From: Structural and Functional Organization of the Neocortex. (1994) B. Albowitz, K. Albus, U. Kuhnt, H.-Ch. Nothdurft and P. Wahle (Eds.). Proceedings of a Symposium in Memory of Otto D. Creutzfeldt, May 1993. Springer-Verlag Berlin, pp. 148-161.

4.5 The Order in Synaptic Circuits of the Cerebral Cortex: Lessons from the Hippocampus

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4.5.1 Introduction: What Is the Basic Cortical Circuit?

Neuronal diversity in the cerebral cortex has fascinated scientists for more than a hundred years, but a basic circuit accounting for interconnections of the existing neuronal types in the cortex is still missing. The structural and functional relationships among cortical cells and their subcortical inputs was a major interest of Otto Creutzfeldt and his associates, who pioneered many approaches for the elucidation of visual cortical circuitry in functional terms (Creutzfeldt 1993; Creutzfeldt and Ito 1968; Creutzfeldt et al. 1974, 1975). In a symposium in his honor it is most appropriate to provide a brief summary of recent insights into synaptic relationships of cortical neurons.

In relation to the main neurotransmitters of its resident neurons the cortex is a simple structure neurochemically consisting of two major cell types: principal cells (pyramidal cells, spiny stellate cells, hippocampal granule cells), which usually have densely spiny dendrites and release excitatory amino acids as transmitters, and non-principal, or local circuit cells, which generally have sparsely spiny or smooth dendrites (for review see McCormick 1992; Somogyi 1989). The latter population forms about 20% of cortical neurons (Gabbott and Somogyi 1986), and releases γ-aminobutyric acid (GABA) as an inhibitory transmitter. The thalamic input to the cortex and long-range associational connections between different cortical areas are mediated by excitatory amino acid mechanisms (for review see McCormick 1992; Tsumoto 1992). Evidence is strong for glutamate as an excitatory amino acid used in cortical connections, and it may be the only acidic amino acid released by thalamo-cortical and corticocortical terminals. Therefore, defining cortical circuitry involved in fast signal processing comes down to defining the origin, relationship and properties of GABAergic and glutamatergic synaptic junctions. Much of the complexity in cortex is due to the diversity of sources of both the glutamatergic and the GABAergic inputs. For example, stereological estimates show that an average cortical neuron receives about 5800 synapses in the cat striate cortex (Beaulieu et al. 1992). Of these, about 960 originate from local, GABAergic, inhibitory neurons, each one making between one and ten synaptic contacts on a single postsynaptic cell. Assuming an average of five, it follows that at least 200 inhibitory neurons, belonging to distinct functional classes, may converge onto a single postsynaptic cortical cell.

The numerical relationship between the terminals using these two classes of transmitters is remarkably stable across species and different cortical areas. About 17% of synaptic boutons are immunopositive for GABA (Beaulieu and Somogyi 1990; Beaulieu et al. 1992) and presumably release it as transmitter. Most of these terminals form morphologically identifiable Gray's type 2 synapses (Gray 1959). Almost all the remaining synaptic boutons form Gray's type 1 synaptic junctions, exhibiting thick postsynaptic densities. Several lines of evidence suggests that the overwhelming majority of these boutons store and release glutamate as neurotransmitter (Liu et al. 1989, Bramham et al. 1990). An additional important element to this somewhat simplified cortical circuit is provided by a sparse, but diverse array of subcortical, nonthalamic, monoaminergic inputs from the reticular formation which, due to lack of space, are not discussed here.

A basic cortical circuit is defined here as the sum of: (a) a subpopulation of principal cells which can be considered homogeneous in terms of their main output, (b) the main excitatory inputs that lead to the activation of these cells, and (c) the local circuit inhibitory neurons involved in

the regulation of both the inputs and outputs of these principal cells. A major difficulty in accounting for the relationships of these three elements *in the neocortex* is that a similar basic circuit is superimposed several times in each column, from layer to layer. In addition, the connections between layers complicate the recognition of the general layout of the basic circuit. Another complexity is introduced by the rich interconnections of the principal cells whose local recurrent axon collaterals overlap in tissue space with the afferents activating the same cells, or may even provide the main excitatory drive to a population of cells. Therefore, in order to define the synaptic relationships in the basic cortical circuit we have investigated the simpler archicortical area of the hippocampal formation.

