FROM EURATOM AND CENTRE D'ÉTUDE DE L'ÉNERGIE NUCLÉAIRE, C.E.N./S.C.K., B-2400 MOL, BELGIUM.

LATE CHANGES IN BIOCHEMISTRY AND BLOOD FLOW IN RAT BRAIN LOCALLY EXPOSED TO 30, 40 OR 60 GY

G. B. GERBER, J. DEROO, J. MAES and J. CASALE

Due to the absence of cell renewal in nerve cells, the central nervous system (CNS) appears to be a suitable system for following late effects of radiation, in particular those related to blood vessels, and this has been the rationale for choosing the CNS as the subject for a cooperative investigation by the European Late Effect Group (EULEP). Vascular abnormalities (Rijswijk) and density (Oxford), the behaviour of the glia population (Mol), blood flow and vascular volume (Louvain) and cell replacement of subependymal cells (Ulm) are being investigated by other members of the group using the same conditions of exposure and animal care. The present report deals with different biochemical parameters and with blood flow after local irradiation of the brain with 30, 40 or 60 Gy, and thus represents an extension to other doses and other parameters in a previous report (GERBER et coll. 1976).

Methods

The conditions of irradiation and the methods of determination have been published previously (GERBER et coll. 1976).

Irradiation is carried out by lateral exposure and is limited to tissue anteriorly and superiorly to the inner corner of the eye. It thus involves nearly the entire cortex with the hippocampus, the corpus callosum and most of the thalamus, but not the hypothalamic area, the medulla and most of the cerebellum. The field had to be restricted in this way to avoid oral death during the second week after exposure. In

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addition to the determinations carried out previously, i.e. DNA, protein, hydroxyproline, sialic acid, β-glucuronidase, acid phosphatase, cathepsin D, serotonin, noradrenalin, dopamine, histamine, diamines and uptake of α-amino isobutyrate, the following determinations were also made: peroxide content and peroxidation in the presence and absence of Fe^{++} ions, sphingosine, phospholipids (by total lipid phosphate content and thin layer chromatography), fatty acids by gas liquid chromatography and relative blood flow (by injection of labeled 15 μ microspheres in the left heart under light avertin anesthesia). The details of these methods have been described previously (GERBER et coll. 1978).

Results

The results of the experiments with 30, 40 and 60 Gy as well as those obtained 2 years after 20 Gy which supplement the previous paper are presented in the Table.

Due to limitations in space, the data are only presented as percentages of the non-irradiated controls of the same age. Statistically significant differences are marked with an asterisk ($p \leq 0.05$). The most noteworthy observations were as follows, in the order shown in the tables:

Body weight decreased soon after exposure and remained at significantly lower levels until at 9 months, when it returned to normal although the animals had become blind and had severe head ulcerations at this time. Such a decrease in body weight did not occur after 20 Gy.

A two-way analysis of variance of all data on brain weight indicated a significant effect of dose ($p \leq 0.01$) but not of time. Student's t-test demonstrated an effect only at 9 months after 60 Gy. No change in brain weight was found previously (GERBER et coll. 1976) after 20 Gy.

DNA content of the brain increased significantly from 3 to 9 months and again after 2 years, an observation which agrees with the results after 20 Gy.

No significant changes were found in protein content, whereas hydroxyproline (i.e. collagen) increased significantly already 6 months after 60 Gy and 2 years after 20, 30 or 40 Gy. However, an analysis of variance indicated that hydroxyproline was increased for all doses at 3 months and for 30 and 40 Gy after one year ($p < 0.05$).

In agreement with the previous data (GERBER et coll. 1976), sialic acid decreased from one month during most of the postirradiation period, with an intermittent return to normal one year after 30 or 40 Gy.

Sphingosine was reduced from one year after all doses, the slight increase on day one being at the borderline of significance ($p \approx 0.05$).

Total lipid phosphate was not significantly changed, except perhaps after 2 years when an analysis of variance of all doses showed a reduction ($p < 0.03$). Thin layer chromatography of phospholipids also gave no possibility to discern an influence of age or radiation, but the variability of these results is considerable. Fatty acids, as measured by gas chromatography, did not exhibit striking changes after irradiation.

