Omega-3 Fatty Acids: Past, Present, and Future

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Introduction
The diverse biological activities and various
natural and fortified food sources of the
multiple types of omega-3 fatty acids present
a challenge in clearly communicating
the nutrition and health benefits of these
essential dietary components. The purpose
of this review is to explain the chemistry,
biochemistry, and nutrition of the omega-3
fatty acids as well as to discuss the role
the International Omega-3 Learning and
Education Consortium for Health and
Medicine plays in disseminating such
information to consumers and professionals.
Established in 2008, The International
Omega-3 Learning and Education
Consortium for Health and Medicine also
known as Omega-3 Learning, aims to
facilitate learning about omega-3 fatty
acids in food, nutrition, and medicine by
providing learning opportunities, references,
and resources to its target audiences.
Comprised of a team of professionals with
expertise in education and communication,
and knowledge in nutrition and food
systems Omega-3 Learning in conjunction
with its partners, such as Dietitians in
Integrative and Functional Medicine (DIFM),
promotes objective, accurate, science-based
information. The key messages include:
bioactivity of eicosapentaenoic acid (EPA)
and docosahexaenoic acid (DHA); differences
between the types and sources of omega-3
fatty acids; nutrition and health benefits as
they relate to inflammation, cardiovascular
disease risk, cellular signaling, growth and
development, aging and cognitive health;
applications to emerging health issues,
global regulations on products and use, and
evaluation of potential risks. The Consortium
communicates said information via its web
page www.omega3learning.purdue.edu. On
this site, consumers may access an electronic
newsletter, “Nutrition & Health”; healthcare
professionals may access “Physicians &
Healthcare Providers”, a newsletter geared
towards them as well as a food product
database which lists the omega-3 fatty acid
content of many common foods.

Omega-3 Fatty Acids: Chemistry and
Biochemistry
Omega-3 fatty acids are classified as
polyunsaturated fatty acids (PUFAs), meaning
there are two or more double bonds in their
hydrocarbon chains. All omega-3 PUFAs
have three or more double bonds. Examples
include α-linolenic acid (ALA), EPA, and DHA.
The differences between the various fatty
acids are based on their chemical structures,
including where double bonds are located
along the fatty acid hydrocarbon chain. All
fatty acid molecules contain a carboxylic
acid (-COOH) group at one end and a methyl
(-CH₃) group at the other, which is referred
to as the terminal or omega end (Figure 1).
When the position of the first double bond
occurs at the third carbon from the methyl
end, as shown in Figure 1, the fatty acid is
considered an omega-3 PUFA. Likewise, fatty
acids with the first double bond at the sixth
carbon from the methyl end are classified
as omega-6 PUFA. Often one will see the
shorthand notation n-3 for omega-3 PUFA or
n-6 for omega-6 PUFA.
When vegetable oils are commercially processed they sometimes undergo hydrogenation. During the hydrogenation process, hydrogen is added to the fatty acid chain, which can convert some PUFA into saturated fatty acids free of double bonds or trans-fatty acids, where the double bonds are in trans configuration. Partial hydrogenation of vegetable oils is used to produce stick margarine and shortening which have less saturated fat than the butter or lard they replace. Reducing PUFA in hydrogenated vegetable oil improves its stability and increases its melting point. The hydrogenation process was adopted several decades ago. Unfortunately, it was subsequently discovered that the trans-fatty acids formed in many margarine brands, shortening, and hydrogenated vegetable oils elevate LDL-cholesterol and reduce HDL-cholesterol. Most naturally occurring double bonds in PUFAs are in the cis conformation as shown in the structures for AA, EPA, and DHA in Figure 3.

Figure 1. Two dimensional molecular structures of some PUFAs. Examples of the omega-6 PUFAs include linoleic acid (LA) and arachidonic acid (AA). The omega-3 PUFAs shown in this figure are ALA, EPA and DHA.

Because it cannot be synthesized by the body, ALA is an essential fatty acid; humans require a dietary source of ALA to prevent deficiency. Besides the omega-3 ALA, at least two other omega-3 PUFAs are important because of their potent biological actions: EPA and DHA. The omega-3 PUFAs are found in foods such as walnuts, canola oil, cold water fish and fish oils. The structures of both EPA and DHA are shown in Figure 1. In the omega-6 family of PUFAs, linoleic acid (LA) is essential, and its elongated product from the biosynthesis is the powerful systemic-acting arachidonic acid (AA). The chemical structures of both LA and AA are also shown in Figure 1. LA is found in a number of vegetable oils including corn, soybean, safflower, and sunflower oils. In essential fatty acids such as LA and ALA, the double bonds are in the cis configuration—the hydrogen atoms are on the same side of the double bonds. In the trans geometric configuration, the hydrogen atoms are on the opposite sides of the double bond as shown in Figure 2.

