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MIROSŁAW J. MOSSAKOWSKI, IRMINA B. ZELMAN

GLYCOGEN DEPOSITION AS AN INDICATOR OF GLUCOSE METABOLISM DISTURBANCES IN THE BRAIN DUE TO VARIOUS DAMAGING FACTORS *)

Department of Neuropathology, Medical Research Centre Polish Academy of Sciences
Head of Department: Prof. M. J. Mossakowski, M.D.

Normal nervous tissue accumulates but a small amount of glycogen. The dependence of polysaccharide accumulation on the stage of maturity of the central nervous system is a very characteristic feature. In our experiments, carried out on rats aged 1, 2, 3, 4, 6 and 10 weeks it was shown that glycogen content in the brain of 1-week-old rats reached the value of 11.3—13.4 mg/100 g of tissue, while that in the brain of 2-week-old ones was already 3 times higher, remaining at this level during the subsequent stages of maturation (Mossakowski et al., 1973).

The observed variations in glycogen content were considered to be related with the shift of glucose metabolism from the pentose monophosphate shunt to the glycolytic pathway occurring at the beginning of the 2nd week of rat life (Winick, 1970; Balasz, 1970), with a significant increase of hexokinase activity at the same time (Wilson, 1972) or with metabolic processes connected with myelination, taking place between the 1st and 6th week of the animal's life (Bass et al., 1968; Eto, Suzuki, 1972).

At the histochemical level, the glycogen deposits occur only in some structures of the central nervous system such as epithelial cells of the choroid plexus, ependyma, mostly of the III ventricle, subependymal and subpial layers, some nuclei of the brain stem (mesencephalic nucleus of Vth nerve, large neurons of reticular formation) and ganglionar layer of cerebellar cortex. Significant species-dependent differences have to be pointed out. The presence of glycogen deposits in large motor

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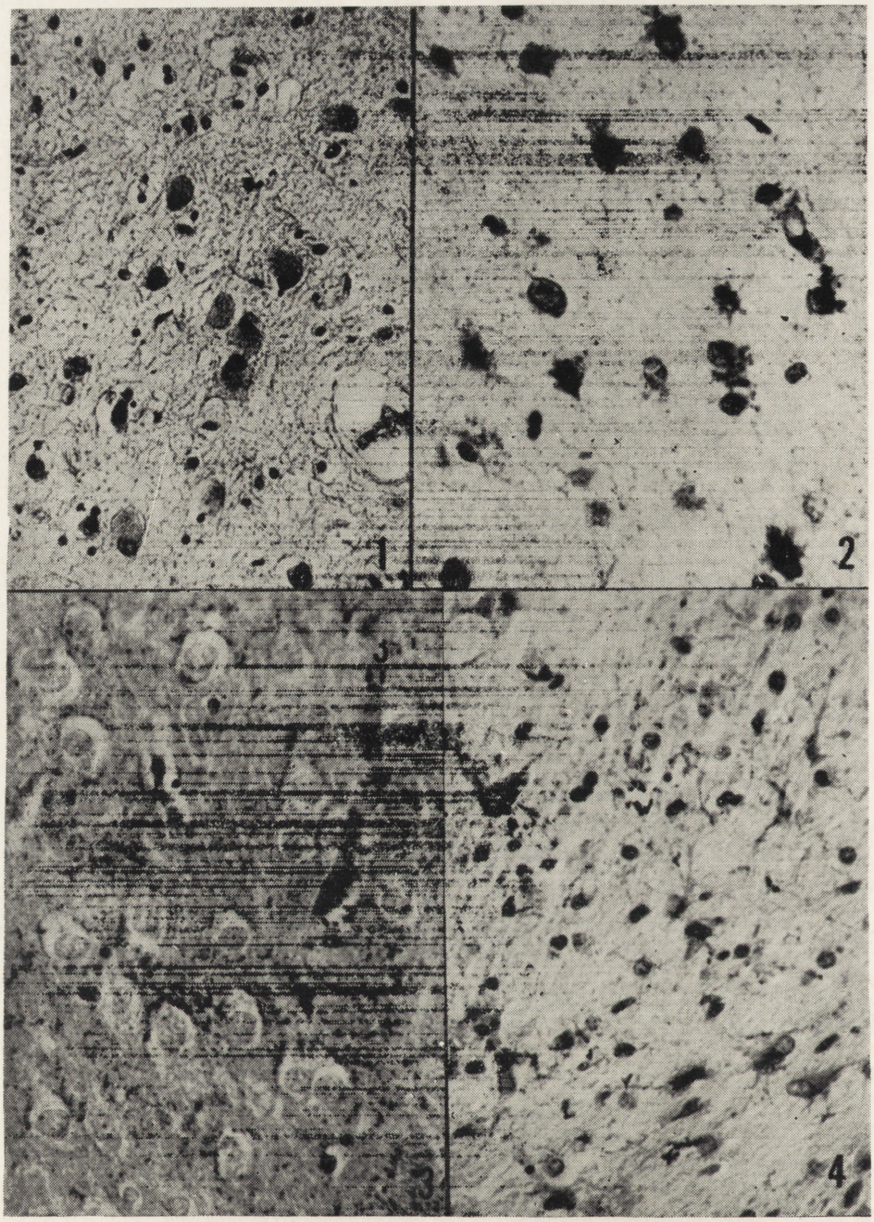

