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Elimination of the delayed postischemic energy deficit in cerebral cortex and hippocampus of aged rats with a dried, deproteinized blood extract (Actovegin ®) [a]

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Summary

In this study, the effect of Actovegin ® (AC) on glucose and energy metabolism of cerebral cortex and hippocampus after 15 minute complete cerebral ischemic (cci) and postischemic recirculation periods of 60 min, 24 h, 48 h, 72 and 96 h was investigated. The study was performed on 2-year-old male Wistar rats which may be designated as aged.

Actovegin is a dried, deproteinized extract of calf blood which acts on mitochondrial respiration and energy metabolism. After cci, the metabolic abnormalities measured as concentrations of glucose, lactate, creatine phosphate (CrP), and adenosine triphosphate (ATP) normalized rapidly. After 48 h and 72 h postischemic recirculation, however, an imbalance in energy metabolism became manifest in cerebral cortex, and even earlier (24 h), longer (96 h), and more severely in hippocampus. AC (1 ml diluted with 1 ml distilled water/day; 1 ml AC contains 40 mg dried deproteinized extract) counterbalanced the postischemic abnormalities in cerebral cortex and hippocampus. This drug may be able to reduce the detrimental effects to the neuron during postischemic recirculation and may thus help the neuron to survive during this critical period.

Aging; Brain; Ischemia; Energy state; Recirculation; Actovegin ®

Introduction

The studies of Framingham and Whitehall documented that age is one of the most important risk factors for brain infarction causing cerebral ischemic cell damage, and its mortality (Fuller et al., 1985; Hubert et al., 1985). There is no doubt

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that the outcome of ischemically damaged neurons highly determines the quality and quantity of patients' deficits in brain functioning. Normal neuronal work depends on the availability of energy as adenosine triphosphate (ATP) to maintain ion homeostasis, cell integrity and transportation processes, as well as to guarantee the production of neurohormones and neurotransmitters. In mammalian brain, ATP is normally formed from the oxidative breakdown of glucose (Siesjö, 1978; Siesjö and Wieloch, 1986). In normal aging, oxidative brain metabolism has been demonstrated to be decreasing while the capacity of the brain to meet stress condition is reduced (Leong et al., 1981; Degrell et al., 1983; Hoyer, 1985, 1988; Hoyer and Krier, 1986).

In ischemia, the oxidative metabolism and the energy production of cerebral cortex were found to be severely damaged. However, these abnormalities normalized nearly completely in the early period after the restoration of cerebral circulation (Ljunggren et al., 1974a, b).

In contrast to metabolic abnormalities subsequent to acute ischemia, observations on cerebral energy metabolism after longer lasting (1 h or more) postischemic recirculation periods are rather scarce. We recently demonstrated that after 48 h and 72 h postischemic recirculation following a 15 min complete cerebral ischemia (cci), disturbances in glucose breakdown and an imbalance in energy metabolism became manifest in cerebral cortex, and were even earlier (24 h), longer lasting (96 h) and more severe in hippocampus (Hoyer and Betz, 1988).

The aim of the present study was therefore to investigate whether or not the above metabolic abnormalities in cerebral cortex and hippocampus can be counterbalanced by appropriate medication. As a drug, it was decided to use Actovegin® (AC), which is a dried, deproteinized extract from calf blood. AC is reported to promote the respiration rate of liver homogenates and of hepatic mitochondria (Jäger et al., 1965), to reduce ultrastructural and functional damage of heart mitochondria (Sotonyi et al., 1980), to stimulate cerebral energy metabolism after barbiturate-induced depression (Baethmann and Oettinger, 1977), to accelerate the recovery or to prevent cold injury-induced damage of cerebral mitochondria (Ryu et al., 1984) and to increase the depressed cerebral metabolic rate of glucose due to chronic alcoholism (Hoyer et al., 1977).

Therefore, it seemed to be obvious to evaluate the efficacy of AC on brain glucose and energy metabolism in aged rats after cci and recirculation periods up to 96 h.

Materials and Methods

Animals

A total of 120 2-year-old male Wistar rats (Breeder Zentralinstitut für Versuchstierzucht, Hannover, FRG) were included in the study. They were allotted randomly to the respective control and ischemic groups (see below), the latter either with or without AC treatment. Twelve experimental groups were formed, each

group comprising 10 animals. Rats may be designated as aged when their strain has a 50% survival rate, and when their survival curve is more or less rectangular. In male Wistar rats, this deflection point was found to be at the age of 24 months (Hollander et al., 1983). Thus, the animals used in this study were indeed aged. All animals had free access to food and water.

