CEREBRAL ENERGY METABOLISM, GLUCOSE TRANSPORT AND BLOOD FLOW: CHANGES WITH MATURATION AND ADAPTATION TO HYPOGLYCAEMIA

A. NEHLIG

SUMMARY - Brain maturation is characterized by a peak of cerebral energy metabolism and blood flow occurring between 3 and 8 years of age in humans and around 14-17 days of postnatal life in rats. This high activity coincides with the period of active brain growth. The human brain is dependent on glucose alone during that period, whereas rat brain uses both glucose and ketone bodies to cover its energetic and biosynthetic needs. The maturation of the density of glucose transporter sites-GLUT1 located at the blood-brain barrier and GLUT3 at the neuronal membrane -parallels the development of cerebral glucose utilization. During moderate acute hypoglycaemia, there are no changes in cerebral functional activity; cerebral glucose utilization decreases and blood flow increases only when hypoglycaemia is severe (lower than 2 \( \mu \text{mol/ml} \)). During chronic hypoglycaemia, the brain adapts to the low circulating levels of glucose: the number of glucose transporter sites is increased, and cerebral glucose utilization and function are maintained at normal levels while cerebral blood flow is more moderately increased than during acute hypoglycaemia. Neuronal damage consecutive to severe and prolonged hypoglycaemia occurs mainly in the cerebral cortex, hippocampus and caudate-putamen as a result of active release of excitatory amino acids.

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Key-words: cerebral maturation, cerebral glucose utilization, cerebral blood flow, cerebral glucose transporters, hypoglycaemia.
Under most conditions, glucose is the principal metabolic fuel of the human brain. Oxidation of other substrates only occurs to a significant degree during abnormal circumstances such as starvation [1] and hypoglycaemia [2]. A few brain regions not lying beyond the blood-brain barrier (BBB) appear to be able to use fats as a source of energy [3] and may not be as dependent on glucose as all other brain regions. Because endogenous levels of glucose and glycogen are rather low, the brain relies on a continuously sustained supply of glucose from the blood [4]. Since the brain is isolated from the regions using the lowest LCBF, glucose passes through endothelial cells and the plasma membranes of neurons and glia. Brain glucose metabolism, unlike that of skeletal muscle, is not transport-limited but rather phosphorylation-limited [5, 6]. Under normal circumstances, the unidirectional blood-to-brain transfer of glucose is in considerable excess (3:1) of the cerebral glucose utilization rate [7, 8]. Even when transport becomes limiting, as in hypoglycaemia, the limitation is at the BBB, not at neuronal or glial cell membranes, since glucose is rapidly transported from cerebral extracellular space to the intracellular compartment [7, 9].

In the present review, we will consider the rates of glucose utilization in the developing brain, the efficiency of glucose transport to the brain in both normoglycaemic and hypoglycaemic conditions and how the brain is able to adapt to hypoglycaemia.

**RELATION BETWEEN CEREBRAL GLUCOSE UTILIZATION AND BLOOD FLOW IN THE ADULT BRAIN**

In adult man as in adult animals, glucose represents the main, if not the sole, substrate of brain energy metabolism. All the glucose extracted by the brain is oxidized, and at most 8-10% are anaerobically degraded or stored in tissues [4]. Thus, cerebral glucose utilization parallels cerebral oxygen uptake, showing the same regional heterogeneity. Local cerebral metabolic rates for glucose (LCMRglc) are very heterogeneous in brain tissue, with a ratio of about 4 between regions using the lowest amount of glucose (hypothalamus, amygdala) and those consuming most (auditory regions) [10, 11]. This is true for all species, e.g. rats [10], cats [12], monkeys [13, 14] and humans [15].

