COMMITTEE V
The Human Food Chain

DRAFT - 10/15/87
For Conference Distribution Only

NUTRIENTS, COGNITION, AND HUMAN BEHAVIOR

by

Shlomo Yehuda
Psychopharmacology Laboratory
Department of Psychology
Bar-Ilan University
Ramat-Gan, ISRAEL

The Sixteenth International Conference on the Unity of the Sciences
Atlanta, Georgia November 26-29, 1987

© 1987, International Conference on the Unity of the Sciences

"Once upon a time there were three little sisters," the Dormouse began in a great hurry; "and their names were Elsie, Lucie and Tillie; and they lived at the bottom of a well--"

"What did they live on?" said Alice, who always took a great interest in questions of eating and drinking.

"They lived on treacle"* said the Dormouse, after thinking a minute or two.

"They could not have done that, you know," Alice gently remarked. "They'd have been ill."

"So they were," said the Dormouse; "very ill."

From: Carroll, L.,
"Alice's Adventures
in Wonderland"

*treacle = most probably a medicinal compound. Wells believed to contain water of medicinal value were sometimes called "treacle wells" (Gardner, M., 1960).

GENERAL

No wonder that Alice "always took a great interest in questions of eating and drinking." After all, Alice is one of the rare examples of a clear-cut demonstration that by drinking (a non-poisonous liquid) or eating (a piece of cake) she can modify her height and possess the ability to communicate with strange creatures. Like Alice, most of us have a deep interest in eating and drinking. "There is no love sincerer than the love of food" (Shaw, G. B.). However, the above citation also emphasizes the common belief that certain water (or other forms of food) may have "medicinal" or health-promoting effects.

Light (Wurtman, 1975, 1982; Wurtman, Baum, & Potts, 1985) and food seem to be among the most important environmental factors which influence the health, physiology and behavior of most vertebrates. While it is easy to agree to this statement, it is difficult to prove it. The relationship between nutrition, nutrients and behavior is very complex. Because of the considerable interest in this field, there are many examples of unscientific, sometimes even dangerous, claims regarding the beneficial effects of certain nutrients on health and behavior.

During the last few years, the number of better-controlled and more scientific-oriented nutritional-behavioral studies has increased. Several scientific disciplines are now involved in the nutrition-behavior studies:

1. Anthropology: Studies of myths and legends about the "magical" power of nutrients. (If you want to be brave,

consume a lion's heart, or if you want to be a fast runner, eat a deer's leg. Also, medicinal properties of rare plants.)

2. Psychology: Each one of us has a clear preference for certain foods. More important--most of the people have a list of foods that they don't eat. The same phenomenon is also on the society level. Most of the cultures that have been studied contain specific instructions about which food is "fit" and which food is "unfit" for eating. Some of these prohibitions don't have an apparent nutritional sense. The main topic here is the study of the psychological process underlying food selectivity.

3. Physiological Psychology: Food intake; Why do we start eating? What are the signals which initiate food consumption behavior? Why do we stop eating? We still don't have a satisfactory explanation for the starting and termination of food intake. The integration between social, psychological and physiological factors in food intake is not entirely clear. These questions become very important when we studied food intake disorders, such as obesity and anorexia nervosa.

4. Neurology: The use of nutrients as drugs in cases where a clear deficit in brain biochemistry was found. The known example is L-Dopa, the precursor of the neurotransmitter dopamine. In Parkinson's disorder a clear decrease in brain dopamine level was found, and L-Dopa is one of the effective anti-Parkinsonian treatments.

5. Immunology: Studies on the effects of nutrients on specific components of the immune system.

6. Neuroscience: Study on nutrients which modified behavioral or cognitive functions via changes in brain biochemistry.

The aims of this chapter are to examine the possible role(s) of nutrients on cognition and behavior, and to evaluate several possible explanations as to the effects of these nutrients.

The basic assumption is that a very strong correlation should be found between changes in behavior and in brain biochemistry. It has been demonstrated that the mode of action of drugs which are able to induce alterations in behavior is the ability of the drug to act upon brain biochemistry, i.e., brain neurotransmitters. Less known are the findings that certain behavioral changes lead to profound changes in brain biochemistry (Yehuda, 1987). One example to this effect is that the behavioral changes observed in rats reared in an "enriched environment" were correlated with changes in cerebral cortex thickness and in acetylcholine level. Therefore, the main question is if nutrients are able to modify behavior or cognitive functions, and if so, if the mode of action of nutrients is similar to the mode of action of drugs, that is, changes in brain biochemistry.

Nutritional studies can be generally divided into two main groups: (a) general or specific nutrition or nutrients deficiency, and (b) present or excessive amount of nutrients. Understanding of models of mode of action of nutrients on brain biochemistry is important for understanding the results of the

nutritional studies on cognitive functions. Therefore, the models will be presented first.

MODELS OF MODE OF ACTION OF NUTRIENTS

BRAIN NEUROTRANSMITTERS PRECURSORS

Wurtman's group was the first to suggest that dietary factors can influence central neurotransmitter functions (Fernstrom & Wurtman, 1971, 1972). They were able to show that, under certain conditions, dietary manipulation of tryptophan (which is the precursor for serotonin and able to penetrate into the brain) causes an increase in brain serotonin level. Similarly, a dietary manipulation of tyrosine leads to an increase in dopamine or norepinephrine, and choline or lecithin to an increase in brain acetylcholine (Anderson, 1980; Benedict, Anderson, & Sole, 1983; Fernstrom, 1981; Sved, 1983; Wurtman, 1982; Wurtman & Wurtman, 1984). The ratio between the level of tryptophan and large neutral amino acids (TRY/LNAA) in the plasma is the key factor in brain tryptophan bioavailability. An increase in the bioavailability of tryptophan was correlated with an increase in serotonin level. An additional finding showed that a carbohydrate-rich breakfast meal causes an increase in the TRY/LNAA ratio, while a protein-rich breakfast causes a decrease in this ratio (Ashley, Liardon, & Leatherwood, 1985).

While many studies were able to show an increase in the level of certain brain neurotransmitters after appropriate dietary

manipulation, the question regarding the effects of dietary manipulation on the functional state of the neurons that use the neurotransmitter is still open. On the one hand, attempts were made to use dietary manipulations in certain neurological and psychiatric disorders, such as L-Dopa in Parkinson's disorder, choline or lecithin in Tardive dyskinesia, Huntington and Alzheimer disorders, Ataxia, Tourtte, myesthenic syndromes, and psychiatric disorders, while tryptophan treatment was suggested for depression, posthypoxic intention myolonus and sleep disturbances. Tyrosine has been tested as an antidepressant (Conlay & Zeisel, 1982; Wurtman, Hefti, & Melamed, 1981; Zeisel, 1981), and a nutritional approach to treatment of pain (Seltzer, Marcus, & Stoch, 1981) and autistic children (Martinau, Barthelemy, Garreau, & Lelord, 1985) has been suggested. Furthermore, a GABA-containing diet induces a decrease in food intake (Tews, Repa, Nguyen, & Harper, 1985).

On the other hand, the mechanisms by which the precursors modify the functional role of the presumed-to-be damaged neurotransmitter system is not clear. In addition, Trulson (1985) has recently claimed that while dietary tryptophan caused an increase in brain-serotonin level, the activity of single serotonergic cells in an awake cat was unchanged by the diet. He concluded that dietary manipulations do not modify the functional activity of the neurons. However, the cats in this study were treated for only three days, and other behaviors (i.e., sleep) were not recorded. The relative failure of lecithin treatment in

Alzheimer's disorder, a disorder in which a decrease in brain acetylcholine level was recorded, is another issue. A possible explanation is that either lecithin does not penetrate into the human brain in large enough quantities, or that the decrease in acetylcholine leve is not the only factor in the dementia associated with Alzheimer's disorder.

A novel explanation of non-precursor dietary manipulation on cognitive functions and behavior emerged from a series of experiments. It is suggested that the dietary manipulation's mode of action is not only on the biochemistry of the neurotransmittal system, but also on the lipid-acids composition of the neuronal membrane. Support for the new hypothesis will be gathered from previously known studies and from a description of a salutary sample of the new line of experiments.

NEURONAL MEMBRANE LIPIDS

In addition to the precursor model for nutritional effects (e.g., via synaptic events) another approach to explain the effects of dietary manipulation is the possible action of nutrients on the lipid composition of the neuronal membrane and on membrane fluidity. Singer and Nicolson's fluid mossaic model of the biological membrane, in which both proteins and lipids are mobile within the membrane, enhances our understanding of the functional role of the membrane. The composition of lipids in the membrane is very important for the normal physiological role of the membrane (Houslay & Stanley, 1982), especially regarding the

function of the neuronal membranes in synaptic transmission and bioelectric responses (Podlubiuk & Kleinrok, 1976; Reiman, 1981; Vergrossen, 1975; Wheeler, Benolken, & Aderson, 1975). The functional role of various membrane receptors seems to be dependent on normal membrane lipid composition (Kirilovsky, Steiner-Mordoch, Selinger, & Schramm, 1985; Spector & Yorek, 1981). For example, phosphotidycholine which is produced in rat symaptosomes in very rich in polyunsaturated fatty acids (Tacconi & Wurtman, 1985).

