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GABAergic Interneurons: Implications for Understanding Schizophrenia and Bipolar Disorder

Francine M. Benes, M.D., Ph.D. and Sabina Berretta, M.D.

A core component to corticolimbic circuitry is the GABAergic interneuron. Neuroanatomic studies conducted over the past century have demonstrated several subtypes of interneuron defined by characteristic morphological appearances in Golgi-stained preparations. More recently, both cytochemical and electrophysiological techniques have defined various subtypes of GABA neuron according to synaptic connections, electrophysiological properties and neuropeptide content. These cells provide both inhibitory and disinhibitory modulation of cortical and hippocampal circuits and contribute to the generation of oscillatory rhythms, discriminative information processing and gating of sensory information within the corticolimbic system. All of these functions are abnormal in schizophrenia. Recent postmortem studies have provided consistent evidence that a defect of GABAergic neurotransmission probably plays a role in both schizophrenia and bipolar disorder. Many now believe that such a disturbance may be related to a perturbation of early development, one that may result in a disturbance of cell migration and the formation of normal lamination. The ingrowth of extrinsic afferents, such as the mesocortical dopamine projections, may "trigger" the appearance of a defective GABA system, particularly under stressful conditions when the modulation of the dopamine system is likely to be altered. Based on the regional and subregional distribution of changes in GABA cells in schizophrenia and bipolar disorder, it has been postulated that the basolateral nucleus of the amygdala may contribute to these abnormalities through an increased flow of excitatory activity. By using "partial" modeling, changes in the GABA system remarkably similar to those seen in schizophrenia and bipolar disorder have been induced in rat hippocampus. In the years to come, continued investigations of the GABA system in rodent, primate and human brain and the characterization of changes in specific phenotypic subclasses of interneurons in schizophrenia and bipolar disorder will undoubtedly provide important new insights into how the integration of this transmitter system may be altered in neuropsychiatric disease.

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Neurons that express the compound, γ-aminobutyric acid (GABA), are broadly present throughout the central nervous system, although telencephalic structures, such as the cerebral cortex, show the most abundant quantities of this neurotransmitter (Jones 1987). In the discussion that follows, the anatomy and physiology of various types of GABAergic interneurons in the cortex and hippocampus will be discussed and related to recent postmortem studies implicating this transmitter system in the pathophysiology of schizophrenia and bi-

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polar disorder and their treatment with neuroleptic drugs (for more comprehensive reviews on cortical and hippocampal neurons see: Hof et al. 1993; Freund and Buzsaki 1996; Somogyi et al. 1998).

NEUROBIOLOGY OF GABAERGIC INTERNEURONS

Based on Golgi-impregnation studies, Ramon y Cajal provided the first descriptions of several different morphological subtypes of interneurons in the cerebral cortex and hippocampus (Ramon y Cajal 1893, 1911). In more recent years, it has been shown that, with some overlap, different morphological subtypes also have distinct distributions, connectivity, neurochemistry, and electrophysiological properties (for reviews see Hof et al. 1993; Freund and Buzsaki 1996). It is interesting to note that every segment of a pyramidal neuron, such as the soma, dendritic branches and spines, and the initial axonal segment, receives dense GABAergic synaptic innervation (O'Kusky and Colonnier 1982; Hendry et al. 1983; Houser et al. 1983; Beaulieu et al. 1992; for reviews see Jones 1993; Freund and Buzsaki 1996). Even more interestingly, each of these segments appears to be innervated by distinct GABAergic neuronal subtypes (see below).

These differences strongly suggest that each of these subtypes plays a fundamentally different role in physiological and pathological mechanisms. In the discussion that follows, cortical interneurons will be described first, since our most basic understanding of GABAergic cells is derived from these populations. In more recent years, however, similar characterizations of interneurons in hippocampus have emerged. Although these cells show some striking similarities to their cortical counterparts, there are also some unique features that distinguish them. For this reason, interneurons in the hippocampus are discussed separately.

Cortex

Neuroanatomical Studies of Cortical Interneurons. Various types of GABAergic neurons can be categorized according to the type of synaptic profiles they are associated with, as this has direct implications for understanding the physiological role of these cells in cortical circuits. These categories are discussed below.

AXO-SOMATIC INHIBITORY SYNAPSES (BASKET CELLS). The most commonly encountered interneurons (Figure 1A) are multipolar in shape, i.e., they may have three or more primary dendritic branches emanating from their cell bodies, some having somata that are as large as those of pyramidal neurons (Jones and Hendry 1984). Using immunocytochemistry to localize the enzyme

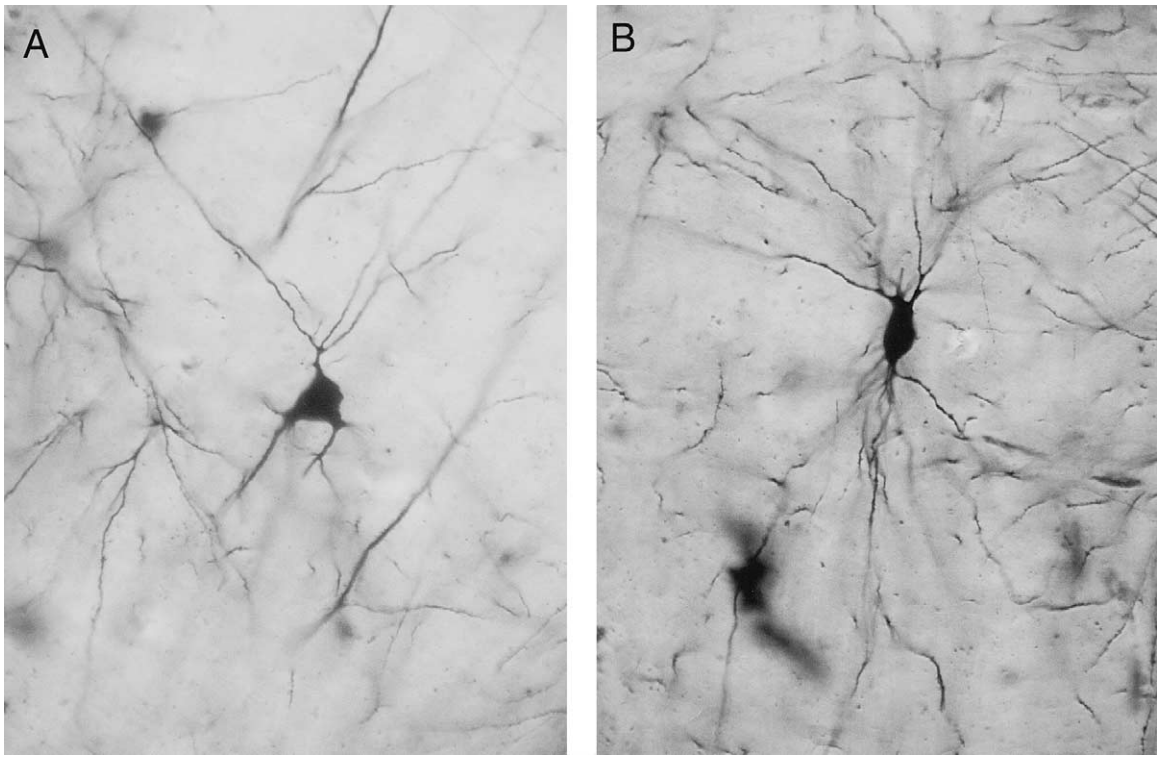

Figure 1. Nomarski photomicrographs of Golgi-impregnated neurons in human prefrontal cortex. **(A)**. A basket cell with multipolar primary dendritic branches exiting from the cell soma. **(B)**. A double bouquet cell that has an apical and basal set of dendritic arborizations that give the cell a somewhat bipolar appearance.

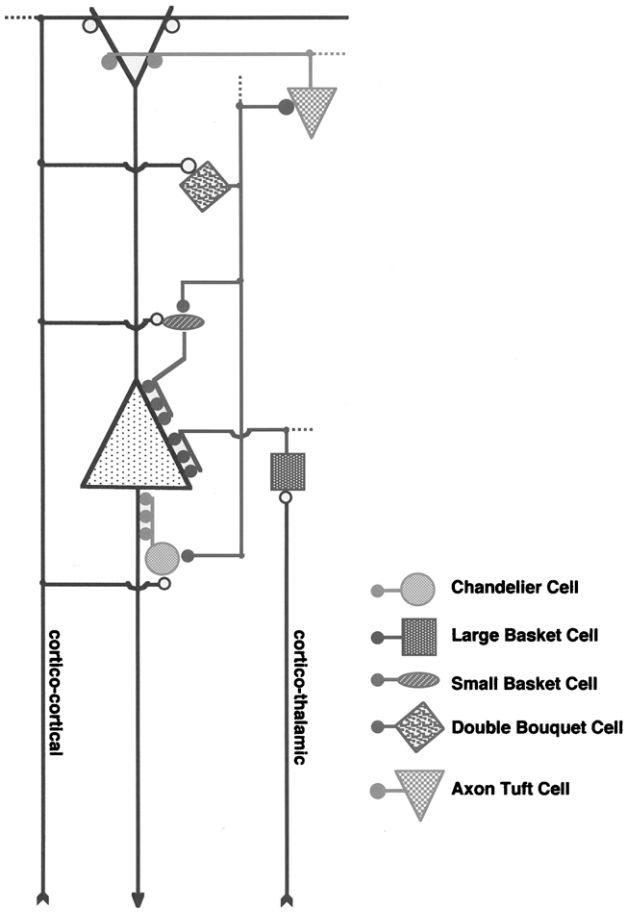

Figure 2. A schematic diagram showing the relationship between various types of GABAergic interneurons, and a pyramidal cell. Small and large *basket cells*, respectively, form axosomatic contacts with the cell body of the pyramidal neuron. A *chandelier cell* forms axo-axonic synapses with the proximal portion of the pyramidal cell dendrite. A *double bouquet* cell is shown forming GABA-to-GABA synapses with a small basket cell and a large basket cell and an axon tuft cell. Not shown are Cajal-Retzius neurons that are primarily found in layer I and to a lesser extent layer II of the cortex. Interneurons are depicted as receiving excitatory inputs from extrinsic afferents from other regions. (Modified from Eccles 1984.)

glutamate decarboxylase (GAD), that synthesizes GABA, the terminal boutons of basket cells have been found to form a basket-like arrangement around a large proportion of the surface of pyramidal cell bodies (Figure 2) (Hendry et al. 1983). These cells also form appositions with the proximal portions of the apical dendrites of these latter projection neurons. Because inputs at the level of the cell body exert much greater influences on the membrane potential of the cell than those located at distal points along the dendritic tree (Rall 1970), the inhibitory effect of basket cells on pyramidal cell firing is a potent one.

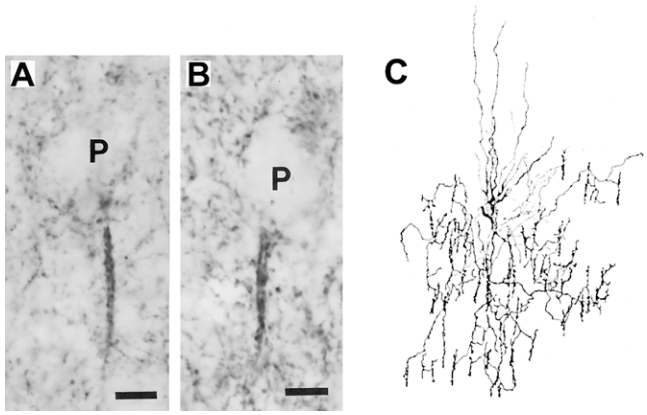

Figure 3. Light photomicrographs showing immunoreactivity for the GABA transporter (GAT-1). GAT-1 immunoreactive axon cartridges in a normal control **(A)** and schizophrenic patient **(B)** are shown to form configurations that appear like the "candles" of the chandelier neuron. (Reproduced with permission from Woo et al. 1998; Pierri et al. 1999.) **(C)** A reproduction of a camera lucida drawing of a Golgi-impregnated chandelier cell. Note the presence of 'candle-'like configurations that are believed to be axo-axonic connections with the initial segment of pyramidal neurons. (Reproduced with permission from Fairen et al. 1982.)