Fig. 1. Brain stem neurons accumulating glycogen in cytoplasm. Type II glycogenosis (Pompe's disease). Best's carmine meth. × 200

Ryc. 1. Neurony pnia mózgu spichrzające glikogen w cytoplazmie w glikogenozie typu II (choroba Pompego). Karmin Besta. Pow. 200 ×

Fig. 2. The same case. Glycogen deposits in astroglial cells in the white matter. Best's carmine meth. × 200

Ryc. 2. Ten sam przypadek. Złogi glikogenu w astrocytach istoty białej. Karmin Besta. Pow. 200 ×

neurons of the spinal cord of rabbits, observed by Schabadasch (1939) in contrast to their absence in the cat spinal cord described by Long et al. (1972) should be stressed. There exist also significant differences in the localization of normal glycogen deposits between mammals and fishes, for instance sharks (unpublished personal data).

Abnormal glycogen deposition in the central nervous system resulting from various pathological conditions seems to be a very common feature. Among those special position has to be attributed to the Pompe's variant of glycogenosis, being an inborn, genetically induced metabolic error, leading to excess glycogen deposition both in neuronal and glial elements of the central nervous system (Fig. 1 and 2). In the most other conditions glycogen accumulation seems to represent entirely non-specific phenomenon. Abundant glycogen deposits were described around experimental brain wounds (Friede, 1954; Shimizu, Hamuro, 1958; Klatzo et al., 1970; Guth, Watson, 1970) as well as an effect of irradiation (Klatzo et al., 1961; Miquel et al., 1963; Miquel, Haymaker, 1965; Ostenda et al., 1970). A wide range of pharmacologically active compounds can also induce an increase of glycogen content in the brain, among these are reserpine (Albrecht, 1957; Estler, 1961), insulin (Nelson et al., 1968), ether (Estler, Heim, 1960), phenobarbital (Estler, 1960; Nelson et al., 1968).

A severalfold increase of glycogen was observed in the central nervous system of rats with alloxan-induced diabetes (Prasannan, Subrachmanyan, 1968) and in rabbits with hereditary ataxia (Tourtellotte et al., 1966). Glycogen deposits were also noticed in areas surrounding human (Oksche, 1958) and animal tumors (Szumańska, Kroh, 1975).

Our experimental studies showed, that hypoxic conditions of various nature involve a common factor leading to the accumulation of abnormal glycogen deposits in nervous tissue.

