Brain Biochemistry: Effects of Diet

The effects of malnutrition on the brain have been studied for many years. Only in the past few years, however, have investigators addressed the question of whether nutritionally adequate "normal" diets affect brain metabolism. At present, evidence is being brought forward indicating that the rates of synthesis by the brain of at least three major kinds of neurotransmitters are affected by diet. Although it is not yet known whether normal fluctuations in dietary nutrients influence behavior by affecting brain metabolism, the recent results relating nutrition and brain chemistry provide a mechanism whereby such behavioral effects could occur.

The best studied of all the brain products whose synthesis is thought to be controlled by diet is the neurotransmitter serotonin (5-hydroxytryptamine). Serotonin is produced in the brain from the amino acid tryptophan, which is carried to the brain by the bloodstream. The source of tryptophan is digested protein.

As a result of their research during the past few years, Richard Wurtman, John Fernstrom, and their associates at the Massachusetts Institute of Technology have obtained information on how diet affects the concentrations of tryptophan in the blood relative to the other neutral amino acids and they have related this to brain serotonin synthesis. They find that when rats are fed a high protein meal the concentrations of tryptophan and serotonin in the brain do not rise, even though the concentration of tryptophan in the blood increases. An explanation of this effect involves results relating to transport of amino acids through the blood-brain barrier. It hinges on the fact that the concentrations in the blood of the competing neutral amino acids also increase when rats eat protein, and therefore the relative concentration of tryptophan does not increase.

Like all other polar molecules, tryptophan requires a transport protein to carry it from the blood into the brain. It is not always easy, however, for tryptophan molecules to gain access to their transport protein. William Oldendorf of the University of California at Los Angeles has shown that tryptophan competes in vivo with eight other neutral amino acids for access to the same transport protein. Moreover, Oldendorf and his colleague William Pardridge of Boston University Medical Center find that this transport protein has a lower affinity for tryptophan than for its four major competitors. This means that increased amounts of tryptophan will enter the brain only if the concentration of tryptophan in the blood is increased relative to the concentrations of the other neutral amino acids that are its competitors.

Wurtman, Fernstrom, and their associates find, however, that one sort of food—carbohydrates—does cause an increase in the relative concentration of tryptophan in the blood. This effect, they explain, is caused by insulin, which is secreted in response to carbohydrates. Insulin facilitates the uptake by body tissues of all the neutral amino acids except tryptophan, thus increasing the relative concentration of tryptophan in the blood. Rats, fed a meal high in carbohydrates, will have an influx of tryptophan in their brains and a proportionate increase in serotonin synthesis. Moreover, Wurtman and Fernstrom find that the increased amounts of serotonin synthesized in brains of animals after an influx of tryptophan are located in neurons that use serotonin as their transmitter. This means that the serotonin is in areas where it might affect behavior.

One reason that increases in the amounts of tryptophan in the brain cause immediate increases in serotonin synthesis is that the brain contains relatively large amounts of the enzymes involved in tryptophan metabolism. Thus, the rate of serotonin formation is limited by the amount of tryptophan in the brain rather than by the activities of these enzymes. Various investigators find, by use of both in vivo and in vitro methods, that the rate at which 5-hydroxytryptophan—the first intermediate in the conversion of tryptophan to serotonin—accumulates in the brain varies directly with the amount of tryptophan available up to concentrations of tryptophan so high that such concentrations would not normally be found in animal brains.

Since amounts of serotonin in the brain seem to be affected by diet, many investigators are trying to determine whether these changes in serotonin concentrations mediate any changes in animal physiology or behavior. Serotonin has been proposed to be involved in avoidance learning, the effects of hallucinogenic drugs, sleep, sensitivity to pain, control of food intake, and the release of pituitary hormones.

