The GAD-given Right of Dentate Gyrus Granule Cells to Become GABAergic

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Janus, the ancient Roman God of Gates and Doors had two faces: one looked into the past, and the other, into the future. Do neurons possess a Janus face when it comes to neurotransmitters, or a given neuron is to be forever solely γ-aminobutyric acid (GABA) ergic, glutamatergic, dopaminergic, peptidergic, or YOURPREFERREDTRANSMITTERergic? The answer is that the terminals of many neurons are homes to even more than two neurotransmitters. All this in spite of the "one neuron–one transmitter" usual misinterpretation of Sir Henry Hallett Dale's postulate, originally meant to indicate that a metabolic process taking place in the cell body can influence all processes of the same neuron. A large variety of neurons in the CNS, many of them GABAergic, produce and release chemicals that satisfy some of the criteria used to define neurotransmitters. The usual scenario for a dual-transmitter terminal is that the fast-acting transmitter such as GABA or glutamate is stored in regular synaptic vesicles, whereas a neuropeptide is stored in dense core vesicles (1). The vesicular zinc found in many glutamatergic terminals also may be considered to be a second neurotransmitter, based on its vesicular packaging with the aid of a specific vesicular transporter, and its postsynaptic actions through high-affinity binding sites and permeation through certain channels (2). Whenever a "fast" and a "slow" neurotransmitter are present in the same presynaptic terminal, it is customary to assume that their release can be differentially regulated (1). There is little convincing experimental support for this phenomenon in the mammalian CNS. The coexistence of two "fast" neurotransmitters in the same terminal is less frequent, but not unheard of. In neonatal sympathetic neurons cocultured with cardiac myocytes, norepinephrine and acetylcholine coexist and have opposite actions on the cardiac muscle cells (3). Very recently we learned that brain-derived neurotrophic factor acting at the low-affinity neurotrophin receptor $p75^{NTR}$, perhaps as part of a programmed developmental switch, can convert the phenotype of the sympathetic neuron from noradrenergic to cholinergic (4). Other examples of two fast neurotransmitters released from the same neuron include GABA and glycine in interneurons of the spinal cord (5) and glutamate and dopamine in ventral midbrain dopamine neurons (6). Of all CNS neurons, the granule cells of the dentate gyrus appear to be the champions of neurotransmitter colocalization: glutamate, enkephalin, dynorphin, zinc, and finally GABA (2,7–9). With this many transmitters in a single neuron, there are probably different ways in which they can be released. Dynorphin and other opioid peptides can be released directly from the dendrites to inhibit excitatory transmission (8). A similar mechanism may take place for GABA, as described in cortical GABAergic neurons (10).

The clear challenge for understanding granule cell function in health and epilepsy is to resolve the release of the transmitter at the synaptic endings, the big mossy boutons that synapse onto CA3 pyramidal cells and their filopodial extensions that form the presynaptic part of synapses onto interneurons. Granule cells in young, but not adult (11), rats and in adult guinea pigs seem to release GABA that apparently finds its way to $GABA_A$ receptors of CA3 pyramidal cells (12). The inhibitory postsynaptic current (IPSC) has a slow rise time, indicating that the receptors might be somewhat removed from the release site, but there is little doubt about the inhibitory nature of the responses in CA3 pyramidal cells (12). To complicate things further, seizures or repetitive stimulation of the perforant path seems to increase the GABAergic phenotype of granule cells both in biochemical studies (13–16) and in physiological experiments (11,17,18). All the necessary enzymes for GABA synthesis seem to be in place (13,14,16), and the vesicular GABA transporter required for packaging GABA into synaptic vesicles also is present (19). The following, with all the possible permutations, are potential consequences of GABA synthesis or release from the granule cell terminals.

1. To produce fast $GABA_A$ receptor–mediated inhibitory events in target cells. These cells include interneurons,

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CA3 pyramidal cells, mossy cells, and, subsequent to the epilepsy-related mossy fiber sprouting, other granule cells.

2. To induce slow $GABA_B$ receptor–mediated inhibitory events in the target neurons mentioned earlier.
3. To cause presynaptic inhibition through $GABA_B$ receptors of glutamate or GABA release from other neighboring terminals, or from the same terminal that just released the GABA (20).
4. To elevate ambient levels of GABA producing tonic GABA conductances in hippocampal neurons equipped with nondesensitizing high-affinity $GABA_A$ receptors (21,22).
5. To buffer pH changes inside the granule cells, akin to the role of GABA in plants (23).

It would be foolish to attempt to speculate on the outcome of all of these possibilities and their interactions. Much of what we want to make of the role of GABA in dentate gyrus granule cells depends on what we believe to be the function of these neurons. They have been described as being the guardians of the hippocampus against an overpowering entorhinal input (24) or as merciless excitotoxic killers of various other cell types (25). Furthermore, the outcome of inhibiting interneurons by the GABA released from phenotypically altered granule cells must be considered. Preliminary findings, after kindling-like repetitive stimulations in slices, point to the existence of granule cell–mediated synaptic GABA responses not only in CA3 pyramidal cells but also in interneurons (11). This disinhibitory alternative must be seriously considered, particularly if we accept that the role of a dentate granule cell is to communicate with a handful of CA3 pyramidal cells while silencing most others. Neuroanatomists tell us that a single granule cell makes synaptic contacts with at least an order of magnitude more interneurons than do the 15 or so CA3 pyramidal cells it innervates (26).

