MINIREVIEW

Ocular Dominance Plasticity: Usefulness of Anesthetized and Paralyzed Preparations

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1. INTRODUCTION: DEVELOPMENTAL PLASTICITY

The cerebral cortex is the crowning achievement of brain evolution, subserving higher brain functions including perception and memory. The results of experiments by WIESEL and HUBEL in the early 60s suggested that the functional architecture of the visual cortex is not complete at birth but undergoes continuous development during a postnatal period toward its maturity [118]. It is during this relatively brief period that properties of individual cortical neurons, and probably the pertinent neural network as well, are extensively modified in response to characteristics of the environment in which young animals are placed. Insight into mechanisms of this developmentally regulated malleability and the impact of “experience” on self-organizing processes of the immature neocortex may help us to understand various adaptive processes of the mature brain in learning, memory, and the restoration of lost functions following brain injuries.

A paradigm of monocular deprivation was devised to study the “experience dependency” of visuocortical plasticity. WIESEL and HUBEL found in 1963 that when the kitten was subjected to monocular vision for a few days many binocular cells in visual cortex lose functional connectivity with the monocularly lid-sutured eye. The majority of visuocortical cells remained excitable only to the stimulation of the unsutured “experienced” eye (ocular dominance, OD, plasticity) [118]. If the period of monocular vision exceeded a certain time limit during early postnatal life (i.e., sensitive period), monocularly deprived kittens became behaviorally “blind,” when tested with the “inexperienced” eye. The effects of monocular deprivation are relatively easy to reproduce, and such physiological consequences as a decrease in the number of binocular cells and an eventual shift in OD toward the open eye would seem to give us a reliable means to measure the extent of OD plasticity.

Temporal requirements for inducing the OD changes caused by monocular

deprivation have been studied in detail [13, 46, 79, 88, 90]. The profile of the sensitive period, particularly near its end, varies among different studies. For example, when examined with long-lasting monocular deprivation (~ 3 months), the sensitive period seems to end 6 months instead of 4 months [22, 32] after birth (see also [34]). Perhaps there is no finite end to the sensitive period: though modifiability is most pronounced early in life, it may persist in a rudimentary fashion throughout adulthood [11]. On the other hand, most investigators agree that in kitten visual cortex OD plasticity starts around the 4th week postnatally, showing peak sensitivity at the 5th–6th week. An unsettled issue here is how rapidly changes in OD can be induced at the height of the sensitivity of immature visual cortex. Answers to this question may give us clues to biochemical and cellular mechanisms underlying OD plasticity.

In the present article, we will first review briefly activity-dependent mechanisms and regulatory factors underlying sensitive-period plasticity in kitten visual cortex and then discuss recent development in the *in vivo* study of cellular and neurochemical mechanisms of the plasticity under acute experimental conditions. The paradigm of OD plasticity was originally formulated for freely behaving, visually alert animals. The presence of a schism is obvious among neural changes occurring in the brain of behaving animals and those from *in vitro* preparations such as cortical slices and cultured cells. We would like, therefore, to promote the usefulness of the whole-animal preparation under acute experimental conditions as a thread to integrate various findings obtained at different levels of analyses, relying on neurochemical changes common to all.

2. ACTIVITY-DEPENDENT MECHANISMS: BINOCULAR COMPETITION

Axons of retinal ganglion cells from the two eyes travel to the lateral geniculate nucleus (LGN) of the thalamus, where their terminals are segregated into separate eye-specific laminae. LGN neurons, in turn, project primarily to layer IV of visual cortex (areas 17 and 18), where their axon terminal arbors are segregated into alternating OD patches, or columns representing the two eyes. OD columns, however, are not detectable by common tracing/staining methods in newborn kittens. Their segregation starts at 3 weeks of age, and at least 3 more weeks are required before attaining the adult form. The peak of cortical sensitivity to monocular deprivation seems to coincide with the time when LGN axons undergo segregation to form the OD patches. Long-term monocular deprivation results in larger OD patches representing the open eye and smaller patches representing the closed eye. Closure of both eyes during the sensitive period causes no changes in the relative width of the respective OD columns [47, 98].

Based on physiological and autoradiographical evidence, it has been thought that both the formation and maturation of OD columns, and the effects of monocular deprivation involve competition between retinal activity present in the two eyes [108, 118].

It has been argued whether rearing young kittens in total darkness (resulting in the lack of visually evoked activity in the two eyes) interferes with the age-dependent formation of OD columns. In dark-reared cats, anatomical segregation of geniculate afferents seems to take place as evidenced by peak-to-trough fluctuation in the density of label through layer IV [81, 108, 109]. Compared to the normal cortex, however, the fluctuations are greatly reduced in extent and show increased irregularity in the shape and width of the labelled patches. MOWER *et al.* concluded that the capacity of the immature brain to segregate geniculate afferents into OD columns and the susceptibility of this anatomical process to monocular deprivation are lost after several weeks of dark rearing [81]. Thus, a notable physiological effect of dark-rearing, the prolongation of the postnatal period of OD plasticity into adulthood [21, 80], is not necessarily mediated by the cellular and neurochemical mechanisms responsible for the anatomical segregation of OD columns in layer IV.

Although its cellular basis requires further clarification, binocular competition remains a leading idea for explaining experience-dependent modification of OD. STRYKER *et al.* carried out an ingenious study in which young kittens were either briefly subjected to lid suture of one eye and tetrodotoxin (TTX, a potent Na^+ -channel blocker) injections in the other eye, or monocularly TTX-injected kittens were left in total darkness. In either case an imbalance in "electrical activity" between the two retinæ was created without involving pattern vision [19]. There was a significant OD shift toward the relatively "active" eye with spontaneous retinal discharges (but see also [40] for a "negative" result). How this shift could occur is not understood, yet the results of this study make clear the vital role of binocular competition or binocular imbalance in determining modes of OD distribution in the immature cortex.

The prime locus for this binocular competition has been thought to be the visual cortex itself. REITER *et al.* reversibly eliminated cortical activity by intracortical infusion of TTX during a period of monocular deprivation [95]. They showed that the cortical-activity blockade completely prevented the OD shift that would normally be seen after a period of monocular deprivation. In this study it was not possible to decide which activity, pre or postsynaptic or both, was eliminated by TTX.