Operation procedure

Animals with postischemic recirculation periods longer than 60 min were first anesthetized by an intraperitoneal injection with chloralhydrate (8 ml/kg b.wt. of a 4% solution). A skin incision was performed above the spinal processes of the upper cervical vertebral column to expose the vertebral arteries at the alar foramina of the atlas. Both arteries were closed by electrocoagulation, and the skin incision was sutured. The common carotid arteries were also exposed and wound around with threads. A 15-min cci was then induced by raising the threads looped around the latter arteries and by hypovolemic hypotension of 30 to 40 mm Hg mean arterial blood pressure (MABP) via an exposed and catheterized femoral artery. Thereafter, MABP was restored to normal by reinfusion of blood, and recirculation of the brain was reestablished in the common carotid arteries. The femoral artery and the incisions were sutured, and the animals were left quiet until the final experiment after either 24, 48, 72 or 96 h recirculation periods.

Animals which underwent a 15 min cci only, and a 15 min cci along with a 60 min recirculation period (acute groups), were ischemically damaged in the same way, but cci was induced in the final experimental procedure as detailed below. Control animals were sham-operated, and were handled also as detailed below.

The final experiment was started with anesthesia with 3.0 vol% halothane. Tracheotomy and intubation were performed. Anesthesia then was continued with 1.5% halothane and nitrous oxide/oxygen 70 : 30. The animals were immobilized with pancuronium bromide (2 mg/kg b.wt.) and artificially ventilated. One femoral artery and vein each were exposed and catheterized for MABP measurement, to sample arterial blood for gas analysis and to measure hemoglobin (Hb), hematocrit (Hc), glucose and lactate concentrations. Via the venous route, bicarbonate was applied to maintain acid-base equilibrium if necessary.

The galea was sagittally incised, and a skin funnel was formed for later brain freezing. Although the compounds of glucose and energy metabolism were demonstrated not to be involved by means of the ischemically induced fall of brain temperature (Busto et al., 1987), a warmed (37 °C) wet sponge was placed into the skin funnel in any case to maintain brain temperature at 37 °C. After this operation procedure, anesthesia was continued with 0.5 vol% halothane and nitrous (oxide/oxygen 70 : 30, until steady state conditions (see below) were established. With the onset of the steady state, halothane anesthesia was discontinued.

Steady state

A steady state of arterial normotension (MABP 100 to 110 mm Hg), normocapnia ($paCO_2$ 36–42 mm Hg), normoxemia to slight hyperoxemia (paO_2 100–170

mm Hg) and normothermia (body temperature 37.0–37.5 °C) was established and maintained over 20 min. Under maintenance of the above steady state, the brains were thereafter frozen in situ by pouring liquid nitrogen into the skin funnel for 3 min. Then the animals were decapitated, and the heads were stored in liquid nitrogen.

In the two acute ischemic groups, a 15 min cci was induced after the above steady state. The brains of the animals without recirculation were then frozen in situ. Animals the brains of which were recirculated for 60 min were maintained in the above steady state after cci, and thereafter their brains were frozen in situ. Animals in which the experimental conditions could not be maintained were excluded.

Analytical techniques

The brain was chiselled out of the skull under liquid nitrogen. Frontoparieto-temporal cerebral cortex and hippocampus were prepared at −20 °C, and powdered under liquid nitrogen. The analysis of glucose, lactate, ATP and creatine phosphate (CrP) in cerebral cortex and hippocampus was performed according to Bergmeyer (1974) and Folbergrova et al. (1972). To evaluate the sum of available energy-rich phosphate from ATP and CrP, ~ P was calculated. Statistical significances were calculated by means of the F test and Student's t test ($2\ p \leq 0.05$).

Actovegin® treatment

The animals randomly allotted to postischemic AC treatment received 1 ml AC diluted with 1 ml distilled water per day intraperitoneally. 1 ml AC contains 40 mg dried deproteinized extract from calf blood. All other animals received the aliquot amount of distilled water only.