The hippocampal formation has two great advantages for the study of basic cortical circuits (for review see Amaral and Witter 1989; Andersen 1975; Witter 1989). (a) The cell bodies of principal cells are arranged into a single layer, resulting in the tangential alignment of functionally equivalent segments of the dendritic fields of individual cells into distinct, well-recognizable laminae. (b) The recurrent local axon collaterals of the principal cells are separated into distinct laminae in the CA1 area and the dentate gyrus. The dentate gyrus in nonprimate species is the only cortical area in which the recurrent collaterals of the principal cells are almost completely separated from the major excitatory inputs to the principal cells (Ramón y Cajal 1893). Although this makes the dentate gyrus unusual in that its principal cells are not normally directly interconnected, the laminar segregation of extrinsic and recurrent inputs offers a unique opportunity to study the relationship of principal cells and local inhibitory cells, both anatomically and physiologically (for review see Scharfman 1992; Mody et al. 1992). The following section focuses on two recent studies of the dentate gyrus (Han et al. 1993; Halasy and Somogyi 1993b) and their implications for other hippocampal areas and the neocortex.

4.5.2 Synaptic Connections in the Dentate Gyrus

Overview. The dentate gyrus is considered the gate to the hippocampal formation through which input from the neocortex arriving via the entorhinal afferents activates the trisynaptic circuit from the dentate area through the CA3 area to the CA1 region (Fig. 1; for review see Andersen 1975; Buzsaki 1989). The principal cells are the granule cells, arranged densely in a cell body layer. Their spiny dendrites ramify in the molecular layer and their axons run in the opposite direction to the CA3 area, where they provide the mossy fiber input to the proximal dendrites of pyramidal cells and local circuit neurons. The granule cell layer is followed by the so-called hilus, containing another set of principal cells, the mossy cells (Amaral 1978;