Table

Biochemical parameters in per cent of control in rat brain from 1 day to 2 years after local irradiation with 30, 40 or 60 Gy. Figures in parentheses denote number of animals

Parameter	1 day (15)			2 weeks (10)			1 month (10)			3 months (5)		
	30 Gy	40 Gy	60 Gy	30 Gy	40 Gy	60 Gy	30 Gy	40 Gy	60 Gy	30 Gy	40 Gy	60 Gy
Body weight	92.3	85.3*	87.7*	69.0*	61.4*	65.4*	75.4*	77.1*	71.3*	95.5	86.6*	88.6*
Brain weight	93.4	96.7	98.0	96.9	96.7	90.1	92.2	91.0	95.3	90.2	91.7	89.9
DNA	89.2	91.9	90.4	94.0	99.3	97.0	108.9	110.2	115.0	114.8*	109.9	121.4*
Protein	102.9	93.8	99.5	97.2	101.2	98.7	94.3	102.7	97.7	101.5	95.3	98.8
OH proline	111.0	118.2	114.1	116.9	124.8	121.6	117.5	123.0	123.9	115.6	118.0	119.4
Sialic ac.	104.7	109.5	115.7	96.4	92.1	87.3*	83.9*	91.0	86.0*	89.6*	83.7*	81.3*
Sphingosin	120.7	127.6	122.7	105.0	110.7	107.2	114.7	123.7	122.4	119.0	97.4	112.6
Lipid p.	106.4	107.7	98.9	113.4	112.6	100.7	98.2	105.9	106.8	110.9	108.0	117.6
Peroxide OHR	84.5	68.5*	69.7*	80.0	76.2*	69.0*	63.1*	55.7*	42.6*	104.3	95.8	111.2
Peroxide 2HR	109.1	103.6	77.0	99.8	119.9	94.4	109.1	76.2	70.0	78.7*	86.5*	67.1*
Peroxide 4HR	109.0	82.3*	46.9*	64.9*	86.0	59.7*	78.1	65.8	55.4	99.7	96.9	91.2
Peroxide 4HR + Fe^{++}	83.8	93.4	86.0	77.8	101.9	51.1*	96.0	89.2*	88.2*	93.5	115.0	74.7*
Serotonin	107.5	105.3	93.5	111.2	115.1	135.7*	116.4	122.1*	124.2*	118.9*	132.2*	127.0*
Nordadrenalin	98.2	106.5	121.1	107.4	107.6	113.6	94.0	107.9	110.4	107.1	99.4	100.8
Dopamine	105.4	115.1	114.0	114.8	97.6	114.2	91.4	118.1	104.6	96.0	109.4	147.8*
Histamine	106.0	77.1	87.7	81.9	92.5	86.3	67.1	64.4	64.9	108.3	104.1	108.0
Diamines	121.6	118.3	111.1	124.6	123.1	122.0	94.7	110.1	81.3	113.4	109.5	113.7
Ac. phosph.-tr.	101.4	94.3	90.7	105.1	105.1	110.7	95.0	111.3	96.4	110.4	98.0	80.0
Ac. phosph. + tr-	94.2	100.7	85.4	105.1	96.2	94.8	84.3	96.5	115.6	86.0	87.7	92.9
