The true impact of brain aging processes on memory

Fleeting Memory

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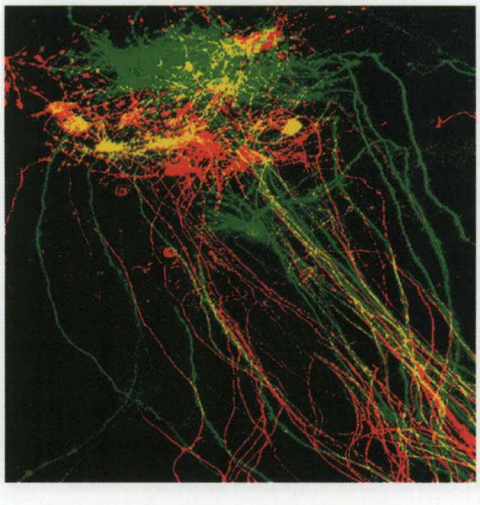
Despite what was thought until recently, the physiological aging process of the brain does not involve the death of neurons. The memory problems that arise at advanced ages are chiefly caused by disturbances in the transfer of information between nerve cells and the degradation of synapses

Recent years have seen a flurry of research on brain aging processes, the mechanisms of learning and memory. As our average lifespan lengthens, degenerative neurological diseases such as Alzheimer's and Parkinson's are posing an ever more important challenge for researchers. Study of the human genome and the mechanisms regulating gene function has given rise to hope that we may soon better understand the causes underlying these diseases and develop improved therapies. Yet we remain unable to simply answer a fundamental question: Why do we age in the first place?



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An image of glutaminergic neurons in the ventrobasal nucleus of the thalamus. Glutaminergic receptors are involved in the mechanisms of memory

The various aging theories that have been put forward can be seen as falling into two groups: evolutionary theories, which try to explain the genesis of the aging process, and molecular theories. Kirkwood's (1997) modern evolutionary theory defines the involvement of three categories of genes: those regulating the processes of maintenance and repair, those which demonstrate antagonistic pleiotropy, and genes which are not subject to selection. This theory reconciled advocates of the genetic and stochastic (time-dependent) hypotheses, by positing that the processes of aging and longevity are affected by both genes and the environment. The theory of somatic mutation accumulation and the free radical theory, accounting for the role of nitric oxide (NO), are now experiencing a renaissance.

Neurons just as numerous

Over the past decade, our research has looked at changes in the expression of the genes for enzymes which take part in NO transformations and NO-dependent transmission processes. Our results have indicated that the free radicals released during the aging process cause damage to the DNA thread and stimulate a key DNA repair enzyme, the polymerase PARP-1. The increased activity of this enzyme in the aging brain could indicate its involvement in the process of DNA repair. It is widely believed that the brain's aging manifests itself in disorders of memory, emotions, and social behaviors. What are responsible for a significant proportion of these changes are numerous infectious, cardiovascular and immunological diseases.

Until recently, a spontaneous process of brain tissue degradation was thought to occur. Yet the physiological process of brain aging itself does not in fact lead to a significant loss of neurons or significant memory disorders. While it is true that the large pyramid neurons do degenerate, they are reinforced by a pool of smaller neurons, their overall numbers remaining unchanged. On the other hand, our research has evidenced changes in

East News/ICONOS

Grandfather and grandson playing a game of chess: whose memory will prove more fallible? Scientists argue that the aging process, in and of itself, does not in fact lead to significant memory lapses

the synthesis of cholinergic and glutaminergic receptors (information transmitters), involved in the mechanisms of learning and memory, as the brain ages. These findings indicate that the age-related impairment of memory (in contrast to Alzheimer's) is caused by disorders of the information transmission process in the nerve endings, not by the death of neurons.

The brain's plasticity

Our nearly 100 billion neurons form a highly specialized network that not only transmits information but also integrates, processes, and stores it. These phenomena enable all the basic functions of the brain to be regulated: they condition learning, memory, emotions, and personality. Neuron functions are supported by glial cells and by proper blood circulation to the brain.

Throughout our lives, numerous neuronal pathways are constantly being reorganized depending on the nature and intensively of incoming stimuli. We gain new experiences and capabilities, we learn and try to remember new information, and all these processes give rise to functional changes in the brain. The brain's capacity for such change during the learning process is called neuroplasticity.

The brain's plasticity is currently a topic of intense research. We do know that it is age-dependent. The number of synaptic connections significantly increases as the body develops: information is transmitted and received in a newborn's cerebral cortex by some 2,500 synapses per neuron, but some 15,000 synapses are already evidenced in 2-3 year olds, and synapse numbers further double in adults. The aging process leads to changes in the nerve endings: the number of synaptic connections is reduced and they are subject to significant degeneration.

