Multiple mechanisms underlying the orientation selectivity of visual cortical neurones

T.R. Vidyasagar, X. Pei and M. Volgushev

For over three decades, the mechanism of orientation selectivity of visual cortical neurones has been hotly debated. While intracortical inhibition has been implicated as playing a vital role, it has been difficult to observe it clearly. On the basis of recent findings, we propose a model in which the visual cortex brings together a number of different mechanisms for generating orientation-selective responses. Orientation biases in the thalamo–cortical input fibres provide an initial weak selectivity either directly in the excitatory input or by acting via cortical interneurones. This weak selectivity of postsynaptic potentials is then amplified by voltage-sensitive conductances of the cell membrane and excitatory and inhibitory intracortical circuitry, resulting in the sharp tuning seen in the spike discharges of visual cortical cells.

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T.R. Vidyasagar is at the Center for Visual Science and Division of Neuroscience, John Curtin School of Medical Research, Australian National University, Canberra, ACT 2601, Australia, X. Pei is at the Dept of Physics, University of Missouri at St Louis, MO 63121, USA, and M. Volgushev is at the Ruhr-Universitaet Bochum, Medical Faculty, Dept of Neurophysiology, D-44780 Bochum, Germany.

THE POSSIBLE mechanism of orientation selectivity of visual cortical neurones first described by Hubel and Wiesel has been intensively studied (for reviews, see Refs 1,2). The striate cortex receives afferents from neurones in the lateral geniculate nucleus (LGN), which can be driven by spots of light and elongated stimuli of any orientation[3]. However, cells in the striate cortex respond vigorously only when bars or edges of appropriate orientation are drifted or flashed over their receptive fields[4]. Hubel and Wiesel suggested that this selectivity arises from the excitatory convergence of a number of LGN neurones onto a cortical cell, with these geniculate neurones having overlapping receptive fields located along a line in visual space (see Fig. 1). This was consistent with their observation that as the length of a bar of optimum orientation was increased, many simple cells showed increasing response up to a length that was usually much greater than the diameters of single LGN receptive fields. The model received further support from the claim that in ferret visual cortex the centres of receptive fields of geniculate afferents at a cortical site tended to form an elongated cloud, paralleling the preferred orientation of cells recorded at the same site[5].

However, many experiments have cast doubt on purely excitatory mechanisms being the basis of orientation selectivity. Inhibition from orthogonal orientation was revealed in a number of paradigms[6,7]. Iontophoretic application of bicuculline, an antagonist of $GABA_A$-mediated inhibition, could markedly reduce orientation selectivity of the spike discharges in many striate cells[8–10]. Another important piece of evidence for the role of inhibition came from intracellular studies, where one could measure the postsynaptic membrane potentials which reflect the excitatory and inhibitory inputs[11]. It was seen that the receptive-field regions from where excitatory postsynaptic potentials (EPSPs) could be elicited were nearly circular, and that inhibitory postsynaptic potentials (IPSPs) could be elicited by stimuli of non-optimal orientation. These studies led to a theory of cross-orientation inhibition, where the excitatory input from the thalamus to a striate cell was not selective for orientation, but intracortical inhibition created the selectivity by being tuned to the orthogonal orientation. However, the source of such selective inhibition remained an enigma. To say that it came from cortical cells tuned to the orthogonal orientation was only evading the issue, since without any orientation selectivity in the input to cortical cells, this argument becomes a circular one. As a solution to the problem it was proposed, in one model implicating intracortical inhibition, that a spatial offset of a pair of non-oriented LGN inputs, one directly excitatory and the other inhibitory via an interneurone, can lead to orientation selectivity[12]. Another possibility is to exploit the orientation biases that are already present in the responses of geniculate and retinal cells[13–18] (Fig. 1). Since these biases are much weaker than the selectivities seen in the cortex, additional mechanisms would be required to isolate and amplify them intracortically.

