ELSEVIER

Brain Research Reviews 26 (1998) 113–135

BRAIN RESEARCH REVIEWS

Salient features of synaptic organisation in the cerebral cortex [1]

Peter Somogyi [a,*], Gábor Tamás [a,b], Rafael Lujan [a], Eberhard H. Buhl [a]

[a] *Medical Research Council, Anatomical Neuropharmacology Unit, Department of Pharmacology, University of Oxford, Mansfield Road, Oxford OX1 3TH, UK*

[b] *Department of Comparative Physiology, József Attila University, Szeged Hungary*

Abstract

The neuronal and synaptic organisation of the cerebral cortex appears exceedingly complex, and the definition of a basic cortical circuit in terms of defined classes of cells and connections is necessary to facilitate progress of its analysis. During the last two decades quantitative studies of the synaptic connectivity of identified cortical neurones and their molecular dissection revealed a number of general rules that apply to all areas of cortex. In this review, first the precise location of postsynaptic GABA and glutamate receptors is examined at cortical synapses, in order to define the site of synaptic interactions. It is argued that, due to the exclusion of G protein-coupled receptors from the postsynaptic density, the presence of extrasynaptic receptors and the molecular compartmentalisation of the postsynaptic membrane, the *synapse* should include membrane areas beyond the membrane specialisation. Subsequently, the following organisational principles are examined:

1. The cerebral cortex consists of: (i) a large population of principal neurones reciprocally connected to the thalamus and to each other via axon collaterals releasing excitatory amino acids, and, (ii) a smaller population of mainly local circuit GABAergic neurones.
2. Differential reciprocal connections are also formed amongst GABAergic neurones.
3. All extrinsic and intracortical glutamatergic pathways terminate on both the principal and the GABAergic neurones, differentially weighted according to the pathway.
4. Synapses of multiple sets of glutamatergic and GABAergic afferents subdivide the surface of cortical neurones and are often co-aligned on the dendritic domain.
5. A unique feature of the cortex is the GABAergic *axo-axonic cell*, influencing principal cells through $GABA_A$ receptors at synapses located exclusively on the axon initial segment.

The analysis of these salient features of connectivity has revealed a remarkably selective array of connections, yet a highly adaptable design of the basic circuit emerges when comparisons are made between cortical areas or layers. The basic circuit is most obvious in the hippocampus where a relatively homogeneous set of spatially aligned principal cells allows an easy visualization of the organisational rules. Those principles which have been examined in the isocortex proved to be identical or very similar. In the isocortex, the basic circuit, scaled to specific requirements, is repeated in each layer. As multiple sets of output neurones evolved, requiring subtly different needs for their inputs, the basic circuit may be superimposed several times in the same layer. Tangential intralaminar connections in both the hippocampus and isocortex also connect output neurones with similar properties, as best seen in the patchy connections in the isocortex. The additional radial superposition of several laminae of distinct sets of output neurones, each representing and supported by its basic circuit, requires a co-ordination of their activity that is mediated by highly selective interlaminar connections, involving both the GABAergic and the excitatory amino acid releasing neurones. The remarkable specificity in the geometry of cells and the selectivity in placement of neurotransmitter receptors and synapses on their surface, strongly suggest a predominant role for time in the coding of information, but this does not exclude an important role also for the rate of action potential discharge in cortical representation of information.

Keywords: Neocortex; Hippocampus; Glutamate receptor; GABA receptor; Synapse; Neurotransmission

Contents

* Corresponding author. Fax: +44 (1865) 271648; E-mail: peter.somogyi@pharmacology.oxford.ac.uk

[1] Published on the World Wide Web on 3 March 1998.

0165-0173/98/$19.00

1. Introduction

In the mammalian brain, the cerebral cortex is the largest structure as defined on the basis of a uniform cellular organisation. The two major classes of cortical cells, the generally densely spiny pyramidal cells, that release excitatory amino acid(s) as transmitter, and the generally smooth dendritic GABAergic cells receive on average 4–6000 synapses, which is not remarkable in the brain. About every fifth neurone and every sixth synaptic bouton synthesises and releases GABA; most of the rest use excitatory amino acids as transmitter [8,7,34]. The great evolutionary success and versatility of the cerebral cortex can be explained by a design which enables the connections to respond to specific localised needs, apparent in the many selective modifications that are manifested in the great variety of neuronal subclasses of the two major cell families. The flexibility of design is also well illustrated by the wide range in the number of synapses, from a few hundred to about 30 000, received by single neurones of distinct types.

The cell type specific adaptations to local processing needs have made the definition of the basic cortical processing circuit and the definition of specific roles for particular synaptic links a daunting task. Nevertheless, although the subclasses of neurone reflect distinct synaptic connections, some basic rules of synaptic connectivity that are a hallmark of the cerebral cortex can be delineated. We consider the salient features to be the following:

1. The cerebral cortex consists of: (i) a large population of output (principal) neurones reciprocally connected to the thalamus and to each other via axon collaterals releasing excitatory amino acids, and, (ii) a smaller population of mainly local circuit GABAergic neurones.
2. Differential reciprocal connections are also formed amongst GABAergic neurones.
3. All extrinsic and intracortical glutamatergic pathways terminate on both the principal and the GABAergic neurones, differentially weighted according to the pathway.
4. Synapses of multiple sets of glutamatergic and GABAergic afferents subdivide the surface of cortical neurones and are often co-aligned on the dendritic domain.
5. A unique feature is the GABAergic *axo-axonic cell* influencing principal cells through $GABA_A$ receptors at synapses located exclusively on the axon initial segment.

Below, we will examine these characteristics from high resolution studies of synaptic organisation in both the isocortex (for definition see [48]) and the hippocampal cortex. The latter has been particularly useful in revealing basic principles, due to the arrangement of the cell bodies of principal cells into a single layer, resulting in the spatial co-alignment of functionally equivalent parts of neurones. In the isocortex the cells are radially scattered, and functionally non-equivalent parts of neurones, such as distal and proximal dendrites from different types of cells, are next to one another. Furthermore, the basic cortical circuit is superimposed in the same space several times, therefore it is much more difficult to decipher from the distribution of neuronal processes which axonal and dendritic populations form synaptic relationships. Before examining the salient rules of cortical connectivity a delineation of the synapse is needed. Since the analysis of cortical connections is often still limited to the anatomically defined synapse, as revealed by electron microscopy, it is worth investigating briefly how the synapse can be defined in those molecular terms that are most relevant to its function.

2. Molecular dissection of cortical synapses

Sherrington [103] used the term synapse to express the functional effect of the axon of one neurone on the dendrites of another, but the precise membrane area responsible for this effect is not well defined. With the electron microscopic identification of membrane specialisations in the presynaptic terminal and the postsynaptic dendrite the synapse came to be considered equivalent to the area of membrane specialisation [94].

For the presynaptic terminal, the site of vesicle accumulation at the presynaptic grid is a good indicator of the

transmitter release site. The calcium channels mediating calcium entry that leads to vesicle fusion are thought to be located in the presynaptic grid [44], but it remains to be established whether they are evenly distributed in the disc of presynaptic membrane specialisation. If some sites in the grid have a higher density of channels, or channels with higher probability of opening, then these sites may provide an increased probability of vesicle fusion and transmitter release, restricting the number of quanta released by an action potential.

The molecular constituents of the plasma membrane involved in vesicle fusion [18] have not been localised at

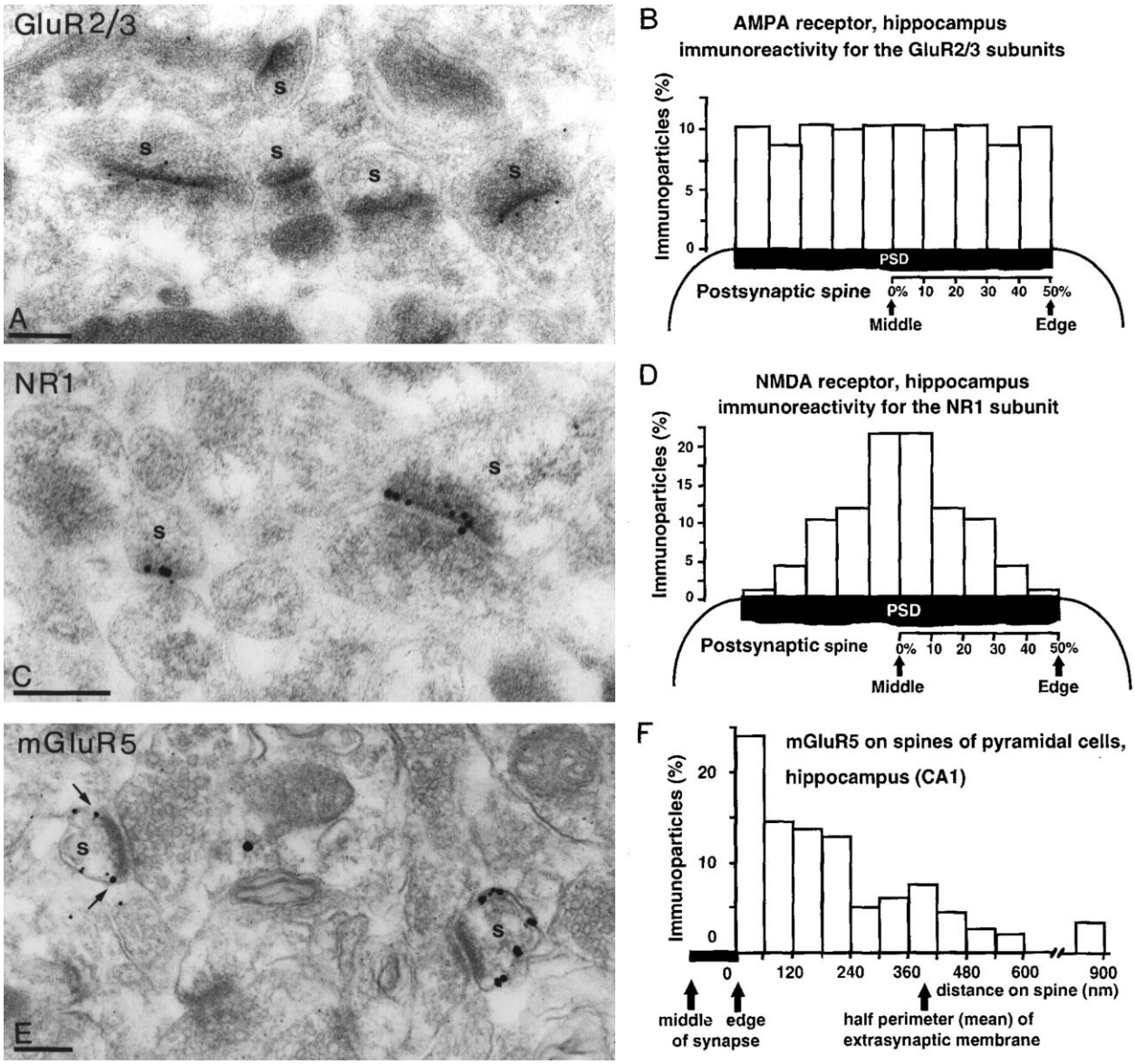


Fig. 1. Differential distribution of three types of glutamate receptor at synapses on dendritic spines (s) in stratum radiatum of the CA1 hippocampal area. Presynaptic terminals most likely originate from CA3 pyramidal cells and postsynaptic spines form CA1 pyramidal cells. (A and B) Electron micrograph (A, postembedding immunogold reaction, 10 nm particles) and quantitative distribution of immunoparticles for the AMPA type glutamate receptor over a large population of spines (R. Lujan and P. Somogyi, unpublished results). In (A), only two of the five spines show immunoreactivity, although all synaptic membranes were equally exposed to the antibody. The differential labelling demonstrates the heterogeneity of spines with regard to synaptic AMPA receptor content. (C and D) The NMDA type glutamate receptor is also enriched over the postsynaptic density (NR1 subunit, postembedding, silver intensified 1.4 nm immunogold reaction, R. Lujan, R.A.J. McIlhinney and P. Somogyi, unpublished), but due to its predominance in the centre of the synaptic membrane specialisation on small spines (to the left) its distribution on a large population of spines as shown in (B) is different from the AMPA type receptors. (E and F) Immunoreactive metabotropic GluR type 5 is mostly located at the *extrasynaptic* membrane of 2 spines (s), one of which also has *perisynaptic* (arrows) immunolabelling (pre-embedding silver intensified immunogold labelling). Quantitative evaluation (F) of immunoparticles shows an annulus of high concentration of mGluR5 next to the edge of the synaptic specialisation (thick line). Note the decrease of receptor density with increasing distance from the synaptic junction. Data based on Baude et al. [5]; Lujan et al. [70] and unpublished quantitative results. Individual spines may only contain some of the receptor species. Scale bars: 0.2 μm.

high resolution. A knowledge of the precise distribution of the fusion machinery in the presynaptic membrane specialisation would allow us to predict whether release can take place at any site in a conventional central synapse, as generally assumed, or if it is restricted to one site as proposed for some specialised synapses [148]. A restriction to, or increased probability of release at one or few sites per synapse could explain the one vesicle hypothesis of transmitter release at central synapses [59].

Due to the introduction of a high resolution immunocytochemical method [6] more information is emerging about the precise distribution of the postsynaptic receptors that mediate the effect of the two main fast cortical transmitters, GABA and glutamate. The postembedding immunogold localisation of receptors revealed that ionotropic AMPA and NMDA type glutamate (Fig. 1) as well as $GABA_A$ receptors (Fig. 2) are highly enriched in the electron microscopically defined postsynaptic membrane specialisation in hippocampal [5,90,91,118] and isocortical [50] synapses. This gives us some confidence to expect that, when connections between neurones are revealed solely on the basis of the synaptic membrane specialisation, then it is likely to be a place of functional interaction. However, in this respect the GABAergic and glutamatergic synapses appear to be different. Whereas most, if not all, GABAergic synapses contain $GABA_A$ receptors [90,91,118] a significant proportion of glutamatergic synapses in the hippocampal CA3 to CA1 pyramidal cell connection could not be shown by immunocytochemistry to contain AMPA type glutamate receptors ([5] and unpublished results, see Fig. 1). These results were obtained under conditions when neighbouring synapses in the same pathway could be shown to contain a high level of AMPA receptor. Therefore, in glutamatergic cortical connections either there are functionally distinct classes of synapses or there may be a wide range in postsynaptic effects, depending on the presence and amount of receptors. Functional studies *in vitro* in developing hippocampus revealed that some synapses in the same pathway may only contain the NMDA type receptor [45,61,65] that can be activated at depolarised membrane potentials. This suggests that the postsynaptic effect of glutamate released even by the same axon can be different according to the postsynaptic receptor composition and the state of the postsynaptic cell.