Results

Steady state parameters

In ischemia, the experimentally induced significant fall in MABP became obvious. No further abnormalities in MABP, $paCO_2$, paO_2, pH and body temperature could be observed in any of the groups under study. Changes were found in the concentrations of hemoglobin and the hematocrit which were both reduced from 24 h recirculation to the end of the experiment in untreated and at 48 h in treated animals, but showed steady improvement towards the end of the experiment (Table I). A slight increase of cerebral blood flow but no changes in cerebral oxygen consumption may be expected at a hemoglobin concentration of 10 g/100 ml as was demonstrated in normovolemic anemia (Borgström et al., 1975). Thus, the changes in tissue metabolism discussed below may not have been influenced by these blood constituents.

TABLE I

Mean values and standard deviations of steady state parameters in control animals, during 15 min cci, and at different postischemic recirculation periods without and with treatment with AC

	MABP (mm Hg)	$paCO_2$ (mm Hg)	paO_2 (mm Hg)	pH	Temp. (°C)	Hb (g/100 ml)	Hc (%)
Control	107 ± 7	38 ± 6	159 ± 37	7.44 ± 0.04	37.1 ± 0.2	13.8 ± 1.2	38.3 ± 2.4
15 min cci	37 ± 5 [a]	37 ± 4	152 ± 35	7.40 ± 0.03	37.1 ± 0.2	12.5 ± 1.4	35.2 ± 5.9
15 min cci + 60 min rec	105 ± 5	39 ± 3	170 ± 43	7.42 ± 0.05	37.2 ± 0.1	12.5 ± 1.6	35.4 ± 4.3
+ AC	107 ± 5	39 ± 3	165 ± 26	7.40 ± 0.06	37.2 ± 0.1	12.8 ± 1.4	35.0 ± 4.1
15 min cci + 24 h rec	101 ± 5	39 ± 3	163 ± 27	7.41 ± 0.04	37.2 ± 0.1	10.5 ± 1.7 [a]	28.8 ± 6.6 [a]
+ AC	105 ± 5	40 ± 3	149 ± 18	7.40 ± 0.06	37.1 ± 0.1	12.8 ± 1.9	36.2 ± 5.3
15 min cci + 48 h rec	103 ± 6	39 ± 3	164 ± 29	7.42 ± 0.05	37.2 ± 0.1	10.5 ± 2.1 [a]	29.8 ± 5.3 [a]
+ AC	105 ± 7	39 ± 2	138 ± 16	7.39 ± 0.03	37.1 ± 0.3	11.1 ± 2.5 [a]	32.0 ± 6.7 [a]
15 min cci + 72 h rec	107 ± 5	39 ± 3	153 ± 20	7.39 ± 0.03	37.0 ± 0.1	11.7 ± 1.8 [a]	32.4 ± 4.6 [a]
+ AC	104 ± 8	39 ± 4	147 ± 16	7.40 ± 0.05	37.1 ± 0.1	13.0 ± 0.9	36.0 ± 2.2
15 min cci + 96 h rec	105 ± 6	39 ± 2	137 ± 28	7.41 ± 0.04	37.0 ± 0.1	11.9 ± 1.5 [a]	33.2 ± 4.6 [a]
+ AC	108 ± 6	38 ± 2	157 ± 22	7.41 ± 0.03	37.1 ± 0.1	13.1 ± 2.5	36.0 ± 6.8

[a] Statistically different from control (2 $p \leq 0.05$). Hb, hemoglobin; Hc, hematocrit; AC, Actovegin®; cci, complete cerebral ischemia; MABP, mean arterial blood pressure; rec, recirculation.

TABLE II

Mean values and standard deviations of glucose and lactate concentrations in arterial blood in control animals, during 15 min cci, and at different post-ischemic recirculation periods without and with treatment with AC

	Glucose (mmol/l)	Lactate (mmol/l)
Control	7.33 ± 0.85	0.707 ± 0.201
15 min cci	13.51 ± 2.93 [a]	4.052 ± 1.326 [a]
15 min cci + 60 min rec	10.63 ± 3.74 [a]	2.024 ± 1.015 [a]
+ AC	12.53 ± 4.64 [a]	4.47 ± 4.05 [a]
15 min cci + 24 h rec	5.47 ± 1.93	1.525 ± 1.015 [a]
+ AC	6.59 ± 1.55	1.15 ± 0.42 [a]
15 min cci + 48 h rec	6.20 ± 2.13	1.912 ± 1.028 [a]
+ AC	7.24 ± 2.05	1.21 ± 0.73 [a]
15 min cci + 72 h rec	6.40 ± 1.31	1.407 ± 0.910 [a]
+ AC	6.34 ± 1.28	0.85 ± 0.55
15 min cci + 96 h rec	6.70 ± 1.34	1.059 ± 0.852
+ AC	6.99 ± 1.65	1.21 ± 0.76 [a]

[a] Statistically different from control ($2\ p \leq 0.05$). For abbreviations consult Table I footnote.

