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Local cerebral glucose utilisation following acute and chronic bilateral carotid artery ligation in Wistar rats: relation to changes in local cerebral blood flow

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Abstract. The effects on local cerebral blood flow (LCBF) and glucose utilisation (LCGU) of permanent, bilateral carotid artery ligation (BCAL) were studied in conscious Wistar rats. LCBF and LCGU were measured using quantitative autoradiographic ^{14}C-iodoantipyrine and the ^{14}C-2-deoxyglucose (^{14}C-DG) techniques in 24 anatomically discrete regions of the brain. LCBF in the cerebral hemispheres 2.5 h (acute) after BCAL significantly decreased to 25–87% of the sham control, with the exception of the mammillary body. After acute BCAL, there was a heterogeneous accumulation of ^{14}C-DG in the caudate nucleus and cerebral cortices. Only in the lateral geniculate body did LCGU significantly decrease after BCAL. One week (chronic) later, LCBF was significantly decreased in 15 (containing the caudate nucleus and all the cerebral cortices) of 24 structures. LCGU in ten (containing the caudate nucleus and all the cerebral cortices) of 24 structures after chronic BCAL significantly decreased to 66–77% of the sham control, except for regions with neuronal damage in which there was a heterogeneous uptake of ^{14}C-DG. The ratio of LCBF/LCGU in chronic BCAL was unchanged in comparison with values in the corresponding sham-operated group. This model of acute and chronic cerebral ischaemia, with impairment in cerebral circulation and/or glucose metabolism, is expected to become a pertinent tool for the neurophysiologist.

Key words: Cerebral ischaemia – Bilateral carotid artery ligation – Local cerebral blood flow – Local cerebral glucose utilisation – Rats

Introduction

Cerebral blood flow and energy states after bilateral carotid artery ligation (BCAL) in Wistar rats have been reported (Eklöf and Siesjö 1972, 1973; Fujishima et al. 1976, 1981; Choki et al. 1977; Umemura et al. 1982); all of these studies were carried out on anaesthetised animals and almost all the investigations were carried out under conditions of acute BCAL.

We have reported on cerebral blood flow and histopathological changes (including selective neuronal damage in the caudate nucleus) following permanent BCAL in Wistar rats (Tsuchiya et al. 1992). In several brain structures there was little or no evidence of neuronal death, even though the decrease in blood flow was similar to that seen in the caudate nucleus. Therefore, selective neuronal damage in the caudate nucleus cannot be explained on the basis of blood flow rate alone. To our knowledge, there is no documentation of local cerebral glucose utilisation (LCGU) following permanent BCAL. In ongoing studies, we noted that LCGU in the caudate nucleus 1 week after permanent BCAL in Wistar rats was significantly lower than that in sham controls. We then investigated LCGU changes after acute and chronic BCAL in relation to residual blood flow in conscious Wistar rats, using ^{14}C-iodoantipyrine (^{14}C–IAP) autoradiography (Sakurada et al. 1978) and the ^{14}C–2-deoxyglucose (^{14}C–DG) technique (Sokoloff et al. 1977).

Materials and methods

Animals and physiological variables

Male Wistar rats (150–270 g; Clea Japan Inc., Tokyo, Japan), were deprived of solid food, but drinking water was given ad lib for 16–20 h. During all surgical procedures, body temperature was kept at around 37° C with a heating lamp. Prior to the LCGU and local cerebral blood flow (LCBF) studies, mean arterial blood pressure(MABP), PaO_2, $PaCO_2$, arterial pH, haematocrit and plasma glucose concentration were checked.

Experimental procedures

Series 1. This series of experiments was undertaken to investigate the LCBF or LCGU 2.5 h after BCAL. Four groups of five to six

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rats each were studied; a BCAL group with LCBF at 2.5 h, a sham group with LCBF at 2.5 h, a BCAL group with LCGU at 2.5 h and a sham group with LCGU at 2.5 h. These rats were anaesthetised with 1.5–2.0% halothane during cannulation of the right femoral artery and vein, and during ligation of the bilateral carotid artery. Both common carotid arteries were exposed through a ventral, midline cervical incision, separated from the vagosympathetic trunks and doubly ligated. In the sham controls, BCAL was not done. After BCAL, the anaesthesia was discontinued and 2.5 h was allowed to elapse before start of the LCBF or LCGU measurements. These rats were partially restrained by a loose-fitting abdominal-pelvic plaster cast and were taped to lead bricks for support.

