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Review

Nicotinic control of adult-born neuron fate

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ABSTRACT

The hippocampus is one of only two regions in the adult brain where neurons are generated in significant numbers throughout the lifetime of the animal. Numerous studies have demonstrated that these adult-born neurons are essential for optimal cognitive function with unimpaired memory formation and retrieval. The extent to which adult-born neurons survive through an early "critical period" and become integrated into functional networks has been shown to depend on the richness of stimulation they receive during these formative stages. The dentate gyrus in the hippocampus – home of the adult-born neurons – receives extensive cholinergic innervation, and newly generated neurons in the adult hippocampus express substantial numbers of both major types of neuronal nicotinic acetylcholine receptors. Early studies indicated that nicotinic signaling may be important for the development of adult-born neurons: repeated exposure to nicotine impaired their long-term survival. Recent studies with mutant mice lacking either one of the two major nicotinic receptor subtypes demonstrate that receptor loss results in fewer adult-born neurons surviving the critical period and becoming integrated into neural networks. The key nicotinic receptor mediating the largest effects is one that has a high relative permeability to calcium. In view of this feature, it may not be surprising that excessive exposure to nicotine can have detrimental effects on survival and maturation of adult-born neurons in the dentate; these same receptors appear to be key. The results pose serious challenges for therapeutic strategies targeting an individual class of nicotinic receptors for global treatment in the recipient.

Contents

1. Introduction

The dentate gyrus of the hippocampus is one of only two parts of the brain that have been shown to generate substantial numbers of new neurons throughout adult life. Adult-born neurons in the dentate are essential for normal cognitive function and memory formation [1–10]. Deficits in generation and function of adult-born neurons contribute to numerous pathological disorders [11–15]. This extends to addictive behaviors where recent evidence indicates that drug seeking is enhanced following loss of adult-born neurons [16].

Adult-born neurons in the hippocampus derive from neural progenitor cells in the subgranular zone of the dentate. During the

Abbreviations: nAChRs, nicotinic acetylcholine receptors; α7-nAChR, homopentameric α7-containing receptor; β2*-nAChR, heteropentameric β2-containing receptor; α7KO, knockout mouse lacking α7-nAChRs; β2KO, knockout mouse lacking β2*-nAChRs; PSCs, postsynaptic currents; MMLV-GFP, Moloney's murine leukemia viral construct expressing green fluorescent protein; RNAi, RNA interference.

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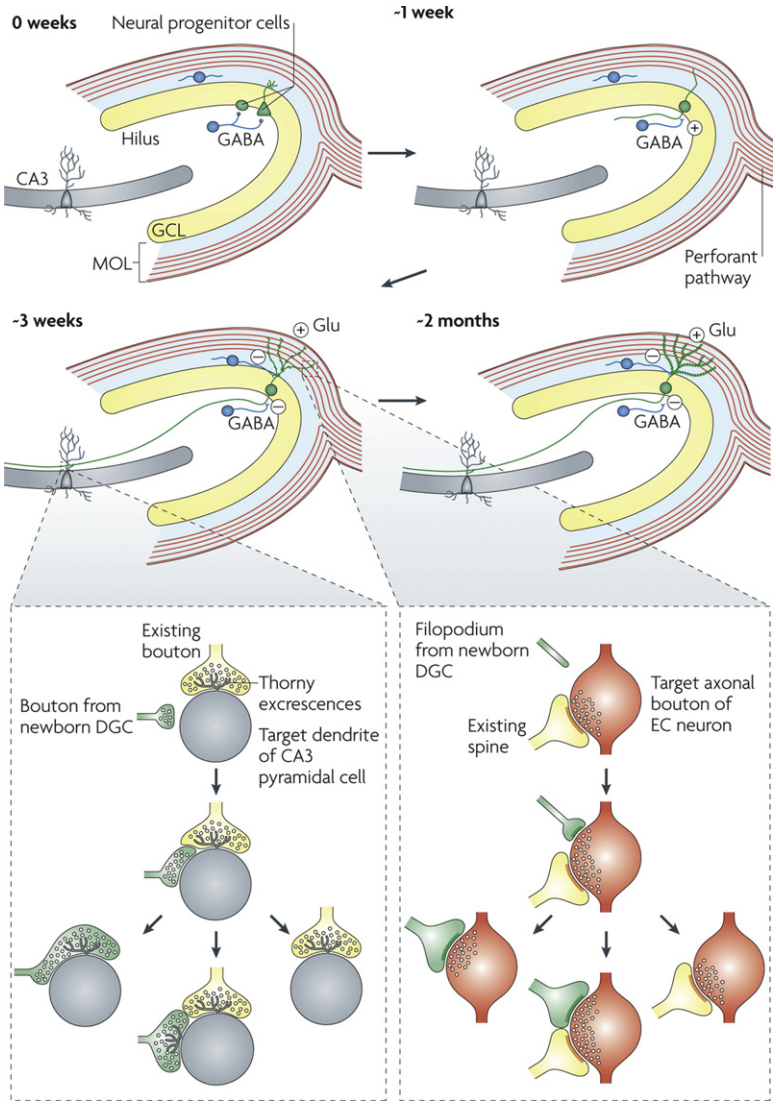

