Chronic Cerebral Hypoperfusion and Impaired Neuronal Function in Rats

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Background and Purpose Studies in acute cerebral ischemia have shown that reductions in cerebral blood flow of up to 50% do not lead to infarction or alterations in neuronal electric activity. Little is known about the effects of chronic reductions in cerebral blood flow. The purpose of this study was to evaluate neuronal electrophysiological function in brain that had been subjected to a chronic reduction of cerebral blood flow of less than 50%. Based on existing knowledge of thresholds of cerebral ischemia, neuronal electrophysiological function should be unaffected by hypoperfusion of this magnitude.

Methods An arteriovenous fistula model in the rat was used to induce chronic cerebral hypoperfusion with reductions of cerebral blood flow of 25% to 50% as measured previously by ^{14}C-labeled autoradiography. Using in vitro electrophysiological brain slice techniques, long-term potentiation in hippocampal CA1 neurons was examined extracellularly after 6 months of chronic noninfarctional cerebral hypoperfusion. Brains were also examined histologically at this time for evidence of cerebral infarction.

Results There was no evidence of cerebral infarction. Long-term potentiation was produced in 9 of 12 control animals and only 2 of 8 hypoperfused animals. This difference was significant ($P<.05$) and demonstrated that long-term potentiation was impaired in animals with chronic hypoperfusion.

Conclusions Noninfarctional reductions in cerebral blood flow of up to 50% do impair neuronal function in chronic cerebral ischemia, a result quite distinct from that seen in acute ischemia. The threshold for neuronal dysfunction in chronic cerebral hypoperfusion is lower than that found in acute cerebral ischemia, suggesting that duration as well as severity of ischemic insult determines cellular viability. Chronic hypoperfusion may lead to a noninfarctional state with impaired neuronal function, a category of chronic cerebral ischemia not previously identified. *(Stroke.* 1994;25: 1022-1027.)

Keywords arteriovenous fistula • cerebral ischemia • hippocampus • rats

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The adverse effects of cerebral ischemia have been recognized since the time of Hippocrates,[1] and although more than 2000 years have passed, only recently have we begun to understand the mechanisms leading to neuronal injury and cell death.[2-3] Our knowledge of the effects and mechanisms of acute ischemia is improving, although little is known about the effects of reductions in cerebral blood flow (CBF) in the chronic situation. Much of this problem has stemmed from the inadequacies of current models emulating chronic hypoperfusion. Morgan et al[4-6] recently described a model incorporating an arteriovenous fistula (AVF) that effectively reduced global CBF in rats chronically by approximately 25% to 50% without an acute ischemic insult (Fig 1). Hence, using this model assessment could be made of the effects of chronic noninfarctional hypoperfusion on brain tissue. Such information may be important in understanding conditions of chronic cerebral hypoperfusion that may occur in humans as a result of ischemic, chronic noninfarctional vascular disease or in perifocal brain tissue associated with arteriovenous malformations.

It has been demonstrated that the severity and extent of ischemic brain damage are dependent on the duration and degree of the hypoperfusion.[7-11] Furthermofe, it has been suggested that if CBF is reduced below 40% to 50% of control values, brain tissue is put at risk with a gradation of effects from inhibition of electric activity to ionic pump failure, membrane disruption, and cell death occurring as CBF is progressively reduced.[12-13] Protein synthesis has been shown to be inhibited at CBF reductions of approximately 50%[14]; however, to date no effect has been demonstrated in terms of altered neuronal function or morphology as a result of more subtle CBF reductions of up to 50%. In chronic hypoperfusion it has previously been thought that only two states may occur (1) hypoperfusion leading to infarction or (2) hypoperfusion with no alteration in neuronal structure or electrophysiological function.