Series 2. This series of experiments was performed to investigate the LCBF or LCGU 1 week after BCAL. Four groups of five to seven rats each were studied; a BCAL group with LCBF at 1 week, a sham group with LCBF at 1 week, a BCAL group with LCGU at 1 week and a sham group with LCGU at 1 week. In all of these rats, the bilateral carotid artery was ligated by the method described above. After BCAL the rats were left to recover from anaesthesia and 1 week later, under light halothane anaesthesia, polyethylene catheters were placed in the right femoral artery and vein. After this cannulation, the anaesthesia was discontinued and at least 2 h was allowed to elapse before the start of the LCBF or LCGU measurements. These rats were partially restrained by the method described above.

Determination of LCBF

LCBF was measured using the ^{14}C–IAP method (Sakurada et al. 1978). To measure LCBF, 25 μCi of ^{14}C–IAP in 1 ml of saline was administered intravenously within 1 min at a constant rate of infusion. Arterial blood samples were collected to measure the concentration of ^{14}C–IAP. At termination of infusion of the tracer, the rats were decapitated and the brains were quickly dissected out and placed in Freon (−40° C), then coronally sectioned (20 μm thick) in a cryostat (−25° C). Autoradiographs were prepared by exposing the brain sections with five precalibrated methacrylic standards (concentration range 96–1675 nCi/g) to X-ray films (Kodak SB–5) in X-ray cassettes for 1 week. Analysis of the resultant images on the X-ray film was made using a computer-based densitometer with an epidiascope and a video display unit (Unigraphy UHG–101, Unique Medical Co., Tokyo, Japan), with reference to the precalibrated standards. ^{14}C–IAP concentrations in whole blood were measured using a Beckman LS 9000 liquid scintillation counter (Beckman Instruments Inc., Fullerton, CA, USA). The cerebral tissue blood partition coefficient used for IAP was 0.8 (Sakurada et al. 1978). Blood flow of each structure was taken as the average of the whole structure. Brain sections used for the measurement of LCBF were stained with haematoxylin and eosin to examine the histopathological changes. LCBF was measured in 24 anatomically discrete regions of the right and left hemispheres, and the mean LCBF of both hemispheres was calculated. LCBF in the area of neuronal damage was measured separately. LCBF of the BCAL-operated groups was compared with values in the corresponding sham-operated group.

Determination of LCGU

LCGU was measured using the ^{14}C–DG technique (Sokoloff et al. 1977). The isotope (25 μCi per rat), dissolved in saline, was given over 15 s. A total of 12 timed samples of arterial blood were withdrawn from the femoral cannula and collected into heparinised, plastic centrifuge tubes over the subsequent 45 min. The volume of the arterial samples was about 100 μl of whole blood: this same volume was replaced by saline solution. The arterial blood plasma was separated by centrifugation within a few minutes of withdrawal. The plasma sample was stored on ice until assay for ^{14}C–DG and glucose concentrations. ^{14}C–DG concentrations in plasma were measured using the liquid scintillation counter. The glucose level was determined by means of a glucose analyser (Seralyzer, Miles Laboratories Inc., USA). At the end of 45 min, the animals were decapitated and the brains were processed for quantitative autoradiography, in the same manner as for the measurement of LCBF. LCGU was calculated from the time course of ^{14}C–DG in the arterial plasma and for the ^{14}C concentration in the cerebral tissue; the equation described by Sokoloff et al. (1977) was used.

Statistical analysis

All data are presented as means ± SD of five to twelve rats. For comparison between the sham- and BCAL-operated groups, Student's *t*-test was used. A P value of <0.05 was considered to have a statistical significance.