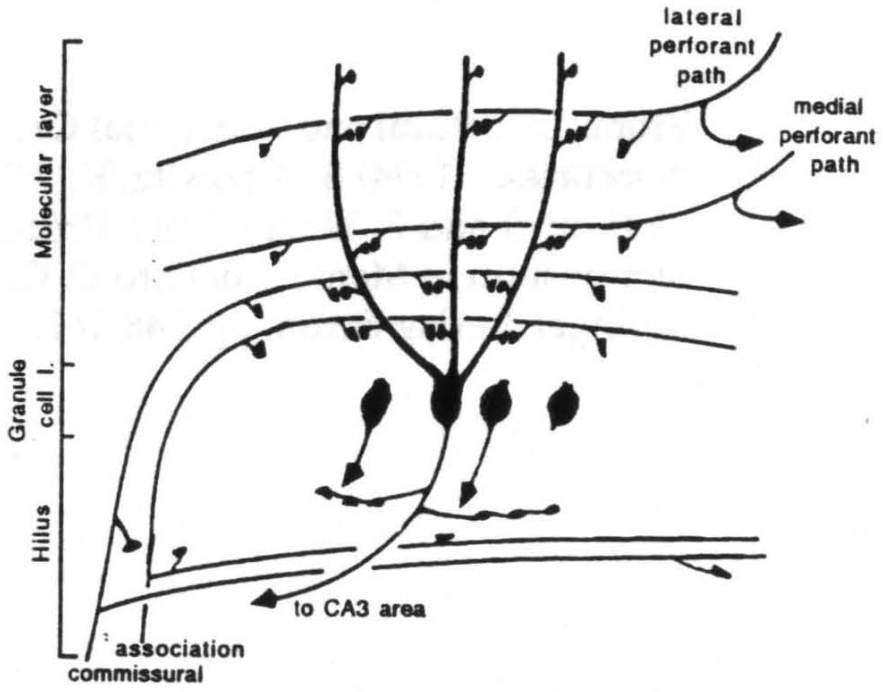

Fig. 4.5–1. Schematic view of the main connections of granule cells in the rat dentate gyrus, demonstrating the lamination of excitatory amino acid inputs to the dendritic field and the spatial segregation of local axon collaterals. Entorhinal afferents innervate the outer two thirds of principal (granule) cell dendrites in the molecular layer, whereas the granule cell local axons mainly innervate the hilus, then run to the CA3 area where they provide the mossy fiber input to proximal dendrites. The hilus contains the excitatory mossy cells (not shown) and a variety of other cell types (see Figs. 2,3). The inner one third of the molecular layer is innervated by ipsilateral association fibers, provided by hilar mossy cells and CA3c pyramidal cells and by commissural fibers from the contralateral hippocampal formation. The association and commissural pathways overlap (not shown)

Frotscher et al. 1991), the local recurrent axon collaterals of granule cells and a variety of cell types whose identity and synaptic relationships are not fully determined (Amaral, 1978; Frotscher 1991; Gulyas et al. 1992), but they are probably all innervated by the granule cells. The entorhinal corticocortical afferents terminate in the outer two thirds of the molecular layer; the medial entorhinal area innervating the middle one-third, and the lateral entorhinal area innervates the outermost one-third of the molecular layer (Hjorth-Simonsen and Jeune 1972). The inner one third of the molecular layer is innervated by ipsilateral association fibers, provided by hilar mossy cells (Buckmaster et al. 1992) CA3c pyramidal cells (Li et al. 1993) and commissural fibers, probably originating from similar cells of the contralateral hilus as the ipsilateral association pathway (Hjorth-Simonsen and Laurberg 1977).

The Question. Is it possible to discern any general rules in the interrelationships between extrinsic and intrinsic excitatory amino acid pathways, the inputs and outputs of local circuit inhibitory neurons and the

inputs and output of the principal granule cells? Local circuit neurons were identified on the basis of their electrophysiological characteristics in intracellular recordings of hippocampal slices in vitro (Han et al. 1993). The cells discussed below generally had short duration action potentials with a fast repolarization phase, and each action potential was followed by a fast, deep afterhyperpolarization. Apart from one cell type, and in contrast to granule cells, the inhibitory neurons showed little spike frequency accommodation. The synaptic inputs of the cells were studied by electrical stimulation of afferent pathways. The cells were identified by intracellular injection of biocytin followed by visualization using avidin-horseradish peroxidase (HRP) conjugates. The nature of transmitter in the terminals of the intracellularly recorded and morphologically identified cells was determined by immunoreacting their labeled synaptic boutons for GABA.

Definition of Cells According to Output. We have found that in the dentate gyrus the principal granule cells receive inputs from at least five distinct types of GABAergic neurons, terminating in four out of five cases, in mutually exclusive domains on the surface of granule cells (Figs. 2,3). They are: (a) hilar cell with cell body and dendrites restricted to the hilus and having ascending axons to the outer two thirds of the molecular layer, where they terminate in conjunction with the perforant pathway (*HIPP* cell); (b) molecular layer cell with both axon and dendrites restricted to the outer two thirds of the molecular layer in association with the perforant pathway (*MOPP* cell); (c) hilar cells with axon restricted to the inner one third of the molecular layer terminating in conjunction with the commissural and association pathways (*HICAP* cell) (d) ***basket cells***, terminating on the somata and proximal dendrites of granule cells; (e) ***axo-axonic cells***, terminating exclusively on the axon initial segments of the granule cells. Basket (Ribak et al. 1978) and axo-axonic cells (Soriano et al. 1990; Soriano and Frotscher 1989) are known to be GABAergic, MOPP and HICAP cells were found to store GABA in their terminals (Halasy and Somogyi 1993b) and more recently HIPP cells were also shown to be immunoreactive for GABA (K. Halasy, E. Buhl, P. Somogyi, unpublished observation). This is in agreement with physiological evidence that some hilar cells generate inhibitory postsynaptic potentials (IPSP) in granule cells (Scharfman et al. 1990; for review see Misgeld et al. 1992; Scharfman 1992).