Recent observations suggest that if we retain the Sherringtonean concept of the synapse, then the membrane area involved in producing the postsynaptic effect has to be expanded beyond the electron microscopically defined

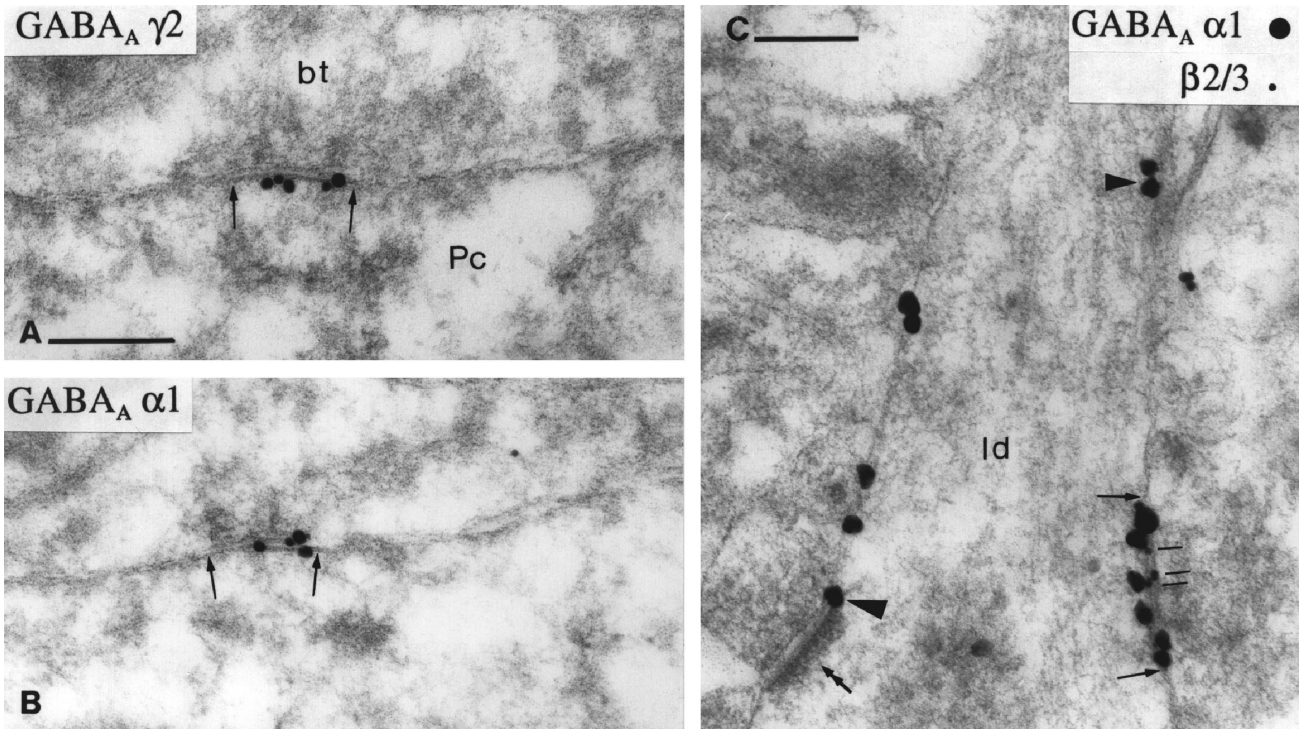


Fig. 2. Concentration of $GABA_A$ receptor subunits in the anatomically defined synaptic junctions (between arrows) in the hippocampal CA1 area. (A and B) A presumed basket cell terminal (bt) makes a synapse containing both the γ2 and α1 subunits, as seen in serial sections of a pyramidal cell body (Pc). (C) An interneurone dendrite (Id) receives a type II synapse containing a high density of both the α1 (large particles) and β2/3 (small particles, bars) subunits. A type I synaptic junction (double arrow) is immunonegative, but note the additional extrasynaptic receptor immunolabelling for the α1 subunit (e.g. triangles) which can occur just outside the synaptic membrane specialisation (lower triangle) of synapses that are unlikely to receive GABA from the terminal giving rise to the type I synapse. Silver intensified postembedding immunoreaction using 1.4 nm gold label, except for the α1 subunit in C (10 nm gold label). Serial sections, same magnification. Data based on Somogyi et al., [118]. Scale bars, 0.2 μm.

membrane specialisation, for the following reasons: (i) First, significant pools of ionotropic AMPA type and $GABA_A$ receptors have been detected outside the synaptic membrane specialisation [5,6,90]. Physiological studies also demonstrated fully functional AMPA, NMDA and $GABA_A$ receptors in the extrasynaptic membrane (Fig. 2C). Although the role of the extrasynaptic receptor pools is not known, it has been suggested for $GABA_A$ receptors that extrasynaptic receptors may contribute to synaptic responses, particularly at high frequency of presynaptic transmitter release [112], and recently tonic inhibitory currents have been demonstrated in cerebellar granule cells that have a particularly high density of extrasynaptic $GABA_A$ receptor [149]. (ii) Second, the G protein coupled metabotropic glutamate receptors have been shown to be outside the postsynaptic membrane specialisation [6,70,71,89]. Nevertheless, most of these receptors show the highest concentration in an annulus around the postsynaptic density (Fig. 1), followed by a cell type and synapse specific gradual decrease in density as a function of distance from the synapse [70,71], and therefore must be considered synaptic in a functional sense. The extent of their activation probably depends on the amount of transmitter released, which in turn reflects presynaptic release frequency. (iii) Finally, the postsynaptic response is strongly influenced by the activation or inactivation of voltage-gated ion channels in the somato-dendritic domain [46,152]. The precise location of voltage-gated ion channels that are influenced by the effects of postsynaptic receptors is not yet known, but high resolution immunolocalisation will be important to define their membrane location relative to transmitter release sites and neurotransmitter receptors.

As more quantitative information becomes available about the molecular mosaic of the postsynaptic membrane it will be possible to define the synapse in terms of the relative amount and location of the molecules involved in the effect of transmitters. Membrane areas outside the postsynaptic membrane specialisation will have to be included in a comprehensive definition of the synapse.

The presence of a presynaptic terminal storing transmitter and having a membrane specialisation and postsynaptic receptors provides an opportunity for synaptic transmission, but whether it actually takes place following the arrival of an action potential depends on the probability of transmitter release which varies from connection to connection and is highly modifiable. The probability of release is influenced by presynaptic auto- and heteroreceptors which appear to have distinct and well defined locations along the preterminal axons. The most precise information is available for the presynaptic metabotropic glutamate receptors which, depending on their pharmacological class, are either restricted to the presynaptic grid [105], the site of vesicle fusion and transmitter release, or are excluded from the release site and are distributed along the extrasynaptic terminal and axon [71,104].

3. Strength and some dynamic properties of cortical synaptic connections

In addition to the neurotransmitter mechanism, out of the many factors influencing the properties of synaptic connections between two neurones, the number and location of synaptic transmitter release sites were amongst the first recognised [24]. In the cortical network where usually connections of a large number of different cell classes overlap in space, the intuitive classification of cell types on the basis of the difference in their inputs, as reflected in the pattern of their dendrites, and outputs, as reflected in the patterns of their axons, has also proven useful. Through the combination of the direct light and electron microscopic analysis of the same visualised cells it became possible to define the cell classes and connections in quantitative synaptic terms [25,110,111]. However, to follow up the quantitative anatomical differences in synaptic connectivity with physiological analysis of the same connections has proved a great challenge and has only been gathering momentum in the last few years. To study the dynamic characteristics, location and extent of synaptic connections, it is necessary to record the activity of both the pre- and postsynaptic neurones together with the visualisation of the sites of interactions. This is most easily achieved by simultaneous recording in vitro followed by electron microscopic determination of synaptic sites mediating the recorded effects. In the following analysis we will consider how the five principles of cortical synaptic organisation are implemented in the connections of the two major classes of cortical neurones.

3.1. Thalamo-cortical reciprocal connections

The reciprocal excitatory connection with the thalamus is a salient feature of the cerebral cortex, but, due to limitations of space, is only dealt with briefly here. Different types of cortical cell receive a different proportion of their synapses directly from the thalamus [150]. Apart from a few cells in the cat visual cortex [32] the extent of innervation of different cell types by a single thalamocortical axon is not known. In the cat, many cells appeared to receive a single synaptic bouton from one axon. The maximal number of synapses was 7 on the basal dendrites of a large pyramidal neurone at the border of layers 3 and 4. Interestingly, all the synapses were on basal dendrites very close to the soma, suggesting small variability in efficacy and little electrotonic attenuation. Large GABAergic neurones received multiple synapses on their soma as well as on their dendrites [30,32,123,150], again suggesting powerful activation by one or a few thalamic axons. The high efficacy of thalamic inputs to many monosynaptically innervated cells is supported by the reliability of synaptic transmission from presumed thalamic axons to spiny stellate cells [126] whose dendrites are restricted to the main termination zone of thalamic inputs. Indeed, cross correlation analysis of the spike discharge of lateral genic-

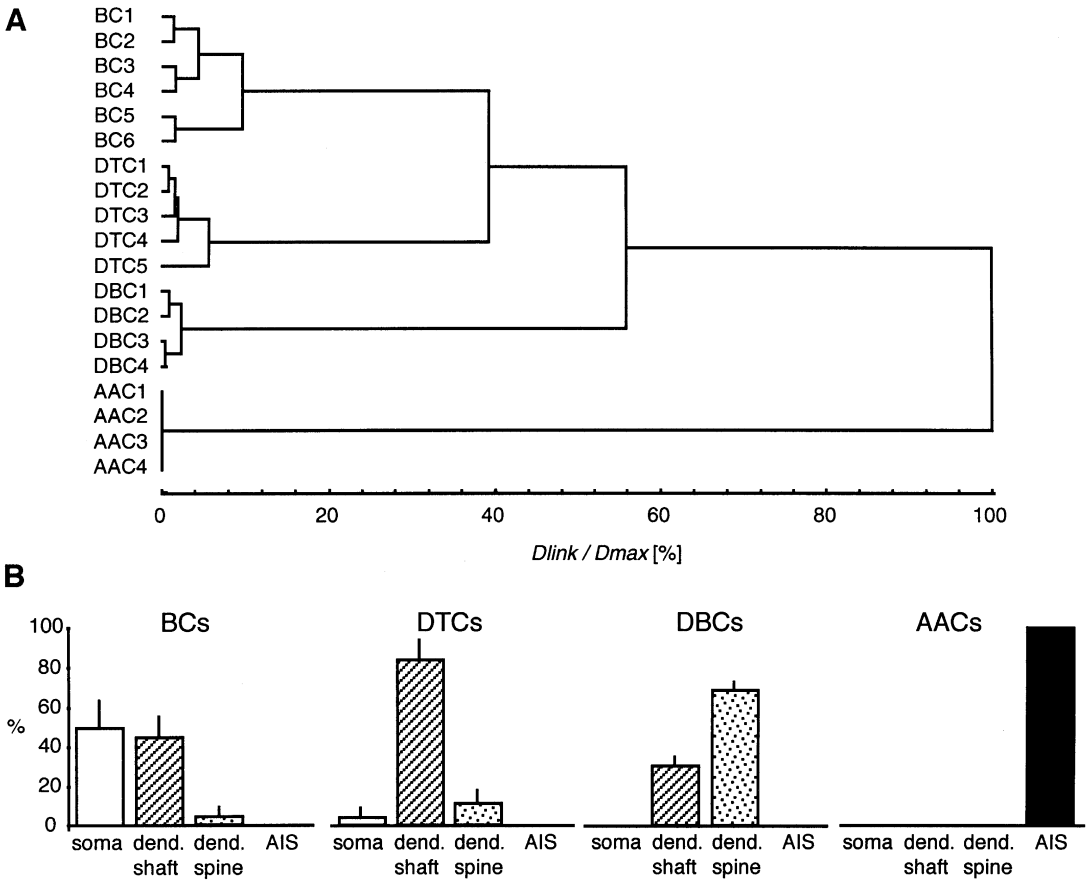


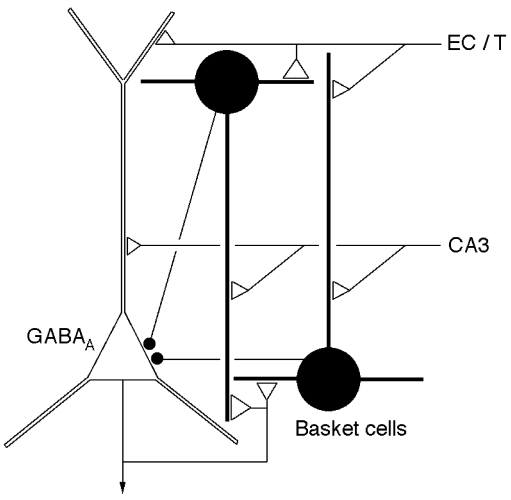
Fig. 3. (A and B) Classification of identified interneurones based on their postsynaptic targets (electron microscopic random samples) in the visual cortex of cat. (B) Interneurones were characterised on the basis of the distribution of their unlabelled postsynaptic targets, including somata, dendritic shafts, dendritic spines and axon initial segments (AIS). Vertical bars denote S.D. Using cluster analysis, joining tree was calculated using Ward's method of amalgamation and Euclidean distances. Interneurones of the 4 clusters had somato-dendritic (basket cells, BC), dendritic (dendrite targeting cells, DTC), spine (double bouquet cells, DBC) and AIS (axo-axonic cells, AAC) synaptic target preference. *Dlink Dmax*: linking and maximal Euclidean distances. Data from Somogyi et al. [116], Freund et al. [31], Tamas et al. [132].

ulate and cortical cells indicated a strong influence of some thalamic neurones on monosynaptically activated cortical cells as well as a wide range of efficacy of different neurones during sensory stimulation [97,135]. The thalamic input to the middle layers and layer 6 of the cortex is closely matched by the local recurrent collaterals of layer 6 cortico-thalamic cells, which provide a numerically larger number of synapses than the direct thalamic input, but with very different physiological properties [126]. It is likely that both the thalamic and the other extrinsic inputs are differentially weighted according to the type of cortical cell.

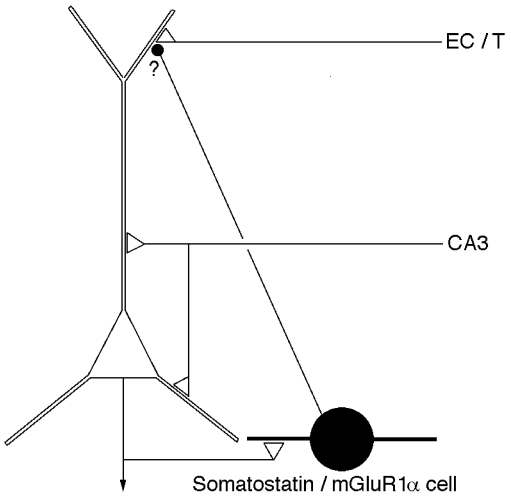
3.2. Local connections between cortical principal cells

Considering the intracortical connections, in physiological terms, a great deal is known about the connections

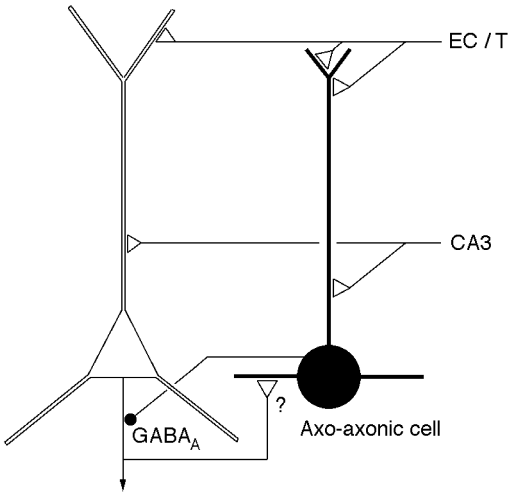
Fig. 4. Schematic diagram of the domain selective input–output relationship of GABAergic neurones (filled circles) with cortical pyramidal cells, as summarised from results obtained in the hippocampal CA1 area. Axonal and dendritic patterns predict unique input–output signatures for the 9 types of GABAergic cells. Basket, axo-axonic, bistratified and Schaffer collateral associated cells have been shown to act through $GABA_A$ receptors, the action of other cells remains to be tested pharmacologically ('?', at terminals). Excitatory amino acid releasing terminals are shown as empty triangles. Most dendritic GABAergic innervation is co-aligned either with the glutamatergic Schaffer collateral/commissural input from the CA3 area (bistratified cells), or (PP-associated cells) with the glutamatergic inputs from the entorhinal cortex (EC) and thalamus (T). Only neurogliaform cells appear to provide substantial innervation to both stratum radiatum and lacunosum-moleculare. Recurrent pyramidal cell input has been shown directly only to basket [14] and somatostatin/mGluR1α expressing cells [11]. Recurrent input to other cell classes having dendrites in the termination zone of pyramidal local axons may exist ('?', at open triangles). Dendritic domains of GABAergic cells cover one, two or three major excitatory input zones. One extrinsic input may provide *cross-influence* to the termination zone of another one by activating zone specific GABAergic output. In some cases, Schaffer collateral and entorhinal inputs to basal dendrites are not shown for clarity. Grouping of cells into feed-back, feed-forward and other categories according to their position in the circuit is arbitrary, since their functional position remains to be established under physiological activation. Scheme based on data from Buhl et al. [14], Halasy et al. [41], Somogyi et al. [122] and for stratum lacunosum-moleculare cells from Vida et al. [147].



