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REVIEW

Brain Aging and Alzheimer's Disease, "Wear and Tear" Versus "Use It or Lose It"

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SWAAB, D. F. *Brain aging and Alzheimer's disease, "Wear and tear" versus "Use it or lose it."* NEUROBIOL AGING **12**(4) 317–324, 1991.—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 and in Alzheimer's disease, possibly by preferentially stimulating the action of protective mechanisms such as DNA repair. This "use it or lose it" principle might explain why certain neurons degenerate in aging or Alzheimer's disease 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.

Aging Alzheimer's disease Longevity Maintenance of neurons Neuronal activation Plasticity Protective mechanisms Regenerative processes

SEVERAL theories on the etiology of aging and Alzheimer's disease are based upon the assumption that during functioning a continuous "wear and tear" of the organism takes place. In this concept increased metabolic activity would result in accelerated cellular aging, which would appear in the form of, e.g., increased lipofuscin accumulation in the cytoplasm. 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 (47). The free-radical theory of aging (31) has provided a plausible mechanism to explain "wear and tear." Free radicals have also been proposed to be involved in the formation of senile plaques in Alzheimer's disease (31).

On the other hand, the "wear and tear" concept does not tally with the therapeutical advice that is generally given to old people or early Alzheimer patients, viz. to stay active and stimulate the brain. Lorand (51) already stated in 1913: "work of any kind, even mental work alone, is a means of preventing precocious senility." More recently, Millard (60) worded the same concept: "until better evidence is available I think I shall tell my mother to go on doing the crossword: like other organs may not brains deteriorate with disuse?".

The present paper is meant to review the question of whether alterations in the functional state of neurons, activation or inhibition, may indeed influence either the normal aging process or dementia and if yes, to what extent and into what direction. First, the oldest parameter for brain aging, i.e., lipofuscin accumulation, is discussed in this context. Moreover, attention is paid to general factors which might influence longevity, i.e., brain size and body metabolism. Subsequently, it is pointed out that during aging and in the Alzheimer brain, not only degenerative processes take place, but also adaptive growth responses and regenerative processes, in which stimulation of neuronal systems might be instrumental. Ten examples are given to illustrate that activation of neurons may have a beneficial effect on neuronal function and survival during aging and in Alzheimer's disease. Finally, some possible mechanisms for this "use it or lose it" principle are proposed.

LIPOFUSCIN

Already one hundred years ago both opposite concepts, i.e., "wear and tear" versus "use it or lose it," were proposed as explanations for neuronal aging in relation to the accumulation of age pigments. In 1883 Schulz (88) attempted to prove that pigmentation of ganglion cells is associated with age and degeneration, whereas Schäfer (85) argued that pigment is evidence of functional activity and not of decay. Also in recent studies arguments in favor of each of the two concepts may be found. The "wear and tear" hypothesis is supported by the observation that lipofuscin accumulates with age in the central nervous system precisely in those regions in which high concentrations of oxidative enzymes are found, suggestive of a relatively high metabolic rate (22,87). In addition, the accumulation of lipofuscin can be slowed down by antioxidants (31). Observations in the visual system of blind patients have also indicated that there may be a correlation between functional activity, oxidative enzymes and deposition of lipofuscin. Those neurons of the lateral geniculate body that receive terminals from the blind eye contain a

lower amount of lipofuscin than neurons in layers connected to the seeing eye (22,87), which would suggest, according to the authors, that the less active neurons are in a better condition. In this concept the accretion of lipofuscin was thought to lead to a decrease in the cellular content of RNA (54).

However, the exact relationship between lipofuscin accumulation and the aging process has remained rather ambiguous so far. The brains of Alzheimer patients do not contain more lipofuscin than those of controls do (55,56). Moreover, a reverse relationship between lipofuscin and the neuronal activity stage was shown in other studies. The observation that activation of supraoptic neurons of aged mice by osmotic stimulation caused a decrease of lipofuscin in these neurosecretory neurons (14) is in favor of the "use it or lose it" concept.

