Topical Review

Target-specific expression of pre- and postsynaptic mechanisms

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Target-specific expression of pre- and postsynaptic mechanisms of synaptic transmission has been shown in a variety of central neurons by a number of laboratories. These data have demonstrated that synaptic transmission between single axons diverging onto distinct target neurons can behave independently, differentially influencing activity in the target neuron. Similarly, single neurons are capable of manufacturing molecularly distinct ligand-gated receptors and targeting them to synapses innervated by distinct converging afferent projections. A picture is emerging consistent with a role for both pre- and postsynaptic mechanisms in influencing the target-specific nature of transmission at numerous diverse synapses throughout the mammalian CNS. This target specificity adds another level of complexity in unravelling the roles played by individual neurons within a computational network. To begin to understand the coordinated activity of large ensembles of neurons it is becoming clear that the nature of transmission between individual pre- and postsynaptic elements within a circuit must first be understood for each and every neural element involved.

New cellular processes do not extend randomly. Instead, they may be oriented along major pathways or even in the direction of intracellular associations mediating repeated solicitations of the will. . . . we saw that mechanism underlying the growth of new axonal branches may be attributed to chemotactic influences.

Ramón y Cajal (*1898*)

Ramón y Cajal was among the first to propose an explanation of how the high degree of specificity among different types of neurons within the mammalian central nervous system developed. The works of Golgi (1884), Ramón y Cajal (1898) and Lorente de Nó (1934) provided the framework for the first classification of the basic cell types that make up the nervous system: the 'principal cells' and cells with 'small axons' which are are today commonly referred to as 'local circuit interneurons'. Furthermore, their work suggested that the highly specific arborization patterns of both dendritic and axonal morphologies were based on the capacity of neurons to select their postsynaptic targets. Surprisingly, the concept of 'synaptic targeting' was born before the existence of different types of neurotransmitters, intracellular proteins, receptors and receptor subunits was known.

Until only recently, it was generally accepted that each presynaptic axon influenced all of its postsynaptic targets in a similar way, regardless of the neuroanatomical/neurochemical identity of the postsynaptic target. Such a configuration would ensure that activity coursing down an axon would be transmitted equivalently to all of the synaptic targets. The first clues that this was too simplified a notion were provided from work at the neuromuscular junction. In the lobster proximal accessory flexor muscle, transmission to different muscle fibres was facilitated to markedly different degrees (Frank, 1973). However, the stimulation of synapses on any single fibre evoked postsynaptic potentials with highly similar facilitation properties. Therefore it was concluded that the presynaptic nerve terminal and the single muscle fibre have 'matching facilitation characteristics'. In the somatogastric system of the lobster two muscles, gm8 and gm9, are innervated by the same motor neuron. The synaptic specializations formed by this common axon were physiologically and anatomically distinct; gm8 muscle contracts slowly and maintains contracture, while gm9 contracts rapidly and then relaxes (Katz *et al.* 1993). Moreover, gm8 was shown to exhibit facilitation of excitatory junction potentials but gm9 did not. At the ultrastructural level, gm9 was shown to have

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larger and more numerous presynaptic bars than gm8. This higher density of release sites suggested a higher output of neurotransmitter, more rapid depletion of vesicles, and consequently the lack of synaptic facilitation on gm9 synapses. Electrophysiological studies in other invertebrate tissue also demonstrated that a single motor neuron axon could have terminals that exhibited different physiological attributes depending on the nature of the target tissue (Atwood & Bittner, 1971; Parnas, 1972; Muller & Nicholls, 1974; Gardner, 1991; Laurent & Sivaramakrishnan, 1992; Davis & Murphey, 1993). These seminal investigations paved the way for our current understanding of the nature of target-specific expression of both pre- and postsynaptic mechanisms. The present review attempts to bring together recent work from a variety of laboratories concerned with such issues. The review is divided into two parts: the first deals with target-specific mechanisms arising from diverging single axon projections; the second will discuss recent observations that single cells can target molecularly distinct receptor subunits across the somato-dendritic axis.

I. Target cell-specific mechanisms of synaptic transmission

In central neurons it had been assumed that the probability of neurotransmitter release (P_r) was identical at all terminals for a given synaptic type. The first evidence that this was not the case came from studying the P_r of synapses formed between cultured hippocampal pyramidal neurons and their targets. Rosenmund *et al.* (1993) demonstrated that the P_r of synapses from a single axon were non-uniform and showed considerable range (0·09–0·54). Although the exact mechanisms responsible for the differential properties of hippocampal synapses were not determined, this study provided the first clue that synapses from a single class of central neuron axon were not all functionally equivalent.

The question of whether axons in the mammalian central nervous system exhibit target-specific differences in the mechanism of synaptic transmission has recently been addressed by several laboratories. The first direct anatomical evidence for the existence of target-specific differentiation of a single central axon came from the laboratory of Peter Somogyi. In an elegant study, Shigemoto *et al.* (1996) demonstrated that axon terminals of hippocampal CA3 pyramidal cells innervating metabotropic glutamate receptor subtype 1α (mGluR1α)-expressing interneurons possessed a >10-fold higher level of presynaptic mGluR7 than axon terminals making contacts with mGluR1α-negative principal cells. The specificity of matching of pre- and postsynaptic receptor composition was extremely high; even a single terminal forming two active zones with different postsynaptic targets formed one mGluR7-containing and one mGluR7-negative synapse (Fig. 1). In the data of Shigemoto *et al.* (1996) the presence or absence of mGluR1α in the postsynaptic cell was not a determining factor since the pattern of mGluR7 expression was identical in genetically altered mice lacking postsynaptic mGluR1α expression. This raised the possibility that presynaptic neurons could regulate the probability of transmitter release at individual synapses according to their postsynaptic target.

