Progress Review: Hypoglycemic Brain Damage

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SUMMARY The central question to be addressed in this review can be stated as “How does hypoglycemia kill neurons?” Initial research on hypoglycemic brain damage in the 1930s was aimed at demonstrating the existence of any brain damage whatsoever due to insulin. Recent results indicate that uncomplicated hypoglycemia is capable of killing neurons in the brain. However, the mechanism does not appear to be simply glucose starvation of the neuron resulting in neuronal breakdown. Rather than such an “internal catabolic death” current evidence suggests that in hypoglycemia, neurons are killed from without, i.e. from the extracellular space. Around the time the EEG becomes isoelectric, an endogenous neurotoxin is produced, and is released by the brain into tissue and cerebrospinal fluid. The distribution of necrotic neurons is unlike that in ischemia, being related to white matter and cerebrospinal fluid pathways. The toxin acts by first disrupting dendritic trees, sparing intermediate axons, indicating it to be an excitotoxin. Exact mechanisms of excitotoxic neuronal necrosis are not yet clear, but neuronal death involves hyperexcitation, and culminates in cell membrane rupture. Endogenous excitotoxins produced during hypoglycemia may explain the tendency toward seizure activity often seen clinically. The recent research results on which these findings are based are reviewed, and clinical implications are discussed.

THE DISCOVERY OF INSULIN in 1921 generated the initial interest in the possibility of brain damage resulting from hypoglycemia. This was due firstly to the occurrence of insulin overdose in the treatment of diabetes mellitus. The second reason for this interest was the deliberate administration of insulin in doses high enough to produce coma (“insulin shock” or insulin coma”), for amelioration of schizophrenia and other psychiatric conditions. This treatment modality was introduced by Sakel in 1933 and led many to suspect that a side effect, or indeed, the mechanism of action of such “therapy” was due to resulting brain damage. Insulin was also given for acne and for morphine addiction.

The pressing clinical issue of the appropriateness of insulin administration for psychiatric disease generated heated controversy. The stage was thus set for a period of intense experimentation in the 1930s. These physiologically uncontrolled experiments were designed to address the question of whether “permanent brain damage” could result from insulin administration.

Early authors tacitly defined “permanent brain damage” as neuronal loss and gliosis. Such changes were easily demonstrable after the long recovery periods used in these early experiments, ranging from days to weeks before insulin administration and sacrifice. The validity of such a definition of brain damage seems self-evident, since neuronal loss and gliosis constitute brain damage by any pathologic criteria. Yet the dark and light neurons which have been recently demonstrated in hypoglycemia followed by no recovery or short recovery periods have aroused controversy, as they do not meet such generally accepted pathologic criteria for “brain damage”.

The rejection of dark and light neurons as spurious observations was due to the well known occurrence of such cells in poorly fixed central nervous tissue, which led to the unquestioned assumption that all dark and light neurons in experimental nervous tissue are due to delayed or inadequate fixation. It now appears that this assumption is not valid. Dark neurons are seen in the brain acutely after excitotoxin administration, or after ouabain injection, neither of which hampers cerebral perfusion. Excitotoxins and dark neurons will be discussed more thoroughly below, but at present it will suffice to emphasize that dark neurons represent early and reversible neuronal injury of a nonspecific nature.

Early workers thus used recovery periods long enough to show neuronal fallout and gliosis, rather than transient and early neuronal alterations. However, they were unable to identify causative factors in the initial pathogenesis of neuronal necrosis. Remarkably, blood glucose levels were not reported in any of these early experiments, nor were physiologic parameters. Insulin itself was felt to be the substance harming the brain, epitomized by one set of experiments in which insulin was injected into the brain, both ante and post mortem. In spite of such shortcomings in experimental design, neuronal necrosis was clearly demonstrated in these early experiments, and its distribution was carefully described.

In the cerebral cortex, most workers described a superficial predilection for damage, although no interpretations of this were made. If hypoglycemia causes superficial cortical damage, with preservation of the remaining cortex clinical cases of irreversible post-hypoglycemic coma which demonstrate continued cerebral blood flow becomes less surprising. Continued perfusion of intact deeper cortical layers would be expected.

In the hippocampus, two research groups observed a relationship of necrotic neurons to CSF spaces. The American neuropathologist Arthur Weil and his collaborators noted involvement of the dentate gyrus near the ventricle, and explicitly stated that in hypoglycemic brain damage, toxic substances in the cerebrospinal fluid should be hypothetically considered, as well as the dominant vascular theories of Spielmeyer and the Vogts, respectively. This pre-
cient observation was then forgotten or overlooked by subsequent workers.