Membrane lipid composition may change the index of "membrane fluidity." At the optimal index of membrane fluidity, the ionic exchange between the cell and the outside is at maximum efficiency. Treatment may modify the membrane lipid composition and its fluidity. An increase in cholesterol level, for example, causes a significant decrease in membrane fluidity (Houslay & Stanley, 1982). There are two methods to modify membrane fluidity via changes in lipid composition. One if through drug treatment. Drugs such as general and local anaesthetics, some steroids, barbituates, alcohol and cannabinoids, cause changes in membrane fluidity (Seeman, 1982; Zubenko & Cohen, 1985). Furthermore, psychotherapeutic (antipsychotic and antidepressant) drugs can also modify the membrane fluidity index (Seeman, 1977, 1982; Zubenko & Cohen, 1985).

The second method to induce changes in the lipid composition is via dietary manipulation (Clandinin, Field, Hargreaves, Morson, & Zsigmond, 1985; Wahle, 1983). Certain fatty acids (mainly

linolenic acid) in the diet can decrease the cholesterol (Balasubramaniam, Simon, Charg, & Hickie, 1985). Furthermore, changes in certain membrane-bound enzymes were found after lipid diet manipulation (Foot, Cruz, & Clandinin, 1983; Heger, 1979).

The role of membrane lipid composition seems to be age-dependent, and many studies show changes in lipid composition during aging, mainly as an increase in cholesterol level (i.e., Calderini, Boretti, Buttistella, Crews, & Taffano, 1983; Carllile & Lacko, 1985; Cohen & Zubenko, 1985; Eddy & Harman, 1975; Harman, Hendricks, Eddy, & Seibold, 1976; Suzuki et al., 1985, 1985; Tappel, Fletcher, & Deamer, 1973). These changes may be related to the cognitive and behavioral changes observed in aging. A soybean oil diet (10%) for one month prevents the increase of plasma cholesterol level in aging rats (Suzuki et al., 1985). Some of the studies on the effect of nutrients on lipid membrane are summarized in Table I.

Insert Table I about here

The following study is an example of the involvement of the neuronal membrane in learning.

LEARNING, CHOLESTEROL LEVEL AND MEMBRANE FLUIDITY

The level of cholesterol in a neuronal membrane is one of the major factors in determing the fluidity index (Houslay & Stanely, 1982). As cholesterol is unable to cross the brain capillaries into the brain (Dhopeshwarker, 1983), any change in cholesterol level in neuronal membrane reflects neuronal activity in the central nervous system. An increased level of cholesterol in neuronal membrane is correlated with a decrease in membrane fluidity index (see above).

The relationship between the level of cholesterol in the neuronal membrane and learning processes was examined recently. Instead of attempting to modify the level of cholesterol neuronal membrane level, the researchers asked the opposite question, e.g., would learning per se induce changes in the level of cholesterol in neuronal membranes which are located in different regions of the brain (Kessler & Yehuda, 1985).

The changes in the level of cholesterol in different brain areas (cortex, hippocampus, hypothalamus, and brainstem) were examined in rats trained in a Y-maze. A second group of rats was also trained in "reversed learning."

The results showed that one-stage learning is enough to modify the cholesterol level in preparations obtained from the hippocampus. The decrease in cholesterol level was associated with a decrease in microviscosity index (i.e., the membrane is more fluid) in the hippocampus and the cortex. Reversed learning induced even lower cholesterol level in the hippocampus and the

cortex as well as a parallel increase in membrane fluidity in both brain areas (Fig. 1). The results of these preliminary studies indicated that learning per se is able to induce significant changes in cholesterol level and in membrane fluidity--and therefore leads to a functional change in the neuronal membrane activity. An additional conclusion is that, most probably, the hippocampus is involved in mediating this type of learning. The hippocampus seems to be involved in long-term memory formations of several types of learning, e.g., spatial (maze) learning, classical conditioning, and in delay alternation tasks (Bloom, Luzerson, & Hofstadter, 1985; Knowlton, McGowan, & Olton, 1985; Olton, Becker, & Hardelman, 1979; Wincour, 1985).

Insert Figure 1 about here

NUTRITIONAL DEFICIENCY

Malnutrition is a very wide term which includes many subcategories. Malnutrition may be associated with a specific disorder, such as cystic fibrosis, pyloric stenosis or other gastrointestinal disorders. In such cases it is almost impossible to evaluate the effect of malnutrition per se. Here we are dealing with malnutrition which is a result of inadequate food intake. There are three levels of malnutrition: (a) Total reduction in all six categories of nutrition (proteins, carbohydrates, lipids, vitamins, and minerals) and therefore a

severe decrease in caloric intake; (b) Deficiency in one of the categories, with or without a decrease in caloric level (i.e., miasmus disorder is the result of a severe decrease in protein and caloric intake, which kwashiorkor disorder is protein deficiency); and (c) Specific deficiency in particular nutrients.

Many studies on general malnutrition have been summarized by Brozek (1978). Most of the studies clearly indicate a general decrease in behavior parameters (apathy, lack of motivation) and a decrease in cognitive functions. However, it is difficult to evaluate in these cases the contribution of a decrease in food intake, as these cases occurred in severe situations of war or natural disaster. Most of the studies also indicate that there is a correlation between the age of onset of malnutrition and the severity of the effects.

An interesting situation is the opposite situation--"overconsumption undernutrition." This paradoxical situation occurs among youngsters who consume large amounts of junk food, which actually consumes "empty calories" because this type of food lacks an adequate amount of nutrients and micronutrients. The symptoms include constipation, muscle pain, lethargy, bad dreams, and a decline in scholastic achievements. Proper nutritional treatment can help in these cases.

Another type of human malnutrition is a short-term malnutrition, induced experimentally. Brief fasting in cats decreased the rate of bar-pressing for brain self-stimulation (Angyan, 1984). Pollitt (Pollitt et al., 1983) found that

skipping breakfast had an adverse effect on late morning problem solving preference in children. While their short-term memory was better (most probably due to an increase in arousal level), their long-term memory was at a low level (Pollitt et al., 1981, 1983). Recently, we (Yehuda & Carasso, unpublished results) were able to repeat Pollitt's experiments with similar results. However, we found that skipping breakfast has a more profound effect on "morning type" children than on "evening type" children.

Another, almost untouched area is the cognitive changes among anorexia nervosa patients. Among non-schizophrenic anorectic patients, the academic level was significantly lower compared with the level before the onset of anoxeria nervosa. Preliminary studies show that the level of IQ score was lower during the anorexia nervosa period compared with the previous period. (This study was carried out on subjects whose previous IQ score was known.)

However, most studies have examined the effects of protein malnutrition (e.g., Dhopeshwarker, 1983; Morgane, Miller, Kemper, Stern, Forbes, Hali, Bronzino, Kissare, Mawrylewicz, & Resnick, 1978; Shoemaker & Wurtman, 1971) on brain growth and morphology (Morgane et al., 1978; Shoemaker & Bloom, 1977) and on brain biochemistry, e.g., the development of catecholamine (Shoemaker & Bloom, 1977; Wiggins, Fuller, & Enna, 1984). Prenatal protein deficiency also cased severe delay in developmental indices both in human and animal offspring. Lipid undernutrition can also modify brain growth and development of children and may even have

long-term effects on adult behavior and cognition (e.g., Dhopeshwarker, 1983; Gosso, Oliverio, Salvati, Serlupi-Crescenzi, Taglimonta, & Tomassi, 1982; Lampety & Walker, 1976, 1978). Dietary deficiencies in many compounds, such as niacin, folacin, thiamin, vitamin B6, magnesium, zinc, copper, etc., have been associated with poor learning and memory (Hamilton, Whitney, & Sizer, 1985). An example of a study on the effects of specific nutrient deficiency is the study on the biochemical and behavioral effects of iron deficiency.

BRAIN IRON DEFICIENCY, BEHAVIOR AND LEARNING

Iron-deficiency (ID) anemia is the most prevalent nutritional disorder in the world (Garby, 1973; Kessner & Kalk, 1973; Pollitt & Leibel, 1982). It causes behavioral abnormalities in children and adults (Jacob & Worwood, 1980; Oski, 1979; Pollitt & Leibel, 1982; Youdim, Green, Bloomfield, Mitchell, Hill, & Grahame-Smith, 1980) as well as in rats made nutritionally iron deficient (Ashkenazi, Ben-Shachar, & Youdim, 1982; Yehuda & Youdim, 1984; Youdim, Yehuda, & Ben-Uriah, 1981).