The Omega-3 PUFA and Their Biological Potencies

The health effects of omega-3 PUFA are frequently reported and include well established evidence for cardiovascular health benefits, improved cognition, and control of inflammation. Emerging evidence suggests other benefits as well. Obtaining adequate omega-3 PUFA can be challenging for the consumer, in part because within the omega-3 family there are different biologically important fatty acids as well as a plethora of food sources from which to obtain these. ALA is the essential omega-3 present in selected plant sources. To a very limited extent,
ALA can be converted to the more biologically active forms such as EPA and DHA. Arterburn et al. reported the conversion of ALA to EPA to be 8% in males and 21% in females. However, Harris et al. reported lower rates of conversion of ALA to EPA. Since the conversion of ALA to EPA and DHA is limited, it is best to consume dietary sources containing these PUFA such as cold water fish (i.e., salmon, mackerel, or tuna [fresh or canned in water]), foods fortified with EPA or DHA, and/or reputable supplements with EPA and DHA.

Figure 4 shows the hepatic pathway and enzymes responsible for the addition of double bonds (desaturases) and elongating (elongsases) the PUFA molecule for the formation of long chain omega-6 and omega-3 PUFAs. The enzymes involved in the formation of long chain fatty acids from the 18 carbon omega-3 and omega-6 PUFAs are the same but as the amount of dietary ALA increases the formation of AA from LA is minimized. The regulation of this pathway resides in the activity of the delta-6 desaturase enzyme. The activity of this enzyme may be impaired in certain health conditions further compounding the adequacy of omega-3 nutrure.

Biological Actions of Omega-3 PUFAs
Omega-6 and omega-3 PUFAs have important biological roles beyond those supporting the growth and development of neural and retinal tissues in the body. These roles include structural lipids in cell membranes, cell signaling molecules, and to a large extent, potent oxygenated products—eicosanoids such as prostanoids and leukotrienes. Many of the diverse physiological actions of PUFA are exerted by the long chain omega-6 PUFA AA and by the omega-3 PUFA EPA and DHA. For example, the prostanoids are biosynthesized from AA and EPA through the actions of the cyclooxygenase enzymes (COX). These enzymes exist as COX-1, a housekeeping enzyme for normal homeostasis and COX-2, an inducible form that is activated during inflammatory responses. There are also a lesser known COX-3 enzyme, a variant of COX-1, exerting approximately 20% of the activity of COX-1. The COX-1 and 2 enzymes and their products are shown in Figure 5.

There are many different metabolites that can be produced with various actions depending on the cell or organ in which they are produced and whether derived from AA or EPA. Although the actions are complex, in general the prostanoids derived from AA tend to be pro-inflammatory while metabolites from EPA are far less so. The prostanoids derived from AA, such as thromboxane, lead to vasoconstriction and platelet aggregation; those from EPA are less potent in exerting platelet aggregation. Hence, the prostanoids can have powerful effects on the vascular system. One of the early discoveries about the COX enzyme is that it is inhibited by aspirin in more recent years the use of low dose aspirin—81 mg/day—has been recommended to decrease platelet aggregation and lower risk of blood clots and heart attack. There are other highly biologically active products derived from the omega-6 and omega-3 families of PUFA. These include those derived from the lipoxygenases.
(LOX) 5-, 12-, and 15- that act on AA or EPA to form leukotrienes (LT). Similar to the formation of prostaglandins, LT from AA tend to promote the inflammatory cascade whereas LT from EPA are far less inflammatory. In recent years a new series of oxygenated products from AA, EPA and DHA was discovered and found to be pro-resolving or involved in the resolution of the inflammatory process. These pro-resolving compounds are formed by the combined actions of COX and LOX enzymes and include lipoxins (from AA), resolvins (from EPA and DHA), docosatrienes (from DHA), and neuroprotectins (from DHA).