Inputs. The analysis of the dendritic distribution of these cell types is most revealing with regard to the spatial selection of inputs (Han et al. 1993). The dendrites of the HIPP cell are restricted to the hilus, hence it has ample access to the recurrent axon collaterals of granule cells but cannot receive significant direct input from entorhinal afferents. Thus, HIPP cells are feedback regulators of the granule cell/perforant path synapse (Figs. 2,3).

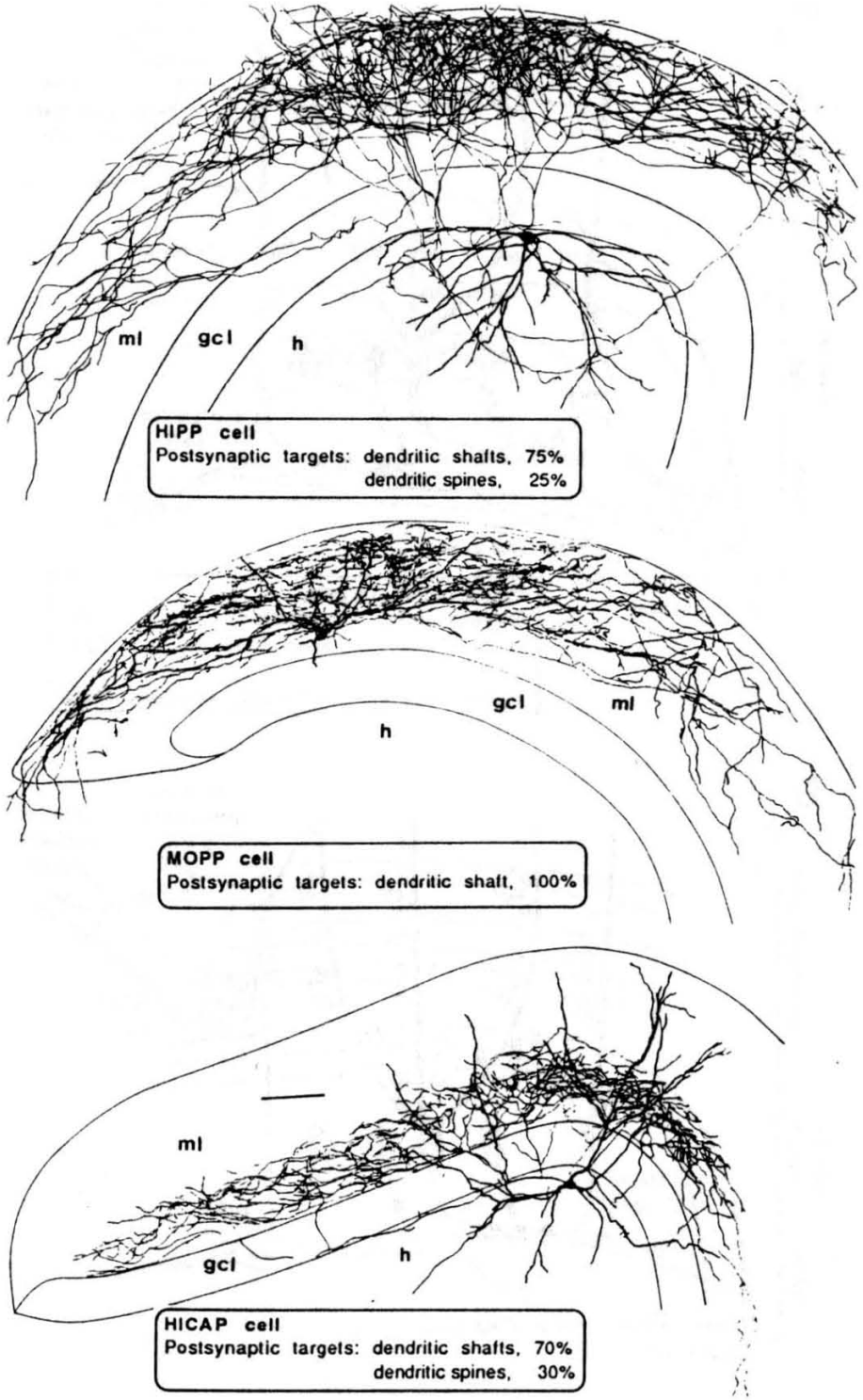

Fig. 4.5–2. Reconstructions of three types of local circuit GABAergic neurons terminating in the dendritic field of granule cells and demonstrating selective axonal and dendritic patterns. Cells were recorded in vitro and visualized with biocytin. Synaptic targets were identified by electron microscopy. HIPP and MOPP cells innervate the outer two thirds of the molecular layer in conjunction with the perforant path. HICAP cells innervate the inner one third of the molecular layer in conjunction with the commissural/association pathway. The dendrites of HIPP cells are restricted to the hilus, whereas those of MOPP cells are confined to the outer molecular layer. HICAP cells have access to all dentate excitatory amino acid afferents. *Scale* for all cells, 100 μm. (Data based on Han et al. 1993; Halasy and Somogyi 1993b)

