EDITORIAL
Imaging Human Brain Development with Positron Emission Tomography

Brain development in most species, including humans, is characterized by both overgrowth and elimination phases. This general phenomenon applies to neuronal populations as well as to their processes and synaptic contacts. Whereas the proliferation and overproduction of neurons in humans occur prenatally, the elimination phase of excessively proliferated neuronal populations begins prenatally and continues until about the second postnatal year (*1*). On the other hand, the overproduction and subsequent elimination (also referred to as "pruning") of neuronal processes and their synaptic contacts in man is largely a postnatal phenomenon with a rather protracted course. Indeed, synaptic concentrations in both human frontal (*2*) and visual (*3*) cortices of children up to 11 yr of age have been shown to exceed those of corresponding regions in adults by nearly a factor of two, despite the fact that adult size and weight of the brain has already been reached by this age. The process of transient exuberant connectivity as a general rule in brain development across many species is believed to be biologically advantageous in reducing the genetic burden that would otherwise be required for specifically programming the enormous numbers of synaptic contacts (on the order of 10^{15} in humans) in the central nervous system (*4,5*).

Postnatal development of the human brain, therefore, is an incredibly dynamic process. The full-term male newborn has an average brain weight of 370 g, which triples to 1080 g by 3 yr. By 6–14 yr, the average brain weight is 1350 g. The processes of dendritic and synaptic proliferation, together with their maintenance, myelination, and various other synthetic processes in the postnatally developing brain undoubtedly demand a great deal of protein synthesis and energy expenditure for their construction and function. Kennedy and Sokoloff (*6*), in their pioneering studies using the nitrous oxide method, demonstrated that the average global cerebral blood flow in children between the ages of 3 and 11 yr exceeded average adult values by a factor of 1.8. Average global brain oxygen utilization similarly exceeded adult rates by a factor of 1.3. Since these were whole brain measurements, local areas of the brain may have exhibited much higher rates.

Due to the development of positron emission tomography (PET) (*7*), a number of biochemic and biologic processes in the maturing brain can now be directly imaged and measured in vivo noninvasively (*8*). With regard to the application of PET in childhood, one is confronted with a dilemma. Ontogenetic changes of various measurements obtained with PET in the normally developing brain must first be established prior to applying PET to the study of childhood disease. It is, however, unethical and unacceptable to perform PET studies on entirely normal children for purely research purposes. Various strategies must, therefore, be employed in order to obtain normative developmental data.

When we reported the ontogenetic changes of local cerebral glucose metabolic rates for glucose (LCMRGlc) obtained with PET and 2-deoxy-2[^{18}F]fluoro-D-glucose (FDG), we had already measured LCMRGlc in well over 100 infants and children. Each had been justified to undergo FDG-PET because of its potential to contribute to the clinical management of the infant or child. We then selected 29 subjects, who in retrospect, had either suffered only transient neurologic events not affecting development or had neurologic disease ruled out altogether. We believed that this subpopulation was adequately representative of normal children to provide an initial description of LCMRGlc ontogeny.

Using this strategy, we found the pattern of LCMRGlc in the human neonate to be markedly different from that of the adult; typically, four brain regions visualized on PET are metabolically prominent in newborns: primary sensorimotor cortex, thalamus, brainstem, and cerebellar vermis. Phylogenetically, these are relatively old structures, which dominate the behavior and participate in the primitive intrinsic reflexes of the normal newborn.