Despite the difficulties in studying the problem, evidence that relative amounts of amino acids in animals' diets may have an influence on their feeding behavior has been obtained. David Ashley and G. Harvey Anderson of the University of Toronto report results that they interpret as indicating that rats may regulate their protein intake as a proportion of their total food intake by sensing how much tryptophan reaches their brains. Rats were offered, over the course of 4 weeks, a choice of diets that differed in both protein content and amino acid composition. The animals consistently ate less protein when the protein contained a high ratio of tryptophan relative to its competing neutral amino acids and more protein when that ratio was lower.

Another behavioral effect of diet was recently reported by Loy Lytle of the Massachusetts Institute of Technology. Lytle fed rats a diet in which corn, which has little tryptophan, was the sole source of protein. The rats were kept on this diet for 14 weeks. During that time, their sensitivity to pain, as measured by response to electric shock, increased significantly. Normal pain sensitivity was immediately restored when these animals were given tryptophan. This result is consistent with previous reports that drugs or lesions that decrease serotonin concentrations in the brains of rats increase their sensitivity to pain.

Several investigators plan to study the effects of diet on sleep since tryptophan apparently induces sleep in laboratory animals and in humans. Ernest Hartmann and his associates at Tufts University School of Medicine report that the ingestion of as little as 1 gram of tryptophan at bedtime (the normal dietary intake of tryptophan is between 0.5 and 2 grams per day) relieves insomnia and enables people to sleep for longer periods of time.

Some investigators, however, believe that effects of diet on serotonin synthesis may not be of sufficient magnitude or duration to bring about physiological or behavioral changes. David Levitsky of Cornell University points out that, even if diets do change brain chemistry, behavioral changes may not occur in the absence of appropriate environmental stimuli. Such stimuli may not be known nor may the reliable measurements of behavior have been developed. Fernstrom points out that whether serotonin affects pituitary hormone secretions is not well established. Evidence implicating serotonin comes from experiments in which animals are injected with drugs that drastically change brain serotonin content and subsequently cause the release of these hormones. This does not necessarily indicate that fluctuations in serotonin content caused by diet will

cause these hormones to be released.

In addition to the effect of serotonin, the rates of synthesis of the neurotransmitter acetylcholine may be affected by diet. Acetylcholine is produced in the brain from choline, which enters the brain from the blood. Lecithin, which is found in meat and eggs, is one dietary source of choline. The other dietary source is proteins since choline is synthesized in the liver from amino acids. A nondietary source of blood choline is the brain, which, although it cannot synthesize its own choline from choline precursors, excretes large quantities of choline that are derived from the breakdown of brain phospholipids. Changes in diet, however, can cause concentrations of choline in blood to vary significantly.

Until fairly recently, it was difficult to determine how much acetylcholine is present in an animal's brain because the enzymes that make acetylcholine are very active after an animal is killed. This problem was resolved, however, by W. B. Stavinoha and S. T. Weintraub of the University of Texas Health Center at San Antonio who found that when rats are killed with microwave irradiation that is focused on their heads, the enzymes that produce acetylcholine are inactivated by the irradiation.

Edith Cohen of the Massachusetts Institute of Technology and Wurtman used the method of microwave irradiation to show that increasing amounts of choline in the diets of rats resulted in proportionate increases in the acetylcholine content of their brains. Cohen and Wurtman attribute this effect to increased synthesis rather than decreased degradation of acetylcholine. They gave the animals a drug that prevents acetylcholine degradation and found that the increase in acetylcholine due to decreased breakdown caused by the drug is additive to the increase in acetylcholine associated with increases in dietary choline.

Donald Jenden of the University of California at Los Angeles cautions, however, that the observation that acetylcholine concentrations in rat brains increase in response to increased dietary choline does not necessarily mean that the newly made acetylcholine is in areas where it can be used. Acetylcholine can, apparently, be synthesized in areas of the brain, such as cell bodies, that are remote from the nerve terminals that use acetylcholine. This question might be resolved by ascertaining whether acetylcholine concentrations also increase in brain regions known to contain terminals of neurons that use acetylcholine as a transmitter. Such neuron terminals occur, for example, in the hippocampus.