The phenomenon was observed in both perinatal asphyxia of newborn monkeys (Mossakowski et al., 1968), hypoxic hypoxia (Mossakow-

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Fig. 3. Granular glycogen deposits lying loosely in the neuropil and in the form of perivascular and perineuronal aggregations in the cerebral cortex of rat. 48 h after carotid ligation. PAS-dimedon-hematoxylin. × 400

Ryc. 3. Ziarniste złogi glikogenu leżące luźno w neuropilu oraz tworzące okołonaczyniowe i okołoneuronalne skupienia w korze mózgu szczura, 48 godz. po podwiązaniu tętnic szyjnych. PAS-dimedon-hematoksylina. Pow. 400 ×

Fig. 4. Glycogen grains in perikarya and processes of astrocytes in rat brain, 12 h after carotid ligation. PAS-dimedon-hematoxylin. × 200

Ryc. 4. Ziarnistości glikogenu w perykariach i wypustkach astrocytów w mózgu szczura, 12 godz. po podwiązaniu tętnic szyjnych. PAS-dimedon-hematoksylina. Pow. 200 ×

ski, Zelman, 1971), ischemia due to ligation of brain or spinal cord arteries (Pronaszko et al., 1971; Long et al., 1972; Mossakowski et al., 1973; Śmiałek et al., 1971; Mrsulia et al., 1975) and hypovolemic ischemia (Sikorska, Śmiałek, 1974; Szumańska, Gadamski, 1974) as well as in acute carbon monoxide intoxication (Śmiałek et al., 1973; Korthals et al., 1973; Szumańska, 1973). An essential characteristic of posthypoxic glycogen accumulation consists in its reversible nature and its localization either in the vicinity of irreversibly damaged areas in the tissue and/or mostly in tissue revealing no histological and ultrastructural lesions whatever. Most glycogen deposits occur in the grey structures, above all in the cerebral cortex. They take the form of fine granular material lying loosely in the neuropile, very often with perivascular and less frequently perineuronal aggregations (Fig. 3). They are very common in the vicinity of astrocytic nuclei, and fill their perikarya and processes (Fig. 4). At the electron microscope level they form abundant rosettes in perivascular astrocytic processes, in perikarya of astrocytes and in their processes not connected with vascular walls (Fig. 5). Their presence in neuronal processes is a very unusual feature. Neuronal glycogen deposition occurs very seldom. In our experimental material deposits were present only in cases of spinal cord moderate ischemia,

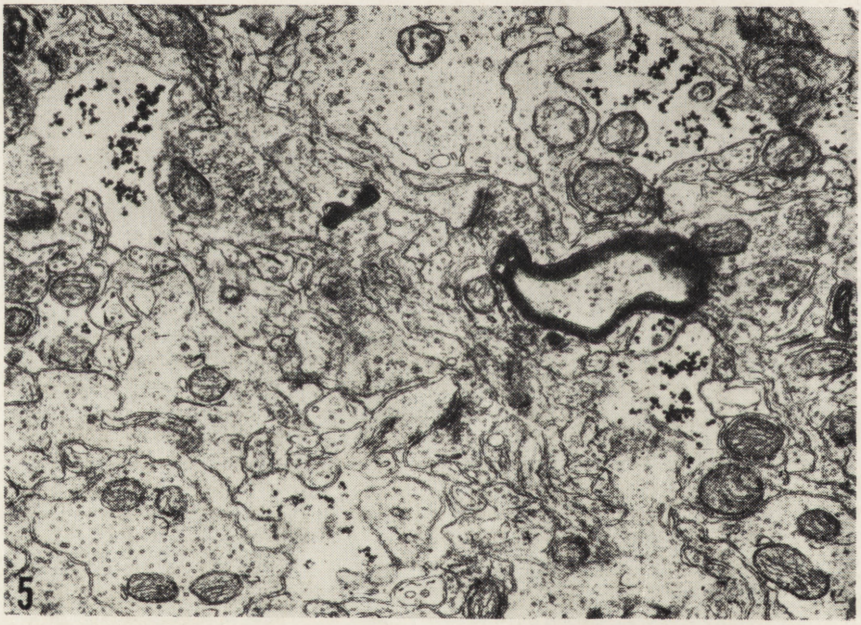

Fig. 5. Typical glycogen rosettes in swollen astrocytic processes in rat brain, 24 h after carbon monoxide intoxication. × 7400

Ryc. 5. Typowe rozetki glikogenu w obrzmiałych wypustkach astrocytarnych, 24 godz. po zatruciu tlenkiem węgla. Pow. 7400 ×

and occurred in large motor neurons accompanying neuropile and astrocyte accumulation (Fig. 6).