In a later study, REITER and STRYKER selectively blocked postsynaptic activity in visual cortex by directly infusing a γ -amino butyric acid (GABA) agonist, muscimol [94]. Monocular deprivation for 5–7 days began 3 days after the start of the muscimol infusion which lasted for an 8- to 11-day period. Recording from the visual cortex after the cortical cells recovered from the muscimol-induced blockade of postsynaptic activity, they found a consistent bias of OD toward the less-active, closed eye. It should be noted that the majority of recorded cells remained binocular (binocularity, 61%), though the authors suggested that the direction of obtained OD change depends on "postsynaptic membrane conductance" but not postsynaptic spike activity. A crucial question is to elucidate neurochemical factors

contributing to this hypothetical "threshold" mechanism based on the fluctuation of membrane conductance.

3. REGULATORY SYSTEMS OF OCULAR-DOMINANCE PLASTICITY

1. *Noradrenaline (NA)- β -adrenoreceptor system*

In 1976, KASAMATSU and PETTIGREW proposed that the catecholamine (CA)-containing system, especially the NAergic one, in the brain is necessary for maintaining OD plasticity at a high level in the visual cortex of developing kittens [61]. The background of this thesis and supportive evidence have been described [62-64, 91] and reviewed extensively [54, 55, 59]. In early experiments, a CA-related neurotoxin, 6-hydroxydopamine (6-OHDA), was repeatedly injected into the lateral ventricle to produce chemical lesions of CA terminal fields in the visual cortex. In later studies, degeneration of CA terminals due to 6-OHDA was confined to the visual cortex by devising a continuous, local microinfusion method [91]. Many binocular cells were found, despite monocular deprivation, in the visual cortex that had been infused with 6-OHDA.

There was a debate on the effects of 6-OHDA. Several groups of investigators failed to replicate the disappearance of OD plasticity despite substantial reduction of endogenous NA in kitten visual cortex [1, 6, 8, 23, 24, 26, 27, 89, 111]. There are, however, characteristic shortfalls in the design of all studies which produced "negative results," as is repeatedly discussed elsewhere [56].

Interestingly, there was little difference between results obtained by other investigators [8, 23, 89] and us [62, 64] when 6-OHDA was directly infused into kitten visual cortex. There were, however, significant differences in their interpretations. First, DAW and colleagues argued that "non-specific effects" of 6-OHDA might have accounted for the observed decrease in plasticity [24, 26, 27]. Second, BEAR and associates have suggested the possibility that non-adrenergic "compensatory" processes heterologously counteract the plasticity-suppressing effect of 6-OHDA [6, 8]. We have suggested a third possibility and examined it in detail: homologous compensation for NA depletion within the NA system. Evidence for the induction of two types of the compensatory processes were obtained: (i) up-regulation of NA-related receptor-binding sites and (ii) reinnervation of the 6-OHDA-affected cortical area with "regenerative" NA fibers and terminals [85, 86].

Encouraged by correlational evidence for the involvement of β -adrenoreceptors in the regulation of OD plasticity (e.g., a characteristic increase in the number of β -adrenoreceptor-binding sites in early postnatal life [52]), the matter was tested directly by infusing a β -adrenoreceptor antagonist, propranolol, using a microinfusion method [65]. In kitten visual cortex infused with *d,l*-propranolol, the expected shift of OD following brief monocular deprivation was suppressed in a concentration-dependent manner [102]. *d*-Propranolol, a biologically inert stereoisomer, was ineffective. In the propranolol-infused visual cortex of kittens, OD

plasticity increased as expected when *in vivo* availability for endogenous NA of unoccupied β -adrenoreceptor increased some time after the termination of continuous infusion of *d,l*-propranolol [103]. Furthermore, recovery of the plasticity was accelerated by a cortical infusion of NA.

In summary, it is very likely that the central NA- β -adrenergic receptor system critically contributes to the regulation of OD plasticity in the developing visual cortex.

2. *Acetylcholine (ACh)-muscarinic receptor system*

The striate cortex receives cholinergic innervation from cells scattered throughout the basal telencephalon [44, 67, 76]. Modulatory roles of iontophoretically applied ACh were studied in some detail while visual cortical units were stimulated by moving a single light slit at optimal orientations through their receptive fields [104]. In most cortical cells, visually evoked responses were augmented by ACh injections. Both facilitatory (majority of units, 74%) and suppressive (minority of units, 16%) effects of ACh on unit firing were blocked by iontophoresis of atropine [97]. In visual cortex ipsilateral to kainate lesions of the basal forebrain, half the recorded cells from area 17 lost visual responsiveness, but the responsiveness seemed to be restored by ACh iontophoresis [96].

A possible role of ACh afferents in the regulation of OD plasticity was suggested. That is, the plasticity decreased in kitten visual cortex following placement of either combined lesions at both the ascending NA bundles and ACh-containing somata in the basal forebrain, or unilateral lesions of the cingulate gyrus, in the region through which cholinergic and noradrenergic axons travel toward area 17 within the white matter [10]. Previously we scrutinized this suggestion positively by testing whether muscarinic activation of ACh receptors restored the plasticity, as was previously shown to occur with an NA infusion, to kitten visual cortex that had been rendered aplastic due to a preceding inactivation of the NA- β -adrenoreceptor system [49].

Effects of direct infusion of a muscarinic ACh agonist, bethanechol, into the 6-OHDA-pretreated cortex was clear: a shift in ocular dominance to the open eye was obtained in visual cortex infused with 1 or 5 mM bethanechol, while the shift was not seen in the control, vehicle-infused hemisphere of the same animals. The "plasticity-enhancing" effect of bethanechol was confined to an area near its infusion site.

To evaluate the potency of bethanechol infusion in restoring OD plasticity, we compared a concentration-effect relationship obtained for bethanechol with that for NA. There was a positive correlation between concentration of bethanechol and the strength of the restored plasticity under the comparable conditions. However the potency of bethanechol in restoring the plasticity was at least 100-fold weaker than that of NA.

