Dietary fat intake and the brain: a developing frontier in biological psychiatry

Carol E. Greenwood, PhD; Simon N. Young, PhD

Some ideas are many years ahead of their time. In the last quarter of the nineteenth century, Thudichum, one of the founding fathers of neurochemistry, studied the composition of the brain. (For reviews of Thudichum’s work and his contributions to the development of neurochemistry, see Sourkes1,2). His aim was to determine the composition of the brain, as far as was possible, in order to discover what changes occur in brain disorders, including mental illness. The major part of his work concerned lipids, the main constituent of the brain after water. The idea that brain lipid content may be important in the etiology or treatment of psychiatric disorders lay dormant until relatively recently, but it is growing in importance.

Lipid is an important constituent of the brain, not only because of myelin, but also because of the large surface-to-volume ratio of neurons — neurons contain a higher proportion of lipid than other cells because lipid is the main constituent of the neuronal cell membrane. The precise characteristics of this lipid bilayer may affect not only the electrical properties of the membrane, but also the properties of proteins embedded in it, such as receptors. However, the extent to which the lipid content of the brain can be altered and the implications this has, both for variations in normal behaviour and for psychopathology, remain uncertain.

Reports of altered plasma, red cell or brain lipid profiles in certain psychiatric disorders, including depression3 and schizophrenia,4 have led some investigators to postulate that impaired fatty acid and phospholipid metabolism may play a major role in the etiology of psychiatric disorders. Specifically reported are lower levels and altered ratios of the omega-6 and omega-3 essential fatty acids.3,4 Whether these changes are secondary to other behavioural attributes of patients (e.g., altered food intake, smoking or alcohol use) or a primary metabolic event associated with the disease has not been unequivocally answered. However, increasing evidence is pointing to altered membrane turnover and release of fatty acids from phospholipids via phospholipase A, in individuals with depression or schizophrenia. These released fatty acids, which are ultimately converted to omega-6 or omega-3 series eicosanoids, contribute to a wide variety of cellular responses, thus implicating genetic disturbances in lipid metabolizing enzymes in the psychopathology of these disorders.

Although genetic disturbances in brain lipid metabolism may be associated with psychopathologic disorders, an important question is whether dietary fat can play a contributory role, a therapeutic role or both. At one time, the lipid content of the brain was considered...
relatively resistant to change induced by dietary intake. However, in the late 1980s, it became apparent that diet could alter the content and function of the rat brain in a short period of time. For example, rats have different brain lipid contents and demonstrate differences in cognition and behaviour after only a few weeks on diets containing soybean oil or lard. The composition of the developing human brain is also dependent on dietary lipid intake. For example, the brains of breast-fed infants have higher levels of total omega-3 fatty acids and lower levels of omega-6 fatty acids than formula-fed infants. The extent to which changes in dietary fat intake alter brain lipid composition in adult human brain is unknown, however.

One of the more common types of diets recommended by physicians is designed to lower cholesterol levels, and, as shown in the nineteenth century, cholesterol levels, and, as shown in the nineteenth century, cholesterol was related more to a measure of impulsivity than to parasuicide. However, a recent study showed that low cholesterol and suicide or accidents. A number of studies found no relationship between low cholesterol and suicide or accidents. However, a recent study showed that low cholesterol was related more to a measure of impulsivity than to parasuicide.

When patients lower their cholesterol intake, they are probably not only lowering their total fat intake, but also substituting other fats for saturated fats and cholesterol. At its extreme, some have argued that the overall trend for decreased consumption of omega-3 fatty acids is associated with the increasing lifetime prevalence of depression seen in the last century. In a cross-country comparison, Hibbeln and Salem found a strong inverse association between omega-3 fatty acid intake and prevalence of depressive illnesses. This could indicate that dietary intake of omega-3 fatty acids has a large enough impact on brain function to significantly affect mental health. Results from therapeutic trials using omega-3 fatty acids in the treatment of depression are inconsistent. However, a preliminary study showed that pharmacological doses of omega-3 fatty acids (9.6 g/day) helped to stabilize patients with bipolar affective disorder. A lower dose (1.5–1.8 g/d) also decreased aggression in students who were stressed by taking final exams. Conflicting results have been obtained in several studies on patients with schizophrenia, but these studies may not have used the best treatment. Preliminary evidence suggests that only the 20-carbon (eicosapentaeanoic acid; EPA), but not the 22-carbon (docosahexaenoic acid; DHA) omega-3 fatty acid results in improvement. The fact that EPA, but not DHA, can inhibit phospholipase A2, which may be elevated in schizophrenia, may help to explain the specificity of this fatty acid.

One of the problems in studying the effects of fat intake on the brain is the large number of fats present in the diet and the many possible mechanisms by which they may alter brain function. It has long been argued that dietary fat, via its ability to alter brain membrane fatty acid composition, can alter membrane fluidity. A recent human study supported this notion by demonstrating that patients taking omega-3 fatty acids show changes in proton magnetic resonance transverse relaxation time, indicating an increase in membrane fluidity. Changes in membrane fluidity, in turn, can influence the availability and activity of membrane-associated proteins (e.g., neurotransmitter receptors and enzymes), as well as the flexibility or movement of ion channels (reviewed in Fenton et al). In addition to alterations in membrane properties, fats are the precursor of a variety of messenger substances, including prostaglandins, thromboxanes and leukotrienes, collectively called eicosanoids. Once released from membrane phospholipids under the action of various phospholipases, the omega-6 and omega-3 fatty acids produce different series of eicosanoids. It has long been known that the essential fatty acids and eicosanoids participate in cellular signal transduction and their deficiency or excess can alter cellular communication. Furthermore, the omega-3 fatty acids can inhibit phospholipase A2 and interfere with the conversion of the omega-6 fatty acids into their respective eicosanoids. However, recent identification of the eicosanoid ligand, anandamide, the endogenous ligand for the cannabinoid receptor, and its ability to increase the production of interleukins and other cytokines, opens the possibility that lipids alter the functioning of the cytokine network. Cytokines have been implicated in the pathophysiology of several psychiatric disorders, including depression and schizophrenia. Finally, evidence is emerging that fatty acids may also have direct nuclear effects. For example, in mouse brain, DHA was re-
cently identified as a ligand for the retinoid X receptor, a nuclear receptor that functions as a ligand-activated transcription factor and that has been implicated in the differentiation of a variety of neuronal subtypes, including cholinergic neurons.

The degree to which any of these changes occur in human brain and their contribution of psychiatric disorders are unknown. Unfortunately, the vast number of potential mechanisms makes it unlikely that a single factor will be identified to explain the complex associations between fat intake, metabolism and brain function.

After more than a century, research relating brain lipid composition and brain function remains in its infancy. On the basic science side, we need to know much more about which specific lipids can influence the brain and the mechanisms mediating these effects. Clinically, more studies are needed to establish the therapeutic effects of pharmacological doses of different fats. Further in the future is an understanding of how dietary fat intake may influence normal and abnormal mood and behaviour. In all probability, the brains of an Argentinian gaucho, a Canadian Inuk and an Indian Hindu have distinctive lipid profiles. Similarly, changes in diet, whether promoted by health professionals or the latest fad, may alter brain composition and function. We are far from understanding the implications of these changes for mental health.

References