Results

Physiological parameters after BCAL

Table 1 shows physiological parameters in the sham- and BCAL-operated groups. At 2.5 h after BCAL, $PaCO_2$ significantly decreased, and PaO_2 significantly increased compared to the sham control. After one week, PaO_2 and

Table 1. Physiological status of Wistar rats in which local cerebral blood flow and local cerebral glucose utilisation were determined

	Physiological variables					
	MABP (mmHg)	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	Haematocrit (%)	pH	Plasma glucose (mg/dl)
2.5 h after BCAL						
Sham ($n=11$)	123 ± 7	86 ± 4	31 ± 2	51 ± 2	7.40 ± 0.03	104 ± 18
BCAL ($n=11$)	128 ± 7	101 ± 5**	26 ± 4**	49 ± 3	7.42 ± 0.03	97 ± 14
1 week after BCAL						
Sham ($n=10$)	122 ± 4	87 ± 5	31 ± 2	50 ± 2	7.40 ± 0.02	96 ± 18
BCAL ($n=12$)	124 ± 6	97 ± 11*	32 ± 3	51 ± 3	7.38 ± 0.04	123 ± 26*

Data are means ± SD and represent the levels measured immediately prior to the measurement
BCAL, bilateral carotid artery ligation
Significant differences from the corresponding sham group: * $P<0.05$, ** $P<0.01$ (Student's *t*-test)

Table 2. Effect of BCAL on local cerebral blood flow in conscious Wistar rats

Structures	Local cerebral blood flow (ml/100 g/min)			
	2.5 h after BCAL		1 week after BCAL	
	Sham ($n=6$)	BCAL ($n=6$)	Sham ($n=5$)	BCAL ($n=7$)
Cortical regions				
Visual	149 ± 17	58 ± 15**	133 ± 16	95 ± 31*
Auditory	210 ± 20	53 ± 11**	213 ± 23	116 ± 35**
Parietal	212 ± 22	65 ± 9**	211 ± 24	128 ± 27**
Sensorimotor	191 ± 17	75 ± 13**	173 ± 15	124 ± 31**
Olfactory	170 ± 22	62 ± 10**	164 ± 14	115 ± 31**
Frontal	185 ± 28	69 ± 9**	168 ± 21	125 ± 32*
Subcortical regions				
Thalamus				
Lateral nucleus	154 ± 11	77 ± 10**	141 ± 17	114 ± 21*
Medial nucleus	169 ± 19	83 ± 7**	139 ± 24	130 ± 20
Ventral nucleus	147 ± 13	85 ± 10**	135 ± 25	116 ± 14
Habenula	177 ± 24	100 ± 5**	146 ± 27	138 ± 21
Medial geniculate body	185 ± 27	101 ± 6**	163 ± 25	155 ± 31
Lateral geniculate body	150 ± 17	62 ± 6**	119 ± 12	77 ± 8**
Hypothalamus	83 ± 6	51 ± 5**	80 ± 7	73 ± 4
Mammillary body	198 ± 41	201 ± 32	175 ± 31	202 ± 40
Hippocampus				
Ammon's horn	118 ± 18	61 ± 8**	108 ± 10	85 ± 16*
Dentate gyrus	108 ± 15	57 ± 7**	98 ± 7	80 ± 15*
Amygdala	82 ± 2	42 ± 5**	77 ± 4	65 ± 9**
Septal nucleus	84 ± 6	50 ± 6**	89 ± 4	65 ± 11**
Caudate nucleus	145 ± 12	61 ± 9**	133 ± 15	86 ± 27**
Nucleus accumbens	166 ± 31	74 ± 12**	154 ± 28	123 ± 23
Globus pallidus	59 ± 4	42 ± 4**	59 ± 3	54 ± 4*
Substantia nigra	79 ± 3	69 ± 8*	69 ± 8	75 ± 5
White matter				
Corpus callosum	41 ± 5	21 ± 3**	42 ± 3	30 ± 4**
Internal capsule	38 ± 3	23 ± 4**	37 ± 7	30 ± 5

Data are means ± SD
Significant differences from the corresponding sham group: * $P<0.05$, ** $P<0.01$ (Student's t-test)

plasma glucose concentration significantly increased to 111% and 128% of the sham control, respectively. There were no differences in MABP, haematocrit and arterial pH between the sham- and BCAL-operated groups.