Youdim's group recently reported a complete reversal of the circadian rhythms of motor activity, thermoregulation (Youdim et al., 1981; Youdim & Yehuda, 1986) and the pain threshold response of rats rendered nutritionally iron deficient (Yehuda & Youdim, 1984). The pain threshold of ID rats, as tested on a hot plate, was elevated during the dark period. Peripheral administration of beta-endorphin and enkaphalines (which have no analgesic effects

in this route of administration in control rats) induced a significant increase in pain threshold. The analgesic effects on ID rats are naloxone-reversible (Yehuda & Youdim, 1986; and unpublished results). In addition, the ID rats were protected from d-amphetamine-induced hypothermia (Yehuda & Wurtman, 1975) when they are exposed to cold (4 degrees C) environment (Youdim et al., 1981).

The overall effect of the ID diet was a significant impairment of learning. The impairment was stronger the longer the rats were exposed to the iron-deficient diet (Table II). Impairment in learning parameters was evident already after 7 days on the diet. This impairment was detected even when the hemoglobin level was still the same (after 7 days) as in control rats.

Insert Table II about here

After the completion of the experiment, the ID rats were fed the control diet for three weeks and their hemoglobin level restored. All rats were tested again. While control rats performed very well in the maze, the ID rats required significantly more trials to reach the criterion (Yehuda, Youdim, & Mostofsky, 1986). In comparison to human studies, impairment of cognitive function was found not only in severely anemic children, but also in children who suffer only from mild anemia (Oski, Honig, Helu, & Howanitz, 1980).

Iron seems to play an important role in regulating the functional activity of dopamine D_2 receptors. Furthermore, the state of the neuronal membrane may also influence the functional level of dopmaine D_2 receptors. It has been suggested that pharmacological manipulation of beta-adrenergic receptors may stimulate the cell plasma membrane to synthesize phosphatidyl choline from phosphatidyl ethanolamine. The importance of this reaction is that it modifies the level of the neuronal membrane fluidity (Houslay & Stanley, 1982). A similar effect may occur also in the dopamine receptors. Another indirect evidence of the role of iron in mediating normal physiological membrane functions is the ability of iron deposits, from electrodes in the brain, to induce epileptic fits. Moreover, injection of $FeCl_3$ into the brain also resulted in epileptic behavior.

On the basis of several studies, it is clear that the physiological and behavioral effects of iron deficiency cannot be attributed to a decreased utilization of oxygen (Ashkenazi et al., 1982; Youdim et al., 1980). The decrease in brain iron level in ID rats (Youdim et al., 1981) was correlated with a diminution of dopamine-dependent behavior and dopamine D_2 receptor number in the striatum (Ashkenazi et al., 1982; Ben-Shachar et al., 1985). Furthermore, it has been shown that like neuroleptic-treated animals, ID rats have a significant increase in serum prolactin level and liver prolactin receptor number (Burkey et al., 1985). The highly localized concentration of iron within dopamine-rich brain areas (Hill & Switzer, 1984) and the observation that

iron-chelators inhibit the binding of H3-spiperon (Ben-Shachar et al., 1985) to dopamine D_2 receptor, led to the conclusion that iron has a role in dopamine receptor functions (Youdim & Yehuda, 1986). Some of the behavioral and biochemical changes induced in rats by iron deficiency can be restored to normal if the animals are fed an iron-supplemented diet leading to an increase in brain iron concentration and dopamine D_2 receptor number (Ashkenazi et al., 1982). However, the deficits in learning and memory capacities remained for a very long time, even after an iron-supplement treatment (Yehuda et al., 1986).

Several studies have examined the effects of iron deficiency on learning capacity (Anonymous, 1983; Findlay et al., 1981; Weinberg et al., 1979). The researchers fed pregnant rat mothers with an iron-deficient diet or started the treatment on very young rats. Recently the effects on learning and memory capacities of adults rats exposed for a short term (4 weeks) to an iron-deficient diet was studied (Yehuda et al., 1986).

The discussion regarding the role of catecholamines in learning and memory processes in general (Zornetzer, 1985) and of dopamine in particular (Sahakian, Sarna, Kantamanci, Jackson, Huston, & Curzon, 1985; Simon, Scatton, & Le Moal, 1980) is beyond the scope of this review. But early reports indicated that dietary restriction of iron may cause many changes in the lipid metabolism in animals (e.g., Rao, Crane, & Larkin, 1985). Furthermore, the ID rats in this study showed deficits both in the acquisition phase of the learning and in the retrieval phase. It is tempting

to speculate that perhaps these results are compatible with a recent learning theory, postulating the adaptive integration of complex physiological and behavioral patterns. Rather than view learning as an isolated demonstration of some artificially associated stimulus-response mechanism, learning and performance are seen as finely tuned adaptive processes. In that case, the persisting changes serve as markers attributable to the biochemistry of iron deficiency. The performance continues even when the primary chemical balance is restored, so that the adaptive and integrative charges persevere for at least three weeks.

VITAMIN DEFICIENCY

"Vitamin deficiency" and vitamin supplement is one of the most popular topics among people who look for "health foods." It should be remembered that vitamin deficiency may occur not because of a low supply of vitamins in the diet, but rather by poor absorption. However, a low level of several vitamins seems to lead to behavioral and cognitive deficit. For example, vitamin B_1 deficiency during the early stages of life induced ataxia and a decrease in body weight. In adults, delirium and loss of long-term memory were found among B_1 deficient patients. A supplement of vitamin B_1 is usually beneficial in these cases. Learning problems and failure to grow seem to be the results of folic acid deficiency. When pantothenic acid was inhibited in humans, apathy and depression were observed (Hamilton et al.,

1986). However, some studies indicated that many people in the USA take much greater vitamin doses than they need. The effects of vitamin overdose is not in the scope of this chapter.

IMPROVEMENTS IN COGNITIVE FUNCTIONS WITH NUTRIENTS

The presence of some nutrient may change behavior. Grain glutens have been considered as major agents evoking schizophrenia in certain genotypes (Dohan, Harper, Clark, Rodrique, & Zigas, 1984). Caffeine may improve attentional deficit disorders (Dolby, 1985) and monosodium glutamate may induce Chinese restaurant syndrome (Hamilton et al., 1985).

In addition, a diet may also influence mood (Leatherwood & Pollitt, 1983). An interesting relationship between nutrition and cognitive function had been suggested by Abalan (1984, 1985) who proposed that malnutrition is one of the etiological factors in Alzheimer's disorder.

FATTY ACID DIET, LEARNING AND BEHAVIOR

Previous research has shown that modifications of the nutrient composition of diets can produce a variety of biochemical and/or behavioral changes in experimental animals. Most of the studies investigated the role of neurotransmitter precursors (see above). In contrast, little is known about the potential importance of dietary lipids to the brain biochemistry and to behavior. Although dietary lipids seem to be non-precursor dietary nutrients, lipids are important and critical constituents of the

neuronal membrane. Modification in lipid composition of the membrane may lead to subsequent changes in neuronal functioning (see above).

Essential fatty acids easily cross from the blood into the brain (Dhopeshwarker, 1983). Feeding pregnant female rats with a diet which does not contain the essential fatty acids caused severe growth problems. Such a treatment induced learning impairment in several types of learning, such as Y-maze and Lashley maze learning (Gosso, Oliverio, Salvati, Serlupi-Crescenzi, Taglimonta, & Tomassi, 1982; Lampety & Walker, 1976, 1978; Morgan, Oppenheimer, & Winick, 1981; Walker, Lampety, & Samulski, 1982). In another study, Ruthrich, Hoffmann, Matthies, and Foerster (1984) showed that depriving pregnant rats of essential fatty acids brought about no change in rate of learning of brightness discrimination (in Y-maze) of their pups; however, it impaired retention. Such a dietary treatment, given to adult rats for four months, also caused impaired retention. On the other hand, pups which were fed with enriched fatty acid diets improved their learning capacity (Borgman, Bursey, & Caffrey, 1975). In addition, some fatty acids are capable of modifying the activity of serotonin N-acetyltransferase (Wainwright, 1985).

The effects of lipid diets on learning and behavior were recently examined in rats. Four experimental diets were used. Two of the diets contained a high level of polyunsaturated fatty acids (sunflower oil source and soybean oil source), and the third was high on saturated fatty acid (lard source). The total lipid

percentage in all three diets was 20%. The fourth diet was standard laboratory chow. Learning capacity was measured in a modified Moon's Place Navigation Task (Sutherland & Dyck, 1984). In addition, several behavioral parameters were tested.

The results (Coscina, Yehuda, Dixon, Kish, & Leprohon-Greenwood, 1986) showed that the dietary treatment did not modify the level of motor activity. On the other hand, it is interesting to note that changes in the diet, i.e., raising the ratio between carbohydrates and proteins, does influence the level of motor activity. As the ratio between carbohydrates and protein was increased rats became more active (Chiel & Wurtman, 1981). Other nutritional factors (i.e., body weight, etc.) were the same in all three experimental groups. Learning was much faster in the soybean source diet group and they showed a higher degree of resistance to extinction than the other groups (Coscina et al., 1986; Yehuda & Carasso, 1986). The effect of soybean-oil diet on learning cannot be attributed to changes in non-specific variables, e.g., as body weight, weight gain, etc. (Fig. 2).