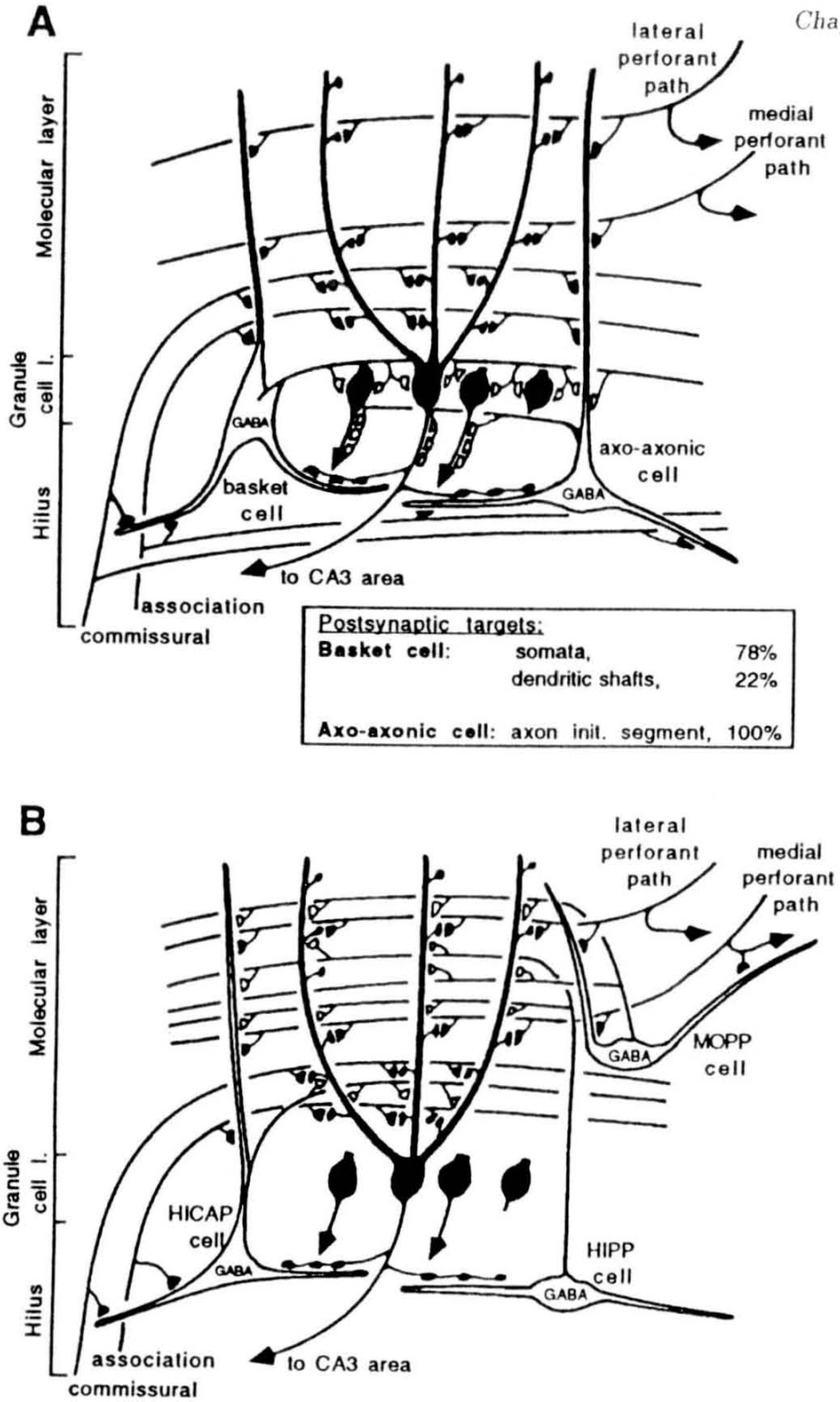

Fig. 4.5–3. Relationships between inputs and subdivisions of the multiple GABAergic innervation of dentate granule cells. **A** There are two levels of output control by the basket and axo-axonic cells, both of them probably receiving the full complement of dentate afferents as well as recurrent granule cell input. **B** Three types of GABAergic neurons (open cells and terminals), innervating the dendritic region, associate their terminals with particular excitatory amino acid pathways (see also Fig. 2). The distribution of dendrites suggests feedforward activation of MOPP cells, feedback (recurrent) activation of HIPP cells and both types of inputs to HICAP cells; the latter could mediate inhibitory cross-influence by the perforant path on the association/commissural input to granule cells

In contrast, MOPP cells have access to entorhinal input that also activates the granule cells but cannot receive significant recurrent input from the granule cells on which they terminate (Fig. 2). Thus, MOPP cells may serve feedforward regulation of the granule cell/perforant path synapse (Fig. 3). Basket, axo-axonic and HICAP cells distribute dendrites in all layers of the dentate gyrus, thus they are in a position to receive input from all the extrinsic afferent pathways (see e.g., Buzsaki 1984; Buzsaki and Eidelberg 1981; Zipp et al. 1989), and from the recurrent collaterals of granule cells (Fig. 3). The relative strength of these inputs is not yet known. The most striking of the latter three cell types is the HICAP cell, which clearly receives perforant path input on its dendrites in the outer two thirds of the molecular layer but restricts its efferent synapses to the inner one-third of the dendritic region of granule cells, where other excitatory pathways terminate. In theory, the perforant path input could provide an inhibitory cross-influence on the commissural/association input to granule cells in a feedforward manner. Much more information is needed, however, on the relative timing and the strength of activation of the different cell types before real functional schemes can be drawn up.

Outputs. The basket and axo-axonic cell types establish their synapses at sites thought to be the most effective place for inhibition to control the final output of granule cells. So called "basket cells" have been frequently described, but without identification of their synaptic output they were not differentiated from axo-axonic or other neuronal types that do not contribute to somatic synapses. It has been suggested that only those cells that provide a substantial proportion of their synaptic terminals to the cell bodies of other neurons should be called basket cells (Halasy and Somogyi 1993b). Axo-axonic cells were identified more recently in the dentate gyrus (Soriano and Frotscher 1989). From our sample it is now apparent that the same individual axo-axonic cells innervate both granule cells and one of their excitatory input cells, the hilar mossy cells.

