depending on the fitness between different chromatin regions and on the presence of transposable elements acting as activators or suppressors. This genome reorganization could cause the slow down of transcription in certain regions and activation in others with a progressive decline and/or a shift in cell functions, i.e., a progressive increase in the entropy of the system. This interpretation of aging that originated from the studies performed with the fibroblast model offers a new concept that can be approached experimentally and could be applied to other cell systems.

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Pharmacological aspects of gerontological brain research

by W. Meier-Ruge

Pharmaceutical Department, Preclinical Research, Sandoz AG, CH-4002 Basle (Switzerland)

One of the cardinal features of aging is polymorbidity. This is not a feature of aging in man alone. An increased incidence of disease is a well-known phenomenon of aging in laboratory animal colonies, as is reflected, to cite but one example, in the age-related increase in tumour frequency[1,2].

The Nestors of descriptive and experimental gerontology, Max Bürger in Leipzig and later Fritz Verzar in Basle, frequently raised the question of whether it might be possible to influence aging processes directly with drugs. No conclusions were reached aside from general assertions to the effect that disease in elderly people is of major concern to the pharmacologist, since aging is a predisposing factor in the development of diseases. Up until now, the experimental pharmacology of aging diseases of the brain has been a field based directly on the results of descriptive gerontology. With increasing age the human brain loses some of its ability to adapt to increased metabolic and functional demands made upon it. The cause is to be sought mainly in a disturbance of glycolytic turnover capacity[3,4] and respiratory-chain oxidation under conditions of increased metabolic demand[5,6].

Changes in transmitter metabolism take the form of a

moderate, but significant reduction in cholinergic activity[7,8]. A reduction in choline acetyl transferase (CAT) activity is a prominent finding. However, reduced activity is also observed in other transmitter systems, e.g. reduced glutamic acid decarboxylase and tyrosine hydroxylase activity in the catecholamine system[9,10].

Functional consequences of these age-related changes in cerebral metabolism are reflected in the decrease in dominant EEG frequencies described by Roubicek[11] and in the rapid loss of vigilance (REF) observed by Matejcek[12] in the EEG chronospectrogram.

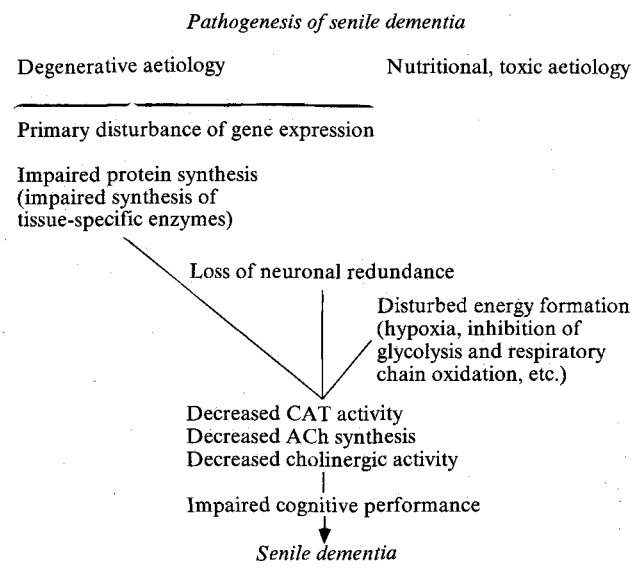
In the light of this reduced ability of the aging brain to adapt to increased metabolic demands, it is understandable that the CNS should be increasingly predisposed to transient ischaemic attacks in old age. Similarly, it is conceivable that dementia might develop, if a second factor adversely affecting the metabolism should supervene (e.g. chronic alcoholism, brain trauma, nicotinamide deficiency, drug intoxication, etc.).

In senile dementia of the Alzheimer type, the temporal region of the brain displays in comparison to normal aging greatly reduced phosphofructokinase activity in association with significantly reduced phosphoglycerate mutase, aldolase, phosphoglucose isomerase and triosephosphate isomerase activity[13].

The enzymes involved in cholinergic transmitter metabolism, choline acetyl transferase (CAT) and acetylcholine esterase (AChE), display greatly reduced activity[8,14,15]. The massive reduction in cholinergic activity is a characteristic feature of Alzheimer's disease. The loss of CAT activity has been shown to correlate with the number of senile plaques and the decline in psychometric test scores[16]. Whereas CAT activity, which is characteristic of presynaptic neuronal function, greatly decreases, the number of postsynaptic muscarinic receptors shows little change in identical age-groups. Recognition of the selective presynaptic impairment of the cholinergic system in Alzheimer's disease has contributed greatly in recent years to our understanding of the pathogenesis of senile dementia.