B-gluc. + tr.	117.5	143.4*	133.2	172.2*	206.4*	174.5*	107.9	134.5*	171.1*	131.6*	117.4*	106.1
B-gluc. + tr.	123.1	141.4*	143.7*	152.4*	165.5*	153.7*	105.4	125.6*	165.9*	106.6	100.8	106.1
Cathepsin	71.9*	81.4*	77.3*	85.7*	46.5*	53.2*	130.8	121.9	129.3*	126.2*	108.6	99.0
AIB brain	87.2*	84.6*	71.5*	86.4	77.2*	59.4*	88.1	71.5*	68.2*	88.7*	62.2*	80.8*
AIB liver	131.6*	135.6*	151.1*	142.7*	155.2*	150.9*	73.8*	66.1*	83.3*	113.7	117.2	116.3
AIB kidney	117.9*	165.1*	181.3*	120.7*	122.9*	130.3*	112.9	94.5	106.4	127.7	130.2*	145.9*
AIB spleen	90.4	93.4	92.4	183.3*	162.4*	137.0	124.1	105.4	120.4	116.2	120.7	122.0
AIB heart	114.5	141.2	139.2	103.6	109.7	106.5	124.5	119.2	118.2	87.6*	79.7*	84.1
AIB muscle	81.7	88.1	113.5	132.0	137.5	135.1	103.1	105.3	110.3	111.6	104.1	154.9*
Microsph. brain	61.8*	69.5*	63.9*	106.8	94.1	51.3*	66.8*	52.9*	72.7*	92.3	111.9	106.7
Microsph. kidney	101.3	119.2	114.6	114.1	107.5	100.3	107.8	111.3	104.2	110.2	97.2	92.0
Microsph. spleen	90.6	62.4*	80.3	130.7	150.0	130.7	123.0	78.8	108.4	111.3	133.8	81.2
FA 16	99.0	106.9	98.5	99.3	100.4	96.5	95.7	90.1	91.6	95.3	119.3	121.2
FA 16-1	74.6	82.5	78.9	120.9	115.0	120.2	112.7	91.1	89.6	115.6	102.3	115.2
FA 18	95.0	95.1	86.4	91.1	88.0	94.5	89.8	84.4*	82.6*	105.8	117.1	111.3
FA 18-1	109.2	99.2	105.3	88.0	90.8	91.0	97.6	82.2*	75.1*	80.5*	86.9	84.8*
FA 18-2	117.6	114.6	114.4	115.7	116.5	117.5	128.6*	124.9*	133.3*	128.5	88.7	81.9
Fa 18-3	115.2	127.9	121.2	90.4	111.2	121.9	119.7	133.0	147.5*	140.0*	91.6	83.1
Fa 20-4	89.3	87.6	89.1	130.2	125.7	117.4	111.5	147.6*	154.0*	116.2	112.0	101.0
Sphingomyel.	93.8	84.0	88.5	108.5	102.6	129.7	98.3	98.7	92.2	96.7	95.9	97.2
P-Cholin	114.8	120.4	113.1	117.1	99.4	115.3	112.0	110.1	114.4	117.7	116.5	111.0
P-serine	95.0	102.9	111.1	112.3	132.9	123.7	94.7	111.4	113.2			
P-eth. amine	98.8	94.5	93.9	86.8	86.1	84.6	84.9	94.3	85.3	118.7	98.2	99.3
Cerebrosides	91.3	86.1	83.6	84.5	103.6	90.8	91.9	87.2	109.7	97.7	120.1	137.3