Results of intracellular recordings using fine-tipped electrodes[19–22] reopened the debate on the mechanisms of orientation selectivity. The strongest EPSPs and maximal IPSPs were observed when optimally oriented bars drifted across the receptive field. Non-optimal bars elicited neither strong hyperpolarization[19–21] nor appreciable shunting inhibition[21]. These experiments supported the model of excitatory convergence[4,5,19] and provided little direct evidence for cross-orientation inhibition. Some studies[20–22] have shown that the intracortical recurrent excitatory connections provide the bulk of the excitation to cortical cells, and have proposed a model[22] of cortical microcircuitry that amplifies the excitation triggered by thalamic inputs. However, they do not address the question of how the selectivity for orientation appears in the first instance.

It is likely that a 'cortical amplifier' would thwart the search for any specific inhibition that contributes

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to orientation selectivity, a point well acknowledged by Douglas *et al.*[20,22]. If such inhibition were to act at an early stage, before recurrent cortical re-excitation is ignited, the initial excitatory load to be overcome by inhibition would be small, and hence this inhibition itself would be weak and difficult to observe. Further, full-blown optimal responses would activate recurrent inhibition to prevent run-away excitation, resulting in strong IPSPs at the optimal orientation. However, such inhibition, being recurrent in nature, cannot lead to orientation selectivity *de novo*. Any early selective inhibition is unlikely to be revealed by the use of moving stimuli that the above studies have employed, since they would strongly activate horizontal excitatory connections as well as side-band and direction-selective inhibitions, all from cells tuned to similar orientations. It is more appropriate to use stationary flashed stimuli, which would cause less excitation through horizontal intracortical inputs and could help detection of any early inhibition. Such studies, however, require stable intracellular recordings over lengthy periods.

Orientation selectivity of postsynaptic potentials studied using *in vivo* whole-cell recordings

Application of patch-clamp techniques to *in vivo* recordings (Box 1) from cat visual cortex[23,24] greatly improved the stability of intracellular recordings, and enabled extensive studies of receptive-field structure and orientation selectivity of postsynaptic potentials (PSPs) of striate cells to be performed[25–27] (X. Pei, PhD thesis, University of Göttingen, 1993). The most important points to emerge are summarized below:

(1) The receptive-field region from which EPSPs could be elicited was only mildly elongated[26]. The mean length-to-width (aspect) ratio for the simple cells was 1.7, a far cry from the elongation that would be required by a purely excitatory model[4,5,19]. These elongations were often not more than the biases shown by single LGN neurones[14–17]. Even if the inputs were to arise from geniculate cells with circular receptive fields, it would not require convergence from more than two LGN fields.

(2) In the majority of first-order cortical cells, IPSPs could be observed at non-optimum orientations[25,26] (Box 2). In early response components, inhibition was often maximal at orientations that differed from the optimal by 45–90 degrees, and was thus capable of contributing to orientation-selective spike discharges. However, cells vary a lot in the magnitude of IPSPs that they exhibit in the non-optimum orientation, reflecting considerable variation in the balance of excitation and inhibition involved in orientation selectivity. In only a small proportion of cells was the orientation selectivity entirely due to specific inhibition or excitatory convergence alone. Most commonly, orientation selectivity was the result of both excitatory and inhibitory mechanisms.

(3) The delay between the appearance of the EPSP and the occurrence of the first spikes is usually between 5 and 12 ms at optimal, and even longer at other orientations[27]. This is sufficient for inhibition to mould the early excitatory response. The feedforward inhibition from the geniculate can be rapid and efficient, since the geniculate afferents that contact the soma of the smooth (putative inhibitory) stellate cells are myelinated up to the terminal boutons[28]. Once the spikes begin to occur, cortical re-excitation between cells tuned to similar orientations would dominate the picture, amplifying the optimal response and masking early orientation-selective IPSPs.