In the cortex, these neurons are abundantly present in layers III-V, but they may have very long axons that typically ascend toward more superficial laminae, become myelinated and give rise to axon collaterals that travel horizontally for distances of 900–1000 μm. Basket cells are, together with neurogliaform cells, the only cortical interneurons found to receive direct thalamic inputs (Figure 2) and might therefore be in the best strategic position for playing a role in shaping receptive field properties of their target neurons (Jones 1993).

AXO-AXONAL INHIBITORY SYNAPSES (CHANDELIER CELLS). These cells have axonal branches that extend at right angles from the cell body and form "candles" with a vertical orientation with respect to the surface layers (Figure 3) (Szentagothai and Arbib 1974; Peters 1984). These axonal terminations form axo-axonic synapses with the initial segment of pyramidal cell axons (Somogyi 1979). As shown in Figures 2 and 3, these so-called 'cartridges' are positioned to produce a short-circuiting of action potential propagation and thus play a major role in modulating the pyramidal neuron output activity. As shown in Figures 3A and 3B, immunolocalization of the GABA transporter (GAT-1) reveals cartridge-like structures that are believed to be the so-called "candles" of the chandelier neuron (Pierri et al. 1999; Woo et al. 1998). In the cortex, chandelier cells are predominantly found in layers II and III and are not contacted directly by thalamic afferent fibers. Thus, these neurons might be involved in modulating the

stimulus-response properties of other neurons, rather than in shaping receptive fields as it has been postulated for basket and neurogliaform interneurons.

AXO-DENDRITIC INHIBITORY AND DISINHIBITORY SYNAPSES (DOUBLE BOUQUET CELLS AND AXON TUFT CELLS). As shown in Figure 1B, double bouquet neurons have axonal arborizations that distribute themselves within narrow, radially oriented columns of the cortical mantle (Fairen et al. 1982). Their synaptic boutons contact mainly dendritic shafts and spines on the side branches of apical dendrites as well as on basal dendrites of pyramidal neurons (Somogyi and Cowey 1981; Somogyi et al. 1982; de Lima and Morrison 1989; DeFelipe et al. 1989b, 1990). Their density is so high that double bouquet neurons are probably an important source of GABAergic synapses on pyramidal neurons in layer III.

The terminations of these interneurons have been found to form synapses with other nonpyramidal cells, some showing immunoreactivity for GAD, and it has been suggested that these may be disinhibitory elements (Somogyi and Cowey 1984). As shown in Figure 2, double bouquet cells could potentially provide inhibitory input to both basket neurons and chandelier cells (see below). If so, the influence of this interneuronal subtype on the activity of local cortical circuits would be potentially complex and far-reaching. Like chandelier cells (see above), double bouquet cells are preferentially localized in layers II and III and are thus not reached directly by thalamo-cortical afferents; their main source of excitatory input is probably provided by cortico-cortical neurons. Axon tuft cells are small multipolar or bitufted cells which send axons in layer I where they form rich arborizations thought to synapse mainly on dendritic spines (Figure 2) (Fairen et al. 1982).

OTHER SUBTYPES OF CORTICAL INTERNEURONS. Neurogliaform cells, bipolar cells, and aspiny neurons in layer I also contact different segments of pyramidal neurons. Neurogliaform cells are of particular interest because they are, together with basket neurons, the only interneuron subtype known to be contacted directly by thalamo-cortical afferents and are thus thought to play a major role in shaping the receptive fields properties of cortical neurons (for review see Jones 1993 #5610).

Neurochemical Markers for GABA Neurons. It has been shown in recent years that different interneuron subpopulations in the cortex, and in other brain regions such as the hippocampus (see below), can be reliably identified by their expression of neurochemical markers such as calcium binding proteins (parvalbumin, calretinin, calbindin D28k) and neuropeptides (e.g., somatostatin, cholecystokinin, neuropeptide Y). Using these markers, cortical interneurons have been characterized in detail using anatomic, biochemical and electrophysiological methods (see below). Thus, cytochemical approaches, such as immunohistochemistry or *in situ* hybridization, offer powerful tools for investigating neuropathological changes selectively affecting neuronal subpopulations expressing calcium binding proteins and/or neuropeptides.

GLUTAMATE DECARBOXYLASE (GAD). GAD is the enzyme that synthesizes GABA and this protein occurs as either a 65 kDalton (GAD_{65}) or a 67 kDalton (GAD_{67}) isoform (Kaufman et al. 1991). While GAD_{65} is primarily localized in axon terminals, GAD_{67} (Anwyl 1991) is found in the somata and dendrites of GABA cells, although some axon terminals also appear to contain this protein. A recent study has demonstrated that both isoforms are co-localized in 95% of GABA cells in rat hippocampus; however, a small percentage of neurons may only express the 67kD isoform under baseline conditions (Stone et al. 1999).

PARVALBUMIN (PVB). PVB has been shown to be expressed mainly by *chandelier* and *basket* cells (DeFelipe et al. 1989a; Hendry et al. 1989; Fonseca et al. 1993; Gabbott and Bacon 1996a). PVB-positive neurons in the cortex, as well as in other brain regions such as the striatum and the hippocampus, have been characterized electrophysiologically as 'fast-spiking' neurons that show: (a) repetitive firing by synaptic activation of depolarized potentials; (b) short duration action potentials with short duration after-hyperpolarizations; (c) relatively negative resting potentials; and (d) lower input resistance with respect to other neuronal subpopulations (Kawaguchi and Kubota 1995; Cauli et al. 1997). 'Fast spiking' neurons have been shown to be connected to each other both through chemical synapses as well as through electrical synapses (gap junctions) so that they have been proposed to form networks that might contribute to the synchronization of electrical activity in cortical neurons (Gibson et al. 1999).

PVB neurons also receive synaptic contacts from calretinin- (CR) positive neurons which have been found to be distributed on the soma and proximal dendrites (Gabbott and Bacon 1996a); this distribution suggests that PVB neurons might be strongly inhibited by CR neurons. PVB-positive neurons have been shown to be GABAergic and, in a small percentage, to also express calbindin D28k (CB), but not other neuropeptides (Kubota et al. 1994).

CALBINDIN D28K. This protein has been reported to be mainly expressed by *double bouquet* cells (Hendry et al. 1989; DeFelipe et al. 1990; Kubota et al. 1994; del Rio and DeFelipe 1995; Gabbott and Bacon 1996a) as well as by some *Cajal-Retzius* neurons in layer I. CB-positive neurons in the cortex were found to correspond to 'low threshold spike' cells: characterized electrophysiologically by broad spikes, pronounced adaptation of firing frequency and low-threshold spikes upon depolarization by synaptic activation (Kawaguchi and Kubota 1993, 1995).

'Low threshold' neurons have been found to be selectively connected to each other through electrical synapses and thus proposed to play a role in generating synchronous inhibitory activity in the cortex (Gibson et al. 1999). CB-positive neurons in the cortex have also been found to be the main target of extrinsic GABAergic projections from the diagonal band of Broca (Freund and Gulyas 1991) and to receive CR-positive synaptic contacts on their distal dendrites (Gabbott and Bacon 1996a).

CALRETININ. This protein appears to be expressed by both *double bouquet* and *bipolar* cells, as well by *Cajal-Retzius* neurons in layer I and by large, otherwise non-identified, neurons in the infragranular layers (Conde' et al. 1994; Gabbott and Bacon 1996a). From an electrophysiological point of view, CR-positive neurons have been classified as 'regular spiking' cells. Consistent with the observation that double bouquet cell synapse with other cortical interneurons (see above), CR-positive neurons have been shown to synapse with PVB- and CB-positive cells (Gabbott and Bacon 1996a), suggesting that at least some subtypes of CR-cells might be disinhibitory interneurons.

SOMATOSTATIN. Somatostatin (SM)-positive neurons in the cortex have been shown to express GABA, CB, and neuropeptide Y, as well as nitric oxide synthase (NOS) (Kubota et al. 1994; Smiley et al. 2000). Morphologically, SM-positive neurons can be either *multipolar* or *bitufted*; some of them have been identified as Martinotti cells (Kawaguchi and Kubota 1996). Electrophysiologically, SM-positive neurons have been characterized as 'regular spiking' neurons that have been found in layers II/III and V and 'burst spiking' neurons that are exclusively localized in layer V (Kawaguchi and Kubota 1996). Different subgroups of SM-cells were found to also express vasoactive intestinal polypeptide (VIP) and CR.

VIP. VIP-positive neurons, have also been found to express somatostatin and parvalbumin (Kubota et al. 1994). Morphologically, VIP-positive neurons have been classified as *bipolar*, *double bouquet*, and *small basket* cells. These neurons showed electrophysiological characteristics typical of 'regular spiking' and 'burst spiking' neurons.

Other Classifying Principles. More recently, a detailed study of morphological, electrophysiological and synaptic (ratio of facilitation/depression of synaptic response) characteristics (Gupta et al. 2000) have lead to the development of guidelines for determining interneuronal subtypes in the cortex. According to this study, when anatomically defined neurons are classified according to their electrophysiological profile and then according to the type of synapse (see above), they form as many as fourteen distinct, non-overlapping interneuronal subpopulations! Because interneurons have been found to form synapses with functionally-related neurons, even ones of different subtypes, 'GABA-groups' are thought to form the most basic functional unit in the cortex (Gupta et al. 2000).

Inputs to GABAergic Neurons

INTRINSIC EXCITATORY INPUTS. The intrinsic excitatory inputs to cortical GABAergic interneurons have been shown to be intriguingly different from those to pyramidal neurons (Thomson and Deuchars 1994). Differences in postsynaptic responses have in fact been found to be due not only to diversity in postsynaptic specializations, but also to differences in presynaptic properties, indicating that the modulation of transmitter release at pyramidal neuron-interneuron synapses might be far more complex than at a pyramidal-pyramidal neuron connections (Thomson and Deuchars 1994, 1997). It is thought that the glutamatergic receptors involved in these connections are mainly non-NMDA in nature (Thomson and Deuchars 1994, 1997; Ling and Benardo 1995).

Recent work using laser scanning photostimulation has demonstrated that differences in laminar sources of excitatory input contribute significantly to the diversity of cortical inhibitory interneurons (Dantzker and Callaway 2000). For example, fast-spiking inhibitory basket cells receive strong stimulation from middle cortical layers, while slow firing ones receive their strongest input from deep laminae.

EXTRINSIC EXCITATORY INPUT. The extrinsic excitatory input to cortical neurons is mainly provided by afferents from the thalamus. It has been shown that thalamic inputs selectively contact and strongly excite 'fast spiking' interneurons, while other interneuronal subtypes such as the 'low threshold spiking' neurons receive weaker or no thalamic input (Gibson et al. 1999). 'Fast spiking' neurons have thus been proposed to be the mediators of fast, feedforward thalamocortical inhibition (Agmon and Connors 1992; Gibson et al. 1999). Interestingly, it has been shown that small changes in membrane potential and synaptic activities in thalamocortical networks, such as those occurring during shifts from states of vigilance to different phases of sleep, can drastically alter basic intrinsic neuronal properties of cortical neurons (Freund and Gulyas 1991; Steriade 1999). These findings imply that neuronal categories based on electrophysiological properties are more labile than previously thought.

