Contents

iv Foreword

1 Undernutrition and Mental Development
S. GRANTHAM MACGREGOR

3 Mechanism for Nutrient Effects on Brain Development and Cognition
R. UAUY

7 Carbohydrate and Fat-Based Appetite Control Mechanisms
W. LANGHANS

10 Diet, Monoamine Neurotransmitters and Appetite Control
J. FERNSTROM

13 Nutrients and Affective Disorders
S. E. MØLLER

15 Nutrition, Serotonin, and Behavior in Anorexia and Bulimia Nervosa
W. H. KAYE

17 Lipids in Neural Function: Modulation of Behavior by Oral Administration of Endocannabinoids Found in Foods
G. CROZIER-WILLI

22 Diet Related Prevention of Alzheimer’s Disease: Different Hypotheses
B. VELLAS

25 Nutritional Pathogenesis and Prevention of Stroke
Y. YAMORI

26 Risk from Exposure to Metals: Deficits and Excesses (Cu, Fe, Mn, Al, Cr, B)
G. ROTILIO
28 Nutritional Reversion of Cognitive Impairment in the Elderly
D. BUNOUT

31 Metabolic Encephalopathies: Liver Disease, Renal Failure, Critical Illness
E. HOLM

34 The Ketogenic Diet and Epilepsy
J. M. FREEMAN

37 Agenda of the Workshop

39 List of Speakers
Foreword

Undernutrition early in life results in impaired growth but also in lower IQ, cognitive deficits, behavioral problems, and impaired motor skills. It has been proven that deficits continue until school-age, adolescence, and even adulthood. Prevention through health care measures and an improved socio-economic environment are of paramount importance in worldwide efforts. It is amazing that adequate nutritional supplements provided during the 3rd trimester of pregnancy and during the first 2 years of life can protect the brain but supplementation later on in life has little effect. Future research focusing on the nutrient-gene interactions in the case of early malnutrition will contribute to the creation of more targeted programs to protect the brain.

Mood disorders in adults have a prevalence of 11% and result in significant disability. The death rate from anorexia nervosa is above 10%. Underdiagnosis and undertreatment of those disorders is common. Nutrient effects on mood, behavior, and psychiatric disorders can be used to prevent disease or even support treatment. The research in the field of aromatic amino acids and long-chain polyunsaturated fatty acids is most encouraging.

Vascular disease is a risk factor for inadequate blood supply of the aging brain. Increased plasma homocysteine as a marker for low B₁₂, folate, and B₆ status has been identified as an indicator for vascular disease. Adequate supply of those vitamins and antioxidants could play an important role in the prevention of stroke and Alzheimer’s disease. In addition, the reversal of age-related impairment in cognitive function by dietary manipulation must be a long-term goal for nutritional intervention.

I would like to take this opportunity to thank the Chairmen, Professor John Fernstrom and Doctors Ricardo Uauy and Pedro Arroyo for their contribution to this workshop. Our thanks to the Nestlé team who organized the workshop, in particular to Mr. Zurita in Mexico and Dr. Philippe Steenhout at the Centre, who helped to set up this workshop.

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Undernutrition and Mental Development

S. M. Grantham-McGregor and C. C. Ani

Childhood undernutrition is extremely common in developing countries: 31% of children under 5 years of age are stunted and 11% wasted. If children’s development is affected by undernutrition the implications for countries with high prevalence are grave. Many factors may modify the effect of undernutrition on children’s development, including the severity and duration of undernutrition, the quality of the home environment, the presence of other infections and nutrient deficits, and the stage of development of the child.

School aged children who suffered from severe clinical undernutrition in early childhood usually have poor cognition, school achievement, and motor skills, and have behavior problems compared with matched controls or siblings. These differences last into adolescence but data are lacking from adulthood. Marked improvements can take place in enriched environments. The duration of moderate undernutrition appears to be more important than a transient episode of severe clinical undernutrition.

Longitudinal studies suggest that undernutrition during the first 2 to 3 years has long term detrimental effects. Supplementation in all stages from pregnancy through the first 3 to 4 years has resulted in concurrent and short term gains. There are only limited data on the long term effects of supplementation. The few available studies suggest that supplementation in pregnancy and up to 6 months of age does not have sustained benefits. Supplementation from the last trimester of pregnancy and through the first 2 to 3 years of life has small benefits in the middle to long term. However, the data concerning long term effects from supplementation beginning in the second year or later are inconsistent.

Findings from all stages of development are summarized as follows: 1. In undernourished populations, supplementation has a concurrent and at least short term effect on children’s development when given in pregnancy or any age during the first $3\frac{1}{2}$ years of life. Between $3\frac{1}{2}$ and 5 years the findings are few and inconsistent [1, 2].
2. Premature babies may be especially sensitive to nutrition in the first few weeks, and effects may be sustained up to 8 years [3].

3. There is no evidence that pregnancy of the first 6 months is an especially sensitive time for nutrition in full term babies [4].

4. The effect of supplementation in pregnancy or the first 6 months may disappear with time [4]. It is unclear what are the long term effects of being born small for gestational age.

5. Supplementation beginning in the last trimester of pregnancy and continued for 3 years at least has small benefits that are sustained for some time [2].

6. Supplementation alone, beginning in the second or third year and given for at least 2 years has no sustained benefits [1] or very limited sustained effects [2]. In contrast, stimulation with or without nutritional supplementation produces sustained benefits [1, 5]

7. Large and sustained improvements can take place in undernourished children with continuous supplementation combined with stimulation, which are probably greater the younger the child [6].

8. Evidence from older children is inadequate to draw conclusions, but school achievement can benefit from school feeding.