Without any detailed experimental evidence, it will take a long time to decide whether the GABAergic phenotype of granule cells is pro- or antiepileptogenic. Nevertheless, by simultaneously releasing fast excitatory and inhibitory transmitters at times of neuronal conflagration, as in epilepsy, granule cells have revealed their ultimate Janus faces. In ancient Rome, of the many temples dedicated to Janus, one was called *Ianus Geminus*. It was a double-gated temple built in the Forum, serving a symbolic function. When its gates were closed, showing only one face, it signified peace within the Roman Empire. When the gates were open, both faces showing, it meant war. Alternatively, if the second face of Janus really looks into the past, the presence of GABA in granule cells during epilepsy may just be the reactivation of a developmental program reminding us of their GAD-given right to be GABAergic.

References

1. Hökfelt T. Neuropeptides in perspective: the last ten years. Neuron 1991;7:867–879.
2. Weiss JH, Sensi SL, Koh JY. Zn^{2+}: a novel ionic mediator of neural injury in brain disease. Trends Pharmacol Sci 2000;21:395–401.
3. Furshpan EJ, MacLeish PR, O'Lague PH, Potter DD. Chemical transmission between rat sympathetic neurons and cardiac myocytes developing in microcultures: evidence for cholinergic, adrenergic, and dual-function neurons. Proc Natl Acad Sci U S A 1976;73: 4225–4229.
4. Yang B, Slonimsky JD, Birren SJ. A rapid switch in sympathetic neurotransmitter release properties mediated by the p75 receptor. Nat Neurosci 2002;5:539–545.
5. Jonas P, Bischofberger J, Sand K. Corelease of two fast neurotransmitters at a central synapse. Science 1998;281:419–424.
6. Sulzer D, Joyce MP, Lin L, Geldwert D, Haber SN, Hattori T, Rayport S. Dopamine neurons make glutamatergic synapses in vitro. J Neurosci 1998;18:4588–4602.
7. Ottersen OP, Storm-Mathisen J. Excitatory amino acid pathways in the brain. Adv Exp Med Biol 1986;203:263–284.
8. Simmons ML, Terman GW, Gibbs SM, Chavkin C. L-type calcium channels mediate dynorphin neuropeptide release from dendrites but not axons of hippocampal granule cells. Neuron 1995;14:1265–1272.
9. Sandler R, Smith AD. Coexistence of GABA and glutamate in mossy fiber terminals of the primate hippocampus: an ultrastructural study. J Comp Neurol 1991;303:177–192.
10. Zilberter Y, Kaiser KM, Sakmann B. Dendritic GABA release depresses excitatory transmission between layer 2/3 pyramidal and bitufted neurons in rat neocortex. Neuron 1999;24:979–988.
11. Gutierrez R. Activity-dependent expression of simultaneous glutamatergic and GABAergic neurotransmission from the mossy fibers in vitro. J Neurophysiol 2002;87:2562–2570.
12. Walker MC, Ruiz A, Kullmann DM. Monosynaptic GABAergic signaling from dentate to CA3 with a pharmacological and physiological profile typical of mossy fiber synapses. Neuron 2001;29:703–715.
13. Schwarzer C, Sperk G. Hippocampal granule cells express glutamic acid decarboxylase-67 after limbic seizures in the rat. Neuroscience 1995;69:705–709.
14. Sloviter RS, Dichter MA, Rachinsky TL, Dean E, Goodman JH, Sollas AL, Martin DL. Basal expression and induction of glutamate decarboxylase and GABA in excitatory granule cells of the rat and monkey hippocampal dentate gyrus. J Comp Neurol 1996;373:593–618.
15. Lehmann H, Ebert U, Löscher W. Immunocytochemical Localization of GABA immunoreactivity in dentate granule cells of normal and kindled rats. Neurosci Lett 1996;212:41–44.
16. Ramirez M, Gutierrez R. Activity-dependent expression of GAD67 in the granule cells of the rat hippocampus. Brain Res 2001;917: 139–146.
17. Gutierrez R, Heinemann U. Kindling induces transient fast inhibition in the dentate gyrus–CA3 projection. Eur J Neurosci 2001;13: 1371–1379.
18. Gutierrez R. Seizures induce simultaneous GABAergic and glutamatergic transmission in the dentate gyrus-CA3 system. J Neurophysiol 2000; 84:3088–3090.
19. Lamas M, Gomez-Lira G, Gutierrez R. Vesicular GABA transporter mRNA expression in the dentate gyrus and in mossy fiber synaptosomes. Brain Res Mol Brain Res 2001;93:209–214.
20. Vogt KE, Nicoll RA. Glutamate and gamma-aminobutyric acid mediate: a heterosynaptic depression at mossy fiber synapses in the hippocampus. Proc Natl Acad Sci U S A 1999;96:1118–1122.

21. Nusser Z, Mody I. Selective modulation of tonic and phasic inhibitions in dentate gyrus granule cells. J Neurophysiol 2002;87:2624–2628.
22. Stell BM, Mody I. Receptors with different affinities mediate phasic and tonic GABA(A) conductances in hippocampal neurons. J Neurosci 2002;22:223.
23. Barker JL, Behar T, Li YX, Liu QY, Ma W, Maric D, Maric I, Schaffner AE, Serafini R, Smith SV, Somogyi R, Vautrin JY, Wen XL, Xian H. GABAergic cells and signals in CNS development. Perspect Dev Neurobiol 1998;5:305–322.
24. Heinemann U, Beck H, Dreier JP, Ficker E, Stabel J, Zhang CL. The dentate gyrus as a regulated gate for the propagation of epileptiform activity. Epilepsy Res Suppl 1992;7:273–280.
25. Sloviter RS. The functional organization of the hippocampal dentate gyrus and its relevance to the pathogenesis of temporal lobe epilepsy. Ann Neurol 1994;35:640–654.
26. Acsády L, Kamondi A, Sik A, Freund T, Buzsáki G. GABAergic cells are the major postsynaptic targets of mossy fibers in the rat hippocampus. J Neurosci 1998;18:3386–3403.