INHIBITORY INPUTS. Inhibitory inputs to GABAergic interneurons can be either *intrinsic*, that is originate from other GABAergic neurons in the cortex, or *extrinsic* such as those originating from the diagonal band of Broca (Freund and Gulyas 1991) and from the zona incerta (Lin et al. 1990, 1997). GABA-to-GABA interactions in the cortex are a particularly intriguing type of connection. They have been shown to form networks

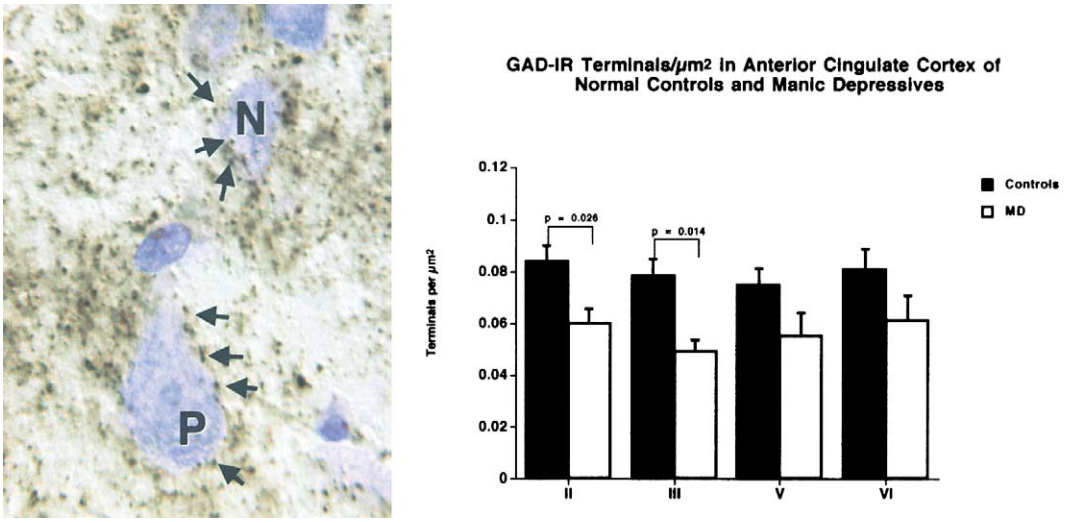

Figure 4. Light photomicrograph showing GAD-IR terminals in the anterior cingulate gyrus. Many of these terminals (arrows) can be detected around the somata of Nissl-stained pyramidal (P) and nonpyramidal (N) neurons. Densities of GAD-IR terminals around pyramidal neurons in the anterior cingulate gyrus were found to be significantly decreased in manic depressive patients as compared to normal controls (schematic diagram).

throughout the cortex in which one specific interneuronal subtype preferentially synapses with neurons of the same type (Gibson et al. 1999). As illustrated earlier these networks are connected through both GABAergic, inhibitory synapses and electrical, excitatory synapses (Gibson et al. 1999).

These networks have also been shown to be able to maintain rhythmic network activity even in the absence of excitatory inputs (Whittington et al. 1995). GABA-to-GABA interactions are likely to attenuate or perhaps even shut off the activity of inhibitory neurons thus creating disinhibition downstream from the postsynaptic inhibitory interneuron (Somogyi and Cowey 1981; Kisvarday et al. 1993). However, when networks of interneurons are interconnected with one another, the final results of such complex interactions are not easily predictable by simple mathematical models (Freund and Buzsaki 1996).

MONOAMINERGIC INPUTS. Based on anatomic studies, a variety of subcortical nuclei such as the nucleus basalis of Meynert (Mesulam et al. 1983), raphe nuclei (Descarries et al. 1975; Lindvall and Bjorklund 1978), locus coeruleus (Levitt and Moore 1978), and ventral tegmental area (Thierry et al. 1973; Lindvall and Bjorklund 1984) send afferents to the cortex. These fibers employ acetylcholine, serotonin, norepinephrine, and dopamine, respectively, as neuromodulators. Some of these monoaminergic fibers seem to project directly to nonpyramidal cells of the cortex and probably influence the activity of GABAergic neurons. For example, GABA neurons in rat medial prefrontal cortex receive direct inputs from dopaminergic fibers (Goldman-Rakic et al. 1989; Verney et al. 1990; Benes et al. 1993). Consistent with this, nonpyramidal cells have been found to express both D1 and D2 receptor binding activities (Vincent et al. 1993, 1995; Davidoff and Benes 1998) or their associated messenger RNAs (Huntley et al. 1992).

More recently, using double immunocytochemistry, the two receptor subtypes have been co-localized in GABAergic interneurons, particularly those that are also positive for PVB (Le Moine and Gaspar 1998). Another study was only able to localize immunoreactivity for the D1 receptor in interneurons (Muly et al. 1998). It is important to emphasize that data obtained from cytochemical approaches, whether they be receptor binding, immunocytochemistry or in situ hybridization, are only useful when a positive localization is obtained; the absence of reaction product may only represent a failure to localize. All of these various neuromodulators can theoretically contribute significantly to the regulation of GABAergic tone in cortical neurons.

Regarding the serotonin system, a complex pattern may also exist. For example, serotoninergic fibers form contacts with interneurons and, like dopamine fibers, most do not show synaptic profiles (Smiley and Goldman-Rakic 1996). CB-/GAD-positive neurons in the cortex have been shown to be the selective target of serotoninergic terminals which tend to form 'baskets' around their somata (Hornung and Celio 1992). Consistent with this, both agonists and antagonists of serotonin receptors can be used to manipulate the activity of GABAergic neurons (Sheldon and Aghajanian 1990; Gellman and Aghajanian 1994). While both pyramidal cells and GABA neurons express the $5HT_{2A}$ receptor subtype (Wu et al. 1998; Jakab and Goldman-Rakic 1998), the $5HT_{1A}$ has been preferentially localized to pyramidal

cells in the hippocampus (Gellman and Aghajanian 1994; Morilak et al. 1993), whereas the $5HT_{1C}$ receptor subtype may be preferentially found in pyramidal neurons in pyriform cortex (Sheldon and Aghajanian 1991). These observations suggest that both projection cells and local circuit cells may be potentially influenced by dopaminergic and serotoninergic projections (Gellman and Aghajanian 1993; Benes 1995). Recently, direct evidence in support of this idea has come from a triple localization demonstrating non-random contacts of tyrosine hydroxylase- (TH-) and 5HT-IR varicosities on GAD-IR neuron somata in rat medial prefrontal cortex (Taylor and Benes 1996; Benes et al. 2000).

Hippocampus

AXO-SOMATIC INHIBITORY SYNAPSES (BASKET CELLS). These neurons show characteristics very similar to those described in the cerebral cortex; however, different subtypes of hippocampal basket neurons can be distinguished on the basis of axonal arborization, location, shape and neurochemical markers (Freund and Buzsaki 1996). The common feature among these neuronal subtypes is a predominant innervation of the perisomatic regions of principal cells, so that most of their synaptic contacts cluster around the somata and the proximal portion of primary dendrites (Figure 4). Like neurons in the cerebral cortex, basket and chandelier cells in the hippocampus have been found to express PVB (Freund and Buzsaki 1996) and show a 'fast spiking' pattern (Kawaguchi et al. 1987). Interestingly, PVB-positive neurons in the hippocampus appear to be connected to each other not only through chemical synapses, but also gap junctions (Katsumaru et al. 1988). A subpopulation of basket cells which is PVB-negative, but CCK- and VIP-positive has also been identified (Gulyas et al. 1991; Acsady et al. 1996a,b).

AXO-AXONAL INHIBITORY SYNAPSES (CHANDELIER CELLS). Like their counterparts in the cortex, these neurons form axo-axonic synapses exclusively with the initial segment of the pyramidal cell axon (Kosaka 1983; Somogyi et al. 1983, 1985). Chandelier cells can be found in both the dentate gyrus and the CA subfields. In the dentate gyrus, the cell body is located within the granule cell layer and the axon arborizes profusely within the granule cell layer forming complex vertical rows of boutons that follow the granule cell axons (Soriano and Frotscher 1989; Buhl et al. 1994). In the CA subfields, the somata are found within or adjacent to the pyramidal cell layer, while their dendrites extend into the stratum radiatum, stratum lacunoso-moleculare and the stratum oriens, so that these neurons are strategically placed for receiving inputs from all major sources of afferents to the hippocampus. The axons of these interneurons form dense arborizations that follow the axons of pyramidal neurons.

AXO-DENDRITIC INHIBITORY SYNAPSES. This type of synapse is associated with neurons that are composed of numerous subpopulations, each showing great differences in the location of their somata, as well as their dendritic and axonal arborizations within the dentate gyrus and CA subfields. Most, however, almost exclusively innervate various segments of the pyramidal or granule cell dendritic tree. Each of these inhibitory cells forms multiple synaptic contacts that are distributed along various branches of a single pyramidal neuron. This distribution implies that each contact may have only a very weak effect on the postsynaptic neuron, suggesting that the activity of dendritic inhibitory cells may have to be synchronized in order to effectively modulate the membrane potential of pyramidal neurons (Freund and Buzsaki 1996; Miles et al. 1996). Another common factor is that the dendritic arborization of these neurons tends to be restricted to only one or two layers so that their influence is limited to selective intrinsic or extrinsic afferents (for a review see Freund and Buzsaki 1996). Different axo-dendritic neurons in the hippocampus have been found to selectively contain calcium binding proteins, such as CB and CR, as well as neuropeptides, such as SM, NPY, and nitric oxide synthetase (NOS) (for a review see Freund and Buzsaki 1996).

INTERNEURON SELECTIVE CELLS (IS). These interneurons, which selectively synapse on other hippocampal interneurons, have been categorized according to at least three subtypes (IS-1, IS-2, and IS-3) based on their connectivity and neurochemistry (for a review see Freund and Buzsaki 1996). IS-1 neurons are CR-positive and their most salient characteristic is that they form long dendrodendritic junctions with each other that appear to connect clusters consisting of 10–15 IS-1 neurons (Freund and Buzsaki 1996). Their synaptic targets are CB-positive neurons, as well as other IS-1 cells (Acsady et al. 1996a; Gulyas et al. 1996); PVB-positive neurons do not receive afferents from IS cells. The principal inputs to these neurons is thought to be intrinsic Schafffer collaterals and extrinsic afferents from the entorhinal cortex. IS-2 neurons express VIP and contact mainly CB-positive, but not PVB-positive neurons. IS-3 neurons also express VIP and appear to selectively synapse with SM-containing neurons.

As discussed above, the simplest interpretation of interneuron-to-interneuron interactions is that activation of one GABA cell will result in the second being inhibited and its follower cell being disinhibited. Activation of complex interneuron networks, however, will probably result in a less predictable outcome.