In addition, lipofuscin is generally no longer considered to be a causal factor in the aging process, but is rather regarded as a by-product of this process, which does not necessarily affect the ability of the cell to function (14, 55, 90), as was already pointed out by Charcot (88). Brody (7) showed that, although 35% of the olivary cells in the 3-month-old child contain pigment and 98% of the cells in the ages of 70 and 80, there is no significant decrease in the number of nerve cells in the inferior olive with age. Observations on the human hypothalamus indicate, in addition, that the absence of lipofuscin does not prevent cells from degenerating. Cells of the suprachiasmatic nucleus (SCN) are devoid of lipofuscin pigment, in contrast to the cells of the supraoptic and paraventricular nucleus (SON and PVN) (6). Yet, selective degeneration of the SCN (Fig. 1), but not of the SON and PVN (Fig. 2), was observed in senescence, and even more clearly in Alzheimer's disease (91–93).

In conclusion, alterations in lipofuscin content of neurons during the process of aging can at present not be interpreted in an equivocal way.

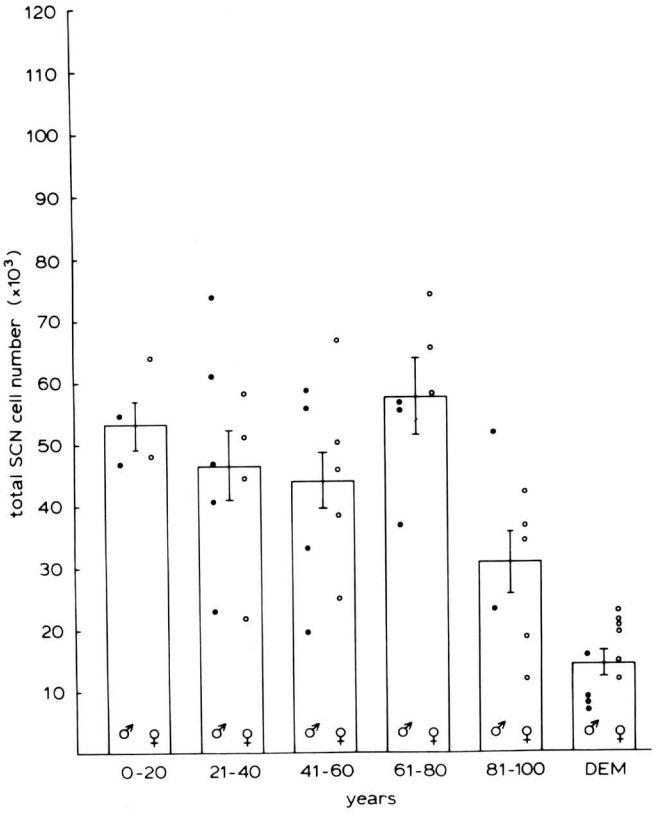

FIG. 1. Total cell numbers in the human suprachiasmatic nucleus show a marked decrease after 80 years of age, which is even more pronounced in Alzheimer's disease [cf. (91,93)]. DEM = dementia (i.e., neuropathologically confirmed Alzheimer's disease, mean age 78 ± 5 years).

BRAIN SIZE, BODY METABOLISM AND LONGEVITY

Alterations in body metabolism have been shown to affect longevity but, in contrast to the idea of Lorand (51) "work" appeared to shorten life. Already in 1924 Pearl (71) concluded that "after roughly age 40 to 45 it appears that a man shortens his life, by definite amounts, in proportion as he performs physically heavy labor." Also, in houseflies, increased metabolic rate caused a decrease in their life span (90). Comparative studies have made it clear that the maximal life span, and hence the rate of aging, is not only inversely related to the basal metabolic rate but also directly related to the evolutionary increase of brain relative to body size (36, 82, 83). It seems therefore essential in studies on life span extension to distinguish between experimental factors causing general metabolic changes and factors stimulating brain size. This point may be illustrated by the problems met when interpreting the data of the only strategy that can, at present, convincingly increase the life span of mammals, i.e., dietary restriction (27,103). Restricted feeding of rats retards the normal age-related loss of dopamine receptors in the corpus striatum (50,81), and it may delay the decline in reproductive cycles and even reinitiate estrus cycles in older rats (75). Furthermore, it improves radial maze learning of 15-month-old mice, and is associated with a reduction in lipofuscin pigment deposition in the neurons of the hippocampus and frontal cortex (39). However, the question of how dietary restriction exerts its effect upon life span is far from resolved. Harman (31) proposed a reduction in free-radical formation in the tissues, whereas others suggested diminished body metabolism or a general (i.e., central?) activation of these animals (103).