This study evaluated long-term potentiation (LTP) in the hippocampus of rats subjected to a considerable period of chronic cerebral hypoperfusion at a level thought not to have detrimental effects on neuronal function. LTP, first described in 1973,[15] is a long-lasting enhancement of synaptic efficacy after brief, repetitive stimulation of afferent pathways and is thought to play some role in the synaptic coding of memory.[16-21] The hippocampus contains neurons selectively more vulner-

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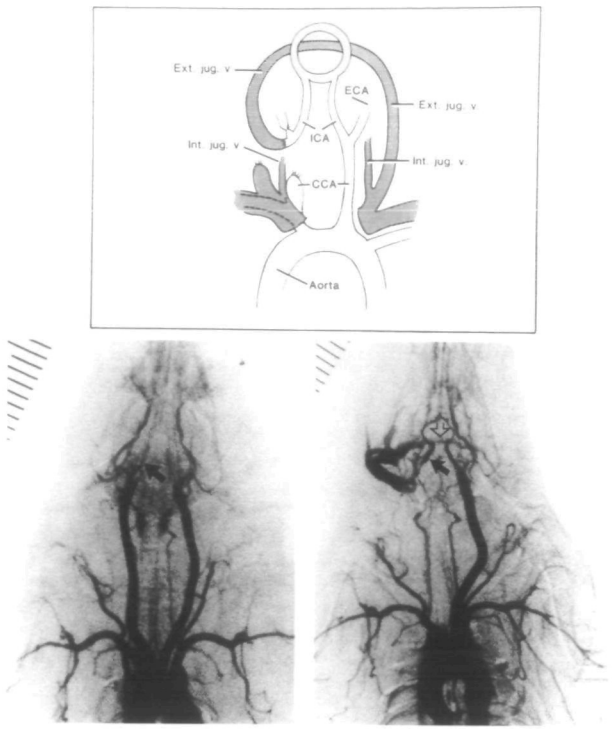

FIG 1. Arteriovenous fistula (AVF) model in the rat used to create chronic hypoperfusion. Top, Schematic representation of the right carotid-jugular fistula anastomosis demonstrating some of the major connections. Ext. jug. v. indicates external jugular vein; Int. jug. v., internal jugular vein; ECA, external carotid artery; ICA, internal carotid artery; and CCA, common carotid artery. Bottom, Angiograms of control rat (left) and AVF rat (right). Closed arrow indicates the right ICA, and open arrow indicates the transverse sinus. The large arteriovenous fistula is clearly visible.

able to ischemia and hypoxia compared with other brain regions[22] and therefore is particularly suitable for a study of this nature.

Materials and Methods

All experimental procedures were approved by our institutional Animal Care and Ethics Committee.

Thirteen male Sprague-Dawley rats (weight, 250 to 350 g; age, approximately 8 to 10 weeks) underwent general anesthesia with 1.6% halothane using a snout mask and spontaneous respiration. Under direct magnification, a carotid-jugular fistula was formed between the right internal carotid artery and right external jugular vein, as described in detail by Morgan et al.[4-6] This formed a functional AVF between the anterior intracranial arterial circulation and extracranial venous circulation and thus created a model of cerebral hypoperfusion without an initial ischemic insult. Morgan et al[4] showed that CBF was reduced from a median of 0.82 to 1.12 mL/g per minute in nonoperated controls to 0.46 to 0.68 mL/g per minute in animals with AVFs using ^{14}C-labeled autoradiography, with no evidence on light microscopy of infarction at 12 weeks after creation of the AVF. Seventeen age-matched rats in our study were used as controls. Unoperated animals were used because of the tolerance of the rat to unilateral ligation of the common carotid artery[23,24] and the finding that in creation of an AVF in rats using similar models, collateral dilatation was maximal by 8 weeks after the initial procedure[25] with subsequent negligible effects of the carotid artery ligation. The rats were allowed to convalesce for 26 weeks after AVF formation in grouped housing climate-controlled facilities with 12-hour day/night cycles. They were allowed free access to food and water and observed daily for abnormalities of activity or diet. At this stage 5 control and 5 AVF animals were anesthetized with 5% halothane, transcardially perfused, and fixed with 10% formalin. Their brains were sectioned into 10-μm slices and stained with cresyl violet for light microscopic examination.

