EDITORIAL

The role of GABA and glutamate on adult neurogenesis

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Adult neurogenesis is a developmental process that includes proliferation and fate specification of adult neural stem cells along with their differentiation, maturation, migration and incorporation into the existing neural circuitry of their progeny in the mature nervous system (Ming & Song, 2005). Active neurogenesis in the adult mammalian brain has been reported in the subventricular zone (SVZ) of the lateral ventricles and in the subgranular zone (SGZ) of the dentate gyrus of the hippocampus (Bordey, 2006, 2007; Ge *et al.* 2007*a*). These limited areas of the adult brain contain dividing neural stem cells that generate intermediate progenitor cells and neuroblasts. Growing evidence suggests that the neurotransmitters GABA and glutamate have a major role in setting the timing for survival, proliferation, migration, synapse formation and integration of newly formed neurons in established synaptic networks. The action of GABA depends on the unique presence and tonic activation of non-synaptic $GABA_A$ receptors that has gained a strong interest recently as a possible target of neurosteroid action and ethanol intoxication. In the SVZ, GABA serves as a feedback regulator of neural production and migration (Bordey, 2007). In the SGZ, GABAergic mechanisms regulate differentiation and the timing of synaptic integration (Overstreet *et al.* 2004; Ge *et al.* 2007*a*). Depolarization by GABA thus provides a mechanistic basis for *in vivo* 'excitation–neurogenesis coupling'. Glutamate receptors, AMPA, kainate and NMDA have also being recognized as crucial players at later stages of neurogenesis and have been clearly identified as critical elements of neuronal plasticity in newly born neurons in the adult brain (Espósito *et al.* 2005).

To highlight recent progress in this field, *The Journal of Physiology* organized a symposium entitled 'The role of GABA and glutamate on adult neurogenesis' at the 2008 Experimental Biology Meeting in San Diego, California. The symposium brought together five speakers from three continents working in this emerging field who have made major contributions to our understanding of the role of the endogenous neurotransmitters GABA and glutamate and their respective receptors in regulating the production, migration, differentiation and integration of adult generating neurons. They used multidisciplinary approaches to delineate the role of neurotransmitter receptors and proteins that controls ambient neurotransmitter level and intracellular ion concentration in regulating the physiological development and network integration of neuronal progenitors found in the adult brain. Conflicting results on the relative roles of the two major neurotransmitters in neurogenesis were presented and discussed. Drs Song, Schinder and Overstreet-Wadiche discussed the SGZ, and Drs Bordey and Alonso the SVZ. This issue of *The Journal* brings together Symposium Reports from each of these speakers and related papers. The symposium offered an appealing framework with a great potential to restore functions after injury to the central nervous system.

Angelique Bordey from Yale University School of Medicine discussed the functions of GABA and glutamate as local signalling molecules on cell proliferation, migration and survival in the SVZ and RMS prior to the acquisition of synaptic inputs. Using mice that express enhanced green fluorescent protein (EGFP) driven by the doublecortin (DCX) promoter, she presented intriguing evidence for the heterogeneity of action of these signals on individual progenitor cells (Platel *et al.* 2008*a*,*b*). These data allow extrapolation to the distinct roles of GABA acting on $GABA_A$ receptors and glutamate acting on kainate receptors in determining the relative abundance of distinct neuronal precursors, in delivering the appropriate number of neuroblasts, and in regulating migration. The exciting findings of these studies suggest that by setting the ambient concentration of both neurotransmitters, cell number control provides a feedback on cell production. Thus GABA and glutamate signalling provides homeostasis in the neurogenic forebrain.

Neuroblasts migrate along the rostral migratory stream (RMS) to the olfactory bulb where they differentiate into interneurons (Luskin, 1993; Lois & Alvarez-Buylla, 1994). Julieta Alonso of the University of Heidelberg, Germany discussed postnatal neurogenesis of distinct GABAergic interneurones in a mouse model where progenitor cells express EGFP driven by the serotonin receptor 5HT3 promoter. Dr Alonso presented evidence that in these mice sections of the RMS branch off in cortical areas following mostly pathways outlined by blood vessels. She further demonstrated that these neuroblasts have great motility that can be controlled with agonist and antagonists of the $5HT_3$ receptors.