Functions of GABAergic Interneurons in the Cortex and in the Hippocampus

Feedback and Feedforward Activity. Basic electrophysiological studies have demonstrated that the action

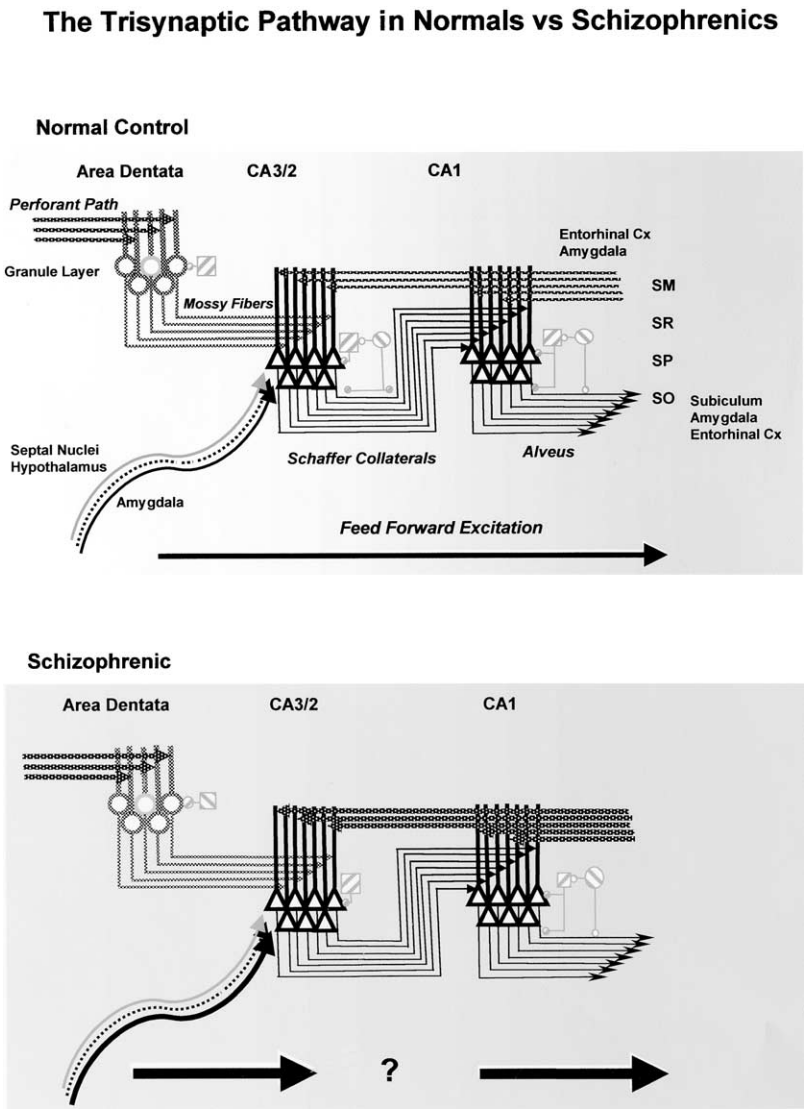

Figure 5. A schematic diagram depicting a model for conduction along the trisynaptic pathway in normal controls (upper panel) and schizophrenics (lower panel). *Normal Controls*: The trisynaptic pathway consists of three components: 1) perforant path fibers providing an excitatory input to the molecular layer in the area dentata; 2) mossy fibers providing an excitatory input to the stratum radiatum of CA3; and 3) Schaffer collaterals that provide an excitatory input to the stratum radiatum of CA1. The activity relayed along the trisynaptic pathway is funneled toward pyramidal cells in CA1 send which sends an efferent output to the subiculum, amygdala, and entorhinal region. The latter two regions also project back into the CA subfields along the stratum moleculare (see text for details). Sector CA3 of the hippocampus also receives direct afferents from the septal nuclei (red arrow), hypothalamus (hatched arrow) and basolateral amygdala (solid arrow). The progressive shading toward the right-hand side of the diagram indicates the direction (arrow) of a "feed forward" excitation that probably results in an amplified signal leaving sector CA1 (see text for details). There are inhibitory interneurons (square cells with hatched filling) providing GABAergic input to pyramidal cells in CA3 and CA1 and to the stratum oriens. Some GABA cells are disinhibitory interneurons (circular cells with hatched filling) that decrease the ability of the GABAergic cell to fire. *Schizophrenics:* A schematic diagram similar to that shown for normal controls, except that there is increased excitatory activity (thickened arrows) entering the trisynaptic pathway from three routes: 1) basolateral nucleus of the amygdala; 2) entorhinal projections to the stratum moleculare of the dentate gyrus; and 3) entorhinal projections to CA1 and CA3 from layers III and II, respectively, that travel along the stratum moleculare of the these subfields. In addition, there is a defect of GABAergic modulation at various points along the trisynaptic pathway. First, inhibitory GABAergic activity appears to be decreased in sectors CA4, CA3, and CA2, but not CA1. There is also a subtle decrease of disinhibitory modulation in the stratum pyramidale of CA3 that would result in an increased inhibition of pyramidal cell firing in this sector. Although it is difficult to understand how a dual defect in inhibitory and disinhibitory modulation in CA3 might impact on the flow of activity along the trisynaptic pathway, it seems likely that there would be an overall increase of excitatory activity along most of the trisynaptic pathway. The latter is indicated as an intensification of the dark shading occurring uniformly from the area dentata

of GABA is typically an inhibitory one (Krnjevic 1987). It seems obvious from the above discussion, however, that different interneuronal subpopulations play different and highly specialized roles in rather complex circuits. On an elementary level of analysis, most inhibitory interneurons in the cortex and hippocampus are involved in either *feedback* or *feedforward* inhibitory mechanisms which are thought to help stabilize the activity of pyramidal neurons. In *feedback* inhibition, an excitatory input activates the pyramidal neuron which, in turn, excites inhibitory interneurons through recurrent collateral fibers (Andersen et al. 1964).

The inhibitory interneurons thus activated inhibit principal neurons, including those that directly excited them. Intracellular recordings from cortical pyramidal cells typically show a depolarization of brief duration that is followed by a longer lasting hyperpolarization (Sillito 1975); it is the latter component of this complex that reflects the action of GABA on the $GABA_A$-chloride ionophore complex expressed by most postsynaptic neurons (Rabow and Farb 1995). Such an arrangement provides a "fail safe" mechanism that ensures pyramidal neurons do not fire excessively. In a *feedforward* system, on the other hand, pyramidal neurons (e.g., in CA3) project downstream to other pyramidal cells in CA1 (refer to Figure 5, upper panel). In addition, however, these excitatory neurons also project to interneurons of CA1, and this ultimately curtails the excitability of pyramidal neurons in this latter sector (Buzsaki 1984).

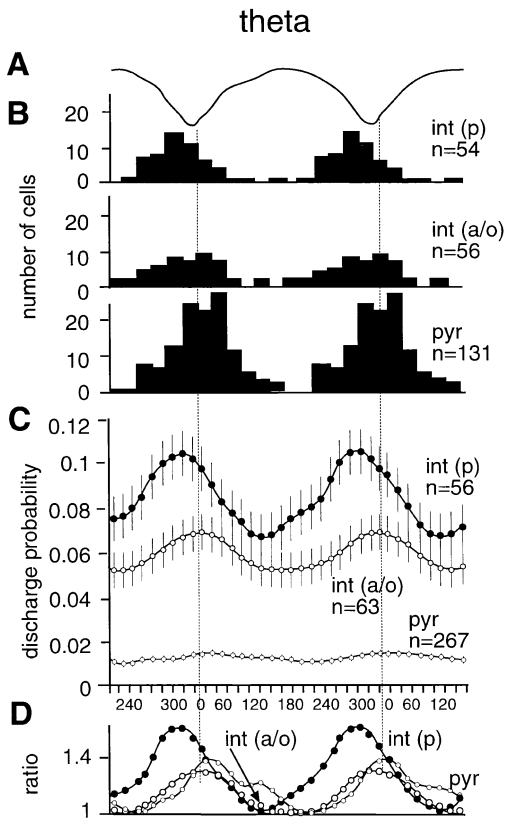

Figure 6. Two theta wave cycles are shown **(A)** together with phase distributions of interneurons in the stratum pyramidale, int(p), and stratum oriens/alveus, int(a/o), as well as pyramidal cells (pyr) with significant phase modulation **(B)**. Both interneurons and pyramidal cells fire during the negative phase of the theta wave, but were much less likely to fire during the positive phase **(C)**. The int(p) and int(a/o) interneurons discharged earlier than the population peak activity of the pyramidal neurons. (Reproduced with permission from Csicsvari et al. 1999.)

Network Oscillations. In both the cortex and the hippocampus, complex interconnections between GABAergic interneurons and pyramidal cells have been found to establish and maintain large scale network oscillations, such as those in the theta, gamma (40–100 Hz), and ultrafast (200 Hz) frequency ranges (Buzsaki and Eidelberg 1983; Fraser and MacVicar 1991; Buzsaki et al. 1992; Soltesz and Deschenes 1993; Amzica and Steriade 1995; Bragin et al. 1995; Buzsaki and Chrobak 1995; Whittington et al. 1995; Ylinen et al. 1995a,b; Freund and Buzsaki, 1996; Jefferys et al. 1996; Buzsaki 1997).

As shown in Figure 6, studies of theta oscillations have demonstrated that both interneurons and pyramidal cells fire during the negative phase of the waveform; however, the interneurons discharge earlier than pyramidal cells. In the cortex, networks of inhibitory interneurons have been found to entrain pyramidal cell discharges. This results in coherent oscillations that have been proposed to 'group' or ' bind' features detected in different cortical areas into a unified perceived object (Whittington et al. 1995). In the hippocampus, these oscillations have been proposed to provide the "context" for the "content" coded by excitatory projection neurons (for review see Buzsaki and Chrobak 1995; Buzsaki 1997). According to this hypothesis, GABAer-

through sector CA1. In the area dentata, the feed forward excitatory drive progressively increases as the conduction of impulses passes toward CA1. Since the changes in GABAergic integration in CA3 are complex and the increase of disinhibitory activity may have the ability to offset some of this excitation potentially offsetting, the arrow is missing in this sector and is replaced by a question mark (?). In CA1, the excitatory drive would attains its highest level of activity, particularly since a decrease of inhibitory modulation appears to be minimally present in this sector in schizophrenics. Taken together, these hypothesized changes would be capable of generating an overall increase of basal metabolism in this region, but an impaired ability to selectively retrieve information when challenged with a specific task (Adapted with permission from Benes and Berretta) (Benes and Berretta 2000a).

gic 'supernetworks' may control pyramidal neurons and provide the temporal structure needed to coordinate and maintain the function of neuronal ensembles in the hippocampus. The available evidence suggests that networks of hippocampal interneurons are capable of generating gamma frequency oscillations (Traub et al. 1997). For the theta rhythm, basket cells have been found to have regular membrane oscillations and the occurrence of rhythmic inhibitory postsynaptic potentials are believed to involve GABAergic inputs from the septal nuclei (Ylinen et al. 1995a). Thus, GABA-to-GABA interactions, even ones involving extrinsic afferents, seem to play a key role in the generation of rhythmic activity by the hippocampus.

Discriminative Processing. Growing evidence supports the hypothesis that cortical interneurons can influence the discriminative responses of pyramidal neurons. For example, in the visual system, GABAergic interneurons play a key role in modulating the activity of geniculate inputs to the primary visual cortex and defining the orientation selectivity of its neurons (Sillito 1975, 1984; Tsumoto et al. 1979). Support for a role of interneurons in shaping of receptor fields has been extended to other cortical areas such as the somatosensory cortex (Alloway et al. 1989; Alloway and Burton 1991; Wilson et al. 1994; Kyriazi et al. 1996). For instance, recordings from layer IV barrel neurons of the somatosensory cortex in the presence of GABA receptor antagonists indicates that inhibitory receptive field properties of barrel neurons can be explained by intrabarrel inhibition and that the expansion of receptive field size during GABA blockade is due to an enhanced effectiveness of convergent, multiwhisker thalamocortical inputs (Kyriazi et al. 1996).

Interestingly, in monkey prefrontal cortex, interneurons have receptive fields similar to those found for pyramidal neurons. This suggests that interneurons carry a specific informational signal (Wilson et al. 1994). In these experiments, the timing of excitatory and inhibitory responses appeared to be phased, a property consistent with a role of interneurons in shaping receptive fields. Furthermore, it has been shown that, in the motor cortex, intrinsic inhibitory circuits maintain and adapt motor representations (Jacobs and Donoghue 1991). Inhibitory interneurons appear to be able to unmask latent connections, so that rather than being static, somatotopic maps can continually reorganize (Jacobs and Donoghue 1991). It can readily be appreciated that similar neurons located in associative cortical regions may help to define the nature and integrity of higher cognitive functions, such as motivation, attention, learning and object recognition. For example, recent findings suggest a role for cortical interneurons in working memory (Wilson et al. 1994; Rao et al. 1999, 2000). In the dorsal prefrontal cortex, 'fast spiking' interneurons have been shown to play an important role in shaping 'spatial memory fields' much in the same way as they have been found to shape 'sensory receptive fields' (Rao et al. 1999, 2000). In addition, blockade of GABAergic inhibition in the inferotemporal area has been associated with a disruption of the normal response of neurons selective for particular object features (Wang et al. 2000).

