SYMPOSIUM REPORT

Molecular diversity of neocortical GABAergic interneurones

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In addition to being the main source of inhibition in the adult brain, GABAergic interneurones are instrumental in pacing the activity of large ensembles of principal cells. GABAergic interneurones have unique features that enable them to contribute to the generation of synchronized network activity thereby shaping principal cell behaviour. Whereas the anatomical and physiological characteristics of certain interneuronal types have been studied extensively over the last decades, the molecular diversity of interneurones is a more recent focus of investigation in this field. Molecular cloning and expression analysis of many receptor families often revealed differential expression in GABAergic interneurones and pyramidal cells. Here we review recent findings regarding the molecular diversity of GABAergic interneurones in the neocortex. Better knowledge about differential gene expression in GABAergic interneurones is the basis for further investigations aimed at understanding the contribution of specific proteins in interneurones to network function.

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The morphological and neurochemical diversity of GABAergic interneurone subtypes is accompanied by an individual repertoire of receptors and ion channels, which is of major functional importance at the cellular and network level. Due to the relatively simple and structured architecture of the hippocampus, GABAergic interneurones have been mostly studied and classified in this structure, rather than in the neocortex. Hippocampal classification criteria have been often extended to 'analogous' cell types in the neocortex, even though the neurochemical and physiological signature of neocortical interneurones does not always match the postsynaptic target distribution as precisely as in the hippocampus. Most importantly, for the accurate classification/characterization of interneuronal cell types, the anatomical features and the molecular–functional properties should be investigated using a systematic and combinatorial approach.

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Molecular techniques

Different anatomical and electrophysiological techniques that were used over the past 20 years to study channel and receptor heterogeneity in the brain and that contributed to revealing molecular diversity are mentioned below. Furthermore, single cell RT-PCR proved to be a particularly valuable technique to correlate functional with molecular data.

Expression studies entailed mainly *in situ* hybridization, and immunocytochemical studies. *In situ* hybridization studies are carried out using either riboprobes or short oligonucleotide probes. Riboprobes have the advantage that they permit double-labelling, which has not been possible so far when using oligonucleotide probes. Double-labelling experiments can be performed either using two different riboprobes (e.g. one radioactively labelled and one non-radioactively labelled probe) or using a riboprobe and an antibody. Oligonucleotide probes are definitely more reliable in this respect since non-specific labelling can clearly be detected when a signal is present in competition experiments using an excess of non-labelled oligoprobe. The complementary use of both techniques is advisable: first establish the 'correct' expression pattern using an oligonucleotide probe, and then establish the

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optimal 'working conditions' for the riboprobe (Laurie *et al.* 2002).

Immunocytochemistry using specific antibodies enables expression analysis at the protein level. Furthermore, colocalization of several proteins can be studied with multiple-labelling techniques. In addition to detecting whether a protein is expressed in GABAergic interneurones or not, the availability of antibodies also permits localization studies with respect to defined cellular compartments (Kanai & Hirokawa, 1995; Waldvogel *et al.* 1999). In particular, electron microscopy techniques enable the subcellular localization of proteins at the ultrastructural level to be discerned.

Molecular cloning permitted functional studies of recombinant receptors in different expression systems (oocytes, cell lines). Studies in heterologous expression systems gave the first hints as to likely subunit composition in different brain regions and sometimes even cell types. Thus, in conjunction with *in situ* hybridization studies, the functional diversity of different receptors in subsets of neurones, including GABAergic cells, was predicted from electrophysiological characterization of recombinant nicotinic, $GABA_A$ or glutamate receptors (for review see: Changeux *et al.* 1984; Levitan *et al.* 1988; Seeburg, 1993). Sometimes, functional studies of recombinant receptors revealed channel properties that had been unknown based on previous studies of native receptors.

Functional studies revealing specific characteristics of GABAergic interneurones were most often electrophysiological studies. The availability of the different cloned channels permitted numerous investigations: whole-cell recordings were helpful as initial screening tests for channel functionality whereas measurements from outside-out patches, particularly in conjunction with fast agonist application, were useful in studies of channel kinetics.