Arterial concentrations of glucose and lactate

In ischemia, the glucose concentration doubled, and lactate increased nearly 6-fold in arterial blood (Table II). Glucose concentration rapidly normalized in untreated and treated animals at 24 h recirculation. On the other hand, lactate concentration fell only slowly but steadily, and remained significantly elevated to the end of the experiment in untreated and treated rats. (Table II). However, the postischemic course of these two blood constituents indicates that they may not influence the changes observed in brain tissue.

Brain tissue metabolite concentrations

The metabolic abnormalities which occurred in cerebral cortex and hippocampus during ischemia and at different recirculation periods have been detailed recently (Hoyer and Betz, 1988). In brief, ischemia caused a severe drop in the concentrations of glucose, ATP and CrP, and in ~ P, too, whereas lactate increased. During early postischemic recirculation, the metabolic abnormalities measured as concentrations of glucose and lactate, and ATP and CrP normalized rapidly. After 48 h and 72 h recirculation, disturbances in glucose breakdown and an imbalance in energy metabolism became manifest in cerebral cortex, and even earlier (24 h), longer (96 h), and more severely in hippocampus.

In this article, the main interest is focused on the groups of AC-treated animals. Therefore, emphasis is laid on the metabolic data under AC treatment and their comparison to those found when treatment is missing.

TABLE III

Mean values and standard deviations in μ mol/g wet wt. tissue of glucose, lactate, ATP, CrP and (calculated) ~ P in brain cortex of rats during and after a 15 min cci without and with treatment with AC

	Glucose	Lactate	ATP	CrP	~ P
Control	2.01 ±0.35	1.39±0.11	2.31 ±0.10	3.41 ±0.27	0.81±0.03
15 min cci	0.284±0.037 [b]	12.97±1.51 [b]	0.216±0.040 [b]	0.519±0.47 [b]	0.11±0.05 [b]
15 min cci					
60 min rec	5.03 ±0.55 [b]	1.82±0.22 [b]	2.24 ±0.20	3.61 ±0.17	0.83±0.03
+AC	5.76 ±0.44 [a,b]	1.65±0.10 [b]	2.16 ±0.17	3.67 ±0.24	0.83±0.04
15 min cci					
+24 h rec	2.29 ±0.36	1.36±0.19	2.56 ±0.20 [b]	3.80 ±0.18 [b]	0.80±0.03
+AC	2.63 ±0.27 [a,b]	1.78±0.17 [a,b]	2.55 ±0.15 [b]	3.43 ±0.21 [a]	0.84±0.03
15 min cci					
+48 h rec	2.50 ±0.31	1.69±0.13 [b]	2.05 ±0.11 [b]	3.23 ±0.12	0.75±0.02 [b]
+AC	2.70 ±0.15 [b]	1.51±0.21 [a]	2.33 ±0.19 [a]	3.61 ±0.11 [a]	0.84±0.02
15 min cci					
+72 h rec	3.45 ±0.21 [b]	1.84±0.08 [b]	2.09 ±0.21 [b]	3.54 ±0.11	0.80±0.03
+AC	2.98 ±0.15 [a,b]	2.30±0.24 [a,b]	2.26 ±0.21	3.25 ±0.17 [a]	0.78±0.03
15 min cci					
+96 h rec	3.21 ±0.13 [b]	1.60±0.07 [b]	2.31 ±0.21	3.80 ±0.21 [b]	0.87±0.03 [b]
+AC	3.14 ±0.10 [b]	1.88±0.23 [a,b]	2.30 ±0.16	3.44 ±0.12 [a]	0.82±0.02

[a] 2 $p \leq 0.05$ between untreated and treated animals.
[b] 2 $p \leq 0.05$ vs. control. CrP; creatine phosphate. For other abbreviations see Table I footnote.