Insert Figure 2 about here

No difference in the activity of choline acetyltransferase was found in the hippocampus, hypothalamus, parietal cortex or in the striatum between the experimental groups (Coscina et al., 1986). It was assumed that such spatial learning would be mediated by the

cholinergic system. In a similar type of spatial learning, i.e., 8-arms maze, lesions in Nucleus Basalis, which caused a decrease in the cholinergic activity level in the cortex (Dubois et al., 1985), an impairment of spatial learning was found, but not a complete blockade. Some aspects of spatial learning seem to not be mediated by the cholinergic system (Sutherland et al., 1982; Whishaw, 1985), and Farelli, Rosenberg, and Gallagher (1985) suggested a role for norepinephrine in spatial learning. The finding that the level of the cholinergic-associated enzyme activity was not changed may indicate that the enzyme is not sensitive to dietary manipulation.

The behavioral effects of fatty-acid diets were tested in two strains of rats, albino rats (Sprague-Dawley) and hooded rats (Long-Evans). After three weeks of experimental diets, the level of motor activity (horizontal and vertical movements) was the same for all experimental and control groups. While d-amphetamine induced hypothermia (Yehuda & Wurtman, 1975) in control and lard-source treated rats, when exposed to an ambient temperature of 4 degrees C, the soybean-source fed rats, of both strains, were protected from the hypothermic effect of the drug. The two strains were found to be different in their pain threshold. While soybean-source fed albino rats exhibited a significant elevation of pain threshold (hot plate), the pain threshold of hooded rats, fed the same diet, was equal to that of the control rats (Yehuda et al., 1986). Although the main difference between soybean-source lipid and lard-source lipid is the high level of

polyunsaturated fatty acids in the soybean oil, it seems that the level of polyunsaturated fatty acids is not the only factor. A preliminary study shows that sunflower oil diet (which contains much more polyunsaturated fatty acids than soybean oil) has no such effect.

On the neurochemical level, preliminary studies of the fatty acid diet failed to detect changes in the functional level of the dopaminergic neurons in the striatum or in the level of brainstem serotonin (unpublished results), or in the level of activity of cholinergic enzymes in different brain regions (Coscina et al., 1986). The inability to detect biochemical changes may reflect a failure to locate the appropriate neurotransmitter in the appropriate brain region or system. But, on the other hand, it is difficult to assume, at this stage of our knowledge, that one particular neurotransmitter is involved in improving learning, increasing the pain threshold, modifying thermoregulation and thermal responses to drug treatment, all this without any effect on the motor activity level.

Another possible explanation is that the dietary manipulation induced changes in the lipid composition of the neuronal membrane. As a result of these changes, the functional roles of the membrane change. At least two groups of membrane-associated molecules are known to be susceptible to dietary fatty acids. The first group is the prostoglandins group (Hiller & Karim, 1979). Prostoglandins are known to be involved in various behaviors including pain and thermoregulation (Carasso, Peled, & Yehuda,

1985; Karim, 1979). The other group is the gangliosides group, mainly ganglioside GD3 (Ando & Yu, 1985; Seyfried & Yu, 1985). The fatty acids dietary manipulation may cause small changes in the lipid composition of the neuronal membrane which cannot be easily measured directly, but these changes may be amplified by triggering very complex changes in the rate of synthesis and function of many membrane-associated enzymes and compounds.

Recently, it was found that the effects of a fatty acid diet are correlated with the length of period of feeding the diet (Yehuda et al., 1987).

CONCLUSIONS

The results of many studies now show that the amount of food intake—in terms of adequate level of proteins, carbohydrates, lipids, vitamins, minerals, and water—is important for maintenance of normal behavioral and cognitive functions. However, it seems that the type of food (which fatty acid or protein) is also very important. The importance of a balanced diet is even more important in critical periods. Nutrients not only may change behavioral or cognitive functions, but also may be used in certain mental disorders or deficits.

It is clear now that environmental factors may have both direct and indirect effects on brain biochemistry and on behavior. Studies over the past decade have demonstrated that the rate of synthesis in the brain of several neurotransmitters (serotonin, acetylcholine and catecholamines) is normally dependent on the

biological availability of their respective precursors (i.e., tryptophan, choline, lecithin, and tyrosine). However, an erroneous conclusion may be that only nutrients which can serve as neurotransmitter precursors and are able to penetrate into the brain can modify brain biochemistry and behavior.

The studies on the effects of learning on brain cholesterol level, on the effects of iron deficiency on brain dopaminergic D receptor function and on learning, memory and behavior and on the effects of fatty acid diet on learning and behavior, all seem to indicate that in addition to the effects of nutrients on the rate of synthesis of brain neurotransmitters, changes in the lipid composition of the neuronal membrane may mediate both brain biochemical and behavioral changes. The interrelationships between the three groups of studies are presented in Figure 3.

Insert Figure 3 about here

The role of the neuronal membrane in mediating biochemical and behavioral changes is still unclear. The role of some membrane-associated molecules is still not known. Furthermore, it is still too early to evaluate the behavioral importance of newly discovered compounds such as choline-kinase (Reinhardt & Wecker, 1983). A possible role for phosphoprotein (proteinkinase C and protein F1) in memory had been suggested by Routtenberg (1985). Moreover, the discovery of the coexistence of neurotransmitters

and peptides in the same nerve-terminal, and the possibility of selective release of each one of these molecules (Wincour, 1985) may change our understanding of the basic principles of brain biochemistry and activity.

Nevertheless, apparent non-precursor diets induce changes in complex functions such as learning and memory, and in regulatory functions such as thermoregulation. Circadian cycle-dependent behavior and the pain threshold were affected by the dietary treatment. These results, together with the findings that learning per se induced modification in brain cholesterol level, strongly indicate a possible role of neuronal membrane in mediating those effects.

Whatever is the mode of action of nutrients in the brain, they are able, under certain conditions, to modify behavioral and cognitive functions. Much more scientific research is needed in order to understand the full range of nutritional effects on human behavior and cognition.

REFERENCES

Abalan, F. (1984). Alzheimer's disease and malnutrition: A new etiological hypothesis. Medical Hypotheses 15, 385-393.

Abalan, F., Achiminov, A., & Pirsolie, M. (1980). Malnutrition and Alzheimer's dementia. British Journal of Psychiatry 147, 320.

Anderson, G. H. (1980). Diet, neurotransmitter and brain function. British Medical Bulletin 37, 95-100.

Ando, S., & Yu, R. K. (1985). Fatty acid and long-chain base composition of gangliosides isolated from adult human brain. Journal of Neuroscience Research 12, 205-211.

Angyan, L. (1984). The effects of feeding and fasting on self-stimulation. Acta Physiologica Hungarica 63, 185-195.

Anonymous. (1983). Iron deficiency and mental development. Nutrition Reviews 41, 235-237.

Ashkenazi, R., Ben-Shachar, D., & Youdim, M. B. H. (1982). Nutrition, iron and dopamine binding sites in rat brain. Pharmacology, Biochemistry and Behavior 17, (Sup 1), 43-48.

Ashley, D. V. M., Liardon, R., & Leatherwood, P. D. (1985). Breakfast meal composition influences plasma tryptophan to large neutral amino acid ratio of healthy young men. Journal of Neuronal Transmission 63, 271-283.

Balasubramaniam, S., Simon, L. S., Charg, S., & Hickie, J. B. (1985). Reduction in plasma and increase in billiary cholesterol by diet rich in n-3 fatty acids in the rats. Journal of Lipid Research 26, 684-689.

Bartfai, T. (1985). Presynaptic aspects of coexistence of classical neurotransmitters and peptides. Trends in Pharmacological Sciences 6, 331-334.

Benedict, C. B., Anderson, G. H., & Sole, M. J. (1983). The influence of oral tyrosine and tryptophan feeding on plasma catecholamines in man. American Journal of Clinical Nutrition 38, 429-435.

Ben-Shachar, D., Finberg, J. P. M., & Youdim, M. B. H. (1985). The effect of chelating agents and dopamine D_2 receptor. Journal of Neurochemistry 45, 999-1005.

Bloom, F. E., Luzerson, A., & Hofstadter, L. (1985). Brain, Mind and Behavior. New York: W. H. Freeman.

Borgman, R. F., Bursey, R. G., & Caffrey, B. C. (1975). Influence of maternal dietary fat upon rat pups. American Journal of Vetrinary Research 36, 799-809.

Brozek, J. (1978). Malnutrition and behavior. Journal of the American Dietetic Association 72, 17-23.