Long-Term Potentiation and Depression. Intrinsic inhibitory interneurons in the hippocampus may also control long-term modifications of synaptic strength induced by synaptic transmission (Buzsaki et al. 1996; Maccaferri and McBain 1996; Miles et al. 1996; Tsubokawa and Ross 1996; McMahon and Kauer 1997; Laezza et al. 1999).

Phenotypical Differentiation. Finally, and of interest for the field of schizophrenia research, hippocampal interneurons have been shown to regulate the differentiation of hippocampal neurons during development (Marty et al. 1996). That many of these functions might involve functional (and presumably structural) neuroplasticity is strongly suggested by the observation that GABA, GAD, and the $GABA_A$ receptors are all regulated in an activity-dependent manner (Jones 1990, 1993). This raises the question as to whether phenotypic changes in the GABA system seen in schizophrenia and bipolar disorder might be related to increases or decreases in the flow of afferent activity into the cortex and hippocampus from other regions with which they are connected (see below).

THE GABA SYSTEM IN SCHIZOPHRENIA

GABA dysfunction is believed to play a role in various neuropsychiatric disorders. For example, as early as 1972, Eugene Roberts postulated that this compound might play a central role in the pathophysiology of schizophrenia (Roberts 1972). Schizophrenia typically involves disturbances of cognitive functioning that include impaired attentional responses (McGhie and Chapman 1961), disruptions of normal information processing (Saccuzzo and Braff 1986; Braff et al. 1991), and a selective impairment in declarative memory (Heckers et al. 1998). Overall, the thought pattern of schizophrenics has been described as being "over-inclusive", i.e. there is an inability to filter out extraneous information (Cameron 1938; Payne et al. 1961; Payne and Friedlander 1962). This has lead to the speculation that an impaired central filtering mechanism may be present in this disorder (Detre and Jarecki 1971), as schizophrenics are unable to distinguish relevant objects in the perceptual field (Matussek 1951).

Using physiological recordings from schizophrenics, a decreased auditory-evoked P50 response to repeated stimuli has been noted (Adler et al. 1982). These authors concluded that such a defect may be related not only to sensory gating difficulties, but also to problems with

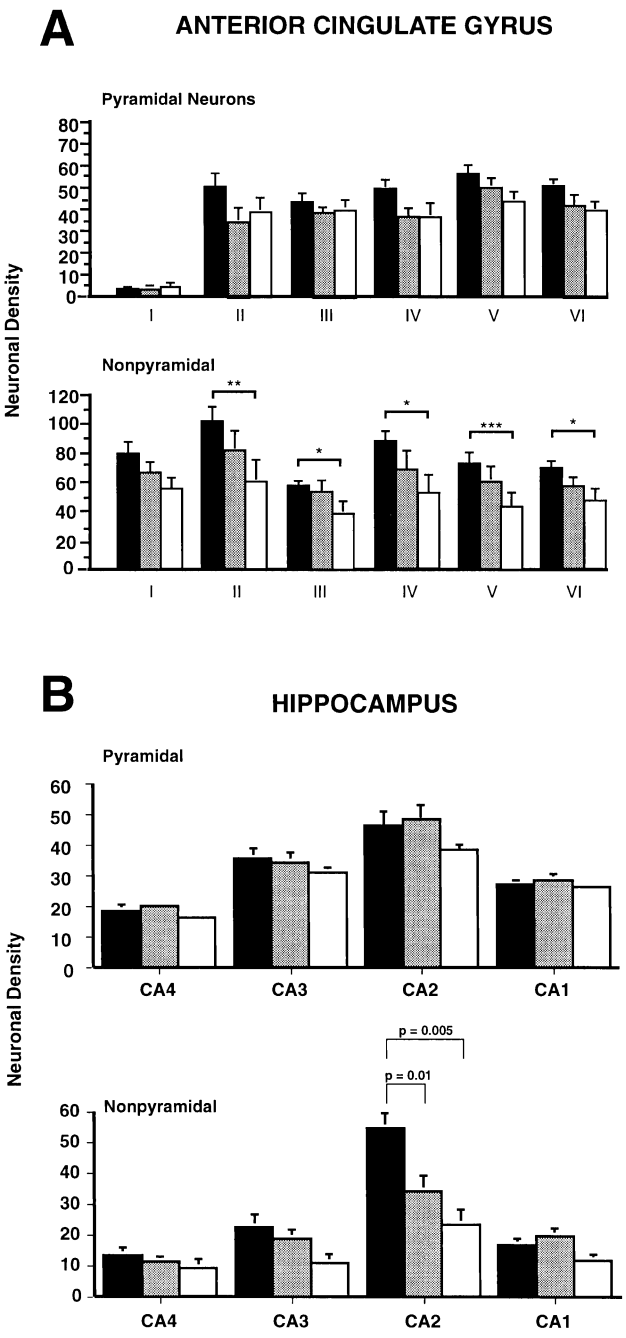

Figure 7. **(A)**. In the *anterior cingulate cortex* the density of pyramidal and nonpyramidal neurons of normal controls (*solid bar*), schizophrenics (*hatched bar*) and schizoaffective (*open bar*) subjects. Pyramidal neurons do not show significant differences among the groups, while nonpyramidal cells are decreased in layers II, III, V, and VI of the schizophrenics and schizoaffectives, particularly the latter where the differences are significant. (Reproduced from Benes et al. 1991.) **(B)**. In the *hippocampus*, the average number of pyramidal neurons also showed no significant differences between the normal controls (*solid bars*), schizophrenics (*hatched bar*) and manic depressive patients (*open bars*) in any of the sectors examined. However, nonpyramidal neurons showed a significant reduction in the average number in sector CA_2 but only a trend in sector CA_3 ($p = .067$ and $p = .065$, respectively). (Reproduced from Benes et al. 1998.)

learning efficiency and accuracy. The most consistent electrophysiological abnormality observed in schizophrenia, however, is a reduced amplitude and increased latency of the P300 evoked potential (Blackwood et al. 1991). These changes are related to a diminished ability to habituate selective attentional responses to a stimulus and could reflect defective GABAergic inhibitory modulation. Consistent with this idea, a recent PET study has demonstrated an increase of basal metabolism in the hippocampal formation of schizophrenic subjects (Heckers et al. 1998) and, as shown in Fig. 5, this finding is consistent with a recent model for how the GABA system in this region may be dysfunctional in schizophrenia (Benes 1999; Benes and Berretta 2000b). On a highly speculative level, it could be hypothesized that decreased GABAergic transmission in specific cortical areas could result in rearrangement, and possibly enlargement, of sensory, memory and 'cognitive' fields and thereby lead to overinclusive, disorganized thought processes.

In order to better understand the functional implications of a dysfunction of the GABA system in schizophrenia, it is necessary to have direct empiric evidence demonstrating alterations of specific markers for this neurotransmitter system. To date, such information has come largely from postmortem investigations as discussed below.

Postmortem Evidence for a GABA Defect in Schizophrenia

Numerical Density of Interneurons.

CELL COUNTING STUDIES. *Cerebral cortex*: In 1991, a postmortem study in which pyramidal and nonpyramidal neurons were differentially counted in cresyl violet-stained sections revealed a decreased density of nonpyramidal cells in layers II-VI of the anterior cingulate area and layer II only of the prefrontal cortex of schizophrenic and schizoaffective subjects (Benes et al. 1991). In the anterior cingulate cortex (Figure 7A), however, these changes were primarily significant in the schizoaffective group, suggesting the possibility that they might show a stronger covariation with affective disorder than with schizophrenia. Nevertheless, this finding is controversial since several other groups have not demonstrated a similar change in the prefrontal cortex of schizophrenics (Selemon et al. 1995, 1998; Akbarian et al. 1995; Arnold et al. 1995) and the anterior cingulate cortex of bipolar subjects (Ongur et al. 1998).

There are significant methodologic factors that may have contributed to these failures to replicate the reduced density of nonpyramidal cells. Not least among

these are the difficulties in comparing data obtained with two dimensional cell counting methods with those obtained with three dimensional techniques. Both have their strengths and weaknesses, although the precision of the 3D optical disector method has been seriously challenged (Benes and Lange 2000). Specifically, with the optical disector method, the size of the window used to count cells in the x/y-plane is very small, while that used with 2D approaches is almost 35-fold larger. This increase of window size provides estimates that take into account the fact that neurons are not distributed in a random or Poisson fashion and marked variations in the size, shape and numerical density of neurons occur within different layers and sublaminae.

Of equal concern is the fact that optical disector counting incurs a marked degree of collapse in the z-axis and this differentially effects the numerical density of neurons, such that the numbers of larger pyramidal neurons would tend to be over-estimated when compared to the smaller nonpyramidal neurons. In contrast, two dimensional counting approaches typically use relatively thin sections (e.g., 20 μm) that collapse to approximately 5–6 μm in thickness when mounted on glass slides. This latter thickness is similar to the depth of focus of a 25X objective lens, making it routinely possible to count all of the cells within the original 20 μm thickness of the section, without the effect of z-axis collapse in this plane. Overall, it is important to consider the type of cell counting method employed in evaluating the differences in findings that have been reported in schizophrenia.

In a subsequent replication study, a 2D method was employed to study a cohort in which both schizophrenics and manic depressives were included as comparison groups. The results of this study showed a pattern similar to that previously reported (Benes and Lange 2001). The manic depressives showed approximately a 30% decrease, whereas the schizophrenics showed a 16% decrease. It is noteworthy that another study in which tyrosine hydroxylase-immunoreactive fibers were analyzed (Benes et al. 1997a) found in a post hoc analysis an 18% reduction in the density of nonpyramidal neurons in layer II of ACCx in schizophrenics (Benes 1998). More recently, the findings from these three studies have been combined and a meta-analysis performed. The data indicate that the reduction in the density of nonpyramidal neurons in layer II of ACCx was 16% in the schizophrenics ($n = 25$), 25% in schizoaffectives ($n = 18$), and 30% in manic depressives (Benes and Todtenkopf 1998). Taken together, these data suggest that a loss of interneurons does occur in affective disorder as well as schizophrenia.

Hippocampus: In a recent study of the hippocampal formation (Figure 7B), a preferential decrease in the number of nonpyramidal neurons was observed in sector CA2; however, in this region, the change occurred to an equivalent degree in both schizophrenics and manic depressives (Benes et al. 1998; Benes and Todtenkopf 1998). Based on these results, it has been postulated that a loss of GABAergic neurons might be related to a factor, such as stress, that both disorders would share to an equivalent degree. It is not straightforward to explain why there is a greater decrease in the density of nonpyramidal neurons in manic depressives, than in schizophrenics. Nor is it obvious why this parameter shows an equivalent change in the hippocampal formation of both disorders; however, it is conceivable that each disorder may involve region-specific alterations of neural circuitry that impact on GABAergic neurons to differing degrees, depending upon the specific diagnostic category.

CALCIUM BINDING PEPTIDES. *Cerebral Cortex*: As discussed above, variety of peptides have been found to be associated with various subtypes of nonpyramidal neurons and are being used to identify specific phenotypes of GABAergic inteneurons (Conde' et al. 1994). An ICC localization of the calcium binding protein parvalbumin has demonstrated a *decrease* of cells showing this immunoreactivity in the prefrontal cortex of schizophrenics (Beasley and Reynolds 1997).

In another study, however, prefrontal areas 9 and 46 showed no differences in the distribution of neurons expressing detectable levels of PVB-IR (Woo et al. 1997). In the anterior cingulate cortex, on the other hand, an *increase* of cells immunoreactive for this peptide has been reported in schizophrenics (Kalus et al. 1997). In attempting to interpret such disparate results, it is important to consider whether differences in the regions studied, tissue handling and perhaps even subject populations may account for the discrepancies. All of these factors may potentially influence whether the amount of PVB-IR is either above or below the level of detection.