Since the results of this early period of intensive research had clearly demonstrated neuronal necrosis, and since the response rate of schizophrenia to insulin coma therapy was disappointing, insulin shock treatment gradually fell out of common use. Research interest in the structural aspects of hypoglycemic brain damage waned thereafter. Hypoglycemia was considered to be a form of ischemia, and the two insults were described as having the same neuropathology. The tacit assumption was that in conditions of either oxygen or glucose deprivation, internal deficiencies of neuronal energy metabolism developed, resulting in selective necrosis of neurons before glia. Neurons were felt to be selectively vulnerable because of their very active metabolism. This view prevailed until accumulating neurochemical data prompted a reexamination of the tenet that ischemic and hypoglycemic brain damage are identical deficiency states of the brain.

**Neurochemical Results**

It soon became apparent that there were considerable problems associated with the concept that ischemia and hypoglycemia were identical insults, producing neuronal necrosis by either substrate (glucose) or electron acceptor (oxygen) deficiency.

Neurochemical whole-brain analyses revealed profound differences between the two insults: in many parameters, the deviations from normal brain were actually in opposite directions. For example, cellular redox systems are reduced in ischemia, but are oxidised in hypoglycemia. Although brain pH is decreased in ischemia due to the formation of lactic acid, it is increased in hypoglycemia. This alkalosis is due both to the formation of ammonia from deamination of amino acids, and to the consumption of metabolic acids and the absence of lactic acid formation. Although alkalosis has been held to be directly responsible for acidophilic neuronal death, reported values for intracellular pH in hypoglycemia have differed among research groups. Derived values calculated from intracellular equilibria of weak acids suggest an alkalosis, conflicting with recent NMR data.

Energy failure, ion fluxes, and lipolysis are common to both ischemia and hypoglycemia. However, energy failure is considerably less severe in hypoglycemia than in ischemia, in spite of the normal dependence of the brain on both oxygen and glucose, which are consumed in a stoichiometric relationship. Depression of cerebral oxygen consumption in hypoglycemia is less than expected in proportion to depression of glucose utilization, indicating the considerable metabolic versatility of the brain in oxidizing non-glucose fuels to maintain its energy state.

Even lactic acid can be burned as fuel, reversing hypoglycemic stupor, but this functions only in immature animals due to the failure of blood lactate to enter the CNS in mature animals. However, production of lactic acid during hypoglycemia is not possible due to glucose deficiency. This likely explains why infarction is not a feature of uncomplicated hypoglycemia (see below).

In hypoglycemia profound enough to cause cessation of electrical activity (“isoelectricity”), ATP levels are still over one third of the normal values due to oxidation of endogenous substrates (proteins and fats) for fuel, whereas in ischemia ATP drops to less than 5% of normal. Lowering of the blood pressure during hypoglycemia results in no increase in neuronal necrosis, in spite of increased cellular release of potassium, and enhanced energy failure. Together, these results indicate that cerebral energy failure per se, as measured in whole brain analyses, does not account for the phenomenon of selective neuronal necrosis within the brain. Selective necrosis of neurons, sparing glia, seems instead to be related to the presence of excitatory receptors (see below) on neurons but not glia. Astrocytes and oligodendrocytes are also exposed to hypoglycemia and energy failure, and in spite of being metabolically active cells, demonstrate reactive changes but not necrosis in hypoglycemia.

When hypotension complicates hypoglycemia, all areas of the brain are not exposed to an equal fall in perfusion. Due to focal loss of autoregulation induced by the hypoglycemia, some regions are grossly underperfused whereas others show almost no fall in local cerebral blood flow. Glucose delivery to the most hyperperfused areas should be most compromised. However, tissue damage is not at all exacerbated in these regions. For example, the cingulate gyrus, severely hypoperfused when hypotension complicates hypoglycemia, does not show focal intensification in the density of neuronal necrosis. Blood flow is evidently not a critical determinant of hypoglycemia-induced neuronal necrosis.

The ionic and chemical changes in hypoglycemia take place abruptly at the onset of cerebral EEG isoelectricity. A prominent change in cerebral amino acids seen in hypoglycemia is a 3 to 4-fold rise in tissue aspartate and a fall in glutamate. This metabolic effect is related to either protein breakdown and/or lack of protein synthesis, with pooling of amino acids and a shift in the aspartate-glutamate transaminase reaction toward aspartate. The rise in tissue aspartate is of importance since this compound is a known neurotoxin by virtue of its excitatory properties (“excitotoxin”, see below).