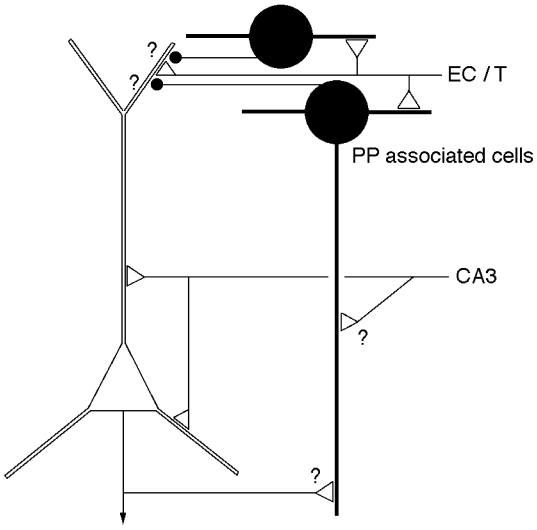
I. Integration control; feed-back+forward



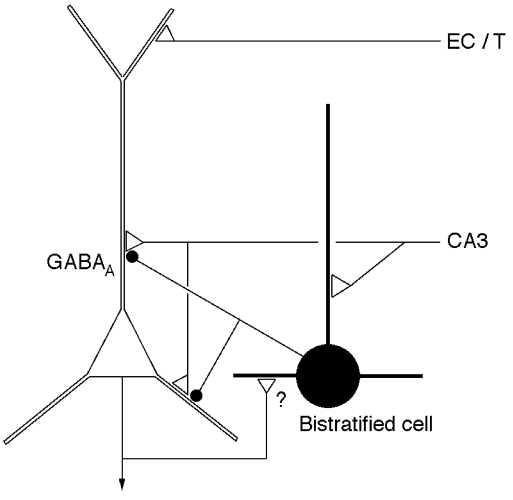
IV. Peripheral feedback only



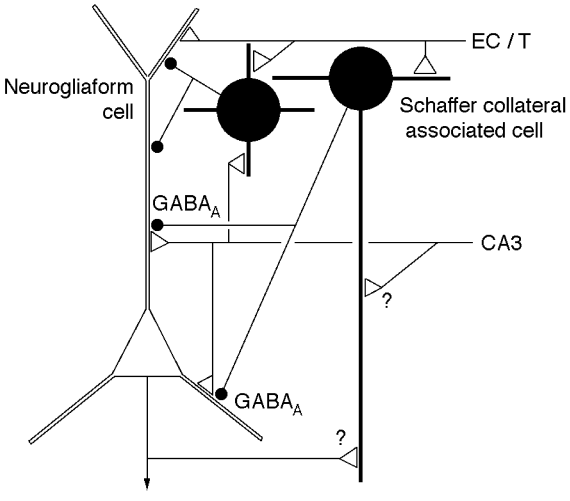
II. Output control; feed-back+forward



V. Feed-forward only. VIa. Cross-influence?



III. Peripheral feed-forward



VIb. Cross-influence

between different cortical areas, which are largely mediated by the long range glutamatergic pathways established by pyramidal cells. For example, the projection from the CA3 to the CA1 area of the hippocampus is the most studied cortico-cortical connection of the cortex, yet the axons mediating the connection have only recently been visualised [64] and the number and relative placement of unitary synapses on individual CA1 cells remains unknown. The study of the rules of single cortical neuronal connections is much easier in the local interactions, i.e. within the functionally and cytoarchitectonically defined cortical area. Not surprisingly, both in the hippocampus and the isocortex, most of the information on unitary synaptic interactions has been obtained between cells within a few hundred micrometers. Therefore, below we will focus on local interactions. However, the results on local connections cannot be extrapolated to the long range connections without direct investigation.

In addition to the inter-areal cortico-cortical connections, all principal cells, the pyramidal, spiny stellate and granule cells, also establish lamina specific local connections in the cortical area where the cell body is located [36,37,63,72,77,96,129]. The spatial extent of local connections ranges from within the dendritic tree of the parent cell to several millimetres, as in the patchy connections of the isocortex or the CA3 area of the hippocampus. Many synapses are established between nearby cells of the same type, e.g. CA1 pyramidal cells [140] or the large tufted layer 5 pyramids [75], whereas others connect to different principal cell populations either in the lamina of the parent cell (e.g. [23]) or more obviously in other cortical layers (e.g. the layer 3 to layer 5, and layer 6 to layer 4 projections). The latter connections form the rich interlaminar excitatory amino acid pathways, a hallmark of the isocortex (see [53,73]). As far as we are aware, only one principal cell population, the granule cells of the hippocampal dentate gyrus of rodents, is not interconnected in the normal cerebral cortex.

Quantitative electron microscopic examination of the synaptic targets of local pyramidal collaterals showed that they establish synapses mostly with dendritic spines and to a lesser extent the dendritic shafts of other principal neurones [23,33,58,75,79,80,111,112]. The proportion of spine as postsynaptic target varies from about 85% between layer 2/3 pyramidal cells [58,79] to about 30% in the layer 6 to layer 4 connection [80,112], and is likely to be dependent on the postsynaptic target cell type. In the hippocampal formation it is apparent that the local connections are restricted to only a certain portion of the dendritic domain so that CA1 pyramids mainly receive their local input on their basal dendrites and CA3 pyramids on dendrites in strata oriens and radiatum, but not on the portion of the dendritic tree in strata lucidum or lacunosum moleculare. In the isocortex, due to the superimposition of several circuits in the same tissue volume, only the accurate tracing of single cell connections can provide information about the possible compartmentalisation of local excitatory inputs. The available data, including both physiological and anatomical information, are limited to layer 5 pyramids [23,75]. The connections between layer 5 large pyramidal cells are mediated by up to eight potential synaptic junctions placed mainly on the basal dendrites and to a lesser extent on apical dendrites [23,33,75]. The potential number of connections between pyramidal cells in layers 2/3 was estimated to be up to 4 [55].

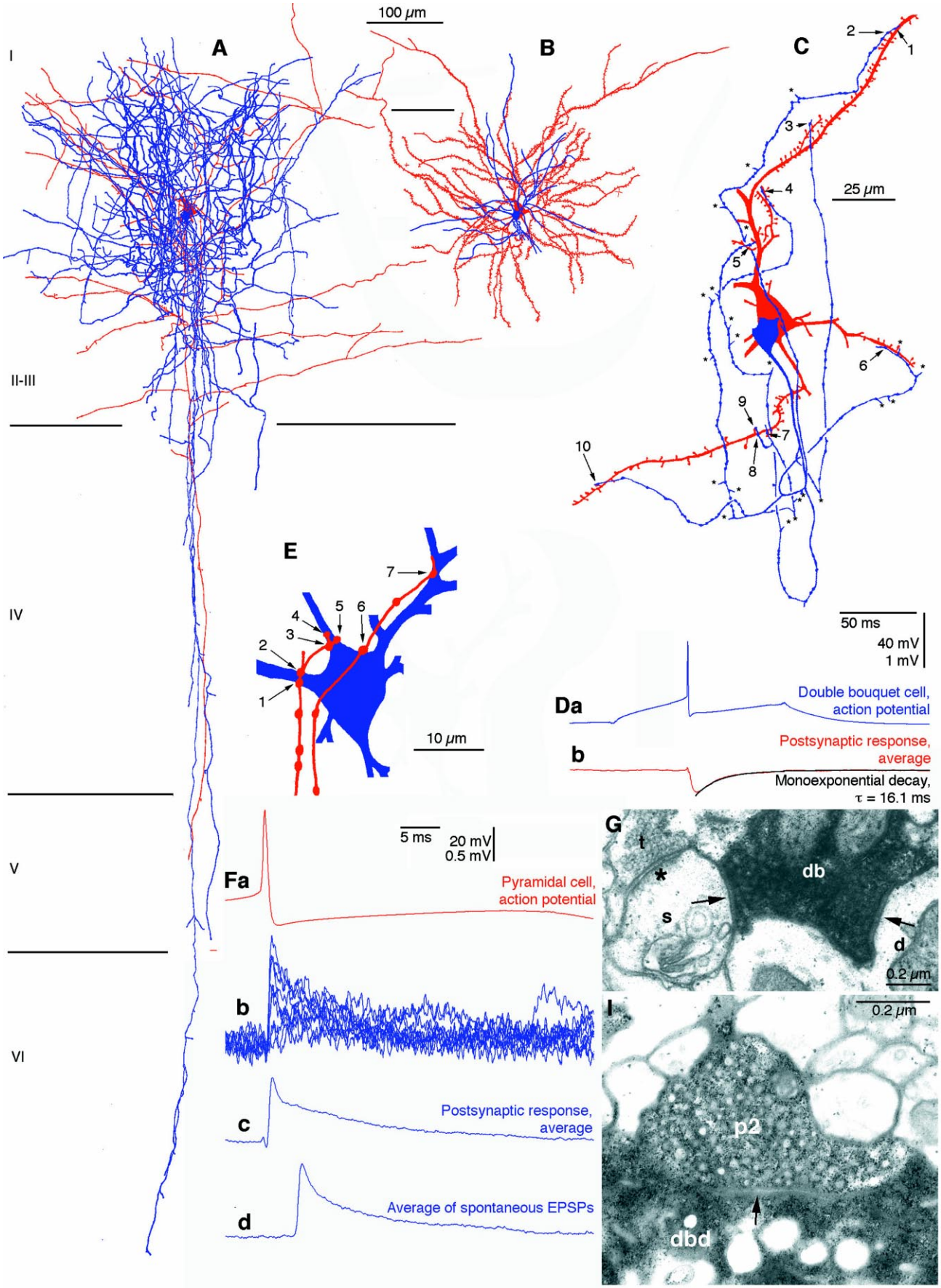
The local connections between pyramidal cells generally show a depression of EPSP amplitudes following repetitive presynaptic firing [75,76,85,136,137,141], but it is likely that the frequency-dependent modification of postsynaptic responses depends on the particular connection, since no change or facilitation has also been reported [126]. Similar to the long range cortico-cortical connections, the local pyramidal interconnections are mediated by both NMDA and AMPA type glutamate receptors [75,139]. The dynamic changes in frequency dependent depression may have fundamental importance for changing synaptic efficacy [76].

In summary, the mutual facilitatory interconnections of large populations of cells via excitatory amino acid releasing terminals are one of the salient features of the cortical network. The extent of these connections, both quantitatively and in the complexity of their selective distribution is unparalleled in the vertebrate nervous system.

3.3. Connections from principal cells to GABAergic cells

Quantitative electron microscopic examination of the synaptic targets of pyramidal collaterals showed that in

Fig. 5. Reciprocal connections and synaptic effects of a pyramidal cell and a double bouquet cell in the visual cortex of cat. (A and B) Axonal (A) and dendritic (B) arborizations of the biocytin labelled double bouquet cell (blue) and the pyramidal cell (red) reconstructed following intracellular recording in vitro. (C) Location of 10 double bouquet cell synapses on the pyramidal cell as identified by electron microscopy. Six synapses were on dendritic spines (2, 3, 5, 7, 9, 10) and four on dendritic shafts (1, 4, 6, 8) at locations relatively distal to the soma. Axonal branch points are labelled by asterisks. (D) Action potentials ($\sim$ 2 Hz) of the double bouquet cell evoked by current injection (a, average) resulted in a short-latency, fast-rising IPSP, with an average amplitude of -0.44 ± 0.23 mV in the postsynaptic pyramidal cell which was held at -48 mV membrane potential (b, average of 273 sweeps). (E) Two collaterals of the pyramidal axon (red) made 7 synapses distributed in 4 groups on (No. 6) or very close to the soma of the DBC. (F) Averaged pyramidal cell action potential (a) and superimposed successive postsynaptic responses (b, MP, -64 mV) in the DBC, indicating a large degree of amplitude variability. Both the averaged identified pyramidal EPSP (c) and the average of spontaneous EPSPs had similar fast rise time and complex decay kinetics. (G) Electron micrograph of a double bouquet cell bouton (db) making type II synapses (arrows) with a dendritic shaft (d) and a spine (s), the latter also receiving a type 1 synapse (asterisk) from an unidentified terminal (t). (I) Electron micrograph of a pyramidal bouton (p2 in I) making a synapse (arrow) on the proximal dendrite (dbd) of the DBC. Data from Buhl et al. [16], Tamas et al. [132]. Scale bars: 0.2 μm.

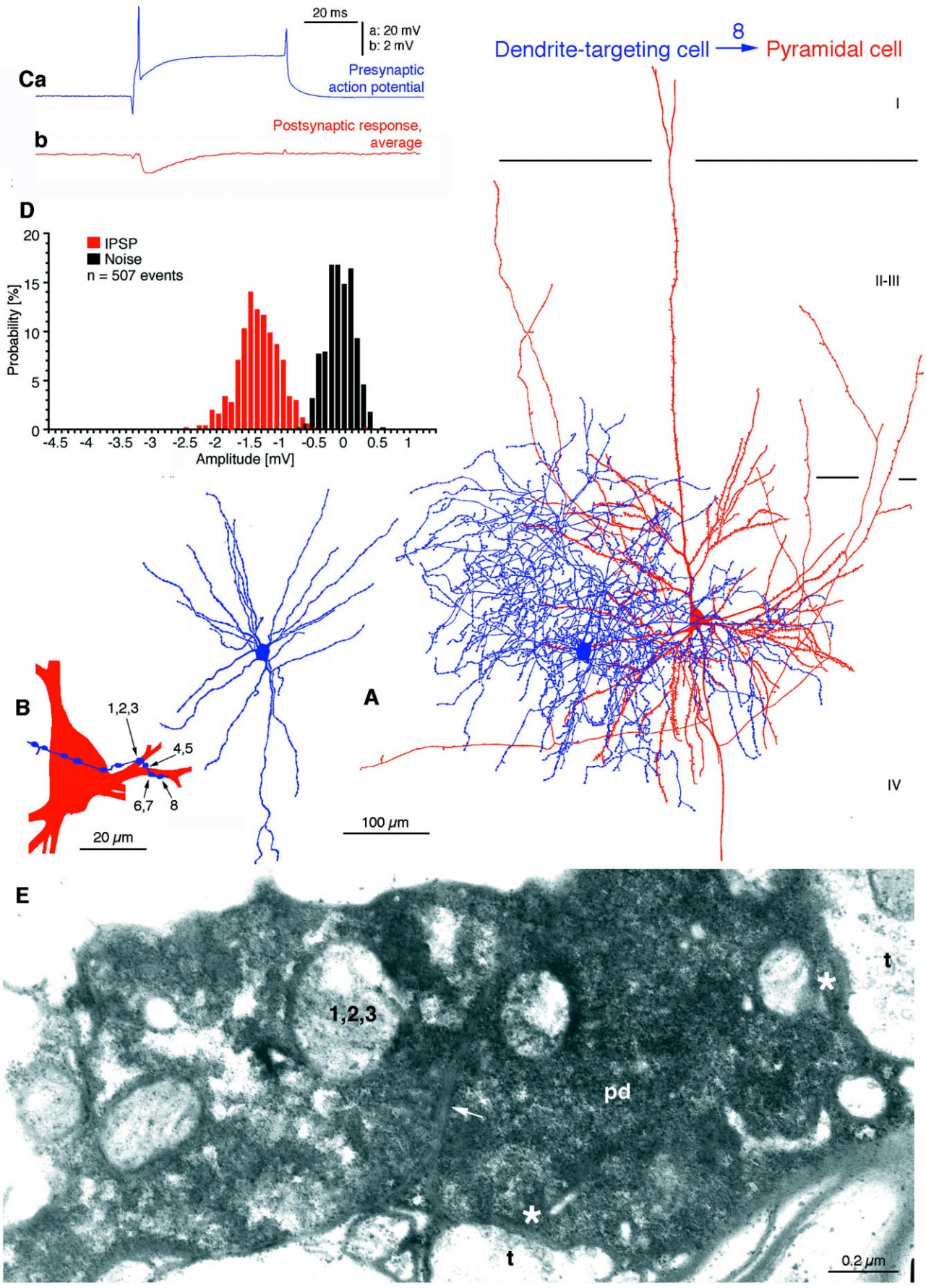

I
II-III
IV
V
VI
A
B
C
100 μm
25 μm
2
1
3
4
5
6
9
7
8
10
E
7
5
6
4
3
2
1
10 μm
50 ms
40 mV
1 mV
Da
Double bouquet cell, action potential
b
Postsynaptic response, average
Monoexponential decay, τ = 16.1 ms
5 ms
20 mV
0.5 mV
Fa
Pyramidal cell, action potential
b
c
Postsynaptic response, average
d
Average of spontaneous EPSPs
G
t
*
s
db
d
0.2 μm
I
0.2 μm
p2
dbd