Burkey, R. J., Ben-Shachar, D., Amit, T., & Youdim, M. B. H. (1985). Increase hepatic and reduced prostatic binding in iron deficiency and neuroleptic treatment: Correlation with changes in serum prolactin and testosterone. European Journal of Pharmacology 104, 193-200.

Calderini, G., Boretti, A. C., Buttistella, A., Crews, F. T., & Taffano, G. (1983). Biochemical changes of rats brain membranes with aging. Neurochemical Research 8, 483-492.

Carasso, R. L., Peled, O., & Yehuda, S. (1985). Flufenamic acid in prostaglandin migraine. International Journal of Neuroscience 27, 67-71.

Carlile, S. I., & Lacko, A. G. (1985). Age-related changes in plasma lipid level and tissue lipoprotein lipase activities of Fischer-344 rats. Archives of Gerontology and Geriatrics 4, 133-140.

Chiel, H. J., & Wurtman, R. J. (1981). Short-term variations in diet composition change in the pattern of spontaneous motor activity in rats. Science 213, 676-678.

Clandinin, M. T., Field, C. J., Hargreaves, K., Morson, L., & Zsigmond, E. (1985). Role of diet fat in subcellular structure and function. Canadian Journal of Physiology and Pharmacology 63, 546-556.

Cohen, B. M., & Zubenko, C. S. (1985). Aging and the biophysical properties of cell membranes. Life Sciences 37, 1403-1409.

Conlay, L. A., & Zeisel, S. H. (1982). Neurotransmitter precursors and brain function. Neurosurgery 10, 524-529.

Coscina, D. V., Yehuda, S., Dixon, L. M., Kish, S. J., & Leprohon-Greenwood, C. E. (1986). Learning is improved by a soybean oil diet in rats. Life Sciences 38, 1789-1794.

Crine, A. F. (1984). Vasopressin effects on food-rewarded learning tasks might be due to its action on carbohydrate/lipid metabolism, not memory. Appetite 5, 233-238.

Dalby, T. J. (1985). Will population decrease in caffeine consumption unveil attention deficit disorders in adults? Medical Hypothesis 18, 163-167.

Dohan, F. C., Harper, E. H., Clark, M. H., Rodrique, R. G., & Zigas, V. (1984). Is schizophrenia rare if gain is rare? Biological Psychiatry 19, 385-399.

Dhopeshwarker, G. A. (1983). Nutrition and Brain Development. New York: Plenum Press.

Dubois, B., Mayo, W., Agid, Y., Le Moal, M., & Simon, H. (1985). Profound disturbances of spontaneous and learned behaviors following lesions of the Nucleus Bsalis Magnocellularis in the rat. Brain Research 338, 249-258.

Eddy, D. E., & Harman, D. (1975). Rat brain fatty acid composition: Effects of dietary fat and age. Journal of Gerontology 30, 647-654.

Farelli, R. J., Rosenberg, R. A., & Gallagher, M. (1985). Role of noradrenergic function in the opiate antagonist facilitation of spatial memory. Behavioral Neuroscience 99, 751-755.

Fernstrom, J. D. (1981). Effects of the diet on brain function. Acta Astronautica 8, 1035-1042.

Fernstrom, J. D., & Wurtman, R. J. (1971). Brain serotonin content: Increase following ingestion of carbohydrate diet. Science 174, 1023-1025.

Fernstrom, J. D., & Wurtman, R. J. (1972). Brain serotonin content: Physiological regulation by plasma neutral amino acid. Science 178, 414-416.

Findlay, E., Ng, K. T., Reid, R. L., & Armstrong, S. M. (1981). The effects of iron deficiency during development on passive avoidance learning in the adult rat. Physiology and Behavior 27, 1089-1096.

Foot, M., Cruz, T. F., & Clandinin, M. T. (1983). Effects of dietary lipid on synaptosomal acetylcholinestrase activity. Biochemistry Journal 211, 507-509.

Garby, L. (1973). Iron deficiency: Definition and prevalence. In S. T. Callender (Ed.), Clinical in Haemotology (Vol. 2, p. 245). London: W. B. Saunders.

Gossi, S., Oliverio, A., Salvati, S., Serlupi-Crescenzi, G., Taglimonta, G., & Tomassi, G. (1982). Effects of dietary phospholipids and odd-chain fatty acids on the behavioral maturation of mice. Food Chemistry and Toxicology 20, 153-157.

Hamilton, E. M. N., Whitney, E. N., & Sizer, F. S. (Eds.) (1985). Nutrition: Concepts and Controversies (3rd ed.). St. Paul, MN: West Publishing.

Harman, D., Hendricks, S., Eddy, D. E., & Seibold, J. (1976). Free radical theory of aging: Effect of dietary fat on central nervous system function. Journal of the American Geriatrics Society 24, 301-307.

Heger, H. W. (1979). Effects of dietary phospholipids on acetylcholinestrase activity in the rat brain and on phospholipid composition in liver and brain. General Pharmacology 10, 427-432.

Hill, J. M., & Switzer, R. C. (1984). The regional distribution and cellular localization of iron in the rat brain. Neuroscience 11, 595-603.

Hiller, K., & Karim, S. M. M. (1979). General introduction and practical implications of some pharmacological actions of

prostoglandins, thromboxines and their synthesis inhibitors. In S. M. M. Karim (Ed.), Practical Applications of Prostoglandins and Their Synthesis Inhibitor (pp. 1-24). Lancaster: MPT Press.

Houslay, M. D., & Stanley, K. K. (1982). Dynamics of Biological Membranes. New York: Wiley.

Jacob, S., & Worwood, M. (Eds.) (1980). Iron in Biochemistry and Medicine. London: Academic Press.

Karim, S. M. M. (Ed.) (1979). Practical Applications of Prostaglandins and Their Synthesis Inhibitor. Lancaster: MPT Press.

Kessler, R. A., & Yehuda, S. (1985). Learning-induced changes in brain membrane cholesterol and fluidity: Implication for brain aging. International Journal of Neuroscience 28, 73-82.

Kessner, J., & Kalk, L. (1973). Strategy for Evaluation Health Service. Washington, DC: Institute of Medicine, National Academy of Science.

Kirilovsky, J., Steiner-Mordoch, S., Selinger, Z., & Schramm, M. (1985). Lipid requirements for reconstitution of the delipidated beta-adrenergic receptor and the regulatory protein. FEBS Letters 183, 75-80.

Knowlton, B., McGowan, M., & Olton, D. S. (1985). Hippocampal stimulation disrupts spatial working memory even 8 h. after acquisition. Behavioral and Neural Biology 44, 325-337.

Lampety, M. S., & Walker, B. L. (1976). A possible essential role for dietary linolenic acid in the development of the young rat. Journal of Nutrition 106, 86-93.

Lampety, M. S., & Walker, B. (1978). Learning behavior and brain lipid composition in rats subjected to essential fatty acid deficiency during gestation, lactation and growth. Journal of Nutrition 108, 358-367.

Leatherwood, P. D., & Pollitt, P. (1983). Diet-induced mood changes in normal populations. Journal of Psychiatric Research 17, 147-152.

Martinau, J. C., Barthelemy, B., Garreau, B., & Lelord, G. (1985). Vitamins B6, Magnesium and combined B6-Mg: Therapeutic effects in children autism. Biological Psychiatry 20, 467-478.

Morgan, B. L. G., Oppenheimer, J., & Winick, M. (1981). Effects of essential fatty acid deficiency during late gestation on brain N-acetyl neuraminic-acid metabolism and behavior in the progeny. British Journal of Nutrition 46, 223-230.

Morgane, P. G., Miller, M., Kemper, T., Stern, W., Forbes, W., Hali, R., Bronzino, J., Kissare, J., Mawrylewicz, E., & Resnick, O. (1978). The effects of protein malnutrition on the developing central nervous system in the rat. Neuroscience and Biobehavioral Review 2, 137-230.

Olton, D. F., Becker, J. T., & Hardelman, G. E. (1979). Hippocampus, space and memory. Behavior and Brain Science 2, 313-365.

Oski, F. A. (1979). The nonheamatologic manifestation of iron deficiency. American Journal of Disorders in Children 133, 315-321.

Oski, F. A., Honig, A. S., Helu, B., & Howanitz, P. (1980). Effects of iron therapy on behavior performance in non-anemic, iron deficient rats. Pediatrics 71, 877-880.

Panakhova, E., Buresova, O., & Bures, J. (1984). Resistance of spatial memory in the Morris water tank task. International Journal of Psychophysiology 2, 5-10.

Podlubiuk, Z. M., & Kleinrok, Z. (1976). Comparison of central action of prostoglandins A, E, E2, E alpha, and F2 alpha in the rat. Psychopharmacology 50, 95-102.

Pollitt, E., & Leibel, R. L. (Eds.) (1982). Iron deficiency. Brain Biochemistry and Behavior. New York: Raven Press.

Pollitt, E., Leibel, R. L., & Greenfield, D. (1981). Brief fasting, stress and cognition in children. American Journal of Clinical Nutrition 34, 1526-1533.

