Chapter 2

Contributions of Ascending Thalamic and Local Intracortical Connections to Visual Cortical Function

Valentin Dragoi, Casto Rivadulla, Mriganka Sur

The emergent properties of visual cortical networks arise from specific features of the cortical circuitry. A mechanistic description of how response properties arise in networks of cortical neurons is central to understanding information processing by the visual cortex. Primary visual cortical (V1) neurons receive their major input through thalamocortical or feedforward excitatory connections, with a role for local recurrent networks and of long-range connections in modulating neuronal responses in different layers of the cortex. We have examined mechanisms underlying three types of emergent responses that are created in V1 of cats—orientation selectivity, direction selectivity and spatial phase invariance—using selective blockade of neurotransmitter systems and selective inactivation of neurons by stimulus-induced adaptation.

Orientation selectivity

Orientation selectivity of neurons in the primary visual cortex (V1) is one of the most thoroughly investigated receptive field properties in the neocortex, and yet its underlying neural mechanisms are still debated (Sompolinsky and Shapley 1997; Ferster and Miller 2000). One prominent model of orientation selectivity is the "feedforward model," which proposes that a cortical simple cell receives input from a row of neurons in the lateral geniculate nucleus (LGN) whose receptive fields are aligned along the axis of orientation of the cortical receptive field (Hubel and Wiesel 1962). However, although it is true that weakly biased feedforward inputs can be sharpened by using high firing thresholds (the "iceberg" effect, Creutzfeldt *et al.* 1974a), the feedforward model incorrectly predicts broadening of orientation tuning with increasing stimulus contrast (Sclar and Freeman 1982; Wehmeier *et al.* 1989). Pure feedforward models also cannot account for the loss of orientation selectivity under iontophoresis of bic culline, a $GABA_A$ antagonist, which reduces inhibition over a localized population of cortical neurons (Sillito 1975; Tsumoto *et al.* 1979; Sillito *et al.* 1980). For this reason, it has been proposed that mechanisms utilizing shunting ("divisive") inhibition (e.g. Koch and Poggio 1985; Carandini and Heeger 1994), or hyperpolarizing ("subtractive")

inhibition at nonpreferred orientations (e.g. Wehmeier *et al.* 1989; Wörgötter and Koch 1991), can sharpen tuning in cells which have mildly oriented thalamocortical inputs; such models can also produce contrast-invariant orientation tuning, and can account for bicuculline-induced tuning loss. However, these inhibitory models are inconsistent with other experimental data. Although shunting inhibition has recently been rediscovered in cortex (Borg-Graham *et al.* 1998; Hirsch *et al.* 1998), it occurs only very transiently and appears insufficient to account for orientation selectivity (Douglas *et al.* 1988; Berman *et al.* 1991; Dehay *et al.* 1991; Ferster and Jagadeesh 1992; Anderson *et al.* 2000).

Moreover, results from our laboratory (Nelson *et al.* 1994) conflict with all orientation models that rely on inhibitory mechanisms to create orientation selectivity. In one set of experiments, intracellular blockade of inhibition in single cells of cat V1 was used to show that the sharpness of orientation tuning of blocked cells remains intact. In these experiments, whole-cell pipettes were used to deliver CsF-DIDS (cesium fluoride—4,4'-diisothiocyanatostilbene-2,2'-disulfonic acid) solution intracellularly to silence inhibitory voltage conductances (Cl−, K+). A mild, fixed hyperpolarizing current was injected to compensate for the increase in spontaneous firing rate. These results appear to conflict with reports that orientation tuning can be abolished by bicuculline-induced extracellular inhibitory blockade (Sillito *et al.* 1980; Nelson 1991). The critical difference between this type of inhibitory blockade and previous reports (e.g., Sillito *et al.* 1980) is the number of cells that lose inhibitory inputs. Disruption of orientation selectivity requires long bicuculline ejection times (Sillito *et al.* 1980; Nelson 1991), suggesting that the drug effects spread across a local population of neurons. In contrast, intracellular blockade (Nelson *et al.* 1994) affects only the recorded neuron. Thus, we infer that inhibition cannot play a major role in the generation of orientation selectivity.

Computer simulations in our laboratory have complemented the physiologic experiments, demonstrating that local, recurrent, cortical excitation can generate sharp, contrast-invariant orientation tuning in circuits that have strong iso-orientation inhibition and weakly oriented thalamocortical excitation (Somers *et al.* 1995). This model primarily addresses the circuitry within a single cortical "hypercolumn" and relies on only three assumptions. First, converging LGN inputs must provide some orientation bias at the columnar population level. Consistent with previous studies (Creutzfeldt *et al.* 1974b; Watkins and Berkley 1974; Jones and Palmer 1987; Chapman *et al.* 1991), this bias may be weak and distributed across a population with many cells that receive unoriented input. The second assumption of the model, that local (<1 mm horizontal distance) intracortical inhibitory connections must arise from cells with an effective broader distribution of orientation preferences than do intracortical excitatory connections, differs from prior inhibitory models in that it is consistent with experimental evidence for strong iso-orientation inhibition (Ferster 1986; Douglas *et al.* 1991a; Anderson *et al.* 2000). Narrowly tuned iso-orientation excitation and more broadly tuned iso-orientation inhibition can be realized by a simple difference-of-gaussian-like

structure in the orientation domain. This idea is supported by cross-correlation data (Michalski *et al.* 1983; Hata *et al.* 1988) and is consistent with a key hypothesis of many models of orientation selectivity development (e.g. Rojer and Schwartz 1990; Miller 1992; Swindale 1992). However, more recent simulations (Somers *et al.* 2001) show that inhibitory inputs can in fact be much narrower than originally thought (Somers *et al.* 1995); inhibitory inputs need only be slightly broader than excitatory cortical inputs. This seems consistent with recent experimental reports (Anderson *et al.* 2000). The final assumption is that cortical inhibition must approximately balance cortical excitation. Too much inhibition produced low response rates, and too little inhibition permitted nonselective amplification of all stimulus responses. However, many sets of parameters satisfied the "balance" requirement. This hypothesis is consistent with reports that EPSP and IPSP strengths roughly covary across orientations (Ferster 1986; Douglas *et al.* 1991; see Pei *et al.* 1994 for a differing view).

Integration of local inputs

Modulation of excitation and inhibition level using focal iontophoresis

Research in our laboratory (Toth *et al.* 1997) has investigated the role of local excitation and inhibition in modulating visual cortical responses. Using a combination of intrinsic signal imaging, single-unit recording, and focal iontophoresis of the $GABA_A$ antagonist bicuculline, as well as focal iontophoresis of GABA, Toth and colleagues have demonstrated that local connections provide strong excitatory inputs that are integrated nonlinearly by postsynaptic neurons. A micropipette was introduced in layer II/III of cat area 18, and intrinsic signal maps were recorded for several millimeters around the pipette (Fig. 2.1A). A critical issue in optical imaging is to avoid artifacts due to heart beat and respiratory movement. The traditional approach in intrinsic imaging experiments is to use a chamber filled with mineral oil and sealed with a glass cover in order to minimize brain movement. However, since perfect sealing cannot be achieved as iontophoresis requires the insertion of a glass micropipette, we had to use an additional method to reduce brain movement. We thus performed a bilateral pneumotorax to eliminate respiratory movements (occasionally, we had to drain the CSF by penetrating foramen magnum). Subsequently, warm agarose (1.5% in distilled water) was poured on the exposed cortex to avoid desiccation, and, finally, we added mineral oil on top of the agarose cushion. The pipette was moved with a mechanical microdrive until the desired position and depth were reached.