The results with bethanechol infusion into the 6-OHDA pre-infused cortex definitely indicated that muscarinic ACh receptors are involved in the regulation of

OD plasticity. We conclude, however, that the contribution of the ACh system to plasticity-enhancing mechanisms is far less than that of the NA- β -adrenoreceptor system for the following reasons: (i) muscarinic cholinergic antagonist, scopolamine infusion was at least 172-fold less effective than the propranolol infusion in reducing OD plasticity under the comparable conditions; and (ii) the "plasticity-enhancing" effect of bethanechol was not expressed when β -adrenoreceptors had been functionally blocked by propranolol.

Recently, GORDON *et al.* have followed up the study of BEAR and SINGER on the effects of a unilateral cingulate lesion [39]. They obtained the expected results: a decrease in OD plasticity with average 60% depletions of NA and choline acetyltransferase activity. The plasticity decrease, however, was seen only when the contralateral eye was monocularly deprived. They assumed that depletion of NA and ACh would have a dual role: reducing facilitatory input, decreasing the ability of cortical cells to potentiate the effect of monocular deprivation and at the same time increasing the visual input required to drive cells. The first is for deprivation of the contralateral eye and the second for the ipsilateral one. Their explanation for the obtained changes in OD is unintelligible and a tautology at best.

Encouraged by the recent advent in studying central effects of lithium (Li) salts [4], we studied visual cortex of monocularly deprived kitten repeatedly injected with a Li solution intraperitoneally or directly into the cortex [60]. We found that OD plasticity was significantly reduced by Li treatments. Thus, it seems quite possible that Li-sensitive second messengers participate in the integration of the multireceptor mechanisms, including NA and ACh, underlying OD plasticity.

3. GABA-GABA_A receptor system

In 1976, DUFFY *et al.* suggested the inclusion of GABA receptor-mediated processes in visuocortical plasticity [28]. They reported that intravenous injections of a subconvulsive dose of bicuculline, a GABA_A antagonist, recovered lost receptive fields for the monocularly deprived eye in visual cortex of adult cats which had been subjected to monocular lid suture since birth. However, none of the recovered receptive fields were dominated by input from the previously deprived eye, suggesting that the observed effect, which lasted very briefly during both intravenous and iontophoretic applications of bicuculline, should not be interpreted as genuine restoration of OD plasticity.

RAMOA *et al.* directly infused kitten visual cortex with 5 mM bicuculline methiodide concurrently with monocular deprivation for a week [92]. The expected shift in OD was significantly reduced compared with that in the saline-infused control hemisphere. The authors' explanation was follows: a loss of selectivity due to bicuculline caused in effect an increase in coupling between presynaptic and postsynaptic activity, which in turn satisfied a necessary condition for the strengthening of Hebbian synapses of binocular cells, effectively counteracting the usual consequence of binocular imbalance. There was, however, a serious drawback in the design of this study. As was the case for continuous

infusion of concentrated glutamate (0.5 M) [99], the majority of visual cortical cells either lost selectivity or became visually unresponsive in the bicuculline-infused cortex. Conceptually, therefore, the situation cannot be distinguished from that of *de facto* binocular deprivation, a condition which interferes minimally with the OD distribution, despite its deleterious effects on the response qualities of visuocortical cells [117].

MOWER and CHRISTEN compared the effects of iontophoretically injected bicuculline on the OD of visual cortical neurons in normal cats and cats reared with abnormal visual experience (monocular deprivation, surgical strabismus, and monocular deprivation after dark rearing) [82]. They found marked differences between cats from different groups: in normal cats only 17% of the recorded cells showed changes in OD caused by bicuculline, whereas in cats reared with abnormal visual experience over 50% showed changes. The results indicate that somehow the effectiveness of GABA inhibition in OD of visual cortical cells is exaggerated in animals reared with abnormal visual experience.

Autoradiographic studies on GABA-replaceable [^3H]-muscimol binding sites in the visual cortex of monocularly deprived kittens have so far produced ambiguous results. Short-term monocular deprivation (3 days) in 5-week-old animals was reported to increase GABA_A receptor binding [107]. MOWER *et al.* found no differences between normal and monocularly deprived cats in the amount or affinity of GABA_A receptor binding in the visual cortex [83]. The binding sites were scattered more or less evenly throughout the 6 cortical laminae, and this laminar pattern stayed the same after long-term monocular deprivation. Using a comparable method, but with 15-fold concentrated [^3H]-muscimol, SHAW and CYNADER obtained different results [100]. In normal cat visual cortex, the laminar distribution of GABA_A binding was not even, but the number of binding sites was highest in the central laminae and lower numbers of binding sites were found near the cortical surface and the white matter. They found that monocularly deprived cats had a greater than 90% increase in the number of muscimol binding sites compared to normal cats, but there was no change in the binding affinity and the laminar distribution pattern. The cause of this increase remains unexplained.

An immunohistochemical/biochemical study showed that monocular deprivation affected neither the glutamic acid decarboxylase (GAD, a GABA synthesizing enzyme) immunoreactivity pattern in kitten visual cortex nor the GAD activity in homogenates of kitten cortex [9].

An autoradiographic study on the ontogeny of muscimol binding showed a rather complicated time course of maturation [101]. This seemingly straightforward study was compromised, however, by the sparseness of the data density for different age groups. More recently, a biochemical study clearly showed that GAD activity in areas 17 and 18 of cats increases gradually during the first postnatal month and reaches the adult level at 5–6 weeks postnatally without reaching any peaks [29].

Taken together, the GABA-GABA_A receptor system may not be directly

responsible for the regulation of cortical plasticity, but it plays a role in maintaining the OD of visuocortical cells. The GABA system may be physiologically modifiable to some extent by changes in excitatory connectivity within the visual cortex and the modified GABA system may in turn contribute to induced changes in the OD pattern.

4. *Glutamate-NMDA (N-methyl-D-aspartate) receptor system*

A unique biophysical feature of NMDA receptors (i.e., voltage-dependent gating of Ca^{2+} influx antagonistically controlled by Mg^{2+} ion and glycine) appears to constitute an ideal ionic mechanism for Hebbian-type synaptic modification [20]. In the CA1 region of the hippocampus, calcium entry through NMDA receptors seems to be necessary, and perhaps sufficient for the induction of long-term potentiation (LTP) [73]. Recently, evidence has accumulated suggesting that thalamocortical afferent projections, including geniculocortical projections and some intrinsic connections in visual cortex, are glutamatergic [5, 110]. The involvement of NMDA receptors has been conclusively demonstrated [2, 3] in the generation of LTP in slice preparations of rat and kitten visual cortex, although induction of LTP without the participation of NMDA receptors has also been reported recently for kitten visual cortex [69].