The obvious experiment to do in respect to the observation that life span is related to the degree of encephalization (36) is to study longevity in rats exposed to an enriched environment, a condition known to enhance (relative) brain size (61, 62, 80). One should, however, also measure metabolism in such an experiment in order to enable proper interpretation of the data.

PLASTICITY OF THE AGING BRAIN

Recently it has become clear that brain aging is not only characterized by the loss of synapses, neurites and neurons. In the first place, degenerative processes in aging have been overestimated due to methodological flaws (9). Shrinkage of cells rather than cell death seems to be the major phenomenon in brain atrophy (32). For instance in the nucleus basalis of Meynert (NBM) a considerable proportion of the cholinergic neurons has probably not died, but rather shrunk and lost their cholinergic marker (1,79). Somatostatin neurons in the cortex of Alzheimer patients also shrink (65). In a recent paper Mann et al. (57), comparing biopsy and autopsy data, found that nucleolar volume of pyramidal cells in the human cortex progressively decreased during Alzheimer's disease. With regard to the hypothesis put forward later in the present paper on the relationship between neuronal activity and cell survival, it is relevant to point out here that neurons that become smaller and have smaller nucleoli are generally considered to become metabolically less active as well (20,37).

Secondly, not only degeneration but also adaptive growth re-

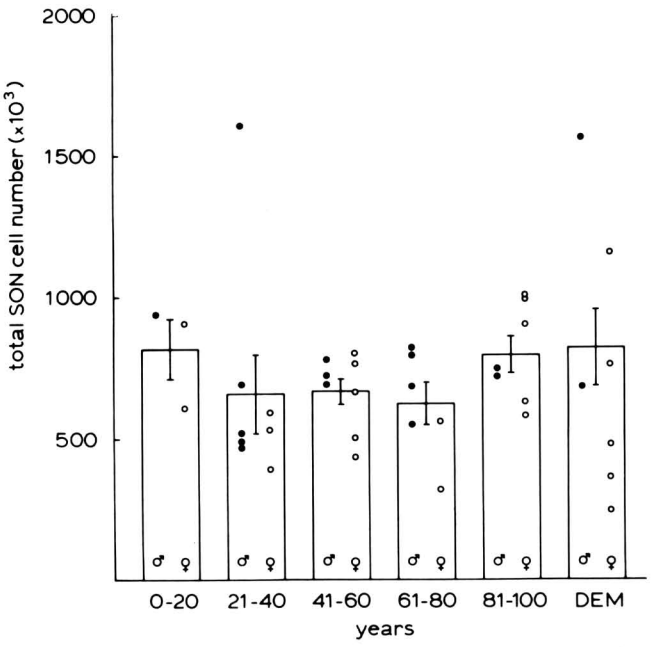

FIG. 2. Total cell numbers in the supraoptic nucleus (SON) do not decrease in sensescence or in Alzheimer's disease (DEM) (E. Goudsmit, unpublished observations) in the same individuals.