Fig. 1. Adult hippocampal neurogenesis. The proliferation of neural progenitor cells (NPCs) with two different morphologies gives rise to adult-born dentate granule cells (DGCs) (shown in green). The fate-committed, adult-born DGCs undergo several stages of development, with gradual changes in morphological and physiological characteristics. About 1 week after birth, the adult-born DGC extends its dendrite into the granule cell layer (GCL) and molecular layer (MOL) and projects the axon into the hilus toward CA3. The DGC receives excitatory GABAergic input, presumably from local interneurons (shown as blue cells). During the third week after birth, the DGC receives glutamatergic input (Glu) from the perforant pathway. At this stage, the GABA input changes from being excitatory to being inhibitory. Both efferent and afferent synapses of the adult-born DGCs begin to form around this time. At around 2 months of age, the basic structural and physiological properties of the adult-born DGCs are indistinguishable from those of mature DGCs. The inset panels illustrate the competitive nature of synapse formation. Left inset: a small bouton (shown in green) from the axon of an adult-born DGC contacts the dendritic shaft (shown in grey) of a CA3 pyramidal neuron at a site near the thorny excrescences that contact an existing axonal bouton (shown in yellow). During the subsequent development of the new synapse, the bouton from the newborn DGC either replaces the existing axonal bouton or forms a new thorny excrescence nearby, or retracts. Right inset: the filopodium (shown in green) from an adult-born DGC dendrite extends to an axonal bouton (shown in red) that is associated with another spine (shown in yellow), which leads to the eventual formation of either a monosynaptic bouton targeting spines from the adult-born DGC or a multisynaptic bouton, or leads to retraction.
(From Ref. [23].)

first week following their final mitosis, the cells differentiate and migrate into the inner granule cell layer (Fig. 1). In subsequent weeks the neurons project axons into the CA3 region and extend dendrites into the molecular layer where they become innervated [7,17–23]. The cells undergo a "critical period" 2–4 weeks after their final mitosis, during which a significant fraction of the cells die [24].

Survival and development of adult-born neurons up through the critical period depends on neuronal activity. GABAergic input is required for precursor proliferation and early dendritic growth [25–27]. This is a time when GABA is depolarizing due to a reversed chloride gradient, as described for the early stages of young neurons in many parts of the developing nervous system [28–30]. Glutamatergic input is also essential, acting through NMDA receptors to promote survival of adult-born neurons through the critical period and integration into functional circuits [24,31].

Endogenous nicotinic cholinergic activity plays a key role in the developing nervous system. Nicotinic receptors (nAChRs) are expressed early [32,33] and drive waves of excitation through many parts of the early postnatal nervous system [34–36]. Activity through a major class of nicotinic receptors, the α7-containing receptor (α7-nAChR), helps drive maturation of the chloride gradient, thereby determining when GABA stops being excitatory and starts being inhibitory in many neurons [37]. The finding that adult-born neurons also display excitatory GABAergic responses early on and that it is critical for their development [26,38] raises the question of whether endogenous nicotinic activity normally shapes the fate of adult-born neurons. This and the related question of

whether exogenous nicotine, e.g. from tobacco consumption, can alter the fate of adult-born neurons are the subjects of this review.