Pollitt, E., Lewis, M. L., Garza, C., & Shulman, R. J. (1983). Fasting and cognitive function. Journal of Psychiatric Research 17, 169-174.

Pollitt, E., Soemantri, A. G., Yunis, F., & Scrimshaw, H. S. (1985). Cognitive effects of iron deficiency anaemia. Lancet 1, 158.

Price, H. C., Byrd, C., Sims, W., & Wilson, R. (1979). Gangliosides and other lipid micelles. A study of amine binding by a dialysis/fluorenscence method. Neurochemistry Research 4, 63-72.

Rao, G. A., Crane, R. T., & Larkin, E. C. (1983). Reduced plasma cholesterol acyl transferase activity in rats fed iron-deficient diet. Lipids 18, 673-676.

Reimann, W., Steinhaur, H. B., Hedler, L., Starke, K., & Hertting, G. (1981). Effects of prostoglandins D_2, E2 and E2 alpha on catecholamine release from slices of rat and rabbit brain. European Journal of Pharmacology 69, 421-427.

Reinhardt, R. R., & Wecker, L. (1983). Evidence for membrane-associated choline kinase activity in rat striatum. Journal of Neurochemistry 41, 623-629.

Routtenberg, A. (1985). Phospoprotein regulation of memory formation: Enhancement and control of synaptic plasticity by protein kinase C and protein F1. In D. S. Olton, E. Gamzu & S. Corkin (Eds.), Memory Dysfunction: An Integration of Animal and Human Research from Preclinical and Clinical Perspectives (Vol. 444, pp. 203-211). New York: Annals, New York Academy of Sciences.

Ruthrich, H. L., Hoffman, P., Matthies, H., & Forster, W. (1984). Perinatal Linoleate deprivation impairs learning and memory in adult rats. Behavioral and Neural Biology 40, 205-212.

Sahakian, B., Sarna, G. S., Kantamanei, B. D., Jackson, A., Huston, P. H., & Curzon, G. (1986, in press). Association between learning and cortical catecholamines in non-drug-treated rats. Psychopharmacology.

Seeman, P. (1977). Antischizophrenic drugs—Membrane receptor site of action. Biochemical Pharmacology 26, 1741-1748.

Seeman, P. (1982). The membrane actions of anaesthetics and tranquilizers. Pharmacological Reviews 24, 583-655.

Seltzer, S., Marcus, R., & Stoch, R. (1981). Perspectives in the control of chronic pain by nutritional manipulation. Pain 11, 141-148.

Seyfried, T. N., & Yu, R. K. (1985). Ganglioside GD3: Structure, cellular distribution and possible function. Molecular and Cellular Biochemistry 68, 3-10.

Sherma, D. C., & Simlot, M. M. (1984). Utilization of dietary tryptophan in iron-deficient rats. Journal of Nutrition 114, 1518-1520.

Shoemaker, W. J., & Bloom, F. E. (1977). Effects of undernutrition on brain morphology. In R. J. Wurtman & J. J. Wurtman (Eds.), Nutrition and the Brain (Vol. 2, pp. 147-192). New York: Raven Press.

Shoemaker, W. J., & Wurtman, R. J. (1971). Perinatal undernutrition: Accumulation of catecholamine in rat brain. Science 171, 1017-1019.

Simon, H., Scatton, B., & Lemoal, M. (1980). Dopaminergic A10 neurons are involved in cognitive function. Nature 286, 150-151.

Spector, A. A., & Yorek, M. A. (1985). Membrane lipid composition and cellular function. Journal of Lipid Research 26, 1015-1035.

Sutherland, R. J., & Dyck, R. H. (1984). Place navigation by rats in a swimming pool. Canadian Journal of Psychology 38, 322-347.

Sutherland, R. J., Wishaw, I. Q., & Regher, J. C. (1982). Cholinergic receptor blockage impairs spatial localization by use of distal cues in the rat. Journal of Comparative and Physiological Psychology 96, 563-573.

Suzuki, H., Hayakawa, S., Tamura, S., Wada, S., & Wada, O. (1985). Effects on the modification of plasma lipids by fish and soybean oil diets. Biochemica et Biophysica Acta 836, 390-393.

Suzuki, H., Kobayashi, T., Hayakaw, S., & Wada, O. (1985). Age-associated changes in rat plasma lipids, platelet fatty acids and prostacyclin release. Biochemica et Biophysica Acta 836, 394-396.

Sved, A. F. (1983). Precursor control of the function of monoaminergic neurons. In R. J. Wurtman & J. J. Wurtman (Eds.), Nutrition and Behavior (Vol. 5, pp. 223-275). New York: Raven Press.

Tacconi, M., & Wurtman, R. J. (1985). Phosphatidylcholine product in rat synaptosomes by N-methylation is enriched in polyunsaturated fatty acids. Proceedings of the National Academy of Science, USA 82, 4828-4831.

Tamir, H. Brunner, W., Casper, D., & Rapport, M. M. (1980). Enhancement by gangliosides of the binding of serotonin to serotonin-binding protein. Journal of Neurochemistry 34, 1719-1724.

Tappel, A., Fletcher, B., & Deamer, D. (1973). Effects of antioxidants and nutrients on lipid peroxidation flurescent

products and aging parameter in the mouse. Journal of Gerontology 28, 415-424.

Tews, J. K., Repa, J. J., Nguyen, H., & Harper A. E. (1985). Avoidance of GABA-containing diets by olfactory Bulbectomized rats. Physiology and Behavior 34, 983-986.

Trulson, M. E. (1985). Dietary affect function of brain serotonin neurons. Life Sciences 37, 1067-1072.

Vergrossen, A. J. (1975). Hypothesis for interaction between acetylcholine and prostoglandin biosynthesis: An introduction. In A. Barbeau, J. H. Growden & R. J. Wurtman (Eds.), Nutrition and the Brain (Vol. 5, pp. 109-112). New York: Raven Press.

Wahle, K. W. J. (1983). Fatty acid modification and membrane lipids. Proceedings of the Nutrition Society 42, 273-287.

Wainwright, G. E., & Wainwright, L. K. (1985). Effects of some fatty acids on serotonin N-acetyltransferase activity in cultured chick pineal gland. Journal of Pineal Research 2, 287-299.

Walker, B. L., Lampety, M. S., & Samulski, M. A. (1982). Polyunsaturated fatty acids and the developing brain. Journal of the American Oil Chemistry Society 59, 290a.

Weinberg, J., Levin, S., & Dallman, P. R. (1979). Long-term consequences of early iron deficiency in the rat. Pharmacology, Biochemistry and Behavior 11, 631-638.

Wheeler, T. G., Benolken, R. H., & Aderson, R. E. (1975). Visual membranes. Specificity of fatty acid precursors for electric response to illumination. Science 188, 1312-1314.

Whishaw, I. Q. (1985). Cholinergic receptor blockade in rats impairs locale but not taxon strategies for place navigation in swimming pool. Behavioral Neuroscience 99, 979-1005.

Wiggins, R. C., Fuller, G., & Enna, S. J. (1984). Undernutrition and the development of brain neurotransmitter system. Life Sciences 35, 2085-2094.

Wincour, G. (1985). The hippocampus and thalamus: Their roles in short- and long-term memory and their effects of interference. Behavioral Brain Research 16, 135-152.

Wurtman, R. J. (1975). The effects of light on human body. Scientific American 233, 68-77.

Wurtman, R. J. (1982). Nutrients that modify brain function. Scientific American 246, 50-59.

Wurtman, R. J., Baum, M. J., & Potts, J. T. (Eds.) (1985). The Medical and Biological Effects of Light (Vol. 453). New York: The New York Academy of Sciences.

Wurtman, R. J., Hefti, F., & Melamed, E. (1981). Precursor control of neurotransmitter synthesis. Pharmacological Reviews 32, 315-335.

Wurtman, R. J., & Lieberman, H. R. (1985). Melatonin secretion as a mediator of circadian variations in sleep and sleepiness. Journal of Pineal Research 2, 301-303.

Wurtman, R. J., & Wurtman, J. J. (1984). Nutritional control of central neurotransmitters. In K. M. Pirke & D. Ploog (Eds.), Psychobiology of Anorexia Nervosa (pp. 4-12). Berlin: Springer.

Yehuda, S. (1987). Effects of alpha-MSH, TRH and AVP on learning and memory, pain threshold and motor activity: Preliminary results. International Journal of Neuroscience 32, 703-709.

Yehuda, S., & Carasso, R. L. (1987). Effects of dietary fats on learning, pain threshold, thermoregulation and motor activity in rats: Interaction with the length of feeding periods. International Journal of Neuroscience 32, 919-925.

Yehuda, S., Leprohon-Greenwood, C. E., Dixon, L. M., & Coscina, D. V. (1986). Effects of dietary fat on pain threshold, thermoregulation and motor activity in rats. Pharmacology, Biochemistry and Behavior 24, 1775-1778.