Functional evidence that differential presynaptic mGluR expression endowed pyramidal cell axons with distinct mechanisms of synaptic transmission came from Scanziani *et al.* (1998). In this study, activation of presynaptic Group III mGluRs decreased EPSC amplitude only at pyramidal neuron axon terminals contacting inhibitory interneurons but not other pyramidal cells, even when recordings were made to show the same presynaptic cell contacting two distinct postsynaptic elements. A differential distribution of other members of the mGluR class of glutamate receptors has also been shown in the mossy fibre axons of dentate gyrus granule cells (Shigemoto *et al.* 1997) suggesting that targeting of mGluRs to specific axonal terminals may be a common feature of cortical synapses.

In cortical and hippocampal circuits, repetitive activation of afferents either progressively increases (facilitation) or decreases (depression) the amplitudes of excitatory synaptic events. Thus synapses can be 'facilitating' or 'depressing' depending on whether subsequent excitatory events are potentiated or depressed, respectively. Cells expressing either depressing or facilitating postsynaptic responses are thought to play distinct roles in a given neuronal network. Facilitation may act to summate, bringing second and subsequent postsynaptic responses closer to threshold for the generation of a postsynaptic action potential. Such a mechanism would increase the reliability of transmission at a given synaptic contact. In contrast, depression could weaken the influence of subsequent responses from the same input at higher firing rates. The depression or facilitation of synaptic transmission in response to a train of stimuli appears to be dictated in part by the target neuron. The use of paired recordings from connected neurons in the *in vitro* hippocampal or cortical slice preparation has generated an extended list of the depressing or facilitating properties of numerous synaptic connections. Consideration of this ever-growing list of synaptic properties suggests that few 'hard and fast' rules exist but serves to underscore that each synaptic connection must be considered a unique entity.

One of the first demonstrations that synaptic transmission from presynaptic cortical pyramidal cells was target specific came from pioneering work from the laboratory of Alex Thomson. By studying connected pairs of neocortical pyramidal neurons–pyramidal neurons and pyramidal neurons–inhibitory interneurons throughout all cortical layers, they demonstrated that pyramidal cell connections could demonstrate either paired pulse depression or paired pulse facilitation at connections with other pyramidal cells. In contrast, pyramidal neuron synapses terminating on two classes of interneuron only showed frequency-dependent facilitation (Thomson, 1997). Similarly, in the hippocampus, CA1 pyramidal neuron inputs onto stratum oriens/alveus interneurons showed facilitatory synaptic responses, while CA1 pyramidal inputs onto basket cells and bistratified cells

demonstrated synaptic depression (Ali *et al.* 1998; Ali & Thomson, 1998). Furthermore, Scanziani *et al.* (1998) demonstrated that short-term transmission between a common CA3 pyramidal neuron and a sequentially recorded CA3 pyramidal neuron and a stratum oriens inhibitory interneuron in organotypic culture was fundamentally different. Unitary EPSCs onto stratum oriens interneurons typically had a greater paired pulse ratio in response to two action potentials than at connections between two pyramidal cells.

Differences not only in short-term, but also in long-term plasticity of synaptic transmission have been observed

