ABSTRACT. Functional neuroimaging techniques such as positron emission tomography have made it possible to investigate brain metabolism noninvasively during development. Studies have revealed a dynamic period of metabolic maturation and neuronal growth corresponding to the processes of synaptic proliferation and pruning of unused pathways. This physiologic plasticity is believed to be the biological basis for a critical period of learning and emotional development. Pediatrics 1998;102:1225–1229; critical period, positron emission tomography, cerebral glucose utilization, infant development, synaptic arborization, synaptic pruning.

ABBREVIATIONS. PET, positron emission tomography; LCMRglc, local cerebral metabolic rates of glucose utilization.

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unctional neuroimaging techniques have made it possible to study energy metabolism noninvasively in the developing human brain. This can be accomplished using positron emission tomography (PET) and the principles underlying the 14C-2-deoxyglucose autoradiographic method developed by Sokoloff and colleagues.1 With PET and the tracer 2-deoxy-2(18F)fluoro-d-glucose, measurements of regional cerebral glucose utilization can be made during different stages of development that are related to behavioral maturation, synaptogenesis, plasticity, and other neuromaturational phenomena.

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, brainstem, and cerebellar vermis.2–4 The cingulate cortex, amygdala, hippocampus, and, occasionally, the basal ganglia also may show a relatively high glucose metabolism compared with most of the cerebral cortex in the newborn period.5 The relatively low functional activity over most of the cerebral cortex during the neonatal period is in keeping with the relatively limited behavioral repertoire of newborns, characterized by the presence of intrinsic brainstem reflexes and limited visuomotor integration.6,7 However, the relatively high metabolic activity of amygdala and cingulate cortex in newborn suggests an important role of these limbic structures in neonatal interactions and, possibly, in emotional development.

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 visuosensorimotor integration, the disappearance or reorganization of brainstem reflex neonatal behaviors, and evidence of increasing cortical contribution to the electroencephalogram.8–10

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 come at a time when cognitively related behaviors, such as the phenomenon of stranger anxiety and improved performance on the delayed response task, begin to appear.11–13 Increased glucose requirement in frontal cortex also coincides with the expansion of dendritic fields and the increased capillary density observed in frontal cortex during the same period of development.14,15 By ~1 year of age, the infant’s pattern of glucose utilization resembles qualitatively that of the adult.

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 anatomic structures preceding that of newer areas.2–4 In addition, the suggestion by Kennedy and colleagues that “at any given developmental age, structures having metabolic rates equal to or exceeding their mature levels are those that dominate the behavior at that age" appears to be the case in human infant development because there is at least a general relationship between the maturational sequence of regional glucose metabolism and the behavioral maturation of the infant.16

GLUCOSE METABOLIC RATES

An important aspect of the PET technique is that it allows for the quantitative measurement of biochemical and physiologic processes. Thus, although the brain of a 1-year-old infant shows a similar distribution pattern of glucose utilization as that of an adult,
the rate at which glucose is being used by various brain regions is different. In fact, a dynamic, protracted, and nonlinear process of metabolic maturation is apparent at birth and lasts until early adulthood (16 to 18 years).

**Birth to 4 Years**

At birth, the regional or local cerebral metabolic rates of glucose utilization (LCMRglc) are ~30% lower than those seen in normal healthy young adults (Fig 4). Between birth and ~3 to 4 years, the cerebral cortex shows a dramatic increase in LCMRglc to reach levels that exceed adult rates by greater than twofold (Fig 4, A, B). Such changes in LCMRglc are not observed in brainstem (Fig 4, C), but a less dramatic increase is seen in the basal ganglia and thalamus (Fig 4, D).

**Middle Childhood**

Between the ages of ~4 years and 9 to 10 years, the LCMRglc for cerebral cortex is essentially at a high plateau greater than twofold the glucose utilization seen in adults (Fig 4, A, B). This observation confirms the earlier results of Kennedy and Sokoloff, who demonstrated that the average global cerebral blood flow (an indirect measure of energy demand in the brain) in nine healthy children (age 3 to 11 years) was ~1.8 times that of normal young adults. Moreover, average global cerebral oxygen utilization was ~1.3 times higher in children than in adults.

**Early and Late Adolescence**

At ~9 to 10 years, LCMRglc for cerebral cortex begins to decline and gradually reaches adult values by 16 to 18 years (Fig 4, A, B). It should be noted that all regions in cerebral cortex studied show the same timing of developmental changes in LCMRglc. The time course is different only for basal ganglia and thalamus, whereas the brainstem does not show significant ontogenetic changes with glucose metabolism measurement.

**REGRESSIVE PHENOMENA IN DEVELOPMENT**

Since the initial description of the ontogeny of cerebral glucose metabolism in children, the relevance of these dynamic changes has been under active investigation. For more than half a century, it has been recognized that the brain of an immature rat consumes more oxygen and glucose than an adult rat brain. For example, the utilization of both oxygen and glucose in excised rat cerebral cortex, striatum, cerebellum, and brainstem was shown to be higher during the period between the 4th and 7th postnatal weeks compared with adult values. 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.