* Difference statistically significant $p \leq 0.05$.

Table (*cont.*)

6 months (5)			9 months (5)			1 year (5)			2 years (5)			
30 Gy	40 Gy	60 Gy	30 Gy	40 Gy	60 Gy	30 Gy	40 Gy	60 Gy	20 Gy	30 Gy	40 Gy	60 Gy
95.1	93.6	85.9*	93.6	88.6*	85.9*	96.4	94.4	94.4	93.9	105.3	106.4	104.2
98.8	91.0	93.4	97.5	93.2	85.6*	94.4	100.4	98.4	98.6	102.3	94.4	97.3
106.2	113.2	117.8*	109.6	122.8*	118.4*	101.0	106.3	105.0	107.5	103.6	118.5*	122.2*
97.4	94.9	97.4	90.6	93.4	94.0	106.9	100.6	100.4	110.8	100.0	109.4	105.9
128.0	122.4	141.1*	109.7	117.5	131.1*	112.6	119.1	128.5*	132.2*	122.4*	136.4*	129.0*
89.6*	81.5*	75.9*	86.1*	78.4*	83.9*	95.7	92.4	73.8*	87.4*	86.7	82.6*	81.3*
103.8	95.1	83.3	119.0	97.7	92.7	79.4*	85.4*	80.0*	74.1*	87.1*	82.4*	77.7*
96.9	97.3	108.7	106.7	100.0	90.3	103.4	98.1	101.3	106.5	90.0	97.7	91.6
108.3	117.1	119.0	108.3	128.6*	129.0*	91.4	145.1*	153.7*	85.5	127.3	103.4	108.6
105.4	111.8	125.4	104.4	111.1	124.2*	80.8	104.4	92.6	87.4	101.7	82.9	96.4
96.8	100.0	111.5	96.1	99.6	110.6	93.0	101.3	96.5	95.8	97.1	85.0	96.1
85.7	87.0	90.5	79.4*	80.4*	84.1*	70.5*	71.9*	57.0*	87.1	95.1	87.2	98.2
125.6*	133.7*	163.6*	130.9*	125.0*	141.6*	98.2	88.0	89.4	97.8	105.1	107.7	114.9
110.2	99.1	91.9	93.4	96.9	113.6	102.6	106.3	93.1	76.4*	90.2	83.3*	97.6
102.1	87.3	98.8	91.4	92.5	112.9	105.5	116.6	126.1	106.8	138.7*	133.3*	122.0
79.6	77.8	83.5	85.9	101.5	119.0	107.6	85.2	88.1	117.8	108.5	122.6	112.7
104.5	116.2	87.2	103.1	126.8	116.2	107.4	93.8	94.2	94.2	122.2	103.9	131.7
98.0	115.8	113.8	84.6	99.0	111.7	105.0	88.6	107.5	94.1	114.2	113.9	155.3*
119.7	106.5	94.0	83.4	92.1	116.5	82.1	90.6	87.6	97.0	124.2	140.9*	150.0*
142.3*	179.4*	132.0*	108.2	113.7	158.4*	97.6	88.0	88.8	89.6	101.9	102.0	108.3
121.6	114.1	104.7	119.4	129.0*	118.9	110.8	105.7	119.4	94.4	85.1	88.1	88.3
120.5	119.6	113.0	117.8	137.1*	153.1*	130.5*	107.7	114.2	112.3	140.8*	146.1*	129.5*
119.9	127.1*	149.6*	109.3	118.2	125.0*	85.0*	100.6	129.0*	96.4	106.0	111.1	119.4
130.7*	144.1*	151.4*	126.2	123.4	117.1	87.1	83.8	90.8	60.1*	89.1*	78.4*	80.9*
128.2	117.3	89.4	131.2	116.5	128.0	110.5	103.2	108.8	100.1	107.7	106.6	116.2
103.5	92.2	98	105.6	102.6	76.1	111.7	117.3	125.0		89.1	98.4	90.5
88.5	81.5*	77.0*	121.1	112.9	115.7	80.7	79.0*	82.5*	109.0	89.5	101.2	94.1
113.7	122.4	124.4	96.8	100.8	71.3	115.5	112.3	121.1	87.0	83.5	81.3	82.0
120.1	134.2*	131.3*	106.8	120.5*	132.1*	143.3*	154.6*	180.0*	109.1	116.8	131.4*	93.6
117.2	109.3	87.3	95.8	88.1	93.0	104.2	96.3	105.3	121.5	106.4	98.3	125.8
78.6	74.9	70.4	88.7	89.9	92.8	80.8	72.1	118.6	117	102.5	107.6	72.9
100.8	99.2	101.4	104.3	115.6	115.0	90.0	86.6	92.0	94.4	109.1	113.6	111.2
89.7	71.7	87.7	94.7	96.6	100.5	93.5	110.8	125.4	118.7	115.1	82.4	104.1
101.9	99.3	100.4	97.8	101.9	88.9	100.8	99.5	86.7	101.4	112.0	93.6	105.0
95.5	95.7	98.5	89.0	78.5*	85.1	97.7	99.5	105.0	96.4	106.0	110.5	102.2
137.7	120.3	100.2	67.9	87.6	105.1	124.2	122.4	103.4	116.2	89.6	79.9	81.2
95.0	78.2	88.9	89.2	87.3	82.8	104.0	94.6	91.6	80.5	85.7	102.8	93.5
89.9	99.5	107.8	86.9	89.2	101.5	110.9	121.8	116.4	113.5	101.5	112.5	99.5
94.9	101.8	97.5				84.1	109.3	91.3	80.0	106.3	95.1	86.0
106.8	115.4	114.0	87.3	104.7	94.7	110.2	92.5	88.7	92.2	100.4	88.2	94.1
75.0	90.5	89.6				96.5	97.9	83.7	127.0	96.4	102.9	94.4
105.4	91.7	93.6	127.8	116.0	92.2	86.7	109.5	99.6	124.5	96.4	99.0	113.0
89.5	86.9	95.1	103.5	94.3	113.3	142.0	132.3	154.4*	89.2	94.4	105.4	95.7

