Neurogenesis

https://doi.org/10.1038/s41583-023-00695-9

(New neurons) singing in the avian brain

During the first half of the twentieth century, the scientific community widely rejected the notion of neuronal regeneration in the adult CNS. Indeed, the first report of continuous neurogenesis in the mammalian brain by Joseph Altman in 1963 was initially received with skepticism by some researchers. However, these discoveries were subsequently supported by numerous studies performed by independent laboratories in which evidence was collected from more than 120 animal species, including humans. The discoveries made by Goldman and Nottebohm in 1983 were the first to demonstrate the continuous addition of new neurons to the adult avian brain.

In 1981, Fernando Nottebohm had described seasonal volume changes in the hyperstriatum ventrale, pars caudale (HVc, a brain nucleus involved in song learning and production) of adult male canaries that coincided with periods of song production, suggesting that such plasticity underlies the learning of new song repertoires. His finding also raised the possibility that the incorporation of new neurons into the HVc might underlie the seasonal volume changes, thereby identifying a possible function for adult neurogenesis and paving the way for the subsequent investigation of neurogenesis in the brains of adult birds under physiological conditions.

In their 1983 study, Goldman and Nottebohm used tritiated (^{3}H) thymidine as a marker of DNA synthesis and, inferentially, of cellular replication. To assess the effect of testosterone on the adult female canary brain, they injected [^{3}H]thymidine into adult female canaries that had previously received implants filled with either testosterone or cholesterol (as a control). At various time points after the injections, the birds were killed and their brains examined by optical and electron microscopy. The cells that took up [^{3}H]thymidine were identified and morphologically classified as neurons, astrocytes, oligodendrocytes, endothelial cells or ependymal/subependymal cells. These experiments revealed the presence of [^{3}H]thymidine-labelled neurons in the HVc of canaries from all the experimental groups 3–5 weeks after [^{3}H]thymidine injections.

The presence of [^{3}H]thymidine-positive cells in both canaries that had received testosterone implants and those treated with cholesterol amazed Goldman and Nottebohm, as it indicated that no hormonal stimulus was required to trigger adult neurogenesis. Indeed, the data demonstrated basal levels of adult neurogenesis (the production of new neurons at a daily average rate of 1.46% of the total HVc neuronal pool) in the female canary brain. Further ultrastructural assessment of some of the labelled cells identified dendrites and axons, which confirmed their neuronal phenotype. The type of implant received did not affect the number of new neurons but did modify the numbers of new glial and endothelial cells. The discovery of the differential responsiveness of these cell populations to hormonal stimuli anticipated later work revealing the functional complexity of neurogenic niches in the adult vertebrate brain, the elucidation of which is still ongoing.

> **"This work robustly demonstrated ongoing precursor cell proliferation in the avian ventricular zone"**

Goldman and Nottebohm found almost no labelled neurons in the HVc of birds killed shortly (≤48 h) after thymidine injections, but abundant labelled cells with a variety of morphologies in the wall of the ventricular zone above the HVc. These data suggested that new HVc neurons were generated in the ventricular zone and subsequently migrated towards their final destination.

Goldman and Nottebohm were cautious and humble in their conclusions. Nevertheless, their discovery provided the foundations for our current understanding of the key principles governing the generation of new neurons in the adult vertebrate brain. This work robustly demonstrated ongoing precursor cell proliferation in the avian ventricular zone and the migration of the cells generated to other regions of the brain, where we now know that they achieve terminal maturation and functional synaptic integration. Their data also suggested the presence and lifetime persistence of a population of stem cells in the avian ventricular system.

Goldman and Nottebohm's seminal discoveries contributed greatly to a growth in interest in adult neurogenesis within both the scientific community and the general public. Indeed, deciphering the permissive mechanisms that allow the generation of new neurons in certain regions of the brain but (apparently) not in others is still a challenge for regenerative medicine and neuroscience research. Strategies to promote the generation of new functional neurons might have important consequences for our understanding of the global functioning of the adult and aged brain, as well as profound clinical implications.

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Competing interests

The author declares no competing interests.

Original article: Goldman, S. A. & Nottebohm, F. Neuronal production, migration, and differentiation in a vocal control nucleus of the adult female canary brain. *Proc. Natl Acad. Sci. USA* **80**, 2390–2394 (1983)

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