2. Effects of nicotinic input mediated by β2-containing receptors

Adult-born neurons express both major classes of nicotinic receptors in the dentate gyrus [39] early on, namely the homopentameric α7-nAChRs and the heteropentameric β2-containing receptors (*β2-nAChRs) [40]. Moreover, cholinergic fibers can be detected immunohistochemically running throughout the region and cholinergic terminals synapse on young adult-born granule neurons, raising the possibility of nicotinic regulation of adult-born neuron development. The first evidence that nicotinic signaling might be important came from nicotine studies in rats [41]. High doses of nicotine, whether self-administered or delivered via intraperitoneal injection or osmotic mini-pump, were found to decrease neurogenesis in the dentate [41–43]. It remains unclear, however, by what mechanism or through which receptors nicotine exerts this effect.

Knockout mice lacking a functional β2-nAChR gene (β2KO) provided the first clear evidence that endogenous nicotinic cholinergic signaling influences the generation of adult-born neurons in the dentate and does so via β2*-nAChRs [44]. Intraperitoneal BrdU injections were used to label dividing neurons, and two hours later animals were perfusion-fixed and taken for analysis. At 7–10 months of age, β2KO mice showed a significant deficit in the number of newborn neurons that could be generated in the dentate (Fig. 2). Interestingly, no deficit was seen either at earlier ages or at substantially later ages. In this respect the results agreed with an earlier study finding no difference in β2KOs vs. WTs at the early time, i.e. 2–4 months of age, when the criterion was the number of adult-born neurons that survived at least 3 weeks after their final mitosis [45].

The results demonstrate a dependence on nicotinic activity via β2*-nAChRs to sustain normal proliferation of neural progenitors to produce adult-born neurons in the middle phase of adult life. This is an interesting finding and raises questions about how β2*-nAChR activation can affect progenitors and why the effect would be confined to "middle age". Importantly, the β2*-nAChR effect seems unlikely to account for earlier reports of nicotine-mediated toxicity that reduce the numbers of adult-born neurons in the dentate [41]. For that effect, attention is drawn to the other major nicotinic receptor expressed by adult-born neurons, namely the α7-nAChR, as discussed below. A remaining question is whether activity through β2*-nAChRs mediates other aspects of neuronal development and innervation, such as generation of dendritic spines. This possibility is suggested by a recent report showing spine deficits in a number of brain regions in adult β2KO mice [46].

3. Role of α7-containing nicotinic receptors in determining the fate of adult-born neurons

Among the most interesting nicotinic receptors are the α7-nAChRs because of their abundance, because of their expression both by neuronal and by non-neuronal cells, and because of their high relative permeability to calcium [39,47,48]. This latter feature enables them to regulate a variety of calcium-dependent events in cells [49]. The availability of knockout mice lacking a functional α7-nAChR gene (α7KO) facilitates analysis of α7-nAChR function in vivo [50]. This has been exploited recently for studies on adult-born neurons in the dentate [51].

BrdU-labeling of adult-born neurons demonstrated that α7KO mice were equivalent to WTs in the numbers of adult-born neurons that survived at least 2 weeks following their final mitosis. A marked difference was seen, however, at the end of the critical period, i.e. 4 weeks post final mitosis. In this case, α7KOs had a third fewer surviving cells than did WTs [51]. Because many of the experiments were done on mice 1–3 months of age, the α7KO effect can be seen as clearly different from that found in β2KOs where only the initial proliferation appears to be affected and only then during middle age for the mouse [44,45].