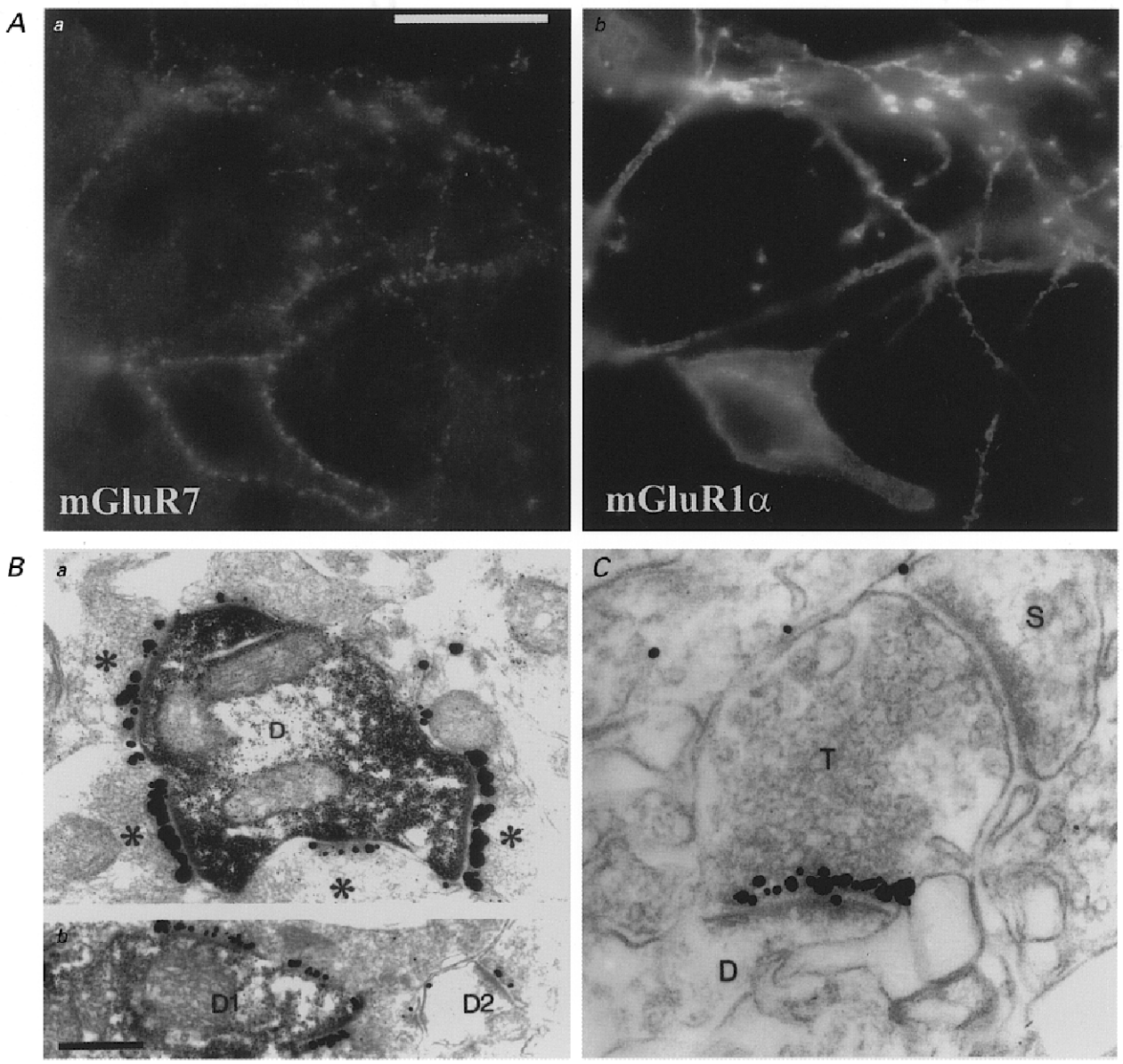

Figure 1. Selective targeting of presynaptic mGluR7 receptors to synapses formed onto mGluR1α-expressing interneurons

A and *B*, correlated distribution of immunoreactivity for mGluR7 and mGluR1α. mGluR7 positive terminals (*Aa*) outline the somas and dendrites of mGluR1α-positive interneurons in the stratum oriens/alveus of the rat hippocampus (*Ab*). Scale bar, 20 μm, applies to all panels. *B*, mGluR7 expression in the presynaptic grid at the electron microscopic level. Synaptic junctions terminating on a mGluR1α-positive dendrite (D) are heavily labelled for mGluR7 (*Ba*), while those on a mGluR1α-negative dendrite (D2) are labelled only weakly for mGluR7 (*Bb*). *C*, mGluR7 is differentially expressed at two synapses of the same terminal (T). The presynaptic specialization facing a dendrite (D) typical of mGluR1α-positive interneurons is heavily labelled for mGluR7, while the other synapse terminating on a pyramidal cell spine (S) lacks mGluR7 immunolabelling, demonstrating the exquisite selectivity of mGluR7 targeting. From Shigemoto *et al.* (1997). Data used by kind permission of the authors and reproduced with permission from *Nature*.

between two different postsynaptic targets innervated by the same input pathway. Single granule cell axons have specialized terminals including large mossy boutons, small *en passant* terminals and filopodial extensions of the mossy boutons (Fig. 2*A*). The interneuron targets of granule cells are preferentially innervated by filopodial extensions and small *en passant* terminals. In contrast, pyramidal neurons are innervated only by the more complex, large diameter mossy boutons and are spared from innervation by the smaller bouton types (Acsády *et al.* 1998). These anatomical specializations were also shown to be functionally distinct. Mossy fibre axons of the dentate granule cells exhibit a well described form of NMDA-independent, cAMP-dependent long-term potentiation (LTP) at synapses onto CA3 pyramidal cells. Maccaferri *et al.* (1998) demonstrated that an induction protocol that induced LTP at mossy fibre synapses onto CA3 pyramidal cells, induced either long-term depression (LTD) or no change in synaptic strength when