**Omega-3 PUFAs and Diet**

**Recommendations for Omega-3 PUFAs**

In 2002, Dietary Reference Intakes (DRIs) for omega-3 fatty acids were published by the Institute of Medicine of the National Academies; in 2005 the Dietary Guidelines for Americans were developed to facilitate healthful eating to achieve the DRIs. The DRI for omega-3 fatty acids places a primary emphasis on adequate intake (AI) of ALA to meet the requirement for all ages and both genders. Although the AI is for ALA, typical diets can include different types of omega-3 fatty acids important to nutrition, metabolism, biological functions, and health. The DRIs recommend an AI for ALA at 1.6 g/day for women, 1.1 g/day for men, and 1.6 g/day for pregnant and lactating women. Therefore, during these life stages women should consume foods rich in omega-3 PUFA to increase DHA concentrations in breast milk and improve infant health outcomes, most notably visual acuity and cognitive development.

Within the 2010 Dietary Guidelines for Americans there is a greater emphasis on omega-3 PUFA, especially EPA and DHA from seafood. The proposed recommendation is consumption of two 4 oz servings of seafood weekly for an average intake of 250 mg/day. The evidence to support this recommendation was considered moderate for reduction of cardiac mortality and sudden death from a cardiac event. Concomitantly, there was limited evidence for plant derived ALA intake above the current recommendations.

Since the publication of the 2002 DRI recommendations there has been considerable research in this area. Expert groups such as the American Heart Association, American Dietetic Association, American Psychiatric Association and other agencies have since made recommendations as shown in Table 1. Recently, the scientific evidence to support a specific requirement for EPA and DHA was assessed by leading researchers who concluded that there is sufficient evidence for the benefit of EPA and DHA intake between 250 - 500 mg/day for cardiovascular outcomes. There is not enough evidence to make a definitive statement for cognitive outcomes, and no apparent benefit for decreased cancer risk. There is no evidence that the 250 - 500 mg/day dosage range has any adverse effect.

**Assessment of Omega-3 PUFA Intake**

The first step in dietary counseling is assessment of the intake of the client or patient. Data from NHANES (1999 - 2000) shows that the average intake of EPA and DHA is approximately 100 mg/day from about 2.9 oz/week of fish. This average meets the current DRI recommendations. However, numerous expert groups and government bodies believe it is below current needs. NHANES data collected via 24-hour recall is a snapshot of Americans’ intake. Fish intake for many individuals is an “all or none” scenario. In the NHANES database when the average intake is calculated, those who consume fish regularly overcompensate for those who never consume fish and fail to meet DRI and other recommendations.

The semi-quantitative food frequency questionnaire (FFQ) used in the Physicians’ Health Study is a reliable and valid tool to assess long-term fish intake. Statistica The FFQ divided seafood into 4 categories: canned tuna fish; 3 - 5 oz dark meat fish (i.e., mackerel, salmon, and swordfish); 3 - 5 oz other fish; and shrimp, lobster or scallops as a main dish. There were seven possible responses ranging from rarely/never to two or more per day. Average consumption was based on the frequency of intake and the nutrient composition for each possible seafood derived from the USDA nutrient database.

Long chain omega-3 PUFA intake can also be assessed by biomarkers of intake. This methodology is often utilized in research settings but may be applied clinically if the instrumentation-primarily gas chromatography—is available. However, one difficulty in the
analytical assessment is that there are multiple tissue types and lipid classes to examine. Some recent attempts to use a value called the omega-3 index in red blood cells are promising for determining cardiovascular disease risk. Unfortunately, there is no agreement for a single biomarker for omega-3 PUFA status. Fekete and colleagues conducted a systematic literature review for assessment methods of long chain omega-3 PUFA status. Of the 41 studies included in the report 18 different biomarkers were evaluated. From these studies, enough data were available to determine that the following are adequate biomarkers of DHA status: plasma DHA, plasma phospholipid DHA, plasma non-esterified DHA, erythrocyte DHA, erythrocyte phospholipid DHA, and platelet DHA. Plasma phospholipid EPA was an effective marker for EPA. The most common biomarker sources are from blood and include total lipid and phospholipid classes of plasma or erythrocytes. In a review of biomarkers for DHA, primarily total and phospholipid classes from both plasma and erythrocytes reflected DHA intake. This data is helpful to determine