During the first year, the ontogeny of glucose metabolic patterns proceeds in phylogenetic order, with functional maturation of older anatomic structures preceding that of newer areas (*9*). This sequence of functional developmental correlated well with the behavioral, neurophysiologic, and neuroanatomic maturation of the infant. As the infant acquires visuo-spatial and visuo-sensorimotor integrative functions in the second and third months of life, and primitive reflexes become suppressed, increases in LCMRGlc are observed in parietal, temporal and primary visual cortical regions, basal ganglia, and cerebellar hemispheres. The last region to undergo a maturational rise in LCMRGlc is the frontal cortex, where maturation of the lateral portion precedes that

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of the phylogenetically newer dorsal prefrontal regions. The metabolic maturation of frontal cortex also progresses from inferior to phyogenetically newer superior levels. Functional maturation of these frontal cortical regions coincides with the appearance of higher cortical and cognitive abilities (*10*). By 1 yr, LCMRGlc patterns *qualitatively* resemble that of the normal young adult.

Quantitative analysis of LCMRGlc during development (Fig. 1) revealed that the brain follows a *protracted* glucose metabolic maturational course. Neonatal LCMRGlc values, which are about 30% lower than adult rates, rapidly increase to *exceed* adult values by 2–3 yr in the cerebral cortex and remain at these high levels until about 8–10 yr, when LCMRGlc declines to reach adult rates by 16–18 yr (*11*).

The biologic significance of the various segments of the LCMRGlc maturational curve remains to be fully understood. We have postulated that the ascending portion of rapid LCMRGlc increase corresponds to the period of rapid overproduction of synapses and nerve terminals known to occur in the developing human brain during that time period (*2,3*). The "plateau" period (Fig. 1) during which LCMRGlc exceeds adult values corresponds to the period of increased cerebral energy demand as a result of transient exuberant connectivity. This phenomenon appears to be common to many species during brain development and is associated with a significant degree of plasticity in the brain. That segment of the metabolic maturational curve describing the LCMRGlc decline corresponds to the period of selective elimination or "pruning" of excessive connectivity, and marks the time when recovery of function following brain insult markedly diminishes in the human (*12*). We believe that the in-depth analyses of LCMRGlc maturational trends in humans that can be accomplished noninvasively with PET will ultimately yield an important index of brain plasticity. It is hoped that these data will provide criteria for prejudging the robustness of compensatory reorganization of the brain to injury or necessary surgical removal of diseased regions.

The potential of expanding PET technology to assess a variety of other biochemic and biologic processes important in the developing brain is indeed exciting. In this issue of the *Journal*, O'Tuama et al. (*13*) illustrate how age-related changes of [^{11}C]L-methionine transport from blood to normal frontal cortex can be measured with PET. These investigators demonstrate that blood-to-brain transport of [^{11}C]L-methionine in children exceeded that of adults, suggesting a developmental accommodation of cerebral metabolic and synthesis requirements of amino acids. Furthermore, competitive inhibition of [^{11}C]L-methionine uptake by neutral amino acid carriers in the brain was already established by 4.6 yr. The strategy employed by O'Tuama et al., which enabled such measurements to be made in children, was to study only patients with brain tumors, sparing the regions analyzed. The radiation exposure from PET in these patients is not an issue because of the much higher radiation therapy doses administered to such patients.

O'Tuama et al. (*13*) purposely restricted the model analysis to the first 2 min of tissue data to isolate unidirectional transport by neutral amino acid carriers. They offer presumptive and literature evidence to support the notion that these increases in neutral amino acid transport capacity during early childhood are to meet the high protein synthesis requirements of the developing brain. This could be defined explicitly by performing studies with L-[1-^{11}C]leucine with a formal compartmental model that allows measurement of the individual rates of facilitated transport, protein syn-