References


Mechanisms for Nutrient Effects on Brain Development and Cognition

RICARDO UAUY, PATRICIA MENA and PATRICIO PEIRANO

Studies over the past five decades have shown that a reduction in the supply of energy or of several essential nutrients during the early stages of life has profound effects on nervous system development. Malnutrition impairs brain development, decreasing the number of cell replication cycles, reducing total brain DNA, restricting dendritic arborization, and thus reducing the connections between neurons. In humans, intrauterine and early postnatal malnutrition affects brain cell number. Alterations in dietary precursors also affect tissue levels of neurotransmitters (serotonin, norepinephrine, dopamine, and acetylcholine) in specific brain regions [1]. Essential and non-essential lipid supplies affect the structural composition of the brain and the myelin sheaths. The functional correlates of these biochemical changes induced by malnutrition are alterations in the waking EEG activity and in visual and auditory evoked responses; motor and cognitive development and social abilities are also affected. Most of these effects are potentiated by other types of environmental deprivation, which interact with poor diet in defining the adverse consequences.

Role of Nutrients in Brain Organogenesis

The traditional view that protein and energy deficits directly affect brain structural development and cognitive performance has been challenged, as malnutrition coexists with other nutritional deficiencies and other elements of psychosocial deprivation that can also disrupt child development. This makes it difficult to separate the role of specific nutrients from multiple other deprivations that interact with nutrition in defining the final outcome of the developmental process [2].

The role of nutrients in brain organogenesis has received renewed attention. If severe enough, a deficit in any essential nutrient can result in abnormal organ development. Cell replication is dependent on a sufficient supply of all essential nutrients. Deficits in vitamin B_{12}, reti-
nol, pyridoxine, pantothenic acid, folic acid, tocopherol, and zinc have all been shown to induce CNS malformations in experimental animals [3]. For most nutrients maternal stores permit adjustments in response to high or low dietary intakes, and in theory maternal stores need to be fully depleted or replete before embryogenesis is affected. In practice, this is not the case because not all nutrients are significantly stored by the mother, or if stored cannot be mobilized effectively. For some nutrients, such as iron, maternal stores are insufficient to meet fetal needs beyond the first half of pregnancy. In addition, genetic polymorphisms that affect nutrient metabolism may determine higher nutrient needs in specific population subgroups. Affected individuals may have an apparently acceptable intake but be depleted in critical tissues affecting embryonic development, for example folate and neural tube closure. Conversely these polymorphisms may determine that nutrients or their metabolic products may become toxic at exposures within the acceptable range for the general population, for example exposure to alcohol causing the fetal alcohol syndrome in subjects with a poor capacity to metabolize alcohol. In the case of folic acid, supplementation not only prevents the recurrence of neural tube defects but has reduced the incidence of this major nervous system malformation by 50-70%.

Iodine dependent thyroid hormone production plays an important role in organ growth and development as well as in the regulation of overall energy metabolism. Human brain development requires thyroid hormone for normal maturation, and the critical period extends from fetal life to 3 years of age. Before the 1980s, iodine deficiency was considered the most common cause of preventable mental retardation; 800 million people were vulnerable to iodine deficiency disorders, while 200 million were affected. The successful implementation of iodization programs has virtually eradicated the clinical forms of the disease, but the less severe forms are still present in some areas of the world. A syndrome that includes severe mental retardation, deafness, mutism, and spastic–rigid motor dysfunction characterizes cretinism secondary to iodine deficiency.

Lipid Effects in Retinal and Brain Development

The effect of essential lipids on the functional maturation of the retina observed in several animal species, including primates, can now be traced to a direct effect on membrane function and photoreceptor differentiation. It has been shown that docosahexaenoic acid (DHA) increases significantly in rod outer segment apical process differentiation; this is the locus for rhodopsin and opsin dependent light transduction. This is paralleled by an increase in opsin expression and content
in the rod photoreceptor apical processes. One of the most significant membrane effects of DHA is its role in photoreceptor signal transduction process. The greater mobility of rhodopsin within the lipid microenvironment most probably explains a change in G protein activation and the corresponding enhanced signal transduction to photon stimuli. The corresponding physiologic phenomenon is the increase in retinal sensitivity to light associated with DHA supply in the diet. We propose that DHA by affecting light transduction early on in life may have long lasting effects on the organization and function of the visual cortex. These potential mechanisms may explain how essential fatty acid supply may affect visual and brain maturation and long term function.

Phospholipids and cholesterol serve as components of specialized cell membranes and organelles. Fatty acid composition of structural membrane lipids can affect membrane function by modifying overall membrane fluidity, membrane thickness, lipid phase properties, and membrane microenvironment, or by interaction of fatty acids with membrane proteins [4]. These effects may modulate receptor activity, transport in and out of cells, and hormonal and other signal transduction processes.

**Temporal Cycles**

Study of the development of fetal states and the organization of their defining parameters, and their modulation and disruption by disease, is a potentially powerful way to assess CNS development. Active sleep is characterized by spontaneous, intense, generalized neuronal firing in most areas of the brain [5]. The CNS shows an increased level of

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**FIGURE 1 – A schematic representation a model for sensory organ integration to CNS function. Nutrients with proven effects on sensory organs and on cortical processing are included.**
endogenous neuronal activation during this state, even in very immature animals. This suggests a key role for active sleep during ontogenesis of the nervous system. Active sleep provides endogenous stimulation to the sensory processing areas in the CNS, while pharmacologic inhibition of active sleep induces structural and functional disturbances during development that become apparent in the adult. The ability to maintain the normal progression in sleep-wake maturation is critical for brain development and may be a way of assessing how environmental factors, including essential nutrient supply, affect central nervous system development.

Effects of Nutrients on Functional CNS Integration

The need for sensory driven activity has been widely recognized as crucial for normal infant brain development. Sensory deprivation induces anatomical and functional deficits in animals and humans. Neural activity is critical in the anatomical development of the intricate circuitry that connects sensory organs to relay centers, primary cortical processing areas, and associative areas necessary for learning and memory. Figure 1 provides a scheme of this generalized model for sensory integration to CNS function and includes nutrients with proven effects on sensory organs and in cortical processing. All systems are more vulnerable during the periods of most rapid functional development. Normal infant development depends both on genetics and on sensory input that provides appropriate patterns of neural activity to shape the developing brain. The combined effect of increased vulnerability reflecting developmental stage and greater severity of nutrient deficits at earlier ages makes infancy a critical time for brain development.