After 1 and 3 months oleic acid was decreased (after one month also stearic acid) in favor of the more unsaturated fatty acids.

Early after exposure, a decrease in preformed peroxides (to one month) and in peroxidation (to 3 months) was discernible. Nine and 12 months after exposure, peroxides were increased and peroxidation was reduced.

Serotonin content in the brain was enhanced beginning from 2 weeks for the highest dose and from 3 months after 30 Gy and ending at 9 months, an observation which agrees with previous findings. Noradrenalin diminished slightly after 2 years. Dopamine increased 3 months after 60 Gy and again 2 years after nearly all doses. Histamine was reduced at 2 weeks and 1 month ($p \approx 0.03$) when all doses were considered together but the variability of histamine determination is rather large. No difference was found with respect to diamines.

Acid phosphatase activity was enhanced after 2 years, but in contrast to the previous observations no increase was found during the early period. β-glucuronidase was activated until 6 months after exposure, whereas cathepsin was reduced until 2 weeks and increased during the rest of the postirradiation period. Only a shortlasting raise in cathepsin after 1 month was noted in previous experiments.

Uptake of alpha aminoisobutyrate (AIB) by the brain was depressed until 3 months, then rose above normal and returned to normal or below normal at one year. After 20 Gy, AIB uptake by the brain was enhanced at day one, and again at 6 and 9 months and reduced at 12 and 18 months. AIB uptake by the liver was increased at 1 and 14 days, diminished at one month and rose again at 6 months. After 2 years, AIB uptake by the liver was greatly reduced. A similar late reduction but starting already at one year was found after 20 Gy. Uptake in the kidney increased similarly to that in the liver but apparently no reduction occurred, whereas that by the spleen was increased after 2 weeks. As in the previous experiments, AIB uptake by the heart was reduced from 3 to 6 months and again after one year. The depression in AIB uptake by muscle observed 1 to 5 months after 20 Gy did not occur in the present experiments with higher doses: instead uptake increased 3 months after 60 Gy. At 2 years, AIB uptake by muscle was found to be significantly reduced when an analysis of variance was carried out for all doses ($p \approx 0.02$).

Blood flow in the brain was diminished from 1 to 30 days after exposure, particularly after higher doses. Later on, it increased significantly to one year and for 40 Gy even to 2 years. Blood flow in the kidney was not affected by irradiation, that in the spleen appeared to be reduced after one day and enhanced after 2 weeks, but the variability of the splenic blood flow was large.

Discussion

The question whether the vascular system, the glia or the nervous structures are the target for late effects in the central nervous system is still debated, but many investigators incline to give the primacy to vascular effects and consider others as secondary at least for doses not exceeding 30 Gy. The general appearance of late

effects in the brain was reviewed in the previous report (GERBER et coll. 1976); recent articles have dealt with brain pathology (WHITE 1975) and the sequelae of radiation therapy (RUBINSTEIN 1972, KRAMER & LEE 1974, FRANKE & LIERSE 1978). In a general manner three phases can be distinguished after local irradiation of the CNS with doses of about 10 Gy; (a) an early one characterized by changes in the blood brain barrier, edema and metabolic disturbances and lasting a few days to about 2 weeks, (b) an intermediate one lasting a few months where clinical symptoms are not apparent but changes in metabolism (lysosomal enzymes, biogenic amines), in blood flow and in brain morphology (beginning demyelisation, vascular injuries and changes in glia population) are detectable, and (c) a late one beginning 6 to 18 months after exposure during which symptoms in man appear and vascular abnormalities, necrosis and glial fibrosis are found.