The possible involvement of NMDA receptors in the regulation of cortical plasticity has been implied [7, 68, 93, 114]. RAUSCHECKER and HAHN showed that an OD shift was prevented in alert kittens that received daily repeated brief periods (20 min) of monocular occlusion immediately followed by ketamine-xylazine anesthesia [93]. Ketamine is known to be a non-competitive NMDA receptor antagonist. Other short-acting anesthetics such as xylazine or methohexital, while providing the same depth of anesthesia, are not NMDA receptor antagonists, and they did not have the same effect on OD plasticity. However, the interpretation of this finding may be compromised, because the drug effect was tested against a small change in OD induced by brief monocular deprivation in control animals. TSUMOTO *et al.* showed that iontophoretic application of 2-amino-5-phosphonovaleric acid (APV), a competitive NMDA-receptor antagonist, suppressed visual responses of cortical neurons twice as often (71%) during the sensitive period of young kittens as it did in adult cats (33%) [114].

In 1987, KLEINSCHMIDT *et al.* reported direct evidence for the involvement of NMDA receptors in the regulation of OD plasticity [68]. They showed that in visual cortex infused with 50 mM APV, many cortical cells remained binocular despite concurrent monocular deprivation. More recently, BEAR *et al.* reported that APV infusion for 1 week combined with monocular deprivation or reverse suture produced a concentration-dependent increase in the percentage of neurons that lacked normal orientation selectivity and visual responsiveness, and that were responsive to stimulation of the deprived eye [7]. They concluded that blockade of NMDA receptors by APV disrupted the experience-dependent plasticity of kitten visual cortex.

We find this conclusion unwarranted for the following reasons. First, results from two control studies, 50 mM L-APV infusion in 2 kittens and 50 mM D,L-APV infusion in 2 adult cats, were described but no data were shown. Especially problematic is that despite the presence of a sizable region of necrosis at the infusion site "as large as 3 mm in diameter in cortex infused only with saline," no histological data were presented whatsoever. That information is crucially important for the assessment of the recording sequences of the individual cells used to construct various histograms. This concern becomes especially acute when alterations in properties of cells are discussed in relation to the intracortical distance from the infusion site. When the region of direct tissue damage was 3 mm or more in diameter at the center of infusion, it might not be possible to record visually responsive cells with a 2 mm radius from the infusion center.

Second, estimation of the extracellular concentration of D,L-APV indicated that a significant decrease in OD plasticity could be obtained with concentrations as low as 20 μ M. This assertion, however, may lack a solid foundation. For an *in vitro* binding study, the concentration of [3 H]-D,L-APV was *a priori* kept as low as 150 μ M (Fig. 14 in [7]), though a concentration of 50 mM was used for *in vivo* infusion to block NMDA receptors in visual cortex. Thus, the coefficient of 0.004 that was used by BEAR *et al.* [7] to convert an APV content *in vivo* recovered at a given cortical site into an estimate of extracellular APV concentration might well be much larger than the number used here, thereby giving the later estimate a value a few orders of magnitude higher than we believe tenable. BEAR *et al.* explained that the prevalence of non-selective binocular cells, more than 3 mm from the infusion center (Fig. 11B in [7]) was due to a decrease in OD plasticity caused by partial suppression of postsynaptic activity. This was contrasted with a histogram showing "reverse shift" toward the deprived eye within 3 mm from the infusion center (Fig. 11A in [7]). However, this scheme is hardly plausible, since the estimated concentration of APV at 5 mm differs very little from that at 2 mm. To make their argument valid, one would have to assume that the concentration of APV decreases exponentially with increasing distance from the infusion center.

Finally, our own study carried out under conditions comparable to those of BEAR and associates showed a clear sign of OD shift after monocular deprivation for a week near (~ 3 mm) the site of 50 mM D,L-APV infusion [58]. Independent of the binocularity value, we found that APV had a distinct effect on the cortical cells' selectivity; a substantial proportion of visually active cells became non-selective for orientation and direction, yet these neurons underwent OD shift toward the open eye.

In short, the large proportion of either visually unresponsive or non-selective cells with poor response quality recorded in these studies would indicate that the chemical environment near the site of 50 mM D,L-APV infusion was probably far from physiological and that the present design of experiments was inadequate to measure changes in experience-dependent plasticity. Rather, as suggested earlier by TSUMOTO *et al.* [114] and elaborated later by MILLER *et al.* [77], NMDA

receptors seem to constitute an indispensable part of the cellular processes for normal impulse transmission in the visual cortex, thus affecting the activity-dependent mechanisms described previously. Indeed, FOX *et al.* [30] showed that iontophoretically injected APV reduced visually evoked responses in layer II/III of cat visual cortex throughout adulthood, though this effect of APV disappeared by 6 weeks of age in layers IV–VI. They also showed that visual stimuli that produce suprathreshold responses activated NMDA receptors [31]. Instead of a threshold for NMDA-receptor activation, a continuous range of NMDA-receptor influence was found over the entire response range. They concluded that NMDA receptors can act to amplify small synaptic signals.

Thus, the available data collectively indicate that at present no specific role may be assigned to NMDA receptors in the regulation of OD plasticity, despite earlier expectations for this based on the results of a few correlation studies [14, 114].

5. Other systems

Several experimental manipulations have been shown to affect OD plasticity. In 1982, MCCALL *et al.* [75] examined in kitten visual cortex the effects of lysergic acid diethylamide (LSD) intraventricularly administered through an osmotic minipump during a one-week period of monocular deprivation. The animals had no obvious anomalies during the administration of the drug. They found that the response properties of recorded units were normal, except that binocularity was significantly lower in the experimental than the control, drug-free animals. This finding suggested that chronic intraventricular administration of LSD affected the sensitivity of cortical neurons to monocular deprivation either directly or indirectly through its interactions with monoamines.