For CB, an *increase* in the numerical density of neurons showing immunoreactivity for this peptide in the dorsolateral prefrontal cortex was observed, whereas there was no change in those containing CR-IR (Daviss and Lewis 1995). Unfortunately, there have not as yet been another studies reporting on this peptide in the prefrontal cortex of schizophrenics.

Hippocampus: CB expression has been shown to be decreased (Takahashi et al. 2000) and CB-IR neurons have been reported to show a marked degree of disarray, particularly evident in sector CA2 (Iritani et al. 1999). Although an overt decrease in the numerical density of these cells was not detected, this study is noteworthy because, as noted above, a selective loss of nonpyramidal neurons has been found in sector CA2 of subjects with schizophrenia and bipolar disorder (Benes et al. 1998).

Taking together the results of cell counting studies using cresyl violet-stained sections with those immunocytochemically localizing antibodies against various

calcium binding proteins, there does not appear to be a definitive answer as to whether a decrease of interneurons is present in the cortex and hippocampus of schizophrenic subjects. On the one hand, studies of cresyl violet stained sections suffer from significant issues regarding cell counting methodology. On the other hand, studies that have localized PVB, CB, and CR are impeded by the factors that influence the retention of immunoreactivity in the tissue and the fact that increases or decreases of detectable levels of peptide may occur without any overt change in the actual number of neurons. Thus, the apparent changes in numerical density of such cells can be quite misleading.

Markers for GABAergic Terminals. In the 1970s, perhaps prompted by the speculations of Eugene Roberts (Roberts 1972), a series of neurochemical investigations focusing on various markers for this system were reported. The first study to appear examined the concentrations of GABA in the nucleus accumbens and thalamus of patients with schizophrenia and compared them with a group of subjects with Huntington's chorea (Perry et al. 1979). The results demonstrated a reduction of this transmitter that was equivalent in the two disorders. Contemporaneously, another study reported that the activity of GAD was significantly reduced in schizophrenics (Bird et al. 1977). Although it began to appear that a pattern of decreased GABAergic activity was emerging, subsequent studies failed to show changes in either GABA levels or GAD activity (Cross et al. 1979), even though one study did show a non-significant decrease of GAD in the prefrontal cortex (Hanada et al. 1987). Because subjects who died suddenly were less apt to show such changes, it appeared that decreases in the specific activity of GAD might be related to the agonal state and might have been confounded in these studies (Bird 1977, #2626).

More consistent findings have come from studies of the GABA uptake site where reductions of this marker have been consistently observed in prefrontal cortex (Simpson et al. 1989), amygdala (Reynolds 1983), and hippocampus (Reynolds et al. 1990) of schizophrenic brain. A recent attempt to replicate this finding in prefrontal and temporal cortex, however, did not show any differences in schizophrenics (Simpson et al. 1998).

More recently, the 65 kDalton isoform of GAD, a marker for GABAergic terminals (Kaufman et al. 1991), has been localized immunocytochemically in the *anterior cingulate cortex*, where schizophrenic patients showed no differences (not shown) while, in bipolar subjects, a marked decrease was detected on pyramidal neurons in layers II and III (Figure 4). In the *hippocampal formation*, no overall differences between normal controls and schizophrenics were detected in the density of GAD_{65}-IR terminals on either pyramidal or nonpyramidal cells in any of the subregions or sublaminae (Todtenkopf and Benes 1998). However, a small number of subjects who were neuroleptic free for at least a year prior to death showed a significant reduction on both neuronal subtypes in sectors CA4, CA3, and CA2, but not CA1. The subjects treated with neuroleptics showed a dose-related increase in terminal density in these sectors, particularly in the stratum oriens of CA3 and CA2. These data suggest that there may be an intrinsic reduction of GABAergic terminals in the hippocampus of schizophrenics and the therapeutic efficacy of the neuroleptic drugs may involve, at least in part, a trophic sprouting of these terminals. This conclusion is consistent with a controlled study in rat medial prefrontal cortex (anterior cingulate region) in which chronic haloperidol administration was associated with a marked increase of GABA-IR terminals (Vincent et al. 1994b).

Whether such changes require blockade of dopamine receptors on GABA cells is not clear; however, the increase in this latter study were most striking in layer II where the dopaminergic projections to this region are most sparse (Lindvall and Bjorklund 1984). Thus, antipsychotic drugs may be capable of inducing changes in GABA cells that are mediated either alone or in combination with other mechanism, such as the $5HT_{2A}$ receptor (Benes 1995) or possibly even direct trophic changes in synapses (Benes et al. 1983, 1985; Kerns et al. 1992).

Other cytochemical studies have employed in *situ* hybridization (ISH) to examine the distribution of mRNA for GAD, particularly that for the 67 kDalton isoform (GAD_{67}) (Kaufman et al. 1991). In the *prefrontal cortex* of schizophrenics, a reduction in the number of cells expressing GAD_{67} mRNA has been reported by two different groups (Akbarian et al. 1995; Volk et al. 2000).

More recently, a decrease in GAD_{67} mRNA, but not GAD_{65}, expression has again been noted (Guidotti et al. 2000). A variety of studies have suggested that GAD_{67} is regulated through transcriptional mechanism. For example, increased expression of mRNA for this protein has been found in relation to lesioning of the substantia nigra (Vernier et al. 1988; O'Connor et al. 1991), climbing fibers of the cerebellum (Litwak et al. 1990) and in the hippocampus in response to systemic treatment with kainic acid GAD_{67} (Feldblum et al. 1990). In contrast, expression of mRNA for GAD_{65} has been found to be relatively stable (Ding et al. 1998; Feldblum et al. 1998). Similarly, expression of GAD_{65} protein also appears to be relatively stable (Martin et al. 1993) and appears to be controlled primarily through post-translational mechanisms (Miller et al. 1991).

The postmortem findings obtained with either immunocytochemistry or ISH showing decreased expression of GAD_{67} , but not GAD_{65}, as well as stable levels of immunoreactivity for GAD_{65} in terminals of the hippocampal formation (Todtenkopf and Benes 1998) are consistent with these ideas. Since mRNA for the two isoforms of GAD are expressed by 95% of the neurons

in rat hippocampus (Stone et al. 1999), it seems likely that complex cellular mechanisms may be influencing the nature of the results observed in these postmortem studies. The fact that changes in GAD_{67} mRNA have been observed not only in schizophrenics, but also in subjects with bipolar disorder (Guidotti et al. 2000; Heckers et al. 2001) suggests that these changes may be related to a nonspecific factor associated with both disorders. Interestingly, differential expression of mRNAs associated with the two isoforms of GAD have been reported in relation to both acute and chronic stress (Bowers et al. 1998), although in this case that for GAD_{67} was increased, rather than decreased as it is in schizophrenia and bipolar disorder.

A recent study in rats has attempted to model for the effects of pre- and/or postnatal stress by injecting rats with corticosterone (Stone et al. 2001). Within 24 hrs of the last injection, a decreases of mRNA for GAD_{67} , but not GAD_{65}, was observed in the dentate gyrus, CA4, CA2, and CA1 of rats exposed both pre- and postnatally. Five days after the last injection, however, the levels of mRNA for GAD_{67} returned to normal, while those for GAD_{65} were markedly increased.

Another finding supporting the presence of disruption of GABAergic networks in schizophrenia, is the decrease of 'cartridges' immunopositive for the GABA membrane transporter (GAT-1) in *prefrontal cortex* (Figures 3A and 3B) (Woo et al. 1998; Pierri et al. 1999). As discussed above, these 'cartridges' represent axo-axonic terminations of chandelier neurons and are strategically positioned within cortical circuitry to modulate cortical output. Thus, their decrease is likely to reflect crucial changes in information processing in the cortex. Other terminals with a more conventional punctate structure did not show differences, thus suggesting selectivity to a population of GABA terminals that accounts for only 1% of the total. It is not known, however, whether GAT-1 containing terminations express GAD_{65} and/or GAD_{67}.

GABA Receptor Binding Activity. The GABA agonist binding of [^{3}H]muscimol, was evaluated in the *prefrontal cortex* of controls and schizophrenics matched for age, but with an average postmortem interval of 8 and 13 hrs, respectively (Hanada et al. 1987). The data indicated that the schizophrenics showed a 48% increase in the B_{max}, but no difference in affinity for [^{3}H]muscimol binding. Addition of the benzodiazepine, diazepam, resulted in a greater increase in binding in the schizophrenics. One limitation of this study was the fact that GABA was used as a competitive inhibitor, rather than bicuculline, a specific antagonist of the $GABA_A$ receptor (Rabow and Farb 1995), making it unclear as to whether the results reflect changes in this latter receptor or possibly the $GABA_B$ receptor and, perhaps, even the GABA transporter.

Subsequent investigations have specifically investigated high affinity binding to the $GABA_A$ receptor complex. Using bicuculline as a selective antagonist, [^{3}H]muscimol binding was found to be increased in the *hippocampal formation* (Figure 8) (Benes et al. 1996b), *anterior cingulate cortex* (Benes et al. 1992) and *prefrontal region* (Figure 9) (Benes et al. 1996b; Dean et al. 1999), of schizophrenic subjects. It is noteworthy, however, that benzodiazepine receptor activity did not show differences in the *hippocampal formation* (Figure 8), suggesting that there might be an uncoupling in the regulation of these two sites on the $GABA_A$ chloride ionophore complex (Benes et al. 1997b). One other study had reported a decrease of benzodiazepine receptor binding in the cortex (Squires et al. 1993), but it is not clear if the subjects in this study were treated with benzodiazepine agents prior to death. It is also important to note that this pattern does not preclude the presence of an allosteric uncoupling in the regulation of the receptor.

SPECT imaging investigations have also attempted to study the $GABA_A$ receptor in schizophrenia using specific ligands, such [^{123}I]iomazenil for the benzodiazepine receptor. While two such studies have found no differences in schizophrenics (Busatto et al. 1997; Abi-Dargham et al. 1999), two others have found a reduction in this binding activity (Verhoeff et al. 1999; Ball et al. 1998). In two of these studies, changes in the benzodiazepine receptor correlated with cognitive impairment (Ball et al. 1998) or severity of illness (Busatto et al. 1997). It is important to emphasize that these studies were probably examining only the benzodiazepine site on the $GABA_A$ chloride ionophore complex so that, in the setting of an allosteric uncoupling in its regulation, the status of the $GABA_A$ site cannot be inferred from such imaging data.

A high resolution microscopic technique has provided specific information regarding the distribution of this receptor binding activity on pyramidal neurons versus nonpyramidal cells (interneurons). In the *prefrontal* (Benes et al. 1996c) and *anterior cingulate* (Benes et al. 1992) cortices, increases $GABA_A$ receptor binding activity has been preferentially found on pyramidal, but not nonpyramidal neurons, particularly in layer II where the effect size was largest (Figure 9). This pattern was thought to be consistent with the hypothesis that a compensatory upregulation of this receptor was occurring in response to a decrease of GABAergic neurons and/or activity. When this form of analysis was applied to the *hippocampal formation* (Fig. 5), a similar pattern was observed in sector CA1 (Benes et al. 1996b). In sector CA3, however, the increase of $GABA_A$ receptor binding activity was found on nonpyramidal neurons, but not pyramidal cells, suggesting that a decrease of GABA-to-GABA interactions might be occurring in this sector of schizophrenics.