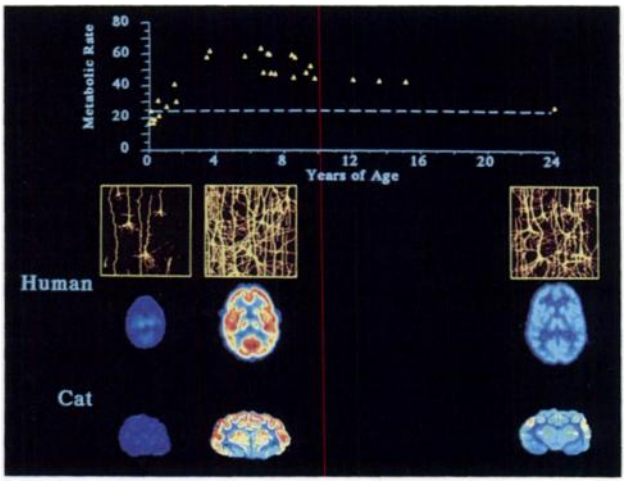

FIGURE 1
Temporal course of changes in LCMRGlc during development. Top: Graph of cortical LCMRGlc in μmole/min/100 g for the human. Dashed line is average adult value. Second row: Density of neuronal processes in human cortex at birth (sparse), at 6 yr of age (exuberant), and young adult. Third row: PET images of LCMRGlc for a mid-level section at 5 days of age (note low cortical and subcortical LCMRGlc, except for phylogenetically older thalamus), 6 yr of age (exuberant), and young adult. Fourth row: LCMRGlc using [^{14}C]-2-deoxyglucose autoradiography in the cat to show the same developmental pattern as observed in the human. The ages in images from left to right are birth, 60 days, and adult. In all images, red is the highest value of LCMRGlc, with orange, yellow, green, and blue representing progressively lower values.

thesis, and amino acid metabolism (*14,15*). Labeled methionine could also be used by employing the compartmental model of Bustany and Comar (*16*). Both approaches require knowledge of the model assumptions, extensive kinetic measurements, and biochemical analysis of plasma.

Where do we go from here? Since the neutral amino acid carrier system is only one of many components that contribute to the synthetic and functional processes of the developing brain, much work remains to be done. Data of O'Tuama et al. (*13*) need to be expanded to include particularly children in the younger age group. It is our supposition that a developmental rise of protein synthesis to levels in excess of adult values, corresponding to the formation of neuronal processes and synaptic connections, must precede the rise in LCMRGlc. This is based upon the assumption that the major portion of excessive LCMRGlc described in our developmental studies is to meet the functional requirements of the exuberant production of established synapses, since protein synthesis is not a process with high energy requirements. This is supported by the fact that synaptic density in the human cortex rises to a peak by about 1–2 yr of age (*2,3*), whereas LCMRGlc peaks a year or two later (Fig. 1). Stated differently, neuronal processes and synaptic connections must be constructed (protein synthesis) before they can function (energy consumption of synaptic maintenance and firing). This, however, remains to be experimentally proven.

Normative developmental data must continue to be acquired in children with strategies that remain within ethical guidelines. These data must not only include those biologic processes mentioned above but also the ontogeny of specific neurotransmitter systems and other processes as new assay methods with PET become available. Studies in humans must be supplemented not only by similar studies in animals, but this work must be the origin of shaping questions and experimental paradigms for much more rigorous mechanistic and ultrastructural studies in animal models, tissue sections, cell cultures, and isolated molecular systems. Taken together, this comprehensive approach will enhance and deepen our fundamental understanding of the rules governing normal human brain development.

As we gain a better understanding of the essential building blocks in normal brain development, we will be better equipped to apply these rules and knowledge to understanding disorders of defective brain development (e.g., microcephaly, Down's syndrome, learning disabilities, etc.) and hopefully to favorably affect the clinical course of these unfortunate individuals. The use of PET to identify and map the area of resection, as well as assess the integrity of the remaining brain, in the surgical treatment of infants and children with refractory seizures stands as an example of the clinical benefit that can be realized from research studies of normal and abnormal development of the brain (*17,18*).