Gangliosides are thought to be involved in cellular differentiation, neurite outgrowth and sprouting *in vivo*, and are capable of protecting neurons from retrograde degeneration and, furthermore, of enhancing the recovery process from various forms of lesions in the central nervous system *in vivo*. CARMIGNOTO *et al.* [18] studied the effects of monosialoganglioside internal ester, AGF₂, on OD plasticity. The AGF₂ treatment (30 mg/kg, i.p. on alternate days) covered the entire period of deprivation from the 35th day to the 4th month of age. They found that the AGF₂ treatment partially prevented the usual shift in OD following monocular deprivation (binocularity and standard deviation, 0.427 ± 0.03 in treated animal v.s. 0.203 ± 0.06 in control).

The presence of immature astrocytes may be a prerequisite for visual cortical plasticity to be causally linked to the maturation of astrocytes. MÜLLER and BEST [84] implanted astrocytes cultured from the visual cortex of newborn kittens into the visual cortex of adult cats. They reported an OD bias toward the nondeprived ipsilateral eye in the astrocyte-implanted adult animal following monocular deprivation that lasted for 4–8 weeks. The effect was not obtained when recordings were made at locations remote from the transplantation site or in visual cortex implanted

with cultured fibroblasts.

DAW *et al.* [25] investigated the effect of an elevated level of cortisol on OD plasticity. Animals were given daily injections of cortisol (i.m.) for 20 days starting around 35 days of age. They found that the cortisol treatment reduced the OD shift usually expected following 10 days of monocular deprivation in a dose-dependent manner.

One result in common for all these studies is that the extent of effects induced by each of these combined manipulations was small compared with those previously described for manipulations of neuromodulator systems. All the authors asserted that the reported changes in the OD distribution were statistically significant. However, it is far less clear how these factors are related to the similar effects of the known neurochemical processes reviewed above in Sections 3-1 to 3-4.

4. APLASTIC KITTEN VISUAL CORTEX: A NEW PARADIGM

Changes in OD resulting from monocular deprivation are known to occur in a relatively short time at the peak of cortical sensitivity as summarized in Table 1. For example, FREEMAN and OLSON reported that monocular occlusion for 4 h causes an abnormally low proportion of binocular cells [36]. Using 4-week-old kittens kept in the dark since birth, BLAKEMORE and MITCHELL reported that as little as 1 h of exposure to gratings of a single orientation was sufficient to produce asymmetries in the distribution of orientations preferred by visuocortical cells [12]. Since the changes could be induced rapidly, they proposed that the processes underlying these changes may be similar to those of other short-term neural events such as learning and memory.

Importantly, OD plasticity has been thought to be effective only when young animals are visually alert, thus being conspicuously absent from anesthetized and paralyzed preparations [33, 48, 106]. For example, monocular exposure lasting for 10–24 h would not induce any significant changes in the OD distribution in visual cortex of anesthetized and paralyzed kittens. The above supposition, if true, would impose a serious constraint on studying cortical plasticity under acute experimental conditions such as cortical slice preparations.

One of a few ways to explore directly the kinetics of experience-dependent changes in individual neurons without using anesthesia and paralysis is to record chronically cell activity with “floating” microelectrodes. Recently, MIOCHE and SINGER utilized this technique to follow changes resulting from monocular deprivation in individual neurons [78]. They found that the earliest effect of monocular deprivation was the disappearance of binocular summation, and that overt changes in OD were observed as early as 6 h after the beginning of monocular deprivation. In the case of reverse occlusion, at least 24 h were required before responses to the deprived eye reappeared. They also reported some intriguing observations, including an experience-independent consolidation period for OD change, the existence of which has been controversial [35, 79]. However, one should be

Table 1. Rapid modification of ocular dominance (OD).

Rearing condition	Age	Monocular deprivation duration	Effects on OD distribution	Comments	Reference
Normal	4-5 weeks	3-4 days	A sharp decline in the number of binocular cells. An overall decline in the relative influence of the deprived eye		HUBEL and WIESEL (1970) [46]
Binocular deprivation	29 days	6-20 h	A shift in ocular dominance toward the open eye	Abnormal cells; 30-44%	PECK and BLAKEMORE (1975) [90]
Normal	29 days	1 day 4-8 days	A sign of shift was detectable Cortical changes comparable to those seen following much longer periods of deprivation	Closure of ipsilateral eye	MOVSHON and DÜRSTELER (1977) [79]
Normal	29 days	4 h	Small but significant changes	Obvious in layer IV and V	FREEMAN and OLSON (1982) [35]

cautious in interpreting these results, since they are based on behavior of multiple units at each site (instead of single cells). There is no guarantee that all units at a given site behave similarly.

A currently popular approach to circumvent the above drawback is the use of slice preparations. For this topic, readers are referred to a recent minireview by TSUMOTO which appeared in this journal [112]. Obviously, an advantage of the slice preparations for studying synaptic plasticity is that they provide a relatively controlled chemical microenvironment for the neurons under study. At the same time, they lack the essential feature of reaction to natural stimuli which is available to *in vivo* preparations. For instance, it is impossible to drive a specific pathway of interest in slices. Furthermore, a number of important and well organized pathways, including long-range intracortical pathways [16, 38], and ascending afferents from subcortical structures are necessarily transected in slices. Both types of afferents are known as to be critically important for the generation of receptive-field properties of individual cortical neurons and thus the regulation of cortical plasticity [17, 66, 105].

In the following sections, we will discuss in detail a third approach. The basic premise here is that visuocortical plasticity is a product of both activity-dependent processes within the visual system and neuromodulator-dependent global processes. Therefore, the objective of the new paradigm is to combine the merits of the above two methods in the anesthetized and paralyzed, whole-animal preparation. We use physiological manipulations of visual afferents such as "associative" presentation of natural visual stimuli or their deprivation, and various pharmacological manipulations such as iontophoresis or direct, continuous infusion of receptor agonists or antagonists. Since anesthetized and paralyzed kittens are to be used throughout the experimentation, changes obtained in the receptive-field properties of visuocortical cells, by counteracting the general suppressive effects of anesthesia and paralysis in this preparation, indicate the involvement of targeted receptors, for example, in the regulation of cortical plasticity.