Although the dual GABAergic innervation of proximal parts of the cortical principal cells by basket and axo-axonic cells is a universal feature of all cortical areas (see Somogyi 1989), the reason for the segregation of inputs is not known. Physiologically identified inhibitory cells of the hippocampal pyramidal layer were found to evoke only fast IPSPs in pyramidal cells in vitro (Miles 1990; Miles and Wong 1984). Recently, Buhl et al. (1993) recorded simultaneously from both a dentate axo-axonic cell and one of its postsynaptic granule cells, followed by anatomical identification of the synaptic contacts that exerted the postsynaptic action on the granule cell through the release sites on the axon initial segment. Action potentials in the axo-axonic cell produced very fast, brief IPSPs in the granule cell with a reversal potential of –78 mV. Identified basket cells evoked similar

postsynaptic effect in the CA1 region (Buhl et al. 1993), and we suggested that the effects of both cell types were mediated through $GABA_A$ receptors. It is possible that the need arose for two different GABAergic output control cells in cortex because the two cells play roles in different aspects of the response of postsynaptic principal cells during their synaptic activation. Axo-axonic cells are ideally placed for synchronization of the output of a large population of principal cells, whereas basket cells may control the degree of depolarization spreading to the initial segment through the soma. In other words, basket cells may rescale excitatory postsynaptic potentials (EPSP) arriving from the dendrites at the somatic level, and therefore indirectly control the threshold of spike generation in the initial segment.

The GABAergic HICAP, MOPP and HIPP cells terminate in precise spatial conjunction with particular excitatory amino acid inputs to the same cell, thus they are in a position to interact selectively with those specific inputs. This idea is reinforced by the observed pairing of a glutamatergic and a GABAergic synapse on a single dendritic spine, although it is probably better to consider the effect of these inputs in a statistical manner and estimate the overall effect of synapses on a dendritic region rather than on a single spine. Measurements of the number of GABAergic synapses on different parts of granule cells show that in numerical terms most of the GABAergic transmission takes place at the dendrites. There are at least three times as many GABAergic synapses on dendrites than on the somata and axon initial segments of granule cells (Halasy and Somogyi 1993a). As in the neocortex (Beaulieu and Somogyi 1990; Beaulieu et al. 1992) the overall proportion of GABA immunopositive synapses is also 17% in the dentate gyrus (Halasy and Somogyi 1993a).

4.5.3 How General Is the Selective GABAergic Innervation of Dendritic Regions?

As elsewhere in the cortex, in the CA1 area the stratum pyramidale is innervated by the somatic basket cells with a small overflow to the adjacent dendritic layers (Ramón y Cajal 1893). Preliminary studies show that in addition there are GABAergic neurons whose axonal output is biased for the dendritic laminae. A local circuit neuron, the bistratified cell, provides its synaptic boutons, in two parallel bands, more to the strata radiatum and oriens than to the stratum pyramidale (Halasy et al. 1993). An even more specialised cell type, the butterfly cell almost completely avoids terminating in the stratum pyramidale and innervates the full depth of the strata radiatum and oriens in precise conjunction with the glutamatergic Schaffer collateral/commissural input (Halasy et al. 1993). Cell bodies of all the above three cell types occur in or near the pyramidal cell layer. Further

GABAergic cells reside in the strata lacunosum moleculare (Lacaille and Schwartzkroin 1988a,b), radiatum and oriens (Lacaille and Williams 1990), but there is only limited information on their axonal termination, although probably they innervate mostly the dendritic regions (see e.g., Kawaguchi and Hama 1987, 1988).

In the neocortex, in addition to basket and axo-axonic cells, there are local circuit neurons that make synapses mainly with dendrites and dendritic spines (for review see Somogyi 1989; and P. Somogyi, Z. Kisvárday, D. Beroukas, unpublished results). It is not yet known whether their terminals are co-distributed in conjunction with particular excitatory inputs to the same postsynaptic cells. In general, because the dendritic regions of many different cell types overlap, very little is known about the precise distribution of particular afferent synapses on the surface of neocortical neurons. Nevertheless, the limited information that is available, particularly from the laminar selectivity of afferents, indicates that stratified dendritic innervation by both glutamatergic and GABAergic afferents exists in many cortical areas.

