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SOME ASPECTS OF THE PATHOMECHANISM OF NERVE TISSUE LESIONS IN ACUTE CARBON MONOXIDE INTOXICATION

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The pathogenetic mechanisms of central nervous system impairment in carbon monoxide intoxication are not fully elucidated, despite a great number of clinical, pathomorphological and experimental observations, which generally point to a complex and ununiform origin of tissue abnormalities. The role of the hypoxic mechanism, resulting from a high affinity of carbon monoxide to blood hemoglobine, exceding in humans 240 times the affinity of oxygen (Forbes, 1970) is generally accepted. The formation of carbon monoxide hemoglobine, varying in its level, leads to anemic hypoxemia with all consequences for the nerve tissue, the nature and intensity of which depends on the degree and duration of hypoxia.

Less univocal is the role of the direct cytotoxic effect of carbon monoxide on the parenchymal elements of the nerve tissue, owing to its affinity to the intracellular respiratory enzymatic system. The reservations, concerning this mechanism of carbon monoxide action *in situ* conditions, originate from the well known relatively low solubility of carbon monoxide in blood serum (Coburn, 1970) and its unknown permeation through the blood-brain barrier. Graziani and Guariano (1965) were not able to prove the presence of CO in the tissues of the central nervous system after 30 min. acute intoxication of experimental animals. Schwedenberg's concept (1952) concerning CO-penetration to parenchymal tissue elements together with edematous fluid may be put in doubt by the fact that in experimental conditions brain edema does not present a permanent pathological feature (Miyagishi, Suwa, 1969; Korthals et al., 1973). On the other hand, Ball et al. (1951) demonstrated that carbon monoxide action *in vitro* appears only at certain level of simultaneous oxygen deficit (below 25%), very rarely reached *in vivo*. This led same authors to the concept of the exclusive hypoxic nature of brain damage in CO intoxications (Brucher, 1967).

The localization of focal tissue lesions in the brain has been attributed by many investigators to the hemodynamic disorders both systemic and local, accompanying carbon monoxide intoxications (Brzezicki, 1930; Lehoczky, 1949; Romanowa, 1959; Környey, 1963; Lapresle, Fardeau, 1967; Preziosi et al., 1970).

A series of experiments performed in our Laboratory, both on animals and on tissue culture seem to offer certain information for a better understanding of this complex problem. In the experiments carried out on rats subjected to carbon monoxide intoxication to the level of 65—70% of CO-hemoglobine in blood accompanied by the reduction of cytochrome oxidase activity in the mitochondrial fraction of brain tissue to 75% of its normal value, no histopathological lesions in the central nervous system were found (Śmiałek et al., 1972). At the same time severe metabolic abnormalities, reversible in their nature were present both during and after intoxication. They consisted in disturbances in the high-energy compounds content (Sikorska et al., 1974), altered activity of main enzymes of the glycolytic pathway (Sikorska, Broniszewska, 1974) as well as that of adenyl-cyclase (Sikorska, 1974). Abnormalities in neuronal and glial protein biosynthesis were found by Albrecht (1973) and Albrecht and Śmiałek (1975). The most striking feature was glycogen content increase during the postintoxication period, accompanied by concomitant changes in the activity of glycogen-metabolizing enzymes (Śmiałek et al. 1972). The above presented metabolic disturbances found their manifestation in the histochemical picture of the brain (Szumańska, 1973), mostly as accumulation of abnormal glycogen deposits, increased activity of UDPG-g-transferase and phosphorylases as well as in reduction of cytochrome oxidase and succinic dehydrogenase activity. Although abnormal blood vessel permeability for protein markers was not a feature, a slight but statistically significant increase of water content in the brain tissue was found after intoxication (Rap et al., 1974).

In electron microscopy no significant abnormalities were present, except swelling of perivascular astrocytic processes and astrocytic glycogen deposition (Korthals et al., 1973). The above presented changes were in their general nature and pattern similar to those observed in many experimental models of brain hypoxia and may be treated as a manifestation of energy deprivation, resulting from the oxygen deficit. In case of a more severe intoxication, the above mentioned abnormalities were superimposed by focal tissue alterations, with an evident prevalence in such areas as Ammon's horn, cerebral white matter, parietal portions of neocortex and striatum. The globus pallidus, cerebellar structures and thalamus were much less frequently the site of irreversible tissue lesions (Korthals et al., 1973).

The location of focal tissue lesions in general corresponds well with the sites of most severe and durable blood supply disturbances as shown in Mossakowski's benzidine studies (1975). This concomitance allowed us to consider the focal tissue impairments as resulting from general, regional and local hemodynamic disturbances, related with systemic hemodynamic abnormalities, accentuated by differences in angioarchitectonics of particular brain structures, and with disorders in autoregulatory mechanisms of brain blood vessels.

At the ultrastructural level the tissue abnormalities consisted in degeneration of neurons, ranging from mitochondrial swelling to complete necrosis as well as in degeneration of axons and myelin sheaths varying in intensity and advancement.