Twenty-six weeks after AVF formation, the remaining 12 control and 8 AVF animals were also anesthetized with halothane and decapitated. The hippocampus was rapidly removed, and 400-μm slices were obtained using a McIlwain tissue chopper. The slices were placed into a chilled incubation chamber bubbled with 95% O_2/5% CO_2 with artificial cerebrospinal fluid (aCSF) concentration of the following (mmol/L): NaCl, 125.3; KCl, 3.5; NaH_2PO_4, 1.25; $MgCl_2$, 2; $CaCl_2$, 2; $NaHCO_3$, 26; and glucose, 25 (pH 7.4). Slices were allowed to recover for at least 1 hour before transfer to a submerged tissue bath superfused with aCSF (at 8 mL/min at 34±0.5°C) of the following composition (mmol/L): NaCl, 124; KCl, 5; NaH_2PO_4, 1.25; $MgCl_2$, 1.3; $CaCl_2$, 2.5; $NaHCO_3$, 26; and glucose, 25 (pH 7.4) bubbled with 95% O_2/5% CO_2. Slices were allowed an additional hour to settle before recording. Extracellular field potentials were recorded from the CA1 pyramidal layer (recording electrode: glass micropipette; impedance, 2 to 20 MΩ; 2 mol/L NaCl) with stimulation via the Schaffer collaterals (stimulating electrode: monopolar stainless-steel wire with paralyene coating; 125-mm 12° tapered tungsten tip; impedance, 2 to 5 MΩ). Baseline stimulation frequency was 0.2 Hz. Control responses were taken using a stimulus intensity that achieved approximately two thirds of the maximal response and recorded for 30 minutes. Measurements of the amplitude and latency of the first and second population spike as well as the number of spikes were used as baseline values for calculating the magnitude of LTP. The population spike amplitude was measured between peak negativity and subsequent maximum positivity, whereas latency was measured to peak negativity. Tetanic stimulation was delivered as 5 trains 6 seconds apart at a frequency of 50 Hz (duration, 400 milliseconds) as described by Andersen et al.[26] After the train, stimulation resumed at 0.2 Hz, and recordings were taken for an additional hour.

Statistical Analysis

For each animal, the mean±SD was calculated for the period of control recording and for the last 30 minutes of recording after tetanic stimulation. All results were then pooled. Control recordings between control and AVF animals were compared via two-sample t tests to determine any differences before the tetanic stimulation. Two-sample adjusted t tests were used for samples with unequal variances.[27] For posttrain data, values in the last half hour of recording were compared between control and AVF animals in the manner previously used for the control period data. Finally, the magnitude of change as a result of tetanic stimulation was compared for each of the five variables between control and AVF animals to determine any difference in the amount of LTP that occurred between the two groups. Again either two-sample t tests or two-sample t tests adjusting for unequal variances were used. A value of $P<.05$ was regarded as significant.

Results

The light microscopic examinations showed no evidence of infarction in any region of the brain and particularly in the hippocampus (Fig 2).

The results obtained from the electrophysiological studies are summarized in Tables 1 and 2. There was no statistical difference between mean values for any variable before the train between control and AVF animals. After the train, 2 of 12 control animals showed immediate posttetanic potentiation (PTP),