References
Carbohydrate and Fat Based Appetite Control Mechanisms

WOLFGANG LANGHANS

The control of appetite is based on positive and negative feedback derived from the sensory properties of food and the postingestive stimulation of pre- and postabsorptive sites [1]. Negative feedback that stops ingestion and maintains satiety is derived from the bulk of the food as well as from the chemical and secretagog properties of the nutrients. In the small intestine, carbohydrates and fat can stimulate vagal sensory fibers directly and through the production of several peptides.

The presence or digestion of lipids in the small intestine stimulates the production of cholecystokinin (CCK), enterostatin, and apolipoprotein A-IV (apo A-IV). All three peptides reduce food intake after parenteral administration in various experimental paradigms and are therefore possible mediators of the preabsorptive feedback control of appetite based on dietary fat.

Glucagon-like peptide 1 (GLP-1) [2], but also CCK [3], may be involved in the preabsorptive feedback control of appetite based on carbohydrates, because the production of both peptides is stimulated by the presence of carbohydrates in the small intestine. GLP-1 also reduces food intake after peripheral administration (man) and central administration (rat). The role of peptides in carbohydrate and fat based appetite control mechanisms is summarized in Fig. 1.

Serotonergic pathways are apparently involved in the central nervous system integration of preabsorptive feedback signals of appetite control based on carbohydrates and fat.

Negative feedback based on the utilization of metabolic fuels may also contribute to the feedback control of meal size, but is primarily involved in the maintenance of satiety after a meal.

Glucose utilization is monitored by glucose sensitive neurons in liver, hindbrain, and hypothalamus. The CNS integration of glucose derived feedback signals apparently involves norepinephrine, neuropeptide Y, and the recently discovered orexin peptide family [4]. Signals from fatty acid oxidation that affect appetite are primarily monitored
FIGURE 1 – Schematic diagram of the carbohydrate (CHO) and fat based preabsorptive feedback control of appetite. Apo A-IV, apolipoprotein A-IV; CCK, cholecystokinin; GLP-1, glucagon-like peptide 1; 5HT, serotonin. Note that enterostatin has not yet been reported to suppress appetite in humans, whereas an appetite suppressive effect of circulating GLP-1 has only been shown for humans but not for rats. The stimuli for central CCK and GLP-1 release or transmission are at present unknown.
in the liver and relayed to the brain through vagal afferents. Galanin [5] and perhaps 5HT appear to be involved in the CNS integration of feedback signals derived from fatty acid oxidation. Pre- and postabsorptive feedback signals also influence taste processing and hence nutrient selection. On the other hand, they have to be associated with familiar oral cues for optimal efficiency.

Thus horizontal as well as vertical interactions between the various feedback signals ensure the characteristic redundancy of the appetite control system. Finally, the carbohydrate and fat based short term appetite control mechanisms are modulated by adiposity signals such as leptin and insulin.

In all, appetite control is part of a complex regulatory system that consists of several intertwined feedback loops which ensure adequate energy intake and nutrient selection, prepare the organism for the arrival of particular nutrients, facilitate their metabolic handling, and control energy storage.

References
Diet, Monoamine Neurotransmitters and Appetite Control

JOHN D. FERNSTROM and MADELYN H. FERNSTROM

The appetite for food is controlled by complex circuitry in the brain. Neurons form the cellular elements of these circuits, and functionally resemble the electronic elements in computer circuits. Neurons process the electrical signals they have received, pass them along, sometimes for great distances, through the depolarization of their cell membrane, and then generate new electrical signals in neurons with which they make contact. Unlike the elements in a computer circuit, however, which are directly linked, neurons do not make direct cellular contact with one another. Instead, they transfer electrical signals through the release of a neurotransmitter, a molecule capable of generating electrical discharges in adjacent neurons through interaction with a specific receptor (Fig. 1). As neurons conduct electrical signals along their membranes by a mechanism common to all types of neuron but transmit their signals through a neurotransmitter that can be unique to a particular neuron, pharmacologists have studied neurotransmitters in the hope of identifying drugs that will selectively alter neuronal function, and thus selectively modify appetite.

Using this approach, monoamines appear at present to be the most convincingly tied to appetite control circuits. Those most studied are serotonin (5HT), dopamine, and norepinephrine. Drugs that target one or other of the monoamines have been found to produce consistent effects on appetite. For example, drugs that selectively enhance the release or the activity of 5HT suppress appetite (for example, fenfluramine, which releases 5HT from neurons), while agents that selectively block 5HT action stimulate appetite (for example, methysergide, a 5HT receptor blocker). Similar relations also hold for dopamine and norepinephrine: drugs like amphetamine (a dopamine releaser) and phentermine (a norepinephrine releaser) are potent appetite suppressants, while dopamine and norepinephrine receptor blockers antagonize these actions.
Much pharmacologic work has focused specifically on the hypothalamus, a brain region long known to contain appetite control circuitry. Neuronal connections responding to dopamine, norepinephrine, and 5HT abound in the hypothalamus, and the local administration of drugs affecting these amines produces appetite effects like those observed when the agents are given systemically [1]. Overall, the importance of the connection between brain monoamines and appetite control mechanisms is perhaps most effectively underscored by the fact that this pharmacologic line of investigation has led to the development of specific norepinephrine, dopamine, and 5HT drugs that are effective clinically as appetite suppressants [2].