In mature animals the glial glycogen deposits were confined exclusively to the grey brain structures, while in animals with immature central nervous system they occurred also in the white matter, mostly in that of myelinating brain hemispheres. This could be seen both in asphyxiated newborn monkeys and 1-week old rats with bilaterally ligated carotid arteries. The age of animals played also important role as far as the dynamics of the phenomenon was concerned .The age dependence of the dynamics of glycogen appearance and disappearance was most clearly demonstrated by polysaccharide accumulation in the brains of rats, the common carotid arteries of which were ligated at various ages. The glycogen content in 1-week-old rats was significantly increased at 24th h after bilateral carotid ligation, while in 6-week-old ones some enhancement was present already after 12 hrs. Return to normal glycogen level in the former age group occurred at the 3rd day, whereas in the latter is was far higher than in controls, even after five days (Mossakowski et al., 1973). The dynamics of the process was also dependent on the kind of hypoxia. The glycogen content in the brain appeared higher much earlier after carbon monoxide intoxication than in the case of moderate brain ischemia or circulatory hypoxia (Śmiałek et al., 1973; Sikorska, Śmiałek, 1974). In asphyxiated newborn monkeys the greatest glycogen accumulation was noted at the 12th hour following experimental procedure, and its return to normal occurred 4 days later. In the spinal cord ischemia glycogen deposition was first observed as early as 30 min following abdominal aorta clamping. Full normalization of the histochemical picture occurred 7 days later.

The dynamics and degree of glycogen accumulation was influenced to a great extent by the tissue composition, as indicated by the differences in glycogen content increase in various portions of rabbit brains in the case of hypovolemic hypoxia.

In all our experiments glycogen deposition was accompanied by changes in the activity of glycogen-metabolizing enzymes, UDPG-g transferase and phosphorylases. They were expressed in the appearance or increase of UDPG-g transferase and phosphorylase activity in astrocytes in all the experiments (Fig. 7) and in neurons in the case of spinal cord ischemia (Fig. 8). The most striking feature consisted in the fact that the increase in UDPG-g transferase activity preceded maximum accumulation of glycogen, this being most early reflected in the case of carbon monoxide intoxication. The greatest increase of phosphorylase activity took place at the time of maximal glycogen deposition.