Cerebral cortex (Table III)

When compared to controls, glucose concentrations were significantly elevated throughout the postischemic recirculation period under AC treatment. At 60 min and 24 h postischemic recirculation, tissue glucose was higher, and at 72 h recirculation was lower under treatment as compared to untreated animals. Tissue lactate remained elevated during the recirculation period under AC treatment with differences to untreated rats at 24, 72 and 96 h recirculation (higher), and at 60 min recirculation (lower).

ATP did not reveal differences from controls except at 24 h recirculation (increase). At 48 h recirculation, ATP dropped in untreated animals so that the difference between untreated and AC-treated rats became significant.

CrP did not show variations under AC treatment as compared to controls. It changed downward at 24, 72 and 96 h recirculation, and upwards at 48 h recirculation under AC treatment as compared to untreated animals.

The sum of ~ P remained in a normal range throughout the postischemic recirculation period under AC treatment. The difference at 48 h recirculation was due to the drop in the untreated group.

Hippocampus (Table IV)

Tissue glucose concentrations were elevated throughout the ischemic recirculation under AC treatment with differences to untreated animals at 72 h recirculation (lower), and at 96 h recirculation (higher).

Hippocampal lactate ranged higher at 72 h recirculation and lower at 96 h recirculation under AC treatment as compared to controls and was variably different to untreated animals throughout the postischemic course.

ATP increased significantly at 24 and 96 h recirculation, but did not show further aberrations from control under AC treatment. Differences were found at 24 h recirculation (lower), and 72 h and 96 h recirculation (higher) as compared to untreated animals.

CrP did not vary from control under AC treatment throughout the recirculation period. It was, in principle, significantly higher as compared to the reduced values of untreated animals.

The sum of ~ P dropped at 48 h recirculation under AC treatment. However, this fall was significantly less marked as compared to the respective untreated group. Differences became also obvious at 72 and 96 h recirculation, when ~ P was reduced in untreated rats.

TABLE IV

Mean values and standard deviations in μmol/g wet wt. tissue of glucose, lactate, ATP, CrP and (calculated) ~ P in hippocampus of rats during and after a 15 min cci without and with treatment with AC

	Glucose	Lactate	ATP	CrP	~ P
Control	1.90 ±0.27	1.76±0.29	2.04 ±0.14	3.83 ±0.46	0.84±0.05
15 min cci	0.375±0.041 [b]	13.63±1.88 [b]	0.347±0.160 [b]	0.318±0.068 [b]	0.10±0.02 [b]
15 min cci					
+60 min rec	5.18 ±0.57 [a]	1.49±0.36	2.00 ±0.25	3.85 ±0.23	0.84±0.04
+AC	5.35 ±0.43 [b]	1.81±0.17 [a]	1.92 ±0.14	3.77 ±0.16	0.82±0.02
15 min cci					
+24 h rec	2.22 ±0.38 [b]	1.86±0.31	2.85 ±0.47 [b]	3.08 ±0.58 [b]	0.83±0.08
+AC	2.22 ±0.18 [b]	1.57±0.11 [a]	2.25 ±0.22 [a,b]	3.79 ±0.16 [a]	0.86±0.02
15 min cci					
+48 h rec	2.54 ±0.22 [b]	2.57±0.35 [b]	1.90 ±0.18	2.82 ±0.25 [b]	0.67±0.04 [b]
+AC	2.34 ±0.28 [b]	1.80±0.29 [a]	1.97 ±0.08	3.55 ±0.36 [a]	0.79±0.03 [a,b]
15 min cci					
+72 h rec	2.91 ±0.20 [b]	2.68±0.30 [b]	1.69 ±0.28 [b]	2.86 ±0.23 [b]	0.65±0.03 [b]
+AC	2.25 ±0.25 [a,b]	2.15±0.17 [a,b]	2.12 ±0.21 [a]	3.61 ±0.36 [a]	0.82±0.05 [a]
15 min cci					
+96 h rec	1.92 ±0.25	1.55±0.31	1.69 ±0.36 [b]	3.42 ±0.27 [b]	0.73±0.05 [b]
+AC	2.60 ±0.30 [a,b]	1.34±0.17 [a,b]	2.25 ±0.14 [a,b]	3.70 ±0.20 [a]	0.85±0.02 [a]

[a] 2 $p \leqslant 0.05$ between untreated and treated animals.