LCBF after BCAL

Table 2 summarises mean LCBF values in the sham- and BCAL-operated groups. At 2.5 h after BCAL, the LCBF significantly decreased to 25–87% of the sham control in 23 of the 24 anatomically discrete regions. LCBF in the structures of heterogeneous accumulation of the tracer in ^{14}C–DG autoradiograph (Fig. 1) revealed a reduction of over 58% in relation to the sham control. Permanent BCAL for 1 week decreased LCBF significantly in 15 of the 24 anatomically discrete regions. There were reductions of over 20% of the sham control values in the six cerebral cortices, lateral geniculate body, hippocampus, septal nucleus, caudate nucleus and the corpus callosum. Blood flow in the area of neuronal damage in the caudate nucleus after chronic BCAL was 51 ± 16 (Mean ± SD of nine hemispheres in seven rats) ml/100 g per minute. Blood flow in the area of neuronal damage in the caudate nucleus was significantly lower ($P<0.01$) than that in the unimpaired area after chronic BCAL.

^{14}C–DG autoradiograph and LCGU after BCAL

Representative ^{14}C–DG autoradiographs from the rat with acute BCAL are shown in Fig. 1. In the cerebral cortex, there were alternating high and dark columns of radioactivity and a disappearance of the high accumulation band of tracer in layer 4. A pattern of small patches of high accumulation of ^{14}C–DG against a background of low accumulation was noted throughout the caudate nucleus. Heterogeneous uptake of the tracer was not seen in other subcortical structures. A total of 17 regions with heterogeneous accumulation of the tracer were present in all five rats; the location was unilateral in the neocortex of three animals, bilateral in the caudate nucleus of five, and bilateral in the neocortex of two. ^{14}C–DG autoradiographs obtained one week after BCAL showed a

