



Excitement keeps your brain cells alive

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A commentary on

NMDA receptors activated by subventricular zone astrocytic glutamate are critical for neuroblast survival prior to entering a synaptic network.

by Jean-Claude Platel, Kathleen A. Dave, Valerie Gordon, Benjamin Lacar, María E. Rubio, and Angélique Bordey (2010). *Neuron* 65, 859–872.

One of the most dynamic features of the postnatal and adult mammalian brain is certainly the continuous cellular replacement taking place in discrete regions of the forebrain. In rodents, the subventricular zone (SVZ) of the lateral ventricles produces 10,000–30,000 neuroblasts daily (Lois and Alvarez-Buylla, 1994), which will migrate and eventually form functional connections within the olfactory bulb (OB) neuronal circuitry.

This unique process is characterized by its extreme complexity, with distinct stages of differentiation controlled in a tight spatiotemporal manner. Neural stem cells (also called neurogenic astrocytes) reside in the walls of the lateral ventricles, where after a transient amplification phase, they generate committed neuroblasts. These neuroblasts migrate great distances via the rostral migratory stream (RMS) to the OB, a journey taking several days. In the olfactory bulb they invade different layers into which they functionally integrate, participating in olfactory processing (see for example, Mouret et al., 2009). This fascinating multistep process needs to be precisely controlled, optimizing the number of newly generated neurons necessary to adapt to a changing olfactory environment (Alonso et al., 2006).

Increasing evidence reveals a central role for neurotransmitters in precisely regulating several key steps of the neurogenic process. In the SVZ, asynchronous release of GABA or glutamate by the neuroblasts and SVZ astrocytes, respectively, antagonistically influence proliferation and therefore ultimately the

size of the newly generated neuroblast pool (reviewed in Platel et al., 2008). Glutamate can bind to different types of receptors. Neuroblasts express one or several of the metabotropic (mGluR5) and ionotropic glutamate receptors (i.e., AMPA, Kainate; reviewed in Platel et al., 2010a), and gradually acquire NMDA receptors while they migrate, as discussed below. These receptors carry out different functions. Neuroblast migration is affected by Kainate receptor blockade (GluK2). In contrast, activation of metabotropic glutamate receptor (mGluR5) has no effect on neuroblast migration but their blockade result in a marked reduction of the number of proliferative cells in the SVZ (Melchiorri et al., 2007). Another level of regulation occurs in the OB, where local activity affects the survival of newborn neurons whilst they synaptically integrate into the OB neuronal circuitry (Alonso et al., 2006; Mouret et al., 2009).

Recent work by Platel et al. (2010b) identifies a new role for the glutamate NMDA receptors (NMDARs) in promoting the survival of migrating neuroblasts through their protracted journeys towards the OB. By performing perforated patch-clamp recording at defined rostro-caudal levels of the RMS combined with calcium imaging, the authors have demonstrated a gradual expression of functional NMDARs in migrating neuroblasts, which are spontaneously activated resulting in transient intracellular calcium increases. They next used an elegant method of electroporation of a Cre-expressing plasmid in the SVZ of Rosa26^{STOP-YFP} neonatal mice, resulting in the conditional but permanent labeling of cohorts of newly generated neuroblasts. This method, when applied in NR1^{flxed}/Rosa26^{STOP-YFP} mice, resulted in single cell knockouts (KOs) for the NMDAR, leading to a significant decrease in the number of neuroblasts reaching the OB. Immunodetection of activated caspase-3 revealed a parallel increase in the number of apoptotic neuroblasts in the RMS, an effect also observed after *in vivo* blockade

of NMDARs. Thus, blocking NMDAR activity by different means increases apoptosis of migrating neuroblasts that results, over time, in a cumulative decrease of OB granule cell neurogenesis (65% at 8 weeks post-electroporation). Importantly, the migration of the electroporated neuroblasts was not influenced by genetic removal of NMDARs indicating that apoptosis alone contributes to defective neurogenesis.

Interestingly, although NMDARs might play a role in the successful synaptic integration of newborn neurons in the OB circuitries, the initial phase of neuroblast apoptosis occurs in the rostral SVZ and RMS, two asynchronous environments. Platel et al., provide detailed analyses of the cell types and mechanisms involved in the asynchronous glutamate release resulting in the activation of NMDARs on migrating neuroblasts. By combining immunostaining for l-glutamate as well as for the vesicular glutamate transporter VGlut1 with astrocytic and neuroblasts markers (Glast and DCX, respectively), they show at the microscopic and ultrastructural level, that within the RMS, only astrocytes express glutamate and the machinery for its vesicular release. Furthermore, a calcium increase in RMS astrocytes induced NMDAR activation in migrating neuroblasts. This was notably shown in acute sagittal forebrain slices prepared from transgenic mice that express the Gq-coupled receptor MrgA1 exclusively in astrocytes, in which a calcium increase can be evoked by using an agonist (FLRF) that does not bind to endogenous receptors in the brain (Fiacco et al., 2007). Altering astrocytic vesicular release by using the *Clostridium botulinum* neurotoxin BoNT/B significantly reduced NMDAR activity in neuroblasts, an effect not observed with the neuronal specific neurotoxin BoNT/A.

Taken together, these results reveal a previously unsuspected role for NMDARs in modulating the survival of neuroblasts migrating within an asynchronous environment. Together with previous work from

the Bordey's lab and others (Melchiorri et al., 2007; Platel et al., 2010a), this work demonstrates that it is the differential expression of distinct receptors that will mediate varied activities of glutamate on cellular processes as diverse as proliferation, migration and survival throughout SVZ neurogenesis.

These findings are significant for several reasons. First, they identify a novel mechanism which, together with the modulation of neural progenitor proliferation in the SVZ and the differential survival of newborn neurons in the OB, might contribute to the tight regulation of neurogenesis in the mammalian forebrain. A wide variety of experimental/environmental manipulations have been shown to modulate OB neurogenesis (Ma et al., 2009). In this context, it will be interesting to assess if stimuli that increase or decrease OB neurogenesis also regulate glutamate release by RMS astrocytes, and to identify the possible mechanisms mediating these changes.

This study might also be of relevance in the context of forebrain repair by endogenous neural stem/progenitor cells. Numerous studies have shown the migration of SVZ-generated neuroblasts to sites of forebrain injury. A striking example is the sustained neuroblast migration to the striatum after stroke. This process persists for several months, but its contribution to repair is tempered by the poor survival of the recruited neuroblasts (Thored et al., 2006). It would be interesting to examine the involvement of NMDARs in mediating this weak survival. RMS astrocytes might differ from astrocytes (quiescent or reactive) in other brain regions (intact or denervated), in their

capacity to release glutamate and therefore to promote the survival of neuroblasts that are recruited to sites of injury. Thus, although it is well known that astrocytes from various brain regions show calcium transients and might release glutamate in response to neuronal activity (Aguilhon et al., 2008), recent research has questioned the significance of this process in the context of synaptic NMDAR activation (Aguilhon et al., 2010).

In conclusion, this work changes our view of the RMS as a passive pathway for neuroblast migration. It highlights that the RMS is a highly specialized forebrain compartment, comparable to the SVZ neurogenic niche, where astrocytes play an intricate role in modulating survival of migrating neuroblasts. Finally, taken together with previous work from the same laboratory and others, these findings illustrate how amino-acid neurotransmitters control multiple steps of a complex cellular differentiation process in the postnatal forebrain.

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