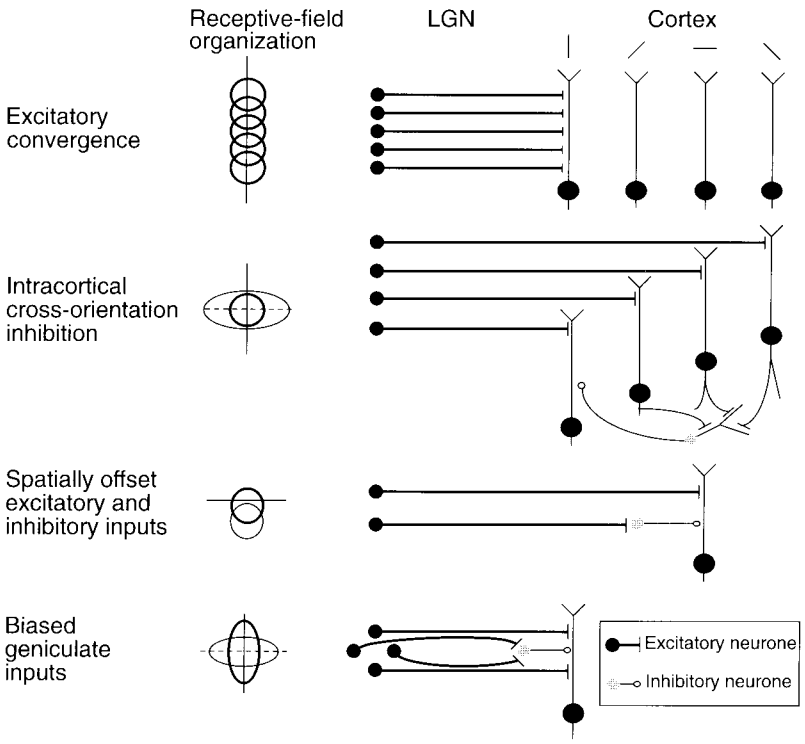

Fig. 1. ***Proposed schemes to explain the orientation selectivity of cells in the striate cortex.*** *The receptive-field organization of various cortical cells are shown in terms of the relevant geniculate inputs, with regions within thick lines marking the excitatory input and those within thin lines marking the inhibitory inputs. The straight line represents the optimum orientation of the cortical-cell response and the dashed line, where shown, represents the optimum orientation of the inhibitory input to the cell. All direct LGN inputs to the cortex are assumed to be excitatory. The inhibitory influences are routed through interneurones in the cortex (shown in lighter grey). The thalamo–cortical afferents in the cross-orientation scheme might also send feedforward inputs to the interneurone. The four short lines shown above the cortical neurones represent optimum orientations of different orientation columns.*

(4) Estimation of orientation tuning within different temporal windows of the PSP response revealed that the early responses were usually more broadly tuned than the later ones[27]. Such improvement of the tuning with response development indicates that several successive mechanisms might contribute to the final sharp tuning for orientation.

(5) Even when using moving stimuli, despite the reservations mentioned earlier, significant PSPs in the non-optimum orientation were often apparent (see Figs 27–29 in X. Pei, PhD thesis, 1993). Both excitatory and inhibitory events could be observed, though of a lesser magnitude than those observed in the optimum orientation.

An outline of the model

In the scheme we propose, orientation selectivity in cortex is generated in two stages, and at each stage a number of mechanisms are involved. At first, a weak initial selectivity is brought about by biases in the thalamo–cortical excitatory inputs. Such biases are likely to be those that are already present in LGN-cell responses[14–18], or might involve convergence of geniculate receptive fields with the centres of the two most distant fields separated by less than the diameter of one field. The exact number of LGN cells with overlapping receptive fields located in between is not crucial for