5. ACUTE ACTIVATION OF THE CENTRAL NA SYSTEM

Some experimental procedures have been reported to counteract anesthesia and paralysis, thereby inducing significant changes in the OD distributions. An early study showed that in lightly anesthetized and paralyzed kittens, binocularity could be significantly reduced by passive eye movement of the visually exposed eye while the other eye was kept occluded [33]. This result corroborates an earlier notion that proprioceptive afferents from extraocular muscles are involved in the expression of OD plasticity in freely behaving kittens [15, 72]. General anesthetics, including barbiturate, are thought to depress the activity of the mesencephalic reticular formation (MRF) [74]. The plasticity-suppressing effect of anesthesia and paralysis were counteracted, at least in part, by electrical stimulation of the MRF for 15 h [106]. In this section, we discuss how the pharmacological

activation of the NA- β -adrenergic receptor system can restore plasticity to the aplastic visual cortex of anesthetized and paralyzed kittens.

The plasticity-enhancing effect of activation of the central NA- β -adrenergic receptor system has been established under various experimental conditions. Briefly, continuous infusion of the striate cortex with exogenous NA restored the plasticity to kitten visual cortex that had lost its plasticity due to a previous lesion of CA terminals by 6-OHDA [63] or the infusion of β -adrenergic receptor antagonists [103]. Even in the adult animal the visuocortical plasticity could be partly restored by either direct cortical infusion of NA or electrical stimulation of the locus coeruleus, from which the ascending NA fibers originate [66]. More recently, we showed that the OD distribution can be rapidly changed under anesthesia and paralysis by "on-line" manipulations of the two visual axes (acute paralysis squint) during recording from the NA infused, otherwise normal, visual cortex of adult cats [43]. Taking advantage of the plasticity-enhancing effects of NA, we showed that OD shift can be induced in anesthetized and paralyzed kittens by combining monocular exposure with a cortical NA infusion [48, 50].

1. Basic findings

Under general anesthesia and paralysis, normal kittens (4–7 week-old) were monocularly exposed to continuous TV shows for about 20 h, concurrently with cortical infusion of the vehicle solution alone. We found that despite monocular exposure, their OD distribution stayed essentially normal, showing a high proportion of binocular cells (binocularity of 0.63, Fig. 1A).

Next, the same visual cortices of the same three kittens were continuously infused with a *l*-NA-containing solution in place of the vehicle solution. This time, physiological recordings from an area close to the infusion site unmistakably revealed a shift in OD to the open eye with a marked reduction in binocularity (binocularity, 0.37) following monocular exposure to TV shows for $\sim$ 20 h. This result was interpreted as suggesting that the cortical *l*-NA infusion restored OD plasticity to the aplastic visual cortex of anesthetized and paralyzed kittens [50].

This plasticity-enhancing effect of *l*-NA was not shared by *d*-NA, a biologically inert stereoisomer of NA [48]. Neither *l*-NA infusion into adult visual cortex combined with moving pattern stimuli nor *l*-NA infusion into kitten visual cortex combined with monocular exposure to electronic noise on the same TV screen for the comparable time duration induced the OD shift [48].

2. Time course

We then examined the time course of the changes in OD under the present acute experimental condition. The number of binocular cells was first significantly reduced after the combined treatment for about 12 h (Fig. 2, top). Binocularity was reduced markedly by 20–24 h. This decrease was accompanied by an increase in the proportion of group-7 monocular cells (G7), a clear sign of OD shift to the open eye (Fig. 2B, C, D).

Fig. 1. Effects of short-term monocular exposure combined or not combined with a direct and continuous infusion of *l*-noradrenaline (*l*-NA) on ocular dominance in visual cortex of acutely anesthetized and paralyzed kittens. A, B: one pair of composite ocular-dominance histograms which comprised three original histograms ($N=3$) were obtained before (vehicle-infused control, A), and after the *l*-NA-infusion (B). Each composite histogram is based on a total of 90 visually active cells ($N=90$), 30 cells being recorded from the cortex of each of the three kittens. Ocular dominance of each cell was determined, using a near optimal stimulus, based on the 7-group scheme of HUBEL and WIESEL. Briefly, group 1 and group 7 refer to monocular cells which are exclusively activated by stimulation of the contra- and ipsilateral eye, respectively. Group-4 cells receive balanced excitatory input from the two eyes. All other groups fall in between. Inhibitory influence is not considered here. GL and U indicate unit activity of lateral geniculate axons and visually unresponsive units, respectively. Filled circles (●) and open circles (○) indicate the closed and the exposed eye, respectively. Binocularity (B) was initially calculated for each original histogram as the ratio of cells in groups 2–6 to the total number of visually responsive cells and then its mean was obtained for the composite histogram. G7 refers to the average proportion of group-7 cells calculated similarly. Vertical bars at the top of columns refer to the standard deviation of the mean in each cell group. A column for group-5 cells in B lacks a standard deviation bar since the three measurements yielded the same value. Timing of experimental manipulations is indicated schematically at the top left. The duration of monocular exposure was comparable among the 6 experiments. In the second monocular exposure, the visual cortex was infused with *l*-NA (top right). The duration of recording time was also comparable among the 6 recordings (modified from [50] with permission).

Fig. 2. Effects of monocular exposure combined with cortical *l*-NA infusion are different depending on the duration of the combined treatment. Top: Eighteen original ocular-dominance histograms were obtained 6–45 h after monocular exposure combined with or without the cortical *l*-NA infusion. Enclosed numbers in the top diagram indicate the duration of the treatment in hour. Squares ($N=15$) represent the results from visual cortex infused with *l*-NA. Circles ($N=3$) represent the results for control animals without *l*-NA infusion. The lower end of the 5% rejection intervals of normal binocularity (0.53, [66]) is shown by a vertical dotted line. Bottom: Each of 6 representative histogram is composed of 30 visually responsive cells recorded along a single recording track in area 17. The convention is the same as for Fig. 1 (modified from [50] with permission).