As Fig. 2.1B indicates, focal disinhibition causes the region around the pipette to become dominated by nearby orientations. Within this region, orientation singularities (or pinwheel centers) disappear and the normal structure of orientation domains is profoundly altered. Figure 2.1D shows that during bicuculline iontophoresis neurons of all orientations within the iontophoresis region shift toward the disinhibited

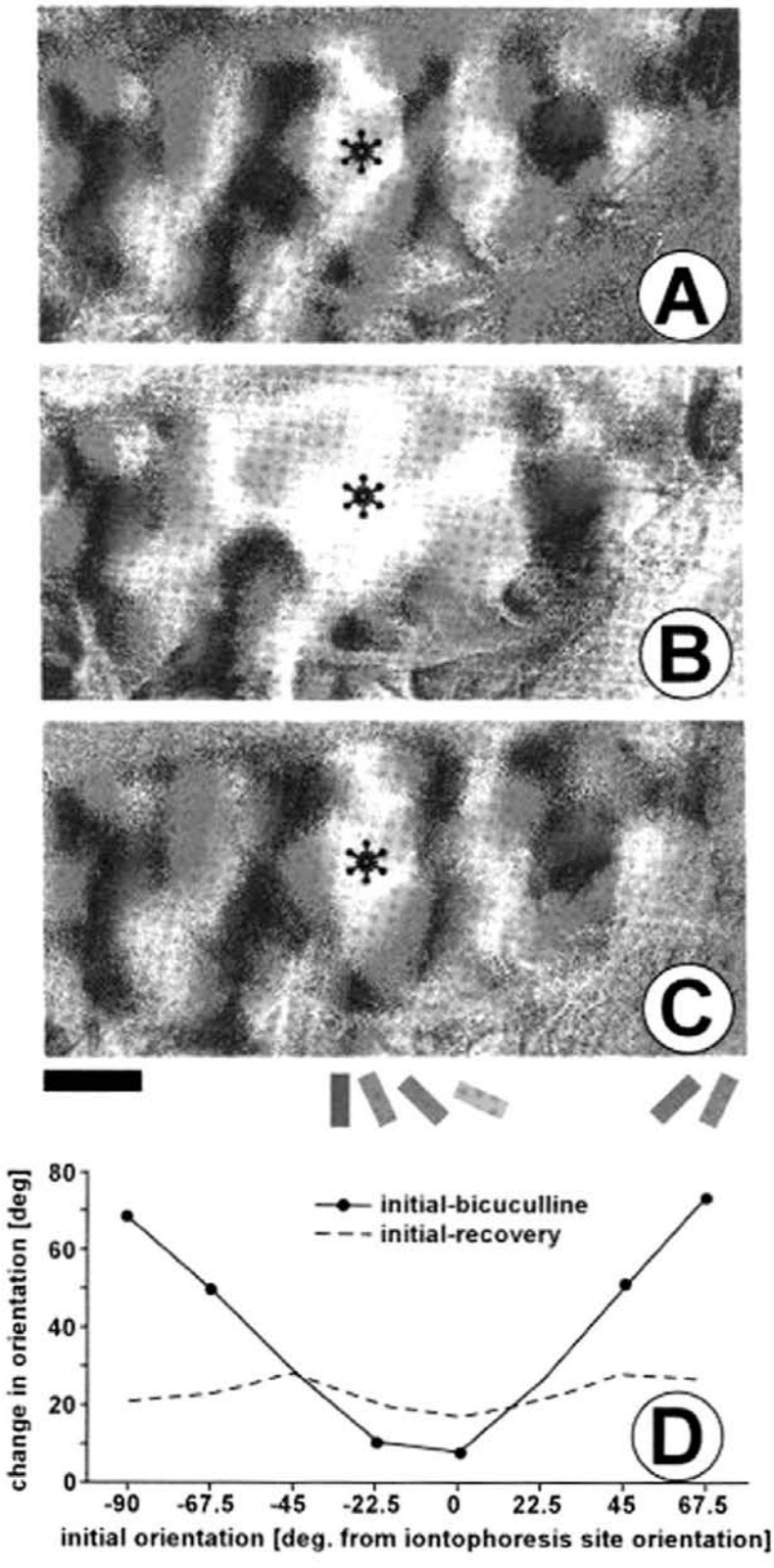

Fig. 2.1 (and color plate 1) Orientation angle maps in cat V2 and the effect of disinhibition with focal iontophoresis of bicuculline. Maps shown are: (A) prior to focal disinhibition, (B) during focal disinhibition and (C) after recovery. The map in (A) is obtained with the pipette in position (asterisk) and retention current applied. During bicuculline iontophoresis (B), the normal orientation map in the region around the pipette is altered, such that the initial orientation at the pipette location is drastically overrepresented. Recovery of the normal map upon cessation of iontophoresis is shown in (C). Scale bar: 1 mm. To produce the vector angle

orientation, and they revert toward control levels after cessation of iontophoresis (Fig. 2.1C). If bicuculline is indeed acting focally and specifically to disinhibit a cortical column, one prediction is that increasing the inhibition to a column, for example by iontophoresis of the inhibitory transmitter GABA, would lead to a reduction of the area preferring the inhibited orientation over a local region; this is found to be the case (Toth *et al.* 1997). These experiments suggest that local connections distribute information to columns of widely varying orientation preference, and that these connections are predominantly excitatory, since an increase in their activity leads to an overrepresentation of the tuning orientation at the iontophoresis location and a decrease to an underrepresentation of the iontophoresis orientation. These results, i.e., altering the balance of excitation and inhibition in cortical columns to affect the orientation tuning of adjacent columns, are well explained by local networks influencing orientation tuning (e.g. Somers *et al.* 1995).

Perturbation of orientation-specific responses induced by adaptation

In the previous section we have shown that changing the efficacy of local inputs by focal iontophoresis affects the orientation tuning of visual cortical neurons. To verify these results, we have subsequently used pattern adaptation (Movshon and Lennie 1979; Saul and Cynader 1989; Carandini *et al.* 1998) to examine how changes in the strength of local intracortical inputs affect orientation selectivity. It is known that adapting neurons to a potent stimulus can reduce responses to subsequent similar stimuli. In a recent study (Dragoi *et al.* 2000), we examined how far the entire profile of the orientation tuning curve changes after short and long-term adaptation to a particular stimulus orientation.

Figure 2.2A shows how the preferred orientation of a representative cell changes after 2 minutes of exposure to one orientation located on one flank of the cell's tuning curve, followed by a period of recovery, subsequent adaptation to a different orientation located on the opposite flank with respect to the preferred orientation, and a final

Fig. 2.1 (continued)
map, imaging data was treated vectorially by assigning each pixel of the 16 single-condition maps a magnitude representing the strength of the signal, and an angle representing 2× the orientation of the inducing stimulus. The 16 vectors at each pixel were added, and the resulting vector angle color coded according to the scheme at the bottom of the figure. (D) shows that the shift in orientation occurs in columns spanning all possible initial orientations. (The x-axis represents the difference in vector angles taken pixel-by-pixel in the original images, and binned for clarity.) The solid curve shows the orientation shift within the affected region [map (B) minus map (A)], and dashed line shows the recovery of the same region [map (C) minus map (A)]. The analyzed region includes 30,793 pixels (18% of image). A strong shift to the bicuculline orientation is seen across all initial values of orientation, nearby orientations changing relatively little, and orthogonal orientations changing nearly 90°, suggesting that areas of all orientation preference receive input from the manipulated orientation column.