In the adult brain, rates of local cerebral blood flow (LCBF) are usually closely related to metabolic demands, so that the regions with the highest LCMRglcs also have the highest rates of LCBF. Likewise, changes in LCMRglcs are accompanied by parallel changes in LCBF rates [16, 17]. This regional relation between cerebral blood flow and metabolism has been demonstrated in both adult humans [18, 19] and animals [16, 17]. The ratio between the rates of LCBF and LCMRglcs for all brain regions is approximately 1.5 in favor of blood flow [11, 16, 17].

**CEREBRAL GLUCOSE UTILIZATION IN THE DEVELOPING BRAIN**

**Human brain** – In human infants of 5 weeks of age, cerebral glucose utilization, as measured by positron emission tomography with $^{18}$F-fluorodeoxyglucose, already represents 71-93% of the adult level in most brain regions, with absolute values ranging from 13 to 25 µmol/100 g/min. At that age, LCMRglcs are highest in the sensorimotor cortex, thalamus, midbrain-brainstem and cerebellar vermis, underlying the predominantly subcortical and primitive sensorimotor level of function at that age. By 3 months, LCMRglcs increase in the parietal, temporal and occipital cortices, as well as in basal ganglia. At that time, many of the intrinsic subcortical reflexes are being suppressed, and more coordinated motions as well as visuomotor integration are appearing. By 8 months, subsequent increases in LCMRglc occur in the frontal cortex and various associative regions, and are accompanied by the appearance of higher cortical and cognitive functions and by more meaningful interaction with surroundings [20, 21].

Adult levels of cerebral glucose utilization (19 to 33 µmol/100 g/min) are reached by 2 years of age. Thereafter, LCMRglcs continue to increase until by 3 to 4 years of age when they reach values ranging from 49 to 65 µmol/100 g/min that are maintained at that age until age 9. They then begin to decline, reaching adult levels by the end of the second decade. The highest increases of LCMRglcs over adult levels occur in the cerebral cortex, while lesser increases are recorded in subcortical structures and the cerebellum. The high levels of brain energy metabolism in children during the first decade of life underlie the basal energy needs of the brain as well as the biosynthetic requirements for the very active maturational processes occurring during that period. Indeed, in children up to 11 years of age, there is an overproduction of neurons, synapses and dendritic spines [22, 23]. At 7 years of age, when the child’s brain has almost the same size and weight as the adult brain, average synaptic density in the frontal cortex is about 40% higher than in the same region of the adult brain [24]. Many neurons subsequently die, and there is a regression of dendritic spines and synapses [25]. Myelination, the other specific process of brain maturation occurring during the first decade of human life, is responsible for excessive energy expenditure [26, 27].

**Rat brain** – Contrary to the human brain, the glucose consumption of whole rat brain is very low at birth.
(2-4 μmol/100 g/min) and then undergoes a sigmoid rise between birth and adulthood, reaching 65-72 μmol/100 g/min in the adult rat brain [10, 28]. The measurement of LCMRglcs in the developing rat brain, as assessed by the quantitative autoradiographic [14C]2-deoxyglucose method [10] applied to the immature rat in our laboratory [29], showed that LCMRglcs are low and quite homogeneous at the early stages of postnatal development in the rat, i.e. between 10 and 17 days (Figs. 1 and 2), with the exception of higher rates in some posterior areas, mainly brainstem regions [29]. Most of the significant increases in LCMRglcs occurring between 10 and 17 days in the rat are correlated with the acquisition of specific functions, such as audition between P10 and P14. Indeed, the rat is deaf at birth. The opening of the external auditory meatus and the appearance of a high sensitivity to sounds and auditory evoked potentials correlate with a specific increase in LCMRglcs in auditory regions between 10 and 14 days. The same kind of correlation has been established for the acquisition of visual function as well as locomotion and playful activities between 14 and 17 days of postnatal life in the rat [28, 29].

