A Critical Period of Brain Development: Studies of Cerebral Glucose Utilization with PET

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Studies with positron emission tomography indicate that the human brain undergoes a period of postnatal maturation that is much more protracted than previously suspected. In the newborn, the highest degree of glucose metabolism (representative of functional activity) is in primary sensory and motor cortex, cingulate cortex, thalamus, brain stem, cerebellar vermis, and hippocampal region. At 2 to 3 months of age, glucose utilization increases in the parietal, temporal, and primary visual cortex; basal ganglia; and cerebellar hemispheres. Between 6 and 12 months, glucose utilization increases in frontal cortex. These metabolic changes correspond to the emergence of various behaviors during the first year of life. The measurement of absolute rates of glucose utilization during development indicates that the cerebral cortex undergoes a dynamic course of metabolic maturation that persists until ages 16-18 years. Initially, there is a rise in the rates of glucose utilization from birth until about age 4 years, at which time the child's cerebral cortex uses over twice as much glucose as that of adults. From age 4 to 10 years, these very high rates of glucose consumption are maintained, and only after then is there a gradual decline of glucose metabolic rates to reach adult values by age 16-18 years. Correlations between glucose utilization rates and synaptogenesis are discussed, and the argument is made that these findings have important implications with respect to human brain plasticity following injury as well as to "critical periods" of maximal learning capacity.

DEVELOPMENTAL PATTERNS OF CEREBRAL GLUCOSE METABOLISM

The pattern of glucose metabolism in the newborn brain is fairly consistent (Fig. 1), with the highest degree of activity in primary sensory and motor cortex, thalamus, brain stem, and cerebellar vermis [1-3]. The cingulate cortex, hippocampal region, and occasionally the basal ganglia may also show a relatively high glucose metabolism compared with most of the cerebral cortex in the newborn period [4]. The relatively low functional activity over most of the cerebral cortex during the neonatal period is in keeping with the limited behavioral repertoire of newborns, characterized by the presence of intrinsic brain stem reflexes and limited visuomotor integration.

Increases of glucose utilization are seen by 2 to 3 months in the parietal, temporal, and primary visual cortex, basal ganglia, and cerebellar hemispheres (Fig. 2). These changes in glucose metabolism coincide with improved skills involving visuospatial and visuomotor integration [5], disappearance or reorganization of brain-stem reflex neonatal behaviors [6], and evidence of increasing cortical contribution to the electroencephalogram [7].

The frontal cortex is the last brain area to display an increase in glucose consumption. Starting between 6 and 8 months, lateral and inferior portions of frontal cortex become more functionally active (Fig. 3) and eventually, between 8 and 12 months, the dorsal and medial frontal regions also show increased glucose utilization. These changes of frontal cortex metabolism are characterized by the tracer 2-deoxy-2-\[^{18}\text{F}\]fluoro-D-glucose. These studies have found that the human brain undergoes a protracted period of development before reaching the adult state. Correlations between regional cerebral glucose utilization and behavioral maturation, synaptogenesis, and plasticity have yielded findings that have important implications for learning and the educational system.

INTRODUCTION

Functional maturation of the human brain has been studied with positron emission tomography (PET) and
FIG. 1. Newborn pattern of cerebral glucose metabolism. At this stage of development, glucose metabolism is most apparent in sensorimotor cortex (a), cingulate cortex (b), thalamus (c), basal ganglia (d), brain stem (e), mesial temporal region (f), and cerebellar vermis (g). Metabolic activity is low in most of the frontal, parietal, temporal, and occipital cortex, as well as in the cerebellar cortex.

FIG. 2. Pattern of cerebral glucose metabolism in a 3-month-old infant. Glucose metabolism has increased in parietal cortex (a), occipital cortex (b), temporal cortex (c), basal ganglia (d), and cerebellar hemispheres (e). Metabolic activity in frontal cortex remains low (f).

FIG. 3. Pattern of cerebral glucose metabolism in an 8-month-old infant. Glucose metabolism has increased in the lateral portion of the frontal cortex (a) prior to the mesial portion (b).

come at a time when cognitively related behaviors, such as the phenomenon of stranger anxiety [8], and improved performance on the delayed response task [9, 10] begin to appear. Increased glucose requirement in frontal cortex also coincides with the expansion of dendritic fields [11] and the increased capillary density [12] observed in frontal cortex during the same period of development. By approximately 1 year of age, the infant’s pattern of glucose utilization resembles that of the adult, at least qualitatively.

From these observations, it appears that in the first year of life, the ontogeny of glucose metabolism follows a phylogenetic order, with functional maturation of older anatomical structures preceding that of newer areas [1–2,3].