Most likely the late effects in the brain of the animal model used, i.e. the upper part of the rat brain, follow the same mechanism of action as those after irradiation of man, but a direct extrapolation of doses is not feasible. Indeed, rats seem to withstand surprisingly well the high doses of radiation which were utilized in the present experiments and which could cause grave brain damage in man. Profound ulcerations often involving the cranium and cataract appear a few months after 40 or 60 Gy; yet brain weight and body weight as well as survival are but little affected. The experiments carried out in Rijswijk and Oxford yielded, however, a shorter survival (12 months after 30 Gy). Apparently greater areas of sensitive midbrain regions had been included in the radiation field at these centres. Nevertheless, it appears from some experiments with 20 Gy where animals irradiated at Rijswijk had been assayed that the general biochemical changes are the same (GERBER et coll. 1976). In general, the biochemical changes occurring after 30, 40 and 60 Gy resemble those found previously after 20 Gy (GERBER et coll. 1976), but they often arise earlier and are more severe although the differences between 20 and 60 Gy are not always as great as one would have expected. During the early and intermediate period, an increase in DNA content and in lysosomal enzymes (but not of acid phosphatase) was again observed. Most striking are the augmentation in serotonin which after 60 Gy occurs as early as at 2 weeks, the permanent increase in cathepsin D, and the early temporary reduction in blood flow and AIB uptake by the brain. Both uptake of AIB and blood flow increase during the intermediary period and fibrosis (collagen) becomes visible after high doses at this time. As in the early investigation, few characteristic biochemical changes occur during the late phase: collagen and cathepsin are increased and blood flow is normal whereas noradrenalin is reduced. From the changes observed it is not yet possible to pinpoint the mechanism of action of late effects in the brain unequivocally, since they suggest the participation of glial cells (? lysosomal enzymes, sialic acid), nerve cells (biogenic amines) and vascular system (blood flow, AIB uptake). The early reduction in flow has also been confirmed by a diffusion technique using antipyrine (HOPEWELL, personal communication) and the intermediate increase was, in addition, observed by an in vivo isotopic

method (KEYEUX 1974, personal communication). The capillary distribution in the cortex is altered from 6 months to one year, depending on the dose, and vascular lesions involving enlargement and tortuosity of capillaries particularly near the corona radiata (REINHOLD, personal communication) become visible. Nevertheless, blood flow as measured by microspheres remains normal or is even elevated at late times.

However, it would be desirable to combine the different procedures to examine in the same animal angioarchitecture, in vivo blood flow and distribution of microspheres.

In contrast to non dividing nerve cells glia cells are renewed slowly. Mitotic activity of the subependymal plate which supplies glia cells for lower brain areas is reduced temporarily after 20 Gy and permanently after higher doses (CAVANACH & HOPEWELL 1972, CALVO, personal communication). Moreover, microglia is diminished and the ratio of astrocytes to oligodendroglia is increased from 1 month after doses as low as 5 Gy (REYNERS, personal communication).