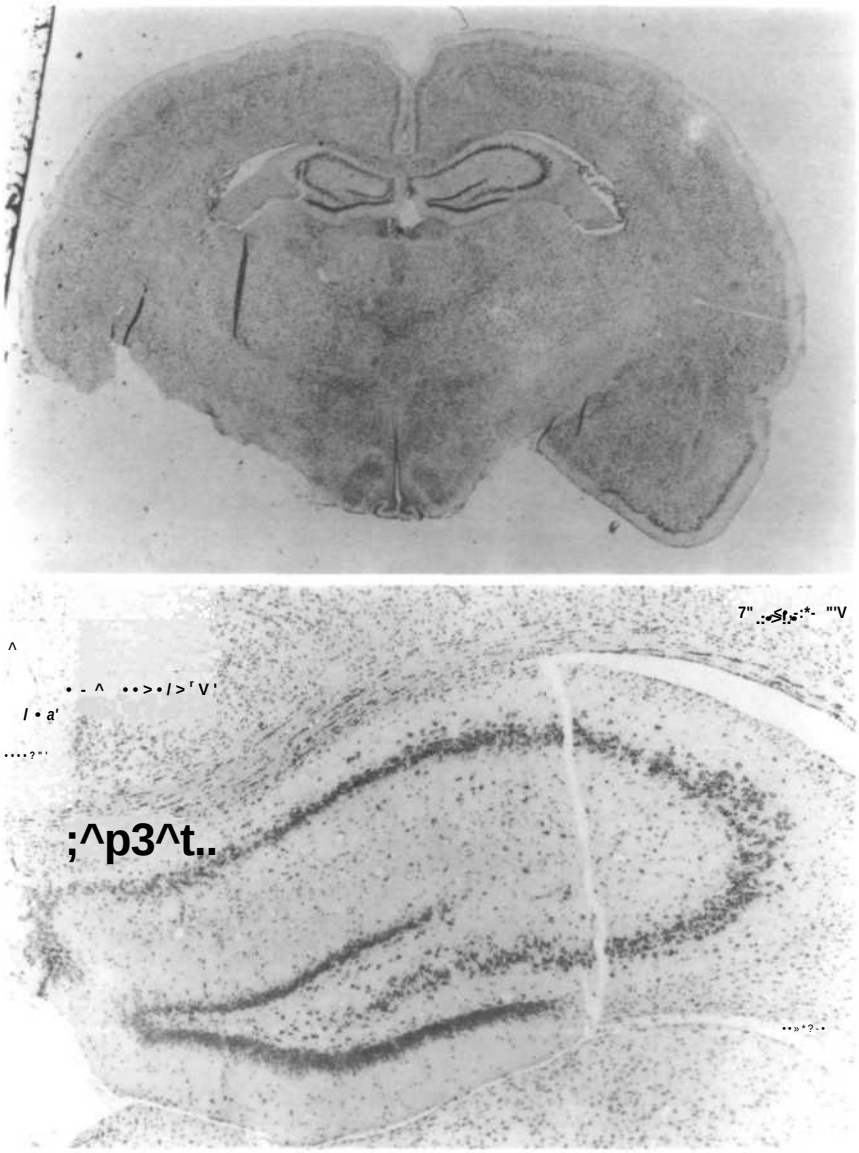

FIG 2. Photomicrographs of sections of brain from typical animals with arteriovenous fistula stained with cresyl violet showing an absence of cerebral Infarction in a coronal section of the whole brain centered on the mid-hippocampal region (original magnification X12) (top) and on higher-power evaluation of the hippocampus (original magnification x63) (bottom).

TABLE 1. Mean Amplitude, Latency, and Number of Spikes by Group

	Control		Fistula		Comparison of Groups (P)			
	Pretrain! (A)	Posttralni (B)	Pretrain! (D)	PosttralnU (E)	A-Bf	D-Et	A-D*	B-E*
First spike								
Amplitude, mV	3.60±1.16	4.16± 1.42	3.30±1.10	3.43±1.30	.001§	.287	.571	.256
Latency, ms	4.26±0.44	4.25±0.40	3.53 ± 1.11	3.44±1.09	.982	.022§	.116t	.079$
Second spike								
Amplitude, mV	1.24±0.77	2.01 ±1.03	1.22±0.94	1.42 ±1.32	.000§	.349	.971	.295
Latency, ms	8.09±0.82	8.01 ±0.68	7.92±0.86	7.70±0.85	.643	.092	.671	.392
Number of spikes	3.00±0.80	3.58±0.55	3.49±1.20	3.43±1.18	.015§	.682	.286	.730*

*Two-sample *t* test
tPaired f tests.
•Two-sample *t* test adjusting for unequal variances.[27]
§Statistically significant, P<.05.
ULast 30 minutes of recording.