A molecular technique that has been used frequently for mRNA expression analysis in GABAergic interneurones is single cell RT-PCR. There are reports on the use of one set of primers to amplify one or several mRNAs belonging to the same family or studies in which several sets of primers were employed to perform multiplex-PCR with the aim of detecting a number of different unrelated mRNAs. Advantages and disadvantages of these methods have been discussed elsewhere (Monyer & Markram, 2004); the choice should be dictated by the scientific question.

With these tools at hand, a number of studies provided evidence that in many instances GABAergic interneurones express a different set of genes compared to their counterparts, the pyramidal cells. Moreover, different types of interneurones are generally characterized by a particular combination of molecular, physiological and synaptic features (Cauli *et al.* 1997; Kawaguchi & Kubota, 1997; Gupta *et al.* 2000; Silberberg *et al.* 2002; Kawaguchi & Kondo, 2002). However, this is a simplified generalization since we have just begun to understand that the existing anatomical diversity (DeFelipe, 1993, 2002; Somogyi *et al.* 1998) is most likely matched by a molecular diversity. In many instances, however, this molecular diversity is inferred based on data obtained in the hippocampus, a structure that, at least with respect to certain aspects, has been studied more than the neocortex.

Receptor diversity

Our knowledge about neocortical GABAergic interneurone diversity based on molecular criteria is patchy at best, but a brief summary will also indicate the need for further studies in this field.

AMPA receptors. The existence of several subunits and splice variants for the three major ionotropic glutamate receptor subfamilies – AMPA, NMDA and kainate – prompted, of course, investigations regarding their expression in GABAergic interneurones. Single cell RT-PCR combined with outside-out patch measurements permitted correlative studies indicating that low abundance of GluR-B accounted for the high Ca^{2+} permeability of AMPA receptors in fast spiking (FS) GABAergic interneurones in somatosensory (Hestrin, 1993) and visual cortex (Jonas *et al.* 1994). In contrast to this specific property of GABAergic interneurones for which one single molecular determinant appears to be responsible, kinetic characteristics of AMPA receptors in GABAergic interneurones are regulated by several molecular mechanisms. In subsequent studies, the same technical approach led to the conclusion that in addition to subunit composition, splicing and editing are involved in determining the faster channel kinetics (Monyer *et al.* 1991; Geiger *et al.* 1995; Lambolez *et al.* 1996; Angulo *et al.* 1997). Although the generalization regarding low GluR-B expression in GABAergic interneurones in the cortex is justified (Catania *et al.* 1995; Leranth *et al.* 1996), differences in AMPA receptor Ca^{2+} permeability and conductance in different GABAergic subtypes have been reported. Thus, in contrast to FS PV-positive interneurones characterized by AMPA receptors with high Ca^{2+} permeability, a number of other GABAergic interneurone subtypes bear AMPA receptors with lower Ca^{2+} permeability. These interneurones comprise vasoactive intestinal polypeptide (VIP)-positive bitufted interneurones (Rozov *et al.* 2001) or calbindin-D28k (CB)- and parvalbumin (PV)-positive multipolar bursting (MB) cells (Blatow *et al.* 2003) in cortical layer II/III. Also, desensitization and recovery from desensitization exhibit marked differences in identified subsets of GABAergic interneurones (Angulo *et al.* 1997; Rozov *et al.* 2001). The existing examples permit at this point the following conclusion: in spite of

some variability between different GABAergic interneurone subtypes, lower GluR-B expression than in pyramidal neurones appears to be a hallmark of AMPA receptor characteristics in this cell population. The differences between GABAergic interneurone subtypes are more pronounced when kinetic properties of AMPA receptors are considered. Although interesting at a phenomenological level, these observations lead to the intriguing question: what is the functional significance of AMPA receptor diversity on GABAergic interneurones at the network level? Making use of a transgenic approach helped in resolving this question not in the neocortex but in the hippocampus. Selective overexpression of the GluR-B subunit in GABAergic interneurones indicated that AMPA receptor properties in this type of cell subserve long-range synchrony (Fuchs *et al.* 2001). Another elegant study merits emphasis in this context: Rozov and colleagues (Rozov *et al.* 2001) could show that the kinetic properties of AMPA receptors on VIP-positive bitufted interneurones in layer II/III of rat somatosensory cortex accounted for the frequency-dependent depressing responses (EPSPs and EPSCs) elicited in these cells upon repetitive stimulation of pyramidal neurones. Fast desensitization and slow recovery from desensitization of AMPA receptors on these GABAergic interneurones enable these cells to contribute to the low-pass feedback inhibition of pyramidal neurones.