Death of nerve cells within a short term after irradiation is only observed in the granular layer of the cerebellum (SAMORAJSKI et coll. 1968, ALTMAN & NICHOLSON 1971, BRIZZEE 1973) but abnormal mitochondria in the cortex have been found after high level irradiation at much later times (SAMORAJSKI 1975). Detailed morphometric analysis will be required to decide whether the nerve cell population in the cortex is affected late after irradiation. The changes observed in biogenic amines, particularly the increase in serotonin, suggest an altered neural activity but its site in the CNS and its meaning for the organism remain obscure. Information on the behaviour of biogenic amines during late periods after irradiation is scanty, although early periods up to a few days have often been examined (cf. Table 4 in ADOLFSSON et coll. 1976, and review, GERBER & ALTMAN 1970) and although a relation between the effects of radiation on biogenic amines and those on brain structure has been suggested (PAUCESCU et coll. 1973). ORDY et coll. (1968) observed a decreased serotonin in the rat brain 16 months after 10 kR, i.e. after a much higher dose than used here. HSU et coll. (1971) reported a decrease in noradrenalin in the monkey brain 6 months after 10 Gy of protons, and HSU & SAMORAJSKI (1974) found increased tyrosine hydroxylase in the mouse brain one year after 100 Gy or more of deuterons, whereas ADOLFSSON et coll. were unable to detect changes in 5 hydroxyindolacetate and homovanillinic acid in the rabbit brain 6 months after 20 to 30 Gy of roentgen rays. Histochemical techniques in conjunction with metabolic analyses should be able to elucidate whether the changes in serotonin are due to particular alterations in metabolism or whether they are confined to brain areas which also display abnormalities in their glia or vascular system.

In conclusion, further investigations are needed to elucidate the interplay of the different systems in the pathogenesis of late radiation effects in the brain, but the present data suggest that already at an early period, glia, nerve cells as well as the vascular system exhibit alterations in their function.

SUMMARY

Rat brain was exposed to 30, 40 or 60 Gy of roentgen rays and different biochemical and physiologic parameters were assayed from one day to 2 years. The most important changes noted were an intermediate increase in DNA, an intermediate to late—dependent on dose—increase in collagen, a decrease in sialic acid, an early to intermediate increase in serotonin, an increase in cathepsin, an early depression, and intermediate enhancement and a late decrease in alpha amino isobutyrate uptake by brain, and an early reduction, an intermediate—and sometimes late—increase in blood flow. These changes suggest that all three principal systems in the brain, nerve cells, glia and vascular system, participate in late changes.

ZUSAMMENFASSUNG

Das Rattengehirn wurde mit 30, 40 oder 60 Gy Röntgen bestrahlt und verschiedene biochemische und physiologische Parameter wurden von einem Tag bis zu 2 Jahren nach Bestrahlung bestimmt. Die wichtigsten Veränderungen waren: Eine Zunahme der DNS von 3–9 Monaten, eine Zunahme von Collagen je nach Dosis von 6 Monaten bis 2 Jahren, eine Abnahme der Neuraminsäure, eine Zunahme des Serotonin je nach Dosis von 2 Wochen (3 Monaten) bis 9 Monaten, eine Zunahme des Cathepsins, eine verminderte Aufnahme der alpha Aminoisobuttersäure bis 3 Monate gefolgt von einer Zunahme bis zu 9 Monaten und einer neuerlichen Abnahme und eine Abnahme des Blutflusses bis 1 Monat, gefolgt von einer Zunahme bis zu einem Jahr. Diese Veränderungen lassen vermuten, dass alle drei hauptsächlichen Systeme des Gehirns, Nervenzellen, Glia und Zirkulation bei den späten Veränderungen beteiligt sind.

RÉSUMÉ

Le cerveau de rat a été exposé à 30, 40 ou 60 Gy de rayons de Röntgen et différents paramètres biochimiques et physiologiques ont été déterminés d'un jour à 2 ans. Les plus importants changements notés sont une augmentation en DNA de 3 à 9 mois, une augmentation en collagène de 6 à 24 mois — dépendante de la dose —, une diminution en acide sialique, une augmentation en sérotonine de 3 à 9 mois, une augmentation en cathepsine, une diminution à 3 mois suivie d'une augmentation à 9 mois et d'une diminution tardive en prélèvement d'alpha amino isobutyrate par le cerveau, une réduction à 1 mois suivie d'une augmentation jusque 1 an du flux sanguin. Ces changements suggèrent que les trois principaux systèmes du cerveau, cellules nerveuses, glie et système vasculaire participent aux changements tardifs.