addition to synapses on other spiny principal neurones, in accordance with the second rule of synaptic organisation, they also innervate GABAergic cells [58,68,111,112,124]. The proportion of synapses targeting GABAergic cells, defined according to their output (Fig. 3) [132], depends on the pyramidal cell type. It is not yet clear whether all GABAergic cell types receive a recurrent local input, but the results from the hippocampus predict a differential innervation (Fig. 4). Since in the CA1 area and the dentate gyrus of the hippocampus the recurrent collaterals of principal cells are restricted to narrow zones, the distribution of interneurone dendrites preferring or avoiding these zones may be a good predictor of their recurrent activation. For example, the visualisation of the dendritic trees of the somatostatin/mGluR1α expressing cells by immunocytochemistry [6] or intracellular labelling [12,43,106,107] led to the prediction that they mainly receive recurrent input which was directly shown in the CA1 area [11,74]. In contrast, the restriction of some interneurone dendrites to the molecular layer, which is devoid of recurrent collaterals, shows that the so-called dentate MOPP cells [43] and their equivalent perforant path-associated cells in the hippocampus proper [147] do not receive local principal cell input, but are exclusively activated by the extrinsic cortico-cortical connections in a feed-forward manner (Fig. 4). Recent in vitro studies in the hippocampus confirmed previously predicted [3] recurrent principal cell input to basket cells [14,35,39] and also revealed the innervation of putative somatostatin/mGluR1α expressing interneurones [39]. A similar approach demonstrated recurrent activation of basket, dendrite targeting, double bouquet (Fig. 4) and sparsely spiny bitufted cells in the isocortex [16,21,143]. The latter probably correspond to the somatostatin/mGluR1α expressing cells of the hippocampus. The recurrent inputs are mediated by 1–7 synaptic junctions (Fig. 5.), probably depending on the postsynaptic cell type and the cortical area.

In the visual cortex [16] unitary EPSPs from pyramidal cells to three distinct types of GABAergic cells were relatively small ($\sim$ 1 mV), fast rising (10–90%; 0.67 ± 0.25 ms) and were of short duration (at half-amplitude 4.7 ± 1.0 ms) at an average membrane potential of -67.6 ± 6.9 mV (Fig. 5). All connections showed considerable amplitude fluctuation at low frequency presynaptic firing (Fig. 5F). Quantal analysis, using a model with quantal variance, predicted quantal sizes between 260 and 657 μV. For three pyramid to basket cell connections, in accordance with the univesicular hypothesis [59], the number of quantal components coincided with the number of electron microscopically determined synaptic junctions (1, 2 and 2), but for both a dendrite targeting cell and a double bouquet cell (Fig. 5) the number of quantal components ($n = 4$) was fewer than the number of synaptic junctions (5 and 7). Interestingly, in the latter connections the synaptic contacts clustered in the same number of groups as the quantal components, each group converging on one dendritic segment or the soma. It is possible that each *group* of release sites contributed one quantum and that closely spaced release sites do not operate independently. Alternatively, the apparent quantal size reflects the synaptic activation of a dendritic segment. The EPSP amplitude fluctuations in two of the four connections that had more than one release site, could be adequately described by a uniform binomial model of transmitter release. The apparent failure rate was relatively low for all connections, ranging from 0.02 to 0.12, suggesting that at these connections transmission occurs with high reliability. The release probability for the individual sites, as calculated from a binomial model, ranged from 0.42 to 0.94. For basket cells receiving 1–2 synapses, using a uniform binomial model for transmitter release, the estimated junctional release probability exceeded 0.7.

Depression [16], facilitation [136,138,142] or a lack of change has been reported in unitary paired-pulse responses of pyramid to interneurone connections, and it is highly likely that the frequency dependent modification of postsynaptic responses is strongly influenced by the postsynaptic GABAergic cell type [2,16,98]. The relationship between presynaptic action potential frequency and postsynaptic responses depends on many factors, such as the dynamics of presynaptic calcium sequestration and the state of presynaptic receptors. One of the presynaptic metabotropic glutamate receptors, mGluR7, has been shown to be restricted to the presynaptic active zone of pyramidal and dentate granule cell terminals [105], and therefore could serve as an autoreceptor. This receptor is distributed highly selectively amongst terminals of the same axon; mGluR7 is expressed at a much higher level in the terminals that innervate the somatostatin/mGluR1α expressing cells than in those terminals that innervate principal cells or other GABAergic neurones [105]. Since group III mGluRs depress presynaptic calcium channels

Fig. 6. Synaptic effect of a dendrite-targeting cell (blue) and location of its synapses on a pyramidal cell (red) in area 18 of the cat visual cortex. (A) Dendritic (left) and axonal (right) arborization of the DTC and the pyramidal cell in layer IV. The axon of the DTC overlaps with a large volume of the somato-dendritic domain of the pyramid. (B) All 8 electron microscopically verified synaptic junctions formed by 4 boutons are located around the branch point of a single basal dendrite. Some boutons made 2 or 3 separate synaptic junctions (numbers linked by commata). (C) Action potentials ($\sim$ 1 Hz) of the dendrite-targeting cell (a, average), evoked by a depolarising current pulse, resulted in a short-latency, fast IPSP with an average amplitude of -1.23 ± 0.32 mV in the postsynaptic pyramidal cell held at -51 mV membrane potential (b). (D) The non-overlapping amplitude distributions of IPSPs (red) and baseline noise (black) demonstrate a highly reliable transmission. (E) Electron micrograph of a large DTC bouton (1, 2, 3, as in B) making a type II synapse (arrow) with the dendritic shaft (pd) of the pyramidal cell, which also receives 2 additional synapses (asterisks) form unlabelled terminals (t). Data from Tamas et al. [132]. Scale bar: 0.2 μm.


20 ms
a: 20 mV
b: 2 mV
Ca
Presynaptic action potential
b
Postsynaptic response, average
D
IPSP
Noise
n = 507 events
Probability [%]
Amplitude [mV]
Dendrite-targeting cell
8
Pyramidal cell
I
II-III
IV
A
B
1,2,3
4,5
6,7
8
20 μm
100 μm
E
1,2,3
pd
t
t
0.2 μm

[131] it was suggested that their selective high level expression at certain synapses allows a single axon to regulate release probability and summation properties at different release sites independently, according to the postsynaptic cell type [105]. In addition to mGluR7, other group III presynaptic mGluRs are also expressed in the presynaptic active zone, in a postsynaptic cell type specific manner in the cortex [104]. The functional properties of the cortical synapses with high levels of group III mGluR are not known, but the role of the receptor would depend on the degree and time course of its activation. If they are not activated at resting conditions and their activation is relatively fast, then release of transmitter by the first action potential would decrease the probability of release by subsequent action potentials as originally suggested [105]. However, if they are tonically activated, as has been suggested at cerebellar synapses for mGluR4 [93], then several action potentials may be necessary to overcome the depression of calcium channels, leading to facilitation of postsynaptic responses by consecutive action potentials. A preliminary report in the hippocampus suggests that cells, which could correspond to the somatostatin/mGluR1α expressing interneurones, decorated by strongly mGluR7 expressing terminals, show strong paired-pulse facilitation [2], and would be activated strongly at a high presynaptic firing rate.

Why do the somatostatin/mGluR1α expressing interneurones need such a specific regulation of presynaptic summation properties? The clue may lie in the pairing of their GABA releasing terminals with one of the cortico-cortical inputs in the hippocampus, the entorhinal glutamatergic pathway to the distal dendrites of principal cells, and several proposals have been put forward [11,74]. Our extension of one of the proposals [11] takes into account the possible tonic depression by mGluR7 (see above) of the recurrent principal cell synapses at low frequency firing of principal cells during exploratory behaviour associated with theta rhythm. Under such conditions these interneurones would not be strongly activated. Only the coincident high frequency firing of several converging pyramidal cells would discharge these cells and result in the release of GABA to the termination zone of the entorhinal pathway (see Fig. 4). Such activity occurs during behavioural rest and is observed as field potential sharp waves [17,28], thought to represent a mechanism for the consolidation of the selective enhancement of synaptic strength. Thus, the primary role of the selectively high concentration of presynaptic mGluR7 that depresses transmitter release is to assist the preference of high frequency, coincident presynaptic inputs for the activation of this GABAergic cell type. If these interneurones are activated during sharp waves, the GABA-mediated depression of entorhinal influence to distal dendrites [74,106] would ensure that the strong activation of synapses receiving glutamate from intrahippocampal terminals is not associated with the strong activation of entorhinal synapses through the reverberating feedback projection from the entorhinal cortex. Hence, somatostatin/mGluR1α expressing interneurones are likely to provide one circuit that allows the independent regulation of synaptic strength at two main glutamatergic synapses, the entorhinal and intrahippocampal inputs, segregated to distinct dendritic segments on the same hippocampal principal cells [74].

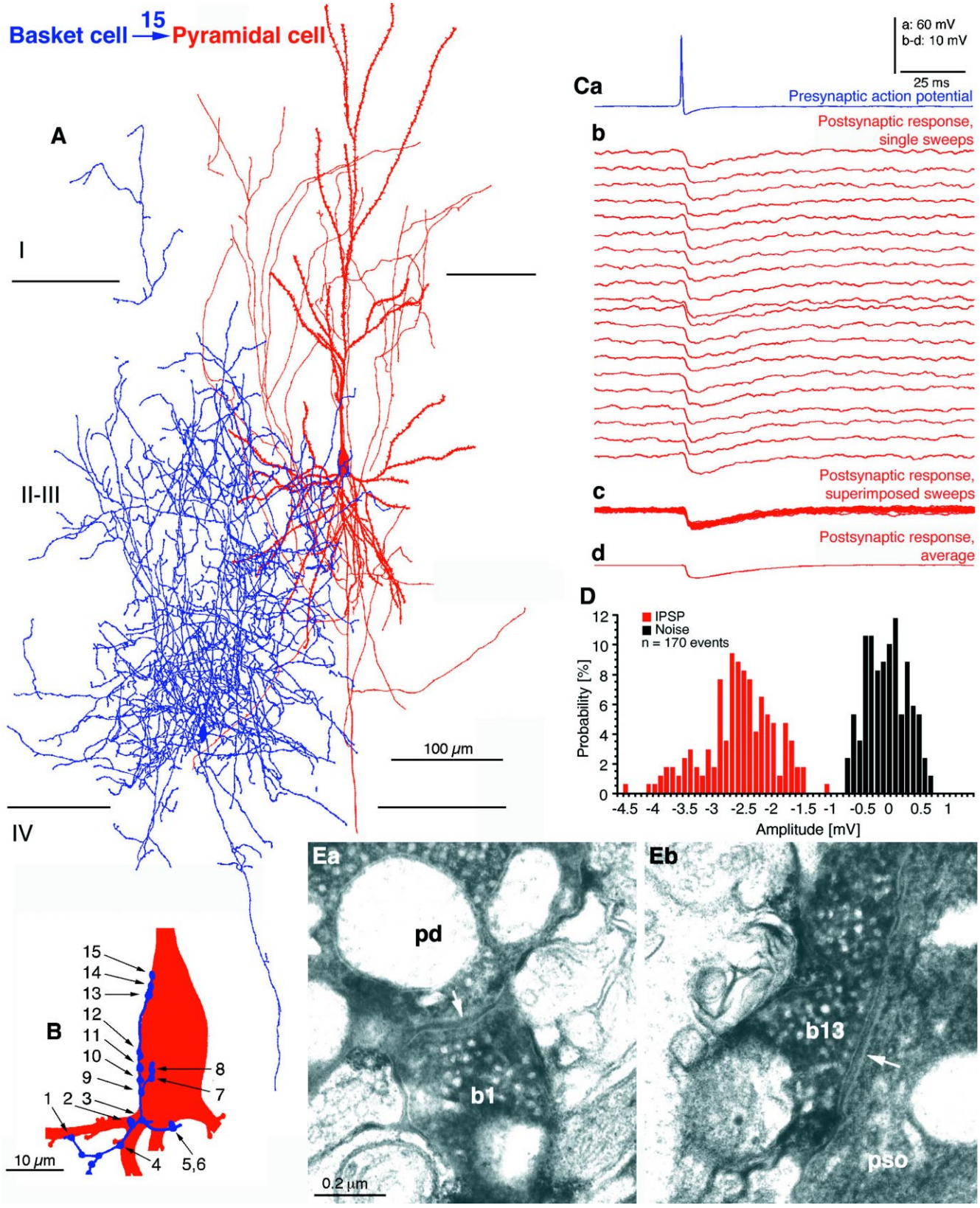
The characteristics of the pyramid connections to other types of GABAergic neurones also suggest that in most cortical areas many inputs are necessary to bring the interneurone to threshold, and the fast kinetics of the EPSCs and EPSPs narrow the window for temporal summation, thus favouring coincident inputs for the activation of cells [16,21,22,35]. Just as for principal cells (see below), conjoint GABAergic inputs to the same dendritic domain which is innervated by the pyramidal cells, and autapses (see below), may further shorten the window for temporal integration, promoting coincidence detection. A different functional connectivity may exist in the CA3 area of the hippocampus, where single pyramidal cells can reliably bring GABAergic interneurones to threshold in vitro [83]. The very rich local, associational and commissural interconnections of these pyramidal cells [64] may have resulted in the development of strong and reliable inputs to some types of interneurones.