Another research direction has also linked monoamine neurons to appetite control in the brain. This approach begins with the facts that monoamines are synthesized from amino acids (dopamine and nore-
pinephrine from tyrosine; 5HT from tryptophan), and that synthesis rates vary directly with the availability of their respective substrate. Hence 5HT synthesis is tied to neuronal tryptophan concentrations, and dopamine and norepinephrine synthesis—in their respective neurons—to local tyrosine concentrations. Being amino acids, the accessibility of tryptophan and tyrosine to brain neurons is subject to normal metabolic phenomena in the body, including the metabolic consequences of consuming food. Through this link, monoamine neurons have been tied to food ingestion. For 5HT neurons, single meals of carbohydrates have been found to raise brain tryptophan and stimulate 5HT synthesis, while protein-containing meals lower brain tryptophan and 5HT. For dopamine and norepinephrine neurons, brain tyrosine concentrations and dopamine and norepinephrine synthesis do not change with the ingestion of carbohydrate meals, but rise when protein meals are consumed [3]. Somewhat different effects are noted for tryptophan and 5HT when examined chronically following the ingestion of high or low protein diets for several weeks: brain tryptophan and 5HT synthesis follows dietary protein content directly (instead of inversely). A similar direct relation is observed between dietary protein content and brain tyrosine concentrations, and dopamine and norepinephrine synthesis.

From these pharmacologic and dietary data, simple mechanisms have been proposed for the control of carbohydrate and protein intakes. While some aspects of these models may be correct, a growing awareness of the complexity of the mechanisms governing body metabolism and appetite suggests that such simple models are at best portions of more complex control circuitry. Future studies will no doubt continue to increase our understanding of such control mechanisms and how monoamine neurons and their dietary links participate, and also suggest new pharmacologic strategies useful in the control of appetite.

References
Affective disorders, including depression, are among the most common disorders in humans and contribute substantially to the global burden of disease [1]. Brain serotonin and norepinephrine play a significant modulatory role in precipitating and sustaining depressive symptoms and in remission from the disease. The formation of these monoamines depends, in part, on the availability from plasma to brain of their respective precursor amino acids tryptophan and tyrosine, which are derived from the food. The metabolic effects of diet and constituents of diet cause alterations in the plasma amino acid profile and thereby change the availability to the brain of tryptophan and tyrosine. When unbalanced amino acid mixtures are given in large doses to vulnerable subjects they experience a relapse of depression [2]. Combined oral contraceptives decrease the tyrosine availability to the brain, which may contribute to precipitation of depression in vulnerable subjects [3]. Use of oral contraceptives is also associated with a change of preference for macronutrients that insufficiently compensates for the decreased plasma tyrosine. Intake of the artificial sweetener aspartame causes significant changes of aromatic amino acid availability to the brain and seems to precipitate affective reactions in susceptible subjects [4].

Acute effects of carbohydrate-rich or protein-rich meals on brain function in normal subjects are, on average, subtle. However, healthy subjects seem to prefer diets that further increase a high, or decrease a low, basal availability of plasma tryptophan to the brain [5]. This raises the question of whether long term metabolic effects of diet, even when modest, contribute to sustaining or accentuating personality features related to brain serotonin function – for example, mood, sleep, pain sensitivity, sexual and aggressive behavior. One study found support for an association between plasma tryptophan level and aggression score in normal individuals [6].

Whether individuals suffering from or vulnerable to affective disorders prefer diets that adversely affect the precursor amino acid availability is not clear. It also remains to be shown whether these individu-
als are more sensitive than healthy subjects to the metabolic effects of diet. There is evidence that at least some psychiatric patients show an abnormal metabolic response to proteins, which could possibly aggravate the central nervous system symptoms related to the cerebral monoamines. Studies of food preferences, of the metabolic effects of diet, and of how diet affects brain function in affective disorders are clearly warranted.

References

Nutrition, Serotonin, and Behavior in Anorexia and Bulimia Nervosa

WALTER KAYE, KELLY GENDALL and MICHAEL STROBER

Anorexia nervosa and bulimia nervosa have not traditionally been viewed as disorders in which biological vulnerabilities contribute to pathogenesis. However, recent studies suggest a potential role of the genetic transmission of a shared biological vulnerability for developing an eating disorder [1, 2]. Several lines of evidence, including the efficacy of serotonin selective reuptake inhibitor (SSRI) treatment, suggest that people with eating disorders may have a trait-related disturbance of serotonin (5HT) [3]. People with eating disorders may have a premorbid increase of brain serotonin 5HT signal transmission, which contributes to increased satiety, extremes of impulse control, and dysphoric mood symptoms. In anorexia nervosa in particular, rigorous dieting behavior appears to result in a reduction of the availability of tryptophan, the precursor of 5HT, which in turn reduces brain 5HT neuronal activity and alleviates dysphoric mood [4, 5]. Conversely, food ingestion which stimulates insulin secretion increases tryptophan availability, which results in increased 5HT release and thus increased anxiety and depression [6, 7]. Self starvation is not conducive to homeostatic adaptation and survival and, in most people, food restriction is not an inherently reinforcing behavior. However, persistent dieting to the point of starvation raises the speculation that food restriction might provide some reward for people with eating disorders.

References


Lipids in Neural Function: Modulation of Behavior by Oral Administration of Endocannabinoids Found in Foods

G. Crozier-Willi, A. Berger, V. Di Marzo, T. Bisogno, L. De Petrocellis, E. Fride and R. Mechoulam

Cannabis (marijuana) has been used medicinally for more than 4000 years for the treatment of disorders that include migraine, anorexia, asthma, muscle spasms, seizures, glaucoma, neuralgia, pain, diarrhea, and nausea. Although the active compound, Δ⁹(-)-tetrahydrocannabinol (THC), is not naturally found in the body, receptors for it have been described in the brain since 1988. These receptors were later named CB1, and a receptor subtype, CB2, has been discovered in the immune system. Their presence in diverse invertebrates is evidence that the cannabinoid signaling system has been conserved for at least 500 million years.