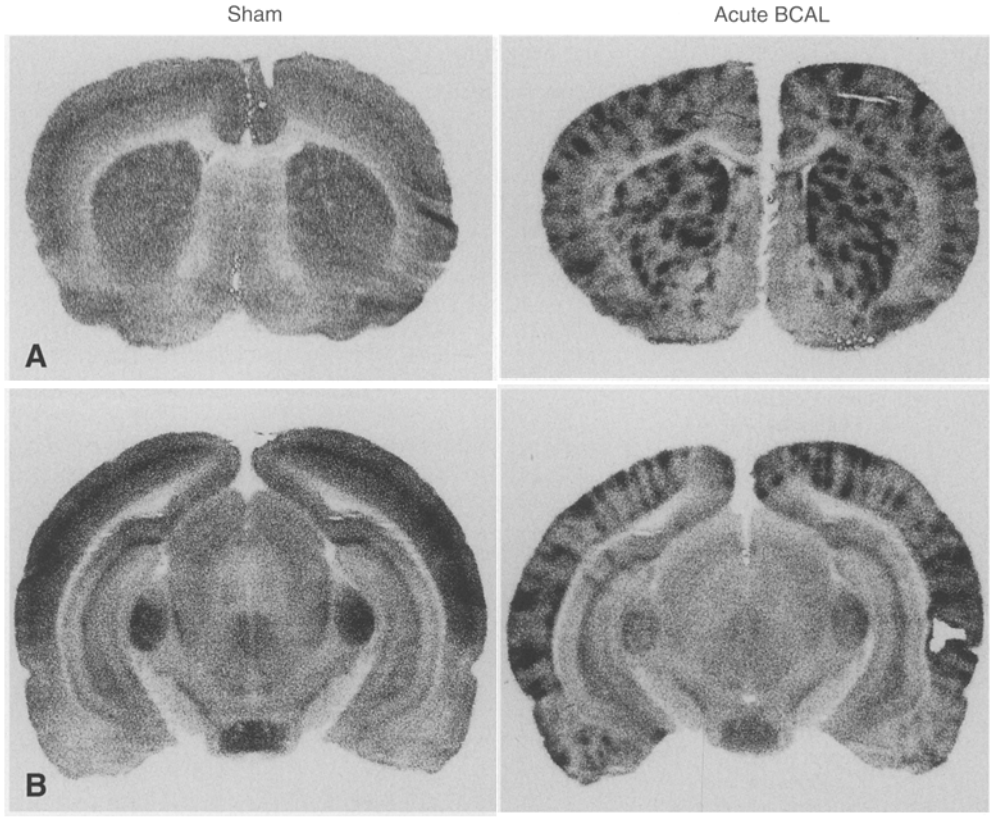

Fig. 1A, B. ^{14}C–2-Deoxyglucose autoradiograms after acute bilateral carotid artery ligation (*BCAL*). **A** Section of sensorimotor cortex; **B** section of medial geniculate body. There was heterogeneous uptake of the tracer in the cerebral cortex and caudate nucleus

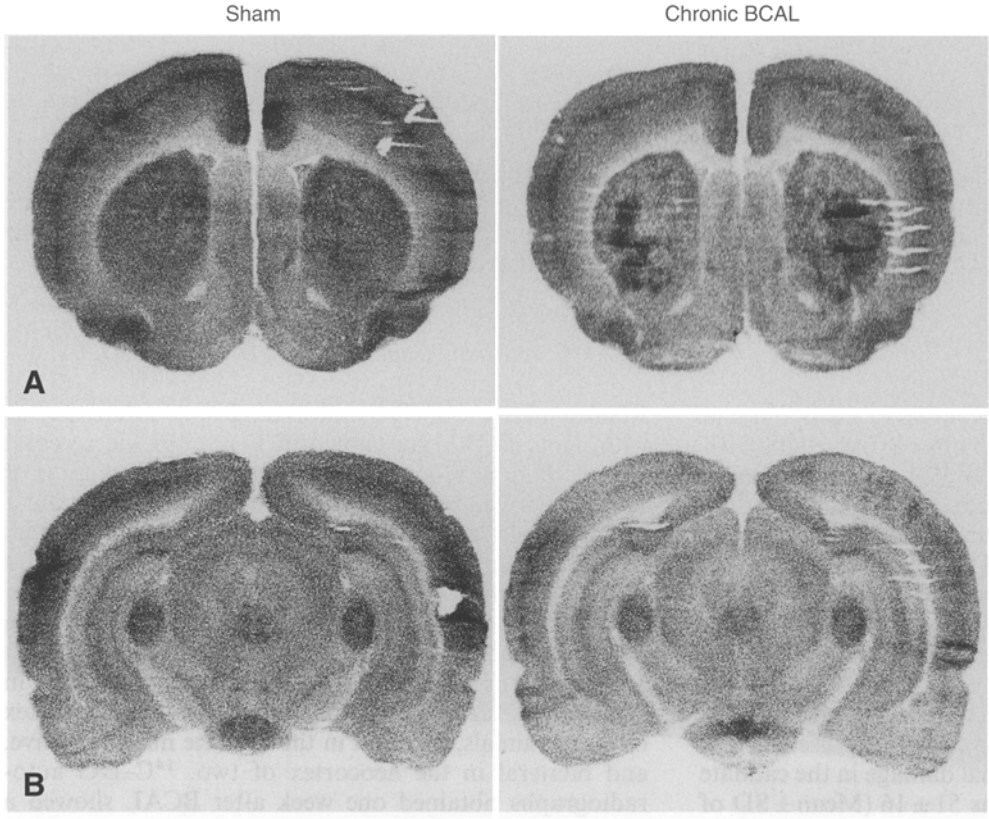

Fig. 2A, B. ^{14}C–2-Deoxyglucose autoradiograms after chronic BCAL. **A** Section of sensorimotor cortex; **B** section of medial geniculate body. Note the decrease in optical density in the cerebral cortex and caudate nucleus