TABLE 2. Comparisons of Amount of Change After Tetanus for Control and Fistula Groups

	Control Group Change After Train (C=B-A)	Fistula Group Change After Train (F=E-D)	C-F* (*P*)
First spike			
Amplitude, mV	0.56±0.46	0.13±0.32	.022†
Latency, ms	−0.01±0.29	−0.09±0.08	.360
Second spike			
Amplitude, mV	0.77±0.58	0.20±0.52	.043†
Latency, ms	−0.08±0.62	−0.22±0.30	.517
Number of spikes	0.58±0.70	−0.06±0.41	.019†

*Two-sample *t* test adjusting for unequal variances.[27]
†Statistically significant, $P<.05$.

followed by posttetanic depression (PTD) lasting several minutes in 7 of 12 animals. By 10 minutes after the train, further sustained potentiation occurred. In the AVF animals 2 of 8 showed immediate PTP, with 4 of 8 then having a PTD of duration similar to that of the control animals (Fig 3). Pooled results for the control animals showed a statistically significant difference in the last 30 minutes after the train compared with the pretrain control values, with increases in the amplitudes of the first and second spike and increases in the number of spikes. Nine of 12 controls showed LTP at 1 hour, with increases in this subgroup in first spike amplitude from 10% to 50% (average increase when potentiated, 19%). Similarly, the number of spikes was increased by 20% to 80% (average, 25%). Pooled results for AVF animals showed a statistically significant difference in mean latency after the train with no significant changes in the mean values of all other variables. Thus, according to the pooled results, LTP did not occur. Only 2 of 8 AVF animals showed potentiation at 1 hour. When the magnitude of change after the train was compared between AVF and control groups (Table 2), a statistically significant difference was shown for the first spike amplitude, second spike amplitude, and number of spikes ($P<.05$). Pooled results after the train in AVF and control animals are shown in Fig 3.