3.4. Connections from GABAergic cells to principal cells

Using Golgi impregnation, Ramon y Cajal [96], Lorente de No [67] and more recently Szentagothai [127–129] presented the striking differences in the axonal arborizations of smooth dendritic or sparsely spiny local circuit neurones which subsequently were shown to use GABA as transmitter. All smooth dendritic cells establish type II synapses made by terminals synthesizing or containing GABA [99,119], therefore these cells are very likely to be GABAergic. As most eloquently formulated by Szentagothai [127,129], the axonal patterns strongly predicted that distinct classes of GABAergic cells subdivide the

Fig. 7. Synaptic effect and sites of innervation of a pyramidal cell by a basket cell in area 18 of the cat's visual cortex. (A) Dendritic and axonal arborization of the postsynaptic pyramidal cell (red) and the presynaptic basket cell axon (blue, dendrites were not recovered). (B) Although the basket axon overlaps with a large part of the pyramidal basal dendritic tree, all 15 electron microscopically verified synaptic junctions are located on the soma or the most proximal basal dendrites. (C) Action potentials (~ 1 Hz) of the presynaptic basket cell (a) were followed by reliable short-latency, fast IPSPs (d, average amplitude -2.43 ± 0.60 mV) in the postsynaptic pyramidal cell (membrane potential held at -49 mV) as shown by twenty consecutive sweeps. (D) The unitary IPSP amplitude distribution demonstrates the absence of postsynaptic response failures. (E) Electron micrographs demonstrating synaptic junctions (arrows) between the basket cell terminals (b1, b13; numbering as in B) and the basal dendrite (pd) or soma (pso) of the pyramidal cell. Data from Tamas et al., [132]. Scale bar for both pictures: 0.2 μm.

somato-dendritic domain of principal cells. Indeed, the very first cell type examined quantitatively for synaptic targets, the chandelier cell discovered by Szentagothai [130] and also described by Jones [47], was shown to innervate only the axon initial segment of pyramidal cells [110] (Fig. 3). Consequently, Szentagothai in his review of



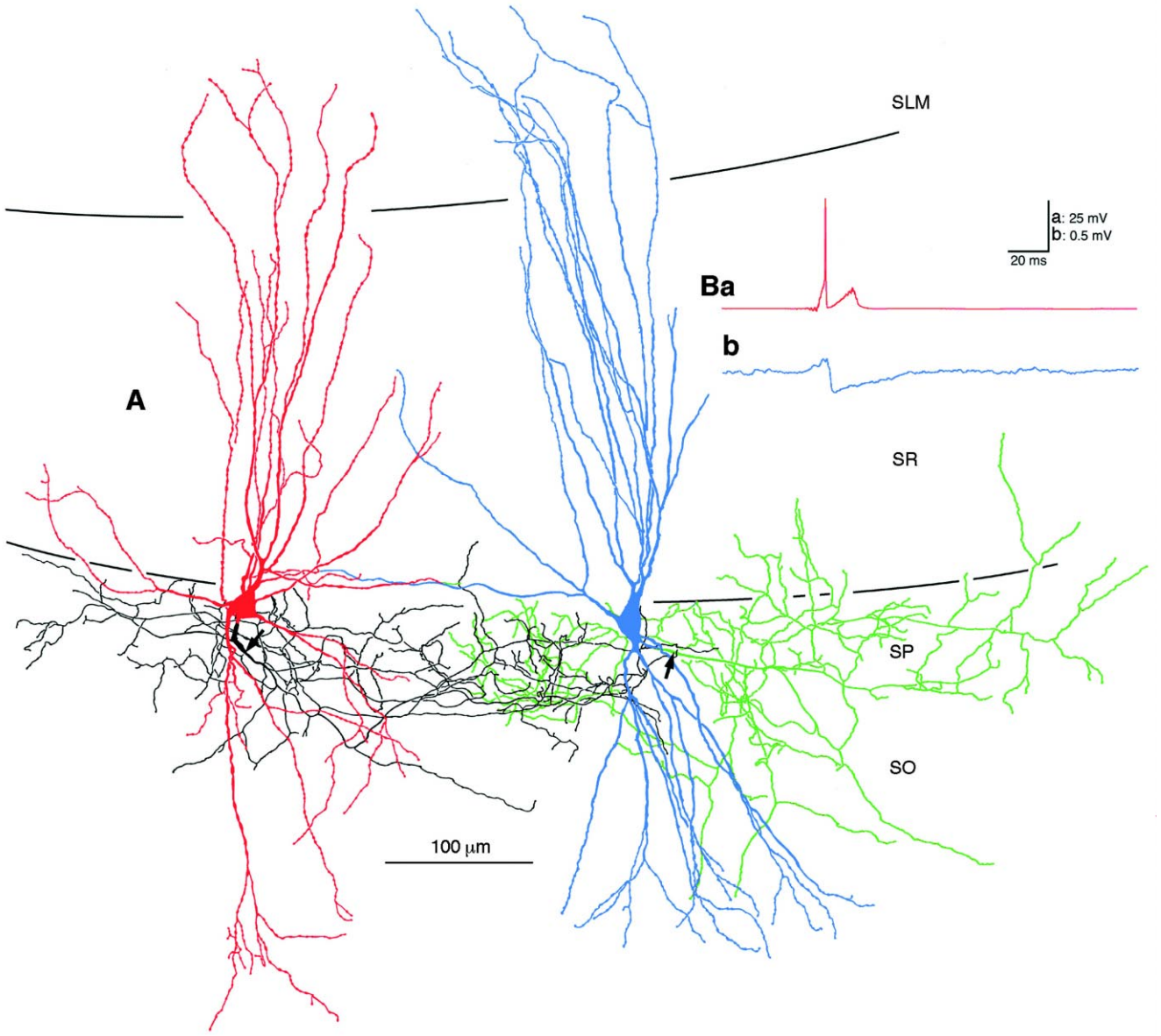
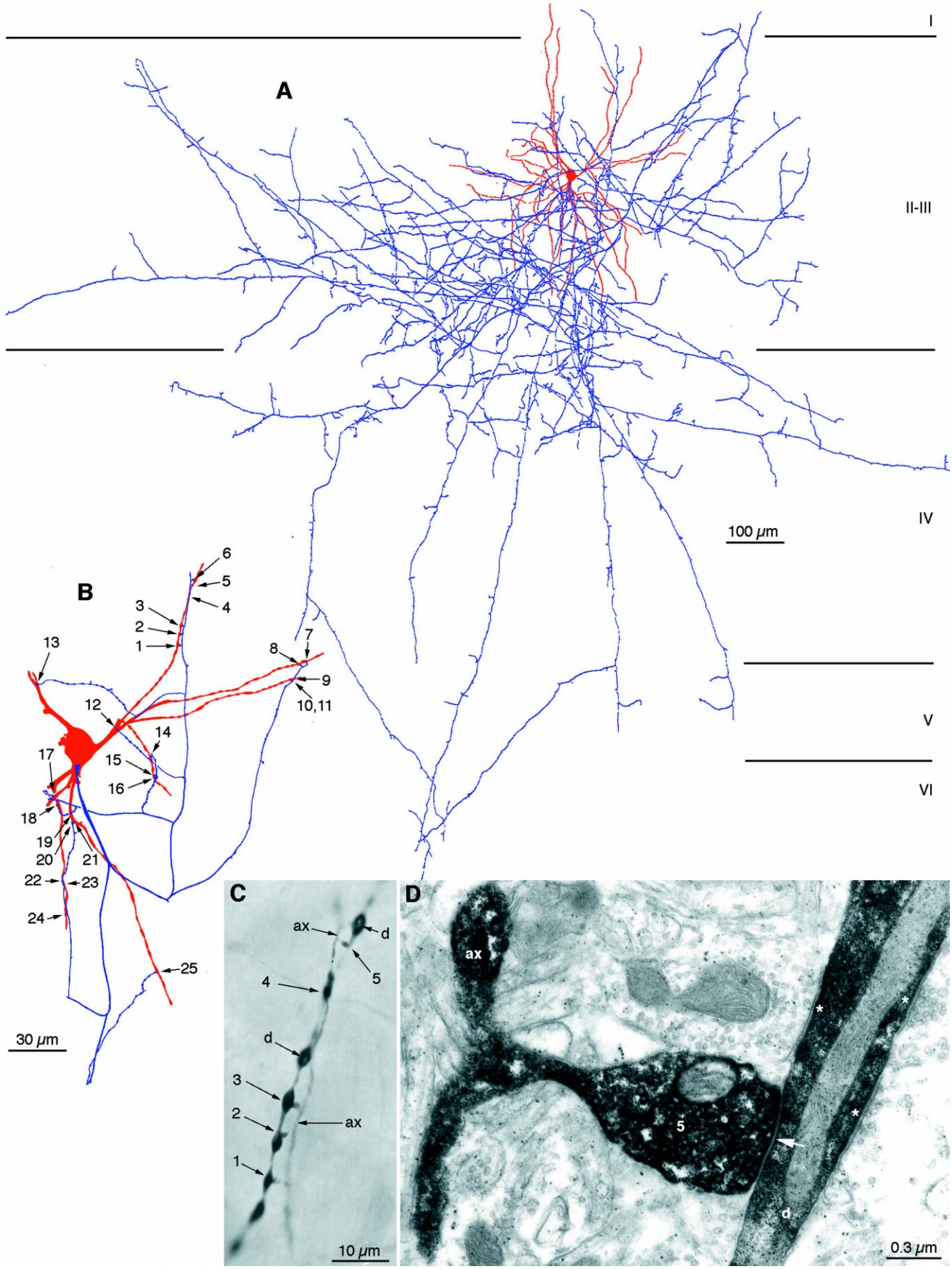


Fig. 8. Interconnection between two GABAergic cortical neurones, as demonstrated by the synaptic action of a basket cell on another basket cell in the CA1 area of the rat hippocampus. Both cells were recorded intracellularly in vitro and labelled with biocytin. Action potentials (Ba, average) in the presynaptic basket cell (dendrites in red, axon in black) evoked a short-latency fast hyperpolarizing IPSP (Bb) in the postsynaptic basket cell (dendrites in blue, axon in green, MP, −59 mV). Basket cells were identified by electron microscopic sampling of their postsynaptic targets. SLM, stratum lacunosum-moleculare; SR, str. radiatum; SP, str. pyramidale; SO, str. oriens. Data from Cobb et al. [20].

the manuscript renamed the cell as *axo-axonal interneurone* [110], becoming axo-axonic cell later [116,117,120,128]. The GABAergic axo-axonic cell is a unique defining feature of the basic cortical circuit, providing the same innervation of principal cells exclusively on their axons in the isocortex [110,116], the hippocampal

Fig. 9. Autaptic self-innervation of a dendrite-targeting cell visualised by intracellular biocytin labelling in area 18 of the cat's visual cortex in vitro. (A) Dendritic (red) and axonal (blue) arborization of the dendrite targeting cell. (B) Location of electron microscopically verified, exclusively dendritic autapses. The cell showed a synaptic target preference towards dendritic shafts (72.7%), and also innervated spines (27.3%) of pyramidal neurons. (C) Light micrograph of autaptic sites derived from a myelinated axonal branch (ax) giving 5 *en terminaux* boutons apposed to a beaded distal dendrite (d) of the parent cell. (D) Electron micrograph of autaptic bouton no. 5 emerging from the axonal trunk (ax) and forming a synapse (arrow) with the parent dendrite. Unlabelled terminals cover the dendrite with synapses (asterisks). Data from Tamas et al. [134]. Scale bars: C, 10 μm; D, 0.2 μm.


A
I
II-III
IV
V
VI
100 μm
B
1
2
3
4
5
6
7
8
9
10,11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
30 μm
C
ax
d
5
4
d
3
2
ax
1
10 μm
D
ax
5
d
0.3 μm

cortex [15,122] and amygdala [78]. Further studies confirmed the target selectivity of many types of GABAergic interneurones (Figs. 3–8), several of which can also be delineated on the basis of neurochemical markers [28,49]. In the isocortex, the distal to proximal progression of GABAergic innervation of pyramidal cells is exemplified by double bouquet cells (Fig. 5) innervating distal dendrites and spines [113,132], to dendrite targeting cells (Figs. 6 and 9.) innervating proximal dendrites [54,132] through basket cells (Figs. 7 and 8) innervating somata and proximal dendrites [47,96,114,121,130,134,143] to axo-axonic cells terminating on the axon initial segment where the action potential may be generated (Fig. 3). These connections are optimised for particular tasks, which are most efficiently executed on a given membrane domain of the postsynaptic cell. The optimisation of synapse placement is strikingly apparent when one compares the overall synaptic target preference of a presynaptic GABAergic cell with the location of synapses in unitary connections. For example, basket cells in the CA1 area provide about half of their synapses to the soma and half to proximal dendrites of single pyramidal cells and the same proportions are found in the overall sample [13,14]. Similarly, a double bouquet cell provided 6 synapses to dendritic spines and 4 to shafts of a pyramidal cell (Fig. 5), reflecting the respective 70% to 30% ratio of targets in the overall sample [132].

The same postsynaptic domain may receive several distinct GABAergic inputs (Fig. 4). For example, the somata of all principal cells are innervated by both parvalbumin and cholecystokinin containing basket cell terminals, with as yet unknown functional differences [28,49]. The situation is particularly intriguing in the innervation of the dendritic domain [109,112] where, in addition to double bouquet cells, neurogliaform cells, bitufted cells and other as yet quantitatively undefined GABAergic cell classes terminate. It was again the hippocampal formation with its segregated laminar excitatory inputs that provided the clue for the design principle in the multiple GABAergic dendritic innervation (see rule 3). It was found that distinct sets of interneurones co-align their axons with a particular excitatory input to the same dendritic segment of principal cells [40,43,109]. Thus, in the dentate gyrus granule cell distal dendrites are innervated by the so called MOPP and HIPP cells whose terminals provide synapses to dendritic shafts and spines in conjunction with the perforant path (PP) synapses [12,43,107]. The proximal dendrites are innervated by the HICAP cell, which terminates conjointly with the commissural/associational glutamatergic input [12,43]. The same principle can be recognised in the hippocampus proper, where basal and stratum radiatum dendrites are innervated by bistratified GABAergic cells [14,41], whereas the termination zone of entorhinal afferents on the distal dendrites is innervated by the somatostatin/mGluR1α expressing GABAergic neurones and perforant path-associated neurones situated in stratum lacunosum moleculare (Fig. 4) [106,147]. Since the same interneurone classes, defined on the basis of targeting dendrites and containing certain neurochemical markers, also exist in the isocortex, the pairing of GABAergic and glutamatergic inputs on the dendritic domains of principal cells is also very likely to apply. Indeed, on the basis of the parallels in the intra- and interlaminar GABAergic [60,114,115] and glutamatergic [53] local connections, Kritzer et al. [60] emphasized such pairing in the primate visual cortex. Furthermore, on the basis of the laminar co-alignment and likely close placement of thalamo-cortical synaptic terminals and the terminals of the dendrite targeting GABAergic cell we suggested that their effects are closely related [132]. However, largely due to our ignorance of the distribution of excitatory terminals of known origin on the surface of neurons, the principle of pairing has not been documented at the level of the single cell in the isocortex.

Explanations for the paired termination of GABAergic and glutamatergic afferents on particular dendritic domains can be grouped into two families, either with predominantly ‘presynaptic’ (i.e. interaction before the postsynaptic membrane that they innervate) or with mostly postsynaptic (i.e. due to change in membrane conductance in the principal cell) consequences, but of course multiple sites of interaction may well be involved.

Genuine presynaptic interactions might take place through: (i) $GABA_B$ receptors on the glutamatergic terminals and/or, (ii) metabotropic glutamate receptors on the GABAergic terminals, and generally would lead to a decrease in transmitter release. The co-alignment would facilitate the effect of presynaptically acting transmitter selectively from the specific source within the termination zone. (iii) Furthermore, indirect ‘presynaptic’ action might be achieved by the well documented selective innervation of particular classes of interneurones by subcortical afferents [28]. Such GABAergic, monoaminergic and cholinergic afferents would selectively influence the termination zone of a glutamatergic pathway by activating or deactivating the conjointly terminating GABAergic interneurones. The co-alignment of terminals would enable the differential modulation of multiple glutamatergic pathways converging onto the same cell.

The paired glutamatergic and GABAergic pathways both form anatomically defined synaptic junctions only on a restricted segment of the dendritic tree, therefore a number of postsynaptic mechanisms may explain their co-alignment. Effects that are in line with an inhibitory role of GABA include: (i) shunting of excitatory currents in dendrites; (ii) the dendritic segment specific local antagonism of depolarisation necessary for NMDA receptor activation [125]. (iii) The dendritically placed GABAergic synapses may prevent or reduce the activation of voltage dependent sodium and high voltage activated Ca^{2+} channels [84,145]. These three mechanisms would tend to reduce the effect of the paired glutamatergic input. How-

ever, *co-operative* GABAergic and glutamatergic interactions have also been suggested: (iv) Appropriately timed local dendritic hyperpolarization may deinactivate sodium channels, low voltage-activated Ca^{2+} channels and deactivate potassium channels, leading to the facilitation of conjointly terminating glutamatergic inputs. (v) Pathway specific GABAergic innervation may also co-operate with the paired glutamatergic input by expanding its dynamic range through the downward rescaling of EPSPs [42]. Which of the above mechanisms operate at particular pathways at a given time depends on the receptor mechanism(s) mediating dendritic GABA action, the membrane potential, the magnitude of the postsynaptic response and, most importantly, its timing relative to that of the glutamatergic effects. There is as yet little information about the latter in the operational network in vivo, and electrical stimulation does not provide information about relative timing.

