Brain Development and Nutrition

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Two questions regarding brain development and nutrition are of particular importance: How long does brain development (i.e., growth and differentiation) continue? and What are the effects of malnutrition on neurotransmitter systems? Many of the research data available today are derived from animal experiments, and the limitations of animal studies are well known. However, knowledge gained from these animal experiments has led to significant research on humans. The knowledge of the effects of malnutrition on brain development in humans will certainly increase thanks to new noninvasive techniques such as nuclear magnetic resonance imaging, permitting longitudinal studies of the metabolism and development of structures in the human brain.

BRAIN DEVELOPMENT

For operational reasons it is useful to divide brain development in humans and in rats into four periods.

First Period

In humans this extends between the 8th and 32nd week of gestation, and in rats from the 3rd day of gestation until birth. This period is characterized by neuroblast proliferation and migration, and aggregation of neurons to form primary layers. There are distinct regional differences in the period of neuroblast proliferation. During this period the formation of the first synapses takes place. These are probably catecholaminergic initially and later serotonergic. The final number of neurons is not attained by the end of this period. In humans the first major neuroblast proliferation takes place between 10 and 18 weeks of gestation (1,2). Despite contrary dogma it is very likely that neuroblast proliferation continues much longer, at least in some areas. In the rat the number of neurons in the dentate granular layer increases steadily until at least 1 year of age (3).

From 18 weeks of gestation, there is an intensive proliferation of glial cells. It is difficult to determine when the number of human brain cells reaches a plateau. In
the cerebellum this occurs at about 15 months, by which time the forebrain has only about 65% of its "adult" cell number, which is reached at about 4 years. In this period the cellular density in the human forebrain decreases, partly due to growth of cells but also due to cell death. At 24 weeks of gestation there are 5,000 cells per unit volume, dropping to 2,000 cells per unit volume at 32 weeks (4). Myelination is already taking place in the human spinal cord at 17 weeks and reaches a first plateau around the end of the first period of brain development.

**Second Period**

In humans this extends between the 32nd week of gestation and birth; the second period in rats is from birth until 10 days of age. This period is characterized by intensive brain growth. Factors contributing to brain growth are mainly cell migration, cell differentiation, and proliferation of glial cells (astrocytes and oligodendrocytes). The cytoarchitecture is further developed. Myelination begins in the brain.

**Third Period**

In humans this extends between birth and 2 years of age; the third period in rats is between 11 and 20 days of age. This is a period of intensive brain growth and differentiation. Adult brain weight is attained at about 2 years. Thus roughly 5/6 of brain growth takes place postnatally. The cytoarchitecture of the brain layers is basically established. This is the period of intensive neuronal differentiation with formation of dendrites and synapses. It is also the period of intensive activity of the oligodendrocytes leading to myelogenesis in the central nervous system. Myelination slows down at the end of this period.

Experiments in mouse brain cell cultures give new insight into the regulation of oligodendrocyte proliferation (5). The postnatal development of mouse brain oligodendrocytes in vivo and in culture can be compared under proper conditions. In vitro the number of oligodendrocytes, identified by immunological markers, reaches a plateau at 14 days, by which time the rate of proliferation has slowed from 26% on day 7 to 10% per day. If oligodendrocytes are completely destroyed on day 14 by complement-dependent cytotoxicity, their number reaches 60% of the normal number 7 days later. These newly appearing oligodendrocytes show a proliferation rate of 25% compared to 10% in the normal controls. These results indicate that precursors of oligodendrocytes are still present in 14-day-old cultures and that proliferation can be induced at a higher rate than in undisturbed controls. Under these experimental conditions there is, therefore, a clear indication that regeneration can occur when the high proliferation rate has slowed down under normal conditions.

**Fourth Period**

In humans this extends from 2 years of age; the fourth period in rats is from 20 days of age onwards. When this period ends remains to be determined. Brain
growth slows down, but differentiation is still active, especially with regard to the formation of the synaptic network. Until recently, this phenomenon was supposed to persist only until about 5 years of age in man. However, it has been shown that in normally aging humans the density and length of dendrites of the neurons in the parahippocampal region increase significantly from 50 to 80 years (6). In presenile dementia, density and length of dendrites decreases during this period. These findings indicate that neuronal differentiation may persist much longer than previously thought (7).

It used to be thought that there was a period of fast myelination in man until about 2 years of age, followed by slow myelination until about 20 years. However, animal experiments indicate that myelination in rats (with a life span of 2 years) does not stop at about 40 days but continues until at least one year of age. Not only should quantitative aspects be taken into account when considering brain development, but also age-dependent changes in the composition of structures. Newer findings show that the number of neurons in certain brain areas is increasing, that myelination continues for a much longer period than previously thought, and that differentiation of neurons in humans takes place for up to 80 years. Development and regression might be a lifelong process, differing from region to region. Nutrition could therefore be of importance to brain development for a much longer period than previously thought. Although brain development later in life may be less intensive than during the first 4 years, it may nevertheless continue to influence human behavior.

