Models of the Visual Cortex

Chapter 54

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CHAPTER 54

Cortical circuitry underlying inhibitory processes in cat area 17

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INTRODUCTION

The early models of cortical organization did not emphasize inhibitory mechanisms, and suggested that specific excitatory connections were sufficient for properties like orientation tuning (Hubel and Wiesel, 1962). Following the discovery of end-inhibition on some receptive fields (RFs; see Hubel and Wiesel, 1965), inhibitory cells were introduced as neuronal components for increasing the selective properties of cortical cells. More recent work using intracellular recording (Benevento, Creutzfeldt and Kuhnt, 1972) or pharmacological agents (Rose and Blakemore, 1974; Sillito, 1975, 1977, 1979; Sillito *et al.*, 1980; Sillito and Versiani, 1977) have shown that most, if not all, specific properties are produced or strongly augmented by inhibitory processes. The inhibitory cells must therefore form the basis of the columnar organization of functional properties in the visual cortex (Hubel and Wiesel, 1963). GABA (γ-aminobutyric acid) is the most likely candidate for the inhibitory transmitter (Krnjević and Schwartz, 1967; Ribak, 1978; Sillito, 1975) and there is strong evidence that it is contained in the cells with smooth dendrites that have been proposed as the inhibitory interneurons (Freund *et al.*, 1983; Ribak, 1978; Somogyi *et al.*, 1983a; Somogyi *et al.*, 1984). The proportion of inhibitory cells in the cortex is small, perhaps only 20 per cent. yet there are a great variety of forms (Lorente de Nó, 1949; O'Leary, 1941; Peters and Regidor, 1981; Ramón y Cajal, 1911; Szentágothai, 1973), suggesting a diversity of function.

The principal reasons for using inhibitory mechanisms rather than excitatory mechanisms for producing RF specificity may be twofold. First, the

system becomes more flexible. Different inhibitory systems superimposed on the same basic pattern of excitation could produce quite different patterns of output. Thus, as new demands are made on the processing system, further inhibitory systems could evolve. Ramón y Cajal (1911) has commented on the apparent increase through the phyla in the number of smooth cell types in the neocortex, with man having the greatest proportion. However, putative inhibitory cells form only about 10 to 20 per cent of the total cells in the cortex (Martin and Whitteridge, 1984; Tömböl, 1974; Winfield, Gatter and Powell, 1980), so the number of additional cells used for additional functions remains relatively small.

A second and related reason for using an inhibitory system is that fewer demands on the specificity of connections are required for each cell if inhibitory processes etch out specific RF properties from a general pool of excitation for each cell. In this manner the inhibitory tuning curves can be broad (as has been found by Benevento, Creutzfeldt and Kuhnt, 1972; Morrone, Burr and Maffei, 1982; Orban, Kato and Bishop, 1979; Sillito, 1979) and yet produce highly selective RF characteristics. To achieve the same degree of selectivity solely by excitatory connections would place great demands on the precision of the intercolumnar excitatory connections that form a large fraction of the intracortical connections. By requiring only a generalized excitation of the cell, only the minimum number of excitatory synapses would be necessary, whereas selectivity produced solely by excitatory connections would require many more connections to achieve specific patterns of excitatory input.

THEORETICAL CONSIDERATIONS

As has been emphasized by theoretical work (Blomfield, 1974; Jack, Noble and Tsien, 1975; Koch and Poggio, 1983), the position of the inhibitory input onto a single neuron is an important factor in determining the net response of the cell. If all the excitation arriving on the cell is to be inhibited, then the optimum position for locating the inhibitory synapses is on the cell soma and axon initial segment. However, if a specific input is to be inhibited, then the optimum location for the inhibitory synapses is just proximal to the excitatory input. The more distal the location of this excitatory/inhibitory combination on the dendrites, the more specific will be its effect (Jack, Noble and Tsien, 1975). Dendritic spines may also receive an inhibitory input that will have its major effect on the single excitatory synapse on the same spine. It has been emphasized that different logical operations can be carried out by particular local interactions of excitatory and inhibitory inputs to the dendritic tree (Diamond, Gray and Yasargil, 1970; Jack, Noble and Tsien, 1975; Koch and Poggio, 1983). Obviously, the output of any single inhibitory/excitatory pair will have little effect on the potential at the soma.

