How to prevent the retiring brain from degenerating

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Summary

In organs other than the brain, cell activation seems to increase “wear and tear”, e.g. by increased free-radical formation, and so to cause an increased rate of aging. However, activation of nerve cells within the physiological range seems to lead to maintenance of neurons during aging, possibly by preferentially stimulating the action of protective mechanisms such as DNA repair. This “use it or lose it” principle might explain why in aging and neurodegenerative diseases certain neurons degenerate while others do not, and why recovery of various neuronal systems during aging has been obtained by restoration of the missing stimulus. Consequently, neuronal activation might provide a means of prolonging its optimal function for the full length of our natural life span, also following retirement.

Introduction

The moment of retirement is a good one to give factors that might influence brain aging a serious thought. Several theories on the etiology of brain aging are based upon the assumption that during functioning a continuous “wear and tear” of the organism takes place, e.g. by free radical formation. In this concept increased metabolic activity would result in accelerated cellular aging. Analogies have been drawn in this connection between biological aging and the wearing out of shoes, clocks, piston rings and rubber bands due to sustained friction and oxidation. The originator of the concept that increasing age might be related to neuronal loss was Hodge, who concluded in 1984: “As the work of life is being done, the cells, one by one, are worn out... Finally this number fails and the functions of life must cease.” It has been postulated that as organisms grow older, changes occur in the DNA template of neurons that ultimately lead to an impairment in RNA and protein synthesis. Free-radicals are produced under normal physiological conditions in aerobic cells. Studies on houseflies indicate, moreover, that oxygen free-radical concentrations tend to increase with age. According to this concept, the relative rest that might occur in the brain of a retiring professor would only be beneficial and even slow down the aging process.

On the other hand, the “wear and tear” concept does not tally with the therapeutical advice that is generally

given to aged people, viz. to stay active and stimulate the brain. Indeed, recent evidence is accumulating that activation of nerve cells within the physiological range seems to lead to maintenance of neurons during aging, possibly by preferentially stimulating the action of protective mechanisms such as DNA repair. This concept is paraphrased as “use it or lose it”.

Ten examples of “use it or lose it”

Various recent observations provide evidence for the possibility that activation of neurons may interfere with the process of aging, and thus prolong their life span or that inhibition of neuronal activity leads to advanced cell death.

I. The neurosecretory neurons of the supraoptic and paraventricular nucleus (SON and PVN) of the human hypothalamus form a population of extremely stable cells. Neither in the course of normal aging nor in Alzheimer patients was any significant cell loss observed. These neurons are not only metabolically highly active throughout life, but they are even extra-activated in senescence as can be judged from (a) the increase in the size of the vasopressin containing perikarya, (b) their enlarged nucleolar size, and (c) the elevated plasma levels of VP and neurophysin. Similar activation of vasopressin neurons was observed in the rat, and is probably due to a loss of vasopressin receptors in the kidney during aging.

II. Aging female rodents develop impairments in the regulation of the estrus cycle and gliosis in the arcuate nucleus of the hypothalamus, one of the sites of origin of

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LHRH-containing fibers. Ovariectomy, which is known to cause an activation of the LHRH neurons, prevents gliosis of the arcuate nucleus, whereas the administration of estrogens, a treatment which inhibits LHRH neurons, advances the occurrence of disturbed estrous cycles and gliosis in the hypothalamus. Following long-term ovariectomy it is also possible to restore regular estrous cycles in old rats by transplantation of a young ovary, whereas without preceding long-term ovariectomy regular estrus cycles do not occur after grafting. The stimulatory action of ovariectomy thus seems to delay the aging process of the LHRH neuron. This idea is consistent with a number of observations showing that in post-menopausal women (as well as in men over 60 years of age!) highly activated nerve cells, showing nucleolar size increase and multiplication and vacuolization, are present in the hypothalamic arcuate and subventricular nuclei. Such neurons remain present even up to the age of 111 years.

III. There is also evidence that an enriched environment continues to stimulate the brain at older ages. Enriched environmental stimulation alleviated a number of age-related changes in the sleeping pattern of 33-month-old rats improved performance in 2-year-old rats and 20-month-old mice and increased the overall dendritic length of pyramidal neurons in old rats.

IV. Also in lower organisms such as *Aplysia*, age-dependent changes in neurons seem to depend upon the function of the pathway they subserve, as is illustrated in two types of gill motor neurons. Neuron L7, which is activated intermittently only when the defensive gill withdrawal reflex is elicited by external stimuli, shows age related alterations, whereas neuron LDG1, which is continuously activated by the respiratory generator, does not change with increasing age. Interestingly, the motor neuronal function of L7 in old *Aplysia* is improved by long-term stimulation of the gill reflex. These observations suggest that baseline levels of excitability might influence the aging process.

V. Vasopressin innervation in the senescent male rat brain is particularly decreased in those regions where the fiber density in young adult males was shown to be dependent upon plasma levels of sex steroids. Plasma testosterone levels decrease progressively with age in the rat, and testicular weight is also reduced in senescence. However, when old rats were treated with testosterone for one month the vasopressin innervation in the rat brain appeared to be reversed. The vasopressin fiber systems responding to the testosterone treatment originate e.g. from the bed nucleus of the stria terminalis and medial amygdala, where testosterone seems to stimulate vasopressin synthesis.