The discovery that derangement of the process whereby carbohydrate is metabolized to produce energy is one of the major general metabolic concomitants of senile dementia[13,17-19], has focused pharmacological interest on possible ways of influencing this metabolic system. In particular, since Gibson et al.[20] and Siesjö and Rehncrona[21] demonstrated that energy-formation and the cholinergic system are directly linked, the working hypothesis has been developed that it may be possible to interfere experimentally with the cholinergic system by inhibition of glycolysis, tricarboxylic acid cycle and/or terminal oxidation.

Age-related cerebrovascular disorders, classified collectively as cerebrovascular insufficiency, appear in the mortality statistics as the third most common cause of death. They are three to four times more prevalent (11-14%) than senile dementia (4-5%)[22]. Intracranial circulatory disorders (stenosing arteriosclerosis, thrombosis, embolism) may give rise to anoxic impairment of brain function, associated with transmitter release, profound depression of EEG activity, reduced cerebral ATP and creatinine phosphate levels, increased lactate level and an impaired permeability of the blood brain barrier, associated finally with oedema and cell death (cerebrovascular accident)[23,24]. Extracerebral, i.e. systemic circulatory disturbances (heart failure, cardiac arrhythmias, cardiac infarction, rheological disorders, etc.) frequently give rise to transient ischaemic attacks or protracted reversible neurological deficits.



Considering these various pathogenetic mechanisms underlying cerebrovascular diseases of old age the question arrises how this knowledge can be utilised to devise experimental models.

Experimental models for gerontological pharmacological studies on the CNS are generally only an approximation of the true situation[25]. In gerontological brain research there exist no standard experimental models such as those found, for example, in cardiovascular physiology. Each model employed in central nervous gerontology permits a study of selected aspects and thus affords only an incomplete insight into processes occurring in the aging brain and the possibility of modifying them with drugs. In seeking to simulate age-related brain disorders for experimental pharmacological purposes, it will be difficult to find an alternative to the very costly aged animals (mouse, rat, monkey) for testing the effect of drugs.

The models of *cerebrovascular insufficiency* are the same as the models of vascular accidents used for pharmacological studies. These are:

hypovolaemic oligaemia,

transient cerebral ischaemia,

high-altitude hypoxia (hypobaric hypoxia), asphyxic anoxia etc.

Similar models have been widely used for many years in the development of drugs for the treatment of cerebrovascular diseases[26-28].

At the present time the greatest progress in the therapy of cerebrovascular insufficiency has been achieved with haemodilution, osmotherapy, platelet aggregation inhibitors and cardiovascular treatment. Drug treatment of senile dementia is still in a preliminary state. Recent findings of fundamental pathogenetic mechanisms of dementia have increased our knowledge to the point where the experimental pharmacologist can make a start by devising suitable models for the development of effective drugs.

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Aging of connective tissues

by L. Robert

Laboratoire de Biochimie du Tissu Conjonctif (GR CNRS N° 40), Faculté de Médecine, Université Paris-Val de Marne, 8 rue du Général Sarrail, F-94010 Creteil Cedex (France)

It is a particularly sad but fascinating task to write about the aging of connective tissues for this memorial issue devoted to Professor Verzár. His historical experiments on the aging of rat tail tendon opened up an important new research area on the molecular and cellular mechanisms of the aging of connective tissues. I had the privilege of meeting Professor Verzár several times during the last twenty years and these conversations and contacts were the prime incentive for our own work in the aging of connective tissues. Having been born in the same country as Professor Verzár and having left it at about fourty years later, my experimental approach may have been inspired by a similar basic biological-medical culture. I wish therefore to consider my work in general, and this article in particular, as a special tribute to the memory of Professor Verzár.

The state of the art in 1980

Our knowledge about the aging of connective tissues can schematically be divided in two distinct areas. The first one concerns the regulation of the biosynthesis of matrix macromolecules such as the collagens of different genetic types, the proteoglycans, elastin and of structural glycoproteins. The macromolecules belonging to these four families of intercellular matrix substances are synthesized in well-defined proportions by the differentiated mesenchymal cells and associate in specific patterns which can be recognized in every differentiated tissue.

The second aspect of aging research in the connective tissue area concerns the post-translational modifications as well as the catabolism of these macromolecules. These modifications are related to the age-