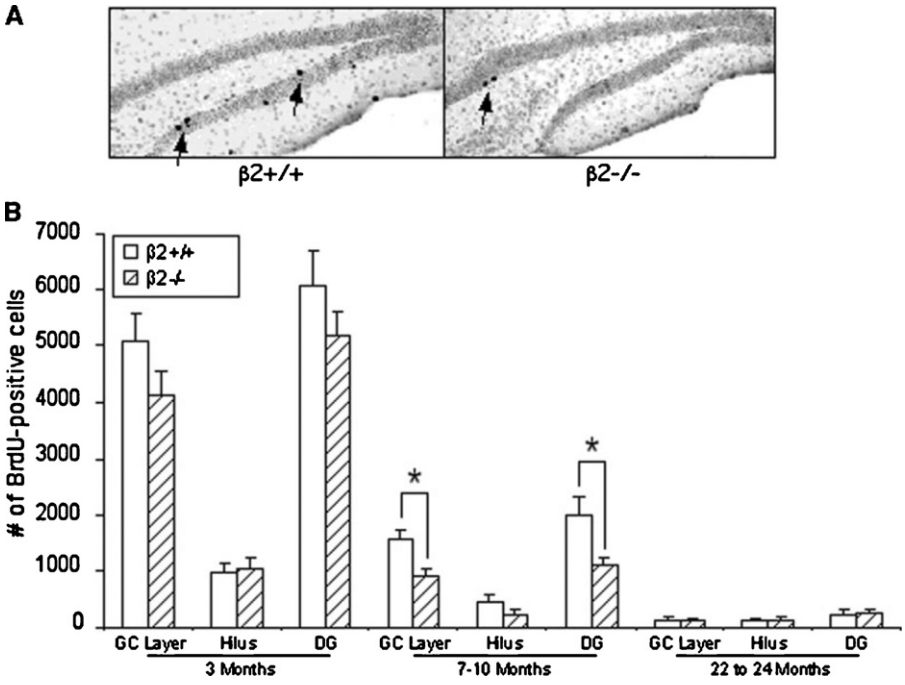

Fig. 2. Numbers of newly divided cells distinguished by BrdU labeling in the subgranular zone of the dentate. (A) Representative sections with BrdU staining in the dentate gyrus of 7–10-month-old WT (β2+/+) and β2KO (β2−/−) mice. (B) Quantification of differences in number of BrdU-stained cells in WT and β2KO hippocampus at 3 months of age, 7–10 months of age, and 22–24 months of age. Data are reported as mean number of BrdU cells/animal ± SEM. Statistical analysis was performed using Student's *t*-test for independent samples; $^{*}p \leq 0.05$. DG = dentate gyrus, GC = granule cell.
(From Ref. [44].)

Loss of signaling through α7-nAChRs was previously shown to delay maturation of chloride gradients in developing neurons in early postnates, thereby extending the initial period during which GABA serves to elicit depolarizing, and often excitatory, responses in the cells [37]. Patch-clamp recording from 4-week-old adult-born neurons in the dentate gyrus of acute slices prepared from α7KO mice indicated that the neurons retain a depolarizing chloride gradient much longer than do age-matched controls in WTs (Fig. 3). Reversal potentials were measured by using a stimulating electrode to elicit postsynaptic currents (PSCs) in the presence of blockers for glutamate receptors. The remaining PSCs, generated by chloride-permeable $GABA_A$ receptors, were measured at a number of different holding potentials so that the reversal potential could be interpolated. A perforated patch-clamp recording technique was used to avoid disruption of the internal chloride concentrations, and neurons were age-dated by stereotaxic intracranial injection of a Moloney's murine leukemia viral construct expressing green fluorescent protein (MMLV-GFP) 4 weeks prior to sacrifice, thereby labeling all neurons undergoing their final mitosis at the time of injection. Though no difference was seen in the resting membrane potential between 4-week-old adult-born neurons in α7KOs vs. WTs, a clear difference was seen