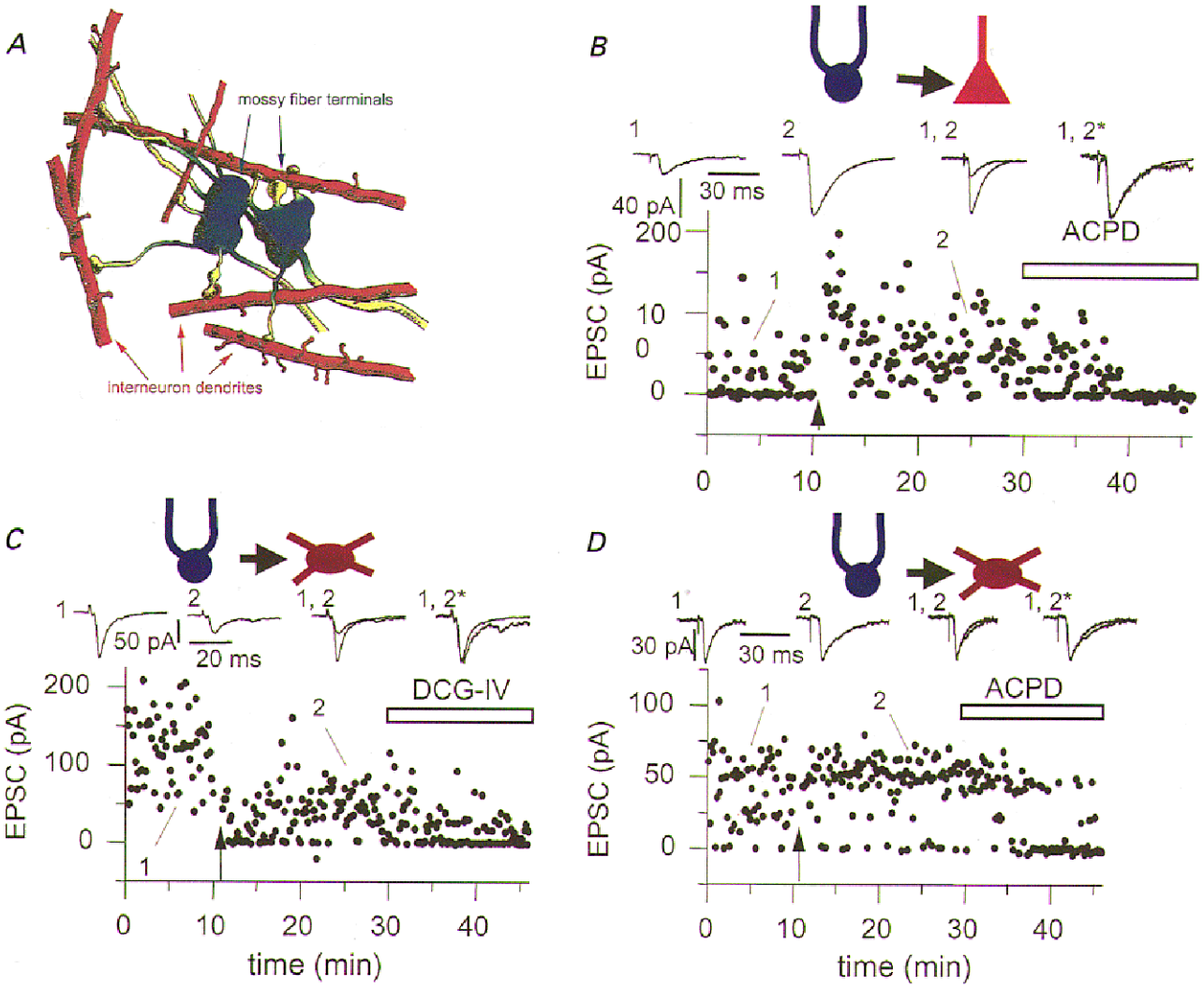

Figure 2. Target-specific expression of mossy fibre long-term potentiation

A, filopodial extensions (yellow) of large mossy fibre terminals (blue) are specialized to innervate GABAergic cells. Artistic impression of two mossy fibre terminals each with four filopodial extensions. All filopodia contact the dendrites or spines of interneurons. *B–D*, differential synaptic plasticity at mossy fibre–pyramidal cell (*B*) and mossy fibre–interneuron synapses (*C* and *D*). Synapses made by filopodial extensions onto interneurons lack a cAMP-dependent form of long-term potentiation (LTP, *C* and *D*) common to mossy fibre synapses onto CA3 pyramidal neurons (*B*). *B*, LTP at synapses onto pyramidal neurons was induced by tetanic stimulation (4 × 100 Hz, 1 s duration, indicated by arrow). Following tetanic stimulation neither short- or long-term potentiation was observed at mossy fibre synapses onto interneurons, instead interneuron long-term depression (iLTD) or no change in synaptic strength was observed. In all experiments activation of Group II metabotropic glutamate receptors (by either ACPD or DCG-IV) blocked synaptic transmission at synapses onto both pyramidal neurons and interneurons confirming their identity as mossy fibres. From Acsady *et al.* (1998) (*A*) and Maccaferri *et al.* (1998) (*B–D*). Data used by kind permission of the authors and reproduced with permission from *Journal of Neuroscience* (for *A*) and *Science* (copyright 1998 American Association for the Advancement of Science; for *B–D*).

the postsynaptic targets were interneurons (Fig. 2*B–D*). Similarly, elevation of cAMP levels by forskolin induced LTP at synapses onto pyramidal cells but failed to alter transmission at synapses onto interneurons. These data demonstrate that different mossy fibre terminals are functionally distinct, and that synaptic terminals arising from a common axon do not behave as a single compartment but are specialized depending on their postsynaptic target. The precise mechanisms underlying this lack of presynaptic mossy fibre plasticity at mossy fibre–interneuron synapses are unclear at this time. It is possible that an essential component of the cAMP-dependent cascade is absent from the pre- or postsynaptic terminals of interneurons.

NMDA-dependent LTP observed between Schaffer collateral axons and CA1 pyramidal neurons is similarly absent at the same synapses onto many inhibitory neurons (Ouardouz & Lacaille, 1995; Maccaferri & McBain, 1995, 1996; McMahon & Kauer, 1997). The lack of NMDA-dependent LTP is thought to result from the absence of calcium–calmodulin kinase II expression in inhibitory interneurons (Liu & Jones, 1996; Sík *et al.* 1998; see review by McBain *et al.* (1999) for further discussion).

Taken together, all of the above data strongly indicate that the synaptic properties of axons belonging to the same type of neuron are influenced by the nature of their postsynaptic targets.

The first direct demonstration that transmitter release could be differentially and simultaneously modulated at individual terminals from the same axon came with a technically demanding series of experiments using triple and quadruple recordings of connected neurons from the laboratories of Bert Sakmann (Reyes *et al.* 1998) and Henry Markram (Markram *et al.* 1998). By simultaneously recording from one presynaptic neocortical pyramidal cell and two postsynaptic cells, one pyramidal, the other interneuronal, Markram *et al.* (1998) showed that the very same presynaptic burst evoked a facilitating response at the interneuron synapse and a depressing response at a synapse onto the pyramidal cell (Fig. 3*A*). In another series of experiments, presynaptic bursts from three pyramidal cells, all converging onto the same interneuron, showed qualitatively similar facilitating and depressing postsynaptic responses (Markram *et al.* 1998). The time course of facilitation and depression, however, differed for each of these convergent connections,