Metabolically derived aspartic acid is also markedly increased when “focal hypoglycemia” is produced in the brain by local administration of halothane compounds, which poison glycolysis. This increase in aspartate occurs in spite of normal serum glucose levels, indicating the metabolic abnormality to be due to inhibition of glycolysis, rather than to low glucose levels per se.

In view of the summarized data that the onset of ionic and metabolic changes of hypoglycemia occur abruptly at the onset of cerebral EEG isoelectricity, it will come as no surprise that neuronal necrosis is ab-
sent in hypoglycemia unless the EEG becomes isoelectric, regardless of the blood sugar level at which the EEG goes flat. Furthermore, the duration of electrocerebral silence roughly determines the degree of resultant brain damage.

Blood-to-brain glucose transfer is effected chiefly by carrier mediated facilitated transport. However, the metabolic changes outlined above occur to a much lesser extent in the cerebellum than in the cerebrum. This may be due to a more efficient blood-to-brain glucose transport system or a denser capillary network in the cerebellum, giving rise to a lesser metabolic perturbation. Structural damage in the cerebrum far exceeds that in the cerebellum, in parallel with the metabolic findings.

Recent Morphological Results

Structural analysis in comparable rat models with long term survival have distinguished hypoglycemia as a brain insult unique from ischemia or epilepsy. Indefinite survival is possible even after 60 minutes of electrocerebral silence due to hypoglycemia in the rat. Thirty minutes of hypoglycemic isoelectricity gives rise to few necrotic neurons. These results in hypoglycemia are in accord with clinical experience.

The desired period of "insulin coma" during the period when this therapy was in vogue was 30 to 60 min. The distribution of brain damage is also unique in hypoglycemia. Necrotic neurons in several brain regions show a conspicuous relationship in the rat to the cisterns of the subarachnoid space. In the rat cerebral cortex (fig. 1), this relationship is seen as a superficial to deep gradient in necrotic neurons: layer 2 is more affected than layer 3, which is in turn more affected than layer 4. It should be noted that neurons in affected cortical laminae include both pyramidal and granule cell types. Thus, cellular necrosis in the cerebral cortex in hypoglycemia is not limited to one type of neuron.

In the hippocampus proper, neuronal necrosis is denser medially, in a gradient along the CA1 pyramidal neurons (Sommer's sector) and subiculum, which form a continuous cell band. Cells die within two hours medially where damage is greater than laterally. A lingering neuronal death often occurs laterally. With severe insults, all neuronal types are destroyed, including the "resistant" CA3 cells.

The dentate gyrus of the hippocampus shows consistent necrosis in hypoglycemia. As in the pyramidal cell band of the hippocampus, however, all dentate neurons are not equally affected. Granule cells related to the subarachnoid cisterns, for example those at the crest of the gyrus (fig. 2), facing the cistern velum interpositum, show early and conspicuous necrosis. The location of the dendritic tree, and not merely the cell body, appears to be a critical factor. Cell bodies with their dendrites facing the cisterna ambiens undergo necrosis whereas cells with dendrites under the fused hippocampal fissure are relatively spared.

Studies of the time course of damage in various
brain regions show that the cortex and hippocampus show early damage already after 10 min cerebral isoelectricity, whereas the caudate nucleus is normal for one hour following isoelectricity. Dark neurons, and then acidophilic neurons finally appear in the caudate, but develop later than in the cortex. Together, these facts suggest that a neurotoxin is carried into the caudate from the cerebral cortex, via the white matter bundles, giving rise to dark, and then necrotic neurons.

Results in other brain regions are in accord with those in the cerebral cortex, hippocampus, and caudate nucleus: Homogeneous neuronal populations are not uniformly affected. Rather, damage is located in well-defined locations often related to CSF spaces and white matter. For example, of the nuclei in the amygdaloid complex, only those portions near the lateral ventricle show necrosis, and in the cerebellum, Purkinje cell necrosis is seen in the folia facing the foramina of Luschka. With such evidence implicating a toxic substance in and around the brain, the question naturally arises as to the possible nature of such a toxin. The following boundary conditions are imposed by the neuropathology:

1. The substance must produce selective neuronal necrosis. This is to say it should be toxic only to neurons and not to glia or other cell types, since selective neuronal necrosis but not infarction is seen in pure, controlled hypoglycemic insults. The substance is thus a neurotoxin, not a histotoxin.