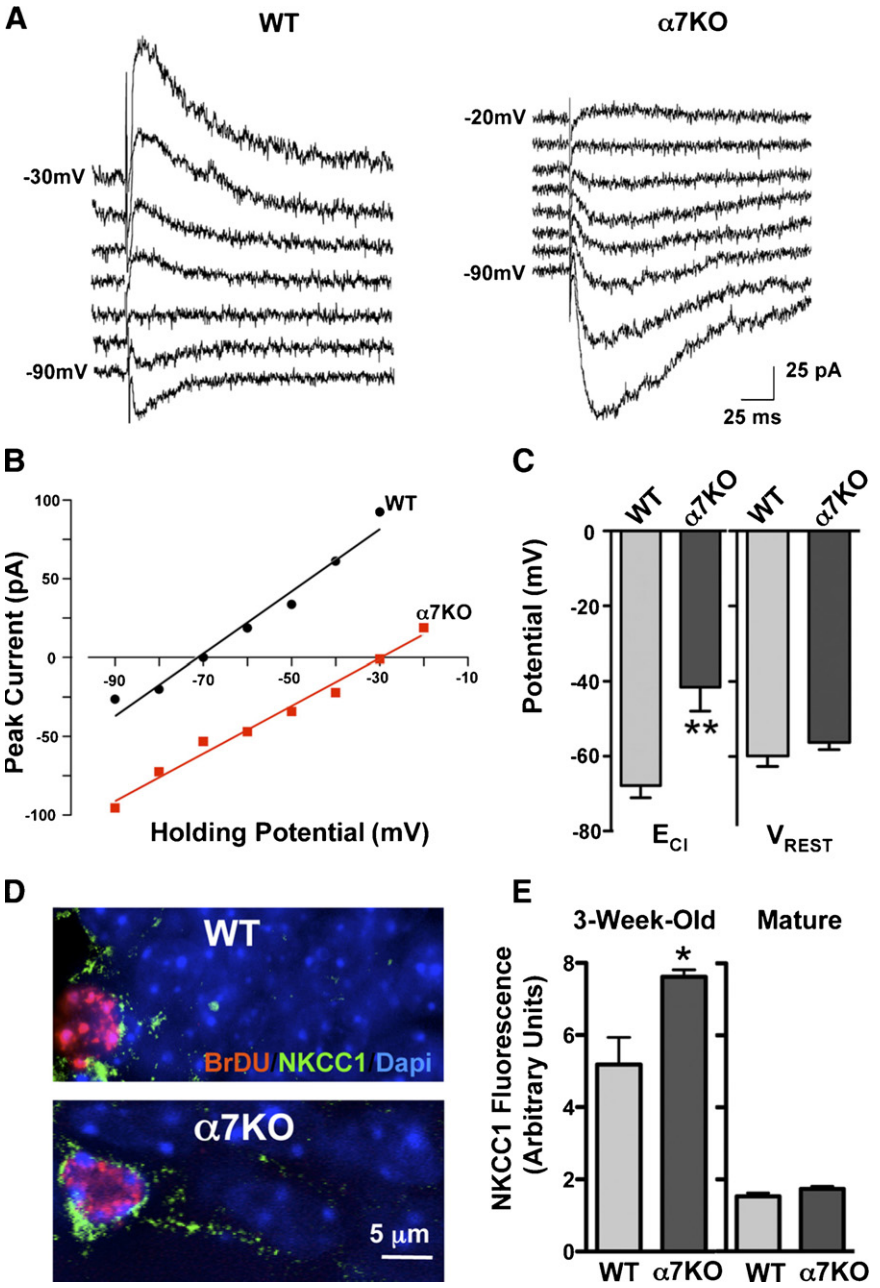

Fig. 3. Delayed maturation of the chloride gradient in adult-born α7KO neurons extends the period of depolarizing GABAergic responses. (A) Superimposed perforated patch-clamp recordings of GABAergic PSCs evoked in 3-week-old adult-born WT (left) and α7KO (right) neurons at the indicated holding potentials. The neurons were labeled in vivo with MMLV-GFP and visualized in freshly prepared slices at the time of recording. (B) Peak amplitude of the evoked GABAergic PSC as a function of voltage in a WT (black) and an α7KO (red) neuron as in A. (C) Interpolated reversal potentials (left; E_{Cl}; $n = 6$ WTs and 5 α7KOs) and resting membrane potentials (right; V_{REST}; $n = 6$ WTs and 8 α7KOs) for WT and α7KO neurons. (D) NKCC1 immunostaining (green) of BrdU-labeled (red) 3-week-old adult-born neurons from a WT (top) and α7KO (bottom) dentate gyrus, mounted in DAPI-containing media to reveal nuclei (blue). (E) Quantification of NKCC1 levels in neurons as in D (3 weeks of age) or from neurons in the outer third of the granule cell layer (mature) from the same mice (mean ± SEM; $n = 3$ animals per condition; ≥10 neurons per mouse). $^*p \leq 0.05$, $^{**}p \leq 0.01$, Student's *t*-test. (From Ref [51].)

in the reversal potential for GABAergic PSCs (Fig. 3C). Immunostaining for the chloride transporter NKCC1, characteristic of young neurons and responsible for generating a "depolarizing" chloride gradient, indicated that adult-born neurons in α7KOs retain high levels of NKCC1 much longer than do their counterparts in WTs (Fig. 3E). These results demonstrate that constitutive lack of α7-nAChRs retards development of adult-born neurons, causing them to retain a chloride gradient that supports depolarizing GABAergic responses much longer than found in WTs.

