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De Fabritiis, A.; Guastarobba, A.; Scondotto, G.; Borgatti, E. (Bologna): Hemodynamic-Pharmacological Effect on Cerebral Circulation Evaluated by Means
Quantitative determination of cerebral blood flow (CBF) and energy metabolism have been exploited to study brain aging since 1950 [1, 2]. The hypotheses to verify were: (a) normal aging is accompanied by a slow decline of CBF and CMRO2, which is parallel, and coupled, to reduced functional activity; (b) chronic diseases of the cerebral vasculature in aging are characterized by a reduction in CBF and an increase in arteriovenous oxygen differences, that is, an increased extraction ratio; (c) chronic brain diseases - such as degenerative brain dementia - show a decline in oxygen consumption that precedes the decline in CBF; particularly, in this latter condition, cerebral vascular reactivity is fully normal, while in chronic vascular diseases reserves of vasoregulation are reduced.

None of these points have received clear experimental support, thus contributing to cast doubts on the whole concept of 'chronic brain arterial disease' for example. Overall, these studies lacked an anatomoclinical correlation, and now are completely displaced by emission computerized tomographic studies, which allow us to perform a regional approach to the measurement of functional cerebral parameters. Nevertheless, none of the above-mentioned questions have a clear-cut answer, which might be due to: (1) the limitations still inherent to the new astonishing technologies, and (2) the still preliminary phase of the neuropsychological correlates of the PET metabolic findings.

It is not entirely surprising that Rapoport [3] in normal subjects, whose eyes were covered and ears plugged to minimize sensory inputs, found no fall in brain oxidative metabolism with age in healthy individuals; while Metter [4] mostly noted a different pattern of intercorrelational distribution of LCMR-glu between young and old (normal) subjects which may reflect 'a better ability of the older brain to focus regional interaction in response to functional demands, with a more selective arousal pattern'. In other words, perhaps aged people are less energetic, but more 'astute' (selective) to compensate. There is still a long way to go, but these findings cast some doubts on the significance of the reported 'subtle' changes in CBF and CMR-glu associated with dementia and aging.
It seems therefore difficult to understand the role of such changes in diagnosis and prevention. Furthermore, it seems more unlikely that from animal studies we may learn much on how the complex human brain ages. Difficult as it is, this seems to be a most promising area of basic and applicative investigations for the forthcoming years.

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References


Introduction

This is the second satellite symposium of the XIth International Symposium on Cerebral Blood Flow and Metabolism. Its topic is the 'Effects of Aging on the Regulation of Cerebral Blood Flow and Metabolism'. This subject has been one of almost uninterrupted interest since the publication of the nitrous oxide method by Kety and Schmidt in 1948 [Kety and Schmidt, 1948]. This method was first applied to problems of aging by Freyhan et al. [1951] who found marked depressions in cerebral blood flow and oxygen consumption in the dementias of senility. Many subsequent studies reviewed by Kety [1956] demonstrated that even without dementia cerebral blood flow and oxygen consumption declined with age. Dastur et al. [1963] addressed the question of whether the decreases in cerebral blood flow and metabolism in the aged were inevitable consequences of aging per se or whether they were secondary consequences of age-related diseases, such as arteriosclerosis, that occur with increasing incidence with increasing age. They studied a population of elderly subjects over 65 years of age who were extremely carefully selected.
for as complete freedom from vascular and other diseases as possible at this age and who were also functioning normally in their homes and communities. The results demonstrated that cerebral blood flow and oxygen consumption do not necessarily decline with age in healthy subjects but do decrease in the presence of vascular disease. In their optimally healthy aged subjects, however, Dastur et al. [1963] did find that cerebral glucose utilization did decline even though cerebral blood flow and oxygen consumption were normal. The nature of the substrates other than glucose that were being oxidized by the brain has remained undefined although there has been speculation that ketone bodies might be utilized by the brain in the aged [Gottstein et al., 1963, 1971; Sokoloff, 1975].

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This was the state of the field for a number of years until the recent introduction of methods for the measurement of local rates of energy metabolism in the brain of laboratory animals and also man. Smith et al. [1980] and London et al. [1981] found selective decreases in glucose utilization in specific regions of the brain of aging rats. The extension of these methods to human aging has led, however, to controversial results, which became a subject of intense discussion at the recent XIth International Symposium on Cerebral Blood Flow and Metabolism in Paris. Kuhl and his group at UCLA in Los Angeles have found a significant negative correlation between cerebral glucose utilization and age in human subjects with some degree of selectivity in various regions of the brain. Frackowiak and the group at the Hammersmith Hospital in London found no changes in cerebral oxygen consumption with age. The combined results of the UCLA and Hammersmith groups are, therefore, in essential agreement with the findings of Dastur et al. [1963]. Rapoport and his associates at the National Institute of Aging in Baltimore, however, have carried out studies similar to those of the UCLA group and found no significant correlations between local cerebral glucose utilization and age. Although it is possible to speculate on the reasons for this discrepancy, it remains unclear whether or not glucose utilization in the brain declines with age. This issue will almost certainly be a topic of discussion at the present Symposium, and it is hoped that a resolution of so fundamental a question will be achieved, if not at this meeting at least in the near future.

Cerebral blood flow and energy metabolism represent only one of the many facets of the problem of aging, both normal and abnormal. Normal aging is an integral part of the living process, and like its reverse counterparts, development and maturation, it involves all aspects of structure and function in the brain. Its effects are manifested in structural, chemical, and
neurophysiological changes which evolve at different rates and to different
degrees in different regions of the brain. The primary effects of aging are
further confounded by the effects of diseases which occur with increasing
frequency with age and are superimposed on the aging process. Great
strides have been made in understanding the pathological physiology and
biochemistry of some of the age-related diseases, such as Parkinsonism and
Alzheimer's disease. The organizers of this satellite symposium have
properly recognized in their formulation of the program the broad range
of the processes and functions that are altered in normal and abnormal
aging. Thanks to their efforts we can look forward to a comprehensive and
stimulating review of the state of aging research today.

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References

Effects of aging on cerebral circulation and metabolism in man; in Birren, Butler, Greenhouse,
Sokoloff, Yarrow, Human aging, a biological and behavioral study, pp. 59-78

Freyhan, F.A.; Woodford, R.B.; Kety, S.S.: Cerebral blood flow and metabolism in psychoses

Gottstein, U.; Bernsmeier, A.; Sedlmeyer, I.: Der Kohlenhydratstoffwechsel des menschlichen

Fettsuren und Ketonkrpern im Gehirn des Menschen. Klin. Wschr. 49:

Kety, S.S.; Schmidt, C.F.: The nitrous oxide method for the quantitative determination of
cerebral blood flow in man: theory, procedure, and normal values. J. clin. Invest. 27:
476-483 (1948).


London, E.D.; Nespor, S.M.; Ohata, M.; Rapoport, S.I.: Regional cerebral glucose utilization

Smith, C.B.; Goochee, C.; Rapoport, S.I.; Sokoloff, L.: Effects of ageing on local rates of cerebral

Sokoloff, L.: Cerebral circulation and metabolism in the aged; in Gershon, Raskin, Aging,

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