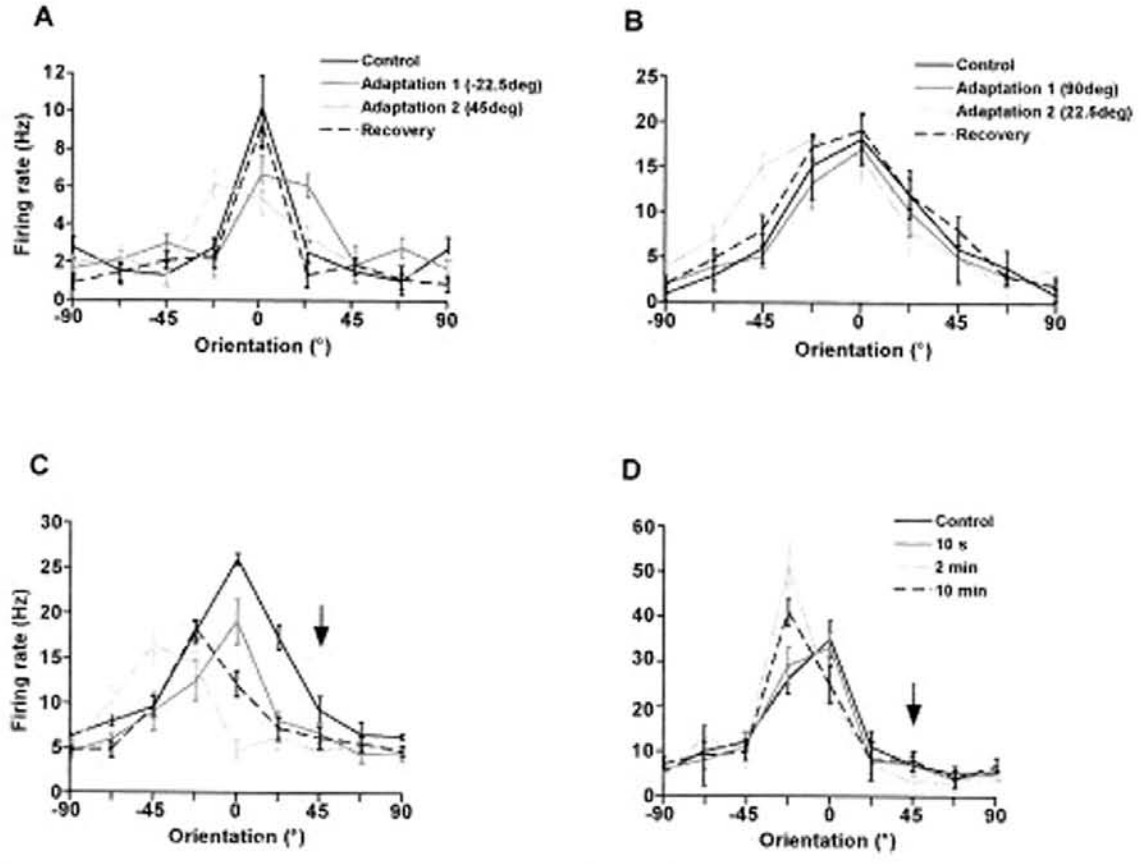

Fig. 2.2 Plasticity of orientation tuning in cat V1 cells. (A, B) Orientation tuning curves of two representative cells that were successively adapted to two different orientations. Each graph represents orientation tuning during four conditions: control (solid black), adaptation to the first orientation (medium grey), adaptation to the second orientation (light grey), and recovery (dashed black). In our tuning curve display convention, the control optimal orientation is represented as 0°, and all subsequent tuning curves (during adaptation and recovery) are represented relative to the control condition. (C, D) Tuning curves of cells that show adaptation-induced response suppression on the near flank and response facilitation on the far flank. Each cell was serially exposed to different adaptation periods: 10 s, 2 mins, and 10 mins. Tuning curves were calculated in each of the four conditions: control, 10 s adaptation, 2 min adaptation, and 10 min adaptation. The adapting orientation is marked by the arrow.

period of recovery. When the difference between the cell's preferred orientation and that of the adapting stimulus ($\Delta\theta$) is −22.5°, there is a shift in preferred orientation to the right, away from the adapting stimulus. In contrast, when the adapting stimulus is presented on the right flank of the tuning curve ($\Delta\theta$=45°), the preferred orientation shifts to the left and then returns to the original value after 10 mins of recovery. However, adaptation to stimuli orthogonal to the cell's preferred orientation ($\Delta\theta$ between approximately 60° and 90°) does not induce any change in preferred orientation. Figure 2.2B illustrates the behavior of one representative cell that exhibits a stimulus-dependent shift after 2 mins of adaptation to a 22.5° stimulus, but the orientation preference remains unchanged when $\Delta\theta$ is 90°.

Interestingly, the shape of the orientation tuning curve undergoes pronounced reversible changes when neurons are serially exposed to different adaptation periods. Figures 2.2C and 2.2D show one cell that exhibits significant shifts in orientation following adaptation for 10 s, 2 mins, and 10 mins to a stimulus oriented 45° away from the cell's peak orientation. Both the response reduction on the near flank (toward the adapting orientation) and facilitation on the far flank of the tuning curve (away from the adapting orientation) build up gradually in time: increasing the adaptation time from 10 s to 10 mins shows a progressive depression of responses on the near flank and a progressive facilitation of responses on the far flank. For the largest adaptation period (10 mins) we found that many cells increase their response at the new preferred orientation by a factor of 2 or more (Fig. 2.2D).

We argue that this type of orientation plasticity involves an active process of network synaptic changes that lead to a new preferred orientation rather than simply a passive reduction of orientation selective responses around the adapting orientation. The shifts in orientation preference by depression of responses on the near flank and facilitation of responses on the far flank imply a network mechanism that reorganizes responses across a broad range of orientations, possibly through changes in the gain of local cortical circuits that mediate recurrent excitation and inhibition (Douglas *et al.* 1995; Somers *et al.* 1995, 2001) and include disinhibitory mechanisms (Dragoi and Sur 2000). For example, if the local cortical circuit includes broadly tuned orientation inhibition, hyperpolarization of neurons representing the adapting orientation could cause disinhibition of responses on the far flank of the tuning curve in the recorded neuron, an effect that could be further amplified via local excitatory interactions.

Altering the efficacy of cortical networks at specific map locations

We subsequently investigated the relationship between orientation plasticity and a neuron's location in the orientation preference map in V1 of adult cats (Dragoi *et al.* 2001). Optical imaging of intrinsic signals was used to obtain the orientation map in a patch of V1 (Fig. 2.3A). We used the vascular pattern of the cortical surface in relation to the orientation map (Fig. 2.3B) to guide electrode penetrations aimed at iso-orientation domains or pinwheel centers. Since pinwheel centers are locations where the preferred orientation of neurons changes rapidly, we determined an orientation gradient map as the two-dimensional spatial derivative at each pixel to identify these foci. The gradient map (Fig. 2.3C) shows that pinwheel centers are included in regions with the highest rate of orientation change, whereas the gradient is low in iso-orientation domains. Figure 2.3D–F illustrates the relationship between location within the orientation map and adaptation-induced plasticity of orientation tuning for representative neurons. Adaptation to a given orientation induces a repulsive shift in orientation preference away from the adapting stimulus. Interestingly, the higher the value of the orientation gradient at the recording site, the larger is the magnitude of the shift in preferred orientation.

