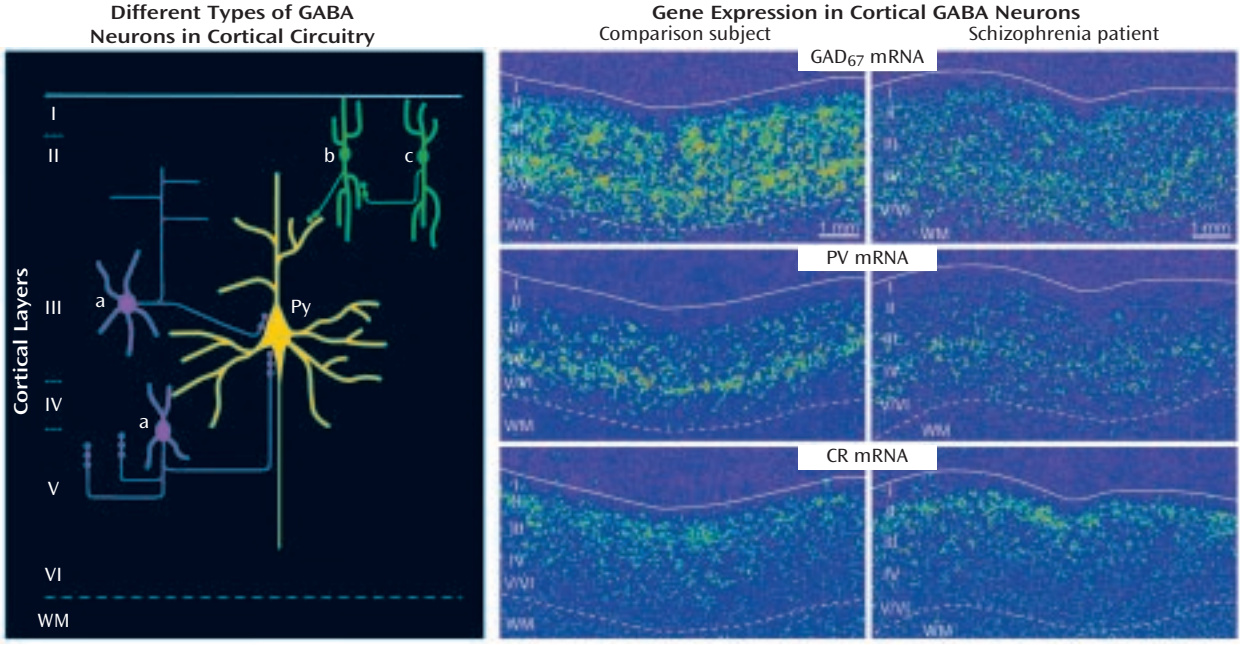
Carol A. Tamminga, M.D., Editor

GABA Neurons in the Human Prefrontal Cortex



About 25% of cortical neurons utilize the inhibitory neurotransmitter, γ-aminobutyric acid (GABA). Subclasses of GABA neurons (left panel) differ in their morphological, biochemical, and functional characteristics, indicating that they likely play distinct roles in regulating cortical circuitry. Some GABA neurons (**a**) provide inhibitory synapses to the cell bodies of nearby excitatory pyramidal neurons (Py) and to their initial axon segments; these appear to be positioned to regulate the firing of pyramidal neurons. Other GABA neurons (**b**) provide inhibitory synapses to the distal portions of pyramidal neuron dendrites, where they modulate neighboring excitatory inputs to pyramidal neurons. The synapses of a third group of GABA neurons (**c**) provide inhibitory inputs to other GABA neurons, resulting in a downstream "disinhibition" of pyramidal neurons. These three subclasses of GABA neurons express different calcium-binding proteins. The (**a**) type of GABA neurons express parvalbumin (PV), whereas the (**b**) and (**c**) types of GABA neurons express calretinin (CR). The cell type-specific expression of parvalbumin and calretinin make it possible to use the expression of the messenger RNA (mRNA) encoding each protein to study the involvement of different subclasses of GABA neurons in brain diseases. As illustrated in the center panels, contiguous sections of normal human brain tissue from Brodmann's area 9 were processed for in situ hybridization to detect the messenger RNA for GAD_{67} (an enzyme that synthesizes GABA), parvalbumin, and calretinin. GAD_{67} mRNA is expressed by all GABA neurons that are principally found in cortical layers II-VI, but not in the subjacent white matter (WM). Parvalbumin and calretinin mRNA are expressed selectively in subpopulations of GABA neurons, and these have different distributions across the cortical layers. The right series of panels illustrates changes in mRNA expression for these proteins in the same cortical region in subjects with schizophrenia. GAD_{67} mRNA expression is decreased, suggesting altered prefrontal GABA-mediated neurotransmission in schizophrenia. Furthermore, the expression of parvalbumin mRNA is decreased, whereas the expression of calretinin mRNA is unchanged. These findings, as a group, suggest that prefrontal GABA neurons regulating pyramidal neuron firing are more prominently affected in schizophrenia than are other subpopulations of GABA neurons. Dysregulation of pyramidal neuron firing may contribute to cognitive dysfunction in schizophrenia.

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