[b] 2 $p \leqslant 0.05$ vs. control. CrP: creatine phosphate. For other abbreviations see Table I footnote.

Discussion

The main biochemical event in cerebral ischemia is the cessation of oxidative metabolism and energy-producing processes. As a consequence, the tissue concentration of lactate rises, and those of glucose, ATP and CrP fall sharply. These repeatedly reported findings were found to be aggravated with age (Ljunggren et al., 1974b; Hoyer and Krier, 1986). With postischemic recirculation, the energy pool is restored more or less rapidly depending on the severity of the ischemic event (Ljunggren et al., 1974b; Mrsulja et al., 1976; Kobayashi et al., 1977; Naruse et al., 1984).

In experimental animals' cerebral ischemia models of different kinds, glucose-related metabolites and high-energy phosphates revealed no homogenous changes during recirculation periods studied up to 96 h after ischemia. The functionally most remarkable variations were found in ATP and CrP metabolism, more pronounced in hippocampus than in cerebral cortex (Pulsinelli and Duffy, 1983; Arai et al., 1986; Hoyer and Betz, 1988; Yasumoto et al., 1988).

Since glucose was above normal, and also lactate rose, the reduction in energy metabolism may not be attributed to a lack of the physiological brain fuel glucose. Moreover, these abnormalities may indicate a severe imbalance between energy production and energy utilization, all the more so since increases in ADP and AMP along with a sharp drop in energy charge potential point to an enhanced energy demand particularly at 48 h and at 72 h postischemic recirculation (Hoyer and Betz, 1988). These changes in energy metabolism might be reflected by the variations that were found in spontaneous neuronal activity after ischemia. During the first 24 h following ischemia, hippocampal CA1 neurons displayed hyperactivity which was followed by isoelectricity 2 days after ischemia although their cellular structure showed general preservation (Suzuki et al., 1983). The delayed postischemic energy deficit may also contribute to both neuronal damage and death via depression of mitochondrial ATP production due to tissue acidosis (Hillered et al., 1984) and loss of synaptic transmission (Whittingham and Lipton, 1981; Lipton and Whittingham, 1982), the latter being assumed to be involved in the death of hippocampal neurons (Onodera et al., 1986; Jørgensen et al., 1987). Furthermore, the enhanced formation of free radicals evidenced in ischemia (Siesjö, 1984; Siesjö et al., 1985) may be capable of stimulating intracellular proteolysis (Davies and Goldberg, 1987). The accumulation of calcium in hippocampus at 48 h and even more at 72 h after ischemia which is highly correlated with the energy deficit as pointed out above, may also contribute to neuronal damage and death (Deshpande et al., 1987). It thus becomes clear that there are a large number of different pathobiochemical parameters which act in a pernicious concerted way in the postischemic recirculation period, and which first contribute to severe functional abnormalities which may precede structural changes, e.g. neuronal death.

Therefore, one of the most important goals of any postischemic therapeutic strategy should be the early interruption of the process of cell-damaging events to avoid neuronal death. Because of the properties of AC to promote oxidation and energy production (see above), the efficacy of this drug was assumed to benefit

postischemic metabolic events although its active constituent has not been elucidated as yet. As becomes obvious from the data listed in Tables III and IV, AC influenced the concentrations of both glucose and lactate in cerebral cortex as well as in hippocampus only to a slight and variable extent as compared to untreated animals. Its effectiveness may be tentatively interpreted as a tendency to normalize the postischemic variations via the reduction of their variability. On the other hand, more uniform and convincing effects of AC could be observed in energy metabolism: the fall in ATP did not happen in cerebral cortex at 48 h and 72 h recirculation, and the sum of ~ P did not fall during recirculation under AC treatment. In hippocampus, the ischemia-induced drops in ATP and CrP were completely counterbalanced by AC throughout the whole recirculation period. The slight but significant fall in ~ P in hippocampus at 48 h recirculation even under AC treatment may point to the particular sensitivity of hippocampal neurons at this time of postischemic recirculation. However, this fall was much less extensive when compared to untreated animals.

It may thus be assumed that this AC-induced improvement of the delayed postischemic disturbances in cerebral energy metabolism may help the neuron to resist the detrimental pathobiochemical events in the course after ischemia more effectively and for a longer period. However, the efficacy of AC on further cellular and molecular mechanisms remains to be elucidated, as well as its clinical relevance in the treatment of acute stroke.

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