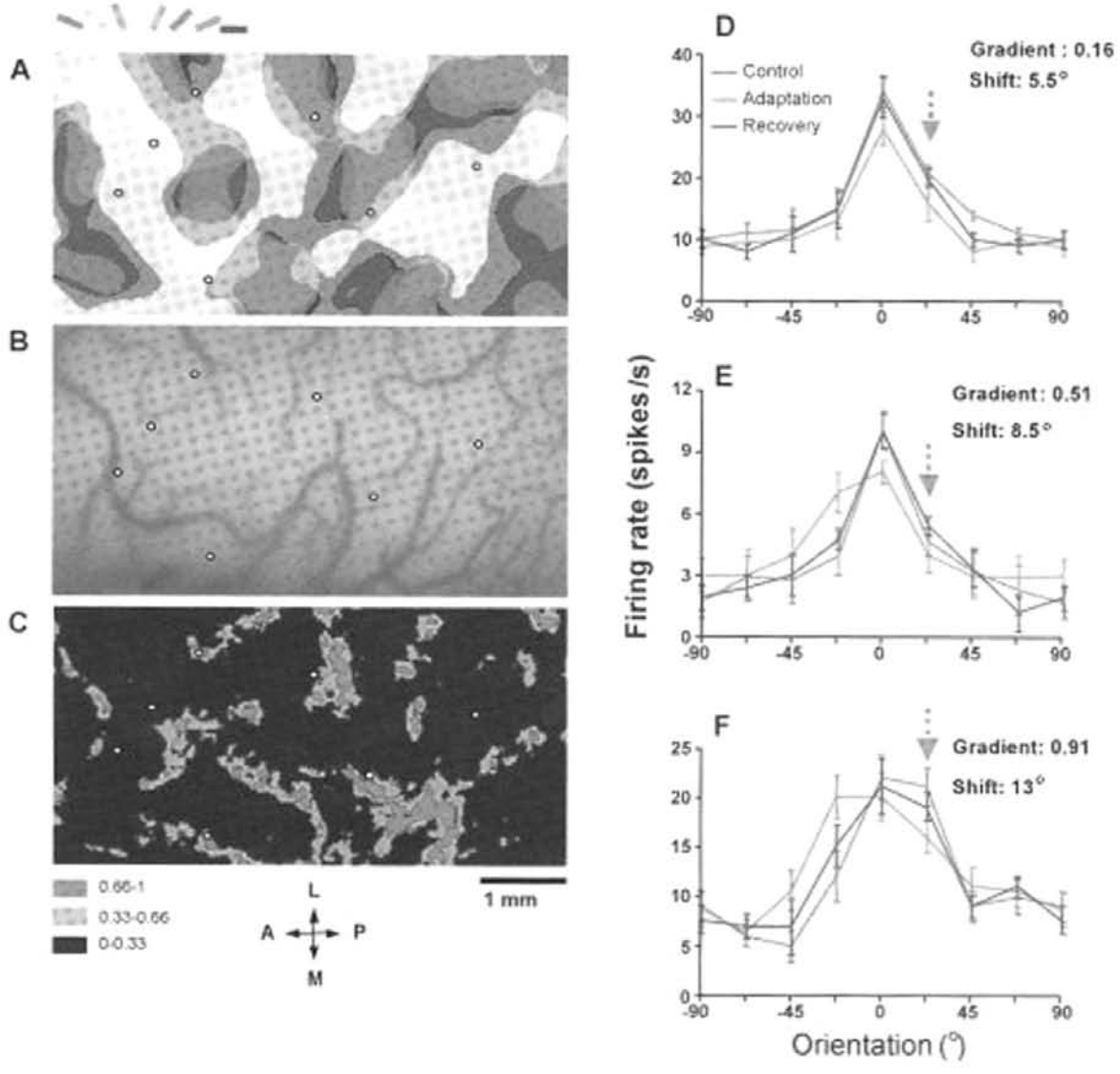

Fig. 2.3 (and color plate 2) Adaptation-induced plasticity of orientation tuning and the orientation architecture of V1. (A) Composite orientation map obtained by intrinsic signal imaging. The angle of preferred orientation of each pixel is shown in pseudo-color according to the key at top. The map was smoothed using a low-pass filter (5×5 pixels) The circles show the location of 7 representative neurons (of 40 that were recorded in this animal) to illustrate the range of orientation and gradient distributions. (B) Vascular pattern of the cortical surface for the region shown in (A) (C) Orientation gradient map, in which gradient was discretized as follows: red (range: 0.66–1), green (range: 0.33–0.66), and blue (range: <0.33). (D–F) Orientation tuning curves of three representative cells during control, adaptation, and recovery conditions. In our tuning curve display convention, the control optimal orientation is represented as 0°, and all subsequent tuning curves (during adaptation and recovery) are represented relative to the control condition. The adapting orientation is marked by the green arrow. Each point in panels (D), (E), and (F) represents mean value +/–S.E.M.

These results could be explained by the nature of inputs to neurons at different locations in the orientation map: Neurons in iso-orientation domains would be only weakly activated by intracortical inputs with orientations that differ from the domain's preferred orientation, while neurons located at or near pinwheel centers would receive

strong local inputs from neurons of all orientations (Dragoi *et al.* 2001). Therefore, altering the efficacy of these inputs through adaptation is likely to induce more profound changes in the orientation preference of neurons at or near pinwheel centers (Fig. 2.3). This suggests that adaptation-induced orientation plasticity in V1 is an emergent property of a local cortical network embedded in a non-uniform orientation map. Indeed, these data indicate the existence of a map of orientation plasticity, closely related to the map of orientation preference, in which pinwheel centers constitute foci of maximal plasticity and the orientation gradient is a measure of the degree of plasticity across V1.

Generation of direction selectivity in superficial layers

Another major emergent response property of V1 neurons is their selectivity for direction of motion. Despite over 30 years of research on the genesis of direction selectivity in V1, the mechanism by which direction selectivity arises in different cortical layers is still imperfectly understood. Most theories rely either on inhibitory mechanisms acting at the nonpreferred direction (Barlow and Levick 1965; Goodwin and Henry 1975; Sillito 1975, 1977; Tsumoto *et al.* 1979; Bishop *et al.* 1980; Ganz and Felder 1984; Nelson *et al.* 1994; Sato *et al.* 1995; Crook *et al.* 1997, 1998), or on recurrent excitation as a mechanism to increase the responses in the preferred direction in a nonlinear fashion (Douglas *et al.* 1995; Suarez *et al.* 1995). Studies on direction selectivity in layer 4 simple cells (Reid *et al.* 1987, 1991; McLean and Palmer 1989; Jagadeesh *et al.* 1993, 1997; Livingstone 1998; Murthy *et al.* 1998) have shown that the receptive fields of these cells have an asymmetric time course of the evoked response, and that a linear summation of these asymmetries could allow us to predict direction preference. However, this procedure overestimates the response in the nonpreferred direction. Most of these considerations apply to the situation in superficial layers. Information about direction selectivity in other cortical layers is limited. An important difference between layer 4 and superficial layers is the presence of NMDA receptors in layer 2/3 (Fox *et al.* 1989, 1990) and the particular properties of these receptors provide new insights into their role in generating direction selectivity.