An extended period of depolarizing GABAergic signaling might have been thought to permit excessive development because numerous studies have shown that manipulations which prevent the early period of GABA depolarization also prevent normal development and integration of neurons [26–29]. The opposite appears to be the case, namely that the extended period of depolarizing GABA in α7KO adult-born neurons reflects retarded development. The neurons have attenuated dendritic arbors measured either as the number of dendritic branch points or total dendritic length 3 weeks after their final mitosis [51]. Patch-clamp recording reveals both reduced frequency and reduced mean amplitude of spontaneously occurring PSCs in the neurons. Moreover, the rise time and decay kinetics of the GABAergic PSCs in α7KO adult-born neurons at this time are delayed compared to those seen in age-matched WT controls [51]. These kinetics are characteristic of $GABA_A$ receptors lacking the α1 subunit, a feature of young neurons [52,53] which provides further evidence that adult-born neurons in α7KOs lag behind those in WTs with respect to developmental time course. The developmental deficits persist for extended periods: adult-born α7KO neurons display reduced dendritic arbors compared to age-matched WTs even 6 weeks after final mitosis [51].

4. Cell-autonomous actions of α7-containing niotinic receptors to support adult-born neuron development

Which α7-nAChRs are critical for adult-born neuron development? The receptors are widely expressed in the nervous system, being found both pre- and postsynaptically at many synapses in the hippocampus and on astrocytes as well [39,54–56]. In the case of adult-born neurons, α7-nAChRs on the neurons themselves appear to be critical for normal development and integration of the neurons into circuits [51]. This was shown by using RNA interference (RNAi) to knockdown α7-nAChR levels in adult-born neurons in vivo and assess the effect on subsequent development. Lentiviral constructs encoding the RNAi sequence along with GFP were stereotaxically injected intracranially, together with an MMLV-mcherry construct that only infects dividing cells. RNAi-expressing adult-born neurons were then identified in the dentate three weeks later by scoring cells expressing both the red and green fluors (yellow). Adult-born neurons expressing the α7RNAi had a significantly reduced dendritic arbor as reflected both by the number of dendritic branch points and by the total dendritic length when compared either to uninfected neurons in the same animal or to neurons of the same age expressing a scrambled RNAi control in other animals (Fig. 4A–C). No off-target α7RNAi effects were apparent because the construct had no effect in α7KOs, as predicted (Fig. 4D and E). The results indicate that α7-nAChRs expressed by the adult-born neurons are essential for normal dendritic development of the neurons, confirming a cell-autonomous effect.

5. Comparisons between hippocampal and subventricular adult neurogenesis

The subventricular zone (SVZ) is the only other major neurogenic region in the adult mammalian brain. Like the hippocampus, it receives rich cholinergic innervation, and the cells go on to express both α7- and β2*-nAChRs [40,57]. Neurons born in the SVZ, however, undergo a radically different path of maturation compared to adult-born neurons in the dentate gyrus. In the latter case, adult neurogenesis produces glutamatergic projection neurons that mature and integrate into the local environment. In contrast, neural precursors from the SVZ migrate in a rostral stream to the olfactory bulb where they differentiate primarily into GABAergic interneurons [58]. These differences raise questions about which nicotinic effects on adult neurogenesis are conserved between the two regions.

Nicotinic receptor expression in adult-born olfactory neurons suggested that β2-nAChRs may play a prominent role. Greater than 95% of the neurons are reported to display β2-nAChR immunostaining while less than 20% display α7-nAChR expression [40]. In the dentate, on the other hand, the two receptor types are both expressed in the vast majority of adult-born neurons. Perhaps not surprisingly, the only demonstration to date that endogenous nicotinic cholinergic signaling controls the fate of adult-born neurons from the SVZ comes from β2KO mice [45]. Intraperitoneal injection of BrdU showed that the absence of β2*-nAChRs causes a significant increase in the number of adult-born neurons that survive to at least 3 weeks of age in 2–4-month-old mice. In contrast, no differences are seen between WT and β2KO adult-born survival at this time in the dentate, and at later times the β2KOs actually show reduced proliferation as noted above [44,45]. These results indicate that endogenous nicotinic cholinergic signaling may exert different regulatory effects on neurogenesis in the two regions.