An endogenous ligand for these receptors was discovered more recently: this is the ethanolamide of arachidonic acid (N-arachidonylethanolamide), and was named “anandamide” from the Sanskrit word “ananda” meaning bliss. When anandamide was injected into animals, the classical behavioral effects of THC administration – hypomobility, hypothermia, analgesia, and catalepsy – were observed [1]. Since this discovery, other endogenous metabolites have been shown to be functional agonists of these receptors. These include several polyunsaturated fatty acid derivatives of ethanolamide and 2-arachidonylglycerol [2]. These compounds are collectively termed “endocannabinoids”. The potent sleep inducing factor, cis-9-octadecanoic amide, although not an agonist for cannabinoid receptors, is now also known to potentiate the activity of anandamide [3].

Many animal studies have shown that anandamide administration influences such brain functions as memory, thermoregulation, control of sleep/wake cycles and movement, food intake, and nociception. Peripheral functions of anandamide decrease gut motility, systemic blood pressure, and intraocular pressure.
<table>
<thead>
<tr>
<th>Material</th>
<th>Ethanolamides</th>
<th>Oleamide</th>
<th>AA MAG</th>
</tr>
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<tr>
<td></td>
<td>Ethanolamides</td>
<td>ng/g Starting material</td>
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<tr>
<td></td>
<td>c16:0</td>
<td>c18:1n-9</td>
<td>c18:2n-6</td>
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</table>

ND, not detected; 2-AG, 2-arachidomylglycerol.
In 1996, a highly publicized study claimed that anandamide had been discovered in chocolate [4], a rather surprising finding as it is known that higher order plants do not synthesize arachidonic acid.

We decided to investigate the possible presence of endocannabinoids in various foodstuffs and to demonstrate that oral administration of these compounds altered classical THC behavioral responses.

Anandamide in foods

The results (Table I) show that anandamide (c20:4n-6) was very low or absent in cocoa powder, dark chocolate, or cocoa beans (unfermented or fermented, unroasted, or roasted). It was not found in coffee cherries, green beans, peanuts, hazelnuts, walnuts, soybeans, oatmeal, millet, or olives. On the other hand, human breast milk was found to contain small amounts. The possible biological significance of this is not known.

In contrast, other N-acyl ethanolamines and oleamide were found in variable concentrations in the materials studied. Oleoyl- and linoleoylthanolamides and some palmitoylthanolamide were present. Palmitoylthanolamide was the most important congener found in milk. All materials contained oleamide, and milk proved to be the richest source of this fatty acid amide of all materials tested. Human milk contained more 2-arachidonylglycerol than bovine milk.

Bioactivity

Anandamide (300 mg/kg), oleamide (200 mg/kg), and 2-arachidonoylglycerol (400 mg/kg) had significant effects on three of the four behaviors tested (Fig. 1) and significantly reduced body temperature, but had no influence on analgesia or intestinal motility. Lower doses of the three compounds were inactive.

Conclusions

From these data it is clear that oral intake of these compounds resulted in significant effects on behavior, although only at high doses. Higher order plants, as expected, do not contain arachidonyl species, although ethanolamides of oleic acid, linoleic acid, and to a lesser extent palmitic acid are present. Oleamide is the most abundant of the fatty acyl amides in plant and animal food sources.

It seems that unreasonably large amounts of food would have to be consumed to achieve levels of ingestion of these compounds of the order of those that influenced behavior in the mouse. However, it is
known that some amide species, while having lesser affinity for the receptor themselves, will potentiate the activity of other species. Therefore a mixture of the compounds may have a synergistic effect, a concept for which there is already some evidence. Second, in the present study, the behavioral responses were clearly evident. The question remains as to whether lower levels result in an attenuated effect, undiscernible with the present methods used. Clearly in the nutrition of normal daily life, a strong effect would be undesirable.

CB receptors are found in many tissues, including the gut and immune tissues. The potential for these lipid compounds to influence enterocytes or gastrointestinal or systemic immune cells deserves further study.

References

Diet Related Prevention of Alzheimer’s Disease: Different Hypotheses

ANNE-SOPHIE NICOLAS and BRUNO VELLAS

Alzheimer’s disease is the leading cause of senile dementia. This disease, which is characterized by progressive loss of memory and cognitive function, affects 15 million people worldwide. The etiology is complex, involving several genes and possibly, environmental factors. Some diet related hypotheses are now proposed.

Oxidative stress and Alzheimer’s disease: the plausible neuroprotector effect of antioxidant

In recent years, there has been increasing interest in the role of reactive oxygen species (ROS), including free radicals, in the normal process of brain aging and in the pathophysiology of Alzheimer’s disease (Fig. 1). Several studies suggest a significant increase in oxidative stress to proteins, DNA, and lipids in Alzheimer’s disease. The oxidative stress hypothesis proposes that oxygen free radicals and hydroperoxides are mainly responsible for specific neuronal degeneration and the development of the principal neuropathological lesion, the neuritic plaque. One of the reasons why this hypothesis has attracted so much attention is its implication that the disease could be influenced by dietary antioxidants. Supplementation results are currently sparse but some preclinical and clinical evidence suggests a valuable role for antioxidant treatment (α-tocopherol, selegiline, ginkgo biloba) [1].

Hyperhomocysteinemia: a new risk for Alzheimer’s disease?

Hyperhomocysteinemia is now known to be an important risk factor for vascular disease, independent of long recognized factors such as hyperlipidemia, hypertension, and smoking. Several recent reports suggest that there may also be a relation between hyperhomocysteinemia and Alzheimer’s disease (Fig. 2) [2]. Although the mechanisms under-
lying the observed associations between hyperhomocysteinemia and Alzheimer's disease are as yet unclear, certain hypotheses should be considered, for example activation of N-methyl-D-aspartate and conversion of homocysteine into homocysteic acid (Fig. 2). Polyvitamin treatment with folic acid and cyanocobalamin are effective in lowering plasma homocysteine in most subjects. Large scale clinical trials in high risk populations are now needed to determine whether lowering blood homocysteine reduces the risk of Alzheimer's disease and other dementias.

Do aluminum and silicon have an influence in Alzheimer's disease?