sponses and regenerative processes take place in the senescent and Alzheimer brain. Coleman and Flood (8) have shown an age-related dendritic proliferation that might be regarded as a compensatory repair system for the loss of neighboring neurons. An increase in the dendritic tree has also been observed in the reticular neurons of the NBM and the diagonal band nucleus in Alzheimer's disease (5). Neuritic plaques from the hippocampal region of Alzheimer patients contain proliferated axons and dendrites from local neurons (74). The capability to restore a loss of synapses in the dentate gyrus following a lesion of the entorhinal cortex is still present in two-year-old rats (35) and treatment with estrogens brought about an increase in synaptic density following deafferentiation of the arcuate nucleus in aged female rats (59). A number of sleep disturbances are restored and the cortical thickness increases in the old male rat following placement in an enriched environment for 1 month (62). The diminished axonal transport rate of motor neurons in old rats can be restored by means of sex steroids (24), and the vasopressin innervation that is strongly decreased in a number of brain areas in the senescent rat can be restored by administering testosterone (28) (Fig. 3), whereas ACTH analogues reverse the loss of type I corticosteroid receptors in the hippocampus of aged rats (78). In the hippocampus of Alzheimer patients an expansion of kainic acid receptor distribution and enhanced acetylcholinesterase activity, indicative of cholinergic afferent sprouting, was found (25,38). The presynaptic loss of cortical nicotinic receptors in Alzheimer's disease goes together with a postsynaptic increase in muscarinic receptors (66). Similarly, the reduced cortical concentration of CRF found in Alzheimer patients is accompanied by reciprocal increases in CRF-receptor binding (15).

Thus plastic changes seem to take place not only during aging but even in the brain of Alzheimer patients at different levels of neuronal complexity. Consequently, a key question seems to be how the restorative plasticity of senescent and Alzheimer brains can be optimally realized. There is evidence that stimulation of a neuronal system might be instrumental in this process.

INFLUENCE OF ACTIVITY STAGE ON NEURONAL SURVIVAL

In the literature two opposite ideas have thus been formulated on the direction of the possible relationship between cell activity

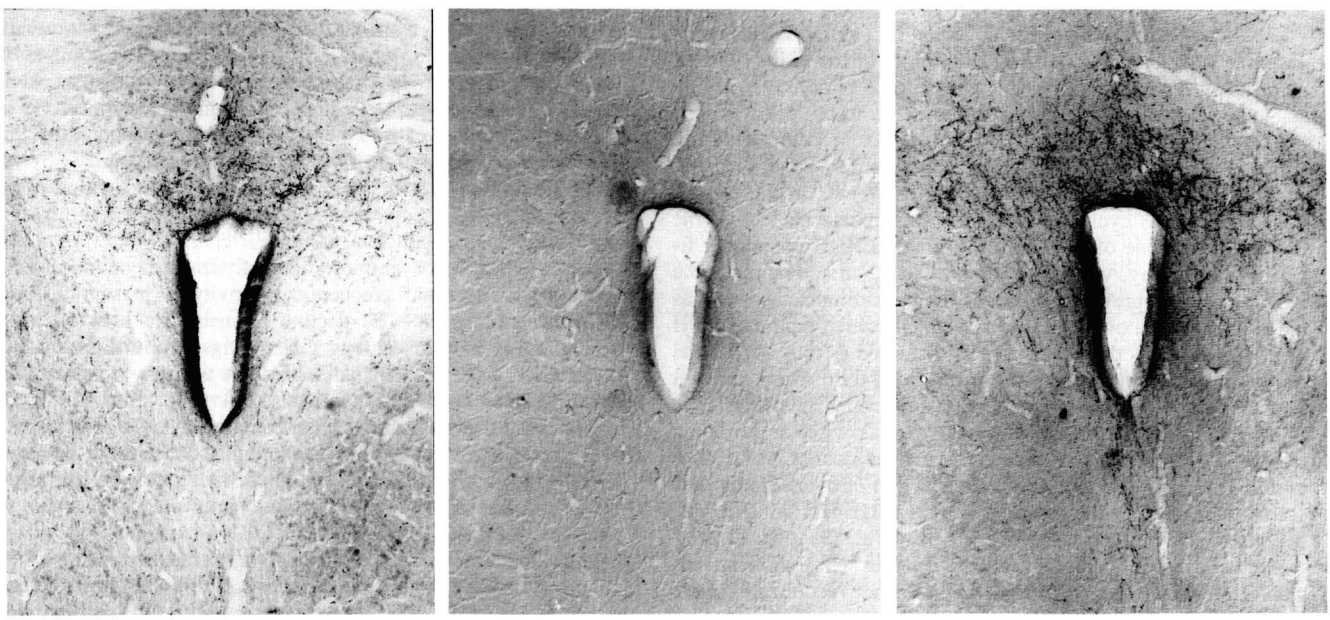

FIG. 3. Immunocytochemical stained vasopressin fibers in the central grey of a 3-month-old young male rat (left), a 37-month-old aged rat (middle) and an aged rat following testosterone supplementation for one month (right). Note the decrease in fiber density with aging which is restored by testosterone treatment [from (28), with permission].

and survival in the process of aging and Alzheimer's disease. In the first place it has been argued that activation of a neuron will lead to "wear and tear" whereas, alternatively, activation of at least some nerve cells is thought to prevent cell death in aging ("use it or lose it").