The two locations also appear to respond differently to nicotine. BrdU labeling was used to show that acute intermittent nicotine treatment increases the proliferation of adult-born neurons in the SVZ by increasing local FGF-2 expression and signaling through FGFR1 receptors [59]. The same treatment has no effect on neuron proliferation in the dentate. In spite of this difference, chronic nicotine exposure supplied by osmotic pump resulted in cell death for both populations of adult-born neurons [43,44]. It is not yet known whether the underlying mechanisms responsible for cell death are the same in the two regions.

Present evidence indicates that adult neurogenesis is responsive to nicotinic signaling both in the dentate and in the SVZ, but much remains to be learned. The role of α7-nAChRs in the SVZ, for example, has yet to be examined in detail. It is far from clear exactly how nicotinic input influences adult neurogenesis in the SVZ and how that compares to nicotinic action in the dentate with respect to the kinds of cellular mechanisms employed, receptor subtypes engaged, and final outcome achieved for cell survival and integration into functional pathways.

6. Future directions

Recent work demonstrates that endogenous nicotinic cholinergic signaling promotes normal development of adult-born neurons in the hippocampus. In contrast, previous work showed that infusion of nicotine could have detrimental effects on adult-born neurons in the dentate. How are these observations to be reconciled? A likely possibility is that either the amount or the timing of nicotinic activity is critical for outcome. Too much or too soon may be detrimental to the progenitors and/or to the neurons. Given the high relative calcium permeability of α7-nAChRs [47,48], excessive stimulation via nicotine may be detrimental at early times [60]. Ongoing work indicates that timing is indeed critical. Nicotine exposure prior to and during neurogenesis seriously diminishes generation and/or early survival of adult-born neurons in the dentate, whereas chronic nicotine infusion starting a week after generation of adult-born neurons markedly