Yehuda, S., & Wurtman, R. J. (1975). Dopaminergic neurons in the nigrostriatal and mesolimbic pathways: Mediation of specific effects of d-amphetamine. European Journal of Pharmacology 30, 154-158.

Yehuda, S., & Youdim, M. B. H. (1984). The increased opiate action of beta-endorphin in iron-deficient rats: The possible involvement of dopamine. European Journal of Pharmacology 104, 245-251.

Yehuda, S., Youdim, M. B. H., & Mostofsky, D. I. (1986). Brain iron deficiency causes reduced learning capacity in rats. Pharmacology, Biochemistry and Behavior 25, 141-144.

Youdim, M. B. H. (1985). Biochemical and behavioral aspects in relation to dopamine neurotransmission. In A. Lajth (Ed.), Handbook of Biochemistry (Vol. 10, pp. 731-755). New York: Plenum Press.

Youdim, M. B. H., & Green, A. R. (1977). Biogenic monoamine metabolism and function activity in iron-deficient rat. In Iron Metabolism (pp. 201-225). CIBA Foundation Symposium 51 (new Ser.). Amsterdam Elsevier, North Holland.

Youdim, M. B. H., Green, A. R., Bloomfield, R., Mitchell, D., Hill, J., & Grahame-Smith, D. G. (1980). The effect of iron deficiency on brain monoamine biochemistry and function. Neuropharmacology 19, 259-267.

Youdim, M. B. H., Yehuda, S., & Ben-Uriah, Y. (1981). Iron-deficiency-induced circadian rhythm reversal of dopaminergic-mediated behaviors and thermoregulation. European Journal of Pharmacology 74, 295-301.

Youdim, M. B. H., & Yehuda, S. (1986, in press). Iron deficiency induced reversal of dopamine dependent circadian cycles: Differential responses to delta-amphetamine and TRH. Pharmacology, Biochemistry and Behavior.

Zeisel, S. H. (1981). Dietary choline: Biochemistry, physiology and pharmacology. Annual Review of Nutrition 1, 95-121.

Zornetzer, S. F. (1985). Catecholamine system involvement in age-related memory dysfunction. In D. S. Olton, E. Gamzu & S. Corkin (Eds.), Memory Dysfunctions: An Integration of Animal and Human Research from Preclinical and Clinical Perspectives (Vol. 444, pp. 242-254). New York: Annals of the New York Academy of Sciences.

Zubenko, G. S., & Cohen, B. M. (1985). Biophysical alterations in cell membranes associated with psychotherapeutic drug exposure,

psychopathology and aging. Psychopharmacology Bulletin 21, 631-640.

TABLE I

Examples of effects of dietary manipulations

Treatment	Subject	Duration of treatment	Results	Reference
Oral tryptophan, tyrosine, caffeine	Human adults	One morning	Changes in mood	Leatherwood & Pollitt, 1983
Brief fasting	Children	One morning	Adverse effects on problem-solving behavior and beneficial effect on short-term memory	Pollitt et al., 1983, 1985
Oral tyrosine, tryptophan	Human adults	3 days per amino acid	Increase in brain catecholamine and decrease in peripheral sympathetic tone	Benedict et al., 1983
Tryptophan	Cats	3 days	No change in functional activity of serotonin neurons	Trulson, 1985
Diet rich in n-3 fatty acid	Young rats	2 weeks	Decrease in cholesterol	Balasubramaniam et al., 1985
10% soybean oil diet	Rats	3 or 14 months	Decrease in cholesterol level only in aged rats	Tappel et al., 1973
Essential fatty-acid deficiency diet	Rat mother progeny	During pregnancy	During gestation: Decrease in polyunsaturated fatty-acid and in learning capacity	Lampety et al., 1976, 1978
Linolic acid deficiency	Rats	During pregnancy, adults 4 months	Impaired learning	Ruthrich et al., 1984
20% soybean oil diet	Rats	3 weeks	Improved learning capacity	Coscina et al., 1985
20% soybean oil diet	Rats	3 weeks	Increased pain threshold, protection for hypothermic effects	Coscina et al., 1985

Learning	Rats	---	Decrease in brain cholesterol level	Kessler et al., 1985
Iron-deficient diet	Rats	10 weeks	Decreased plasma lecithin cholesterol transferase activity	Pollitt et al., 1985
Iron-deficient diet	Rats	4 weeks	Reversal of circadian cycle of pain threshold. Potentiation of analgesic effects of beta-endorphin and enkephaline	Yehuda & Youdim, 1985
Iron-deficient diet	Rats	4 weeks	Impaired learning and memory	Yehuda et al., 1986

Table II

Effects of ID diet on learning

Days on diet	Delta % of no. of trials*	Delta % of mistakes*	Delta % of time to reach platform*
0	+ 5.2	+ 10	- 4.5
7	+31.5	+ 44.4	+20.5
14	+41.7	+ 68.9	+49.2
21	+59.2	+ 94.1	+46.3
28	+70.3	+111.2	+48.5

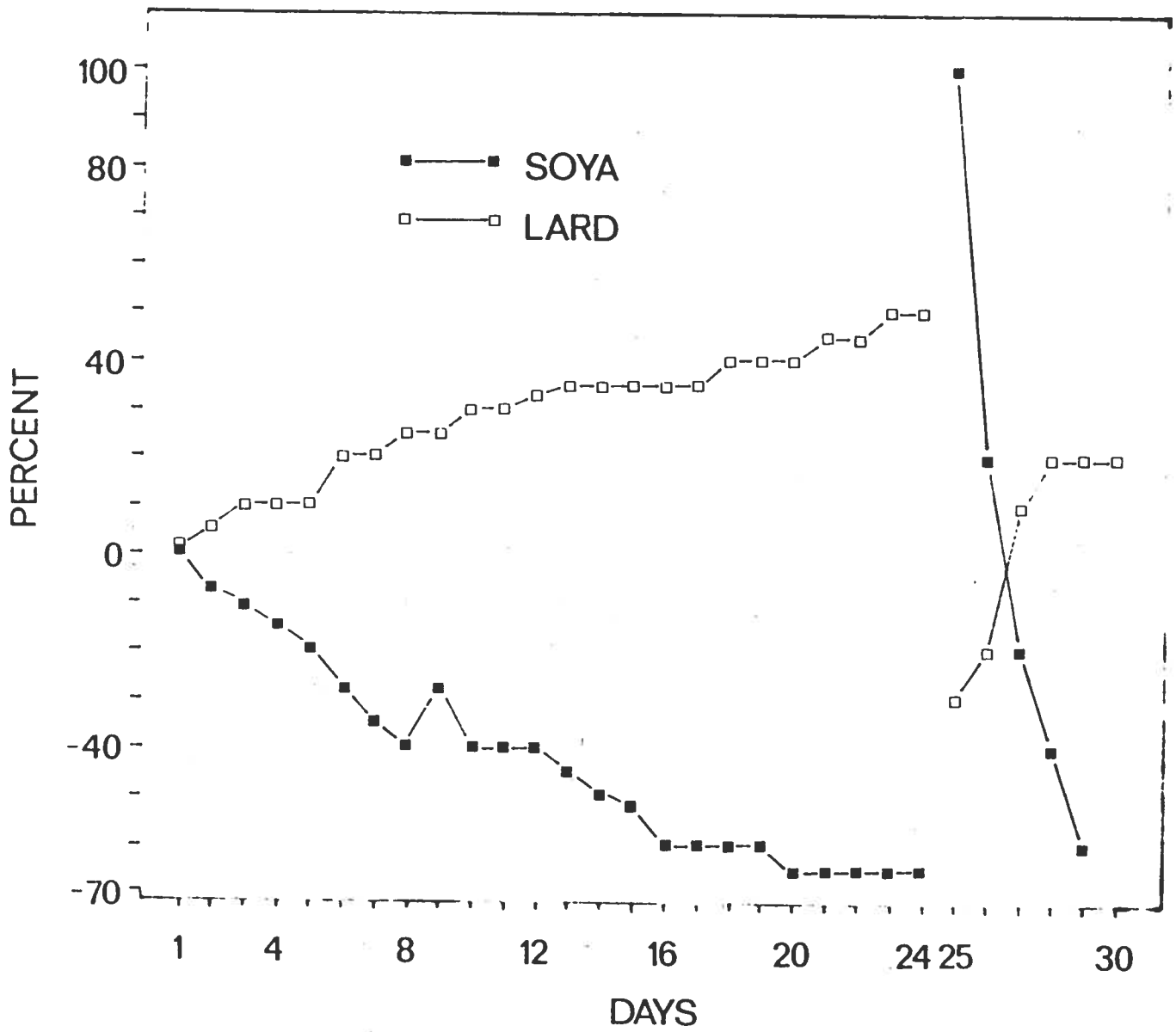
*Compared with rats fed control chow diet