Wear and Tear

The originator of the concept that increasing age might be related to neuronal loss was Hodge (34), 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 (2,102). Radiation (47) and oxidative damage of neurons due to the cell's own metabolism (31) have been mentioned as a causal factor. Free-radicals are produced under normal physiological conditions in aerobic cells, whereas the concentrations increase following physical exercise in rats. Studies on houseflies indicate, moreover, that oxygen free-radical concentrations tend to increase with age [for review see (90)]. However, we are not aware of similar data for mammalian brain tissue under different stages of activity and during the process of aging.

Use It or Lose It

Various recent observations provide evidence for the alternative possibility, viz. 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:

1) 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 (29a,92) (Fig. 2). 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 (20), (b) their enlarged nucleolar size (37), and (c) the elevated plasma levels of VP (23) and neurophysin (48). Similar activation of vasopressin neurons was observed in the rat (19,29) and is probably due to a loss of vasopressin receptors in the kidney during aging (76). The hypothesis that the neurosecretory cells are so stable because they are extra-activated needs to be tested experimentally, e.g., by long-term inhibition of these neurons during aging in which case degeneration should occur.

2) 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 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 estrus cycles in old rats by transplantation of a young ovarium, whereas without preceding long-term ovariectomy regular estrus cycles do not occur after grafting (18, 75, 86). The stimulatory action of ovariectomy thus seems to delay the aging process of the LHRH neuron. This idea is consistent with the observation of Ule et al. (95) that in postmenopausal women, 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. However, proper immunocytochemical identification of these putative LHRH neurons and cell counts still have to be made in order to see whether LHRH cells are indeed activated and are not lost during aging.

3) Environmental stimulation of the rat was shown to stimulate the neocortex of the adult rat in a generalized fashion, i.e., it increases the size, thickness and weight of the cortex, dendritic branching (40,96) and the number of glia, and it enhances the protein synthesis of the brain, the activity of the cholinergic system, the number of synapses per neuron and the animal performance in complex mazes [for reviews see (62,77)]. 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 (97), improved performance in 2-year-old rats (17) and 20-month-old mice (101), and increased the overall dendritic length of pyramidal neurons in old rats (10, 11, 30). Although enriched conditions thus seem to delay the aging process, neither longevity studies nor cortical cell counts have so far been performed following environmental stimulation.

4) 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 (72). 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 (104). These observations suggest that baseline levels of excitability might influence the aging process.

5) 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 (21). Plasma testosterone levels decrease progressively with age in the rat, and testicular weight is also reduced in senescence (76). However, when old rats were treated with testosterone for one month, the vasopressin innervation in the rat brain appeared to be reversed (28) (Fig. 3). The vasopressin fiber systems responding to the testosterone treatment (28) originate, e.g., from the bed nucleus of the stria terminalis and medial amygdala, where testosterone seems to stimulate vasopressin synthesis. In castrated male rats, in which axonal transport was blocked by means of colchicine, testosterone increased the number of BST neurons expressing vasopressin (98). The increased vasopressin fiber staining in aged animals by testosterone treatment is thus an example of how activation of the synthetic activity of peptidergic neurons (i.e., BST neurons) may reverse the age-related changes in their endings.

6) 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 metabolic 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 (53) and a further decrease within those neurons that contain neurofibrillary tangles (58). Interestingly, a similar observation has been made by Doebler et al. (16), 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 (67), 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 that the metabolic rate of the cells is

decreased secondary to the disease process, should also be considered seriously.

