Restoration: Potential for Compensatory Changes in Numbers of Neurons in Adult Human Brain

Adult neurologists live perpetually in the fall. Just as we see the leaves turn brown and fall off the trees each autumn, adult neurologists dealing with neurodegenerative diseases are used to seeing populations of neurons fail and die in our aging patients. Like the trees, some of which lose their leaves much earlier than others and some not at all, neuronal loss is often selective, with preservation of some neuronal populations even in patients with Alzheimer disease.[1,2]

With the demonstration over the past 2 decades of neuronal precursor cells that continue to generate new neurons even in adult brains, neurologists were awakened to the possibility that in some cases neurons could be replaced.[3,4] Initially, these findings led to great hope that we could replace neurons in adult brains, and although this hope remains, the journey has been much longer and more difficult than many of us expected. It has turned out that most of the new neurons that are spontaneously generated in adult brains are targeted for the hippocampus, and the rate of new neuronal generation is slow. Results in recent years have dimmed our expectation that this process would provide a useful compensation for neurodegenerative disorders or dramatically increase any neuronal population in the brain.

Yet the latter process is precisely what 2 new papers published in this issue of *Annals of Neurology* claim. Valko and colleagues[5] and John and coworkers[6] both investigated the histamine-producing neurons in the postmortem brains of patients who had narcolepsy with cataplexy (NC). Since the discovery of orexins (also known as hypocretins) as neuropeptides in lateral hypothalamic neurons in 1998,[7,8] a large body of evidence has accumulated that in most patients with NC there is >90% loss of the orexin-producing neurons.[9,10] This work has been a major milestone in neurology, as NC has assumed its place among the very few human neurological disorders that appear to be due to the loss of a single neurotransmitter. Humans with null mutations of the gene coding for the orexins, and animals with null mutations in the orexin gene or its receptors, have shown essentially all of the features of naturally occurring NC.[10–12] However, unlike these genetic disorders, which are present at birth, most patients with NC develop the disorder during the second or third decade of life. Careful studies have shown selective loss of orexin neurons in the lateral hypothalamus (the only part of the brain where orexin cell bodies reside in adult mammals), but not of other nearby hypothalamic cell populations.[9,10,13] The striking precision of the attack on orexin neurons in narcolepsy is believed to be due to an autoimmune process, perhaps associated with the H1N1 influenza A virus or one of the vaccines against it.[14]

Against this background, both groups of investigators examined the histamine neurons in NC brains. The histamine neurons are found only in the tuberomammillary nucleus of the hypothalamus in mammals, located nearby the orexin neurons.[15] There is an intense excitatory input from the orexin neurons to the histamine neurons, which is believed to be important for the wake-promoting effects of orexin.[12] As a result, there has been renewed interest in stimulating the histamine neurons (by blocking their H3 inhibitory autoreceptor) as a mechanism for increasing wakefulness in NC.[16,17] However, if the histamine neurons are also attacked by the same disease process as the orexin neurons, this strategy might not work. Hence, it became important to determine whether the histamine cells are preserved in patients with NC.

The results of that investigation by 2 independent groups are stunning and congruent. Both groups found an increase in the number of histamine neurons in NC patients compared to controls. The changes are not trivial. One group reported a 64% increase and the other a 94% increase, that is, nearly a doubling of the histamine neurons in patients with NC. In the latter study, the gain in histamine neurons was actually higher in the subjects who had the greatest loss of orexin neurons. To my knowledge, these are the first reports of a massive increase in numbers of neurons in one part of the adult human brain in compensation for loss of neurons in a different region.

As always, there are a number of possible technical confounds that could have crept into these experiments. Immunohistochemical staining for histidine decarboxylase (HDC), the enzyme that synthesizes histamine and is used as a marker for histamine neurons, is challenging in postmortem human brain. Both groups considered the possibility that the brains of the NC subjects were simply better preserved, and hence showed more stained neurons, and as a result they also examined brains from genetically narcoleptic mice to see whether the same phenomenon occurred in an experimental setting where peri- and postmortem events could be better controlled. The Valko group found a 54% increase in histamine neurons in mice with deletion of the orexin gene, and a 28% increase in mice genetically engineered so that the orexin neurons died a few months after birth. However, the John group failed to find a significant increase in numbers of histamine cells in these and several other genetic models of NC. Although these differences are puzzling, there were major differences in the methods employed by the 2 studies. These included use of different protocols for the immunohistochemistry, different antibodies, and different methods for counting neurons. As a result, the John study found smaller numbers of histamine cells in both the human and mouse control brains (eg, approximately 75,000 per human brain in the John study compared with 120,000 per brain in the Valko study). These differences suggest that the Valko group may have used a more sensitive (or perhaps less specific) method for identification.

Such large differences in neurons detected are common between immunohistochemical studies, and they suggest that any immunohistochemical method is likely staining only a percentage of the total population. In other words, some neurons may produce HDC at levels below the detection threshold for the method. As a result, additional HDC-immunoreactive neurons may appear because of an overall upregulation of HDC levels in the entire histaminergic population. Another possibility is that neurons that otherwise do not make HDC at all may have induction of the enzyme in compensation for loss of the orexin neurons. Admittedly, these 2 alternatives would be difficult to distinguish with the methods employed here, and the distinction between very low production of HDC and no production at all at baseline may not matter. Thus, the appearance of more histamine neurons in the hypothalamus in NC patients may reflect an upregulation or induction of HDC, so that more neurons express it at a level that can be detected immunohistochemically.

Another possibility is that the additional HDC-immunoreactive neurons may actually be new neurons that are generated in the adult brain. There are hints in the literature that under certain conditions, neurogenesis along the third ventricle can produce new neurons in the hypothalamus.[18] It would be very exciting for neurology if we found that certain cell types could be produced and become functional in adult brains, and if we learned how to control that process.

Distinguishing these alternatives will require more research, probably in experimental animal models. However, whether the compensation comes by production of new neurons, or upregulation of expression of relevant genes by existing neurons, the possibility of restoring function by assisting that process gives new hope to our patients who suffer from neurological degenerative disorders.

Potential Conflicts of Interest

Nothing to report.

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