Contrary to what occurs in the human brain, LCMRglcs in the rat do not undergo a transient increase during maturation. Instead, LCMRglcs of the immature rat brain undergo a sigmoid rise during postnatal development and are never higher than those found in the adult brain (Fig. 2). LCMRglcs increase by about 50% between 17 and 21 days of age, and this rise is widespread and unspecific. After weaning time, i.e. 21-22 postnatal days, LCMRglcs increase in all brain regions by a mean value of about 25% until 35 days of age. Finally, between 35 days and the young adult stage (about 60 days), cerebral glucose utilization matures further in some brain regions (mainly cortical, motor and limbic forebrain areas), whereas the hypothalamus has reached maturity by 35 days, i.e. at the age of puberty in the rat [29].

**Fig. 1.** [14C]2-Deoxyglucose and [14C]β-hydroxybutyrate autoradiograms of brain sections of rats between postnatal age (P) 10 and 21 days obtained at the level of the substantia nigra. Grain density is low and quite homogeneous in sections representing cerebral glucose utilization in P10 and P14 rats, except in mammillary body (MB). By P21, the distribution of grain density increases and becomes heterogeneous in many regions, resembling the distribution of labeling in adult rat brain. Grain density is quite high in regions such as the medial geniculate body (MG), the auditory cortex (TeAud), the hippocampus (Hi) and the substantia nigra pars compacta (SNC) which appears as a dark line bordering the substantia nigra pars reticulata (SNR) whose grain density is much lower. Concerning β-hydroxybutyrate uptake, grain density is highest at P14, at which age its distribution within regions is more homogeneous than that of [14C]deoxyglucose.
We may conclude that increases in LCMRglcs in the human infant and the rat pup are in good agreement with behavioural, neurophysiological and anatomical changes known to occur during brain development, as shown in other species such as lambs [30], monkeys [31] and cats [12].

**CEREBRAL KETONE BODY UTILIZATION IN DEVELOPING RAT BRAIN**

Because of the high lipid, low carbohydrate content of maternal milk, the rat pup develops a nutritional ketosis soon after birth which lasts throughout the whole suckling period [for review, see 28]. During that period, ketone bodies constitute an important proportion (22-76%) of the total energy metabolism balance of the brain, and positive cerebral arteriovenous differences for β-hydroxybutyrate and acetoacetate, proportional to their concentration in arterial blood, are recorded [1, 32-34]. The development of autoradiographic techniques has recently allowed the measurement of regional rates of β-hydroxybutyrate uptake in the adult [35, 36] and the suckling rat brain [37].

These studies show that the uptake of β-hydroxybutyrate by the immature rat brain is quite high during the whole suckling period, from 10 to 17 days, reaching peak levels at 14 and 17 days (Fig. 2) [37, 38]. These results are consistent with previous studies reporting that the rate of β-hydroxybutyrate utilization is highest in brain from 11 to 15 days [39, 40]. Between 17 and 21 days, regional rates of β-hydroxybutyrate uptake decrease by 50 to 60% in all brain regions [37, 38]. This decrease is concurrent with a marked increase in local cerebral glucose utilization during the same period [29]. Thereafter, from 21 to 35 days, β-hydroxybutyrate tissue accumulation decreases further, by about 50% in most brain areas, except in cerebral cortex where the decrease is less marked (10-20%) [37]. These data are consistent with the high permeability of the BBB to ketone bodies and the high activity of the enzymes of ketone body metabolism in the suckling rat brain [for review, see 28]. Whereas regional rates of cerebral glucose utilization show marked heterogeneity, those of ketone body uptake are more homogeneous, even at 14 days when they are highest (Fig. 1). Ratios between the most highly labeled (vestibular nucleus or inferior colliculus) and least labeled structures (globus pallidus or hypothalamus) reach a value of 1.3-2.0 during suckling [41, 42]. This quite relative interregional homogeneity of ketone body uptake during suckling is consistent with the important role of ketone bodies as precursors for aminoacid and lipid biosynthesis, thus for membrane and myelin edification [for review, see 28]. It is thus quite likely that ketone bodies participate in these biosynthetic processes at a comparable efficiency in all brain regions during early development. In 35 day-old control [37] and adult rats [35, 36], the highest levels of β-hydroxybutyrate uptake are found in cerebral cortex, mainly in the deeper layer. The high levels of β-hydroxybutyrate accumulation in specific regions of the adult rat brain are attributed to a regional heterogeneity in the permeability to ketone bodies [35, 36], which does not exist in the suckling rat brain when rates of ketone body transport are very efficient [43-46]. Moreover, in immature rat brain, which is dependent on both glucose and β-hydroxybutyrate for its energy metabolism and biosyntheses, changes in LC-
MRGlc is region-specific and underlie functional changes [29], as in the human brain [20,21], whereas ketone bodies appear to be oriented towards cellular edification. Conversely, in the human brain, active brain growth occurs mainly between 3 and 9 years of age when glucose is the sole cerebral substrate in normal conditions.