Linda Overstreet-Wadiche of the University of Alabama at Birmingham discussed GABAergic signalling to adult generated neurons. Her research team utilizes propiomelanocortin (POMC)–EGFP transgenic mice that allow a 'snapshot' of newborn dentate gyrus granule cells (DGCs) at an early developmental stage at any age of the mouse. In her presentation and in the review paper in this issue (Markwardt & Overstreet-Wadiche, 2008) she explored the involvement of $GABA_B$ receptors in adult neurogenesis, a neglected topic as much research focused on chloridepermeable $GABA_A$ receptors. The starting hypothesis was that hyperpolarization via $GABA_B$ receptor-mediated activation of inward-rectifying K^+ channels would counteract $GABA_A$-mediated depolarization. Her results showed that $GABA_B$ receptor-mediated K^+ responses are absent in newborn granule cells but it is not know if this is due to the lack of functional $GABA_B$ receptors, GIRK channels or coupling between the two. She concluded that GABAergic signalling in newly developed DGCs is optimized for depolarization-mediated functions.

Alejandro F. Schinder at the Neuronal Plasticity Laboratory, Leloir Institute in Buenos Aires discussed how neurogenesis in the adult hippocampus has the potential to rewire the brain. Dr Schinder reported data from SGZ granule neuron in adult mice after retroviral injections with an EGFP

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expressing virus at embryonic day E15 and at postnatal day 42. Expression of bacterial channel rodhopsin ChR2 fused with GFP illustrated the pattern of excitation of newly developing DGCs with distinct stimulation frequencies. He reported unique roles of newly born DGCs in regulating feed-forward inhibition of CA3 cells and polysynaptic oscillatory response. In the current issue (Morgenstern *et al.* 2008), using retroviral fluorescence labelling and confocal microscopy, Dr Schinder's group also report that neurons born in the ageing dentate gyrus can develop typical DGC morphology and spine density. Ageing reportedly reduces proliferation and neuronal differentiation of neural progenitor cells, which has been proposed as a factor in the age-related decline of cognitive ability. Yet data shown here demonstrate that surviving neurons achieve a high degree of complexity with a density of afferent glutamatergic connections comparable to that of neurons born in young adult mice. This suggests that surviving adult-born granule cells may be less sensitive than neural progenitor cells to environmental alterations of the ageing brain.

Immature DGCs exhibit a striking propensity for synaptic plasticity, suggesting that they could make a unique contribution to experience-dependent modification of the mature neural circuit. Hongjun Song from Johns Hopkins University School of Medicine reported on activity-dependent regulation of adult hippocampal neurogenesis comparing progenitor derived neurons at 4 and 8 weeks post-injection. His data were a follow-up of his earlier studies (Ge *et al.* 2007*b*) that illustrate synaptic plasticity of excitatory inputs to newborn cells. DGCs between 4 and 6 weeks old display an increased magnitude of LTP compared to both younger and older granule cells. Intriguingly, the application of the $GABA_A$ receptor antagonist bicuculline methiodide blocks long-term potentiation (LTP). He also elegantly provided evidence for a critical period of synaptic plasticity in adult born granule neurons similar to that shown during early development of the dentate gyrus. The conclusion of his study summarized in this issue (Ge *et al.* 2008) suggests the exciting hypothesis that adult neurogenesis represents an ongoing developmental process in the adult brain rather than just a replacement mechanism for lost neurons. It is clear that this mechanism provides expanded plasticity of the existing neural circuitry in response to experience throughout life.

In support of this hypothesis, an additional paper by Stocca *et al.* (2008) used confocal Ca^{2+} imaging to investigate dendritic Ca^{2+} signalling in young and mature hippocampal granule cells, identified by the expression of the immature neuronal marker polysialated neural cell adhesion molecule (PSA-NCAM). With Ca^{2+} imaging and patch clamp recordings they found that both young and mature granule cells showed large action potential evoked dendritic Ca^{2+} transients with similar amplitude indicating active backpropagation of action potentials. However, the decay of the dendritic Ca^{2+} concentration back to baseline values was substantially slower in young than in mature cells, leading to a more efficient temporal summation of Ca^{2+} signals during theta-frequency stimulation. They concluded that the low buffer capacity and slow extrusion rates in young granule cells may contribute to the activity-dependent growth and plasticity of dendrites and new synaptic connections. This will finally support differentiation and integration of young neurons into the hippocampal network.

In addition this special issue includes a review from Dr Vittorio Gallo's laboratory on the occurrence and potential roles of GABA and glutamate mediated synapses in a subclass of progenitor cells positive for the marker NG2 in the adult brain (Gallo *et al.* 2008). They suggest the exciting possibility that synaptic transmission to these progenitor cells via activation of GABA and/or glutamate receptors will produce oligodendrocytes or neurons accordingly to specific physiological and/or pathological conditions.

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