If some brain regions develop for longer periods these regions might also be vulnerable for longer periods. But persistence of structural development also implies possibilities for regeneration. Thus we arrive at a concept where brain development, in the widest sense of the word, is a lifelong process during which the brain is vulnerable to exogenous factors such as nutrition but also retains the capability for repairing damage.

NUTRITION AND BRAIN DEVELOPMENT

The effect of nutrition on myelination has been extensively investigated in the past. Less attention has been given to the effect of nutrition on neurons (8). However, numerous studies have shown important effects of undernutrition on neurons, such as retarded neuropil development (9), decreased dendritic arborizations (10), decrease in the size and density of presynaptic endings (11), and a decrease in the number of synapses per unit area (12). There are indications that in the long term nutrition affects the structural and functional development of these systems. Nutrition may also directly affect neurotransmitter (NT) metabolism in the brain and hence affect behavior. Recent work has shown that food intake can directly affect NT synthesis in the brain (13,14). If brain NT synthesis is modified by changes in food intake, it must be influenced by precursor availability. NT synthesis is precursor dependent if the following four requirements are met (13,14): (a) Precursor levels in plasma must depend on intakes; (b) the brain must not be able to synthesize as much of the precursor as it needs; (c) a low affinity transport system must mediate
uptake across the blood–brain barrier; and (d) a low affinity enzyme must catalyze the key step converting the precursor into the neurotransmitter, and its activity may not be under feedback control.

These criteria are met for the synthesis of acetylcholine, catecholamines, and serotonin, which are dependent on the availability of choline, tyrosine, and tryptophan, respectively (15). Most of the basic research in this field has been done in the rodent brain and will be briefly reviewed. At birth, activity of enzymes involved in NT synthesis is relatively low, and the number of sites for NT uptake as well as of receptors is also relatively small. They increase during the first 3 to 4 weeks after birth. During this period of intensive brain growth, including myelination and synaptogenesis, both systems show a very high metabolic activity and are therefore particularly dependent on adequate nutrition. Thus myelinogenesis and synaptic development might thus both be affected by inadequate nutrition with possible consequences on behavior.

Acetylcholine

Whole brain acetylcholine (ACh) is reduced in undernourished animals. However, undernutrition does not cause irreversible defects in ACh synthesis and storage (16), as levels return to normal when a normal diet is reintroduced. Undernourished suckling rats initially show reduced choline acetyltransferase (ChAT) activity. But total brain ChAT activity becomes normal by day 21 despite continuing nutritional deprivation. Low ChAT activity persists in olfactory bulbs and in the hypothalamus but normalizes after five weeks of nutritional rehabilitation. ChAT activity in the brain stem does not recover, indicating more severe damage in this region. In contrast, no reduction of ChAT activity is observed in the brain stem when undernutrition starts after weaning, indicating the crucial importance of the time of exposure. It is not known whether the reduction of enzyme activity is due to reduced enzyme synthesis, increased enzyme turnover, structural changes of the enzyme protein, or modifications of activators or inhibitors.

Animals undernourished until weaning and then given a normal diet for one week show a significant reduction of cholinergic muscarinic receptor binding in the corpus striatum and hypothalamus, a slight increase in the midbrain, and no changes in the cerebral cortex and cerebellum (15). These changes are due to alterations in the concentrations of binding sites and not to changes in the affinity of receptors. No data are available on the possible functional effects of these modifications.

Catecholamines

Dopamine concentration in the brain is reduced in early malnutrition, mainly in the corpus striatum (17). Nutritional rehabilitation seems to normalize dopamine content. Undernutrition in adult rats has no effect on brain dopamine content.

Early undernutrition reduces norepinephrine concentration in the brain stem and
telencephalon (18). Several months of normal diet can reverse this deficit. Since undernutrition does not affect the supply of the precursor (tyrosine) for catecholamine synthesis and since in vivo conversion of tyrosine to dopamine is enhanced and tyrosine hydroxylase activity is elevated in cases of undernutrition (19), the reduction of the content of catecholamines does not seem to be due to deficient synthesis but to enhanced turnover.

Early undernutrition in rats reduces the number of catecholamine receptors in adult life but not their affinity characteristics (20). Dopamine receptors in the corpus striatum are reduced in animals that have been undernourished before weaning. This finding might explain the reduced response to apomorphine (a direct dopamine receptor agonist) observed in rats when protein-malnourished during postnatal development (21).

Serotonin synthesis is related to brain tryptophan content. In undernutrition free tryptophan concentration in serum is increased, probably because of increased competition of nonesterified fatty acids for binding sites on albumin and because of the reduction of serum albumin concentration. Thus the pool of tryptophan that can enter the brain is increased (21,22). Concomitantly the activity of tryptophan hydroxylase in brain is increased in undernutrition. Both factors can explain why serotonin concentration is elevated in the brain of undernourished animals. The content of 5-hydroxyindolacetic acid (a serotonin metabolite) is also increased in the brain of undernourished animals, indicating an increased turnover of serotonin (24). Thus undernutrition seems to increase serotonin synthesis as well as its release. Increased concentrations of serotonin and of its metabolites are mainly observed in the diencephalon and in the brain stem. This seems also to be the case in short-term fasting (24). These experiments do not prove that serotonic transmission is increased. Nevertheless, one could question whether the apathy observed in undernourished animals is due in part to the increased serotonin content of the brain, and whether a comparable mechanism also operates in undernourished humans, in whom apathy is a major problem.