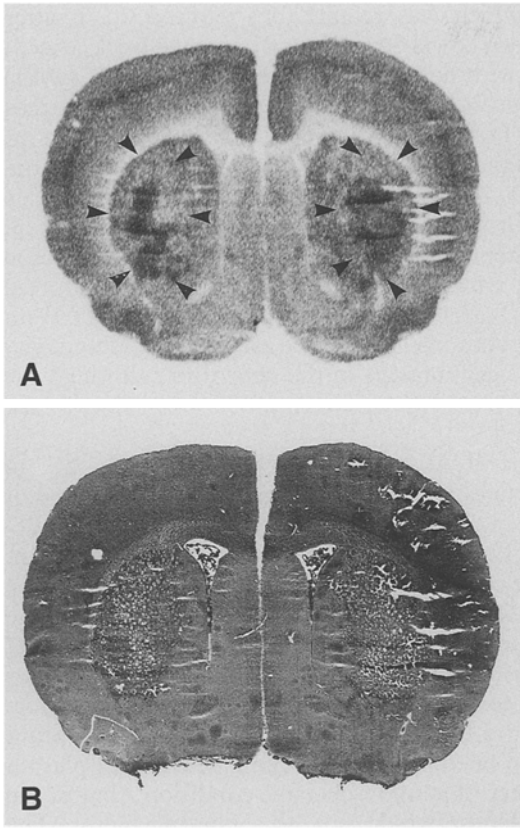

Fig. 3. A Representative ^{14}C–2-deoxyglucose autoradiogram and **B** histopathological change (haematoxylin and eosin stain) in the caudate nucleus after chronic BCAL in the same rat. The zone of the lesion epicentre with focal infarction is confined to dorsolateral neurons of the caudate nucleus

heterogeneous accumulation of the tracer in the area with neuronal damage (Figs. 2, 3).

Table 3 shows mean LCGU values in the sham- and BCAL-operated groups. LCGU in structures with a heterogeneous uptake of ^{14}C–DG (i.e. caudate nucleus and all the cerebral cortices after acute BCAL) could not be taken as the average for that structure. Permanent BCAL for 2.5 h significantly decreased LCGU in only the lateral geniculate body. At 1 week after BCAL, the LCGU significantly decreased to 66–77% of the sham control in ten of 24 anatomically discrete regions studied. LCGU reductions of over 20% of the sham control values were evident in six cerebral cortices, lateral nucleus of thalamus, lateral geniculate body, caudate nucleus and corpus callosum. LCGU in regions with neuronal damage in which there was a heterogeneous uptake of ^{14}C–DG could not be taken as the average of the whole region.

Relationship between LCGU and LCBF after chronic BCAL

For the sham-operated and chronic BCAL-operated rats, there was a good correlation ($P<0.001$) between LCGU and LCBF values (Fig. 4), with the mean levels for each variable taken from 24 cerebral regions (Tables 2 and 3). Calculation of the correlation lines showed that the slopes were 1.45 for the sham-operated group and 1.53 for the chronic BCAL-operated group. There was no difference in the slope of the correlation line of LCGU and LCBF between the sham-operated and chronic BCAL-operated groups.

Table 3. Effect of BCAL on local cerebral glucose utilisation in conscious Wistar rats