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Organization</th>
<th>Organization Type</th>
<th>Target Population</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>World Health Organization</td>
<td>Authoritative Body</td>
<td>General adult population</td>
<td>n-3 PUFA: 1-2% of energy/day</td>
</tr>
<tr>
<td>Global</td>
<td>International Society for the Study of Fats and Lipids (ISSFAL)</td>
<td>Expert Scientific Organization</td>
<td>General adult population</td>
<td>DHA+EPA: 0.65 g/2000 kcal/day; DHA at least 0.22 g/2000 kcal/day; EPA at least 0.22 g/2000 kcal/day</td>
</tr>
<tr>
<td>United States</td>
<td>American Dietetic Association</td>
<td>Expert Scientific Organization</td>
<td>Pregnant/nursing women</td>
<td>DHA: 300 mg/day</td>
</tr>
<tr>
<td>United States</td>
<td>March of Dimes</td>
<td>Expert Scientific Organization</td>
<td>General Adult Population</td>
<td>500 mg/day long-chain PUFA intake</td>
</tr>
<tr>
<td>United States</td>
<td>American Heart Association</td>
<td>Expert Scientific Organization</td>
<td>Pregnant and Nursing Women</td>
<td>200 mg DHA from fish, fortified foods or supplements</td>
</tr>
<tr>
<td>United States</td>
<td>American Psychiatric Association</td>
<td>Expert Scientific Organization</td>
<td>All adults without CHD</td>
<td>Eat fish (particularly fatty fish) at least two times a week; include oils and foods rich in ALA</td>
</tr>
<tr>
<td>United States</td>
<td>American Psychiatric Association</td>
<td>Expert Scientific Organization</td>
<td>Patients with CHD</td>
<td>Consume approximately 1 g/day of EPA+DHA preferably from oily fish</td>
</tr>
<tr>
<td>United States</td>
<td>American Psychiatric Association</td>
<td>Expert Scientific Organization</td>
<td>Patients with high triglycerides</td>
<td>2-4 g/day EPA+DHA as capsules under a physician’s care</td>
</tr>
<tr>
<td>United States</td>
<td>American Psychiatric Association</td>
<td>Expert Scientific Organization</td>
<td>All adults</td>
<td>Consume fish at least 2 times a week</td>
</tr>
<tr>
<td>United States</td>
<td>American Psychiatric Association</td>
<td>Expert Scientific Organization</td>
<td>Patients with mood, impulse control or psychotic disorders</td>
<td>Consume 1 g/day of EPA + DHA</td>
</tr>
<tr>
<td>United States</td>
<td>American Psychiatric Association</td>
<td>Expert Scientific Organization</td>
<td>Patients with mood disorders</td>
<td>Supplement 1-9 g/day may be useful. Use of &gt; 3 g/day should be monitored by a physician</td>
</tr>
</tbody>
</table>
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if a biomarker is sensitive enough to detect small changes in fish intake or supplemental dosage modifications. The two reviews by Fekete et al.33 and Kuratko and Salem34 gave direction on how to interpret the use of omega-3 PUFA biomarkers. As stated in both reviews, there is not a consensus for the most appropriate biomarker for EPA and DHA intake, but the above mentioned outcomes show that some of the most commonly used measures are appropriate and correlate well with intake.

Disappearance data from The National Marine Fisheries revealed that seafood intake from 1994 to 2004 increased. The data ranked shrimp as the top type of seafood consumed followed by canned tuna and salmon.35 This type of data is helpful for understanding food patterns for the US population; however, individual assessments can aid in personalized recommendations for intake and the use of biomarkers, when appropriate, can help assess compliance to recommendations.

How to Meet the Omega-3 PUFA Recommendations: Dietary Sources of Omega-3 PUFAs

Inconclusive evidence leaves the research community unable to make recommendations for certain populations. However, healthy diets for all segments of the population should consist of omega-3 PUFA in amounts recommended by the DRI and other scientific organizations and authoritative bodies. The ADA is one such organization. Its recommendations were made in 2007 and included 5 additional years of research since the establishment of the most recent DRI published in 2002. The ADA and Dietitians of Canada, recommends that the general population consume 500 mg/day of long-chain omega-3 PUFAs.23 PM.</Authors_Primary><Authors_Primary><Innis,S. How can these recommendations be put into practice?

The omega-3 PUFA content of seafood products can vary widely. Fatty cold water fish—salmon, tuna, mackerel, rainbow trout, anchovies and sardines—have the highest omega-3 content. Other varieties have moderate to very low omega-3 content. When purchasing canned fish, it is advisable to select water packed instead of oil packed to obtain a greater intake of omega-3 PUFAs relative to omega-6 PUFAs. A quick, useful resource to determine the EPA and DHA content of a seafood variety is the food product database on the Omega-3 Learning website (www. omega3learning.purdue.edu/diet-health/view/consumers/productdatabase/food-products). Additionally, recommendations for intake of seafood with low levels of mercury and other toxins can be found on state department of public health websites. Table 2 lists the amount of omega-3 PUFA in one, 3 oz serving of fish. With the exception of halibut, one serving as listed meets or exceeds the ADA recommendation of 500 mg/day for EPA and DHA.