We have used pharmacological blockade of AMPA and NMDA receptors (Rivadulla *et al.* 2001), and the blockade of inhibition to assign specific roles to these receptors in the generation of direction selectivity in the superficial layers. This section presents results obtained in cells recorded extracellularly in V1 of anesthetized cats using multibarrel pipettes to eject blockers into cortex and to record responses (Rivadulla *et al.* 2001). As expected from their different properties, our experiments show that AMPA and NMDA receptors play different and specific roles in direction selectivity.

Figures 2.4A and 2.4B show the effect of blocking AMPA and NMDA receptors in two visual cortical cells. Five or seven barrel pipettes were hand-made in our laboratory from individual glass capillaries. We used barrels of 1.5 mm outer diameter (OD) and 0.75 mm inner diameter (ID) with inner filament (note that slight changes in the OD/ID ratio provokes considerable changes in the final properties of the pipette that

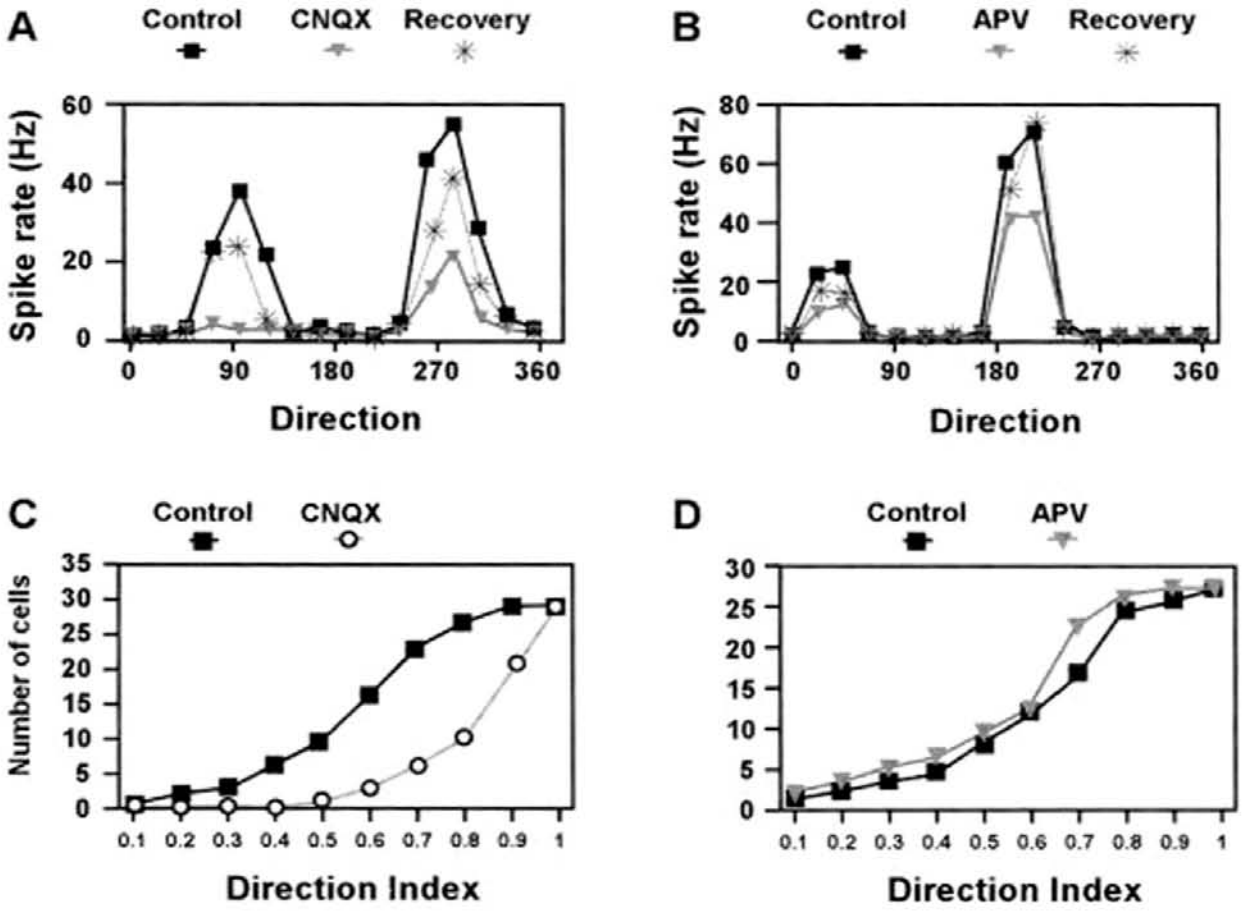

Fig. 2.4 CNQX and APV have different effects on direction selective visual responses of layer 2/3 cells in cat V1. (A) Direction tuning curves of a complex cell in the control condition, during CNQX iontophoresis, and after recovery. (B) Direction tuning curves from another complex cell in the control condition, during APV iontophoresis, and after recovery. (C, D) Effect of CNQX and APV on the direction index of layer 2/3 cells. (C) Cumulative histogram showing the effect of CNQX ($n=30$ cells) (D) Cumulative histogram showing the effect of APV ($n=27$ cells) The x-axis represents the direction index (DI). The y-axis represents the number of cells in each bin.

affect the quality of both recording and ejection). The barrels were attached using heat shrink cable and twisted around by hand approximately 270° using a burner (pipettes were pulled with a vertical puller). In order to avoid the mixing of drugs during the filling process and to eliminate possible artifacts during recording, we ensured that the top of each barrel was slightly separated from all others. The barrel tip was broken under the microscope to achieve the desired diameter (3–8 M, corresponding to a resistance around 8–12 MΩ). One of the barrels was used for recording, and thus filled with a solution of NaCl 3 M, whereas the others were filled with a combination of D-2-amino-5-phosphonovaleric acid (APV; 50 mM, pH 8), a selective NMDA receptor antagonist, 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX; 1 mM, pH 8), a selective AMPA receptor antagonist and bicuculline methiodide (20 mM, pH 4), a potent and selective antagonist of the $GABA_A$ receptor. Using this technique, we were able to eject

together or individually all the drugs inside the pipette (ejection currents were in the range of 10–40 nA). Unlike using pressure ejection, our method affects only a small area of tissue (less than 150 μm radius), and ensures stability of drug concentration during a continuous ejection. In order to reach a stable drug concentration, we started the ejection and waited until the visual response of the cell was diminished with respect to the control condition, usually after 2–3 minutes of continuous ejection of CNQX or APV. Stability was evaluated by comparing responses collected during the first and the last set of trials and calculating whether the observed differences were significant.

During CNQX ejection (1 mM pH 8) there is a decrease in the response of the cell, with the reduction being clearly more prominent in the nonpreferred direction (Fig. 2.4A). The effect of APV (50 mM, pH 8), shown in Fig. 2.4B, is similar in the preferred and nonpreferred direction. During CNQX blockade, since the residual response is mediated by NMDA receptors, and because of the pronounced effect on the nonoptimal response, neurons exhibit significant changes in direction selectivity (Fig. 2.4C). Direction index [DI = maximum response—opposite response/maximum response] is represented for the whole population ($n = 29$) and compared to control values in Fig. 2.4C. Note that during CNQX ejection there is a displacement of the curve to the right, showing that DI values are increased relative to control. Blockade of NMDA receptors does not change the DI for the population (Fig. 2.4D). These results show that responses during CNQX ejection (i.e. NMDA mediated responses) are highly direction selective, postulating a prominent role for NMDA receptors in mediating direction selectivity.

