was positioned and secured in a sound chamber.

The owls remained calm for the duration of the experiment. We conducted the experiments in the rostrolateral ICX, where neurons are tuned to frontal space in normal owls (ITDs range from 0 to 20 μs, contralateral ear leading). In prism-reared owls, the ITD tuning of neurons in this region has been shown to shift reliably in response to juvenile prism experience (*3, 16*). We recorded unit activity with a five-barrel glass microelectrode, the central barrel of which contained a carbon fiber 7 μm in diameter. The remaining four barrels had 2- to 4-μm tips and were used to apply bicuculline methiodide (Sigma) (10 mM in 0.9% saline, adjusted to pH 3.0 with HCl). Units were isolated with a waveform detector. We consistently attempted to isolate the largest unit waveforms. We do not know, however, the degree to which these waveforms corresponded to the discharges of single neurons. We used unit response properties (tuning for frequency, ITD, and interaural level difference) and the progression of these properties with electrode advance to indicate that the recording sites were in the ICX (*3, 8*). The experimental protocol was approved by the Animal Care and Use Committee at Stanford University School of Medicine.

10. Auditory stimulation: ITD tuning properties were characterized as described in (*3*). Briefly, broadband (4 to 12 kHz) noise stimuli were generated digitally and presented dichotically at 10 dB above unit threshold. We determined unit tuning for ITD by presenting a series of 50-ms noise bursts in which ITD was varied in a random, interleaved pattern. We measured ITD tuning by using the optimal interaural level difference for the site. Responses were defined as the number of spikes in the 100 ms after stimulus onset minus the number of spikes in the 100 ms before stimulus onset (baseline).
11. Iontophoresis protocol: At each site, we first assessed ITD tuning three to seven times without drug ejection by using a 20-repetition stimulus series. We then applied bicuculline iontophoretically at a current that resulted in a clear increase in responses; this current ranged from 30 to 60 nA. Once responses were stable, we reassessed ITD tuning three to seven times by using the same 20-repetition stimulus series. Finally, we halted drug ejection, allowed responses to recover to the predrug level, and assessed ITD tuning again.
12. Rearing conditions: This study is based on neurophysiological recordings from eight barn owls (*Tyto alba*), all of which were raised together in our colony. Two of the owls were raised normally and six were raised wearing Fresnel prismatic lenses (VisionCare/3M), mounted in spectacle frames, that displaced the visual field horizontally 23° to the left or right. The spectacle frames were secured with a bolt that was cemented to the skull when the owls were 60 to 70 days old, the age at which they are full grown and leave the nest. The flight room in which they lived provided them with a rich visual and auditory environment. Neurophysiological recordings began when the owls were 130 days old, after they had worn spectacles continuously for at least 60 days.
13. Predicting normal best ITD: The value of ITD to which a site in the ICX will be tuned in a normal owl can be predicted (±10 μs) by recording units along a transect that passes through the representation of a given value of ITD both in the central nucleus of the inferior colliculus (ICC) and in the optic tectum (*3*). In normal owls, sites in the ICX that lie along this transect are also tuned to this same value of ITD. In prism-reared owls, the representation of ITD in the ICC is not altered from normal, and normal ITD tuning in the optic tectum can be inferred from the location of a site's visual receptive field, which is also unaltered by prism experience (*3*). In this study, the predicted normal ITD tuning for a transect was determined at the beginning of each experiment from the best ITD measured in the ICC and from the best ITD inferred from the visual receptive field measured in the optic tectum. All ICX recordings were made along this transect.
14. We calculated effectiveness of inhibition for each ITD that evoked at least 15% of the maximum response at each site. To compare the effectiveness of inhibition across different groups of owls (Fig. 3A), we averaged the values of this metric across all sites from each group for a given ITD value [C. Koch, T. Poggio, V. Torre, *Proc. Natl. Acad. Sci. U.S.A.* **80**, 2799 (1983); N. Qian and T. J. Sejnowski, *ibid.* **87**, 8145 (1990)].
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17. To evaluate whether an ITD tuning curve was fully returned back to normal after prism removal, we compared the responses on the two flanks of the tuning curve. A tuning curve was deemed fully returned back to normal when the sum of the responses to ITDs 30, 40, and 50 μs on each side away from the predicted normal best ITD were not significantly different (two-tailed t test, $P > 0.05$).
18. Unpaired two-tailed t tests were used throughout this study.
19. At 12 of 28 ICX sites tested in prism-reared owls, responses to normal ITDs were significantly weaker than responses to learned ITDs when inhibition was blocked (two-tailed t tests, $P < 0.05$; Fig. 3B, filled circles) (at the remaining 16 sites, responses to normal and learned ITDs were not significantly different when inhibition was blocked; $P > 0.05$). In addition, with inhibition blocked, responses to normal ITDs were weaker in prism-reared owls than in normal owls ($P = 0.009$; Fig. 3B, open circles versus filled circles) even though there was no difference between the strengths of responses to normal ITDs in normal owls and responses to learned ITDs in prism-reared owls ($P = 0.19$).
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Inheritance of Resistance to *Bacillus thuringiensis* Toxin (Dipel ES) in the European Corn Borer

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Resistance in the European corn borer, *Ostrinia nubilalis* (Hübner), to a commercial formulation of *Bacillus thuringiensis* (*Bt*) Berliner toxin, Dipel ES, appears to be inherited as an incompletely dominant autosomal gene. This contrasts with the inheritance of resistance to *Bt* in other insects, where it has usually been characterized as a recessive trait. The proposed high-dose/refuge strategy for resistance management in *Bt* maize depends on resistance being recessive or partially recessive. If field resistance turns out to be similar to this laboratory resistance, the usefulness of the high-dose/refuge strategy for resistance management in *Bt* maize may be diminished.

Maize and several other crops have been bioengineered to express, in plant tissues, endotoxins derived from *Bacillus thuringiensis* (*Bt*) Berliner (*1, 2*). Such transgenic maize hybrids are known as *Bt* maize (*Bt* corn) hybrids. *Bt* maize hybrids have been developed to protect the crop against corn borers such as the European corn borer, *Ostrinia nubilalis* (Hübner) (order Lepidoptera, family Crambidae). *Ostrinia nubilalis* ranks among the most important pests of maize in North America, causing losses in excess of $1 billion annually (*1*). The efficacy of *Bt* crops against this insect has been impressive and is resulting in widespread adoption of this bioengineered technology. Selection for pest resistance to *Bt* is expected to be intense and is likely to result in the evolution of resistance to *Bt* endotoxins. An effective resistance management program will be needed to preserve the long-term utility of this technology. The U. S. Environmental Protection Agency (EPA) has approved conditional registrations for several *Bt* maize transformations and is requiring the development of a scientifically sound resistance management strategy by the year 2001 (*1, 2*). The currently favored resistance management strategy for *Bt* maize is the "high-dose/refuge strategy" (*1*). Implicit in this strategy is the assumption that genes promoting resistance in the insect will be recessive or partially recessive (*1, 2*).

We analyzed resistance to Dipel ES in a laboratory colony of *O. nubilalis* (*3*). Dipel ES is a commercial formulation of *Bt* endotoxins (*4*). Our results suggest that resistance to Dipel ES in *O. nubilalis* is inherited as an incompletely dominant autosomal gene. In

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