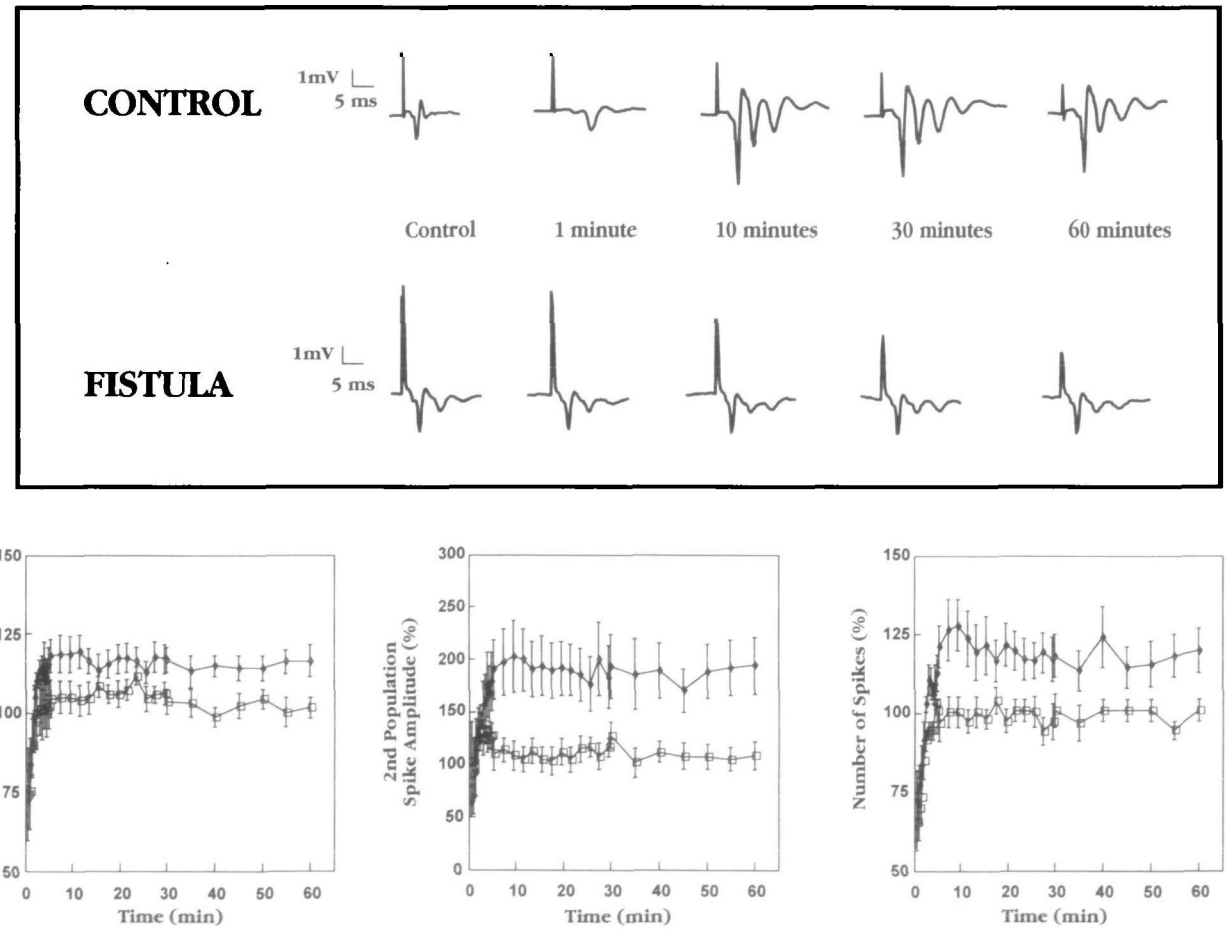

FIG 3. Top, Typical extracellular field potentials recorded from a single control and single arteriovenous fistula (AVF) animal. The pretrain response is shown (top left) with the changes associated after tetanus subsequently shown in minutes after the train. Bottom, Plots for pooled data (mean±SEM) of control (♦, n=12) and AVF (□, n=8) animals for amplitude of the first population spike (bottom left), amplitude of the second population spike (bottom middle), and total number of spikes (bottom right) are shown. Normalized values that were expressed as a percentage of the mean control value were used. Note that both groups show initial depression followed by a more sustained increase in controls and a return to near normal values in the AVF animals with regard to amplitudes of the population spikes and number of spikes. The change in spike amplitudes and number of spikes showed a statistically significant increase in control animals that was not observed in AVF animals (see Tables 1 and 2).

Discussion

Our results revealed many interesting properties of hippocampal function in chronic hypoperfusion. The degree of reduction in CBF did not lead to cerebral infarction, which would imply that CBF was not reduced beyond 50%. Field potential recordings in both control and AVF animal groups were the same before the train, with no statistical differences in mean values of population spike amplitudes, latencies, or numbers of spikes. The incidence of PTP and PTD was also fairly similar. It therefore appears that synaptic transmission was intact in the AVF animals and identical to that in control animals. When the data from 30 to 60 minutes after the train were compared, marked differences emerged. Seventy-five percent of control animals were able to sustain LTP, but only 25% of AVF animals had similar results. As a whole there was no significant LTP in AVF animals, in contrast to the potentiation seen in the control animals. These data suggest that LTP is impaired by chronic hypoperfusion with otherwise intact synaptic transmission.