Box 1. Application of patch-clamp electrodes to whole-cell recordings *in vivo*

The remarkable success of patch-clamp electrodes in studying ion channels[a] is due to the ease with which a clean pipette with a relatively large tip can be brought into contact with a cell membrane under microscopic control and made to form a high-resistance seal. On rupturing the underlying cell membrane, one can obtain low-resistance electrical access to the interior of the cell. This technique was first used on isolated cells, but was later applied to brain slices[b,c]. Adapting the method to *in vivo* recordings from the intact mammalian neocortex first appeared a bit daunting, because the instability of the preparation (due to brain pulsations) and the blind penetration into a medium of neuronal elements, glial tissue and extracellular matrix prevented the formation of gigaohm seals. However, it was finally possible to achieve at least partial seals and stable conditions for whole-cell recording[d]. The patch-clamp electrode is kept relatively clean of tissue debris by applying a continuous positive pressure during penetration. The electrode resistance is continually monitored, and various visual stimuli that are likely to excite the cells in that cortical region are presented. When the tip of the electrode is near a neurone the positive pressure is reduced. Close contact to a cell is denoted by an increase in the electrical resistance or the occurrence of extracellular action potentials either spontaneously or in response to visual stimuli, or both. When the pipette tip is finally resting on the cell membrane, the positive pressure is released and a small negative pressure is applied to the electrode. This often results in the formation of a seal of reasonably high resistance and gradual access to the cell interior. Even though seals comparable in resistance to those with isolated cells and brain slices are rare, the input resistances in the whole-cell configuration[d] (50 to 200 MΩ) are considerably greater than when classical fine-tipped microelectrodes are used (for example, range of 10–153 MΩ, mean of 69 MΩ)[e]. The recordings are also stable and often last for an hour or two. It is likely that the intracellular contents rapidly get replaced by the pipette solution, but this seems to make little difference to the responses of the cells to visual stimuli. However, different solutions can be used to fill the pipette to yield specific results. For example, Cl^--channel blockers can be added to the pipette solution to counteract the effect of specific inhibitory inputs to the cell[f].

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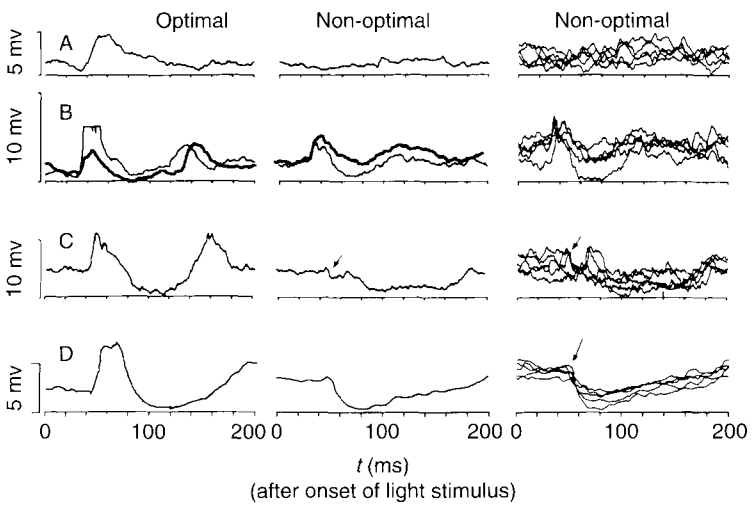
the model. Feedforward inhibitory inputs from the LGN (via cortical interneurones) could also be biased for orientation. The presence of some bias in either the excitatory or the inhibitory input[18] or in their spatial offset[12] can lead to the elongation seen in the PSP fields (aspect ratios of about 1.7) and to some initial selectivity of the early PSP responses. The selectivity established at this stage might be only mild, but we consider it as crucial for generating the final sharp orientation tuning of first-order cortical cells.

Box 2. Orientation sensitivity of postsynaptic potentials



While flashing a bar of optimum orientation elicits a robust depolarization often followed by a mild hyperpolarization, flashing the same bar in the orthogonal orientation leads to different results in different cells. The figure shows the postsynaptic potentials (PSPs) of four cortical simple cells (from Ref. a), with averaged responses to five stimulus repetitions in the optimum (left) and non-optimum (middle) orientations. On the right, the individual traces are shown for the non-optimum orientation. Trace A represents the group that showed no specific excitatory or inhibitory PSPs to non-optimal stimuli. However, only a few of these cells were first-order cells directly excited by the lateral geniculate nucleus. Traces B, C and D represent cells that showed significant PSP activity for stimuli of non-optimal orientation, implicating a role for inhibition in generating the orientation sensitivity. A bar flashed in the non-optimum orientation for the neurone in B elicited a strong excitatory postsynaptic potential (EPSP), followed by an inhibitory postsynaptic potential (IPSP). When the IPSP was suppressed by a continuous hyperpolarizing current (thick traces in the left and middle columns), the first hump of EPSP elicited was equal in amplitude and duration in both orientations. While the averaged trace in the non-optimum orientation for the cell in C does not seem to show any obvious IPSPs, the individual traces exhibit specific, stimulus-locked inhibition. In D, both EPSPs and IPSPs appear to be well-tuned to orthogonal orientations. (Figure reproduced with permission of Society for Neuroscience.)