The question of receptor mechanisms at particular synapses has been addressed in vitro, using paired intracellular recording and the identification of synaptic sites through the visualisation of both pre- and postsynaptic cells, as well as by immunocytochemistry [90,91]. Unitary IPSPs in postsynaptic cells have been reported to be mediated by $GABA_A$ receptors, irrespective of the termination zone of the presynaptic cell, ranging from the axon initial segment to distal dendrites [13,14,22,83,143,147], but not all types of GABAergic cell have been tested. The possibility that in addition $GABA_B$ receptors may be recruited due to prolonged presynaptic firing has also been raised [87,143], and in the isocortex IPSPs with slow kinetics, reminiscent of $GABA_B$ receptor-mediated responses, were evoked by local activation of neurones by exogenous glutamate [9]. If these responses were evoked by cells that activate only $GABA_B$ receptors, their identity remains to be established. The $GABA_A$ receptor mediated responses also show kinetic heterogeneity [92]. Differences in subunit composition of synaptic $GABA_A$ receptors is one potential mechanism that could lead to pharmacological and kinetic differences in the postsynaptic response. The first such difference has been found between the synapses of axo-axonic cells that are rich in both the $\alpha 1$ and $\alpha 2$ subunits and those of basket cells largely lacking the $\alpha 2$ subunit [91]. Other subunits, such as the $\beta 2/3$ and the $\gamma 2$, appear to be distributed at most GABAergic synapses on the surface of principal cells [90,118].

The subdivision of the neuronal surface by specific sets of GABAergic neurones strongly suggests a division of labour in distinct circuits (Fig. 4). As suggested earlier, perisomatic inputs appear to be best suited for the phasing of action potential discharge and subthreshold activity [19]. Such phasing may be particularly important during oscillatory cortical activity. The role of dendritic segment specific GABAergic inputs has been discussed above and is related to the modulation of subsets of glutamatergic inputs. Clearly, the key to the understanding of why so many separate circuits are needed will be information about their activity in the behaving animal [108], but the subsets of GABAergic neurones have not been identified in relation to behaviour. Characterising the activity of identified cells in anaesthetised animals in relation to specific behaviourally relevant network activity has already proved very informative [28]. Further studies in vitro may also reveal the constraints on the timing of identified interneuronal activity.

3.5. Connections between GABAergic cells

The early immunocytochemical studies showed that many cortical GABAergic neurones are surrounded by GABAergic synaptic terminals [31,99], some of which were shown to originate from subcortical areas, such as the medial septum, for the hippocampal formation [27] or the basal forebrain [26] and zona incerta [66] for the isocortex. The study of the synaptic output of interneurones also revealed that a small but significant proportion of their synapses are given to other interneurones [14,29,42,52,56,57,88,106,113,121]. Interneurones respond to local synaptic stimulation by both $GABA_A$ and $GABA_B$ receptor-mediated mechanisms [15,51,62,86,101,106], and following the blockade of excitatory amino acid transmission, connections between GABAergic interneurones are able to maintain rhythmic network activity [82,151].

Recently, we have investigated the degree and cell type selectivity of GABAergic interconnections both in the hippocampus [20] and in the visual cortex [133] by intracellular recordings from pairs of interneurones in vitro. The examined interneurones innervated mainly pyramidal cells, only a few percent of their synapses targeted other interneurones. The postsynaptic domain selectivity in the placement of synapses on other interneurones is maintained and is similar to the location on pyramidal cells (Fig. 8). Thus, basket cells innervated the perisomatic region of interneurones [20,121,133] and the dendritic region of interneurones was innervated by cells innervating the dendrites of pyramidal cells [133]. The number of synapses formed by a basket cell on an individual interneurone was 10 in the hippocampus and, depending on the postsynaptic cell, up to 20 in the visual cortex, being very similar to the numbers reported for unitary connections to pyramidal cells [14,20,132,133]. Frequently, the connections could be shown to be reciprocal. The structural similarity was paralleled by the similarity of postsynaptic unitary IPSPs evoked by both basket and other interneurones in different types of interneurones and principal cells [20,102,133]. The responses evoked by low frequency presynaptic activity appeared to be mediated exclusively by $GABA_A$ receptors. The evaluation of the strength of interactions in terms of the number of synapses to a given neurone showed that in the visual cortex the connections between basket cells, mediated by up to 20 synapses, are stronger than their connections with double bouquet cells targeting dendrites [133].

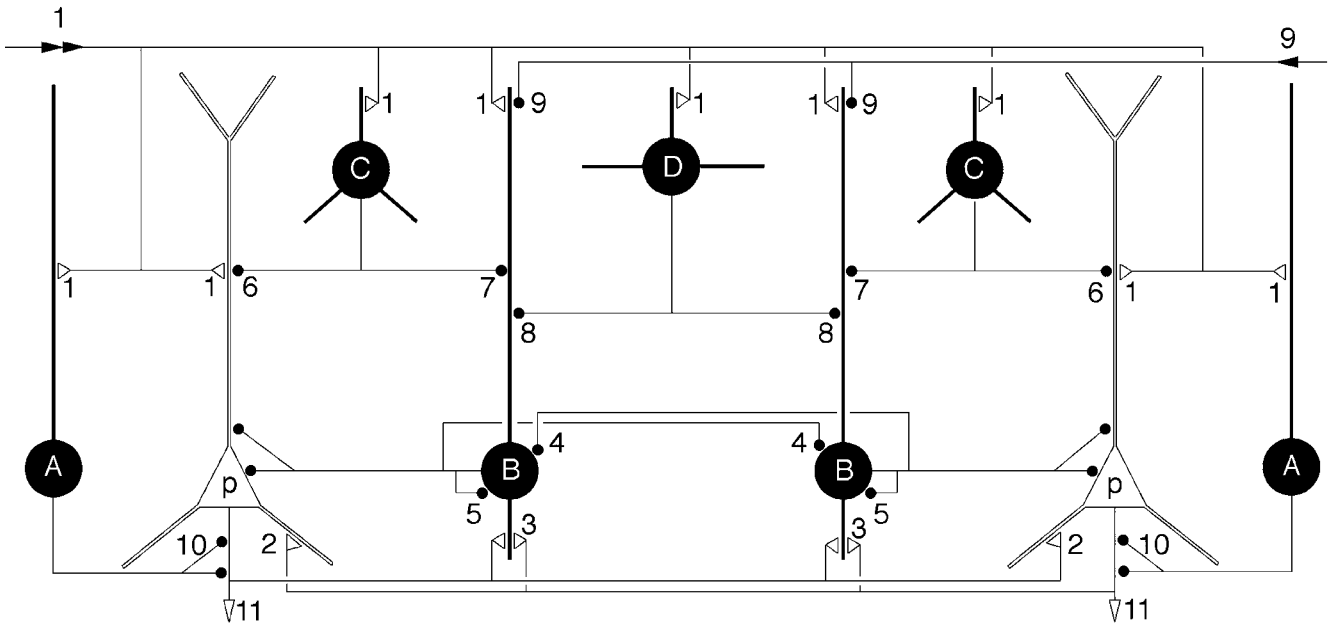


Fig. 10. Simplified summary of the salient features of the basic cortical circuit, consisting of only one type of pyramidal cell (p) and a set of local circuit GABAergic cells (filled circles) innervated by sets of extrinsic glutamatergic pathways (double arrow, here only one (1) shown for clarity). Ensembles of pyramidal cells are extensively interconnected (2) and also innervate some classes of GABAergic cell (3). The perisomatically terminating basket cells (B) are also extensively interconnected(4) and innervate themselves through autapses (5). Distinct classes of GABAergic cells (C, one class shown for clarity) innervate the pyramidal cells (6) and other GABAergic cells (7) in a domain specific manner, co-aligning their termination zone with glutamatergic pathways (1). Some GABAergic cells (D) specialise in the innervation (8) of other GABAergic cells. Extrinsic GABAergic (9, filled arrow) and monoaminergic (including ACh, not shown) afferents innervate (9) specific interneurone classes. The output of the circuit is predominantly via the pyramidal axons (11, open arrows), influenced by the GABAergic axo-axonic cells (A), which are unique to the cortex and selectively innervate (10) the axon initial segments. In the isocortex, this circuit is repeated in each layer, sometimes several times as multiple sets of output neurones evolved, and both tangential and columnar connections are established between the basic circuits through additional specific links, involving both the GABAergic and the glutamatergic neurones.

The above described connections could be viewed as being of no functional consequence, demonstrating a lack of selectivity in GABAergic output from neurones that are not equipped to differentiate between the principal cells and other GABAergic neurones. However, the differential weighting and the large number of synapses involved argue against this scenario. It is unlikely that all GABAergic interconnections have a single functional explanation such as disinhibition downstream of the postsynaptic GABAergic cell [52,88,101,113]. Disinhibition resulting from the inhibition of GABAergic cells can be demonstrated experimentally [10,100,144], and in intracortical circuits could be evoked by selective and unidirectional connections (see below) to interneurones. Connections between distinct types of neurones targeting different domains of the same postsynaptic principal cell population could lead to switching the balance of excitation and inhibition from one membrane domain to another. For example a basket cell providing simultaneous fast GABAergic influence to the dendritically terminating bistratified cell and to pyramidal cells [20] could lower dendritic inhibition while increasing the somatic one. The result of strong reciprocal GABAergic connections, e.g. between basket cells, in fully operational networks may depend on the state of the system, such as the presence or absence of oscillatory population activity. Indeed, the ability of GABAergic connections to maintain rhythmic activity has been argued to be the basis of fast gamma frequency oscillatory cortical activity [28,151].

In an exciting new development, the study of the synaptic target selectivity of GABAergic cells in the hippocampus has led to the discovery of three novel classes of GABAergic cells that mainly or exclusively target subclasses of other GABAergic cells [28]. Similar connections may also exist in the isocortex [81]. These unexpected and remarkably selective GABAergic circuits provide the best scenario for both the domain specific disinhibition of principal cell populations, and the synchronisation of specific interneurone populations [1,38].

3.6. Cell type specific self-innervation of cortical cells

In addition to subcortical, local nonselective or selective GABAergic innervation of interneurones the fourth source of GABA arises from self-innervating terminals forming autapses on the soma and dendrites [20,95,133]. The number of autapses formed by GABAergic dendrite targeting cells in the visual cortex can be up to 32, so far the most numerous junctions reported for a single axon innervating any cortical cell [132,134]. The autapses were both cell

type specific, i.e. basket and dendrite targeting cells established massive self-innervation, double bouquet cells made few, if any, and axo-axonic cells lacked self-innervation. Moreover, autapses are domain specific, i.e. those formed by basket cells concentrated on the perisomatic region, whereas those formed by dendrite targeting cells were located on more distal dendrites (Fig. 9). These two features of selectivity argue for a functional significance of autapses, which are unlikely to result from random connectivity. Although, in developing cortex, a number of autapses have been reported for layer 5 pyramidal cells [69], we found that out of 10 supragranular pyramidal cells only one formed autapses in the adult cat's visual cortex. Therefore, large numbers of autapses appear to be a specific feature of basket and dendrite targeting cells, presumably related to the summation properties of their inputs and the timing of their action potentials. Unlike other IPSPs evoked in the cell, those mediated by autapses will be precisely timed to the cell's action potentials and those EPSPs that evoked them. These cells can sustain very high frequency regular discharge, when activated by depolarising somatic current injection. They appear to fire much more irregularly, when driven by sensory stimuli in the visual cortex [4]. It is possible that autapses in self-innervating cells contribute to the pattern of discharge only at relatively low excitatory drive. Activating a large $GABA_A$ receptor-mediated conductance by the first action potential would effectively shorten the time constant of the cell, shortening EPSPs and favouring the activation of the cells by coincident inputs, as well as making the subsequent steady state discharge more reliable. As evidenced by the high current-evoked discharge, this mechanism would be overridden by strong excitatory drive when inputs from other neurones and network activity would govern the discharge of self-innervating cells. Although these ideas remain to be tested, it is likely that regulation of the frequency and timing of GABAergic discharge was a major driving force for the development of massive self-innervation.

4. Conclusions

The analysis of the salient features of cortical synaptic connections has revealed a remarkably selective array of connections (Fig. 10). Yet, a highly adaptable design of the basic circuit emerges, when comparisons are made between cortical areas. The basic circuit is best seen in the hippocampus, where a relatively homogeneous set of spatially aligned principal cells allows an easy visualization of the organisational rules. Those principles which have been examined proved to be identical or very similar in the isocortex. Here, the basic circuit, scaled to specific requirements, is repeated in each layer, sometimes several times, as multiple sets of output neurones evolved, requiring subtly different needs for their inputs. Tangential intralaminar connections, present in both the hippocampus and isocortex, connect output neurones with similar properties, as best seen in the patchy connections in the isocortex. The additional radial, layer by layer superposition of distinct sets of output neurones, each representing and supported by its basic circuit, requires a co-ordination of their activity, that is mediated by highly selective interlaminar connections, involving both the GABAergic and the excitatory amino acid releasing neurones. The remarkable specificity in the geometry of cells and the selectivity in placement of neurotransmitter receptors and synapses on their surface, strongly suggest a predominant role for time in the coding of information, but this does not exclude an important role also for the rate of action potential discharge in cortical representation of information [146].

Acknowledgements

The authors thank Dr. Ole Paulsen for his comments on an earlier version of the manuscript. G.T. was supported by the European Blaschko Visiting Scholarship during the preparation of this paper. E.H.B. holds a Medical Research Fellowship at Corpus Christi College, Oxford. Some of the work reported here has been supported by the European Community Grant BIO4-CT96-0585.

References

[1] L. Acsady, T.J. Gorcs, T.F. Freund, Different populations of vasoactive intestinal polypeptide-immunoreactive interneurons are specialized to control pyramidal cells or interneurons in the hippocampus, Neuroscience 73 (1996) 317–334.

[2] A.B. Ali, A.M. Thomson, Brief train depression and facilitation at pyramid-interneurone connections in slices of rat hippocampus; paired recordings with biocytin filling, J. Physiol. (Lond.) 501 (1997) 9P.

[3] P. Andersen, J.C. Eccles, Y. Loyning, Recurrent inhibition in the hippocampus with identification of the inhibitory cell and its synapses., Nature 198 (1963) 540–542.

[4] R. Azouz, C.M. Gray, L.G. Nowak, D.A. McCormick, Physiological properties of inhibitory interneurons in cat striate cortex, Cerebral Cortex 7 (1997) 534–545.

[5] A. Baude, Z. Nusser, E. Molnar, R.A.J. McIlhinney, P. Somogyi, High-resolution immunogold localization of AMPA type glutamate receptor subunits at synaptic and non-synaptic sites in rat hippocampus, Neuroscience 69 (1995) 1031–1055.

[6] A. Baude, Z. Nusser, J.D.B. Roberts, E. Mulvihill, R.A.J. McIlhinney, P. Somogyi, The metabotropic glutamate receptor (mGluR1α) is concentrated at perisynaptic membrane of neuronal subpopulations as detected by immunogold reaction, Neuron 11 (1993) 771–787.

[7] C. Beaulieu, Z. Kisvarday, P. Somogyi, M. Cynader, A. Cowey, Quantitative distribution of GABA-immunopositive and -immunonegative neurons and synapses in the monkey striate cortex (area 17), Cerebral Cortex 2 (1992) 295–309.

[8] C. Beaulieu, P. Somogyi, Targets and quantitative distribution of GABAergic synapses in the visual cortex of the cat, Eur. J. Neurosci. 2 (1990) 296–303.

[9] L.S. Benardo, Separate activation of fast and slow inhibitory postsynaptic potentials in rat neocortex *in vitro*, J. Physiol. (Lond.) 476 (1994) 203–215.