**CORRELATION BETWEEN RATES OF CEREBRAL ENERGY METABOLISM AND BLOOD FLOW IN THE DEVELOPING BRAIN**

In the human infant, postnatal changes in regional CBF rates are similar to those of LCMRGlces. At birth, cortical CBF rates are lower than those of adults; after birth, they increase until 5 to 6 years of age, reaching values 50-85% higher than adult rates. Thereafter, they decrease to adult level by 15 to 19 years of age. Neonatal values of CBF in the thalamus and cerebellum are slightly higher than corresponding adult rates, but after 1 year of age they follow the common pattern for cortical curves [47]. Thus, the highest rates of LCBF occur in all brain regions at the period when the highest LCMRGlces are recorded, i.e., from 3 to 9 years of life [20, 21, 47-49], and the cognitive development of the child is related to changes in blood flow in the different brain regions [47].

Contrary to the situation in the human brain, postnatal changes in LCBF rates in the rat differ significantly from the maturation of LCMRGlces. Like LCMRGlces, LCBF rates remain low and homogeneous in the rat until 10 days of age, representing 18-35% of adult levels. However, after 14 days, they increase by 110-240%, reaching a quite high value at 17 days similar to LCBF rates recorded at 35 days. Between 17 and 21 days, LCBF rates decrease by 15-40%. After weaning time, LCBF rates increase again in the manner of LCMRGlces changes during the same period until they reach adult levels [50]. In the rat, the most active brain growth phase takes place before weaning when the animal depends on both glucose and ketone bodies as substrates for metabolic and biosynthetic pathways. When average brain levels of glucose and 3-hydroxybutyrate utilization are summed up to represent the total supply of metabolic substrates, the peak level of energy metabolism is situated at 14 days [28], i.e., at the same period as the LCBF peak [50].

Thus, in the human infant and the rat pup, rates of cerebral energy metabolism and blood flow remain associated during development, with the highest rates occurring for both species during the period of active brain growth. The difference is that the peak of functional activity during early development is higher than adult rates of LCBF and LCMRGlces in humans and about equal to adult rates in rats.

**GLUCOSE TRANSPORT TO THE BRAIN**

Glucose enters the brain via a carrier-mediated, facilitated diffusion process, which is saturable and stereospecific as well as energy-, Na+- and insulin-independent [7, 8]. This process is mediated by facilitative glucose transporter proteins. Seven members of this multigene family have been identified to date, which are known as GLUT1-7 for the order in which they were cloned [for review, see 51, 52]. Two of them, GLUT1 and GLUT3, have been detected in brain [53, 54]. GLUT1 is located at the BBB and GLUT3 allows the transport of glucose across the plasma membrane of neurons [51, 55]. Human brain microvessels are richly endowed with a glucose transporter moiety similar to the GLUT1 transporter characterized in other mammalian species [56]. Likewise, GLUT3 is expressed in the mature neuronal processes of human brain regions, which suggests that it plays a role in regulating fuel requirements for dendritic and axonal trafficking, thereby mediating neurotransmission [57].