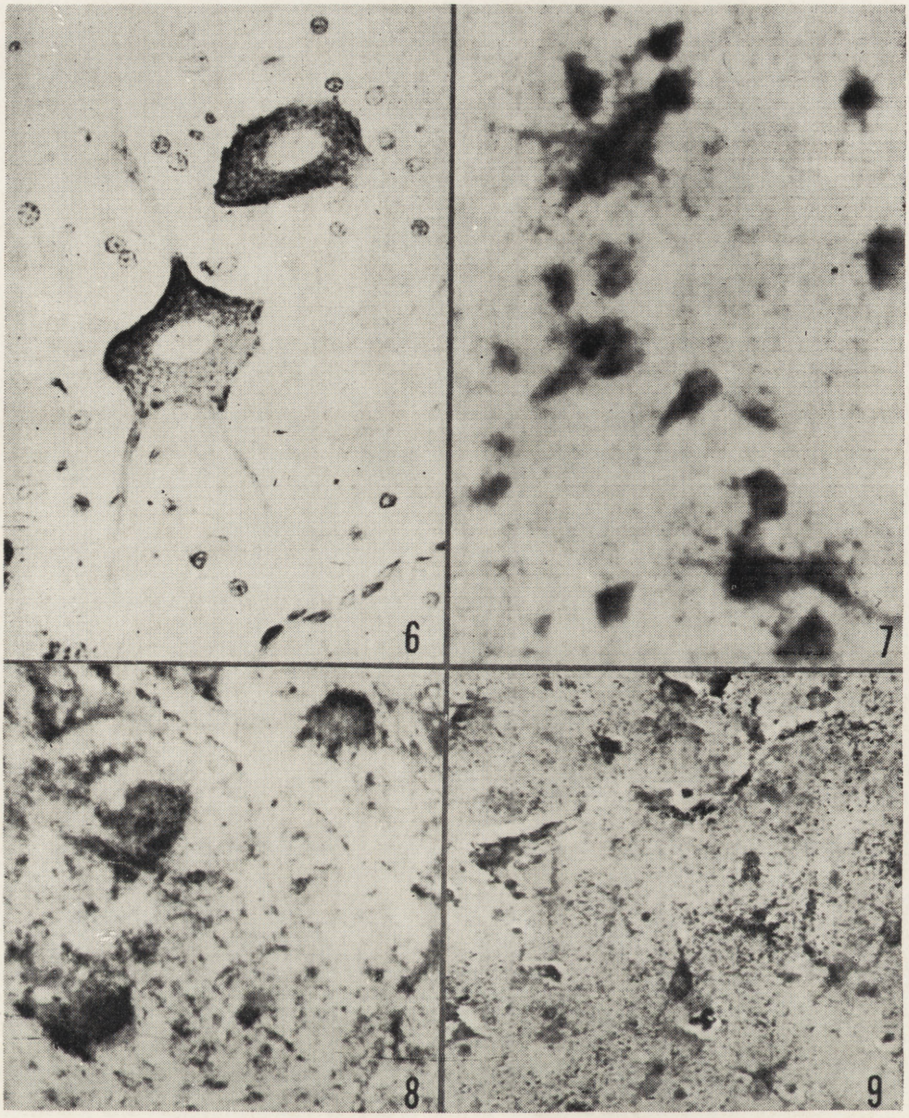

Fig. 6. Large motor neurons from the lumbar segment in cat sacrificed 12 h following ligation of aorta. Different pattern of glycogen granules within neuronal cytoplasm. PAS-dimedon-hematoxylin. × 600

Ryc. 6. Duże neurony ruchowe odcinka lędźwiowego rdzenia kręgowego u kota, 12 godz. po podwiązaniu tętnicy głównej. Złogi glikogenu w perikarialnej i wypustkowej cytoplazmie neuronu. PAS-dimedon-hematoksylina. Pow. 600 ×

Fig. 7. Subcortical white matter in a monkey sacrificed 1 h after asphyxia. Astrocytes with UDPG-glycogen transferase activity in their cytoplasm. × 460

Ryc. 7. Istota biała podkorowa u małpy w 1 godz. po asfiksji. Astrocytarna aktywność transferazy UDPG. Pow. 460 ×

The same phenomenon, consisting in glycogen accumulation and in changes of glycogen-metabolizing enzymes activity occurred also in nerve cells and astrocytes cultured in vitro and subjected to anoxic conditions or to carbon monoxide intoxication (Kraśnicka, Renkawek, 1972; Hoppe, 1974).

Glycogen accumulation resulted also from intracerebral injection of ouabain, a well known membraneous ATP-ase inhibitor, and leading when given intracerebrally to profuse cytotoxic brain edema. In the above experimental conditions astrocytic aggregation of polysaccharide, accompanied by considerable changes in glycogen-metabolizing enzymes activity were observed (Fig. 9). Abnormal glycogen accumulation in these conditions deserves special attention because of its bilateral distribution exceeding by far the area of glycoside diffusion in the brain tissue, as indicated by radioisotopic studies of Towfighi and Gonatas (1973), the long duration of the process and its entirely different dynamics as compared to that in cases of brain hypoxia or ischemia (Zelman, Pronaszko-Kurczyńska, 1975).

Similar changes were observed by Szumańska et al. (1974) in experimental vasogenic brain edema induced by brain compression caused by a supradurally located balloon. However, they were much less pronounced, this probably being related with early stages of brain edema. Their mechanism owing to dominating hemodynamic disturbances was considered to be similar to that in cases of brain ischemia.