NMDA receptors. Studies on NMDA receptor expression and their functional implication in cortical GABAergic interneurones are rare. In analogy to the hippocampus, it is probably safe to assume that cortical GABAergic interneurones also express NR2A and NR2B, alone or in combination (Monyer *et al.* 1994). The finding of the preferential expression of the NR2D subunit in somatostatin (SOM)- and PV-positive interneurones is based on an *in situ* hybridization study in different brain regions, including the neocortex (Standaert *et al.* 1996). Of note is that in the neocortex SOM-positive cells exhibit higher NR2D expression compared to PV-positive neurones. However, the functional role of this subunit in these GABAergic interneurones is not clear. Whilst the long deactivation time constant (more than 4 s) of NR2D-containing recombinant receptors suggests a possible function for the integration of presynaptic input over longer periods, this hypothesis remains speculative since such long NMDA receptor deactivation kinetics have not been found in neurones. In contrast to pyramidal neurones where it is known that both NR2A and NR2B are synaptically expressed, there is no information about the subcellular localization of NR2A, -B or -D in GABAergic interneurones. Based on the peculiarity of glutamate receptor subunit expression, both NMDA and AMPA receptors can contribute to Ca^{2+} entry in GABAergic interneurones, hence the question as to the relative contribution and functional role of these two glutamate receptor-mediated Ca^{2+} entry sources. Ca^{2+} imaging studies in different types of layer II mouse visual cortex interneurones indicate that Ca^{2+}-permeable AMPA and NMDA receptors differentially contribute to subthreshold Ca^{2+} dynamics in distinct GABAergic interneurone subtypes. Whilst dendritic Ca^{2+} influx through NMDA receptors is functionally important in PV-positive FS and calretinin (CR)-positive irregular spiking cells, synaptic Ca^{2+} influx through AMPA receptors is functionally relevant only in FS cells contributing to a larger peak and faster Ca^{2+} kinetics in this cell type (Goldberg *et al.* 2003).

Metabotropic glutamate receptors. Expression of mGluRs in cortical interneurones has been given little attention so far. Only one study investigating mGluR1a expression concluded that most mGluR1a-positive cells in the neocortex were GABAergic interneurones (Stinehelfer *et al.* 2000). Although purely descriptive (being an *in situ* hybridization study), these results revealed differential expression not only between different GABAergic interneurone subclasses but also within a class. There was no homogeneity of expression of mGluR1a even within one subclass as judged by double-labelling for biochemical markers: most, but not all SOM-positive neurones, about 50% of CR-positive cells, 30% of CB-positive cells and almost no PV-positive cells expressed mGluR1a.

$GABA_A$ receptors. The cloning of the first ionotropic $GABA_A$ receptor subunits goes back to the early eighties and the paucity regarding information as to their differential expression in GABAergic interneurones is surprising. This is in stark contrast to the growing body of evidence that $GABA_A$ receptors on GABAergic interneurones are also a key requirement for the generation of oscillatory activity in different frequency ranges (Whittington *et al.* 1995). It was shown for a GABAergic interneurone network formed of low threshold spiking (LTS) cells in layer IV of somatosensory cortex that for the induction of theta frequency oscillations, the activation of $GABA_A$ receptors was necessary (Gibson *et al.* 1999). In another network of chemically and electrically coupled MB cells (Blatow *et al.* 2003) in frontal and somatosensory cortex layer II/III, theta frequency oscillations also depended on interneurone $GABA_A$ conductance. However, little is known about the exact $GABA_A$ receptor subunit composition in the different GABAergic cell populations. The authors of a recent study performed in layer V of the somatosensory cortex (Bacci *et al.* 2003) came to the conclusion that functional differences in spontaneous and induced IPSCs recorded in FS and LTS cells can be accounted for at least in part by differential expression

of the $GABA_A$ receptor subunits. The higher expression of $\alpha 1$ as well as $\beta 2$–3 subunits in FS cells may underlie the higher amplitude and faster kinetics of IPSCs in these GABAergic interneurones. The authors used pharmacological tools and knockout animals to correlate IPSC waveform with differential $GABA_A$ receptor subunit expression in FS and LTS cells. Faster kinetics of IPSCs have also been reported for FS PV-positive interneurones in the hippocampus (Bartos *et al.* 2002), suggesting that fast IPSCs may be a feature that is shared by FS cells in hippocampus and neocortex.