GLUT1 is present in mammalian (including human) placentae. It is generally abundant in placental cell populations bordering on the maternal and foetal circulations and may therefore facilitate effective glucose supply to the foetus and placenta [58]. In rodent brain, GLUT1 is located at the BBB and distributed rather homogeneously in the different brain areas. It is not abundant at birth, constituting about 15% of the adult level, but increases fourfold between 14 days of age and the adult stage [55, 59, 60]. These data are concordant with postnatal maturation of the capacity for glucose uptake from the blood to the brain [61-63]. The lack of regional heterogeneity in GLUT1 expression is consistent with its regulation by the growth and nutritional state of the animal.

GLUT3, which is specifically located in neurons, has a very low density in rat brain at birth and increases concurrently with LCMRGlces [29], attaining a regional heterogeneous distribution in the mature brain [55]. In the human brain, the density of GLUT3 is 2-3 times lower at birth than in the adult [57]. The regulation of neuronal GLUT3 appears to be more closely related to the maturation of functional activity in neuronal populations and directly reflects postnatal changes in cerebral glucose utilization [55].

During mild hypoglycaemia resulting from starvation, GLUT1 mRNA and protein are increased by 31 and 25% respectively. During moderate insulin-induced hypoglycaemia (4.5 μmol/ml), GLUT1 mRNA and protein increase by 41-43%. These increases are specific for brain, as no changes are observed in liver or kidney [64]. GLUT1 mRNA also increases in rat cell cultures in a dose- and time-dependent fashion, with the maximum effect observed 20-24 h after the onset of hypoglycaemia [65]. GLUT3 mRNA expression is also regulated by hy-
hypoglycaemia and increases twofold with a blood glucose level of 1.7 μmol/ml. This increase occurs in selective brain regions including the hippocampus, dentate gyrus, cerebral cortex and piriform cortex, but not the cerebellum [66]. These data show that glucose, nutritional and endocrine status can directly regulate the expression of brain glucose transporters.

In humans, the data are less clear. In one study, mild hypoglycaemia (about 3.0 μmol/ml) resulted in a threefold increase in hexose transfer across the BBB compared to saline-infused or euglycaemic controls [67]. In another study, the same range of hypoglycaemia (2.7 μmol/ml) was found to decrease glucose clearance through the BBB by 50 % [68].

### EFFECTS OF ACUTE HYPOGLYCAEMIA ON CEREBRAL GLUCOSE UTILIZATION

When arterial glucose concentration falls below a critical level, abnormal electroencephalographic (EEG) activity and mental symptoms ranging from lethargy to confusion, stupor and coma appear. Cerebral energy metabolism is altered, and energy failure may eventually occur [69-71]. All these symptoms vary according to the severity of hypoglycaemia. The EEG correlates with the degree and duration of carbohydrate depletion in cortical tissue. The rapid decline of brain glucose levels occurs without remarkable EEG changes. Slow-wave and paroxysmal activity appear in the EEG when the intracellular concentration of glucose reaches zero, and the EEG finally becomes isoelectric when glycogen and glucose-6P are depleted [71-73].

**Energy metabolism changes** – When plasma arterial concentration falls from a normal level of 6-7 μmol/ml to about 2.5-3 μmol/ml, cerebral glucose content decreases in a directly proportional manner to whole blood glucose concentration [72], while cerebral energy metabolism remains unchanged. Below 2.5 μmol/ml, glucose transport into the brain diminishes to a point where brain glucose no longer saturates hexokinase and becomes rate-limiting and insufficient to support brain energy metabolism [74, 75]. At that concentration, tissue glucose content is so low that it mainly represents glucose contained in blood vessels and extracellular fluid [75], and LCMRglcs decrease as a function of plasma glucose levels [70, 77-80].