Reference

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We propose that once such a selectivity is established in the postsynaptic response, a number of amplificatory mechanisms boost it. There is now evidence for the involvement of voltage-sensitive conductances[29,30], which are capable of amplifying EPSPs *in vitro*[31,32]. Our data suggest that such mechanisms are indeed involved in amplifying visually elicited EPSPs (Ref. 33). When there is already a bias for orientation, the EPSP elicited by optimal orientation would reach spike threshold more easily than the EPSP elicited by non-optimal stimuli. Once spikes begin to occur, recurrent excitation within a column and mutual excitation between iso-orientation columns would further amplify the excitatory responses[22]. Such re-excitation would occur only for optimal stimuli because the intracortical excitatory connections are largely between cells tuned to similar orientations[34,35]. At this stage, inhibitory mechanisms can further sharpen the tuning for orientation by suppressing responses for non-optimal stimuli. Inhibition from cells tuned to orthogonal orientations[36,37] or to adjacent orientations[38] would reduce responses to orientations other than optimal. Also, nonspecific inhibition would sharpen the tuning by shifting the whole EPSP tuning curve downwards, and preventing the weaker responses to non-optimal orientations from being amplified by the above-mentioned mechanisms and reaching spike threshold – a 'tip of the iceberg' effect. Recurrent inhibition is not shown in Fig. 2, since it is not directly involved in contributing to orientation selectivity in our scheme. However, it is very likely to be present in the cortical network as a negative feedback not only for preventing run-away excitation and stabilizing the system, but also to normalize responses and make them relatively invariant to contrast[39].

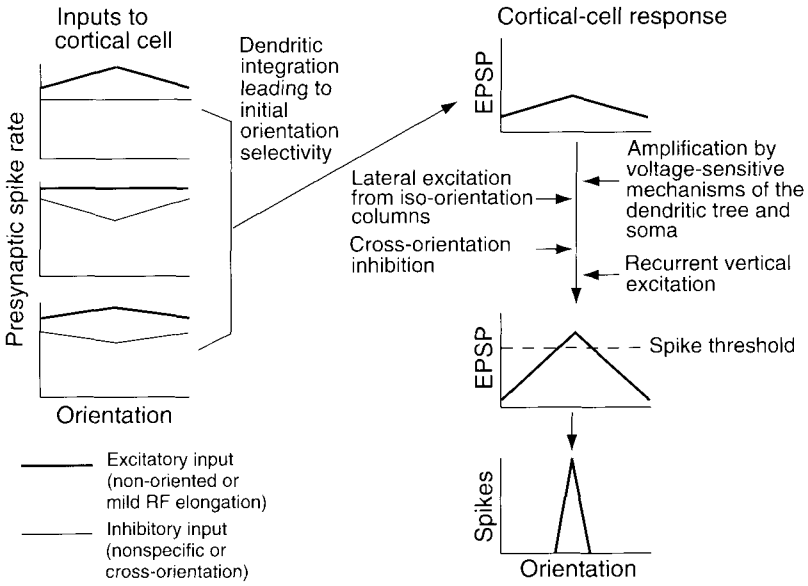

Fig. 2. ***A model for visual cortical orientation selectivity.*** *An initial mild sensitivity can be produced in the postsynaptic potential (PSP) responses of a striate cortical cell by any one of the three possible combinations of excitatory and inhibitory inputs that are shown in the left column (inhibitory input being via cortical interneurones). The biases of thalamic inputs might reflect the biases seen in individual cells of the lateral geniculate nucleus (LGN), or arise from a modest convergence of up to two LGN fields in a row. Once a mild selectivity of the PSP response is established by the thalamic input, this is amplified by a number of cortical mechanisms as shown on the right. Our data suggest that the contribution of each of the different mechanisms might vary from cell to cell, in particular, the overall balance between orientation-selective excitation and inhibition. Abbreviations: EPSP, excitatory postsynaptic potential; RF, receptive field.*