Intriguingly, the present acute study clearly revealed the dynamic nature of OD changes that had long been suspected but not openly discussed. The same combined treatment extended to periods longer than 24 h did not necessarily enhance the shift, although the *state of reduced binocularity* was sustained (Fig. 2). The predominance of group-1 monocular cells weakened, in effect, the degree of the shift toward the open eye (Fig. 2E, F). The relatively large proportion of group-1 monocular cells, which responded exclusively to stimulation of the deprived eye, appears to resemble that seen in a few OD histograms derived from visual cortex of monocularly deprived kittens that were chronically infused with either muscimol [94] or D,L-APV [7]. However, one would not imagine the presence of mechanisms common to the above two studies and the present one, because the binocularity value ($\sim 60\%$) in the above two studies was twice as large as that obtained in our study ($\sim 30\%$), indicating that the physiological condition was dissimilar among the three studies.

3. Age dependency

The susceptibility of visual cortical cells to the effects of closure of one eye varies with the age of animals. It is possible that OD plasticity restored by *L*-NA infusion in acutely anesthetized and paralyzed preparations is also age-dependent. We tested this possibility by monocularly exposing 11 anesthetized and paralyzed animals (4–36 week-old) for about 20 h in combination with cortical *L*-NA infusion. Binocularity and G7 values were compared among two age groups: 5 kittens 13 weeks or younger and 6 kittens older than 13 weeks. The effects of combined treatments were smaller in the older animals than the younger ones. Both indices are significantly different between the two groups. These results suggested the existence of a “sensitive period” for the effect of short-term monocular exposure under the acute experimental condition as known in the chronic condition [50].

4. Comments

At present, we cannot fully explain why the extent of the NA-induced changes in the OD distribution fluctuates between the two extremes represented by OD histograms with predominantly either group-1 or group-7 monocular cells. However, we can exclude the possibility that cyclic fluctuations simply reflect an “increased variability” in the normal OD distribution caused by NA infusion. Because the standard deviations in the OD histograms of Fig. 1, obtained with or without NA infusion, always retain small changes in the shape of a given OD histogram, they cannot be a product of increased variability in the sampling of single cells belonging to different OD groups. Furthermore, we found that the acutely induced cortical effects of monocular exposure, combined with the cortical *L*-NA infusion, were strongest immediately after the end of the treatment, and that the effects gradually became less obvious as physiological recording progressed. The gradual change in the OD pattern from the first to the last segment of the same recording tracks is hardly explained by the “increased variability” hypothesis [50].

Another possible explanation for the NA-induced changes is that weak responses to the stimulation of one eye simply were suppressed by the inhibitory effects of NA, leaving the dominant responses the same, or even enhanced, presumably due to an NA-induced increase in signal-to-noise ratio for visual cortical cells. However, this is highly unlikely for the following reasons. First, the thesis that NA works primarily as an inhibitory agent in the brain is incorrect; iontophoretic studies of NA's action on visually evoked single-cell discharges have shown that cortical responsiveness either increased, decreased or was left unchanged at about the same frequency [57, 116]. Second, the assumption that NA inhibits cortical activity, preferentially weakening relatively weak responses more than strong ones, would predict a gradual and smooth decline in binocularity without monocular exposure. This has never been shown. For example, KUPPERMANN and KASAMATSU reported that no change in the OD distribution was obtained in NA-infused, otherwise normal, visual cortex of kittens kept in the dark during the NA infusion [70]. Lastly, it is known that NA is highly reactive and autooxidized rapidly in the physiological condition. Therefore, exogenous NA infused into the visual cortex becomes ineffective unless it is taken up by tissue and stored in the special compartment including small dense-cored vesicles in nerve terminals. Only NA molecules bound to NA-related receptors are able to exert physiological effects thereafter. The specific uptake of exogenous NA begins rapidly and is completed within a few hours at most [51]. Therefore, if NA has a direct chemical effect on the cortical network responsible for binocularity, changes in binocularity would have been completed much faster than those observed in our study, because we always began physiological recording a few hours after the end of the NA infusion. These considerations, taken together, suggest that the fluctuation of binocularity, superimposed on its steady decrease, may be caused by the concurrent presence of two competing factors. One is a coercive force set in action in favor of the open, ipsilateral eye following monocular deprivation of the contralateral eye. The other is dominance of the contralateral afferents whose strength is exaggerated by the acutely restored cortical plasticity in the NA-infused, but otherwise normal, visual cortex. Consistent with this hypothesis, we earlier obtained an OD histogram dominated by the contralateral eye with normal binocularity in normal kitten visual cortex chronically infused with *l*-NA [70]. In this case, the extent of binocular competition is minor in comparison to the background of the elevated OD plasticity.

A remaining issue concerns how the present data are related to those obtained in previous studies. There is some evidence for a gradual OD shift towards the experienced eye following monocular deprivation in alert kittens. This orderly progress, however, did not occur with the present acutely induced changes. This apparent discrepancy raises doubts whether acutely induced changes in OD are related to experience-dependent changes in waking animals.

It is certainly a possibility that the two phenomena are not related. Our explanations, as summarized above, must be incomplete, since they cannot explain

asynchrony between the fluctuation of binocularity and a unimodal peak of G7 values. Nevertheless, other qualifying properties such as the presence of a "sensitive period" and a significant decrease in binocularity when challenged by strong binocular imbalance suggest the likelihood of a similarity between the "restored" plasticity in the acute study and OD plasticity in the visual cortex of alert animals. Indeed, a U-shaped OD distribution is commonly seen shortly after the start of monocular deprivation of the contralateral eye, before the eventual shift to the open eye is established [46, 87]. In this connection, we would like to mention in particular that misalignment of the two visual axes *during* electrophysiological assay resulted in a smaller number of binocular cells in the NA-infused, otherwise normal visual cortex of adult cats under anesthesia and paralysis [43]. This finding is surely comparable with that of a similar lack of binocular cells in the visual cortex of strabismic cats [45].

Taken together, the available data suggest that the NA- β -adrenergic receptor system functions, at least in part, as a neurochemical mechanism underlying visuocortical plasticity in both "traditional" chronic preparations and in acute ones.

6. "ON-LINE" ANALYSIS OF OD CHANGES: A PHYSIOLOGIST'S DREAM

An ultimate goal of neurophysiology is to show, directly and not by inference, moment-to-moment changes occurring in the brain. It would be exciting to show that OD of single cells can be changed during physiological recording. Results obtained on the basis of pooled data are not free from the inherent problem of "sampling bias" in a population study. Assessment of changes before, during and after comparisons is, however, straightforward when the same single cells are studied.