Only the net result of hundreds of such local interactions will determine whether the cell fires or not. In addition, the operations carried out on the distal portions of the dendrites may be further modulated by events occurring more proximally, especially around the soma and axon hillock region. Blomfield (1974) has emphasized one further aspect of the location of inhibitory synapses: if the inhibitory conductances are large, then inhibitory synapses located at the soma will produce a division-like change in the cell's response, whereas inhibitory synapses located on the dendrites will produce a subtractive change in response.

Thus in assessing the significance of a particular type of inhibitory neuron it is essential as a first step to identify the particular location of the synapses on its postsynaptic target. In attempting to apply these theories to cortical organization, one must appreciate that there are only a few instances where the synaptology of the putative inhibitory cells has been examined. The studies described below show that there are very marked differences in the postsynaptic targets of different cell types.

THE SYNAPTIC CONNECTIONS MADE BY THE AXONS OF PUTATIVE INHIBITORY CELLS IN THE CAT

The Axo-axonic cell

The axo-axonic cell, so named because it forms synapses on the initial segment of the axon of pyramidal cells (Somogyi, 1977, 1979), is the most selective of the putative inhibitory cells in its choice of postsynaptic target. Although the physiological properties of the axo-axonic cells are not known, there is now direct evidence that the terminal boutons of the axo-axonic cell contain the synthesizing enzyme for GABA, glutamate decarboxylase (GAD), indicating that this cell is probably inhibitory in function (Freund *et al.*, 1983). About five axo-axonic cells converge on a single pyramidal cell axon, and a single axo-axonic cell may contact several hundred pyramidal cells (Somogyi, Freund and Cowey, 1982). The axo-axonic cell seems to provide the bulk of its innervation to pyramidal cells in the superficial layers of the cortex (Freund *et al.*, 1983; Somogyi, Freund and Cowey, 1982). Since these pyramidal neurons provide most of the corticocortical connections it has been suggested that the axo-axonic cell controls the transfer of information between different cortical areas (Peters, Proskauer and Ribak, 1982; Somogyi, Hodgson and Smith, 1979). This may not be their only role since many of the pyramidal cells projecting to other cortical areas also provide a substantial collateral input to the deep layers of the same cortical area (Martin and Somogyi, Chapter 53 in this volume). Inhibition of the output of the pyramidal cells of the superficial layers could then markedly affect the activity

of cells in the deep layers and hence the output to subcortical regions. Thus, given the appropriate input, the axo-axonic cells could provide a most effective control of the output of projection neurons. If this control were applied selectively to specific cortical regions, it could provide a basis for the mechanism of selective attention.

If the cortex uses positive feedback circuits (the pyramidal cells of layer 6 that project to layer 4 and the LGN may be one such example) then it may be necessary to insert inhibitory cells as governors to prevent epileptiform activity being initiated by positive feedback. If the axo-axonic cell had a relatively high threshold for activation then it would be a suitable candidate for such an inhibitory cell (Freund *et al.*, 1983). Physiological evidence has been obtained for the presence of an inhibitory mechanism that operates only at high levels of discharge of pyramidal cells (Sillito, 1979).