VI. In aging, and even more markedly in Alzheimer's disease, a decline in neuronal biochemical activity is present in many different brain areas. The decline in metabo-

lic activity during normal aging is clear, among other things from the decrease in brain RNA. In Alzheimer's disease there appears to be an accelerated general decline in neuronal RNA and a further decrease within those neurons that contain neurofibrillary tangles. Interestingly, a similar observation has been made by Doebler et al., who found that in Alzheimer's disease neurons of the hippocampus and the subiculum that were positive for the abnormal antigen Alz-50 had lower RNA contents than Alz-50 negative neurons did. This suggests that the expression of the abnormal antigen, which is labeled by Alz-50 and probably consists of tau proteins, is closely related to a diminished neuronal metabolism. The possibility that the cells that are already metabolically less active become affected the most in Alzheimer's disease, rather than the possibility that the metabolic rate of the cells is decreased secondary to the disease process, should also be considered seriously.

VII. Changes in neuronal RNA content during aging might be reversed by activation. Neurons in the auditory cortex of 40-week-old mice contained less RNA than those of 10-week-old mice. After auditory stimulation by continuous noise, the neurons of older mice contained the same amount of RNA, if not more, than the younger ones did.

VIII. The observation of Landfield and Sapolsky et al., that glucocorticoids enhance the aging process in rat hippocampus, would also fit in with the "use it or lose it" hypothesis, since chronically elevated levels of corticosterone, the major glucocorticoid secreted by the rat adrenal, may decrease glucose uptake in the hippocampus. This view is reinforced by Pfaff's data, showing that hippocampal single unit activity in freely moving rats was decreased by corticosterone.

IX. Aged rats normally show a decrease in type I corticosteroid receptors in the hippocampus, but this can be reversed by the administration of centrally active ACTH analogues. These compounds are known to enhance glucose utilization of hippocampal neurons containing these receptors and to delay features of hippocampal aging. Hippocampal aging was retarded in a similar way by administration of the neural stimulant pentylenetetrazole.

X. The observation, that osmotic stimulation of neuronal functioning of the neurosecretory neurons of the supraoptic nucleus of aged mice causes a decrease in lipofuscin content, is also in favor of the "use it or lose" it concept.

Stimuli for the aging neurons

The classes of activating stimuli that may prevent or protract the aging process seem to be, in principle, the same ones that normally affect neuronal functioning, i.e.

environmental stimuli, hormones, transmitters and trophic factors.

The existence of all these different stimulatory factors means that, in order to critically test the "use it or lose it" hypothesis, the manipulation of a single experimental factor will probably not be sufficient. Although some stimuli will almost certainly prove to have a more generalized stimulatory effect on the brain than others, each neuronal system will have to be kept in an activated state by a different means and, as a consequence, a combination of factors will undoubtedly be necessary if one is to obtain functionally relevant effects.

Possible mechanisms of "use it or lose it"

"Wear and tear" may certainly play a role in the process of aging. Enhanced metabolism of cells in various organs might result in enhanced cell damage, e.g. through the formation of free-radicals, and consequently in a shortening of the life span. However, activation of nerve cells seems not only to stimulate cell metabolism, and thus the possibility of increased cell damage, but even more to activate protective mechanisms. Factors protecting against oxygen toxicity include superoxide dismutase, glutathione peroxidase and catalase. Superoxide dismutase might, according to correlations in comparative studies, be involved in the determination of life span differences among different species. DNA repair, which effectively counteracts the continuous deterioration of DNA, might be another class of crucial protective mechanisms in the cell. The possibility exists that Alzheimer's disease is due to accumulation of DNA damage, e.g. caused by defective DNA repair. We have recently found supportive evidence for such a mechanism in cerebral cortex samples from Alzheimer patients and controls obtained from rapid autopsies. Alzheimer patients appeared to have at least 2-fold higher levels of DNA breaks in the cortex than the controls. The finding that food restriction which increases life span has an antilipoperoxidation effect and positively influences DNA repair increases with transcriptional activation agrees with this

possibility. In addition, in HeLa cells the rate of DNA repair is greater in the transcriptionally active chromatin than in the inactive chromatin. Moreover, it has recently been shown that DNA repair was decreased in the mouse brain by anesthesia, again indicating a direct relationship between decreased metabolic rate and decreased DNA repair.

The hypothesis that stimulation of activity is necessary to prevent neuronal damage during aging might also explain, at least partly, the fundamental question of why certain neurons degenerate in aging or in neurodegenerative diseases while others do not. For those areas that do show such degenerative alterations, one should search for sensory, endocrine, neurotransmitter or trophic stimuli which have disappeared, and investigate whether or not recovery is possible with restoration of the missing stimuli. In addition, protective mechanisms should be studied particularly in vulnerable cell populations. The protective mechanisms in these vulnerable structures might either be relatively underdeveloped or not be sufficiently activated by neuronal excitation. Moreover, in the case of neurological diseases, it seems worthwhile to try and prevent or slow down degeneration in certain brain areas by a well-directed program of stimulation of the affected area. The hypothesis that the activity level of neurons affects their survival can, in principle, be tested experimentally. It may provide a means of prolonging the optimal function of neurons for the full length of our natural life span.

For you, George, this means that it may be good to keep using that fabulous brain of yours, preferably by helping me to find examples for this hypothesis in neurodegenerative diseases in order to further illustrate and test this concept. That way your encyclopedic knowledge of the central nervous system might not only help me but also your own neurons to stay active and healthy! Take care!

References

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