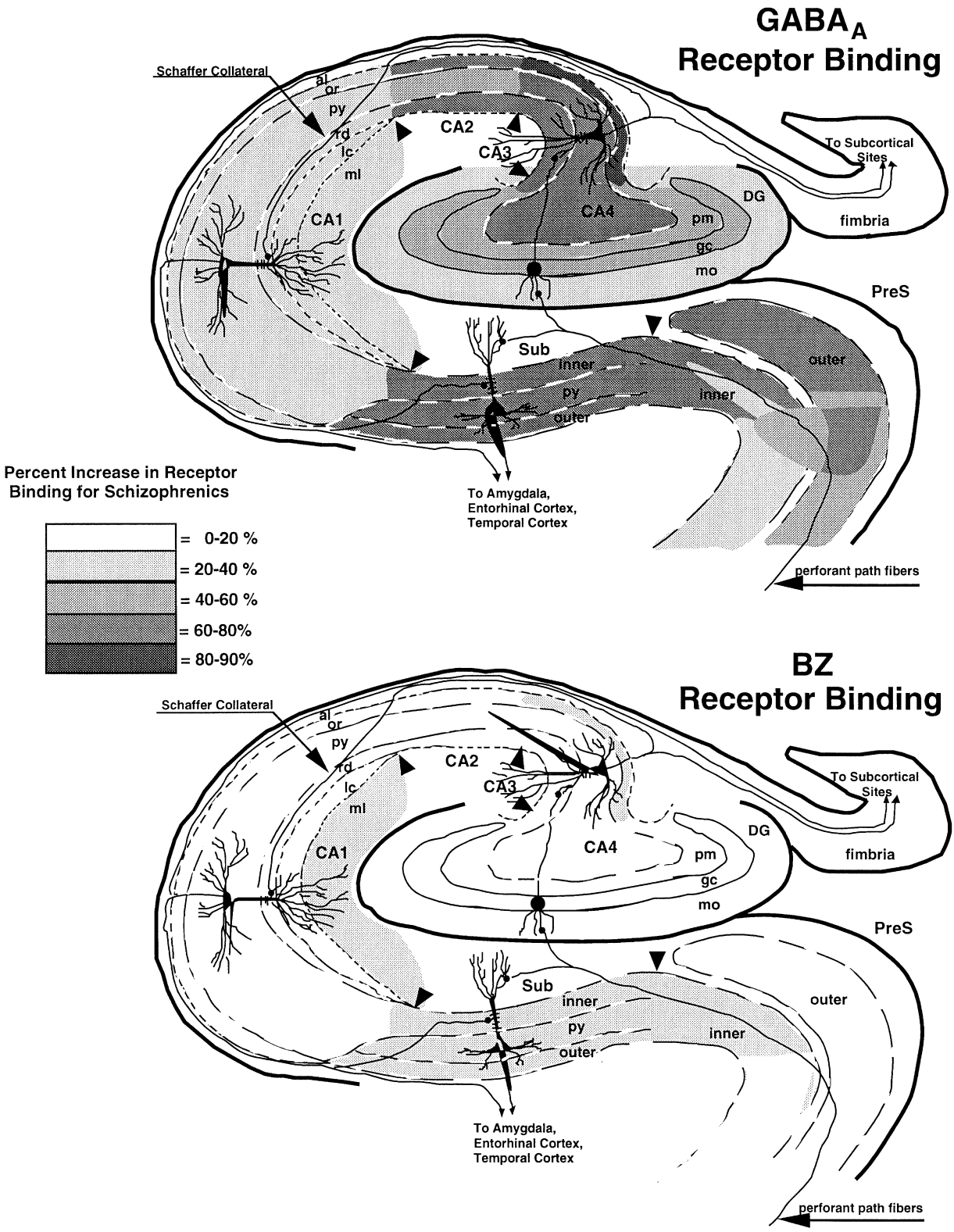

Figure 8. A schematic diagram of human HIPP depicting relative increases of specific $GABA_A$ (upper panel) and specific BZ (lower panel) receptor binding activity in SZ s compared to normal controls. The degree of shading in each diagram is proportion to the percent increase of receptor binding in SZs (refer to key in diagram). (Modified and reproduced from Benes et al. 1996b with permission.)

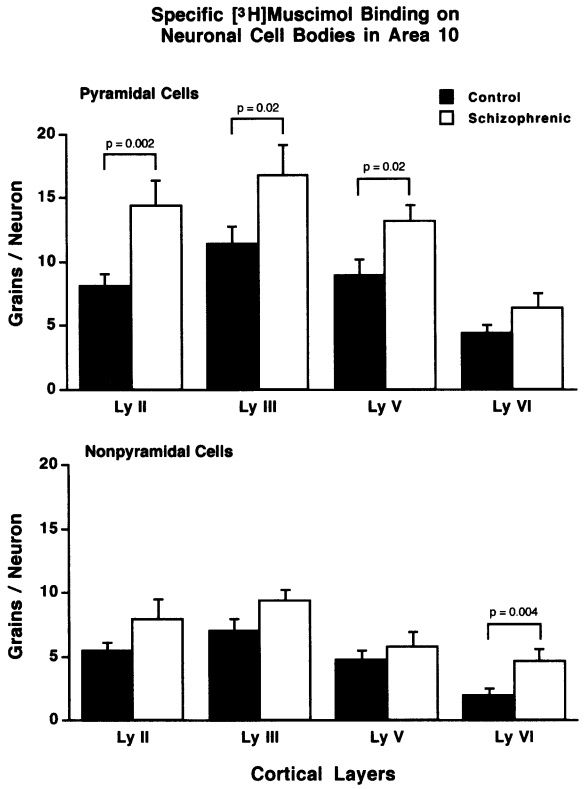

Figure 9. High resolution studies of $GABA_A$ receptor binding activity in various layers of the prefrontal cortex from normal controls (*solid bars*) and schizophrenic subjects (*open bars*). There is a marked increase of $GABA_A$ binding in layers II, III and V of the schizophrenics, but no change in layer VI. These changes are thought to represent a compensatory upregulation of this receptor in response to a loss of GABAergic cells and/or activity in this and other regions of the corticolimbic system. These data do not exclude the possibility, however, that the GABA receptor complex may be genetically abnormal in schizophrenia and that the increase of binding to the $GABA_A$ site might represent a primary defect. (Adapted from Benes et al. 1992.)

Taken together, these results consistently indicate that a disruption of inhibitory GABAergic neurons occurs in selective regions of the cerebral cortex. In the hippocampus, however, there appear to be more complex alterations that involve both inhibitory and disinhibitory GABA cells along the trisynaptic pathway of schizophrenics (Benes 1999; Benes and Berretta 2000b) and these changes would likely result in disruptions of the normal feedforward activity of this region (see Figure 5).

Altered Inputs to GABA Cells. The dopamine system has long been suspected of playing a role in the pathophysiology of schizophrenia (Kety and Matthysse 1972), even though convincing empiric evidence for a primary defect in this system has been lacking (Carlsson 1978). Seymour Kety was the first to suggest, however, that subtle changes in connectivity could occur in the absence of any discernible biochemical alterations (Kety 1959). To determine whether such a defect is present in schizophrenia, it is now possible to visualize dopamine fibers using antibodies against TH (Lewis et al. 1987; Gaspar et al. 1989; Noack and Lewis 1989; Samson et al. 1990; Williams and Goldman-Rakic 1993).

A recent study of the distribution of TH-IR varicosities in the *anterior cingulate* and *prefrontal cortices* of schizophrenic brain has suggested that there may be a decrease of these fibers on pyramidal neurons, but an increase on interneurons in layer II of the anterior cingulate; this change was not observed in the prefrontal cortex (Benes et al. 1997a). In layers V and VI, there was a significant reduction in the density of TH-IR varicosities and this compares favorably with an analysis of fiber length in the prefrontal cortex of schizophrenics where a significant reduction was found in layer VI (Akil et al. 1999). In the anterior cingulate cortex, however, this change was only found in patients treated with neuroleptic drugs, whereas the apparent shift of TH-IR varicosities from pyramidal to nonpyramidal cells of layer II was found in all schizophrenic subjects, whether or not they were treated with antipsychotic medication (Benes et al. 1997a).

A subsequent *post hoc* analysis in which several different working models were considered suggested that these data might best be explained by a trophic shift of TH-IR fibers from pyramidal to nonpyramidal neurons (Benes 1998). A loss of GABAergic interneurons was not required for this pattern to occur, although it could co-exist with such a shift. If these findings were correct, they would suggest that dopaminergic afferents might be providing a non-adaptive hyperinnervation of a subpopulation of GABAergic interneurons, perhaps ones that are intrinsically impaired in schizophrenia. Since dopamine appears to exert an inhibitory effect on cortical GABA cells (Retaux et al. 1991), these findings would predict that an excessive release of dopamine under conditions of stress (Thierry et al. 1976; Roth et al. 1988) could lead to an impairment of GABAergic function and ultimately to a decompensation of the intrinsic circuitry in layer II of anterior cingulate cortex (Benes 1997).

The Neurodevelopmental Hypothesis

Cell Migration. The findings of a variety of changes in layer II of the anterior cingulate and prefrontal cortices has suggested the possibility that there might be a disturbance in the migration of neurons in the developing cortex of subjects with schizophrenia (Benes 1993). To investigate this possibility further, the distribution of nicotinamide adenine dinucleotide diaphorase (NADPH diaphorase) was examined in the prefrontal cortex of normal controls and schizophrenics (Akbarian et al. 1993). As shown in Figure 10, the results demonstrated

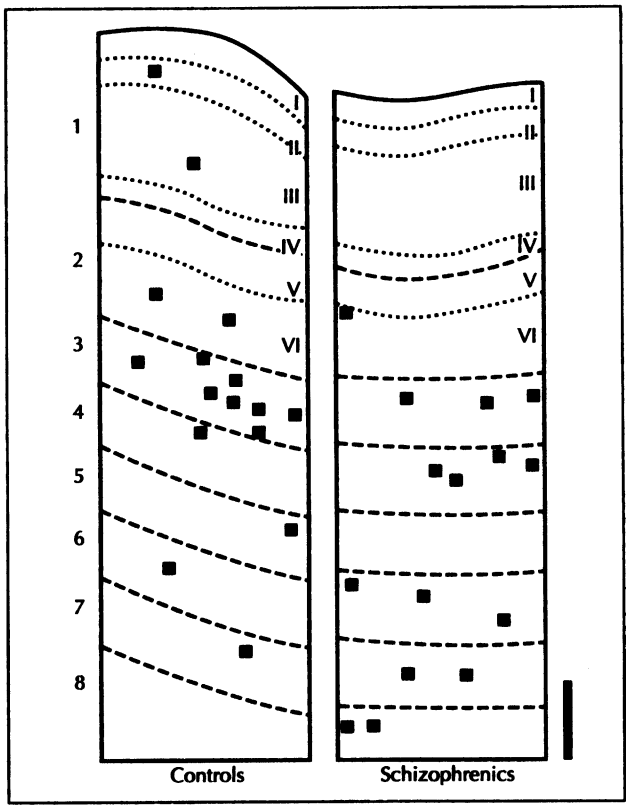

Figure 10. A schematic diagram depicting a disturbance in the migration of neurons in the prefrontal cortex of schizophrenic subjects. An increase of NADPH diaphorase positive neurons has been found in the subcortical white matter, while a decrease was observed in the cortical mantle. (Reproduced with permission from Akbarian et al. 1993.)

a significantly higher density of cells showing this marker in the subcortical white matter when compared to the cortical mantle. A similar pattern has been observed with MAP-2 staining (Andersen et al. 1996). Of significance to the current discussion is the fact that NADPH diaphorase has been co-localized to subpopulations of interneurons that are GABAergic in nature (Chesselet and Robbins 1989; Spike et al. 1993; Valtschanoff et al. 1993a,b; Davila et al. 1995; Gabbott and Bacon 1995, 1996a,b; Gabbott et al. 1997).

Reelin and Cortical Lamination. Another line of investigation that has pointed to a possible neurodevelopmental mechanism playing a role in the induction of a GABA defect in schizophrenia has come from studies of Reelin, a protein extracted from the Reeler mouse mutant. Reelin is believed to be secreted by a subclass of interneuron called Cajal-Retzius cells that may be GABAergic in nature (Pesold et al. 1998, 1999). These neurons are among the first to appear and are localized in layer I (Marin-Padilla 1984). During early development of the cortex, they interact with Martinotti cells in deeper laminae and may play a role in the formation of laminar patterns (Marin-Padilla 1984).