Because of its proven neurotoxicity, aluminum may be another factor that could play a role in Alzheimer's disease. Several epidemiologic studies have reported an association between exposure to aluminum and Alzheimer's disease. An interesting complementary hypothesis has also been proposed by Birchall on the role of silicon, particularly in water, as a protective factor against aluminum toxicity [3]. However, there is much controversy on both the biological and the epidemiologic findings and their interpretation.
Conclusions

There is convincing evidence that nutrition may influence the pathogenesis of Alzheimer’s disease. Most results are from clinical and epidemiological studies which cannot establish a causal link. Large scale randomized trials are necessary to determine whether nutrition can protect against the development of Alzheimer's disease. Because it is a common and severe illness with no known preventive measures, demonstration by such trials of even a small to moderate protective effect would be of substantial public health importance.

References
Stroke-prone spontaneously hypertensive rats (SHRSP), which develop rapid onset severe hypertension and stroke, are an appropriate model for analyzing the pathogenesis of stroke. This applies to genes related to hypertension and stroke, as well as to the investigation of the role of sodium, protein, and other nutrients in the pathogenesis and prevention of hypertension and stroke.

Recent genome-wide linkage analysis on SHRSP revealed the gene loci contributing to excess-salt-induced hypertension. This information may also indicate genetic differences in salt sensitivity in human populations. In addition, there is experimental evidence in SHRSP that stroke is preventable by adjustments to nutrition, such as increasing the intake of protein, some amino acids, fatty acids, calcium, magnesium, potassium, dietary fiber, and other nutrients. The mechanisms of dietary stroke prevention have been further analyzed experimentally.

The effectiveness of the nutritional prevention of hypertension or stroke was indicated by the WHO coordinated study on Cardiovascular Disease and Alimentary Comparison (WHO-CARDIAC study) covering 60 populations in 25 countries. Age adjusted mortality rates for stroke in particular were positively related to 24 hour urinary sodium excretion and to the Na/K ratio, while they were inversely related to serum total cholesterol concentrations, which reflect at least in part the animal's protein intake. Moreover, higher blood pressure – the major risk factor for stroke – was positively related to 24 hour urinary sodium excretion and to body mass index but inversely related to 24 hour urinary magnesium excretion and to urea nitrogen, a biological marker of protein intake.
Risk from Exposure to Metals: Deficits and Excesses (Cu, Fe, Mn, Al, Cr, B)

G. Rotilio

Risks associated with exposure of the brain to deficits of essential microelements (Cu, Fe, Mn, Cr, B) or to an excess of metals, either essential or non-essential (Al), can conveniently be studied by analyzing the molecular markers and underlying mechanisms now being uncovered in research on neurodegenerative diseases.

Copper-linked diseases are representative of the nutritional risks for the brain from abnormal exposure to metals. Neurological symptoms are predominant in two inherited disturbances of copper homeostasis, Menkes’ and Wilson’s diseases, which are associated with loss of transmembrane copper transporting ATPases. As the two mutated ATPases are expressed in different tissues, Menkes’ disease serves as a model for copper deficiency and Wilson’s disease as a model for copper intoxication. However, in both cases there is neurodegeneration associated with increased oxidative injury of the tissues. Under conditions of cop-

<table>
<thead>
<tr>
<th>TABLE I – Factors determining brain vulnerability to oxidative stress.</th>
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</thead>
<tbody>
<tr>
<td>1. Excess production of oxygen radicals</td>
</tr>
<tr>
<td>• High rate of oxidative metabolic activity</td>
</tr>
<tr>
<td>• Endogenous generation of oxygen radicals by specific neurochemical reactions, for example, dopamine oxidation</td>
</tr>
<tr>
<td>• Increased deposition of transition metals with age</td>
</tr>
<tr>
<td>2. Deficit of defense</td>
</tr>
<tr>
<td>• Low levels of protective antioxidant enzymes with respect to other tissues like liver or blood</td>
</tr>
<tr>
<td>3. Propensity of the target</td>
</tr>
<tr>
<td>• High concentration of readily oxidisable substrate, in particular, membrane lipid polyunsaturated fatty acids</td>
</tr>
<tr>
<td>• High ratio of membrane surface area to cytoplasmic volume</td>
</tr>
<tr>
<td>• Neuronal anatomical network vulnerable to disruption</td>
</tr>
<tr>
<td>• Neuronal cells are non-replicating</td>
</tr>
</tbody>
</table>
per deficiency, inactivation of cytochrome oxidase and superoxide dismutase leads to mitochondrial dysfunction and increased generation of oxygen radicals by damaged mitochondria. In copper intoxication, excess metal will be involved in redox cycling, with oxygen again causing an augmented flux of oxygen radicals. Factors determining brain vulnerability to oxidative stress are outlined in Table I.

For iron, analogous situations are represented by aceruloplasminemia and Friedreich’s ataxia. In Alzheimer’s disease, aluminum intoxication leads to iron accumulation and consequent oxidative stress, while interference with mitochondrial function is likely to be source of oxidative stress in manganese linked parkinsonism. Also, metal mishandling by normal proteins altered for genetic or environmental reasons is a potential source of oxidative stress: copper binding to Cu Zn superoxide dismutase in familial amyotrophic lateral sclerosis, to Aβ amyloid in Alzheimer’s disease, and to the prion protein in spongiform encephalopathies are relevant models for risks associated with exposure of brain to metals in particular predisposing situations.

Further reading

The decline in neurocognitive function among elderly people is widely considered to be a biological imperative of aging. However, it now appears that the decline in memory, problem solving, and related cognitive skills can be postponed or prevented [1]. In that light, a whole range of interventions based on physical activity and nutrition has been proposed. Few of those have been adequately studied in randomized controlled trials and thus the definitive information needed to prescribe interventions that will be effective across genetically and experientially diverse populations is lacking. However, given the knowledge we do have about the roles of specific nutrients in the function of the nervous system, coupled with measures which have been taken to relate cognitive function to the circulating levels of those nutrients, it now appears that in some instances cognitive function in the elderly can be protected.