[10] D.K. Bilkey, G.V. Goddard, Medial septal facilitation of hippocampal granule cell activity is mediated by inhibition of inhibitory interneurones, Brain Res. 361 (1985) 99–106.
[11] J.M. Blasco-Ibanez, T.F. Freund, Synaptic input of horizontal interneurons in stratum oriens of the hippocampal CA1 subfield: structural basis of feed-back activation, Eur. J. Neurosci. 7 (1995) 2170–2180.
[12] P.S. Buckmaster, P.A. Schwartzkroin, Physiological and morphological heterogeneity of dentate gyrus-hilus interneurons in the gerbil hippocampus in vivo, Eur. J. Neurosci. 7 (1995) 1393–1402.
[13] E.H. Buhl, S.R. Cobb, K. Halasy, P. Somogyi, Properties of unitary IPSPs evoked by anatomically identified basket cells in the rat hippocampus, Eur. J. Neurosci. 7 (1995) 1989–2004.
[14] E.H. Buhl, K. Halasy, P. Somogyi, Diverse sources of hippocampal unitary inhibitory postsynaptic potentials and the number of synaptic release sites, Nature 368 (1994) 823–828.
[15] E.H. Buhl, Z.-S. Han, Z. Lorinczi, V.V. Stezhka, S.V. Karnup, P. Somogyi, Physiological properties of anatomically identified axo-axonic cells in the rat hippocampus, J. Neurophysiol. 71 (1994) 1289–1307.
[16] E.H. Buhl, G. Tamas, T. Szilagyi, C. Stricker, O. Paulsen, P. Somogyi, Effect, number and location of synapses made by single pyramidal cells onto aspiny interneurones of cat visual cortex, J. Physiol. (Lond). 500 (1997) 689–713.
[17] G. Buzsaki, L.-W. Leung, C.H. Vanderwolf, Cellular bases of hippocampal EEG in the behaving rat, Brain Res. Rev. 6 (1983) 139–171.
[18] N. Calakos, R.H. Scheller, Synaptic vesicle biogenesis, docking, and fusion: a molecular description, Physiol. Rev. 76 (1996) 1–29.
[19] S.R. Cobb, E.H. Buhl, K. Halasy, O. Paulsen, P. Somogyi, Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons, Nature 378 (1995) 75–78.
[20] S.R. Cobb, K. Halasy, I. Vida, G. Nyiri, G. Tamas, E.H. Buhl, P. Somogyi, Synaptic effects of identified interneurons innervating both interneurons and pyramidal cells in the rat hippocampus, Neuroscience 79 (1997) 629–648.
[21] J. Deuchars, A.M. Thomson, Innervation of burst firing spiny interneurons by pyramidal cells in deep layers of rat somatomotor cortex: paired intracellular recordings with biocytin filling, Neuroscience 69 (1995) 739–755.
[22] J. Deuchars, A.M. Thomson, Single axon fast inhibitory postsynaptic potentials elicited by a sparsely spiny interneuron in rat neocortex, Neuroscience 65 (1995) 935–942.
[23] J. Deuchars, D.C. West, A.M. Thomson, Relationships between morphology and physiology of pyramid-pyramid single axon connections in rat neocortex *in vitro*, J. Physiol. (Lond.) 478 (1994) 423–435.
[24] J.C. Eccles, Excitatory and inhibitory mechanisms in brain, in: H.H. Jasper, A.A. Ward, A. Pope (Eds.), Basic Mechanisms of the Epilepsies, J. and A. Churchill, London, 1969, pp. 229–252.
[25] A. Fairen, A. Peters, J. Saldanha, A new procedure for examining Golgi impregnated neurons by light and electron microscopy, J. Neurocytol. 6 (1977) 311–338.
[26] R.S. Fisher, N.A. Buchwald, C.D. Hull, M.S. Levine, GABAergic basal forebrain neurons project to the neocortex: the localization of glutamic acid decarboxylase and choline acetyltransferase in feline corticopetal neurons, J. Comp. Neurol. 272 (1988) 489–502.
[27] T.F. Freund, M. Antal, GABA-containing neurons in the septum control inhibitory interneurons in the hippocampus, Nature 336 (1988) 170–173.
[28] T.F. Freund, G. Buzsaki, Interneurons of the hippocampus, Hippocampus 6 (1996) 347–470.
[29] T.F. Freund, Zs. Magloczky, I. Soltesz, P. Somogyi, Synaptic connections, axonal and dendritic patterns of neurons immunoreactive for cholecystokinin in the visual cortex of the cat, Neuroscience 19 (1986) 1133–1159.
[30] T.F. Freund, K.A.C. Martin, I. Soltesz, P. Somogyi, D. Whitteridge, Arborisation pattern and postsynaptic targets of physiologically identified thalamocortical afferents in the monkey striate cortex, J. Comp. Neurol. 289 (1989) 315–336.
[31] T.F. Freund, K.A.C. Martin, A.D. Smith, P. Somogyi, Glutamate decarboxylase-immunoreactive terminals of Golgi-impregnated axoaxonic cells and of presumed basket cells in synaptic contact with pyramidal neurons of the cat's visual cortex, J. Comp. Neurol. 221 (1983) 263–278.
[32] T.F. Freund, K.A.C. Martin, P. Somogyi, D. Whitteridge, Innervation of cat visual areas 17 and 18 by physiologically identified X- and Y-type thalamic afferents. II. Identification of postsynaptic targets by GABA immunocytochemistry and Golgi impregnation, J. Comp. Neurol. 242 (1985) 275–291.
[33] P.L.A. Gabbott, K.A.C. Martin, D. Whitteridge, Connections between pyramidal neurons in layer 5 of cat visual cortex (area 17), J. Comp. Neurol. 259 (1987) 364–381.
[34] P.L.A. Gabbott, P. Somogyi, Quantitative distribution of GABA-immunoreactive neurons in the visual cortex (area 17) of the cat, Exp. Brain Res. 61 (1986) 323–331.
[35] J.R.P. Geiger, J. Lubke, A. Roth, M. Frotscher, P. Jonas, Submillisecond AMPA receptor-mediated signaling at a principal neuron-interneuron synapse, Neuron 18 (1997) 1009–1023.
[36] C.D. Gilbert, T.N. Wiesel, Clustered intrinsic connections in cat visual cortex, J. Neurosci. 3 (1983) 1116–1133.
[37] C.D. Gilbert, T.N. Wiesel, Morphology and intracortical projections of functionally characterised neurones in the cat visual cortex, Nature 280 (1979) 120–125.
[38] A.I. Gulyas, N. Hajos, T.F. Freund, Interneurons containing calretinin are specialized to control other interneurons in the rat hippocampus, J. Neurosci. 16 (1996) 3397–3411.
[39] A.I. Gulyas, R. Miles, A. Sik, K. Toth, N. Tamamaki, T.F. Freund, Hippocampal pyramidal cells excite inhibitory neurons through a single release site, Nature 366 (1993) 683–687.
[40] A.I. Gulyas, R. Miles, N. Hajos, T.F. Freund, Precision and variability in postsynaptic target selection of inhibitory cells in the hippocampal CA3 region, Eur. J. Neurosci. 5 (1993) 1729–1751.
[41] K. Halasy, E.H. Buhl, Z. Lorinczi, G. Tamas, P. Somogyi, Synaptic target selectivity and input of GABAergic basket and bistratified interneurons in the CA1 area of the rat hippocampus, Hippocampus 6 (1996) 306–329.
[42] K. Halasy, P. Somogyi, Subdivisions in the multiple GABAergic innervation of granule cells in the dentate gyrus of the rat hippocampus, Eur. J. Neurosci. 5 (1993) 411–429.
[43] Z.-S. Han, E.H. Buhl, Z. Lorinczi, P. Somogyi, A high degree of spatial selectivity in the axonal and dendritic domains of physiologically identified local-circuit neurons in the dentate gyrus of the rat hippocampus, Eur. J. Neurosci. 5 (1993) 395–410.
[44] P.G. Haydon, E. Henderson, E.F. Stanley, Localization of individual calcium channels at the release face of a presynaptic nerve terminal, Neuron 13 (1994) 1275–1280.
[45] J.T.R. Isaac, R.A. Nicoll, R.C. Malenka, Evidence for silent synapses: implications for the expression of LTP, Neuron 15 (1995) 427–434.
[46] D. Johnston, J.C. Magee, C.M. Colbert, B.R. Christie, Active properties of neuronal dendrites, Ann. Rev. Neurosci. 19 (1996) 165–186.
[47] E.G. Jones, Varieties and distribution of non-pyramidal cells in the somatic sensory cortex of the squirrel monkey, J. Comp. Neurol. 160 (1975) 205–268.
[48] J.H. Kaas, The evolution of isocortex, Brain Behav. Evolution 46 (1995) 187–196.
[49] Y. Kawaguchi, Y. Kubota, GABAergic cell subtypes and their synaptic connections in rat frontal cortex, Cerebral Cortex 7 (1997) 476–486.
[50] V.N. Kharazia, K.D. Phend, A. Rustioni, R.J. Weinberg, EM colocalization of AMPA and NMDA receptor subunits at synapses in rat cerebral cortex, Neurosci. Lett. 210 (1996) 37–40.

[51] R. Khazipov, P. Congar, Y. Ben-Ari, Hippocampal CA1 lacunosum-moleculare interneurons: modulation of monosynaptic GABAergic IPSCs by presynaptic $GABA_B$ receptors, J. Neurophysiol. 74 (1995) 2126–2137.
[52] Z.F. Kisvarday, C. Beaulieu, U.T. Eysel, Network of GABAergic large basket cells in cat visual cortex (Area 18): implication for lateral disinhibition, J. Comp. Neurol. 327 (1993) 398–415.
[53] Z.F. Kisvarday, A. Cowey, A.D. Smith, P. Somogyi, Interlaminar and lateral excitatory amino acid connections in the striate cortex of monkey, J. Neurosci. 9 (1989) 667–682.
[54] Z.F. Kisvarday, A. Cowey, P. Somogyi, Synaptic relationships of a type of GABA-immunoreactive neuron (clutch cell), spiny stellate cells and lateral geniculate nucleus afferents in layer IVC of the monkey striate cortex, Neuroscience 19 (1986) 741–761.
[55] Z.F. Kisvarday, U.T. Eysel, Cellular organization of reciprocal patchy networks in layer III of cat visual cortex (area 17), Neuroscience 46 (1992) 275–286.
[56] Z.F. Kisvarday, D.-S. Kim, U.T. Eysel, T. Bonhoeffer, Relationship between lateral inhibitory connections and the topography of the orientation map in cat visual cortex, Eur. J. Neurosci. 6 (1994) 1619–1632.
[57] Z.F. Kisvarday, K.A.C. Martin, D. Whitteridge, P. Somogyi, Synaptic connections of intracellularly filled clutch cells: a type of small basket cell in the visual cortex of the cat, J. Comp. Neurol. 241 (1985) 111–137.
[58] Z.F. Kisvarday, K.A.C. Martin, T.F. Freund, Zs. Magloczky, D. Whitteridge, P. Somogyi, Synaptic targets of HRP-filled layer III pyramidal cells in the cat striate cortex, Exp. Brain Res. 64 (1986) 541–552.
[59] H. Korn, D.S. Faber, Quantal analysis and synaptic efficacy in the CNS, Trends Neurosci. 14 (1991) 439–444.
[60] M.F. Kritzer, A. Cowey, P. Somogyi, Patterns of inter- and intralaminar GABAergic connections distinguish striate (V1) and extrastriate (V2, V4) visual cortices and their functionally specialized subdivisions in the rhesus monkey, J. Neurosci. 12 (1992) 4545–4564.
[61] D.M. Kullmann, Amplitude fluctuations of dual-component EPSCs in hippocampal pyramidal cells: implications for long-term potentiation, Neuron 12 (1994) 1111–1120.
[62] J.-C. Lacaille, Postsynaptic potentials mediated by excitatory and inhibitory amino acids in interneurons of stratum pyramidale of the CA1 region of rat hippocampal slices in vitro, J. Neurophysiol. 66 (1991) 1441–1454.
[63] J.B. Levitt, D.A. Lewis, T. Yoshioka, J.S. Lund, Topography of pyramidal neuron intrinsic connections in macaque monkey prefrontal cortex (Areas 9 and 46), J. Comp. Neurol. 338 (1993) 360–376.
[64] X.-G. Li, P. Somogyi, A. Ylinen, G. Buzsaki, The hippocampal CA3 network: an in vivo intracellular labeling study, J. Comp. Neurol. 339 (1994) 181–208.
[65] D. Liao, N.A. Hessler, R. Malinow, Activation of postsynaptically silent synapses during pairing-induced LTP in CA1 region of hippocampal slice, Nature 375 (1995) 400–404.
[66] C.-S. Lin, M.A.L. Nicolelis, J.S. Schneider, J.K. Chapin, A major direct GABAergic pathway from zona incerta to neocortex, Science 248 (1990) 1553–1555.
[67] R. Lorente de No, Studies on the structure of the cerebral cortex. II. Continuation of the study of the ammonic system, J. Psychol. Neurol. 46 (1934) 113–177.
[68] P.R. Lowenstein, P. Somogyi, Synaptic organization of corticocortical connections from the primary visual cortex to the posteromedial lateral suprasylvian visual area in the cat, J. Comp. Neurol. 310 (1991) 253–266.
[69] J. Lubke, H. Markram, M. Frotscher, B. Sakmann, Frequency and dendritic distribution of autapses established by layer 5 pyramidal neurons in the developing rat neocortex: comparison with synaptic innervation of adjacent neurons of the same class, J. Neurosci. 16 (1996) 3209–3218.
[70] R. Lujan, Z. Nusser, J.D.B. Roberts, R. Shigemoto, P. Somogyi, Perisynaptic location of metabotropic glutamate receptors mGluR1 and mGluR5 on dendrites and dendritic spines in the rat hippocampus, Eur. J. Neurosci. 8 (1996) 1488–1500.
[71] R. Lujan, J.D.B. Roberts, R. Shigemoto, H. Ohishi, P. Somogyi, Differential plasma membrane distribution of metabotropic glutamate receptors mGluR1α, mGluR2 and mGluR5, relative to neurotransmitter release sites, J. Chem. Neuroanat. 13 (1997) 219–241.
[72] J.S. Lund, G.H. Henry, C.L. MacQueen, A.R. Harvey, Anatomical organization of the primary visual cortex (area 17) of the cat. A comparison with area 17 of the macaque monkey, J. Comp. Neurol. 184 (1979) 599–618.
[73] J.S. Lund, T. Yoshioka, J.B. Levitt, Comparison of intrinsic connectivity in different areas of macaque monkey cerebral cortex, Cerebral Cortex 3 (1993) 148–162.
[74] G. Maccaferri, C.J. McBain, Passive propagation of LTD to stratum oriens-alveus inhibitory neurons modulates the temporoammonic input to the hippocampal CA1 region, Neuron 15 (1995) 137–145.
[75] H. Markram, J. Lubke, M. Frotscher, A. Roth, B. Sakmann, Physiology and anatomy of synaptic connections between thick tufted pyramidal neurones in the developing rat neocortex, J. Physiol. (Lond.) 500 (1997) 409–440.
[76] H. Markram, M. Tsodyks, Redistribution of synaptic efficacy between neocortical pyramidal neurons, Nature 382 (1996) 807–810.
[77] K.A.C. Martin, D. Whitteridge, Form, function, and intracortical projections of spiny neurones in the striate visual cortex of the cat, J. Physiol. 353 (1984) 463–504.
[78] A.J. McDonald, J.L. Culberson, Neurons of the basolateral amygdala: a Golgi study in the opossum (*Didelphis virginiana*), Am. J. Anat. 162 (1981) 327–342.
[79] B.A. McGuire, C.D. Gilbert, P.K. Rivlin, T.N. Wiesel, Targets of horizontal connections in macaque primary visual cortex, J. Comp. Neurol. 305 (1991) 370–392.
[80] B.A. McGuire, J.-P. Hornung, C.D. Gilbert, T.N. Wiesel, Patterns of synaptic input to layer 4 of cat striate cortex, J. Neurosci. 4 (1984) 3021–3033.
[81] V. Meskenaite, Calretinin-immunoreactive local circuit neurons in area 17 of the cynomolgus monkey *Macaca fascicularis*, J. Comp. Neurol. 379 (1997) 113–132.
[82] H.B. Michelson, R.K.S. Wong, Excitatory synaptic responses mediated by $GABA_A$ receptors in the hippocampus, Science 253 (1991) 1420–1423.
[83] R. Miles, Synaptic excitation of inhibitory cells by single CA3 hippocampal pyramidal cells of the guinea-pig in vitro, J. Physiol. (Lond.) 428 (1990) 61–77.
[84] R. Miles, K. Toth, A.I. Gulyas, N. Hajos, T.F. Freund, Differences between somatic and dendritic inhibition in the hippocampus, Neuron 16 (1996) 815–823.
[85] R. Miles, R.K.S. Wong, Excitatory synaptic interactions between CA3 neurones in the guinea-pig hippocampus, J. Physiol. (Lond.) 373 (1986) 397–418.
[86] U. Misgeld, M. Frotscher, Postsynaptic-GABAergic inhibition of non-pyramidal neurons in the guinea-pig hippocampus, Neuroscience 19 (1986) 193–206.
[87] I. Mody, Y. De Koninck, T.S. Otis, I. Soltesz, Bridging the cleft at GABA synapses in the brain, Trends Neurosci. 17 (1994) 517–525.
[88] M.G. Nunzi, A. Gorio, F. Milan, T.F. Freund, P. Somogyi, A.D. Smith, Cholecystokinin-immunoreactive cells form symmetrical synaptic contacts with pyramidal and non-pyramidal neurons in the hippocampus, J. Comp. Neurol. 237 (1985) 485–505.
[89] Z. Nusser, E. Mulvihill, P. Streit, P. Somogyi, Subsynaptic segre-