One advantage of using iontophoresis is the possibility to study the effects of several compounds independently or in combination on the same cell, and thus we studied the effect of APV and CNQX on direction selectivity in the absence of inhibition achieved by ejection of Bicuculline (20 mM, pH 4). Application of bicuculline causes a larger increase in the response in the nonpreferred direction as compared to the increase in the preferred direction, leading to a decrease in the direction selectivity index (Fig. 2.5A, 2.5C, 2.5D). As in Fig. 2.4, application of CNQX alone increases the direction index by causing a larger reduction in the nonpreferred response. Surprisingly, ejection of CNQX in the presence of bicuculline caused a similar reduction in the preferred and nonpreferred directions, when compared with bicuculline alone, leading to a similar DI in both conditions (Fig. 2.5C). This result indicates that the response in the nonoptimal direction contains an NMDA mediated component that, in normal conditions, is removed by GABAergic inhibition. This effect is detailed in Fig. 2.5B where peristimulus time histograms are shown for preferred and nonpreferred conditions. During bicuculline ejection (notice the different scale on the y-axis), the responses increase preferentially in the nonpreferred direction and the neuron becomes less directional. This is the opposite of the effects observed with CNQX application. Removing inhibition during AMPA blockade increases the response in both directions but, again, the effect is preferentially on the nonoptimal response, causing the DI to be similar to that obtained with bicuculline alone (Fig. 2.5C). These results

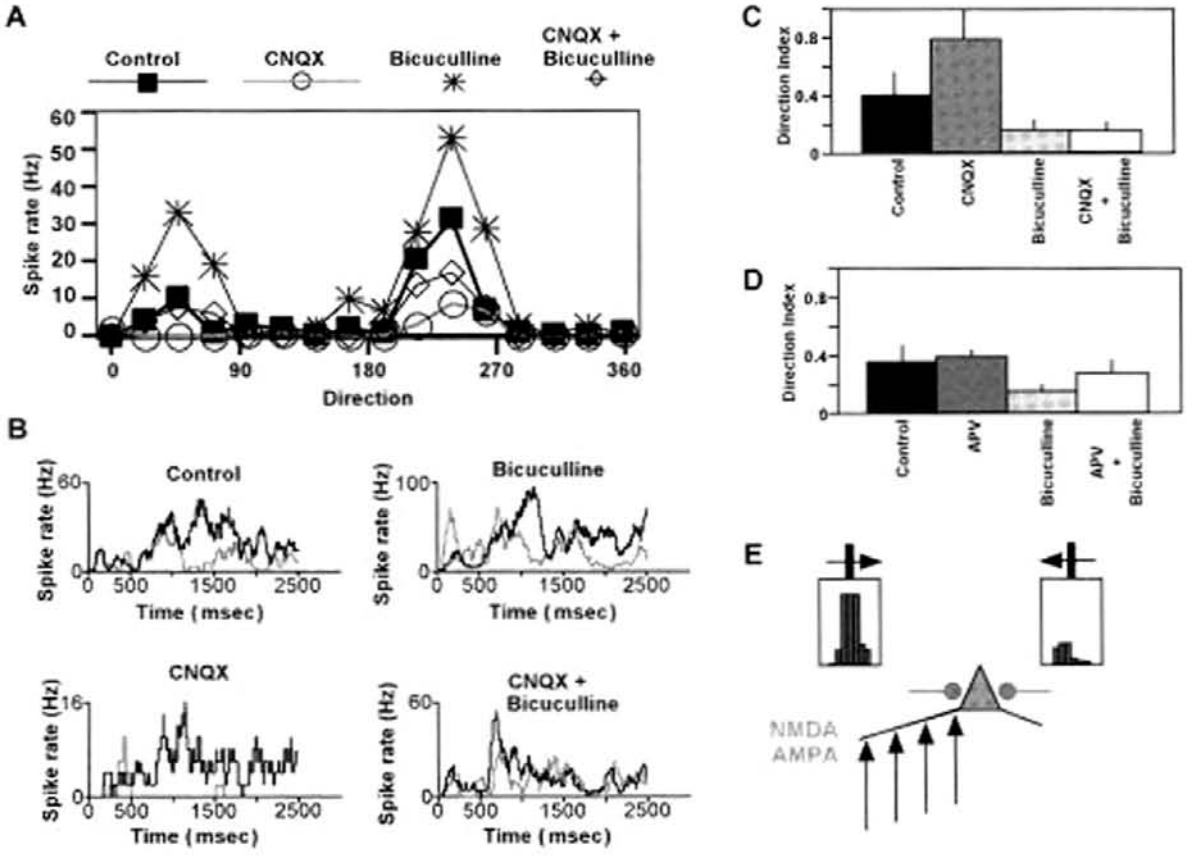

Fig. 2.5 Interactions between AMPA and GABA receptors during direction-selective responses. (A) Direction tuning curves of a complex cell in the control condition and during ejection of CNQX, bicuculline, and both simultaneously. (B) Peri-stimulus time histograms of responses from another complex cell showing the control response and the effect of the drugs on the preferred (shown in black) and nonpreferred (gray) directions. Each histogram is the average response to seven stimulus presentations and shows the entire 2.5 sec of stimulus duration: the grating was stationary for the first 500 msec and drifted for the next 2 sec. (C) Bar histogram showing the mean value (standard deviation [SD]) of the direction index for the population of cells in the different conditions ($n=4$ cells). (D) Modulation of NMDA activity by GABA during generation of direction selective responses. Bar histogram showing the mean (+/−SD) of the direction index for the population of cells in the different conditions ($n=4$ cells). (E) Schematic showing that NMDA and AMPA receptors together provide direction selective feedforward input to layer 2/3 cells. NMDA receptors contribute prominently to responses in the preferred direction (left response histogram), while their contribution to responses in the nonpreferred direction (right response histogram) is reduced substantially by GABAergic inhibition (circles). Such inhibition may be greater in the nonpreferred direction (right to left).

indicate the presence of an excitatory NMDA-mediated component in the nonpreferred direction that is absent during the control condition because of GABAergic inhibition. We have seen consistently during our experiments that the DI varies from trial to trial. This variability could be due to a continuous modulation of the NMDA mediated response through GABAergic inhibition. This idea is supported by data obtained while simultaneously ejecting APV and bicuculline (Fig. 2.5D). The effect of

bicuculline on the DI is reversed by simultaneous ejection of APV, showing that bicuculline acts mainly on the NMDA-mediated component of the response.

Taken together, our results demonstrate that both AMPA and NMDA receptors contribute to the generation of direction selectivity in the superficial layers of V1. However, their effects can be delimited (Fig. 2.5E). During control conditions, AMPA receptors are sufficient for generating direction selectivity, but NMDA receptors are needed to increase the response in the preferred direction in a nonlinear fashion. In the nonpreferred direction, the NMDA mediated component of the response is suppressed by inhibition (Artola and Singer 1987; Shirokawa *et al.* 1989; Schroeder *et al.* 1997). A possible interpretation of these results is that NMDA mediated responses are only effective during stimulation in the preferred direction because a sufficient amount of excitation is provided in this condition. However, a comparison of CNQX effect on nonpreferred responses (when CNQX causes an average reduction of 90%) and spontaneous activity (when CNQX causes an average reduction of 28%, and there is less excitation) supports the presence of an active inhibitory component in the response to the nonpreferred direction. This modulatory action of inhibition provides a rich substrate for a dynamic control of neuron responses based on stimulus configuration or spatial and temporal history and context.