In addition to the above mentioned generalized or focal brain pathology, glycogen accumulation occurs in some reversible neuronal degenerative processes, namely in cases of experimentally induced axonal reaction. Damage of the peripheral nerves, as in experiments of Szumańska and Rap (1971), resulted in polysaccharide accumulation in cer-

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Fig. 8. Glycogen phosphorylase a activity in the anterior horn neurons in cat sacrificed 24 h after ligation of aorta. High enzyme activity in neuronal cytoplasm and processes. Takeuchi, Kuriaki. × 200

Ryc. 8. Aktywność fosforylazy a w rogu przednim rdzenia u kota w 24 godz. po podwiązaniu tętnicy głównej. Wysoka aktywność w cytoplazmie perikarialnej i wypustkowej motoneuronów. Takeuchi, Kuriaki. Pow. 200 ×

Fig. 9. Cerebral cortex of rat, 48 h following intracerebral ouabain injection. Abundant astrocytic and neuropil glycogen deposits. PAS-dimedon-hematoxylin. × 200

Ryc. 9. Kora mózgu szczura, 48 godz. po domózgowej injekcji ouabainy. Obfite ziarniste złogi glikogenu w astrocytach i neuropilu. PAS-dimedon-hematoksylina. Pow. 200 ×

tain motor neurons, related with damaged axons. The phenomenon occurred at the time of advanced tigrolysis, and disappeared with tigroid formation. Increase of UDPG-g transferase and phosphorylases activities, taking place at corresponding time intervals was an accompanying feature. The same phenomenon was represented by glycogen accumulation in neurons of dorsal root ganglia grown in vitro cultures. The polysaccharide accumulation and increased activity of the metabolizing enzymes disappeared at the time of tigroid reconstruction (Kraśnicka, 1969).

The review of the literature and the presented results of our own experiments indicate that glycogen accumulation and abnormalities in the activity of glycogen-metabolizing enzymes are a nonspecific manifestation of disturbances of nerve tissue metabolism, accompanying various pathological conditions. The full reversibility of the process, its occurrence in areas of entirely undamaged tissue or in elements of the latter revealing features of reversible abnormalities (axonal reaction) allow to consider glycogen accumulation as a manifestation of early and reversible metabolic disturbances, showing no histopathological or ultrastructural exponents. This process expresses undoubtedly abnormalities in glucose metabolism. Time sequences of polysaccharide accumulation and variations in glycogen-metabolizing enzymes activity as well as isotope studies of Guth and Watson (1970) and Sikorska et al. (1975) are strongly suggestive of an increased glycogen synthesis rather than inhibition of its enzymatic breakdown. The mechanism of abnormal glycogen accumulation remains unknown. Numerous pathogenetic theories have been offered. The most attractive explanation of the phenomenon seems to be that based on the assumption of reduced glucose utilization by the tissue. The occurrence of glycogen accumulation in conditions of reduced tissue metabolism (reserpine, ether, barbiturates) or in cases of excess of glucose (alloxan-induced diabetes), as well as in processes, in which, owing to the preceding hypoxia, the rate of metabolic processes is diminished (reduced protein and nucleotide biosynthesis, shown by Yap and Spector (1965) and Albrecht (1972) to follow hypoxic accidents) is strongly suggestive of such a possibility. Astrocytic or mostly astrocytic localization of glycogen might be related with their transport functions, although our tissue culture studies indicate the possible role of disturbances of their own metabolism. Neuronal glycogen deposition according to Long's and his colleagues (1972) opinion — occurs only in those nerve cells, which posses the necessary enzymatic apparatus for glycogen synthesis. However, molecular mechanisms of glycogen accumulation still remain to be elucidated.