gation of metabotropic and ionotropic glutamate receptors as revealed by immunogold localisation, Neuroscience 61 (1994) 421–427.
[90] Z. Nusser, J.D.B. Roberts, A. Baude, J.G. Richards, W. Sieghart, P. Somogyi, Immunocytochemical localisation of the α1 and β2/3 subunits of the $GABA_A$ receptor in relation to specific GABAergic synapses in the dentate gyrus, Eur. J. Neurosci. 7 (1995) 630–646.
[91] Z. Nusser, W. Sieghart, D. Benke, J.-M. Fritschy, P. Somogyi, Differential synaptic localization of two major γ-aminobutyric acid type A receptor α subunits on hippocampal pyramidal cells, Proc. Natl. Acad. Sci. USA 93 (1996) 11939–11944.
[92] R.A. Pearce, Physiological evidence for two distinct $GABA_A$ responses in rat hippocampus, Neuron 10 (1993) 189–200.
[93] R. Pekhletski, R. Gerlai, L.S. Overstreet, X.-P. Huang, N. Agopyan, N.T. Slater, W. Abramow-Newerly, J.C. Roder, D.R. Hampson, Impaired cerebellar synaptic plasticity and motor performance in mice lacking the mGluR4 subtype of metabotropic glutamate receptor, J. Neurosci. 16 (1996) 6364–6373.
[94] A. Peters, S.L. Palay, The morphology of synapses, J. Neurocytol. 25 (1996) 687–700.
[95] A. Peters, C.C. Proskauer, Synaptic relationships between a multipolar stellate cell and a pyramidal neuron in the rat visual cortex. A combined Golgi-electron microscope study, J. Neurocytol. 9 (1980) 163–183.
[96] S. Ramon y Cajal, Histologie du Système Nerveux de l'Homme et des Vertèbres, Vol. II, Maloine, Paris, 1911.
[97] R.C. Reid, J.-A. Alonso, Specificity of monosynaptic connections from thalamus to visual cortex, Nature 378 (1995) 281–284.
[98] A.D. Reyes, B. Sakmann, Target-specific short-term modification of synaptic potentials in layer 2/3 neurons, Soc. Neurosci. Abs. 23 (1997) 365.
[99] C.E. Ribak, Aspinous and sparsely-spinous stellate neurons in the visual cortex of rats contain glutamic acid decarboxylase, J. Neurocytol. 7 (1978) 461–478.
[100] M. Satou, K. Mori, Y. Tazawa, S.F. Takagi, Long-lasting disinhibition in pyriform cortex of the rabbit, J. Neurophysiol. 48 (1982) 1157–1163.
[101] H.E. Scharfman, Paradoxical enhancement by bicuculline of dentate granule cell IPSPs evoked by fimbria stimulation in rat hippocampal slices, Neurosci. Lett. 168 (1994) 29–33.
[102] H.E. Scharfman, D.D. Kunkel, P.A. Schwartzkroin, Synaptic connections of dentate granule cells and hilar neurons: results of paired intracellular recordings and intracellular horseradish peroxidase injections, Neuroscience 37 (1990) 693–707.
[103] C.S. Sherrington, The Integrative Action of the Nervous System, Yale Univ. Press, New Haven, 1906.
[104] R. Shigemoto, A. Kinoshita, E. Wada, S. Nomura, H. Ohishi, M. Takada, P.J. Flor, A. Neki, T. Abe, S. Nakanishi, N. Mizuno, Differential presynaptic localization of metabotropic glutamate receptor subtypes in the rat hippocampus, J. Neurosci. 17 (1997) 7503–7522.
[105] R. Shigemoto, A. Kulik, J.D.B. Roberts, H. Ohishi, Z. Nusser, T. Kaneko, P. Somogyi, Target-cell-specific concentration of a metabotropic glutamate receptor in the presynaptic active zone, Nature 381 (1996) 523–525.
[106] A. Sik, M. Penttonen, A. Ylinen, G. Buzsaki, Hippocampal CA1 interneurons: an in vivo intracellular labeling study, J. Neurosci. 15 (1995) 6651–6665.
[107] A. Sik, M. Penttonen, G. Buzsaki, Interneurons in the hippocampal dentate gyrus: An in vivo intracellular study, Eur. J. Neurosci. 9 (1997) 573–588.
[108] W.E. Skaggs, B.L. McNaughton, M.A. Wilson, C.A. Barnes, Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences, Hippocampus 6 (1996) 149–172.
[109] P. Somogyi, The order in synaptic circuits of the cerebral cortex: Lessons from the hippocampus, structural and functional organization of the neocortex, in: B. Albowitz, K. Albus, U. Kuhnt, H.-Ch. Nothdurft, P. Wahle (Eds.), Structural and Functional Organization of the Neocortex, Springer, Berlin, 1994, pp. 148–161.
[110] P. Somogyi, A specific 'axo-axonal' interneuron in the visual cortex of the rat, Brain Res. 136 (1977) 345–350.
[111] P. Somogyi, The study of Golgi stained cells and of experimental degeneration under the electron microscope: a direct method for the identification in the visual cortex of three successive links in a neuron chain, Neuroscience 3 (1978) 167–180.
[112] P. Somogyi, Synaptic organisation of GABAergic neurons and $GABA_A$ receptors in the lateral geniculate nucleus and visual cortex, in: D.K.-T. Lam, C.D. Gilbert (Eds.), Neural Mechanisms of Visual Perception, Proc Retina Res Found Symp, 2, Portfolio Publ., The Woodlands, Texas, 1989, pp. 35–62.
[113] P. Somogyi, A. Cowey, Combined Golgi and electron microscopic study on the synapses formed by double bouquet cells in the visual cortex of the cat and monkey, J. Comp. Neurol. 195 (1981) 547–566.
[114] P. Somogyi, A. Cowey, Z.F. Kisvarday, T.F. Freund, J. Szentagothai, Retrograde transport of γ-amino[^{3}H]butyric acid reveals specific interlaminar connections in the striate cortex of monkey, Proc. Natl. Acad. Sci. USA 80 (1983) 2385–2389.
[115] P. Somogyi, A. Cowey, N. Halasz, T.F. Freund, Vertical organization of neurons accumulating ^{3}H-GABA in the visual cortex of the Rhesus monkey, Nature 294 (1981) 761–763.
[116] P. Somogyi, T.F. Freund, A. Cowey, The axo-axonic interneuron in the cerebral cortex of the rat, cat and monkey, Neuroscience 7 (1982) 2577–2607.
[117] P. Somogyi, T.F. Freund, A.J. Hodgson, J. Somogyi, D. Beroukas, I.W. Chubb, Identified axo-axonic cells are immunoreactive for GABA in the hippocampus and visual cortex of the cat, Brain Res. 332 (1985) 143–149.
[118] P. Somogyi, J.-M. Fritschy, D. Benke, J.D.B. Roberts, W. Sieghart, The γ2 subunit of the $GABA_A$ receptor is concentrated in synaptic junctions containing the α1 and β2/3 subunits in hippocampus, cerebellum and globus pallidus, Neuropharmacology 35 (1996) 1425–1444.
[119] P. Somogyi, A.J. Hodgson, Antisera to γ-aminobutyric acid. III. Demonstration of GABA in Golgi-impregnated neurons and in conventional electron microscopic sections of cat striate cortex, J. Histochem. Cytochem. 33 (1985) 249–257.
[120] P. Somogyi, A.J. Hodgson, A.D. Smith, An approach to tracing neuron networks in the cerebral cortex and basal ganglia. Combination of Golgi staining, retrograde transport of horseradish peroxidase and anterograde degeneration of synaptic boutons in the same material, Neuroscience 4 (1979) 1805–1852.
[121] P. Somogyi, Z.F. Kisvarday, K.A.C. Martin, D. Whitteridge, Synaptic connections of morphologically identified and physiologically characterized large basket cells in the striate cortex of cat, Neuroscience 10 (1983) 261–294.
[122] P. Somogyi, M.G. Nunzi, A. Gorio, A.D. Smith, A new type of specific interneuron in the monkey hippocampus forming synapses exclusively with the axon initial segments of pyramidal cells, Brain Res. 259 (1983) 137–142.
[123] J.F. Staiger, K. Zilles, T.F. Freund, Distribution of GABAergic elements postsynaptic to ventroposteromedial thalamic projections in layer IV of rat barrel cortex, Eur. J. Neurosci. 8 (1996) 2273–2285.
[124] J.F. Staiger, K. Zilles, T.F. Freund, Recurrent axon collaterals of corticothalamic projection neurons in rat primary somatosensory cortex contribute to excitatory and inhibitory feedback-loops, Anat. Embryol. 194 (1996) 533–543.
[125] K.J. Staley, I. Mody, Shunting of excitatory input to dentate gyrus granule cells by a depolarizing $GABA_A$ receptor-mediated postsynaptic conductance, J. Neurophysiol. 68 (1992) 197–212.

[126] K.J. Stratford, K. Tarczy-Hornoch, K.A.C. Martin, N.J. Bannister, J.J.B. Jack, Excitatory synaptic inputs to spiny stellate cells in cat visual cortex, Nature 382 (1996) 258–261.
[127] J. Szentagothai, The 'module-concept' in cerebral cortex architecture, Brain Res. 95 (1975) 475–496.
[128] J. Szentagothai, The neuron network of the cerebral cortex: a functional interpretation. The Ferrier Lecture, 1977, Proc R Soc Lond B 201 (1978) 219–248.
[129] J. Szentagothai, Synaptology of the Visual Cortex, in: R. Jung, H. Autrum, W.R. Loewenstein, D.M. McKay, H.L. Tenber (Eds.), Handbook of Sensory Physiology, VII/3B, Springer, Berlin, 1973, pp. 269–324.
[130] J. Szentagothai, M.A. Arbib, Conceptual models of neural organization, Neurosci. Res. Prog. Bull. 12 (1974) 305–510.
[131] T. Takahashi, I.D. Forsythe, T. Tsujimoto, M. Barnes-Davies, K. Onodera, Presynaptic calcium current modulation by a metabotropic glutamate receptor, Science 274 (1996) 594–597.
[132] G. Tamas, E.H. Buhl, P. Somogyi, Fast IPSPs elicited via multiple synaptic release sites by distinct types of GABAergic neurone in the cat visual cortex, J. Physiol. (Lond.) 500 (1997) 715–738.
[133] G. Tamas, E.H. Buhl, R.S.G. Jones, P. Somogyi, Interactions between distinct GABAergic neuron types eliciting fast IPSPs in cat visual cortex: number and placement of synapses, Soc. Neurosci. Abs. 23 (1997) 1265.
[134] G. Tamas, E.H. Buhl, P. Somogyi, Massive autaptic self-innervation of GABAergic neurons in cat visual cortex, J. Neurosci. 17 (1997) 6352–6364.
[135] K. Tanaka, Cross-correlation analysis of geniculostriate neuronal relationships in cats, J. Neurophysiol. 49 (1983) 1303–1318.
[136] A.M. Thomson, Activity-dependent properties of synaptic transmission at two classes of connections made by rat neocortical pyramidal axons in vitro, J. Physiol. (Lond.) 502 (1997) 131–147.
[137] A.M. Thomson, J. Deuchars, D.C. West, Large, deep layer pyramid–pyramid single axon EPSPs in slices of rat motor cortex display paired pulse and frequency-dependent depression, mediated presynaptically and self-facilitation, mediated postsynaptically, J. Neurophysiol. 70 (1993) 2354–2369.
[138] A.M. Thomson, J. Deuchars, D.C. West, Single axon excitatory postsynaptic potentials in neocortical interneurons exhibit pronounced paired pulse facilitation, Neuroscience 54 (1993) 347–360.
[139] A.M. Thomson, J. Deuchars, Synaptic interactions in neocortical local circuits: Dual intracellular recordings in vitro, Cerebral Cortex 7 (1997) 510–522.
[140] A.M. Thomson, S. Radpour, Excitatory connections between CA1 pyramidal cells revealed by spike triggered averaging in slices of rat hippocampus are partially NMDA receptor mediated, Eur. J. Neurosci. 3 (1991) 587–601.
[141] A.M. Thomson, D.C. West, Fluctuations in pyramid–pyramid excitatory postsynaptic potentials modified by presynaptic firing pattern and postsynaptic membrane potential using paired intracellular recordings in rat neocortex, Neuroscience 54 (1993) 329–346.
[142] A.M. Thomson, D.C. West, J. Deuchars, Properties of single axon excitatory postsynaptic potentials elicited in spiny interneurons by action potentials in pyramidal neurons in slices of rat neocortex, Neuroscience 69 (1995) 727–738.
[143] A.M. Thomson, D.C. West, J. Hahn, J. Deuchars, Single axon IPSPs elicited in pyramidal cells by three classes of interneurones in slices of rat neocortex, J. Physiol. (Lond.) 496 (1996) 81–102.
[144] K. Toth, T.F. Freund, R. Miles, Disinhibition of rat hippocampal pyramidal cells by GABAergic afferents from the septum, J. Physiol. (Lond.) 500 (1997) 463–474.
[145] R.D. Traub, J.G.R. Jefferys, R. Miles, M.A. Whittington, K. Toth, A branching dendrite model of a rodent CA3 pyramidal neurone, J Physiol (Lond) 481 (1994) 79–95.
[146] M.V. Tsodyks, H. Markram, The neural code between neocortical pyramidal neurons depends on neurotransmitter release probability, Proc. Natl. Acad. Sci. USA 94 (1997) 719–723.
[147] I. Vida, K. Halasy, C. Szinyei, P. Somogyi, E.H. Buhl, Unitary IPSPs evoked by interneurons at the stratum radiatum lacunosum-moleculare border in the CA1 area of the rat hippocampus in vitro, J. Physiol. (Lond.) 506 (1998) 55-73.
[148] H.J. Wagner, Presynaptic bodies ('ribbons'): From ultrastructural observations to molecular perspectives, Cell Tissue Res. 287 (1997) 435–446.
[149] M.J. Wall, M.M. Usowicz, Development of action potential-dependent and independent spontaneous $GABA_A$ receptor-mediated currents in granule cells of postnatal rat cerebellum, Eur. J. Neurosci. 9 (1997) 533–548.
[150] E.L. White, Termination of thalamic afferents in the cerebral cortex, (1986) 271–289.
[151] M.A. Whittington, R.D. Traub, J.G.R. Jefferys, Synchronized oscillations in interneuron networks driven by metabotropic glutamate receptor activation, Nature 373 (1995) 612–615.
[152] R. Yuste, D.W. Tank, Dendritic integration in mammalian neurons, a century after Cajal, Neuron 16 (1996) 701–716.