We first review below results of several early studies on "on-line" modification of OD, then consider whether activation of the NA- β -adrenoreceptor system might be useful in such modification.

In 1976, KASAMATSU [53] created in young kittens a drastic but reversible imbalance in the total output from the retina by direct application of a small amount of local anesthetic to one optic nerve distal to the optic chiasm. The subsequent nerve-silencing effect lasted for one minute or less at the injection site while evoked potentials in the LGN were suppressed for 7 min in average. In 13 of 20 visuocortical cells studied for at least 1 h under acute recording conditions, the blockade of tonic retinal discharges from one eye caused cortical cells to respond better to the stimulation of the other eye. No such changes were observed in similarly treated adult cortex. The results were interpreted as suggesting the existence of constant binocular competition between the two sets of visual afferents impinging on single cells in the developing visual cortex. This observation was extended by TSUMOTO and SUDA [115], who found that conditioning tetanic stimulation of one optic nerve of the normal kitten enhanced visual cortical evoked potentials in response to stimulation of the conditioned optic nerve, whereas similar

potentials induced by stimulation of the other optic nerve were concurrently suppressed. This effect lasted up to 9 h after delivery of the tetanic stimulation.

TSUMOTO and FREEMAN [113] stimulated the internal medullary lamina (IML) of the thalamus to elicit conjugated eye movement in 4-week-old anesthetized and unparalyzed kittens. During electrical stimulation of the IML for 15–20 min, one eye was occluded and the other was visually activated with optimal stimuli. They found that 11 of 42 cells underwent changes in OD which lasted for 1 h or more (22 cells for over 15 min). They considered a change to have occurred if the shift was in two or more OD groups. This criterion was used to exclude the contribution of spontaneous changes in OD. It is worth mentioning that they never observed OD changes to occur in the inappropriate direction, i.e., toward the occluded eye. These results corroborate those of a previous study in which binocularity was significantly reduced in lightly anesthetized and paralyzed kittens [33] by passive eye movements of the visually exposed eye while the other eye was occluded.

FRÉGNAC *et al.* [37] reported that OD and the best orientation of single neurons in area 17 can be modified during the period of recording. They employed a differential pairing procedure, during which iontophoresis of potassium was used to increase artificially visual responses to a given stimulus, and to decrease (or block) the response to a second stimulus which differed in ocularity or orientation. Modification of OD and orientation selectivity were produced in 33 and 43% of the recorded cells ($N=121$), respectively. The largest changes were obtained in dark-reared kittens at the peak of the sensitive period, but similar changes were also observed in adults. Changes were sometimes obtained in the size of receptive fields, probably due to unmasking initially subliminal zones, but no response appeared *de novo* (e.g., no change from monocular to binocular). These results are consistent with the “Hebbian” model of shifts in OD and best orientation.

Using a similar pairing procedure, GREUEL *et al.* [41] showed that 9 of 19 single cells in kitten visual cortex changed OD in less than one hour when monocular stimulation was paired with iontophoretic applications of cocktails of ACh, *l*-NA, NMDA, and L-glutamate simultaneously. The observed changes in response properties consisted of an enhancement of the responses to conditioned stimuli (homosynaptic potentiation via Hebbian mechanisms) or a reduction of the responses to nonconditioned stimuli, or both. Decreases in the conditioned responses (homosynaptic depression via “anti-Hebbian” mechanisms) were also observed at about an equal frequency. Their results seem to indicate that neuro-modulators such as ACh and NA, and NMDA receptor agonists promote experience-dependent modification of neural response properties in kitten visual cortex. They also reported that these chemical agents were more effective when applied in combination, suggesting synergy between their actions. However, it is unclear to what extent the induced changes are attributable to each of the few agents used here in combination with monocular visual stimulation.

In all these “on-line” analyses, discrimination of reported modification from

Fig. 3. Changes in ocular dominance of single cortical neuron following monocular visual stimulation combined with *l*-NA microinfusion. This cell was originally classified as group 2 (A, B, basal responses) and was located in layer V. A marked increase of ipsilateral response was observed following the treatment for 15 min (C, D). Further treatment for 30 min did not increase the ipsilateral response, though the contralateral response seems to have been reduced slightly (E, F). Both conditionings and tests were carried out by moving a single light slit with optimal parameters (Imamura *et al.*, unpublished data).

spontaneous variation of measurements is of critical importance. There are some studies suggesting that OD varies continuously under acute experimental conditions [42, 71]. The lack of universal criteria for changes in OD is an acute limitation to studies of this kind. Given the heterogeneity of visual cortical cells, it would be very informative if one could characterize modifiable cells by other known properties such as cell type, location by cortical lamina, and relationship to the

columnar/horizontal organization. Recently, we found that changes in OD can be induced by pairing monocular visual stimulation with iontophoretic or pressure applications of *l*-NA (Fig. 3). In 9 of 21 neurons examined, we have observed significant changes in the OD ratio 15–75 min after monocular conditioning. We plan to correlate the modifiability of single cells with functional cell type, laminar localization and location in relation to OD column in the near future.

7. CLOSING REMARKS

We have critically reviewed here early findings related to roles of activity-dependent mechanisms and global neurochemical factors in the regulation of the OD plasticity. Anesthesia and paralysis reduce plasticity in the kitten visual cortex even when the animal is at the peak of the sensitive period. Taking advantage of the plasticity-enhancing effect of activation of the β -adrenoreceptors, we have introduced a new paradigm in that OD plasticity is possibly restored to aplastic visual cortex of anesthetized and paralyzed kittens. We have argued that the direct activation of the NA- β -adrenoreceptor system, enhances cortical plasticity, in principle, independent of the general conditions of the experimental animals. This NA-restored plasticity may be further augmented by the simultaneous manipulation of other neuromodulatory/receptor systems such as muscarinic ACh receptors, NMDA receptors and others. It is hoped that future studies will combine specific manipulations of visual afferents with rapid induction and maintenance of a high level of cortical plasticity by pharmacological means in the same preparation under acute experimental conditions. The characterization of modifiable cells in relation to the known properties of single cells and networks in neurochemistry, physiology and anatomy is essential for understanding the cellular and molecular mechanisms of visuocortical plasticity.

Key words: cat, developmental plasticity, neurochemical control, striate cortex, synaptic modification.

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