Only two studies to date have examined chronic reductions in CBF and the effects on neuronal structure and function. De la Torre et al[28-31] used a three-vessel occlusion model in the rat but had reductions of CBF greater than 50% 3 weeks after the initial procedure accompanied by marked early pathological and magnetic resonance changes, suggesting that an acute ischemic insult was inflicted. Kudo et al[32] described a model of cerebral ischemia in gerbils using carotid artery clips. Although CBF in their study was reduced to 73% to 76% of that measured in control animals by the hydrogen clearance method at 8 weeks after initial surgery, the measurements were performed under deep barbiturate anesthesia, with quite markedly abnormal CBF in both control and treated animals. As such, an acute ischemic insult could not be excluded, and it would be difficult to estimate the proportionate reduction in CBF in the awake unanesthetized animal, which could possibly have been less than 50%. In subsequent studies the severity of the ischemia was worsened.[33,34] Thus, both groups assessed cerebral hypoperfusion for durations far shorter than presented in this study and with reductions in CBF very likely greater than 50%, a threshold known to impair neuronal structure and function.

Studies in monkeys,[8,35] cats,[36] and humans[37] have all shown that a critical CBF threshold exists (at approximately 0.18 to 0.23 mL/g per minute), below which spontaneous and evoked brain electric activity cease. This threshold forms the upper border of the so-called ischemic penumbra zone.[38] Further reductions of CBF below 0.10 to 0.12 mL/g per minute lead to loss of cellular ion homeostasis[12,13] and eventually membrane disruption and cell death. On a cellular level, failure of ATP synthesis is one of the terminal events, with lactic acidosis, glutamate activity, and edema formation being some of the mediators leading to this loss of ATP synthesis.[2,3] The mechanism of the cell dysfunction demonstrated in chronic noninfarctional hypoperfusion is not known, but unlike acute cerebral ischemia, it is not thought to involve loss of ATP synthesis. Whatever mechanism is eventually identified as mediating cell damage in chronic cerebral ischemia, it is likely that it will be quite distinct from that which occurs in acute cerebral ischemia.

These results show that current thinking regarding cerebral ischemia needs modification. LTP has been shown to be impaired in animals undergoing noninfarctional cerebral hypoperfusion with reductions of CBF of 25% to 50%. It is suggested that a new subtype of chronic hypoperfusion exists. Previously chronic hypoperfusion was thought to lead to infarction if CBF was reduced by greater than 60% to 75% and was thought to have no effect with reductions of a lesser magnitude. We suggest that a third category exists whereby chronic hypoperfusion with CBF reductions of 25% to 50% may lead to impaired neuronal function in the absence of cerebral infarction.

Acknowledgments

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Editorial Comment

In this interesting article, the authors evaluate neuronal electrophysiological function in brain subjected to a chronic reduction of cerebral blood flow (CBF) of approximately 50%. The authors suppose that reductions in CBF of up to 50% impair neuronal function in chronic cerebral ischemia. This result is important because these data would suggest that moderate ischemia is accompanied by changes in brain function, and these changes could explain the alteration in cognitive function in patients with mild reduction in CBF. The authors present interesting histopathologic data that demonstrate an absence of cerebral infarction with reference to the hippocampus in animals 26 weeks after fistula formation, and thus they assume that CBF is reduced by less than 50%. The major aspect of this study which needs to be dealt with is that the authors needed to measure CBF directly to be sure that the reduction did not exceed 25% to 50%. It is clear that there was indeed impaired neuronal function in the absence of major cerebral infarction; however, to demonstrate this absolutely, CBF must be measured. Another aspect is the question of the mechanism of cell dysfunction. The authors offer two potential mechanisms, one involving protein synthesis and the other the potential resistance of inhibitory interneurons with cerebral ischemia. Clearly, the mechanism of this interesting finding needs to be elucidated.

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