Structures	Local cerebral glucose utilisation (μmol/100 g per minute)			
	2.5 h after BCAL		1 week after BCAL	
	Sham ($n=5$)	BCAL ($n=5$)	Sham ($n=5$)	BCAL ($n=5$)
Cortical regions				
Visual	95±19	ND	99±18	72± 8*
Auditory	123±12	ND	121±14	83±14**
Parietal	116±18	ND	108±13	83±20*
Sensorimotor	116±14	ND	111±13	84±15*
Olfactory	107±13	ND	106±21	78±17*
Frontal	117±13	ND	113±19	85±13*
Subcortical regions				
Thalamus				
Lateral nucleus	116±16	97±34	108±14	91±24
Medial nucleus	117±13	108±29	128±16	93±22*
Ventral nucleus	101±12	93±37	100±17	86±20
Habenula	131±12	123±37	126±20	115±32
Medial geniculate body	119±13	97±28	108± 9	94±20
Lateral geniculate body	97±11	63±21*	87±10	57± 9**
Hypothalamus	57± 4	58±14	52± 8	45± 4
Mammillary body	120±12	102±23	113±19	108±19
Hippocampus				
Ammon's horn	84± 7	84±20	79± 8	69±16
Dentate gyrus	75± 7	70±17	72± 8	63±14
Amygdala	49± 5	49±11	44±11	44± 7
Septal nucleus	65± 3	64±11	61± 7	50± 8
Caudate nucleus	109±13	ND	106±16	76±22*
Nucleus accumbens	97± 9	104±18	96±18	73±16
Globus pallidus	54± 4	48± 8	53± 8	49± 9
Substantia nigra	56± 5	56±12	56±10	59± 7
White matter				
Corpus callosum	31± 2	33± 4	29± 5	22± 5*
Internal capsule	31± 3	36±11	30± 3	22± 8

Data are means±SD
ND, not determined
Significant differences from the corresponding sham group: * $P<0.05$, ** $P<0.01$ (Student's t-test)

Discussion

In the caudate nucleus and cerebral cortices, there was a heterogeneous uptake of ^{14}C–DG after acute BCAL. What the LCGU shows is a heterogeneity in tissue metabolism of glucose. The acute BCAL studies suggest that there are small areas of increased LCGU after 2.5 h. The "columnar" incorporation of ^{14}C–DG in the cerebral cortices has a pattern suggesting vascular anat-

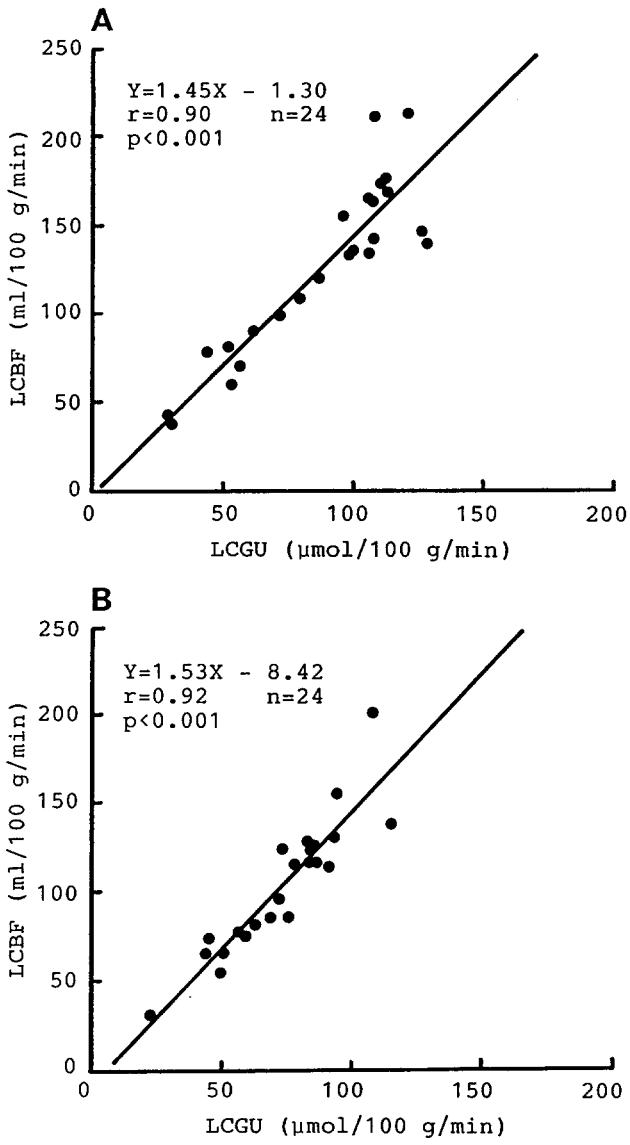

Fig. 4. Relationship between the mean local cerebral glucose utilisation (*LCGU*) and local cerebral blood flow (*LCBF*) values in the 24 cerebral regions in **A** the sham-operated rats and **B** the chronic BCAL-operated rats