7) Changes in neuronal RNA content during aging might be reversed by activation. Neurons in the auditory cortex of 40-week-old mice contained fewer RNA than those of 10-week-old mice did. 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 (2).

8) The observation of Landfield (45) and Sapolsky et al. (84) 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 (46). This view is reinforced by Pfaff's data (73) showing that hippocampal single unit activity in freely moving rats was decreased by corticosterone and increased by ACTH. That Dafny et al. (13) could not confirm the former experiments might be due to the fact that he used a different type of steroid, i.e., cortisol.

9) 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 (78). These compounds are known to enhance glucose utilization of hippocampal neurons containing these receptors (52) and to delay features of hippocampal aging (44). Hippocampal aging was retarded in a similar way by administration of the neural stimulant pentylene tetrazole (44).

10) The observation that enhanced neuronal functioning of the neurosecretory neurons of the supraoptic nucleus causes a decrease in lipofuscin content (14) has already been mentioned earlier.

These examples indicate that activation of neurons within a physiological range during the process of aging may well have a beneficial effect on neuronal function and survival.

STIMULI FOR THE AGING NEURON

The classes of activating stimuli that may prevent or protract the aging process are, in principle, the same ones that normally affect neuronal functioning. Consequently, neurons could be stimulated by:

(a) *environmental stimuli*, e.g., enriched environment (cf. 3);

(b) *hormones* and other chemical factors from outside the brain, e.g., the effect of testosterone substitution on vasopressin innervation (cf. 5), of manipulation of the LHRH neurons on the estrus cycle (cf. 2), sex hormones restoring axonal transport rate (24), corticosterone and ACTH analogues influencing hippocampal function (cf. 8, 9), osmotic stimulation of AVP synthesis in relation to cell survival (cf. 1) and lipofuscin decrease (cf. 10);

(c) *transmitters* (cf. 3, 4 and 7). An interesting example of stimulating effects of a transmitter on postsynaptic neurons was published by Arendash et al. (4). They showed that a long time after NMB lesions have been made in rats, cortex changes mimic neuropathological Alzheimer changes in the human cortex. Plaques, tangles, atrophy and cell loss in the cortex might thus be secondary to the disappearance of innervation of the cortex following degenerative changes in the NBM. In addition, the observed loss of various receptors (63) might be a basis for a diminishment of stimulatory neurotransmitter input, both in aging and Alzheimer's disease;

(d) *trophic factors*. As already appeared from the pioneering work by R. Levi-Montalcini and V. Hamburger (49), trophic factors may enhance neuronal resistance to damage. The disappearance of cholinergic markers containing neurons in the basal forebrain of the rat following lesions could be prevented by intraventricular application of nerve growth factor (NGF) (99), or IP administration of GM1 gangliosides (89). Although there is no evidence for a lack of NGF in Alzheimer's disease, there may be a lack of other trophic factors [for reviews see (3,33)] or, alternatively, a diminished responsiveness of neurons for trophic factors.

The existence of all these different stimulatory factors means that in order to critically test the hypothesis that brain stimulation can protract or even prevent aging, 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 (12,69). DNA repair, which effectively counteracts the continuous deterioration of DNA (26,100), 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 two-fold higher levels of DNA breaks in the cortex than the controls (64). The finding that food restriction which increases life span has an antilipoperoxidation effect (43) and positively influences DNA repair might provide an interesting model in this respect, too. The evidence presented for the "use it or lose it" hypothesis suggests that activation of neuronal activity within the physiological range could preferentially stimulate the action of such protective mechanisms, and therefore shift the balance towards maintenance of the neuron. The observation that DNA repair increases with transcriptional activation (68) 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 (70). Moreover, it has recently been shown that DNA repair was decreased in the mouse brain by anesthesia (41,42), again indicating a direct relationship between decreased metabolic rate and decreased DNA repair.

On the other hand, outside the brain cell activation might activate wear and tear more than protective mechanisms do, and so cause an increased rate of aging in such tissues.

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 Alzheimer's disease while others do not, and why age and Alzheimer pathologies are not manifested to the same degree in different brain structures. 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 such as the substantia nigra, NBM, hippocampus and locus coeruleus. 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 protract 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.

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