GLUCOSE METABOLIC RATES

At birth, the regional or local cerebral metabolic rates of glucose utilization (LCMR\textsubscript{glc}) are about 30% lower than those seen in normal healthy young adults (Fig. 4). Between birth and approximately 4 years, the cerebral cortex shows a dramatic increase in LCMR\textsubscript{glc} to reach levels that exceed adult rates by over twofold (Fig. 4). Such changes in LCMR\textsubscript{glc} are not observed in brain stem, but a less dramatic increase is seen in the basal ganglia and thalamus.

Between the ages of about 4 years and 9–10 years, the LCMR\textsubscript{glc} for cerebral cortex is essentially at a high plateau of over twofold the glucose utilization seen in
FIG. 4. Absolute values of LCMRglc in cerebral cortex plotted as a function of age in normal infants and children, and corresponding values in seven normal young adults.

adults [2, 3] (Fig. 4). This observation confirms the earlier results of Kennedy and Sokoloff [13], who demonstrated that the average global cerebral blood flow (an indirect measure of energy demand in the brain) in nine normal children (ages 3 to 11 years) was approximately 1.8 times that of normal young adults. Moreover, average global cerebral oxygen utilization was approximately 1.3 times higher in children than in adults.

At about 9–10 years, LCMRglc for cerebral cortex begins to decline and gradually reaches adult values by 16–18 years (Fig. 4) [2, 3].

REGRESSIVE PHENOMENA IN DEVELOPMENT

Since the initial description of the ontogeny of cerebral glucose metabolism in children [2], the relevance of these dynamic changes has been under active investigation. Studies performed in other species using either in vivo autoradiography or PET have confirmed the presence of a developmental period during which local cerebral energy demand, as measured by local cerebral blood flow and, more directly LCMRglc, exceeds that of the adult [14–16].

The ontogeny of cerebral glucose metabolism described in Fig. 4 is not surprising considering the fact that regressive phenomena are not uncommonly seen during development of the nervous system [17–19]. Thus, there are periods during development when neurons, neuronal processes, synaptic contacts, neurotransmitters and various receptors are in excess of those seen in the adult. The proliferation and overproduction of neurons in humans occur prenatally, whereas programmed cell death (apoptosis) begins prenatally and continues until about the second postnatal year [20]. Surviving neurons undergo a similar phenomenon postnatally characterized by overproduction of their arborization and synaptic contacts, followed by an elimination or “pruning” phase [21–23]. Synaptic elimination in humans probably continues well into adolescence; for example, synaptic density in frontal cortex of children up to 11 years of age has been shown to exceed that in adults [21].

Synaptic pruning is not a random phenomenon, but rather is based on activity-dependent stabilization. In other words, repeated neuronal activity involving certain circuits during a critical period will result in stabilization of those circuits rather than elimination during the pruning process [24]. The advantage of activity-dependent stabilization of neuronal pathways is that there will not be an unnecessary expenditure of genes to code precisely for the large number of connections in the brain. Rather, repeated early environmental exposure will serve to guide the molding of an optimum cortical cytoarchitecture for the individual’s future.
needs. The molecular basis for the stabilization and retention of some pathways and vulnerability of others to be pruned or eliminated is an area of intense investigation.

NEUROBIOLOGICAL CORRELATES OF GLUCOSE METABOLISM ONTOGENY

Under normal circumstances, the major portion of glucose used by the brain is for the maintenance of resting membrane potentials [25–27]. Therefore, there should be a direct relationship between the degree of “connectivity” and the energy demand of the brain in the resting state. This is, in fact, the case when one compares the ontogeny of LCMRglc in cerebral cortex (Fig. 4) with the developmental curve for synaptogenesis in humans [21–23]. Similar comparisons performed in the developing kitten [16] and rhesus monkey [15] have confirmed this notion.

The ontogeny of LCMRglc in cerebral cortex may, therefore, provide an indirect measure of synaptogenesis in the brain. An analysis of the glucose metabolism curve (Fig. 4) suggests that the ascending portion of the curve seen between birth and 4 years represents the period of synaptic proliferation in cerebral cortex. The “plateau” period of the curve seen during middle childhood represents the period of synaptic excess and exuberant connectivity associated with increased energy requirement by cortex compared with adults. This is also the critical period in development when the process of activity-dependent synaptic stabilization is at a maximum. With adolescence and synaptic elimination, LCMRglc in cortex begins to gradually decline as shown by the gradual down slope of the metabolism curve because of diminishing energy requirement [3,28].

The notion of an extended period during childhood when activity-dependent synaptic stabilization occurs has recently received considerable attention by those individuals and organizations dealing with early intervention to provide “environmental enrichment” and with the optimal design of educational curricula. Thus, it is now believed by many (including this author) that the biological “window of opportunity” when learning is efficient and easily retained is perhaps not fully exploited by our educational system.

REFERENCES