M. J. Mossakowski, I. B. Zelman

ODKŁADANIE SIĘ GLIKOGENU W MÓZGU JAKO WYKŁADNIK ZABURZENIA PRZEMIANY GLUKOZY W NASTĘPSTWIE DZIAŁANIA RÓŻNYCH CZYNNIKÓW USZKADZAJĄCYCH

Streszczenie

Zawartość glikogenu w prawidłowym mózgu jest niewielka, a histochemicznie wykrywalne złogi spotyka się tylko w niektórych strukturach ośrodkowego układu nerwowego. Zwiększenie zawartości tego polisacharydu występuje jako zjawisko fizjologiczne w okresie dojrzewania tkanki nerwowej oraz w stanach patologicznych o różnej etiologii. Oprócz glikogenozy, w której odkładanie się glikogenu w ośrodkowym układzie nerwowym jest wynikiem uwarunkowanego genetycznie zaburzenia przemiany, obserwowano gromadzenie się glikogenu jako zjawisko przejściowe w następstwie niedotlenienia, uogólnionego i miejscowego niedokrwienia, po zatruciu tlenkiem węgla, po domózgowym podaniu ouabainy oraz w innych procesach prowadzących do zaburzeń przemiany w tkance nerwowej ale nie powodujących zmian strukturalnych, lub wyłącznie zmiany odwracalne. Zmianom zawartości glikogenu towarzyszą zaburzenia w aktywności enzymów biorących udział w jego przemianie, UDPG-g transferazy i fosforylaz. Dynamika rozwoju tych zmian jest różna w zależności od stopnia dojrzałości ośrodkowego układu nerwowego, rodzaju czynnika patogennego oraz gatunku zwierząt doświadczalnych. Złogi glikogenu gromadzą się przede wszystkim w neuropilu, perikarionach i wypustkach astrocytów, rzadko i tylko w niektórych strukturach również w perikarionach dużych neuronów ruchowych. W dojrzałym mózgu glikogen obserwowano wyłącznie w strukturach szarych, w niedojrzałym, a zwłaszcza mielinizującym się również w istocie białej. Wzrost zawartości glikogenu, którego mechanizm nie jest wyjaśniony, stanowi niespecyficzny wykładnik zaburzeń przemiany glukozy w tkance nerwowej, wyprzedzający pojawienie się histologicznych i submikroskopowych uszkodzeń ośrodkowego układu nerwowego.

М. Я. Моссаковски, И. Б. Зельман

ОТЛОЖЕНИЕ ГЛИКОГЕНА В МОЗГУ, КАК ПОКАЗАТЕЛЬ НАРУШЕНИЯ ОБМЕНА ГЛЮКОЗЫ В РЕЗУЛЬТАТЕ ДЕЙСТВИЯ РАЗЛИЧНЫХ ПОВРЕЖДАЮЩИХ ФАКТОРОВ

Резюме

Содержание гликогена в нормальном мозгу невелико, а гистохимически обнаружимые отложения встречаются только в некоторых структурах цнс. Увеличение содержания этого полисахарида выступает как физиологическое явление в период созревания нервной ткани и в патологических состояниях с разной этиологией. Кроме гликогеноза, при котором отложение гликогена в цнс является результатом генетически обусловленного нарушения обмена, наблюдалось накопление гликогена в цнс как преходящее явление в результате гипоксии, общей и местной ишемии цнс, после отравления окисью углерода, после внутримозгового введения оуабаина, а также других процессов, приводящих к нарушениям обмена в нервной ткани, но не вызывающих каких-либо структурных изменений в цнс или вызывающих только обратимые изменения. Изменения содержания гликогена сопровождались нару-

шениями активности ферментов, участвующих в его обмене, УДФТ-г трансферазы и фосфорилаз. Динамика развития этих изменений различна в зависимости от степени зрелости цнс, характера патогенного фактора и вида опытных животных. Отложения гликогена накапливаются прежде всего в нейропиле, перикарионах и отростках астроцитов, редко и только в некоторых структурах также в перикарионах больших двигательных нейронов. В зрелом мозгу гликоген наблюдали только в серых структурах, в несозревшем и, особенно, миелинизирующемся мозгу — также в белом веществе. Возрастание содержания гликогена, механизм которого не выяснен, является неспецифическим показателем нарушений обмена глюкозы в нервной ткани, опережающим появление гистологических и субмикроскопических повреждений цнс.

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Authors' address: Department of Neuropathology, Medical Research Centre, Polish Academy of Sciences. 00-784 Warszawa, Dworkowa Str. 3.