2. The neurotoxin must be capable of killing all neuronal types in the hippocampus, cerebral cortex, caudate nucleus and spinal cord, as necrosis of all these neuronal elements has been observed after controlled experiments delivering a “pure” hypoglycemia insult. Dentate granule cells and CA1 pyramidal cells must be more sensitive than CA3 pyramidal cells in the hippocampus. Small and medium sized neurons should be more vulnerable than large neurons in the caudate.

Molecules fulfilling these two basic criteria exist, and are termed excitotoxins, due to their parallel excitatory and neurotoxic properties. They bind to receptors located on neuronal dendritic trees and perikarya, causing increased neuronal spiking and neuronal depolarization. The sequence of critical events subsequently leading to neuronal death are as yet unclear, but there is no question that these compounds are capable of killing neurons. The characteristic neuropathology is destruction of dendrites in the neuropil due to the location of receptors for these substances on the dendrites, while axons, which lack such receptors, are spared. Selective neuronal necrosis results when cell membrane destruction spreads from dendrites to neuronal perikarya. The glia survive.

Is there evidence in hypoglycemia that the neurotoxin is an excitotoxin? Recent results give an affirmative answer. Examination of the dendritic trees of hippocampal neurons destined to undergo necrosis reveals early dendritic, axon-sparing lesions (fig. 3). Swollen dendrites, containing swollen mitochondria
Removal of the excitatory cortico-striatal inputs to the caudate by cortical ablation, a procedure which would lead to degeneration of excitatory amino acid receptors on caudate neurons, virtually abolishes neuronal necrosis in the caudate nucleus. Furthermore, removal of the dopaminergic input to the striatum with 6-OH dopamine lesions of the substantia nigra also reduces selective neuronal necrosis in the caudate. The latter procedure does not even remove a pathway using an excitotoxic amino acid (e.g., glutamate, aspartate) as a neurotransmitter, but merely one which may modulate neuronal excitation in the caudate (See Lindvall et al for discussion.) Clearly, the degree of excitotoxic neuronal necrosis is affected by inhibitory and excitatory inputs.

Pharmacologic blockade of excitotoxin receptors also prevents neuronal necrosis. Together with the morphologic findings, these results lend considerable support to an excitotoxic mechanism of neuronal death in hypoglycemia, rather than catabolism due to a glucose deficiency state directly killing the neuron.

Conclusions

It is possible to draw eight conclusions regarding hypoglycemic brain damage, which can now be summarized:

1. In the rat, neuronal necrosis is absent in hypoglycemia unless the EEG becomes isoelectric.
2. Quantitated neuronal necrosis increases as the duration of EEG isoelectricity increases.
3. Both the density and the distribution of brain damage is unique in hypoglycemia.
4. Although different neuroanatomical cell types are differentially susceptible to necrosis, eventually all neuronal types can undergo necrosis with a high dose of insult.
5. The same neuroanatomical cell type may be only partially affected in a "subanatomic distribution".
6. In the rat, with progressively longer periods of isoelectricity, neuronal necrosis appears first in susceptible brain regions exposed to subarachnoid spaces, second in portions of brain apposed to other brain surfaces, and lastly in deeper regions. This suggests a toxic substance accumulating in the CSF.
7. The fact that only selective neuronal necrosis and not infarction is seen in even severely damaged brains after purely hypoglycemic insults indicates the hypoglycemic toxin is a neurotoxin, and not a histotoxin.
8. The axon-sparing, dendrosomal nature of the neuronal lesion, and its prevention by antagonists of excitotoxin receptors, indicates that the hypoglycemic neurotoxin is an excitotoxin.

Synthesis

A synthesis of the likely events leading to neuronal death in hypoglycemia can now be made. As the blood glucose falls to the range of 2.0–2.5 mM, slowing of the EEG appears. As energy failure progresses, ionic pumps cannot be maintained and ions run down their concentration gradients. These events begin focally, but spreading depression of cortical activity occurs, often asynchronous within or between the hemispheres. EEG silence ensues. A new metabolic homeostasis is achieved, with an ATP level of roughly 25% of control, maintained due to oxidation of endogenous substrates within the brain. The aspartate-glutamate reaction reaches a new steady state, the equilibrium being markedly shifted toward aspartate. This metabolically-derived aspartate is released into the extracellular space of the brain, first into the interstitial space and ultimately into the CSF.