The third kind of neurotransmitter whose synthesis may be affected by diet is the catecholines, such as dopamine and norepinephrine. Catecholamines are synthesized from the neutral amino acid tyrosine which enters the brain from the blood.

Tyrosine can enter the blood directly, when proteins containing it are degraded, or indirectly, when the amino acid phenylalanine, which also is supplied to animals by dietary protein, is metabolized in the liver to tyrosine (*p*-hydroxyphenylalanine). Enough tyrosine, relative to the other neutral amino acids, is released into the blood after animals eat high protein meals so that the tyrosine concentrations in their brains increase after such meals.

Difficulties arise in attempts to determine whether increases in brain tyrosine concentrations cause increases in brain catecholamine synthesis. Brain catecholamine synthesis is apparently subject to feedback regulation. This means that when excess catecholamines are made, they can inhibit the activity of a key synthetic enzyme by binding to it and thus turning off their own synthesis. The step in catecholamine synthesis that is inhibited by this feedback loop is the first step: the conversion of tyrosine to dopa (dihydroxyphenylalanine), which is catalyzed by the enzyme tyrosine hydroxylase.

To circumvent this feedback loop, Arvid Carlsson of the University of Göteberg in Sweden devised a method in which he gives animals a drug that prevents the conversion of dopa to catecholamine but does not affect the conversion of tyrosine to dopa. When they use Carlsson's method, Candace Gibson of the Massachusetts Institute of Technology and Wurtman find that diet does affect the rate of synthesis of dopa in the brains of rats.

Rats that are fasted overnight and then fed a high protein meal subsequently have more than twice as much tyrosine and dopa in their brains as rats that are fasted but not fed, according to Gibson. Since both groups of rats are given a drug to prevent them from converting dopa to the catecholamines, this result does not necessarily mean that diet plays a significant role in the control of catecholamine synthesis. It remains possible that when rats have increased amounts of tyrosine in their brains, they are prevented from making more catecholamines by feedback inhibition of tyrosine hydroxylase. On the other hand, in some brain neurons more catecholamines could be made and used under these circumstances.

H. J. Chiel of the Massachusetts Institute of Technology and Wurtman do have some evidence, however, that when the amount of tyrosine in an animal's brain is decreased, in the absence of drugs that affect catecholamine synthesis, the animal may synthesize less dopamine. They inject rats with amino acids that compete with tyrosine for entry into the brain, thus decreasing brain tyrosine concentrations. They find that these animals are no longer sensitive to the temperature-lowering effect of *d*-amphetamine—an effect thought to be mediated by newly synthesized dopamine.

Even if diet turns out not to affect behavior by affecting neurotransmitter synthesis, the developing theory of how the availability of neurotransmitter precursors affects neurotransmitter synthesis promises to lead to clinical applications. For example, Kenneth Davis, Philip Berger, and Leo Hollister of Stanford University School of Medicine are administering large doses of choline to patients with motor disorders thought to be caused by a lack of acetylcholine in their brains. Patients with tardive dyskinesia, which is caused by the prolonged administration of antipsychotic drugs, may be helped by this procedure. Davis, Berger, and Hollister gave one such patient 16 grams of choline per day and report his tardive dyskinesia was substantially improved.

Josef Fischer and his associates of Massachusetts General Hospital note that rats, dogs, and humans in hepatic comas have blood in which the concentrations of the amino acids tyrosine, tryptophan, and phenylalanine are abnormally high relative to the concentrations of the other neutral amino acids that compete with them for uptake from the blood to the brain. These investigators bring dogs and humans out of hepatic comas by injecting them with the competing neutral amino acids.

Now that the idea that normal diets can affect brain metabolism is becoming established, many researchers are joining the search for such effects and are investigating the possibility that the synthesis of brain products other than serotonin, acetylcholine, and the catecholamines may also be affected by diet. According to Pardridge, there is evidence that the synthesis of brain histidine, *S*-adenosylmethionine, and proteins may be subject to dietary effects. The biochemical and clinical implications of these studies may open a new era in the understanding and treatment of neurological disorders.—GINA BARI KOLATA