As long as arterial glucose levels are at least equal to 2.6 μmol/ml, LCMRglcs remain normal in the adult rat [81]. When they drop to 2.0-2.4 μmol/ml, they tend to decrease in all brain regions, but this decrease reaches significance only in specific areas. In one study, the greatest reductions occurred in brainstem regions in which glucose utilization is normally high, suggesting that glucose delivery and transport become rate-limiting first in the structures with the greatest metabolic demands for glucose [82]. In another study, rates of cerebral glucose utilization were decreased in brainstem, but also in cerebral cortex, thalamus and caudate-putamen [83]. Unlike the other studies that quantified glucose utilization by the [14C]2-deoxyglucose method [10], the latter one used [6-14C]glucose for the measurement of LCMRglcs and encountered methodological problems [84, 85].

During severe acute hypoglycaemia (1.0-1.4 μmol/ml), when EEG activity is isoelectric, LCMRglcs become limited by an influx in all brain areas and markedly decrease (20-65 %). Metabolic depression was generalized to all structures in one study [83], and to all except the hypothalamus and the cerebellum in another [81]. The relative protection of brain glucose content and energy metabolism in the cerebellum, as compared to the cerebral cortex, has also been demonstrated by biochemical techniques [86].

In humans, the Kety-Schmidt method and the positron emission tomography technique have shown that there is a uniform decrease in the rates of cerebral glucose utilization induced by moderate hypoglycaemia [68, 87, 88]. Contrary to the rat, a 40 % decrease in cerebral glucose consumption was recorded in humans after a 55 % reduction of blood glucose, i.e. 2.7 μmol/ml [68]. However, the effects of hypoglycaemia on LCMRglcs in humans should be more extensively studied, possibly by more precise anatomical methods than positron emission tomography.

**Utilization of other substrates** – During acute hypoglycaemia of moderate intensity, the ratio of the arteriovenous difference in glucose to the arteriovenous difference in oxygen in the cerebral cortex does not change until arterial blood glucose levels reach a value of about 2 μmol/ml. Below that value, the decrease in LCMRglcs always exceeds that of LCMRO 2 in the rat [80] and the cat [89], indicating that the brain is using other substrates from endogenous and exogenous sources. Endogenous carbohydrate reserves such as glycogen are exhausted quite rapidly after insulin injection [2, 80] and thereafter contribute negligibly as an oxidative fuel. Brain amino acids [72] and phospholipids [90] can serve as metabolic substrates, and the latter represent a potentially large energy reserve. The cerebral uptake of β-hydroxybutyrate, an exogenous substrate, is also largely increased during hypoglycaemia [80]. Cerebral metabolism of ketone bodies is limited by their rate of transport through the BBB [33, 34, 38, 91]. However, during acute hypoglycaemia in the rat, the arterial concentration of ketone bodies in arterial blood is comparable to the level in normoglycaemia, suggesting that transport of ketone bodies across the BBB is facilitated, as occurs in prolonged starvation [92]. Hypoglycaemia producing...
isoelectric EEG is accompanied by an oxidation of NADH, demonstrating that the supply of reducing equivalents to the respiratory chain is decreased and that alternative substrates cannot fully replace glucose as a source of reducing equivalents to the respiratory chain [89].

During hypoglycaemic coma, the cerebral uptake of β-hydroxybutyrate becomes negligible and amino acid metabolism, as reflected by ammonia accumulation, is enhanced. The cerebral concentration of free fatty acids increases four- to sixfold during that state, thus inhibiting the metabolism of β-hydroxybutyrate by competition for available coenzyme A [80].

In humans, the brain can use ketone bodies in sufficient quantities to influence its function during acute glucose deficit in the postabsorptive state. Articr concentration of fatty acids and ketone bodies is not changed during short-term hypoglycaemia but increases 150-200 % above basal levels during prolonged hypoglycaemia [93]. This acute use of ketone bodies produces immediate changes in neurohormonal responses to hypoglycaemia [93, 94]. Likewise, the infusion of lactate substantially diminishes catecholamines, growth hormone, cortisol, and symplomatic responses to hypoglycaemia in humans [95] and animals [96]. Lactate is also associated with a significant lowering of the plasma glucose level at which the brain deteriorates, suggesting that lactate protects neuronal function [95].

