



NEUROSCIENCE FACTS

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The GABAergic Synapse in Neuronal Circuits of the Brain

All neurons of the central nervous system (CNS) appear to be responsive to γ -aminobutyric acid (GABA), and GABA is a transmitter at approximately 20% of CNS synapses. Many GABAergic neurons make long-range connections; for example, the cerebellar corticonuclear, striatonigral, striatopallidal, nigrothalamic, nigrotectal, septohippocampal, and cerebellum-to-inferior olive pathways release GABA as a transmitter. In addition, most areas of the CNS contain neurons whose local axon terminals release GABA.

Perhaps the greatest complexity in GABAergic connections has evolved in the cortex, where the action of GABA also can be related directly to physiological processes. In the visual cortex, approximately one in five neurons and one in six synaptic boutons synthesize GABA. Stereological estimates show that an average cortical neuron receives approximately 5800 synaptic inputs in the cat striate cortex. Of these, about 960 (17%) originate from local GABAergic inhibitory neurons, each one making one to 10 synaptic contacts on a single postsynaptic cell [Beaulieu and Somogyi, *Eur. J. Neurosci.* 2, 296 (1990)]. Taking a value of five, it follows that at least 200 inhibitory neurons converge onto one postsynaptic cortical cell. These statistics hide, however, the intricacy of organization; these 200 cells comprise highly specialized types that spatially subdivide the surface of the postsynaptic cell among themselves [Somogyi, in *Neural Mechanisms of Visual Perception*, Lam and Gilbert, Eds. (Portfolio, Texas, 1989), p. 35]. This conclusion follows from the target selectivity of specific types of GABAergic cortical neurons. For example, the bitufted and neurogliaform cells terminate on the spines and distal dendrites; other cells, such as those of the basket cell family, terminate on the proximal dendrites and somata; and the axoaxonic cells terminate exclusively on the axon initial segment of the spiny principal cells, which use excitatory amino acids as transmitters.

The selectivity of interneuronal con-

nections is more easily seen in the hippocampal formation, where the homogeneous population of principal cell bodies and equivalent parts of their dendrites are aligned. In the dentate gyrus, granule cells receive inputs from at least five distinct types of GABAergic neuron, four of which terminate in mutually exclusive domains on the granule cell surface (Han *et al.*, *Eur. J. Neurosci.*, in press; Halasy and Somogyi, *ibid.*, in press): (i) Hilar cells whose cell bodies and dendrites are restricted to the hilus and which have ascending axons to the outer two-thirds of the molecular layer terminate in conjunction with the perforant pathway. (ii) Molecular layer cells whose axons and dendrites are restricted to the outer two-thirds of the molecular layer terminate in conjunction with the perforant pathway. (iii) Hilar cells whose axons are restricted to the inner one-third of the molecular layer terminate in conjunction with the commissural and association pathways. (iv) Basket cells terminate on the somata and proximal dendrites of granule cells. (v) Axoaxonic cells terminate exclusively on the axon initial segments of the granule cells. The latter two cell types terminate at sites thought to be the most effective for inhibitory control of the final output of granule cells. In contrast, the specific local inhibitory neurons [types (i) to (iii)], which terminate in conjunction with particular excitatory amino acid inputs to the same cell, are in a position to interact selectively with those specific inputs on the same dendritic segments. This interaction is reinforced by the frequent pairing of one glutamatergic and one GABAergic synapse on a single dendritic spine. That most of the GABAergic transmission takes place in the peripheral processes of cells is evident from measurements in the visual cortex, in which twice as many GABAergic synapses are on dendritic spines, and four times as many are on dendritic shafts, as are on the somata of cells [Beaulieu and Somogyi (1990)]. This arrangement is highly appropriate for separate adjustment of the gain of different corticocortical excitatory inputs.

This sophistication in wiring is amply matched by the molecular diversity of amino acid transmitter receptors. Diversity of action of a transmitter can arise from the differential expression of receptor subtypes in different brain areas or on different cell types in the same area. Further selectivity and specificity of action could come from a differential placement of receptor subtypes on the surface of a cell. The granule cells of the dentate gyrus, for example, express at least 11 subunits of the GABA_A receptor [Wisden *et al.*, *J. Neurosci.* **12**, 1040 (1992)]. This repertoire would certainly be adequate for supplying different GABAergic synapses with receptors of different subunit composition, resulting in different physiological actions of the same transmitter. Unfortunately, except for the cerebellum [Somogyi *et al.*, *J. Neurosci.* **9**, 2197 (1989)], little is known about the precise distribution of receptor subtypes at identified synapses.

High-resolution immunocytochemistry has shown the $\alpha 1$ and $\beta 2,3$ (the $\beta 2$ and $\beta 3$ subunits are recognized by the same anti-

body) subunits of the GABA_A receptor to be localized at GABAergic synaptic junctions in the cortex, thalamus, hippocampus, and cerebellum. However, these subunits are also distributed over the entire surface of the cells at nonsynaptic sites [Somogyi (1989); Somogyi *et al.* (1989)] and therefore do not appear to be selectively associated with particular synapses. Such a distribution cannot be generalized for all subunits, however. Cerebellar granule cells express at least eight GABA_A receptor subunits, although most cells receive GABA from only one source, the Golgi cells. In contrast to the $\alpha 1$ and $\beta 2,3$ subunits, which are found over the entire surface of the cells, the $\alpha 6$ subunit is concentrated in the synaptic glomeruli at the junctions established with Golgi cells [Baude *et al.*, *Neuroscience* **51**, 739 (1992)]. The presence of $\alpha 1$ at the same synaptic junctions demonstrates that GABA released from a single terminal may act at receptor complexes of different composition. ●

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