omy, i.e. that tissue around the penetrating arterioles is best supplied. Perhaps the high LCGU areas in the cerebral cortices are those farthest away from the arterioles, i.e., the classic "dead corners" of the Krogh tissue cylinder. They depend entirely on how low LCBF goes in that cortex. The LCBF in all the cortices decreased to 25–39% of the sham control. However, the "spotty" incorporation of ^{14}C–DG in the caudate nucleus cannot be clearly explained by vascular anatomy and blood flow rate. In the lateral geniculate body there was no evidence of heterogeneous uptake of ^{14}C–DG, even though the decrease of blood flow was similar to that in the caudate nucleus. Therefore, heterogeneous uptake of the tracer in the caudate nucleus may relate to an unique heterogeneity in the tissue that is made up of grey and white matter.

LCBF, which was remarkably reduced 2.5 h after BCAL, tended toward recovery within one week, except for regions with neuronal damage. Tamura et al. (1981) reported that the average value for blood flow, in areas of the rat brain that showed consistent evidence of ischaemic damage following middle cerebral artery occlusion, was 24 ml/100 g/min. In addition, collaterals may have formed in the ischaemic regions; enlargement of major cerebral collateral arteries following unilateral or bilateral carotid artery ligation has been reported (Coyle and Panzenbeck 1990; Lehman et al. 1991). With these interpretations, it might be easy to understand why there is little cell damage in the neocortex, although the LCBF after acute BCAL fell to 25–39% of values in the sham control.

In chronic BCAL, there was a reduction in LCGU in cerebral cortices and caudate nucleus without histological change. LCGU in these regions significantly decreased to 72–77% of the sham control. In addition, slopes of the correlation lines of LCBF and LCGU in the sham-operated and chronic BCAL-operated groups gave similar values. This suggests that LCBF and LCGU reductions after chronic BCAL were coupled. By way of explanation for this LCGU reduction, a secondary effect of decreased LCBF seems unlikely because the brain tissue should be able to extract the glucose from plasma in the presence of a mild ischaemic condition; that is, the supply of glucose would not be a limiting factor. The most likely explanation for the decrease in LCGU is a reduction in cerebral functions, but without morphological changes. More definitive experiments such as passive avoidance test and receptor assay should provide clarification.

In the caudate nucleus, there were multiple areas of neuronal death, an almost confluent area of "incomplete infarction". The pathological feature of subacute infarct was a "softening", not the structureless caseous ischaemic necrosis seen after extreme ischaemia. There was a heterogeneous uptake of ^{14}C–DG in the area of histopathological change in the caudate nucleus. In this area of active necrosis, LCGU was higher than in the remaining area of the caudate. Since LCBF in this area is again increased via collateral flow, this suggests that this increased LCGU is aerobic, not anaerobic as in the acute phase. We reported that glial nodules or neuronophagia were observed in most cases of histopathological change (Tsuchiya et al. 1992). Komatsumoto et al. (1989) found that increases in local cerebral glucose metabolism following temporary middle cerebral artery occlusion may be due to phagocytotic activity and, if so, then this phagocytotic activity may increase aerobic glucose metabolism in the area of subacute infarct in the caudate nucleus.

We reported changes in physiological parameters (except for plasma glucose) after permanent BCAL in Wistar rats (Tsuchiya et al. 1992) and the present study provided support for these findings. The increase in plasma glucose in rats with chronic BCAL, though not negligible, would be within a physiological range. Ischaemic stress by ligation of the bilateral carotid artery for 1 week may explain the slight increase in plasma glucose.

This permanent BCAL model can serve as an acute and chronic model of cerebral ischaemia, with impairment in cerebral circulation and/or glucose metabolism.

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