STEM CELLS

# Exciting neurogenesis

Does activity modulate the formation of new neurons in the mammalian brain? Fundamental steps towards answering this question have been made by Rob Malenka and colleagues. Their *Neuron* paper reveals that excitatory stimuli act directly on adult hippocampal cells to encourage neurogenesis.

The team began their comprehensive investigation by culturing neural progenitor cells (NPCs) from adult rat hippocampi in the presence of mature neurons and glia. Under conditions that favour neuronal differentiation, application of excitatory stimuli — $K^+$-mediated depolarization or glutamate — to these cultures enhanced the production of neurons. The number of functional excitatory synaptic connections also increased. These effects were specific for NPCs — depolarization of postmitotic cells did not significantly alter the abundance of new neurons.

Ethanol-fixed cultures were used to determine whether excitatory stimuli were acting directly on NPCs, or exerting their effect through intermediates. Fixation created an *in vitro* milieu that was permissive for neurogenesis, but in which NPCs were the only viable — and therefore potentially excitation-responsive — cell type. Greater numbers of neurons and enhanced connectivity were again induced by depolarization or glutamate, showing that the response to excitation is mediated directly by NPCs.

Elevated intracellular calcium concentrations in stimulated cultures indicated to the authors that calcium channels might have a role in transducing the excitatory signal. Treatment of both ethanol-fixed and unfixed cultures with the L-type calcium channel (LCC) antagonist nifedipine blocked excitation-induced neurogenesis. Conversely, the formation of new neurons was enhanced in the presence of an LCC agonist. Observation of this latter effect even without excitation indicates that activation of LCCs is sufficient to promote neurogenesis.

Real-time PCR showed that rapid transcriptional modulation of genes related to neuronal fate mediated the cellular effects of excitation on NPCs. Within 2 hours of depolarization, expression of the anti-neuronal genes *HES1* and *Id2* was downregulated. Antagonising LCCs had the opposite effect, whereas constitutive expression of *Id2* blocked excitation-induced neurogenesis completely. Concomitant with excitation-induced inhibition of anti-neuronal genes was a rapid and persistent increase in the expression of *NeuroD*, which encodes a regulator of genes that are necessary for neuronal differentiation.

But how well do these *in vitro* data reflect the *in vivo* situation? Administration of diazepam to adult rats showed that impaired activity in the hippocampus reduced the proportion of cells that assumed a neuronal phenotype. In addition, injection of an LCC agonist induced a long-term stable increase in the size of the neuronal fraction.

Malenka and his colleagues neatly rounded out their study by modelling the effect on memory storage of this coupling between neurogenesis and excitatory input. Surprisingly, incorporation of neurogenesis into a simple, three-tiered Hebbian neural network had a dual effect. Previously stored memories were cleared from storage more efficiently, and recall of new memories was improved.

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**References and links**

**ORIGINAL RESEARCH PAPER** Deisseroth, K. *et al*. Excitation–neurogenesis coupling in adult neural stem/progenitor cells. *Neuron* **42**, 535–552 (2004)