Phase invariance in visual cortex

It is known that most cells in layer 4 are simple cells, while those in layers 2/3 are predominantly complex (Hubel and Wiesel 1962). How simple cell responses are converted to complex cell responses is still an open question. The main excitatory and inhibitory input to the superficial layers of the cortex is provided by feedforward connections from layer 4 and by intracortical connections within layer 2/3. Experiments blocking the inhibitory inputs have reported a widening of ON and OFF subregions of simple cells and an increase in the overlap between ON and OFF subfields, suggesting that under these conditions simple cells responses can become similar to those of complex cells (Pernberg *et al.* 1998; Sillito 1975). These data suggest a combination of feedforward and intracortical inputs as generating complex cell properties. Indeed, Chance *et al.* (1999) have proposed a model in which complex cells properties arise as a consequence of decreasing the phase selectivity of simple cell responses by recurrent intracortical connections. A key test for this model is whether blockade of intracortical excitation causes complex cells to respond like simple cells.

An important difference between simple and complex cells is their temporal pattern of response when they are stimulated with drifting gratings (Movshon *et al.* 1978a,b; Skottun *et al.* 1991). We used this difference to classify simple and complex cells based on the ratio between the first two Fourier harmonics of the response (F1/F0 ratio). We studied the effect of blocking AMPA and NMDA receptors on the F1/F0 ratio in layer 2/3 cells. Figure 2.6A shows two subpopulations in our sample: cells with a F1/F0 ratio less than 1 were classified as complex cells and those with a F1/F0 ratio greater than 1

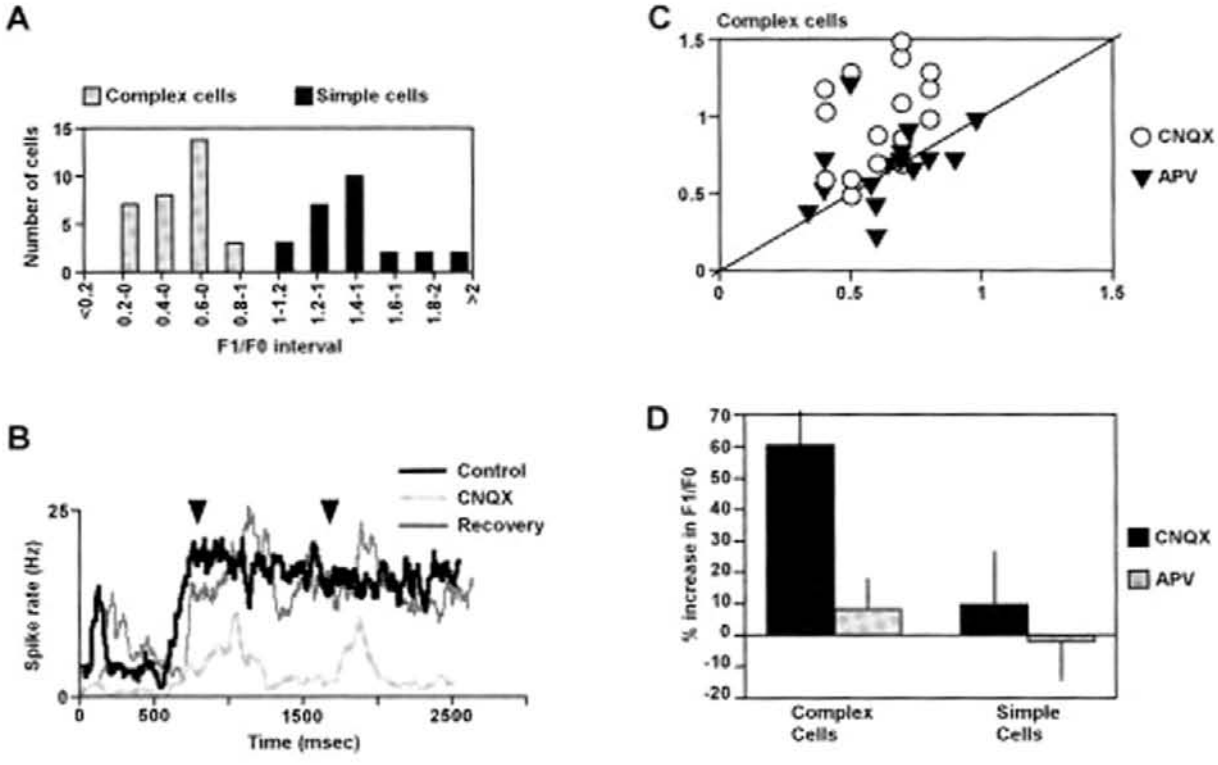

Fig. 2.6 Effect of CNQX and APV on responses of simple and complex cells. (A) Histogram of F1/F0 values of simple and complex cells in the control condition. F1: amplitude of the first Fourier component of response, showing modulation at the grating temporal frequency. F0: the dc or mean response level. (B) Peri-stimulus time histograms showing the response of one complex cell to a drifting grating moving in the preferred direction during the control condition, ejection of CNQX, and after recovery. (C) Scatter plot showing the change in F1/F0 for each complex cell ($n = 16$ cells) during CNQX and AMPA ejection. (D) Histogram showing the variation in the F1/F0 ratio under CNQX and APV for simple and complex cells. The F1/F0 ratio increases significantly for complex cells under CNQX, denoting an increase in the temporal modulation of responses by the grating.

were classified as simple cells. The most important result (Fig. 2.6B) is that AMPA blockade makes complex cells behave like simple cells. The visual stimulus is a drifting grating at the optimal orientation presented for 500 ms. During the control condition, the response of the cell shows an absence of modulation characteristic of complex cells, while during AMPA blockade the response decreases and changes the temporal pattern of response to exhibit a modulation by the grating cycle, in a manner that is typical for simple cells. Figure 2.6C shows a scatter plot representing the change in the F1/F0 ratios during CNQX and APV ejection on all the complex cells recorded. APV decreases the response of the cell but does not change the temporal structure of the response, while CNQX increases the F1/F0 ratio of complex cells and alters the temporal pattern of responses.

In simple cells neither APV nor CNQX affects the temporal response pattern. Figure 2.6D shows population data for simple and complex cells during APV and CNQX ejection and it is clear that only CNQX applied to complex cells modifies the temporal

structure of the visual response. We also tested the effect of bicuculline on simple and complex cell properties and the interactions with AMPA and NMDA receptors. Intracortical inhibition has been related to the generation of simple cell subfields. However, in our experiments (Fig. 2.7) we do not find any effect of bicuculline on the temporal modulation of the responses in simple and complex cells. Figure 2.7A shows a PSTH from a simple cell responding to a grating drifting in the preferred direction. During bicuculline ejection a clear increase in the response is achieved, but no change in the modulation of the response (F1/F0=1.59 in the control condition and 1.34 during bicuculline application; this result holds for the population). Our data apparently disagree with previous experiments (Pernberg *et al.* 1998) showing that in absence of inhibition different subregions of simple cells overlap, a typical complex cell property. However, several methodological differences could explain this discrepancy. For example, Pernberg *et al.* (1998) used the reverse correlation method with flashed bar stimuli to study the spatial separation of On and Off subfields of cells in area 18. We studied changes in the temporal modulation of responses in area 17 using drifting gratings. Of course, a relationship between receptive field structure and temporal properties of responses must exist, but it may not relate in a simple way to the temporal structure of

