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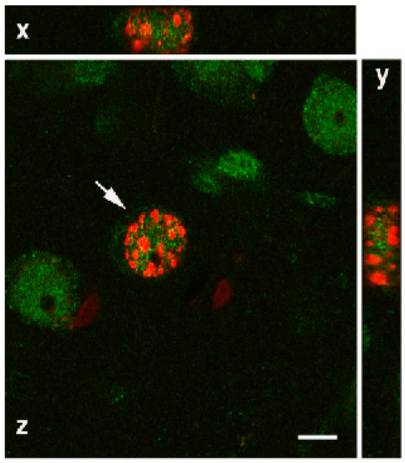

Confocal image of a new neuron in the anterior cortex of the adult rat stained with BrdU (red) and the neuronal marker NeuN (green). The cell is rotated in orthogonal planes to show that it is double labeled throughout its extent.

Neurogenesis and hippocampal function

My laboratory studies the production of new neurons in the early postnatal and adult mammalian brain. Several decades ago, new cells with neuronal characteristics were reported in the hippocampus, olfactory bulb and neocortex of adult brains first by Altman and then by Kaplan. Despite these early reports, relatively little progress has been made toward understanding the control of neuron production in these areas and neurogenesis in the adult neocortex remains controversial. My laboratory explores issues related to the regulation of cell production and survival in these three brain regions in rodents and primates (marmosets and macaques). Quantitative estimates by Cameron and McKay (JCN 2001) have shown that ~ 9,000 new cells are generated everyday in the adult rat dentate gyrus, the majority of which become neurons. Considering the fact that this structure is estimated to contain between 1.5-2 x106 neurons, the number of new cells added per month of adult life is substantial (~2.7x105).

We are trying to answer the following basic questions: How do hormones modulate the production of new neurons? Does experience affect new cell production and if so, through what underlying mechanisms? What possible function could late-generated cells serve? We use a variety of approaches to resolve these issues. The following subtopics explain a few representative studies.

Hormonal regulation of cell production: We have found that the ovarian steroid estrogen enhances cell proliferation in the dentate gyrus of the adult rat. This effect can be seen following ovariectomy and hormone replacement as well as under naturally occurring changes in hormone levels. Cell proliferation peaks during proestrus, a time when estrogen levels are highest. Conversely, steroid hormones of the adrenal glands inhibit cell proliferation in the dentate gyrus but they do so indirectly via an NMDA receptor dependent mechanism.

Experience-dependent changes in neurogenesis: We have shown that exposure of aversive stimuli results in a decrease in cell proliferation in the dentate gyrus of adult rats, tree shrews and marmoset monkeys. In a series of studies, we have shown that social stress inhibits cell production in these three species. Furthermore, exposure of adult rats to the odors of natural predators, but not other novel odors, suppresses the proliferation of cells in the dentate gyrus. This effect is dependent on adrenal steroids because prevention of the stress-induced rise in glucocorticoids (by adrenalectomy and replacement with low dose corticosterone in the drinking water) eliminates the inhibitory effect of fox odor on cell production.

Animals living in semi-naturalistic settings: We have observed that many new cells in the hippocampus of adult rats and monkeys do not survive in animals living under standard laboratory conditions. In the rodent, these

cells can be rescued by exposing animals to more complex environments. These results may reflect the deprived laboratory conditions in which experimental animals live, a phenomenon that is probably even more pronounced in primates with high social needs than in rodents. We are exploring this issue by examining the brains of adult rats living in a visible burrow system and adult monkeys living in semi-naturalistic conditions with opportunities for foraging and other natural activities.

The functional role of new neurons: The function of new neurons in the adult brain is unknown. However, because so many new neurons are generated in the hippocampus and these cells appear to be a sensitive to experience, it is likely that they participate in hippocampal function. We are exploring the possibility that new neurons participate in two functions of the hippocampus, learning and modulation of the stress response. We have shown that learning enhances the number of new neurons but only under certain conditions. Furthermore, experimental depletion of new neurons is associated with impairment in certain types of learning but not others. A decrease in the number of new neurons following treatment with anti-mitotic drugs impairs trace eyeblink conditioning but not spatial learning in a Morris water maze, both hippocampal-dependent tasks.

Publications

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