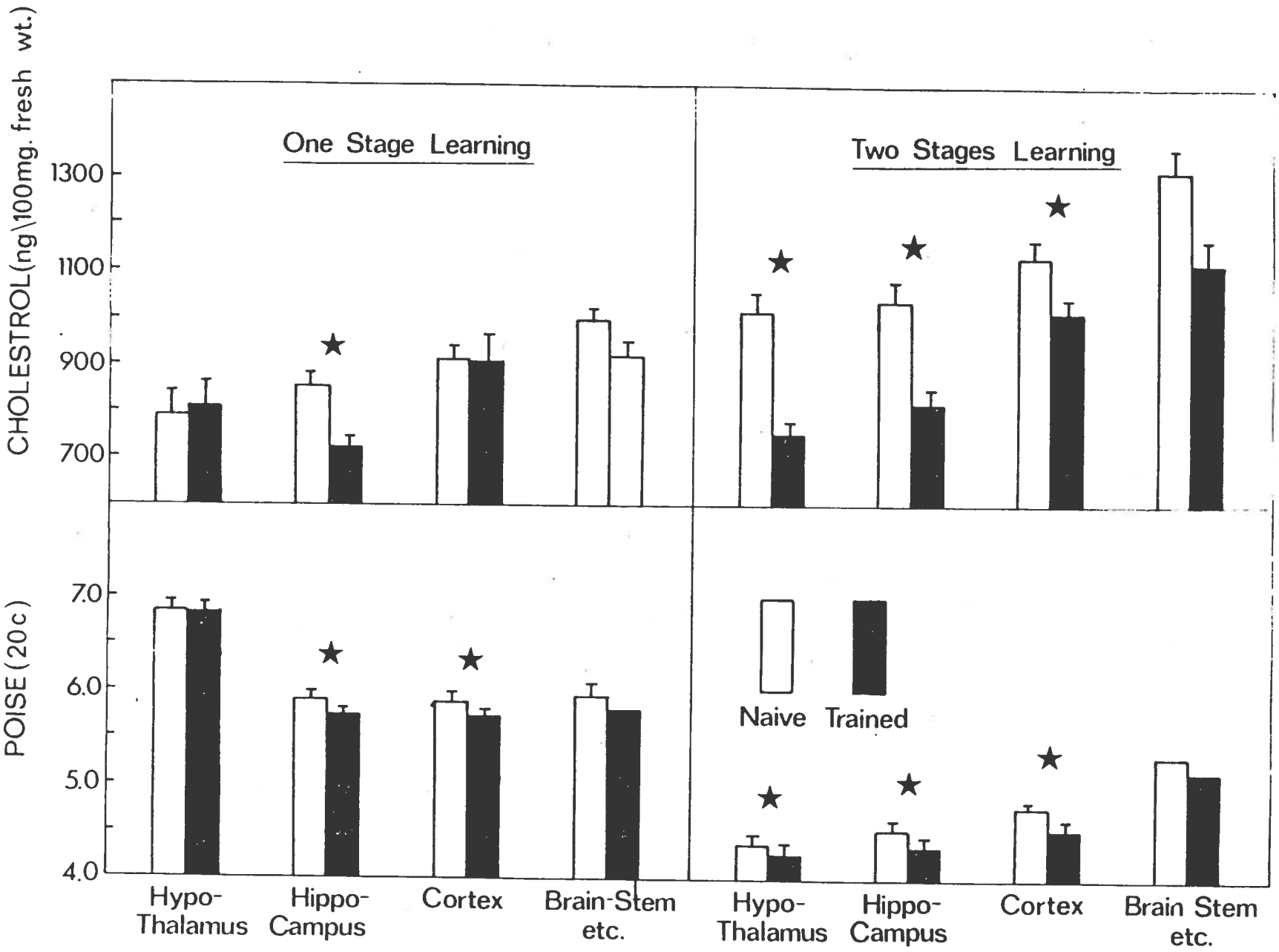
FIGURE LEGEND

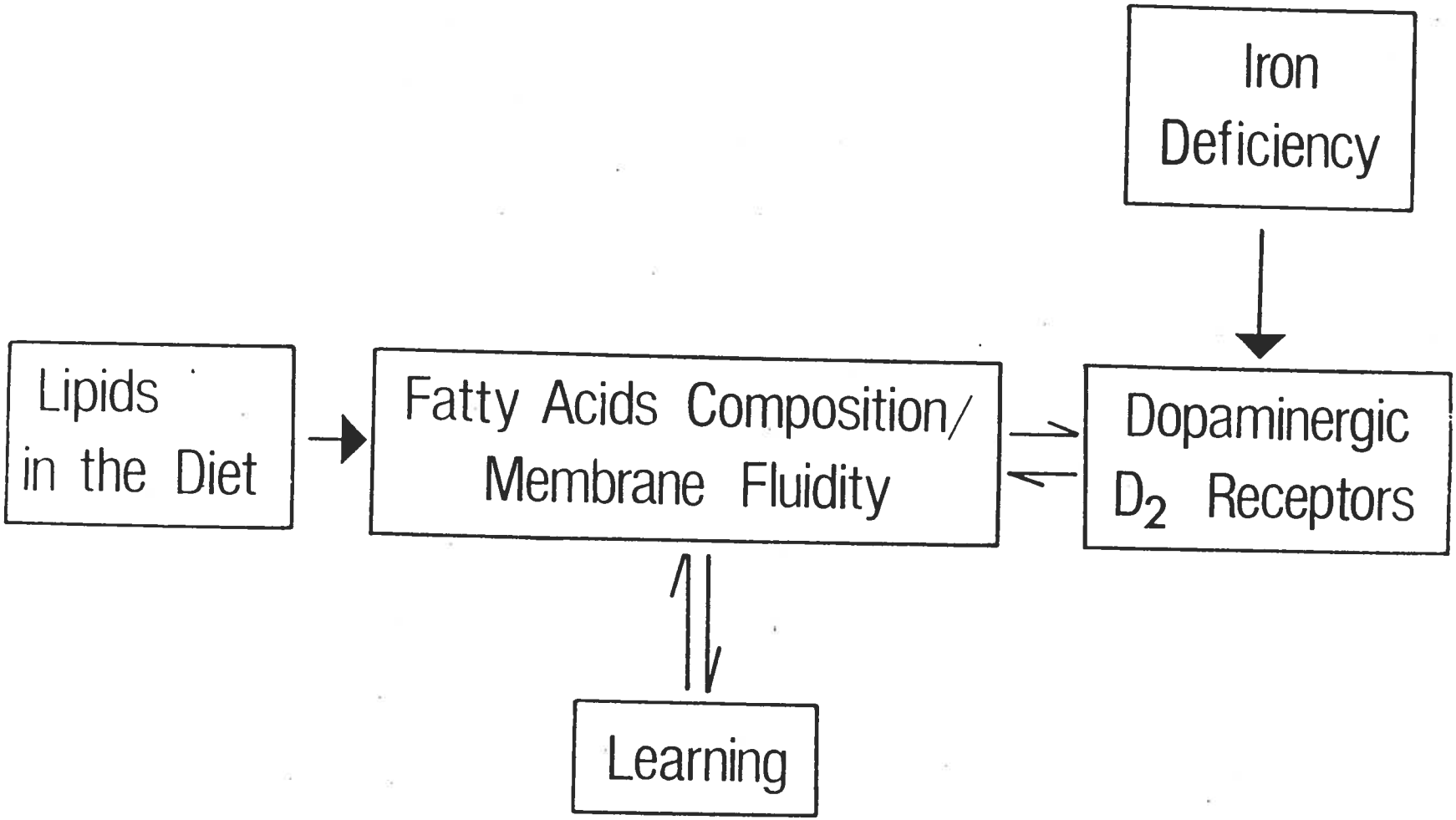
FIGURE 1 The effects of one- or two-stage learning on the levels of brain cholesterol and microviscosity in four different brain areas. Data are presented as mean plus/minus SD.

FIGURE 2 The effects of two lipid diets (soybean and lard sources) on spatial learning. During trials 1-24, the platform was in one location. Between the 24th and 25th trial, the platform was relocated. Data are presented as percent of change in the time required to reach the platform by diet-treated rats compared to control chow-treated rats.

FIGURE 3 Membrane fluidity as a possible mediator of nutritional effects of iron deficiency and fatty acids on learning.


100
80
40
0
-40
-70
PERCENT
SOYA
LARD
1
4
8
12
16
20
24
25
30
DAYS


One Stage Learning
Two Stages Learning
CHOLESTROL(ng\100mg. fresh wt.)
1300
1100
900
700
POISE (20c)
7.0
6.0
5.0
4.0
Naive
Trained
Hypo-Thalamus
Hippo-Campus
Cortex
Brain-Stem etc.
Hypo-Thalamus
Hippo-Campus
Cortex
Brain Stem etc.


Iron
Deficiency
Lipids
in the Diet
Fatty Acids Composition/
Membrane Fluidity
Dopaminergic
D_2 Receptors
Learning