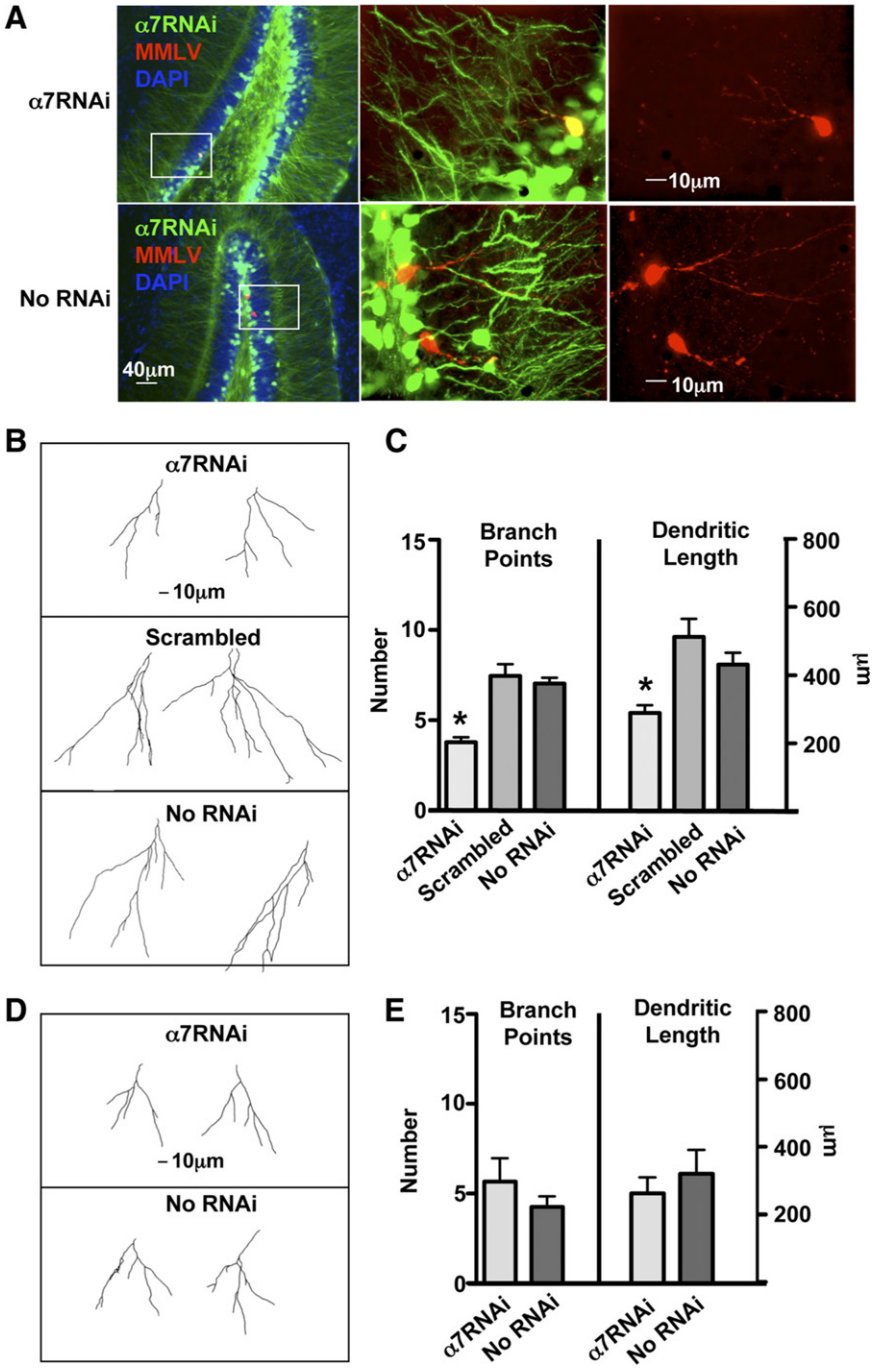

Fig. 4. Cell-autonomous signaling through α7-nAChRs supports dendritic maturation of adult-born granule neurons. (A) Stereotaxic co-injection of lenti-α7RNAi (green) and MMLV-mcherry (red) yields both adult-born neurons expressing α7RNAi (top row; yellow cell) and adult-born neurons lacking RNAi expression (bottom row; red cells) in the same animal. Images are shown at 10× (left) and magnified for the region of interest (white box) to 63× (middle and right). (B) Dendritic arbor traces of 3-week-old adult-born neurons expressing α7RNAi (top), scrambled RNAi (middle), or lacking RNAi expression in animals injected with lenti-α7RNAi (bottom). (C) Dendritic branch points (left) and dendritic length (right) of 3-week-old adult-born neurons infected as in (A) and (B) (mean ± SEM; $n = 3$ mice per condition with 4 cells per animal). (D) Dendritic traces of 3-week-old α7KO adult-born neurons expressing α7RNAi (top) or lacking RNAi expression in animals injected with lenti-α7RNAi (bottom). (E) Dendritic branch points (left) and dendritic length (right) of 3-week-old α7KO adult-born neurons (mean ± SEM; $n = 4$ mice per condition). $^*p \leq 0.05$, one-way ANOVA with Bonferroni's *post hoc* test for multiple comparisons.
(From Ref. [51].)

enhances their survival through the critical period and their dendritic development (N. Campbell, D. John, A. Lozada, W. Kem, and D. Berg, manuscript under review). In both cases these nicotinic effects on adult-born neurons depend on α7-nAChRs.

Pharmaceutical intervention targeting nicotinic receptors is potentially a powerful strategy to combat a variety of neurological disorders. In the case of adult-born neurons and their contributions to memory formation and performance, the challenge is huge. This is because α7-nAChRs have potentially contradictory effects, depending on timing and dose-dependence of agonists. Moreover, global strategies that target the entire nervous system may have beneficial effects for α7-nAChRs in some regions such as the cortex or CA1 of the hippocampus, while at the same time having negative effects on adult-born neurons expressing the receptors. These

issues raise the question of whether partial agonists or noncompetitive antagonists might achieve an appropriate balance, aiding desired populations while not harming others. A different strategy might be to infuse the active compounds locally, but that poses other kinds of challenges. Nonetheless, the importance of nicotinic receptors in general, and α7-nAChRs in particular, in guiding neural development and function, not to mention their roles in mediating nicotine addiction, render them highly attractive targets for therapeutic strategies in humans.

Conflicts of interests

The authors declare they have no actual or potential conflicts of interest.

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