5-HT_3 and nicotinic receptors. A less confusing picture emerged upon studying 5-HT_3 receptors in neocortex. *In situ* hybridization and immunocytochemistry (Morales *et al.* 1996; Morales & Bloom, 1997) results are in agreement with data obtained using RT-PCR (Ferezou *et al.* 2002). 5-HT_3R, the only ionotropic serotonin receptor, is expressed in a subset of GABAergic interneurones, namely the cholecystokinin (CCK)/VIP-positive neurones. This rule appears to hold for all cortical layers. Interestingly, in the RT-PCR study, the authors reported the coexpression of 5-HT_3 and nicotinic receptors in CCK/VIP-positive GABAergic interneurones. The nicotinic receptors mediating the excitatory effect are presumably composed of $\alpha 4$, $\alpha 5$ and $\beta 2$ subunits as indicated by previous pharmacological and RT-PCR results (Porter *et al.* 1999). This and other studies on nicotinic receptors are of note because they clearly indicate that caution needs to be exerted when extrapolating data and drawing conclusions based on findings from one brain region in a species. Thus, in the rat neocortex nicotinic receptors are selectively expressed in CCK/VIP-positive interneurones and are not present in pyramidal neurones. But, the restricted expression of nicotinic receptors to a subset of GABAergic interneurones may differ between species since in the developing visual cortex there is functional evidence for their presence on pyramidal neurones as well (Roerig *et al.* 1997). Also, it appears that nicotinic receptors in interneurones of the hippocampus may not be restricted to CCK/VIP-positive neurones and in addition the nicotinic receptor subunit composition appears to be different in hippocampal and neocortical interneurones.

Other receptors. GABAergic interneurone diversity is also manifested in the differential expression of the μ-opioid receptor in a subset of GABAergic interneurones in the cortex (Taki *et al.* 2000). Whilst absent from interneurones expressing PV or CB, μ-opioid receptor expression was found to a varying degree in a non-homogeneous interneurone population, expressing any of the following markers: VIP, corticotrophin-releasing factor (CRF), choline acetyltransferase (ChAT), CR or CCK.

Although not specifically expressed in GABAergic interneurones but also found in pyramidal neurones, D1 and D2 dopamine receptor subunits are more often found in PV-positive compared to CB-positive neurones in the neocortex (Le Moine & Gaspar, 1998). Functional implications are not clear at a cellular level, let alone at a network level. The study is mentioned here for the sake of completion. Similarly, expression of the cannabinoid receptor CB1 is not restricted to GABAergic interneurones in most brain areas. Activation of CB1 receptors exerts modulatory effects onto glutamatergic and GABAergic neurones. However, in the neocortex, at least in rat and mouse brain, there is an excellent correlation between CB1 expression and GABAergic interneurones. Expression diversity within the GABAergic system is illustrated best by mentioning the two extremes: CCK-positive neurones exhibit the highest expression levels; PV- and CR-positive cells are CB1 negative (Matsuda *et al.* 1993; Tsou *et al.* 1998; Marsicano & Lutz, 1999).

The above-mentioned studies clearly revealed that a number of modulatory effects mediated by nicotinic, 5-HT_3 or CB1 receptors are exerted both in the neocortex as well as in the hippocampus exclusively or preponderantly on the GABAergic system.

Potassium channels

The differential expression of voltage-gated channels in neocortex is best studied for K^+ channels. *In situ* hybridization experiments indicate that in the neocortex the expression of the four K^+ channels (Kv3.1, Kv3.2, Kv3.3 and Kv3.4) is restricted to GABAergic interneurones (Weiser *et al.* 1994). Layer-specific expression and differential expression levels were indications of combinatorial possibilities of heteromeric assemblies. Subsequent analysis concentrated on the fast activation/deactivation channels Kv3.1 and Kv3.2 that, based on functional analysis in oocytes, were thought to be the molecular substrate for fast spiking. Cellular distribution analysis revealed the presence of Kv3.1 in PV-positive cells in all cortical layers, whereas Kv3.2 was found mainly in deeper cortical layers. Since the latter was not only detected in PV-positive neurones but also in SOM- and CB-positive cells, a simple correlation between Kv3.1 and/or Kv3.2 and fast spiking could not be made. In fact, one study supports the notion that, at least in the hippocampus, the combination of Kv3.1 and Kv3.4 underlies fast spiking in PV-positive interneurones (Baranauskas *et al.* 2003). The functional significance at a network level of these K^+ channels, that are prominent in the GABAergic system, is apparent in Kv3.1 knockout mice and manifests itself in altered oscillatory activity (increased gamma and decreased delta power; Joho *et al.* 1999).These findings support the notion that GABAergic interneurones are critically involved in the generation of