The Basket cell

The main input to the soma of pyramidal cells probably comes from the large basket cell (Kisvárday *et al.*, 1983; Martin, Somogyi and Whitteridge, 1983; Somogyi *et al.*, 1983b), although one other cell has now been found which provides somatic input to pyramidal cells (Kisvárday *et al.*, in preparation; see below). The evidence that the basket cells are GABAergic is indirect, but the finding that most if not all of the boutons providing somatic synapses on pyramidal cells contain GAD is strongly suggestive of their inhibitory role (Freund *et al.*, 1983). So far only the basket cells of the superficial layers have been investigated in detail at the electron microscopic (EM) level, but our observations of the basket cells of layer 5 suggest they have similar postsynaptic targets. The synapses of the basket cell are concentrated on the soma (30 to 40 per cent. of the basket cell's synapses) and proximal dendritic shafts (24 per cent.) of pyramidal cells. This location of the synapses suggests that their action may produce division-like changes in the cells response. Two RF properties, orientation tuning and directionality, have been examined for this purpose (Dean, Hess and Tolhurst, 1980; Morrone Burr and Maffei, 1982; Rose, 1977). In both instances increasing amounts of inhibition produce division-like changes in the cell's firing rate, suggesting that the relevant inhibitory synapses are positioned around the perisomatic region of the cell and may therefore have the basket cells as their source. We have suggested that different subsets of basket cells may be involved in producing many of the specific RF properties, like orientation tuning, directionality, binocular depth tuning and end-inhibition, that are known to be under inhibitory control (Martin, Somogyi and Whitteridge, 1983; Somogyi *et al.*, 1983b). This is because the circuitry required to generate these properties in a single cell becomes very complicated if the same set of basket cells are used as the final common path for all inhibitory mechanisms. It may also be useful for

cells to use the same subset of inhibitory cells for those properties they have in common (e.g. end-inhibition), but would obviously have to use different inhibitory cells for generating dissimilar properties (e.g. different orientation selectivities).

The axon of the basket cell does not contact every pyramidal cell in the region occupied by its axon. Instead it appears to pick out columns of pyramidal cells located in small patches of cortex. Thus although the axon covers about 1.5 mm of cortex in the anteroposterior and mediolateral dimensions (the largest tangential spread of any smooth type so far encountered), only about 200 to 300 pyramidal cells are contacted by a single basket cell (Kisvárday *et al.*, 1983; Martin, Somogyi and Whitteridge, 1983; Somogyi *et al.*, 1983b). Each basket cell only provides about four or five of the synapses (about 5 to 10 per cent. of the total somatic input) on the soma of a pyramidal cell. If, as we have suggested (Martin and Somogyi, Chapter 53 this volume), 100 to 300 active excitatory synapses are required to bring the cell to threshold for firing, then it seems unlikely that the input of a single basket cell would be sufficient to produce a significant reduction in the response of the target cell, even if the inhibition is producing a shunt rather than a hyperpolarization of the membrane (Jack, Noble and Tsien, 1975). Thus controlling the pyramidal cell output by basket cell inhibition may require the coordinated action of several basket cells.

The basket cells also provide a substantial input to dendritic spines (20 per cent. of basket cell synapses; Somogyi *et al.*, 1983b). An inhibitory input to a spine probably has a very localized effect on the excitatory input (Jack, Noble and Tsien, 1975) and that effect will be subtractive. As yet a subtractive change in firing rate has not been related to a specific RF property, but the localized nature of spine inhibition suggests that a specific excitatory pathway is being inhibited by the basket cell input to the spines.

The Clutch cell

The other cell that gives a strong somatic input to its postsynaptic targets is located in layer 4. It is a multipolar cell (Martin, Somogyi and Whitteridge, 1983) which we have called a 'clutch' cell. Although the general distribution of its synapses between soma and dendrites is similar to that of the large basket cell, its axon is very much more restricted than that of the basket cell. Unlike the basket cell, the major portion of the axonal arborization of the clutch cell is in layer 4 and it probably makes synapses on many spiny stellate cells. Some collaterals of the clutch cell extend into lower layer 3 and into layer 5 and synapse on pyramidal cells (Kisvárday *et al.*, in preparation). Many of the spiny cells in layer 4A have widespread connections to other layers (Martin, 1984). Thus an inhibitory cell with a localized axon system within layer 4, such as the clutch cell, could have a widespread

influence. The much more extensive collateral system of the basket cells in deep and superficial layers may in part be required to inhibit cells with a common excitatory source in layer 4.