The question naturally arises as to why there should be a relationship of necrotic neurons or their dendrites to CSF spaces, if an excitotoxin is endogenously produced by the brain parenchyma. It is known that the interstitial fluid of the brain is derived from the arterial end of the microcirculation at the capillary-glial complex, most of it undergoing resorption into the blood stream at the venular end of the microcirculation. The balance of unresorbed interstitial fluid courses through the brain parenchyma toward the CSF to be ultimately resorbed by the arachnoid villi. Dilution of any excitotoxin produced and locally released by the brain into the CSF occurs only via mixing with CSF from the distant choroid plexus. Cerebral interstitial fluid, in contrast to CSF, is renewed in closer proximity to its source at the arterial end of the microcirculation by blood pressure driven production. Thus, an endogenously produced excitotoxin might still appear in higher concentration in the CSF than at its site of production, due to proximal "washout" and constant renewal of cerebral interstitial fluid. Subarachnoid CSF, especially that surrounding the spinal cord, is known to be relatively stagnant due to relative remoteness from choroid plexus tissue, and poor exchange of spinal and cerebral CSF.

The released excitotoxin, likely aspartate, then
binds to neuronal dendrites, initiating a lethal chain of cellular events. Further experiments are necessary to clarify the exact events responsible for excitotoxic neuronal death, and their sequence.

**Future Research**

How do excitotoxins kill neurons? Once an excitotoxin binds to neuronal dendrites, definite mechanisms leading to neuronal death are still unclear, but ionic fluxes probably play a crucial role. Excitotoxins cause an influx of Ca$^{2+}$ ions into neurons, with calcium dependent neurotoxic effects. Lipolysis is cayctivated by calcium. Should degradation of dendritic cell membranes occur in this process of Ca$^{2+}$ activated lipolysis, then neurons would be effectively open to the extracellular space and unable to compartmentalize cytoplasm. Such a sequence may occur in excitotoxic neuronal death.

Excitotoxins can be classified into those which produce only local lesions, and those which produce both local and "distant" lesions, the latter arising in a brain region remote from an injection site. The distant lesions appear to arise by transsynaptic mechanisms, and are seen with excitotoxins capable of producing a seizure-related brain damage (SRBD) syndrome. The latter consists of severe status epilepticus and selective neuronal necrosis in a trans-synaptic distribution. In contrast to findings in epilepsy, where a trans-synaptic distribution is seen, no brain regions show a trans-synaptic distribution in hypoglycemia. An SRBD syndrome has not been seen in experimental studies of hypoglycemia.

Excitotoxin with a predominantly local effect is thus implicated.

Increased aspartic acid levels in brain tissue during hypoglycemia, and a largely local neuronal destruction resulting from injections of aspartate into brain tissue, make endogenously produced aspartic acid the most likely excitotoxic agent mediating the neuronal necrosis in hypoglycemia. However, quinolinic acid, an endogenous cerebral tryptophan metabolite, is lethally excitotoxic in nanomole quantities and might also be produced during hypoglycemia. Quinolinic acid levels have not yet been measured during hypoglycemia.

In hypoglycemia, it is necessary to measure cerebral interstitial fluid levels of excitotoxins using either intracerebral microdialysis or push-pull cannulae, comparing them with CSF levels of excitotoxins. The obvious experiment suggested by the data available is transfer of either cerebral interstitial fluid or cerebrospinal fluid from a hypoglycemic rat into the brain of a recipient animal. If excitotoxic pathology could be demonstrated by light microscopy (selective neuronal necrosis), and by electron microscopy (ie an axon-sparing lesion), this would constitute definite evidence for a fluid-borne excitotoxin in such a "transfer bioassay" experiment.

**Neonatal Hypoglycemia**

Neonatal hypoglycemia in all probability constitutes an entirely different situation from the adult with regard to hypoglycemic brain damage. Metabolically, the immature brain has the capability to oxidize lactate for fuel, an apparent protective response to neonatal hypoglycemia.

Pathologic responses in the immature brain are also different from that seen in adult animals. The dark cell phenomenon in aldehyde fixed tissue, a non-specific neuronal reaction to excitotoxic administration, ouabain administration, or mechanical injury prior to fixation is not seen prior to a certain stage of neuronal maturation. Thus, the dark neuron, a cellular response of the brain seen acutely in hypoglycemia, and likely representing neuronal ion and water shifts, does not occur in the neonatal brain.