Recovery from hypoglycaemia – The rate and degree of recovery after glucose administration depends on the duration and severity of hypoglycaemia and the neurological state of the animal before the insult. After 10 min of glucose infusion, rats subjected to hypoglycaemia inducing at most 1 min of coma fully recover their high-energy phosphate stores as well as a normal neurological state. However, when normalization of plasma glucose levels is delayed for more than 1 min of coma, CMRO₂, remain depressed and high-energy plasma glucose levels is delayed for more than 1 min neuronal state. However, when normalization of their high-energy phosphate stores as well as a normal cerebral function [95].

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108]. In addition to changes in blood flow in response to hypoglycaemia, autoregulation of LCBF is lost in all cortical regions, the thalamus and the hippocampus, whereas the other regions have well-preserved LCBF rates at low blood pressures. Thus, during severe hypoglycaemia, even relatively moderate arterial hypotension may add a circulatory insult to the hypoglycaemic one and affect some brain structures more than others [109].

During the recovery period, LCBF rates are notably reduced in some brain areas, i.e. cerebral cortex, hippocampus and caudate-putamen, which show blood-flow rates of only 20-35% of control values. In other regions, namely pontine reticular formation and cerebellar cortex, hypoperfusion does not occur [100]. The regions in which flow is reduced during the recovery period also show a marked concomitant reduction in LCMRgls [81]. However, the reductions in flow levels are more marked than those in LCMRgls, thus inducing a mismatch between cerebral bloodflow and glucose utilization rates during the recovery period which could lead to the final cell damage incurred [81, 100].

**COMPARISON OF EFFECTS OF ACUTE AND CHRONIC HYPOGLYCAEMIA**

Chronic hypoglycaemia induced by 48-72 h glucose deprivation in neuronal cell culture leads to an upregulation of the glucose transporter located at the BBB, i.e. GLUT1 [65], as well as of the one located at the neuronal cell membrane, GLUT3 [66]. The same phenomenon is observed in vivo after 3-5 days of hypoglycaemia induced by starvation or insulin injection [64, 66, 110]. The upregulation of the two cerebral glucose transporters in response to chronic hypoglycaemia represents a protective mechanism against energy depletion in the brain. Moreover, only hexose transport across the BBB is affected during chronic hypoglycaemia, while amino acid, monocarboxylic acid and choline transport are unchanged. These data argue against the possibility of greater capillary recruitment during chronic hypoglycaemia and in favour of an increased number of glucose transporter sites [110].

Glucose transfer from blood to brain is increased in several brain regions (sensorimotor cortex, hypothalamus, thalamus, hippocampus and brainstem) during chronic vs acute hypoglycaemia of the same intensity (2.2-2.3 μmol/ml). These brain areas are mainly those in which LCMRgls are increased by chronic as compared to acute hypoglycaemia [111]. In all brain regions studied, LCMRgls during chronic hypoglycaemia do not differ from those recorded in control animals. Furthermore, chronically hypoglycaemic rats are able to sustain normal somatosensory-evoked responses at levels of hypoglycaemia (1.5 μmol/ml) which, when imposed acutely, result in attenuated response in both humans [112] and rats [72]. Thus, the enhanced blood-brain glucose transport capacity accompanying chronic hypoglycaemia in many (but not all) brain regions allows the brain to function in a relatively normal fashion, even in the face of further glycaemic reductions to levels associated acutely with profound cerebral functional disturbances [72, 111, 113]. These regulatory phenomena in turn increase LCMRgls and improve the general function of the individual as compared to that seen during acute hypoglycaemia [111].