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REFERENCES

1. Rabinowicz T. The differentiated maturation of the human cerebral cortex. In: Falkner F, Tanner JM, eds. *Human growth, volume 3. Neurobiology and nutrition.* New York: Plenum; 1979: 97–123.
2. Huttenlocher PR. Synaptic density in human frontal cortex—developmental changes and effects of aging. *Brain Res* 1979;163:195–205.
3. Huttenlocher PR, de Courten C, Gray LJ, van der Loos H. Synaptogenesis in human visual cortex-evidence for synapse elimination during normal development. *Neurosci Lett* 1982;33:247–252.
4. Changeux JP, Danchin A. Selective stabilization of developing synapses as a mechanism for the specification of neuronal networks. *Nature* 1976;264: 705–712.
5. Jacobson M. *Developmental neurobiology*, 2nd edition. New York: Plenum; 1978:302–307.
6. Kennedy C, Sokoloff L. An adaptation of the nitrous oxide method to the study of the cerebral circulation in children; normal values for cerebral blood flow and cerebral metabolic rate in childhood. *J Clin Invest* 1957; 36:1130–1137.
7. Phelps ME, Hoffman EJ, Mullani NA, et al. Application of annihilation coincidence detection to transaxial reconstruction tomography. *J Nucl Med* 1975;16:210–224.
8. Phelps ME, Mazziotta JC. Positron emission tomography: human brain function and biochemistry. *Science* 1985;228:799–809.
9. Chugani HT, Phelps ME. Maturation changes in cerebral function in infants determined by [^{18}F]FDG positron emission tomography. *Science* 1986; 231:840–843.
10. Kagan J. Do infants think? *Scientific American* 1972;226:74–82.
11. Chugani HT, Phelps ME, Mazziotta JC. Positron emission tomography study of human brain functional development. *Ann Neurol* 1987;22:487–497.
12. Chugani HT, Hovda DA, Villablanca JR, et al. Metabolic maturation of the brain: a study of local cerebral glucose utilization in the developing cat. *J Cereb Blood Flow Metab* 1990:in press.
13. OTuama LA, Phillips PC, Smith QR, et al. L-Methionine uptake by human cerebral cortex: maturation from infancy to old age. *J Nucl Med* 1991; 32:16–22.
14. Keen RE, Barrio JR, Huang SC, et al. In vivo cerebral protein synthesis rates with leucyl-transfer RNA used as a precursor pool: determination of biochemical parameters to structure tracer kinetic models for positron emission tomography. *J Cereb Blood Flow Metab* 1989;9:429–445.
15. Hawkins RA, Huang SC, Barrio JR, et al. Estimation of local cerebral protein synthesis rates L-[1-^{11}C]leucine and PET: methods, model, and results in animals and man. *J Cereb Blood Flow Metab* 1989;9:446–460.
16. Bustany R, Comar D. Protein synthesis evaluation in brain and other organs in human by PET. In: Reivich M, Alavi A, eds. *Positron emission tomography.* New York: Alan R. Liss, Inc.; 1985:183–201.

17. Chugani HT, Shewmon DA, Peacock WJ, Shields WD, Mazziotta JC, Phelps ME. Surgical treatment intractable neonatal onset seizures: the role of positron emission tomography. *Neurology* 1988;38:1178–1188.
18. Chugani HT, Shields WD, Shewmon DA, Olson DM, Phelps ME, Peacock WJ. Infantile spasms. I. PET identifies focal cortical dysgenesis in cryptogenic cases for surgical treatment. *Ann Neurol* 1990;27:406–413.

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JANUARY 1961

The Radioisotope Renocystogram

Delores E. Johnson, George V. Taplin, Earl K. Dore, and Jane Hayashi

The radioisotopic renogram is a tracer method for evaluating individual kidney function and patency of the upper urinary passages by external gamma ray scintillation counting techniques. Certain modifications have improved the renogram since its introduction in 1956, but it may be improved further in several ways.

This work demonstrates an efficient arrangement of detection equipment and points out the superiority of ^{131}I-labeled hippuran for this procedure.