Some of the nutrients exert an effect on cognitive function through their effects on the circulatory system, others may act by protecting against oxidative damage, while others inhibit the build up of metabolites that impair neurocognitive function or are involved as co-factors and as nutrient or metabolite carriers which are important to neurocognitive function.

Antioxidants

As Alzheimer's disease involves oxidative damage, it is suggested that increased antioxidant intake may inhibit age related loss of cognitive function. There have been some prospective clinical trials of antioxidant treatment and cognitive function. These have involved vitamin E or ginkgo biloba extract, but the results have been uncertain. A meta-analysis of four papers using standard inclusion criteria and a double blind design suggested a 3% difference in cognitive perform-
ance between subjects treated with ginkgo biloba extract and controls [2]. A study of α tocopherol supplementation suggested a beneficial effect of 2000 IU/d [3].

Dietary Modulation of Inflammation

Long term users of anti-inflammatory drugs have lower odds ratios for the development of cognitive decline [4]. Amyloid β, a peptide accumulating in the brain in Alzheimer’s disease, may exert damaging effects by eliciting an inflammatory response. Inflammatory responses can be modulated by altering the intake of ω-3 fatty acids. Evidence that altering the intake of fatty acids can affect cognitive decline is epidemiological and circumstantial, and no prospective studies have been published.

Dietary Manipulation of Cholinergic Transmission

Defects in cholinergic transmission are observed in Alzheimer’s disease. Dietary manipulation of cholinergic transmission has been attempted, for example using acetyl-L-carnitine [5], but with no significant improvement. The use of thiamine has also been suggested, but no prospective trials have been done.

Phytoestrogens

Postmenopausal women receiving estrogen replacement therapy appear to experience less cognitive decline than unsupplemented women [6]. Estrogens have various neurotropic and neuroprotective effects, and clinical trials of natural plant estrogens (phytoestrogens) would be worthwhile.

Glucose enhancement

Modest increases in circulating glucose affect various brain functions including learning and memory. Provision of beverages with glucose enhances memory performance [7].

Homocysteine

There is an association between hyperhomocysteinemia and dementia in the elderly, linked to vitamin B-12 and folate undernutrition [8]. Work is needed to clarify the role of deficiency of these latter nutrients in the pathogenesis and treatment of dementia.
Conclusions

It is unlikely that there is a “magic bullet” to protect neurocognitive function, but the association of nutritional or dietary factors with cognitive decline in the elderly provides a field for continuing clinical and experimental research.

References

Disorders of brain function not induced by primary lesions of brain structure may become apparent as acute, chronic, or acute on chronic encephalopathies.

Liver Disease

Hepatic encephalopathy includes any neuropsychiatric disorder induced by liver disease. A dualistic concept is proposed to explain the pathogenesis of hepatic encephalopathy (Fig. 1), which distinguishes between the sequelae of liver insufficiency and those of hyperammonemia [1]. Hepatic failure in patients gives rise to only a modest increase in the plasma ammonia concentration, while another factor – portal–systemic shunting, which occurs independently of liver insufficiency – is usually responsible for pronounced hyperammonemia (Fig. 1). Liver cell damage causes an accumulation of methionine and aromatic amino acids, whereas hyperammonemia appears to reduce the plasma levels of branched chain amino acids by depleting intracellular glutamate (Fig. 1). The term “portal–systemic encephalopathy” by definition only means brain dysfunction brought about by portal–systemic shunting.

Whether or not neurotoxic compounds derived from accumulated amino acids contribute to hepatic encephalopathy in liver insufficiency remains unclear. However, a derangement of neurotransmission owing to altered concentrations of substances such as taurine, octopamine, and tryptamine is likely to be a causative factor. The metabolic deviations associated with hepatic failure depress the reticular activating system even at an early stage. In contrast, a clinically relevant hyperammonemia only interferes with the activity of the cerebral cortex and other brain structures located above the mesencephalic reticular formation. Portal–systemic encephalopathy mostly represents a sub-
clinical encephalopathy. However, in conditions of long lasting hyperammonemia the brain becomes extremely sensitive to an additional ammonia load, as glutamine formation is limited. Here nitrogenous substances may precipitate a manifest acute on chronic encephalopathy. Synergistic neurotropic effects of liver insufficiency and hyperammonemia take place, at least in part, at the blood–brain barrier, where hepatic failure increases the entry of ammonia into the brain and hyperammonemia facilitates the transport of neutral amino acids.

The treatment of encephalopathy in cirrhosis should include the branched chain amino acids, which improve the mental state but do not reduce the mortality rate in patients with clinical complications [2]. If hyperammonemia outweighs liver insufficiency, ornithine aspartate is indicated.

Renal Failure

In chronic renal failure, the steady decline in the glomerular filtration rate is most probably mediated by an increase in the intraglomerular hydrostatic pressure. Dietary protein contributes to disease progression by augmenting this pressure. Furthermore, toxic influences
of protein derived waste products are involved in the pathogenesis of the uremic syndrome, with parathyroid hormone and disorders of transmembrane ion transport playing an additional part [3]. A low protein diet (0.7 to 0.8 g of protein/kg.day) has been found to slow down the progression of renal disease [4]. Protein restriction also ameliorates uremic encephalopathy. However, in order to prevent malnutrition, sufficient energy has to be provided. Regardless of the beneficial effects of protein restriction, patients with chronic renal failure should, whenever possible, be given early dialysis.

Critical Illness

Diabetic ketoacidosis and the hyperglycemic hyperosmolar non-ketotic syndrome should not be viewed as separate nosological entities, because they are the extremes of a continuum of emergencies caused by an insufficient secretion or action of insulin. They differ only in the extent of metabolic acidosis and hyperglycemia induced dehydration, the latter being crucial in producing neurological symptoms. Brain dysfunction associated with either hyper- or hyponatremia results from alterations of the “effective osmolality.” When abnormal serum sodium concentrations develop over many hours or days, a regulatory change of brain cell volume takes place, which has to be considered in the treatment schedule [5]. Encephalopathy caused by hypophosphatemia, for instance in the refeeding syndrome, is mediated mainly by a decay of ATP production and a decrease in the 2,3-diphosphoglycerate content of red blood cells, with impaired oxygen delivery to tissues.