The ontogeny of cerebral glucose metabolism de-
scribed in Figure 4 is not surprising, considering the fact that regressive phenomena are not uncommonly seen during development of the nervous system.23–25 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 approximately the second postnatal year.26 Surviving neurons undergo a similar phenomenon postnatally, characterized by overproduction of their arborization and synaptic contacts, followed by an elimination or “pruning” phase.27–29 Synaptic elimination in humans probably continues well into adolescence; for example, synaptic density in frontal cortex of children to 11 years of age has been shown to exceed that in adults.27

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 in elimination during the pruning process.30 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. Recent studies have suggested that in the visual cortex of kittens, activity-dependent stabilization may involve activation of the N-methyl-d-aspartate subclass of glutamate receptors, associated perhaps with the expression of specific neuronal proteins.31,32

NEUROBIOLOGICAL CORRELATES OF GLUCOSE METABOLISM ONTOGENY

Relationship to Synaptogenesis

Under normal circumstances, the primary portion of glucose used by the brain is for the maintenance of resting membrane potentials.33–35 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 comparing the ontogeny of LCMRglc in cerebral cortex (Fig 4, A, B) with the developmental curve for synaptogenesis in humans.27–29 Similar comparisons performed in the developing kitten and rhesus monkey have confirmed this notion.21,22

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, A, B) 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 also is the critical period in development when the process of activity-dependent synaptic stabilization is at a maximum. With adolescence and losses from synaptic elimination, LCMRglc in cortex gradually begins to decline, as shown by the gradual downslope of the metabolism curve because of diminishing energy requirement.4,36

Brain Plasticity

There have been many studies relating synaptogenesis to a critical period of developmental brain plasticity. Because the ontogeny of LCMRglc appears to be related to synaptogenesis, it may provide indirectly a marker for a critical period of developmental brain plasticity in humans and, therefore, analyses correlating synaptogenesis, LCMRglc, and brain plasticity may have important implications.

This relationship has been characterized in area 17 of the kitten visual system. In the kitten, synapses are sparse in this region at birth, and LCMRglc values are correspondingly low.37,38 During the second and third postnatal weeks, there is a well-documented rapid increase of synaptic density that reaches a peak at ~70 days; this phase of synaptogenesis coincides with the period when LCMRglc values rise dramatically in area 17.38,39 Moreover, the same period is characterized as a critical period in the visual system of kittens. During this time, there is considerable plasticity manifested when the visual system is injured or manipulated experimentally.40-44 This critical period of development in kitten visual cortex extends from 3 weeks to ~3 months of life, during which LCMRglc values are high in this brain region. Subsequently, there is diminishing plasticity associated with regression of exuberant synapses and connections and a corresponding decline of LCMRglc presumably attributable to diminished energy requirement.45-47

Interestingly, in the cat, the decline of LCMRglc in cerebral cortex is followed by a second, larger peak occurring at ~180 days. Only after 180 days did LCMRglc decrease to reach final adult values. The period at ~180 days appears not to coincide with any known major neuroanatomic changes in the cat brain, but rather is the time when cats undergo sexual maturation.48 This timing of the gradual decline of LCMRglc in the cat at puberty is analogous to that in humans (Fig 4, A, B). A similar relationship between synaptogenesis and LCMRglc has been shown in the developing rhesus monkey.24,49

CLINICAL IMPLICATIONS OF GLUCOSE METABOLISM ONTOGENY

The ontogeny of cerebral glucose metabolism appears to have profound implications in the study of human brain development, plasticity, and, possibly, child psychopathology. A central hypothesis in our laboratory is that at ~10 years, when LCMRglc in cerebral cortex begins to decline (Fig 4), developmental brain plasticity also begins to diminish in children. There is much support for this hypothesis in the clinical literature, only some of which will be reviewed below.

Children who have been deprived of exposure to language since birth, as, for example, those raised in the wilderness (so-called feral children), can still acquire reasonably normal language skills but only if intense speech and language therapy is introduced before the age of 10 years.30 After damage to the language-dominant hemisphere, there is better recovery of language skills if the injury occurs before ~8 to 10 years than if the injury occurs later.31,52 In fact, based on an extensive review of this subject, Lenneberg postulated that there must be a “critical period for language acquisition” ending at approximately the age of 10 years, after which there is a more limited (but not absent) potential to acquire language skills.53

Analyses in the human visual system also have suggested a similar timing of diminished plasticity in children. A number of studies have evaluated the upper age limit beyond which stimulus deprivation of one eye in young children, caused by monocular occlusion such as a cataract or certain kinds of strabismus, will induce an irreversible reduction of visual acuity known as amblyopia.54 Two large clinical surveys have found that amblyopia can be prevented from occurring if the monocular occlusion is corrected before ~8 to 10 years of age, but not after.55,56 In addition, the compromise in visual depth perception induced by unilateral enucleation (eg, for orbital tumors) can be minimized if enucleation is performed before ~8 years of age.57

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

Finally, there are investigators who believe that the onset of some forms of psychopathology may be related to various segments of the synaptogenesis curve. For example, Feinberg and colleagues have noted that the maturational curves for LCMRglc, synaptogenesis, and δ wave amplitude during sleep in children are similar and can be described best with a γ distribution model.58 The proposal is made that because the early symptoms of schizophrenia occur at early adolescence when the maturational curves begin their downslope, errors in synaptic pruning localized to certain areas of the brain (eg, frontal cortex) may play an important role in the pathophysiology of this disorder.

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