In schizophrenia and bipolar disorder, both Reelin and GAD_{67} mRNA have been found to be decreased in layer I and, to a lesser extent, layer II (Impagnatiello et al. 1998). These latter findings are consistent with both a cell counting study (Benes et al. 1991) and high resolution analyses of $GABA_A$ receptor binding activity (Benes et al. 1996c) showing preferential changes in layer II of the prefrontal cortex. These authors propose that a down-regulation of Reelin expression in this region of schizophrenic and bipolar brain may be due to either a genetic or an epigenetic factor. Since this protein is reduced in both schizophrenia and bipolar disorder, it seems more likely that the changes noted might be related to an environmental factor common to both. In this regard, it is noteworthy that obstetrical complications have been found to occur in both schizophrenia (Jacobsen and Kinney 1980) and bipolar disorder (Kinney et al. 1993, 1998), making it plausible that an insult early in life could influence the expression of this protein during adulthood.

Postnatal Ingrowth of Extrinsic Afferents. Important questions regarding the role of a neurodevelopmental disturbance in the induction of altered phenotypes of GABA cells are when and how such changes become manifest during the life cycle in individuals who carry the susceptibility genes for schizophrenia and bipolar disorder. One possibility is that the GABA cells are abnormal from birth; however, the clinical observation that most subjects with schizophrenia are relatively normal during childhood and early adolescence argues against this possibility. It is important to emphasize, however, that studies in rat suggest that the cortical GABA system continues to develop until the equivalent of early adolescence (Coyle and Yamamura 1976; Candy and Martin 1979; Johnston and Coyle 1980; Johnston 1988; Vincent et al. 1995).

Taking together these observations, a second possibility is that the GABA cells are relatively normal during childhood when they are also relatively immature, but become abnormal as their maturation process is completed as putative gene(s) associated with schizophrenia or bipolar disorder begin their expression. In this latter case, it would be assumed that both disorders would share common genes and these would be capable of altering the normal functioning of GABA cells. A third possibility is that the GABA cells are either relatively normal or abnormal during childhood, but their activity is quiescent while they await the ingrowth of an extrinsic fiber system, such as the dopaminergic afferents to the cortex (Verney et al. 1982; Kalsbeek et al. 1988). These latter fibers continue forming increased numbers of appositions with GABAergic interneurons until the early adult period (Benes et al. 1996a).

Influence of Pre- and Postnatal Stress. The role of stress in the induction of changes in the cortical GABA system in schizophrenia and bipolar disorder is an interesting issue to explore. For example, glucocorticoid hormones have the ability to bind to the $GABA_A$ receptor (Sutanto et al. 1989) and have been found to directly increase its activity (Majewska et al. 1985; Lambert et al. 1987). In this regard, it is noteworthy that the binding of [^{3}H]corticosterone is greatest in sector CA2 (McEwen 1982; Stumpf et al. 1989) where schizophrenics and bipolars both show a marked decrease of nonpyramidal neurons and also the largest increase of $GABA_A$ receptor binding (see above). It is important to point out, however, that stress is believed to *increase* rather than decrease the activity of the GABA system (Woodbury 1952; Feldman and Robinson 1968; Pfaff et al. 1971; Miller et al. 1978), although it is possible that chronic stress, particularly when preceded by stress in utero, might result in an eventual decrease in the activity of this transmitter system. This possibility is particularly intriguing when the marked sensitivity of GABAergic neurons to excitotoxic injury (Schwarcz and Coyle 1977) is taken into account. It is believed that cell death in this setting probably requires both an increase of excitatory activity and an increased release of glucocorticoid hormone (Sapolsky 1992).

Another important component to the stress response is the increased release of dopamine that occurs in the medial prefrontal cortex (see above). Relevant to this discussion is the fact that an increase of dopamine varicosities forming appositions with interneurons has been induced by exposing rats both pre- and postnatally to stress-related doses of corticosterone (Benes 1997). Thus, it is possible that the postnatal maturation of GABA cells in the cortex may be normally influenced by the ingrowth of dopamine fibers, but abnormally affected when this occurs in individuals for whom pre- and postnatal stress are co-morbid factors. In this latter case, it would have to be assumed that gene(s) involving the dopamine system and perhaps also cortical GABA cells would be affected by prenatal exposure to stress and would be permanently sensitized in such individuals.

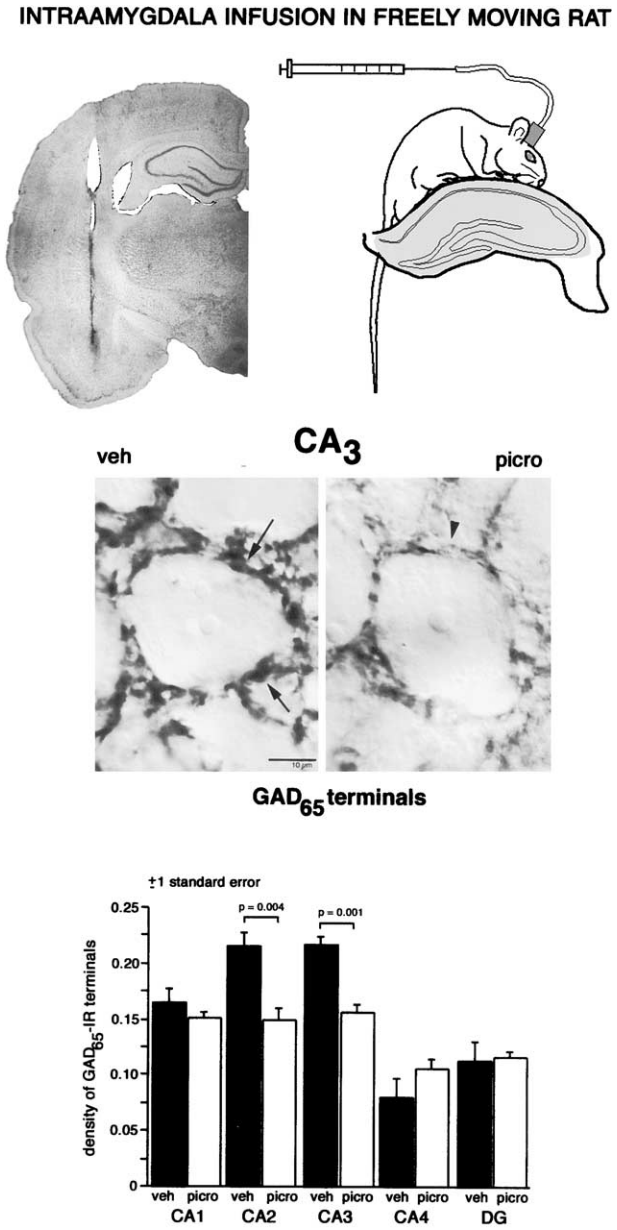

Figure 11. Stereotaxic local infusion of the $GABA_A$ receptor antagonist picrotoxin in the amygdala (needle track shown in upper left panel) of awake freely moving rats induced significant changes in densities of GAD_{65}-positive terminals in hippocampus. The decrease, detectable around cell bodies of pyramidal neurons (middle panel), were selectively observed in sectors CA3 and CA2, but not CA1 (lower panel).

MODELLING ACTIVITY-DRIVEN CHANGES IN HIPPOCAMPAL GABA CELLS

A conundrum that has presented itself from postmortem studies of the GABA system in schizophrenia and bipolar disorder is the following: Why are abnormalities preferentially detected in layer II of the anterior cingulate cortex and sectors CA3 and CA2 of the hippocampus? A potentially important clue that will help answer this question comes from studies of the connectivity of these regions. Layer II of the anterior cingulate cortex is known to receive a 'massive' projection from the basolateral nucleus of the amygdala (Van Hoesen et al. 1993), whereas sectors CA3 and CA2 also receive a substantial input from this same complex (Pikkarainen et al. 1999). Taken together with other evidence (Longson et al. 1996; Benes and Berretta 2000a), it seems plausible that the changes in the GABA system described above may potentially be related to an increased inflow of ac-

tivity from this key limbic region. To explore the possibility that changes in the cortical and hippocampal GABA system in schizophrenia could be related to an increased inflow of activity originating in the amygdala, a 'partial' animal model has been developed (Berretta et al. 2001).

When the $GABA_A$ antagonist, picrotoxin, is infused locally into the basolateral nuclear complex of awake, freely moving rats, within 2 hours, a marked decrease in the density of both the 65 and 67 kDalton isoforms of GAD-IR terminals can be detected on neuron somata in sectors CA3 and CA2, but not CA1 (Figure 11). In anterograde tracer studies, amygdalo-hippocampal projection fibers show a similar distribution. Overall, these results suggest that activation of afferents from the basolateral nucleus is associated with the induction of significant changes in the GABA system in the hippocampus with a subregional distribution that is remarkably similar to that found in schizophrenia and bipolar disorder. Under pathological conditions, an excessive discharge of excitatory activity emanating from the amygdala could be capable of altering inhibitory modulation along the trisynaptic pathway and may potentially contribute to disturbances of GABAergic function in neuropsychiatric disorders. Such 'partial' modelling in rodents will provide an important strategy for deciphering the effect of altered corticolimbic circuits in schizophrenia and bipolar disorder.

CONCLUSIONS

The cortical and hippocampal GABA systems consists of many different subclasses of interneurons, each having unique phenotypes defined by their morphology, neuropeptide content, electrophysiological properties, and synaptic connectivity. GABAergic cells engage in complex interactions not only with projection neurons, but also with one another. The intricate networks derived from these interactions are associated with the generation of both oscillatory rhythms and detailed aspects of discriminative information processing. A defect in even one component of such a system could potentially have profound implications for the functioning of local circuits, as well as larger scale macrocircuits within the corticolimbic system. Stated simply, GABAergic interneurons are critical to the formulation of complex behaviors and a defect in their functioning can give rise to a broad array of disturbances in cognitive function, like those seen in schizophrenia.

In reviewing the postmortem investigations that have been directed at the study of this system, it is clear that there have been some inconsistencies, particularly with regard to cell counting findings. There are many different confounding factors that can be invoked to explain failures to replicate and these vary according to the types of methodology that have been employed. Nevertheless, when this literature is viewed as a totality, including not only cell counting studies, but also cytochemical ones in which immunocytochemistry, receptor binding autoradiography and in situ hybridization have been employed, some form of dysfunction in the GABAergic system brain appears to be present in the cortex of schizophrenics. The fact that similar findings are also being reported in bipolar disorder suggests that such a defect may be related to a common environmental factor, perhaps that related to obstetrical complications. Indeed, the neurodevelopmental hypothesis of schizophrenia (and by extrapolation, bipolar disorder) has received its most convincing evidence from studies of the GABA system.

An important question raised by these findings is whether the GABAergic interneuron might potentially be a common site for the action of drugs that are used in the treatment of both schizophrenia and bipolar disorder. Indeed, GABA-mimetic drugs, such as mood-stabilizing anticonvulsants, show efficacy in the treatment of both schizophrenia (Wassef et al. 1999) and bipolar disorder (Bowden 1998), although patients with affective disorder show a more striking beneficial effect. Recent studies demonstrating direct interactions between the dopamine and serotonin systems with GABAergic neurons in the cortex, as well as the expression of their respective receptor systems in these interneurons, are also consistent with this idea.

In the years to come, continued investigations of the GABA system in rodent, primate, and human brain and the characterization of changes in specific phenotypic subclasses of interneurons in schizophrenia and bipolar disorder will undoubtedly provide important new insights into how the integration of macro- and microcircuitry in the corticolimbic system is altered in health and disease. Most importantly, it will be important to use increasingly sophisticated information regarding GABAergic cells to identify the precise ways in which neuroleptic drugs can influence the structural and functional integrity of this transmitter system. Information of this type may eventually point the way toward novel approaches to the treatment of devastating neuropsychiatric disorders.

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