REFERENCES

ADOLFSSON R., GOTTFRIES C. G., HASSLER O., ROOS B. E. and WINBLAD B.: Late effects on brain morphology and monoamine metabolites produced by ^{60}Co irradiation. Acta radiol. Ther. Phys. Biol. 15 (1976), 433.

ALTMAN J. and NICHOLSON J. L.: Cell pyknosis in the cerebellar cortex of infant rats following low-level X-irradiation. Radiat. Res. 46 (1971), 476.

BRIZZEE K. R.: Quantitative histological studies on aging changes in cerebral cortex of Rhesus monkey and albino rat with notes on effects of prolonged low-dose ionizing irradiation in the rat. Progr. Brain Res. 40 (1973), 141.

CAVANACH J. B. and HOPEWELL J. W.: Mitotic activity in the subependymal plate of rats and the longterm consequences of X-irradiation. J. neurol. Sci. 15 (1972), 471.

FRANKE H. D. und LIERSE W.: Strahlenbedingte Reaktionen des Gehirns und des Rückenmarks. Strahlentherapie 154 (1978), 587.

GERBER G. B. and ALTMAN K. I.: Radiation biochemistry, pp. 223, 308. Academic Press, New York 1970.

— MAES J., GILLIAVOD N. and CASALE G.: Brain biochemistry of infant mice and rats exposed to lead. Toxicology Letters 2 (1978), 51.

— DEROO J., BESSEMANS B., REINHOLD H. S. and VERWEY-VERSTEEG A. A. C.: Late effects in the central nervous system. A study of biochemical alterations after local exposure of the rat brain to 2 krad. Strahlentherapie 151 (1976), 530.

HOPEWELL J. W., REINHOLD H. S., WILKINSON J. and BLACKIEWICZ B.: Changes in the architecture of blood vessels in the rat brain after local irradiation. Brit. J. Radiol. 51 (1978), 561.

HSU L. L. and SAMORAJSKI I.: Irradiation of mouse brain: Effects on incorporation of Tyrosine-^{14}C into catecholamines in vivo and on uptake of NE-^{14}C by brain slices in vitro. Neurobiology 4 (1974), 419.

— ORDY J. M., BOSE H. and CURTIS H. J.: Regional changes in brain catecholamines after proton irradiation of the striate cortex in the squirrel monkey. J. Neurochem. 18 (1971), 1719.

KRAMER S. and LEE K. S.: Complications of radiation therapy. *In:* The central nervous system. Sem. Roentgengenol. Ser. 9, p. 75. Grune Stratton, New York 1974.

KEYEUX A.: Blood flow and permeability in the central nervous system. Curr. Topics radiat. Res. Quart. 10 (1974), 135.

ORDY J. M., SAMORAJSKI T., HORROCKS L. A., ZEMAN W. and CURTIS H. J.: Changes in memory, electrophysiology, neurochemistry and neuronal ultrastructure after deutron irradiation of the brain in C57Bl/10 mice. J. Neurochem. 15 (1968), 1245.

PAUSESCU E., CHIRVASIE R., TEODOSIU T., LUGOJAN R. and MUBTIU M.: Early effects of ^{60}Co gamma-radiation on cerebral catecholamines, serotonin and related compounds. Strahlentherapie 145 (1973), 76.

RUBINSTEIN L. J.: Tumors of the central nervous system. Armed Forces Inst. Path. 2nd series, part 6, p. 350. Washington D.C. 1972.

SAMORAJSKI T.: Late ultrastructural changes in neuronal mitochondria after ionizing radiation of the brain. J. comp. Neurol. 161 (1975), 255.

— ROLSTEN C. and CURTIS H. J.: Changes in neurochemistry and neuronal morphology after exposure of the mouse brain to lethal levels of focal irradiation. Anat. Rec. 168 (1970), 203.

— ORDY J. M., ZEMAN W. and CURTIS H. J.: Early and long-term effects of deuteron irradiation on cells in the cerebellum of adult mice. J. Cell Biol. 38 (1968), 213.

WHITE D. C.: An atlas of radiation histopathology. TID 26676. Oak Ridge, Tennessee 1975.