synchronous, oscillatory network activity (for review see McBain & Fisahn, 2001).

Gap junction-forming proteins

Another example of differential expression of a protein in GABAergic interneurones and its functional implication at the network level is the gap junction-forming protein connexin 36 (Cx36). In the neocortex, Cx36 is preferentially expressed in GABAergic interneurones as documented by *in situ* hybridization and RT-PCR. Most of the PV-positive cells in all cortical layers express Cx36 (Belluardo *et al.* 2000). It certainly is the molecular substrate of gap junction coupling as reported for LTS (Deans *et al.* 2001), FS (Hormuzdi *et al.* 2001) and MB cells (Blatow *et al.* 2003). Functional evidence for gap junction coupling in SOM-positive layer IV LTS cells (Gibson *et al.* 1999) and in SOM-positive layer II/III bipolar neurones (Venance *et al.* 2000) indicates that gap junction coupling is not a prerogative of PV-positive neurones. However, only interneurones of the same subtype seem to be electrically coupled (Gibson *et al.* 1999; Galarreta & Hestrin, 1999; Tamás *et al.* 2000; Meyer *et al.* 2002; Amitai *et al.* 2002; Blatow *et al.* 2003; Fukuda & Kosaka, 2003). The segregation of electrically coupled networks appears to be very strict indeed, since the expression of Cx36 does not imply functional gap junctions between different neurones. As a striking example two subsets of PV- and Cx36-expressing neurones, FS cells and MB cells, belong to distinct networks each delineated by electrical coupling amongst neurones of the same subtype (Blatow *et al.* 2003). Although PV positive, these two cell types were different with respect to most criteria that were studied. More recently we have characterized two members of a new gap junction-forming protein family, the pannexins (Pxs) (Bruzzone *et al.* 2003). Albeit not selectively expressed in GABAergic interneurones, mRNA expression levels of Px1 and Px2 are higher in cortical (and hippocampal) GABAergic interneurones compared to pyramidal cells (H. Monyer, unpublished observation). Their presence in PV-positive interneurones (H. Monyer, unpublished observation) raises the intriguing question of whether they colocalize or not with Cx36 and, if so, to which cellular compartment are the gap junction proteins targeted.

Perspectives

Although often merely descriptive, the above-mentioned examples have been major contributions to a better understanding of GABAergic interneurone diversity at a functional level. The information gathered so far regarding the individual morphological, molecular and functional characteristics of particular interneurone subtypes suggest that these cells subserve distinct roles in the frame of larger circuitries. Indeed, different interneurone subclasses, e.g. FS, LTS and MB cells, appear to form discrete networks participating in various oscillation phenomena.

In a recent review, a number of techniques for studying GABAergic interneurone diversity have been discussed (Monyer & Markram, 2004). It certainly is clear that GABAergic interneurone diversity on the one hand and the scarcity of certain subtypes on the other makes the functional characterization of identified GABAergic interneurones a daunting task. Significant progress in this field of research will be heralded by the following molecular approaches: (1) combinatorial approaches using RT-PCR in conjunction with anatomical and functional characterization; (2) *in vivo* labelling of GABAergic subpopulations; (3) selective knockouts of key molecules in GABAergic interneurones; (4) functional silencing of distinct GABAergic networks. These approaches will enable the role of GABAergic cells in the living animal to be assessed. To this end a first attempt has been reported recently by Margrie *et al.* (2003) where genetically labelled PV-positive cells were patched *in vivo* using two-photon microscopy. Ultimately the need is for electrophysiological recordings and functional imaging studies from identified GABAergic interneurones during defined network activity in the live, awake animal.

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