Newborn pups born to dams fed an isocaloric, low protein diet (8% casein instead of the normal 25%) prior to mating and throughout gestation may have normal body and brain weights but show alterations in serotonin metabolism in the central and peripheral nervous system and abnormal spontaneous activity of single neurons in the frontal cortex (25). These changes seem to be irreversible and are not affected by cross-fostering at birth with dams fed on a 25% casein diet. In this model normal growth does not correlate with normal brain development. Similar results have been obtained in small-for-gestational-age rats born to mothers fed an isocaloric 6% casein diet, nursed by dams also fed a 6% casein diet (26).

Food intake can influence the synthesis of neurotransmitters and serotonin, since it affects plasma concentrations of amino acids which share with tryptophan the same transport system into the brain. There has been speculation that diet, particularly the carbohydrate-to-protein ratio, may directly influence the flux of NT precursors to the brain and hence the level of NT synthesis (27). This could have an influence on such functions as appetite, sleep, level of aggression, and so on. It is
not known whether prolonged periods of altered diet could affect behavior in the long term and in this way disturb the normal interactions with the environment. These interactions by themselves can affect development. Doerner (28) compared the ratio of plasma tryptophan to neutral amino acids (valine, isoleucine, phenylalanine, and tyrosin) in formula-fed and breast-fed infants. In formula-fed infants the ratio of tryptophan to neutral amino acids was significantly lower due to an increase in the concentration of the neutral amino acids. The authors conclude that this might lead to a decreased entry of the precursor tryptophan into the brain and thus to a decrease in serotonin synthesis, with possible consequences such as developmental obesity and/or permanent changes of mental capacity. It is evident that these conclusions are purely speculative and need further research.

GABA

Dietary restrictions cause a reduction in the activity of the GABA synthesizing enzyme glutamic acid decarboxylase (GAD) in all brain areas except the cerebellum and brain stem (29). The enzyme activity becomes normal with time, even with a restricted diet. The findings suggest that development of GAD activity is delayed and not arrested (30).

GABA receptor binding is significantly increased in undernutrition, especially in the cerebral cortex, corpus striatum, midbrain, and hypothalamus. The changes in receptor binding are probably due to an increase in the number of receptors and not to alterations in their affinity (8). Using a different model of undernutrition it has been shown that undernutrition enhances the binding of GABA by increasing the availability of high affinity sites and the number of low affinity receptors.

These studies suggest that undernutrition decreases the production of some endogenous inhibitors that normally mask the high affinity sites. These could be GABA-modulin or GABA itself (8). No data are yet available showing any functional consequences of these apparent receptor modifications.

In summarizing the various findings regarding neurotransmitter synthesis, turnover, and binding, one must bear in mind that experimental results depend on the type of under- or malnutrition, the timing of dietary alterations, and the species studied. However, a general pattern is emerging, suggesting that undernutrition reduces the activity of cholinergic and GABAergic systems in the developing brain, whereas the activity of catecholamine and serotonin systems increases. This selective effect on brain neurotransmitter activity might have several functional consequences, but none is yet established. Many of the neurochemical disturbances described so far normalize when dietary intakes return to normal, even after the period of intensive brain development.

CONCLUSION

Recent research suggests that brain development (growth and differentiation) lasts much longer than previously thought. This is particularly true of structural and
biochemical differentiation in distinct brain areas. Structural and biochemical brain development in humans needs to be carefully studied and possible correlations with the development of behavior evaluated.

There are indications that regeneration at a cellular level may take place in the central nervous system of rodents. Regeneration may be due to increased differentiation or increased proliferation of precursor cells or both. Future research should address the question of cellular regeneration processes in the human brain.

Nutrition affects the structural and biochemical development of neurotransmitter systems and myelin. Functional consequences of these structural and biochemical changes need to be evaluated.

Food intake has a direct influence upon the synthesis of neurotransmitters such as acetylcholine, catecholamines, and serotonin. These neurotransmitters seem to have direct effects on behavior. Possible effects of food intake on human behavior such as appetite, sleep, aggressivity, and arousal need to be studied. Fine but distinct alterations in food intake may perhaps affect brain development or be used in a therapeutic way to correct abnormal brain development.

ACKNOWLEDGMENT

This work was supported by grant 3.493.083 from the Swiss National Research Foundation, a grant from the Swiss Multiple Sclerosis Society, and a grant from the Swiss Foundation for Encouragement of Research in Mental Retardation.

REFERENCES