Rates of LCBF are increased in all brain regions except the cerebellum and hypothalamus during severe chronic hypoglycaemia (1.97 μmol/ml) induced by continuous infusion of insulin for 6-7 days. However, the magnitude of the increase recorded during chronic hypoglycaemia is not as great as that measured during acute hypoglycaemia of the same degree [114]. Therefore, adjustments in the regulation of LCBF occur during chronic compared to acute hypoglycaemia. The regulation of LCBF increases during chronic hypoglycaemia seems to be due solely to the non-β-component, while the β-component appears to be non-functional. Either the β-receptors adapt to the presence of the agonist or the agonist is absent from the receptor site [104].

**HYPOGLYCAEMIA-INDUCED NEURONAL DAMAGE**

The distribution of hypoglycaemic brain damage has been well described in humans, monkeys and rats. The brain appears to be relatively resistant to hypoglycaemia-induced neuronal damage. Indeed, neuronal necrosis is not observed unless the EEG shows periods of isoelectricity [115]. Necrosis of neuronal cells in the cerebral cortex, the striatum and both the CA1 area and the dentate gyrus of the hippocampus can be seen in human hypoglycaemic brain damage [116-118]. In rats and monkeys, neuronal damage is found in the cerebral cortex, hippocampus and caudate-putamen [119-122]. As noted previously for energy metabolism and blood flow, the cerebellum appears to be a structure quite resistant to hypoglycaemia-induced neuronal damage [123].

Hypoglycaemia causes neuronal death, though not by depriving neurons of glucose and energy simply and directly. Instead, experimental data indicate that activation of neuronal excitatory receptors [124] of the N-methyl-D-aspartate (NMDA) subtype [125] mediates hypoglycaemic neuronal death. The nature of the endogenously produced brain excitotoxin causing hypoglycaemic brain damage has not been clearly established. Hypoglycaemia causes a marked increase in aspartate levels in whole brain tissue [123] plus a 16-fold increase in aspartate concentration and a
3-fold increase in glutamate in extracellular space [125, 126]. Both aspartate and glutamate are capable of activating various types of excitatory amino-acid receptors, including NMDA receptors. During hypoglycaemia, blockade of NMDA receptors reduces both the efflux of excitatory amino acids from brain cells [127] and neuronal injury in several major brain regions, including the striatum, CA1 area and dentate gyrus of the hippocampus [127-131]. Neuronal necrosis may be reduced by administration of MK-801, a non-competitive antagonist of the NMDA receptor, even at the stage of profound hypoglycaemia, accompanied by slow wave activity on the EEG, even if coma with isoelectric EEG activity ensues [131].

The potential deleterious role of calcium in hypoglycaemia-induced neuronal injury remains debatable. Hypoglycaemic coma, like ischaemia, is accompanied by a translocation of extracellular calcium to intracellular fluids. The recovery of extracellular calcium content occurs in two phases, possibly because a large fraction entering the cell in hypoglycaemic coma is sequestered and/or bound, allowing partial preservation of nucleoside triphosphate stores and the absence of acidosis [132]. These data are confirmed by the fact that no protection, but rather a worsening of neuronal necrosis, was observed when hypoglycaemic rats were treated by a dihydropyridine calcium channel antagonist [133].

CONCLUSION

The consequences of hypoglycaemia on cerebral glucose transport, metabolism and blood flow have been almost exclusively studied in adult animals and humans. Very few data are available in the literature for these parameters with respect to the consequences of hypoglycaemic exposure on functional activity in the developing brain of humans or animals. Only the neonatal period, during which hypoglycaemia is of great concern, has been more extensively studied. However, there is still no consensus as to the level of hypoglycaemia that might be deleterious to the full-term or premature newborn, especially in terms of associated pathologies. It would thus seem necessary to develop further studies on the possible adaptation of brain function during childhood hypoglycaemia when the brain is dependent on a great supply of glucose to support energetic and biosynthetic needs.

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