METHODODLOGY

Renogram. The patient is seated comfortably in the "renogram chair" to ensure immobilization. Kidney probes are centered over the renal areas against the skin. A third detector, aimed at the bladder, is centered at the sacrococcygeal junction. Tracer dose is measured in a syringe before and after injection in an ^{131}I calibrated phantom. A test dose of 0.6 mCi ^{131}I-hippuran per kilogram of body weight is used to obtain peak count rates of 70,000–90,000 cpm in normal subjects. Quantitative in vivo measurements of tracer excretion are made immediately after completion of the 10-15-min qualitative test.

Urinary Excretion Measurement. Bladder phantom studies were made to select an optimum arrangement of detection equipment for accurate in vivo bladder measurements. The detector utilized has a 2x2-inch thallium-activated sodium iodide crystal housed in a shield. The surface of the crystal is retracted 4 inches from the opening of the shield to which a multi-stage collimator is attached.

With the patient positioned against a wall to secure immobilization, the centering stick of the detector is placed against the upper border of the symphysis pubis and pressure is exerted along its axis to ensure a firm location at this bony landmark. After counts per minute are taken, tissue background is measured over the upper posterior chest. Immediately after voiding, bladder measurement is repeated to check for retention.

RESULTS

The present procedure with its supplemental bladder recording and in vivo measurement of tracer excretion has been employed during the past several months in the performance of 323 renocystograms using ^{131}I-hippuran. The more rapid renal accumulation and excretion of hippuran is reflected in the renograms by more steeply rising and falling tubular and excretion segments. In marked constrast, the miokon renogram has rather shallow tubular and excretion segments and peak activity is reached in 7.5 min versus 2.5 min with hippuran.

Hippuran, by virtue of its rapid renal turnover and organ specificity, is the ideal tracer agent for the radioistopic renogram. The greater sensitivity in detecting renal and upper urinary tract abnormalities has been demonstrated by comparative studies with other test agents in the same patients and by serial renograms in individuals with fluctuating renal disease.

JANUARY 1976

Measurement of Acute Myocardial Infarcts in Dogs with Technetium-99m-Stannous Pyrophosphate Scintigrams

Ernest M. Stokely, L. Maximillian Buja, Samuel E. Lewis, Robert W. Parkey, Frederick J. Bonte, Robert A. Harris, Jr., and James T. Willerson

Cardiac pump failure in patients following acute MI has been shown to be directly related to the mass of irreversibly damaged myocardial tissue. Estimates of infarct size following acute MI could, therefore, have important implications for patient treatment. Several methods have been used to measure infarct size in animals, but none has gained universal acceptance. The present study assesses the use of ^{99m}Tc-PYP (stannous pyrophosphate) myocardial scintigrams to estimate acute MI in dogs.

Adult dogs weighing between 15 and 35 kg were anesthetized with i.v. chloralose and ventilated with a Harvard respirator using 95% O_2 and 5% CO_2. Imaging was performed 1 hr after an i.v. injection of 3 mCi of ^{99m}Tc-PYP. Scintigrams were made using a Searle Radiographics Pho/Gamma III HP camera with a high-resolution collimator. Data were collected by a PDP-8/I computer interfaced to the scintillation camera and recorded on seven-track magnetic tape. Histologic quantification of infarct size was performed by utilizing the methods of Alonso and Reimer.

In most histologic sections, areas of infarction were relatively homogeneous and contained relatively small border zones with mixtures of necrotic and nonnecrotic myocardium. In PAS-stained sections, differences in intensity of staining were accounted for on the basis of abundant PAS-positive glycogen deposits, glycogen depletion and diffuse diastase-resistant PAS-staining of necrotic muscle cells in the infarcts, and PAS staining of neutrophils in the infarcts.

The results of this study show that infarct size can be adequately measured with ^{99m}Tc-PYP myocardial scintigrams in dogs with proximal left anterior arterial ligation. The potential application of this approach in man is uncertain, but the data provide sufficient encouragement for future clinical evaluation of this imaging technique. Additionally, comparative measurements of infarct size in experimental animals and patients, using precordial mapping and creatine phosphokinase clearance measurements, should be made.