References
The Ketogenic Diet and Epilepsy

JOHN M. FREEMAN

Despite many new anticonvulsant drugs, approximately 20% of children and adults will continue to have seizures that are hard to control. Some are candidates for epilepsy surgery to remove a seizure focus. Many must continue trying drugs. For some children, a ketogenic diet represents a promising alternative therapeutic approach to improved seizure control, and is a potential but untested treatment for adults [1]. A schematic diagram of the course of seizures and epilepsy, and of the role of the ketogenic diet is shown in Fig. 1.

The “classic” ketogenic diet a high fat, adequate protein, low carbohydrate diet, developed in the 1920s. The diet was initially designed to mimic the effects of starvation, which had been shown to have dramatic and long lasting effects on the control of seizures [1]. After the discovery of phenytoin, the “classic” ketogenic diet was used less often. Recent prospective studies (Table I) have documented the continued efficacy of the diet in children with uncontrolled seizures, and a recent review stated “this improvement is in the range of, or greater than, that reported with the addition of newer AEDs (antiepileptic drugs)” [2].

The diet must be individually calculated to achieve and maintain ideal body weight for the child and must be supplemented with multivitamins, calcium, and trace minerals. It must ONLY be used under medi-

![FIGURE 1 – The place of the ketogenic diet in the management of seizures.](image-url)
cal supervision, working with a knowledgeable dietician [3].

The diet achieves more than a 50% decrease in seizure frequency in more than half the children treated (Table I). It appears equally effective at various ages and in different seizure types, and appears to have a dramatic effect in many children with the atonic/myoclonic seizures of the Lennox-Gastaut syndrome. The diet is tolerated in adolescents when sufficiently effective. Its effectiveness in adults remains to be determined.

The ketogenic diet mimics starvation by restricting carbohydrate ingestion and replacing 90% of the dietary energy with fat. In the absence of sufficient carbohydrate, the fatty acids are incompletely oxidized, resulting in increased levels of β-hydroxybutyrate. Raised blood concentrations of β-hydroxybutyrate (> 4 mM) are thought to be critical for achieving seizure control, but the mechanisms by which the ketogenic diet exerts its anticonvulsant effects are still unknown. The precise correlation (if any) of blood levels of β-hydroxybutyrate with seizure control remains to be determined. How, or indeed if, β-hydroxybutyrate is the active anticonvulsant factor in the brain is a question also under active laboratory investigation.

The ketogenic diet, when supplemented with vitamins, calcium, and trace minerals, appears to be nutritionally adequate to permit normal linear growth, even while restricting weight gain. Kidney stones occur in 5-8% of children and can often be prevented by increased fluids and alkalization of the urine with citrates. A mild dyslipidemia is common, with mean cholesterol of 220 mg/dl (5.7 mmol/l) and mean high density lipoprotein of 50 mg/dl.

As we begin to learn how the diet works and understand more about this difficult to use alternative treatment for intractable seizures in childhood, we will perhaps develop a new understanding of the mechanisms underlying epilepsy, and thereby develop less burdensome forms

<table>
<thead>
<tr>
<th>Number initiating</th>
<th>Seizure control and diet status</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure-free</td>
<td>4 ( 3%)</td>
<td>5 ( 3%)</td>
<td>11 ( 7%)</td>
<td></td>
</tr>
<tr>
<td>&gt;90%</td>
<td>46 (31%)</td>
<td>43 (29%)</td>
<td>30 (20%)</td>
<td></td>
</tr>
<tr>
<td>50-90%</td>
<td>39 (26%)</td>
<td>29 (19%)</td>
<td>34 (23%)</td>
<td></td>
</tr>
<tr>
<td>&lt;50%</td>
<td>36 (24%)</td>
<td>29 (19%)</td>
<td>8 ( 5%)</td>
<td></td>
</tr>
<tr>
<td>Continue diet</td>
<td>125 (83%)</td>
<td>106 (71%)</td>
<td>83 (55%)</td>
<td></td>
</tr>
</tbody>
</table>
of anticonvulsant treatment.

References
Agenda of the
5th Nestlé Nutrition Workshop
Clinical & Performance Program

Mexico 27 to 29 March 2000

“Nutrition and Brain”

Chairmen: Prof. John D. Fernstrom
            Dr. Ricardo Uauy
            Dr. Pedro Arroyo

Undernutrition and mental development
S. Grantham MacGregor

Micronutrient & cognitive function (iron deficiency and neurofunctional development)
P. Peirano

Mechanism by which nutrients affect brain development & cognition
R. Uauy

Carbohydrate and fat-based appetite control mechanisms
W. Langhans

Neuropeptides and the control of energy homeostasis
S. Woods

Diet, neurotransmitters and appetite control
J. Fernstrom

Nutrients and affective disorders
S. E. Møller

Eating disorders-nutrient/behavior interaction
W. H. Kaye
Lipids in neural function: modulation of behavior by oral administration of endocannabinoids found in foods
G. Crozier-Willi

Nutritional impact on sleep-wake cycle
R. Drucker-Colin

Mechanism by which nutrients affect the brain aging process
I. Rosenberg

Diet-related prevention of Alzheimer’s disease: different hypotheses
B. Vellas

Nutritional pathogenesis and prevention of stroke
Y. Yamori

Risk from exposure to metals: deficits and excesses
(Cu, Fe, Mn, Al, Cr, B)
G. Rotilio

Reversal of age-related impairment in cognitive function by dietary manipulation
D. Bunout

Metabolic encephalopathies: liver disease, renal failure, critical illness
E. Holm

The ketogenic diet and epilepsy
J. M. Freeman
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