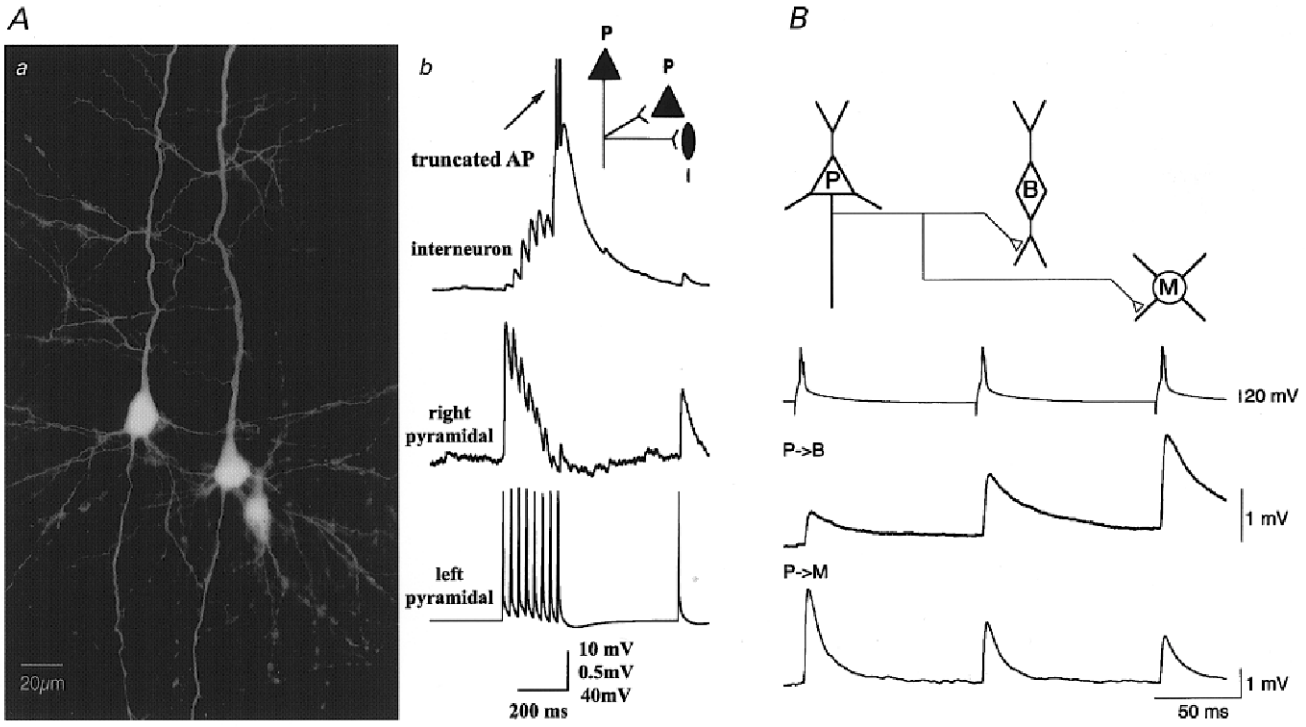

Figure 3. Differential synaptic signalling via the same axon innervating two distinct targets

Aa, light microscopic image of three biocytin filled neurons. The pyramidal cell on the left innervated the pyramidal cell on the right and the bipolar interneuron on the right. *Ab*, single trial responses (30 Hz) to the same action potential train from the pyramidal cell on the left evoked a facilitating response in the interneuron and a depressing response in the pyramidal cell. *B*, triple recordings reveal differential short-term plasticity in two classes of interneurons innervated by a single cortical layer 2/3 pyramidal neuron. When the pyramidal cell was fired at 10 Hz (upper trace) the amplitude of unitary EPSPs evoked successively in the bitufted cell increased (middle trace), whereas the amplitude of those EPSPs evoked simultaneously in the multipolar cell decreased (lower trace). From Markram *et al.* (1998) (*A*) and Reyes *et al.* (1998) (*B*). Data used by kind permission of the authors and reproduced with permission from *Proceedings of the National Academy of Sciences of the USA* (copyright 1998 National Academy of Sciences, USA; for *A*) and *Nature Neuroscience* (for *B*).

suggesting that different pre- to postsynaptic interactions underlie quantitative differences in synaptic properties.

Further evidence that the nature of the postsynaptic target alone (i.e. principal neuron *versus* inhibitory interneuron) did not determine the pattern of postsynaptic activity was demonstrated by Reyes *et al.* (1998), who demonstrated that synaptic transmission via a single pyramidal cell axon generated different responses in two distinct inhibitory interneuron classes. Simultaneous recording from a layer 2/3 pyramidal cell connected to a bitufted inhibitory cell and a multipolar inhibitory cell demonstrated that the same train of presynaptic action potentials resulted in facilitation at synapses onto bitufted cells, while synaptic depression was observed at multipolar cells (Figure 3*B*).

Evidence that depressing or facilitating synapses may reflect a developmental process was established by Bolshakov & Siegelbaum (1995) who demonstrated that the probability of release and the incidence of long-term potentiation were developmentally regulated. In young animals (< 8 days postnatal) the probability of release at Schaffer collaterals synapses onto CA1 hippocampal neurons is initially high (∼0·9), and at this stage normally occludes the expression of LTP. In contrast by 2–3 weeks postnatal the P_r fell to ∼0·5 and LTP was associated with an increase in P_r from a single synaptic site.

Further evidence for a developmental process underlying transmitter release was shown in recordings made between layers 2/3 and 5 of the rat sensorimotor cortex (Reyes & Sakmann, 1999). In the immature cortex (postnatal day (P)14), EPSPs evoked in all connected cells, whether between layers or within layers, showed depression in response to a short train of stimuli. The degree of depression was determined by the identity of the presynaptic neuron; responses evoked by stimulation of layer 5 neurons depressed significantly more than those evoked from layer 2/3 neurons. In the mature cortex (P28), however, the EPSPs evoked in connected cells were facilitated to a comparable degree, regardless of the layer in which the pre- or postsynaptic cell was located.

Whether a synapse facilitates or depresses in response to a short train of presynaptic stimuli is based on changes in the probability of evoked transmitter release (for review see Zucker, 1989, 1999). Analysis of the frequency-dependent changes in synaptic transmission at various cortical synapses has revealed complex heterogeneity of the synaptic transfer function. Markram *et al.* (1998) have suggested that such heterogeneity allows multiple synaptic representations of the same presynaptic action potential train, which depends in part on the precise synaptic parameters and the history of presynaptic action potential activity. Target-specific facilitation or depression could, in part, be due to the combined processes of Ca^{2+} dynamics in the distinct presynaptic terminals (i.e. the type of voltage-gated calcium channels expressed, mechanisms of Ca^{2+} buffering, differences in the Ca^{2+} domains in the active zone), magnitude and time course of presynaptic action potentials, differential expression of presynaptic voltage-gated potassium channels, the depletability of the readily releasable neurotransmitter pool, presynaptic autoreceptors, neurotransmitter concentration *versus* time profile, degree of transmitter spillover, density of neurotransmitter uptake transporters, geometry of synaptic cleft. Postsynaptic mechanisms such as receptor desensitization may also play a role (however see Markram *et al.* 1998; Reyes & Sakmann, 1999). Whether any or all of these mechanisms are involved will need to be determined one synapse at a time.