4.5.4 What Are the Possible Functional Consequences of the Conjoint Excitatory and Inhibitory Dendritic Inputs?

Any hypothesis must consider the effect of the inhibitory cell in the context of the effect on the excitatory input located on the same dendritic segments.

Selective Subcortical State Control. Innervation of nonprincipal cells in neocortex and hippocampus by nonthalamic subcortical afferents (Freund 1992; Mulligan and Tork 1987) provides an opportunity for different subcortical afferents to control particular excitatory inputs selectively via the GABAergic cells that terminate in conjunction with them.

Presynaptic Inhibition of Glutamate Release. Glutamate release is reduced by the activation of presynaptic $GABA_B$ receptors (Thompson and Gähwiler 1992). The costratification of GABAergic axons and glutamatergic inputs provides an opportunity for GABAergic influence on a particular pathway and not on the others. However, the GABAergic terminals in the dendritic region are neither in preferential membrane apposition nor do they form axo-axonal synapses with glutamatergic terminals. Instead the anatomically defined synaptic junctions are formed with postsynaptic dendrites and spines, so GABA can reach glutamatergic terminals only by diffusion from the presumed release site at the synaptic junction. Obviously, the probability of GABA diffusion to nearby terminals is greater, and the costratification may thus ensure preferential influence on some, but not on other input pathways.

Regulation of NMDA Receptor Activation. The activation of *N*-methyl-D-aspartarte (NMDA) receptor mediated excitatory postsynaptic effect is voltage dependent, increasing with depolarization, and GABAergic hyperpolarizing and shunting influences decrease the NMDA receptor mediated effect (Davies et al. 1991; Staley and Mody, 1992). The selective pairing of GABAergic and glutamatergic inputs could lead to the differential adjustment of the probability of NMDA receptor activation and/or effect at the synapses of different pathways that converge on to the same cell. This could result in a differential, long term modification of synaptic strengths of only some inputs to a cell, as has been demonstrated for long term potentiation (for review see e.g., Bliss and Collingridge 1993).

Increasing the Dynamic Range of EPSP. Postsynaptic GABAergic influences reduce both the amplitude and the duration of glutamate-mediated EPSPs. The *pathway specific* GABA-mediated events, with appropriate gain and timing (Staley and Mody, 1992) could rescale the EPSPs arriving at the same dendritic segment and thereby extend their dynamic range. This mechanism would work by reducing EPSPs, which are suprathreshold in the absence of GABAergic influence, into the subthreshold domain and render them available for spatial and temporal summation. This may be a general role for those GABAergic terminals which are selectively co-aligned with glutamatergic terminals in the dendritic tree in many parts of the central nervous system. The arrangement found in the dentate gyrus and elsewhere is highly appropriate for the separate adjustment of the gain of different corticocortical excitatory inputs. The downward rescaling would also dampen spurious variability in EPSP strength and make inputs more reliable. The mechanisms discussed above are not mutually exclusive. The recognition of the order in synaptic circuits opens them up for physiological exploration.

4.5.5 Conclusions

What are the lessons from the hippocampus that are likely to be applicable to cortical circuits in general? Studies of the hippocampal circuitry lead to the following predictions: (a) Populations of principal output cells of the cortex receive segregated excitatory glutamatergic input on their dendrites. (b) Excitatory inputs to a cortical area always activate both excitatory and inhibitory cells in parallel. (c) Some inhibitory cells are connected primarily in a feedforward manner, others primarily in a feedback manner, but some types receive both inputs. (d) Inhibitory cells terminating on the somatic region (basket cells), or on the axon initial segment (axo-axonic cells) of principal cells receive the same excitatory inputs as the principal cells and in addition a recurrent input from the cells that they innervate. (e) Some

inhibitory cells terminate only on the dendritic tree of principal cells in conjunction with subsets of excitatory inputs, and their inhibitory effect is likely to be pathway specific. Certain elements of these predictions remain to be proven in the neocortex, but the strategy applied in the hippocampus could provide useful guidelines for their investigation.

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