Excitotoxic neuronal death would be theoretically impossible prior to developmental maturity of neurotransmitter systems and cell surface receptors. Hypoglycemia to less than 20 mg/100 ml usually gives rise to cerebral EEG isoelectricity and consequently brain damage in the mature brain. In the neonate, glucose levels in this range uncommonly give rise to a permanent neurologic deficit if the hypoglycemic episode is asymptomatic. Work is needed specifically on neonatal hypoglycemia and at present, an excitotoxic mechanism should not be assumed by transfer of findings obtained in adult animals to neonates. The few studies that have addressed the problem of neonatal hypoglycemia have demonstrated structural brain damage in both man and experimental animals, the mechanism of which remains unclear.

**Clinical and Medico-Legal Aspects**

Although a SRBD syndrome of continuing and intractable seizures does not characterize hypoglycemia, it is well known clinically that seizures are a manifestation of profound hypoglycemia, prior to the stage of coma. When the EEG becomes isoelectric, corresponding to clinical coma, the energy failure and cortical depolarization make seizure manifestations impossible. But the onset of EEG isoelectricity is not a simultaneous event over the cerebral hemisphere. Rather, the wave of ionic shifts and cortical depolarization spread over the hemisphere, not unlike cortical spreading depression. Portions of the cortex which are already isoelectric may well release excitotoxin before an adjacent cortical region. The resulting excitation, possibly combined with the depletion of the inhibitory neurotransmitter GABA may account for seizure phenomena in hypoglycemia. Focality of initial electrical events and energy failure may also explain the focal symptoms often seen in hypoglycemia, when no focal perfusion deficit can offer a satisfactory explanation. Another explanation for focal symptoms in hypoglycemia may be focal hyperperfusion, probably operating via decreased glucose delivery to the tissue. However, it is to be emphasized that focal hyperperfusion in hypoglycemia can account for reversible functional deficits, but not neuronal necrosis.

Although amyotrophy in diabetic patients may be due to peripheral neuropathy of the axonal type, rather
than to anterior horn cell damage, necrosis of the motor neurons of the spinal cord has been reported after profound hypoglycemia. Lower motor neuron paresis develops slowly and is delayed after the episode of hypoglycemia, possibly reflecting a delayed excitotoxic death of susceptible motor neurons of the anterior horn due to accumulation of an excitotoxic amino acid in the stagnant CSF surrounding the spinal cord.

It is apparent that structural damage to the nervous system in humans resembles that seen in animals, appears independent of the agent causing the hypoglycemia, having been seen in patients after oral hypoglycemic agents or islet cell adenoma of the pancreas in addition to insulin overdose in diabetes. The etiology of the hypoglycemia is thus not important in the immediate clinical situation, and clinical efforts are best directed toward rapid return of plasma glucose levels to normal and avoidance of cerebral EEG isoelectricity. Death due to severe brain damage from therapeutic “insulin shock” for psychiatric disease is fortunately no longer seen.

The third conclusion listed above may have medicolegal implications: If a superficial laminar necrosis of neurons is demonstrable in the cerebral cortex in an autopsy case of possible insulin overdose, as has been demonstrated, then hypoglycemic brain damage is very likely, as this pattern has not been reported after ischemia. A laminar distribution of neuronal necrosis to the middle cortical laminae would favor ischemic brain damage, and a transcortical distribution of necrotic neurons would be unhelpful in distinguishing ischemic from hypoglycemic brain damage.

The absence of infarction in experimental models of hypoglycemic brain damage may tempt one into attributing infarction only to primary ischemic insults. However, when glucose is administered following profound hypoglycemia, there is considerable post-hypoglycemic hyperperfusion. More importantly, lactic acid levels rise to supra-normal levels in the tissue. As high lactic acid levels in brain tissue appear to promote infarction, it may be judicious to administer glucose slowly and continuously when recovering clinical cases of hypoglycemic coma, in order to prevent infarction in the recovery phase. The EEG is useful in monitoring recovery, returning in minutes after a mild hypoglycemic insult, but after longer periods following a more prolonged period of hypoglycemia.

The presence of absence or infarction should thus not be used by the neuropathologist in a medicolegal situation in attempting to differentiate, with certainty, ischemic from hypoglycemic brain damage. Infarction may well develop secondarily in the recovery period after hypoglycemia, due to tissue lactic acidosis after too rapid glucose administration.

Acknowledgments

The author is grateful to Drs. Bo K. Siesjö, Tim Watson and Rolando Del Maestro for comments on the manuscript, and to Caroline Collins for typing the manuscript.

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Stroke. 1986;17:699-708
doi: 10.1161/01.STR.17.4.699

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