GABA Comes First to Newly Generated Neurons. Focus on “GABAergic Signal to Newborn Neurons in Dentate Gyrus”

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Using a transgenic mouse that transiently expresses enhanced green fluorescent protein (EGFP) in newborn granule cells, Overstreet Wadiche et al. (2005) in this issue of the Journal of Neurophysiology (p. 4528–4532) describe that during the first 2 wk of their existence, adult-generated granule cells remain isolated from extrinsic excitatory input while they receive GABAergic synapses. These GABAergic inputs derive from local interneurons that at the same time innervate adult and well-differentiated granule neurons in close proximity. It is quite likely as proposed by Overstreet Wadiche et al. (2005) that newborn granule cells receive exclusively GABAergic input because of their location in a region rich in GABAergic terminals with their short dendrites that do not extend into the region containing excitatory input from the perforant path. The study of Overstreet-Wadiche et al. (2005) illustrating that the appearance of GABAergic before glutamatergic activity synaptic events in adult-generated granule cell contrasts with studies of synaptogenesis in the progeny of adult stem cells in vitro (Song et al. 2002). This highlights the need for comparative in vivo—in vitro studies in stem cell neurobiology.

The immature synaptic inputs in the newly generated neurons, although deriving from presumably similar GABAergic interneurons, differ from those received by adult neurons as they are endowed with properties typical of GABAergic synapses established early in development (Hollrigel and Soltesz 1997). Among these properties, the enhanced contribution of α2/3 versus α1 subunits in postsynaptic GABA A receptors diminishes the sensitivity to the hypnotic imidazopyridine Zolpidem and prolongs the decay of the synaptic currents. This has the net effect to increase the charge transfer during synaptic activation, a phenomenon of likely significance in development, possibly to compensate for the lower rate of synaptic activation. Another striking property that newly generated granule neurons in the adult hippocampus display is a depolarized equilibrium potential for chloride as compared with neighbor mature neurons. This has been extensively studied in developing neuron and brings support to the hypothesis that during development, GABA can have trophic effects on cell proliferation, migration, and neurite outgrowth (Ben-Ari 2002; Owens and Kriegstein 2002). At the moment, the role of GABA and that of activity in general in the progressive developmental switch from depolarization to hyperpolarization is hot topic of controversy (Ganguly et al. 2001; Ludwig et al. 2003; Titz et al. 2003). Consensus, however, exists on GABA trophic actions and a depolarized GABA reversal potential. In this regard, it has been thought that depolarizing GABA responses would supply the drive in the immature brain for action potential generation that ultimately drives network development. The conclusion of the elegant study reported here by Overstreet-Wadiche et al. (2005) demonstrates that while GABA is likely depolarizing, it does not loose its shunting effect. The consequence of this is that GABA does not cause spontaneous action potential firing in newly generated neurons although the depolarization generated by synaptic GABA channel activation is probably sufficient for activation of voltage-gated calcium channels and the required role of calcium entry for proper cellular development. Thus GABA maintains the proposed trophic role in the developing neuron leaving intact the proper activity-dependent network development.

References