Relation to other models

Some of the mechanisms proposed in our scheme have been included in other models[39–43]. Computer simulations performed in these studies show that orientation selectivity can be produced by any of a number of mechanisms, but the required degree of specificity of each mechanism is so high, that it conflicts with experimental data. For example, to achieve the observed tuning with only receptive-field elongation, aspect ratios of receptive fields should have a value of at least four or more[40], which is more than twice that observed with intracellular recordings[11,26]. Our scheme differs from previous models in some important respects. One is the significance of voltage-sensitive conductances in amplifying the early orientation bias resulting from the excitatory and inhibitory inputs. A second point is the combination of several different mechanisms, starting from orientation biases in the thalamo–cortical input to recurrent cortical excitation for achieving orientation selectivity (see Fig. 2). Simulations based on combination of different mechanisms, though more limited than in our scheme, have been fairly successful in demonstrating sharp orientation selectivity[40,42]. Recent computer simulations also show that features such as gain control and contrast invariance of orientation tuning can be achieved by a combination of recurrent excitation with feedback and feedforward inhibition[39,41,42].

The proposed model lowers substantially the demands on specificity for any one of the mechanisms and makes the selectivity more robust. For example, while responses of neurones from area 21a could be gradually reduced and finally entirely blocked by cooling area 17, the orientational tuning remained constant throughout the cooling[44]. Furthermore, since the degree of involvement of each mechanism can vary from cell to cell[25], our scheme is compatible with many apparent discrepancies in the published data.

Critical evaluation of the model

Our scheme's denial of excitatory convergence from a long row of geniculate fields might appear to contradict cross-correlation[45] and morphological studies[28] that suggest that at least 10 LGN neurones converge on a cortical cell. However, since a single retinal ganglion cell diverges onto a number of LGN cells (estimated ratio of four for X cells and 20–30 for Y cells[46]), there is considerable overlap in LGN fields, and the summed receptive field of a pool of LGN cells could have dimensions not very different from that of a single retinal cell or just two cells in a row. Convergence from such a pool onto a cortical cell is consistent both with the studies mentioned above and with our model. In fact, cross-correlation between retinal and striate-cell responses indicates that the excitatory input to a cortical cell originates from only one or a very small number of retinal ganglion cells[47]. Our wiring scheme can be achieved during development with simple Hebbian rules without recourse to extensive genetic instructions[18]. Cells of the LGN with a common retinal input would have a tendency for synchronous firing, and therefore their inputs to the same cortical cell will be strengthened.

The presence of length summation in many cortical cells[4,48] over an extent that is much longer than the average diameter of single LGN fields might be taken as support for the model of excitatory convergence.

However, not only is an extended excitatory-input region at variance with much of the experimental data[11,26,49], but length summation can be explained without assuming such convergence. Long-range intracortical excitatory connections between cells tuned to similar orientations[34,35] is one possibility. Another reason for length summation could be disinhibition, since end-zone inhibition of the inhibitory interneurone would be expressed as length summation in the target cell[18]. Consistent with this proposal, cortical cells with length summation showed complete summation within much shorter lengths, when the $GABA_A$ antagonist, bicuculline, was iontophoretically applied[50,51] and profiles of receptive-field responses were much shorter than the extent of length summation[52].

How does the model rest with the failure of some experiments to show clear and convincing hyperpolarizations or shunting inhibition in the non-optimum orientation[21,24]? Summarizing points mentioned earlier, the problem might be related to the masking of relatively weak orientation-selective feed-forward inhibition not only by the excitatory input, but also by nonspecific inhibition and recurrent inhibition in the optimum orientation that are essential to prevent run-away recurrent excitation. Thus the most relevant inhibition for the generation of orientation selectivity might be the weakest of the three types and the most difficult to detect. Furthermore, since non-optimum orientations elicit reasonable-sized EPSPs, only the strongest inhibitory drives with weak concurrent excitation might be apparent as significant hyperpolarizing inhibition in somatic recordings. Instances where strong IPSPs in the non-optimum orientation have been seen were usually those where the EPSPs were significantly smaller at non-optimal than at optimal orientations (see trace D in Box 2).