Plasticity processes enable the brain to adapt to the environment throughout our whole lives. Altered synapses get eliminated, while active connections get maintained and strengthened, conditioning the proper functioning of neurons.

Long term memory

Newly obtained information initially gets stored in the form of short-term memory, which is based upon electrical and chemical phenomena. It is chiefly this form of memory that is impaired by the aging process. After a certain period of time, information comes to be stored in the form of long-term memory, the result of anatomical and biochemical changes. Two well-known information transmitters, NO and arachidonic acid (AA), play a crucial role in the processes of learning and long-term memory, being responsible for transmitting information from the post-synaptic portion of the nerve endings to the pre-synaptic part. Such information transmission phenomena from one part of the cell to another have interested our research team for years.

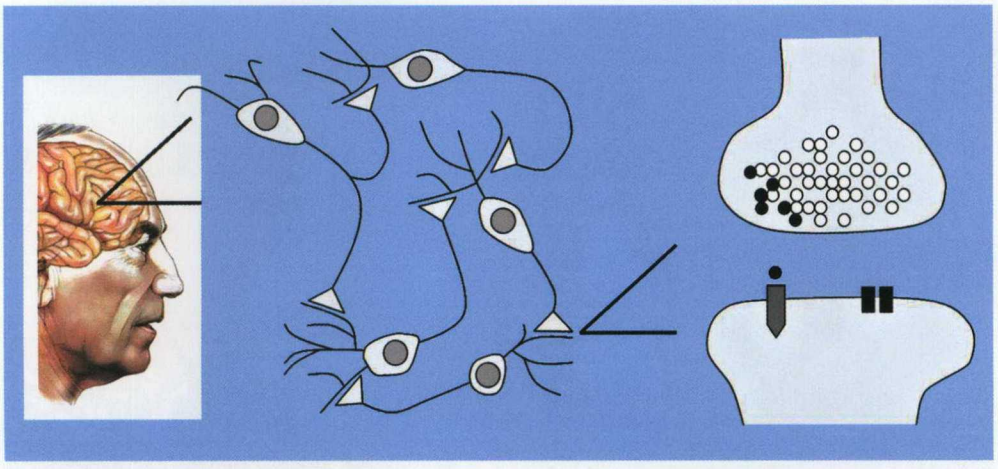

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Diagram illustrating the exchange of information between nerve cell endings in the human brain

The aging process affects different information transmission pathways differently. It selectively modifies receptors, the level of neurotransmitters, and effector-postreceptor systems.

Inexorable process

Aging causes two types of changes that influence neurotransmission, studied in detail by our team. The first pertains to the level of receptors in the cell tissues. Aging reduces the density and sensitivity of many receptors including the cholinergic and glutaminergic systems, in the hippocampus, the cerebral cortex, and the cerebellum. The level of the ionotropic receptors NMDA and AMPA, and also muscarinic and nicotinic receptors, is reduced, while acetylcholine, an important neurotransmitter, binds much more weakly to receptors. The function of the important GABA receptors is also disrupted.

The second type of change pertains to biochemical processes. The altered function of certain transcription factors changes the expression of genes in the cell nucleus and cell phenotype. New proteins, new receptors, and neurotransmitters are synthesized. Aging influences the level of neurotransmitters and information transmitters of the I and II orders, such as AA and NO. These processes can be modified, such as by using specific inhibitors of the enzymes taking part in transformations of AA or NO and the NO-dependent cyclical nucleotide cGMP. Applying such specific inhibitors to animals significantly improves memory in both adult and old specimens.

It is worth bearing in mind that if the physiological aging process proceeds properly, the numerous changes mentioned here in the neurotransmitter systems contribute to memory disorders only to a small degree. Nonetheless, few individuals manage to reach old age in healthy condition and retaining their full intellectual fitness, without any brain function disorders.

Healthy lifestyle!

What is crucial is leading a healthy, intellectually and physically active, way of life. Genetic factors of course also have a very important impact on the aging process, increasing or reducing the risk of degenerative diseases like Alzheimer's and Parkinson's and other diseases causing dementia. The discoveries made by the 2006 and 2007 Nobel Prize winners have uncovered the fundamental mechanism controlling the flow of genetic information and have given rise to techniques for precisely manipulating the genome. We are presently able to identify the involvement of specific genes in the aging process and in degenerative neurological diseases. New research discoveries could have broad application in the treatment of these diseases. ■

Further reading:

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