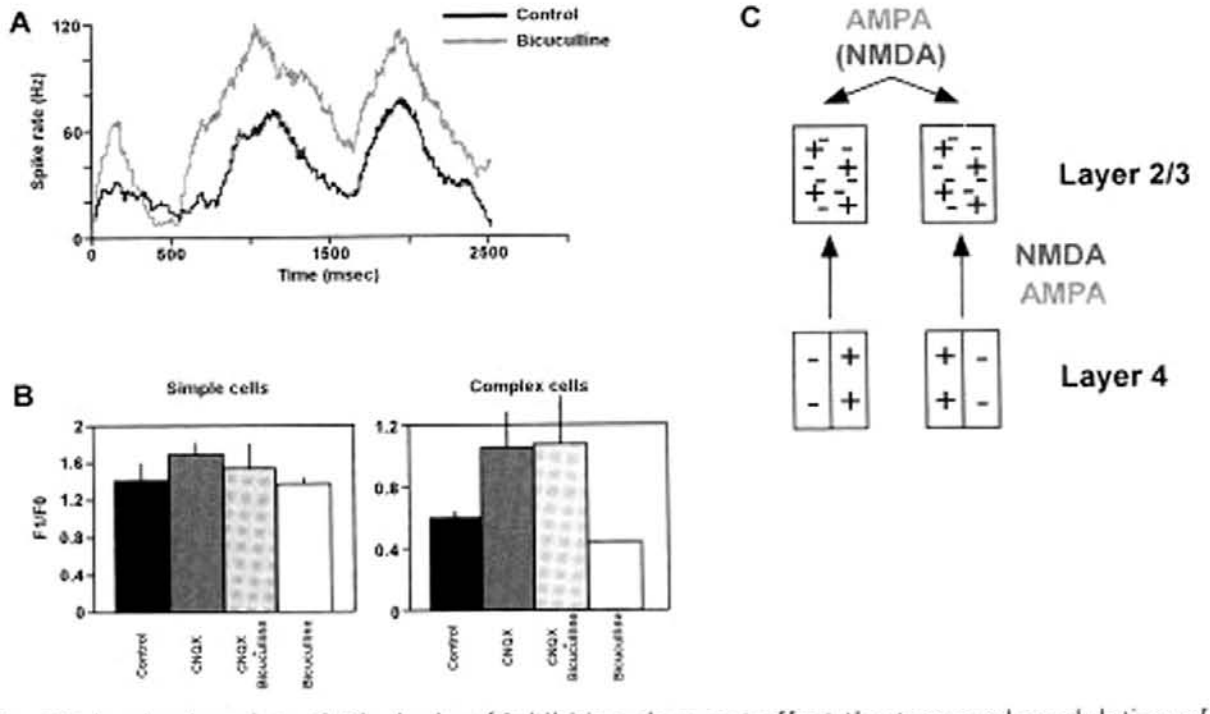

Fig. 2.7 (and color plate 3) Blockade of inhibition does not affect the temporal modulation of simple or complex cell responses. (A) Peristimulus histogram of the response of a simple cell to a grating drifting in the preferred direction, in the control condition and during bicuculline application. (B) The effect of bicuculline, CNQX and bicuculline+CNQX on F1/F0 values of simple cells (left) and complex cells (right) Bars show mean (+/−SD). (C) Cartoon showing that simple cells in layer 4 provide feedforward input to cells in layer 2/3 via NMDA and AMPA receptors. Our data suggest that short-range recurrent excitatory connections in layer 2/3 via AMPA receptors are responsible for reducing the spatial phase-selectivity of simple cells and creating phase-invariant complex cell responses.

the grating response, during which orientation selectivity, stimulus motion and full field stimulation are all involved. In our experiments we also analyzed the effect of removing inhibition on complex cells. In this case, there was a possible decrease in the F1/F0 ratio during bicuculline application (p=0.2). Importantly, bicuculline did not modify the change in F1/F0 produced by AMPA blockade. Figure 2.7B represents the average values obtained for the F1/F0 in the different experimental conditions. Thus, blockade of inhibition does not affect temporal response modulation in simple or complex cells, and the effect of blocking AMPA receptors is to increase phase-selective modulation even when inhibition is removed.

In summary, CNQX ejection (i.e. AMPA receptor blockade) increases the modulation of complex cell responses by a drifting grating stimulus. Thus, AMPA receptors decrease the selectivity of complex cells for spatial phase or the spatial location of visual stimuli. Blocking NMDA receptors or inhibition has little effect on the temporal modulation of simple or complex cell responses.

Our results provide a new view on cortical networks by proposing specific roles for different subtypes of glutamate receptors in the generation of phase selectivity in visual cortical cells. Our data suggest that a specific input to a cortical cell primarily uses one type of receptor. We propose that AMPA and NMDA receptors in layer 2/3 have different spatial distributions on cells, with both present on the same cell but in different proportions at different inputs. In this model (Fig. 2.7C) feedforward connections are mediated through both AMPA and NMDA receptors while local recurrent connections are mainly mediated through AMPA receptors only. These latter connections are responsible for smearing the phase-selectivity of simple cells to create phase-invariant complex cell responses.

Conclusions

We have used orientation selectivity, direction selectivity, and modulation of phase selectivity in V1 neurons as experimental models that could help understanding the role of excitatory and inhibitory cortical networks and the action of specific receptor types in visual information processing. By combining extracellular recording, iontophoresis of receptor blockers, and optical imaging of intrinsic signals, we demonstrate the following results:

First, blockade of local inhibition and excitation causes profound changes in the layout of orientation maps. Specifically, blockade of inhibition by bicuculline iontophoresis (Toth *et al.* 1997) causes a shift in the orientation preference of neurons toward the preferred orientation at the ejection location, whereas blockade of excitation through GABA iontophoresis (Toth *et al.* 1997) or visual adaptation (Dragoi *et al.* 2000) causes a shift in the orientation preference of neurons away from the iontophoresis or adapting orientation. These results argue strongly that local excitation balances the effect of inhibition to maintain stable orientation preference during vision. These changes in orientation selectivity imply a network mechanism that reorganizes responses across a broad range of orientations, possibly through changes in the gain of local cortical circuits that

mediate recurrent excitation and inhibition (Ben-Yishai *et al.* 1995; Douglas *et al.* 1995; Somers *et al.* 1995) and include disinhibitory mechanisms (Dragoi and Sur 2000).

Second, disruption of excitation and inhibition in local cortical networks depends on cortical location. The structure of the orientation map in V1 implies that the orientation distribution of local connections would vary with a neuron's position within the map: neurons in pinwheel centers are likely to be connected to neurons of a broader range of orientations than neurons in iso-orientation domains. Thus, altering the efficacy of intracortical orientation-specific inputs to neurons in different locations of the orientation map through adaptation induces changes in the tuning properties of neurons in a manner that depends on cortical location, i.e., more pronounced changes in the orientation preference of neurons at or near pinwheel centers (Dragoi *et al.* 2001).

Third, blocking AMPA receptors reduces responses to nonpreferred directions stronger than to preferred directions and, consequently, increases direction selectivity, while blocking NMDA receptors removes proportional components from preferred and nonpreferred responses which eventually preserves direction selectivity at the same level (Rivadulla *et al.* 2001). On the other hand, blocking inhibition enhances the contribution of NMDA receptors to nonpreferred responses to reduce direction selectivity.

Finally, blocking AMPA receptors increases the modulation of complex cell responses by drifting gratings; thus there is an increase in the selectivity for spatial phase or the spatial location of visual stimuli. Blocking NMDA receptors or inhibition has little effect on the temporal modulation of simple and complex cell responses (Rivadulla *et al.* 2001). Thus, AMPA receptors have a major role in creating phase-insensitive complex cell responses in the superficial layers of V1.

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