II. Afferent-specific innervation of molecularly distinct glutamate receptors

A large number of both voltage- and ligand-gated ion channels are polarized across the dendritic-somatic-axonal axis. The mechanisms underlying this polarization across neurons are poorly understood; however, distribution of membrane proteins is maintained by specialized domains situated at the axon initial segment of neurons, which prevents diffusion of proteins between axon and the somato-dendritic surface (Winckler *et al.* 1999). However, segregation of receptors is not only restricted to the axonal or somato-dendritic compartment. A single cell has several hundred dendritic branches that receive inputs from numerous distinct excitatory and inhibitory afferent pathways. Since Gray's pioneer work (1959) on the ultrastructure of the nervous system we know that two types of synapse exist, type I, or asymmetric, and type II, or symmetric. Later, type I synapses were shown to be excitatory, while type II were inhibitory in nature (Andersen *et al.* 1963; Eccles, 1964). At the neuromuscular junction, acetylcholine receptors are localized precisely on the opposite side of the presynaptic terminal (Fertuck & Salpeter, 1976). In the central nervous system, however, although many receptors are concentrated at synapses, in many cases they are also sparsely distributed at the non-synaptic membrane surfaces, i.e. extrasynaptic receptors (Richards *et al.* 1987; De Blas *et al.* 1988; Somogyi *et al.* 1989; Soltesz *et al.* 1990; Martin *et al.* 1993; Molnar *et al.* 1993; Baude *et al.* 1993, 1994; Nusser *et al.* 1995, 1998). The cellular and subcellular distribution of glutamate (Petralia & Wenthold, 1992; Martin *et al.* 1993; Molnar *et al.* 1993; Baude *et al.* 1993, 1994) and GABA receptors (Richards *et al.* 1987; De Blas *et al.* 1988; Somogyi *et al.* 1989; Soltesz *et al.* 1990; Nusser *et al.* 1995, 1996*a*, 1998) in fixed animal tissue showed that they are predominantly expressed in only one type of synapse; glutamate receptors in asymmetric synapses and GABA receptors in symmetric synapses (but see Nusser *et al.* 1996*b* who show α6 GABA subunits in glutamatergic synapses).

It is well established that many native ligand-gated receptors comprise several distinct subunits and that the subunit composition of a receptor can greatly influence the physiological parameters associated with that receptor. Since synaptic specializations exist to facilitate the precise transmission of signals between two adjacent neurons, the

selective targeting of distinct receptor populations to synapses associated with a given set of afferents would be a powerful mechanism to increase the computational power of any given neuron. The question of whether single central neurons express receptors with different subunit composition on their surface, or are 'committed' to a certain subunit composition has only recently begun to be explored. Furthermore if a single neuron can express receptors with different molecular composition how are they distributed on the membrane surface? Is expression uniform or are certain receptor types facing different afferent inputs? The answers to these questions are of fundamental importance for our understanding of the computational power of a single neuron within a given network.

The first evidence that presynaptic innervation could influence synaptic receptor expression was provided by Sakmann & Brenner (Sakmann & Brenner, 1978; Brenner & Sakmann, 1983) working at the neuromuscular junction. During synapse development a neurally controlled conversion of ACh receptor channels occurs about 2–3 weeks after establishment of the nerve–muscle contact.