Differences in ultrastructural abnormalities of astrocytes, consisting in swelling of their cytoplasm and those in oligodendroglial cells seem to be worth mentioning. In the latter, selective damage of mitochondria contrasted with the relatively well preserved structure of other subcellular elements.

To elucidate the question of the possible cytotoxic effect of carbon monoxide action exerted on parenchymal elements of the nerve tissue, tissue culture studies were performed (Hoppe, 1974). The severe damage to all neuroectodermal cells was a striking feature. It consisted in remarkable glial cell swelling and vacuolar degeneration with increased cell membrane permeability and significant reduction of the activity of all respiratory enzymes.

At the EM level severe vacuolization of glial cell cytoplasm and damage to mitochondrial system were permanent features (Korthals et al., 1973). The oligodendrocytes happened to be the most sensitive cellular element. Their sensitivity exceded that of neurons. The cytotoxic effect of CO was exerted in conditions of entirely normal oxygen content; this contradicts the observations of Ball et al. (1951), at least under the conditions applied. Keeping in minde, all differences concerning tissue culture experiments, their comparison with the results of our experiments performed with animals is strongly suggestive that the cytotoxic effect of carbon monoxide has to be taken into consideration even in *in situ* conditions. The difference in the dynamics of metabolic abnormalities observed in CO intoxications as compared with other hypoxic and ischemic conditions, concerning mostly glycogen accumulation and protein biosynthesis supports this supposition. The same is suggested by the results obtained by Śmiałek (1974) in experiments with isolated nerve cells from the brain of intoxicated animals.

On the basis of experiments with animals and tissue culture it would seem that myelin impairment in experimental conditions does not depend so much on brain edema as on the oligodendroglial damage. However, the possible role of brain edema, postulated by numerous authors cannot be ruled out, as the cerebral white matter is the site of predilection for severe, persisting venous hyperemia, which favours development of brain edema (Mossakowski, 1975).

To sum up, the brain tissue damage, occurring in carbon monoxide intoxication results from several factors, such as anemic hypoxemia and ischemia due to both systemic and local hemodynamic disorders, accentuated by regional angioarchitectural factors as well as the cytotoxic action of the poison exerted directly on the parenchymal elements of the central nervous system. All these factors overlap each other and all have in common oxygen deprivation or its limited utilization in tissue metabolic processes.

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WYBRANE ZAGADNIENIA PATOMECHANIZMU USZKODZEŃ TKANKI NERWOWEJ W OSTRYM ZATRUCIU TLENKIEM WĘGLA

Streszczenie

W oparciu o badania doświadczalne wykonane na materiale zwierzęcym i w hodowli tkankowej autorzy omawiają udział poszczególnych czynników patogenetycznych w kształtowaniu obrazu patomorfologicznego ostrej encefalopatii tlenkowęglowej. Autorzy zwracają uwagę na trzy podstawowe czynniki odgrywające rolę w metabolicznym i strukturalnym uszkodzeniu tkanki nerwowej w następstwie działania tlenku węgla — hypoksyjnego, związanego z wysokim powinowactwem tlenku węgla do hemoglobiny, niedokrwiennego, stanowiącego następstwo ogólnoustrojowych i miejscowych zaburzeń hemodynamicznych, pogłębionych przez właściwości angioarchitektoniczne poszczególnych struktur ośrodkowego układu nerwowego i zaburzenia autoregulacyjnych mechanizmów krążenia mózgowego, oraz cytotoksycznego, wynikającego z blokowania przez tlenek węgla wewnątrzkomórkowych układów oddechowych. Szczególną uwagę zwrócono na uszkodzenia gleju skąpowypustkowego, jako czynnika prowadzącego obok obrzęku mózgu do rozpadu osłonek mielinowych.

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ИЗБРАННЫЕ ВОПРОСЫ ПАТОМЕХАНИЗМА ПОВРЕЖДЕНИЙ НЕРВНОЙ ТКАНИ ПРИ ОСТРОМ ОТРАВЛЕНИИ ОКИСЬЮ УГЛЕРОДА

Резюме

Основываясь на экспериментальных исследованиях, проведенных на животном материале и тканевой культуре, авторы обсуждают в работе участие отдельных патогенных факторов в становлении патоморфологической картины острой энцефалопатии, вызванной окисью углерода. Авторы обращают внимание на три основных фактора повреждений нервной ткани в результате отравления окисью углерода — гипоксический, связанный с высоким сродством окиси углерода к гемоглобину, исхемический, являющийся результатом гемодинамических нарушений как местного, так и общего характера и усиленных ангиоархитектоническими свойствами отдельных структур центральной нервной системы и нарушениями авторегуляционных механизмов мозгового кровообращения, и цитотоксический, возникающий в результате блокирования окисью углерода внутриклеточных дыхательных систем. Особое внимание уделяется повреждениям олигодендроглии как фактору, ведущему наравне с отеком мозга к распаду миелиновых оболочек.

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