Physiologically the clutch cells and the basket cells are heterogenous (Martin, Somogyi and Whitteridge, 1983). They can have either S- or C-type RFs and be activated monosynaptically or polysynaptically by X- or Y-like LGN afferents. In addition, two basket cells with RFs near the vertical meridian were driven by callosal afferents. This heterogeneity of RF type and serial position is not surprising, given that the cortex may be organized in a parallel fashion and that similar inhibitory processes act on different parallel paths at all levels.

The Double Bouquet cell

The fourth putative inhibitory cell whose synaptology has been investigated in the cat is the double bouquet cell (Somogyi and Cowey, 1981, 1984). While the three types described above concentrate their input at the perisomatic region of spiny cells, the double bouquet cell shows just the opposite trend. The vast majority of contacts it makes are onto small- or medium-sized dendritic shafts of non-pyramidal cells that may themselves be inhibitory. As has been pointed out (Somogyi and Cowey, 1981, 1984), this would provide a mechanism for the disinhibition seen in physiological studies. However, disinhibition may not be the primary role of the cell. It has been found (Martin, Somogyi and Whitteridge, 1983) that the tuning curves and RF properties of putative inhibitory cells are qualitatively no different from those of the pyramidal and spiny stellate cells. Since the RF properties of the inhibitory cells are presumably also produced by inhibition, it is inevitable that they should themselves receive an inhibitory input and that this would produce the disinhibition effect seen using electrical stimulation. The convergence of a number of inhibitory cells with different RF properties probably accounts for the broad inhibitory tuning curves that have been found (Burr, Morrone and Maffei, 1981).

Although both the basket and the clutch cell also contact putative inhibitory cells (Kisvárday *et al.*, in preparation; Martin, Somogyi and Whitteridge, 1983; Somogyi *et al.*, 1983a) these constitute 10 per cent. or less of the postsynaptic targets. The double bouquet cell, by contrast, contacts a far higher proportion of putative inhibitory cells, perhaps as high as 60 to 70 per cent. (Somogyi and Cowey, 1981). The reason for this may be that the activity of inhibitory cells needs to be coordinated because many converge on the same target cell. The double bouquet cell, with its localized vertically oriented axon passing through several layers, would be well-suited to such a coordinating role, especially for specific properties that are arranged in a columnar fashion.

CONCLUSION

It seems likely from the admittedly small amount of data available that any single cell receives inhibitory input from more than one inhibitory cell type, as in the case of the input to pyramidal cells from both the basket cell and the axo-axonic cell. Presumably the activities of these different convergent inhibitory paths must be coordinated in some way, and this would require rich interconnections between inhibitory cells. Also, those inhibitory cells that are involved in more than one inhibitory mechanism may receive their excitatory input from several independent local circuits. This organization would necessitate a much greater synaptic input to inhibitory cells than excitatory cells, and there is some evidence that cells with smooth dendrites do have a higher synaptic density on their dendrites than cells with spiny dendrites (Freund *et al.*, 1983; Ribak, 1978; Somogyi, Freund and Cowey, 1982).

All of the four putative inhibitory cells described above connect either to different cell types or to different positions on the same type of cell. There are many varieties of putative inhibitory cells whose synaptology has yet to be investigated. It is probable, on the basis of the survey to date, that they will also have particular cell types and postsynaptic sites of preference, reflecting yet further functional differentiation. We have suggested that some inhibitory cells, like the axo-axonic cell, may not be directly involved in producing RF selectivity. Other cells, like the double bouquet cells, because of the distal location of their particular input, may be involved only in the fine tuning of the cell's responses, with the coarse tuning being carried out by cells whose input is at a more strategic location on the cell, like the basket and clutch cells. Clearly we need to know a great deal more about the dendritic and somatic location of inputs from different inhibitory and excitatory sources and their postsynaptic targets before we can devise a realistic and integrated model of area 17. Nevertheless, the power of the methods described here is cause for optimism that the previously intractable problems in studying local circuitry are now potentially soluble.

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