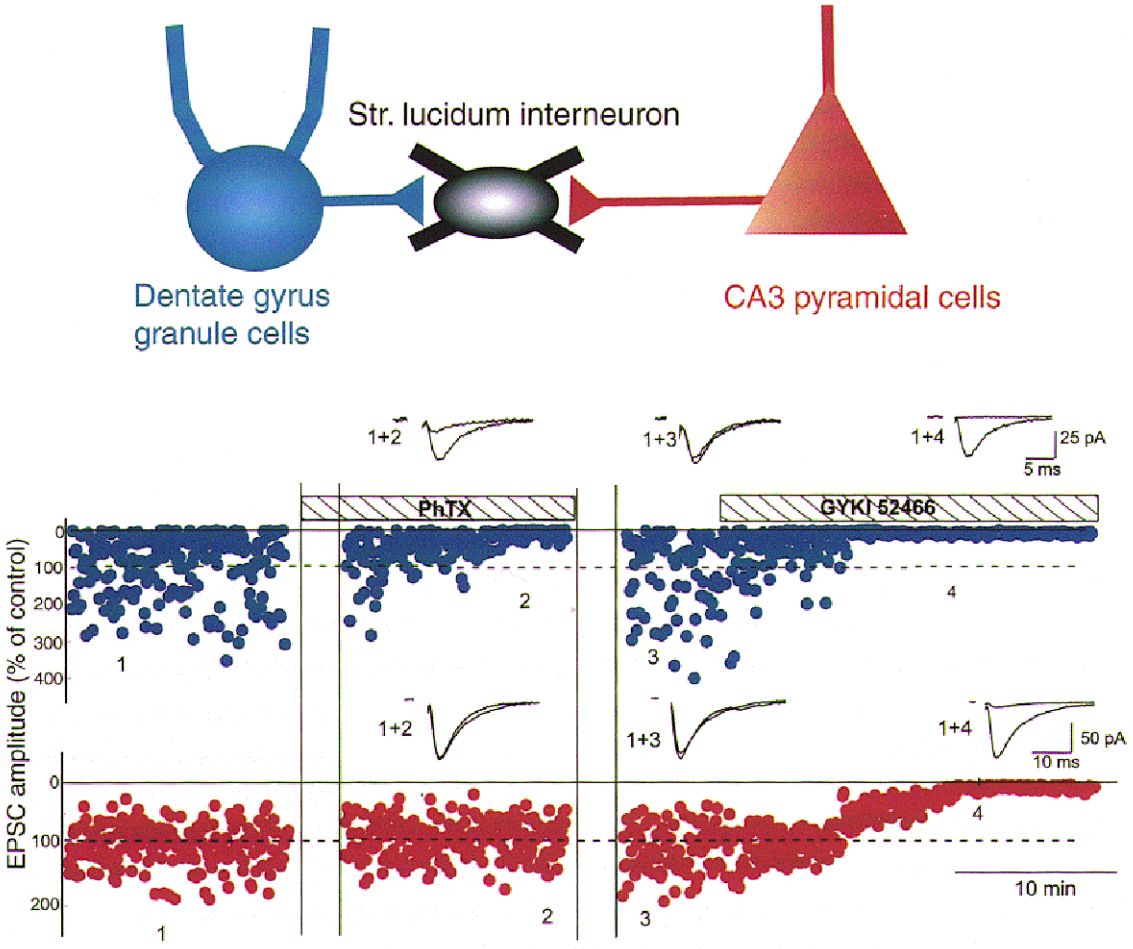

Figure 4. Single hippocampal inhibitory interneurons express both calcium-permeable and calcium-impermeable AMPA receptors

Upper panel, schematic diagram illustrating that a single stratum lucidum interneuron of the CA3 hippocampus receives afferent input from two distinct sources; the mossy fibre axons of dentate gyrus granule cells and the collaterals of CA3 pyramidal neurons. Lower traces, stimulating electrodes were positioned within the stratum radiatum and the dentate gyrus granule cell layer to stimulate either the CA3 pyramidal cell collaterals or the mossy fibres, respectively. A single experiment demonstrates that EPSCs evoked by alternate stimulation of mossy fibres (blue points) and CA3 collateral inputs (red points) can be detected on the same cell. On application of the polyamine toxin PhTX only the EPSC evoked by mossy fibre stimulation was blocked (traces 1 + 2); in contrast the CA3 recurrent collateral input remained unchanged. A 10 min portion of the initial exposure to PhTX was removed for clarity (first set of vertical lines). Following a 30 min washout period (second set of vertical lines) the mossy fibre EPSC recovered to control amplitude (trace 3). At the end of the experiment the selective AMPA receptor antagonist GYKI-52466 was added to the recording medium. Both mossy fibre- and CA3 collateral-evoked EPSCs were blocked (trace 4) confirming that they were generated by AMPA receptor activation. From Tóth & McBain (1998). Data reproduced with permission from *Nature Neuroscience*.

Embryonic ACh synapses between nerve and muscle comprise $\alpha_2\beta\gamma\delta$ subunits. Shortly after innervation, ϵ subunit mRNA expression is induced locally via a signal restricted to the end-plate region and dependent on the presence of the nerve only during a short period of early neuromuscular contact (Brenner *et al.* 1990). A concomitant reduction in the expression of the γ subunit is observed. Mature ACh receptors are then composed of $\alpha_2\beta\epsilon\delta$ subunits and are localized precisely on the opposite side of the presynaptic terminal (Fertuck & Salpeter, 1976). This developmental regulation of a synaptic receptor results in a reduction in the mean open time of ACh receptors, demonstrating that a change in gating behaviour accompanies the maturation of ACh receptors.

In frog sympathetic ganglion, B and C cells are innervated by two distinct classes of preganglionic axons (B and C fibres). Transmission at these two synapses differs 2-fold in kinetics, resulting from differences in the mean open time of the nicotinic ACh ion channels underlying each EPSC. By denervating B cells and then allowing them to become innervated solely by preganglionic C fibres, Marshall (1985) demonstrated that B cell EPSCs acquired kinetics normally characteristic of C cells, providing the first evidence that the kinetic properties of postsynaptic channels can be determined by the particular class of axon innervating them.

Examples of afferent-specific expression of molecularly distinct receptors in central neurons include expression of $\delta2$ glutamate receptors in cerebellar Purkinje cells, the differential distribution of AMPA receptors in hippocampal interneurons and neurons of the cochlear nucleus, and compartmentalization of $GABA_A$ receptors on single hippocampal pyramidal neurons.

At the anatomical level, differential distribution of most glutamate receptor subunits has been described at the electron microscopic level. The so-called 'orphan' glutamate receptor subunit $\delta2$ is prominently expressed in the cerebellum; however, $\delta2$ subunits do not form functional channels alone nor have they been shown to modify the properties of other glutamate receptor subunit combinations. However, knockout of the $\delta2$ subunit leads to a loss of activity-related depression of parallel fibre–Purkinje cell synapses highlighting a poorly understood but important role for the $\delta2$ subunit (Kashiwabuchi *et al.* 1995). Electron microscopic investigation of $\delta2$ glutamate receptor distribution demonstrated that in cerebellar Purkinje cells they are exclusively expressed at postsynaptic specializations of parallel fibre synapses and are absent from climbing fibre–Purkinje cell synapses (Landsend *et al.* 1997; Zhao *et al.* 1997). Even when both climbing fibre and parallel fibre synapses were identified on the same dendritic tree, $\delta2$ expression was associated only with parallel fibre synapses. Similarly, parallel fibre–inhibitory interneuron synapses also lacked $\delta2$ expression. These data would suggest that the expression pattern of $\delta2$ glutamate receptors is controlled by the combined identity of both the pre- and postsynaptic targets.