In a recent ingenious modification of the whole-cell recording technique[53], Nelson *et al.* added Cl^--channel blockers to a CsF-based pipette solution to block inhibition in the cell under study without affecting neighbouring neurones. They found that blocking inhibition in this way did not appreciably reduce the orientation selectivity of the spike responses of the cell to moving stimuli. They concluded that the selectivity is primarily due to the pattern of excitatory inputs and not due to inhibition which selectively counteracts the effect of excitation at non-optimal orientations. While this interpretation seems to be inconsistent with the present scheme, the results are not. Their application of a strong hyperpolarizing current to prevent excessive depolarization due to the Cl^-- and K^+-channel blockers, effectively acts as a substitute for natural nonspecific inhibition. Such hyperpolarization, acting on even a mildly biased excitatory thalamo–cortical input could lead to sharp orientation selectivity of spike responses. Furthermore, the intact cortical circuitry provides normal, sharply tuned excitatory inputs to the cell via lateral and recurrent connections. It would be interesting to study the orientation specificity of the earliest PSPs in their preparation.

Implications of the model for columnar architecture

An important feature of visual cortical organization is the columnar nature of the spatial representation of orientation-selective cells (for review, see Ref. 54). If the orientation biases in the excitatory input to cells in the striate cortex reflect mostly the biases in responses of retinal and LGN cells, this might provide a possible basis for orientation columns. That these biases might be important for cortical orientation selectivity is supported by the finding that the radial pattern of orientation biases observed in the retina and LGN is also apparent in the striate cortex[55,56] and by the reduction of cortical orientation selectivity if bicuculline is iontophoresed in the geniculate to attenuate the biases in the LGN (Ref. 57).

It has been suggested[58,59] that pyramidal-cell modules (with diameters of 56 μm) are basic neuronal aggregates in the cat visual cortex, each module being excited by a different set of thalamic afferents to produce columnar systems related to ocular dominance and orientation preference. Even though we know that the extent of the axonal arborization of individual thalamo–cortical afferents can be considerable[28], it is not too speculative to suppose that the cortical cells receiving the most dominant input from any one retinal cell via the LGN cells that it projects to would be topographically aggregated in one or a few pyramidal-cell modules, and would be receiving the same orientation bias. Nonspecific inhibition and amplificatory mechanisms described in our scheme would sharpen the tuning of these cells, but would not affect the optimum orientation, providing the common preferred orientation for the cells in a vertical module. The gradual progression of preferred orientations across the horizontal domain can be established by self-organizing cortical networks[60] that elaborate a full set of orientations from the primary orientations coded by retinal cells and their corresponding cortical modules[18,56].

Concluding remarks

We have proposed a model for the orientation selectivity of primary visual cortical neurones that includes a number of mechanisms – excitatory input bias from the LGN, nonspecific as well as specific intracortical inhibition, amplification and sharpening of early orientation bias through voltage-sensitive conductances, lateral and vertical excitation from cells tuned to similar orientation and cross-orientation inhibition. The model provides a framework to reconcile the spectrum of conflicting hypotheses regarding the basis of orientation selectivity, and also provides clues to the origins of the columnar architecture of the visual cortex.

Note added in proof

Ferster *et al.*[61] recently reported that cooling the visual cortex to inactivate intracortical circuitry did not affect the orientation selectivity of postsynaptic potentials elicited by moving sine-wave gratings. This finding is not necessarily supportive of the model of excitatory convergence as claimed and could be due to: (1) orientation biases seen in responses of geniculate cells to moving gratings; (2) spatially offset ON and OFF excitatory subregions of the cortical receptive field; or (3) incomplete silencing of the cortical network, or a combination of these. For further details, see http://jcsmr.anu.edu.au/~sagar/orient.html

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