The first functional demonstration of molecularly distinct AMPA receptor synapses on the same cell was demonstrated at mossy fibre *versus* CA3 commisural afferent inputs onto single interneurons of the CA3 hippocampus. Tóth & McBain (1998) demonstrated that mossy fibre synaptic inputs were blocked by philanthotoxin-433 (PhTx), a polyamine toxin that blocks GluR2-lacking AMPA receptors i.e. calcium-permeable AMPA receptors (Fig. 4) (Herlitze *et al.* 1993; Brackley *et al.* 1993; Isa *et al.* 1996; Washburn & Dingledine, 1996; Iino *et al.* 1996; Bähring & Mayer, 1998). In contrast synaptic transmission at CA3 pyramidal cell collaterals onto the same cell occurs through receptors composed of Ca^{2+}-impermeable AMPA receptors. These data clearly demonstrate that afferent-specific innervation is also functionally distinct. At this time no data exist concerning the precise distribution of Ca^{2+}-permeable and Ca^{2+}-impermeable AMPA receptors on single hippocampal interneurons. It is unclear whether the two types of synaptic input innervate functionally distinct compartments of the interneurons or whether they are homogeneously distributed over the dendritic tree. The similarity in the rise times and decay time constants of the two EPSC populations, however, suggests overlapping electrotonic locations (authors' unpublished observations).

Evidence that particular glutamate receptor subunit expression can be polarized across the dendritic tree comes from analysis of different synaptic inputs to neurons of the dorsal cochlear nucleus. Fusiform cells of the dorsal cochlear nucleus receive excitatory input onto their apical dendrites from granule cell parallel fibres. Cochlear auditory nerve terminals synapse onto their basal dendrites. Several types of glutamate receptor subunits are found at both populations of synapses. However, the GluR4 AMPA receptor subunit, and the metabotropic receptor, mGluR1α, are both selectively targeted to basal dendrites and are associated only with synapses formed by the auditory nerve (Hunter *et al.* 1993; Rubio & Wenthold, 1997; Wang, 1998). AMPA receptors containing the GluR4 flop subunit gate rapidly (Mosbacher *et al.* 1994), which may be a receptor property essential in encoding timing information for proper sound localization (Raman *et al.* 1994; Trussell *et al.* 1994). Recently Gardner *et al.* (1999) demonstrated functional correlates of the molecular differences associated with inputs onto cochlear nuclear neurons. Miniature EPSCs arising from auditory nerve inputs possessed rapid kinetics and were blocked by PhTx. In contrast, mEPSCs associated with parallel fibres were resistant to PhTx and possessed slower kinetics. These data suggest that in addition to GluR4 segregation, GluR2, the AMPA receptor subunit responsible for conferring the presence or absence of calcium permeability, is also differentially targeted across the cochlear neuron somato-dendritic axis (however see Rubio & Wenthold, 1997).

A highly divergent population of inhibitory interneurons of the hippocampus and cortex possess axons that ramify extensively across different domains of both pyramidal

neurons and inhibitory interneurons to strongly influence their activity (for review see Freund & Buzsaki, 1996). These cells, which use GABA as their neurotransmitter, activate $GABA_A$ receptors on their postsynaptic target to mediate fast inhibitory synaptic transmission. Evidence that $GABA_A$ receptors may also be segregated within individual neurons, similar to glutamate receptors, was provided by the laboratory of Pearce (1993), who demonstrated the presence of two anatomically segregated and pharmacologically distinct $GABA_A$-mediated inhibitory postsynaptic currents (IPSCs) on single CA1 pyramidal neurons. IPSCs arising at the soma and presumably mediated by axo-axonic cells have a rapid time constant of decay (3–8 ms) and are blocked by furosemide (frusemide). In contrast an IPSC with a distal generation site possessed extremely slow kinetics (30–70 ms decay time constant) and was resistant to block by furosemide (Pearce, 1993; Banks *et al.* 1998). At this time the precise anatomical identity of the inhibitory interneurons generating these inhibitory synaptic events is unclear. Given the large number of anatomically distinct inhibitory interneurons that exist within the hippocampal formation it is likely that at least two inhibitory circuits exist to innervate pharmacologically distinct $GABA_A$ receptors on single pyramidal neurons.

How then do different inputs influence postsynaptic receptor distribution? As our understanding of the molecular machinery at synapses evolves it is apparent that multiple mechanisms are involved in the clustering of specific neurotransmitter receptor subunits at specific synapses. If one considers AMPA receptors alone, most mRNA for AMPA receptor subunits is largely confined to the cell soma (Craig *et al.* 1993; Benson, 1997) suggesting that the synaptic targeting of AMPA receptors requires both protein transport and local stabilization for precise positioning of each receptor form. Discussion of the machinery involved in synaptic targeting is out of the scope of the present review and the reader is referred to several excellent reviews for further reading (Sheng & Kim, 1996; Kennedy, 1997, 1998; O'Brien *et al.* 1998; Hsueh & Sheng, 1998). It is worthwhile pointing out that while these previous investigations have considered questions related to targeting and receptor sorting they provide little insight into how specific inputs control receptor distribution in a single cell.

Conclusions

The issues discussed in this review illustrate our increased understanding of the complexities of mechanisms of synaptic transmission via either a single axon diverging onto two distinct postsynaptic targets or two distinct afferent projections converging onto a common postsynaptic cell. Our understanding of how pre- and postsynaptic specializations target specific cellular elements essential for precise encoding of information at individual synapses is in its infancy. The identities of proteins known to bind to glutamate receptors are only beginning to be described. These proteins are important not only for receptor targeting and clustering but also for modulation of receptor activity and activation of appropriate signalling cascades. How these proteins are targeted at specific sites across the myriad spines and pre- and postsynaptic specializations remains a challenge for neurobiologists well into the next millenium.

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