A greater challenge is to help ensure adequate omega-3 PUFA intake for individuals who do not consume fish frequently or at all because of limited access, cultural or religious beliefs, vegetarianism, allergies or personal preference. One way to facilitate adequate intake of essential PUFAs is consumption of vegetable oils. Omega-6 and omega-3 PUFA are found in a variety of vegetable oils. Safflower, corn, sunflower, and soybean oils all contain high amounts of LA while flaxseed oil has the most omega-3 ALA. The quantities shown in Table 3 indicate grams of LA and ALA present in 1 tablespoon of oil.

The addition of omega-3 fortified food products to the naturally occurring omega-3 food sources affords the consumer yet another way to improve omega-3 nutrity. Over the past few years numerous foods—whole eggs and egg products, breads, juices, and dairy foods—have been fortified with omega-3 PUFAs. Table 4 lists select food products that meet the 500 mg/day recommendation for EPA and DHA for those not consuming seafood.

Unfortunately, most omega-3 fortified foods do not specify the amount or type of ALA, EPA or DHA, and only list the source of omega-3 PUFAs on the ingredient list. The Omega-3 Learning database includes such fortified foods and lists the amount (when available) and/or source of omega-3 fortification in food product such as beverages, baked goods, and eggs.

Determining how much and what types of omega-3 PUFAs are in a fortified food can be difficult. There are no requirements for listing omega-3 PUFA content on the Nutrition Facts label. Many fortified food products will state on the front of the package that the product contains omega-3 fatty acids; however, the amount and type of PUFAs are not required to be listed. Because all ingredients must be listed on the package, the ingredient list can help to determine the source and therefore type of fatty acid, but not the amount. Milk is an example of a food that has been fortified with omega-3 PUFA. Depending on the brand, milk can be fortified with fish oil to add EPA and DHA, whereas fortification with algae oil will

<table>
<thead>
<tr>
<th>Food Product</th>
<th>Serving Size</th>
<th>Total omega-3 (mg)</th>
<th>EPA (mg)</th>
<th>DHA (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmon, Atlantic Farmed</td>
<td>3 oz (85 g)</td>
<td>2131</td>
<td>733</td>
<td>938</td>
</tr>
<tr>
<td>White Canned Tuna in Water</td>
<td>3 oz (85 g)</td>
<td>808</td>
<td>198</td>
<td>535</td>
</tr>
<tr>
<td>Halibut (Atlantic and Pacific)</td>
<td>3 oz (85 g)</td>
<td>444</td>
<td>60</td>
<td>248</td>
</tr>
<tr>
<td>Rainbow Trout Wild</td>
<td>3 oz (85 g)</td>
<td>690</td>
<td>142</td>
<td>357</td>
</tr>
</tbody>
</table>

Table 2. Quantity of Omega-3 PUFAs, EPA and DHA, in Select Fish Varieties
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Table 3. Quantity of Omega-6 and Omega-3 PUFA in Select Vegetable Oils

<table>
<thead>
<tr>
<th>Oil</th>
<th>Serving size (Tbsp)</th>
<th>Omega-6 linoleic acid (g)</th>
<th>Omega-3 alpha-linolenic acid (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soybean oil</td>
<td>1</td>
<td>6.86</td>
<td>0.92</td>
</tr>
<tr>
<td>Safflower oil</td>
<td>1</td>
<td>10.15</td>
<td>0</td>
</tr>
<tr>
<td>Corn oil</td>
<td>1</td>
<td>7.24</td>
<td>0.16</td>
</tr>
<tr>
<td>Canola oil</td>
<td>1</td>
<td>2.61</td>
<td>1.28</td>
</tr>
<tr>
<td>Sunflower oil</td>
<td>1</td>
<td>8.94</td>
<td>0</td>
</tr>
<tr>
<td>Flaxseed oil</td>
<td>1</td>
<td>1.73</td>
<td>7.25</td>
</tr>
</tbody>
</table>

Table 4. Quantity of Omega-3 PUFA, EPA and DHA in Select Functional Foods

<table>
<thead>
<tr>
<th>Food Product</th>
<th>Serving Size</th>
<th>Total omega-3 (mg)</th>
<th>EPA (mg)</th>
<th>DHA (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fortified Eggs</td>
<td>2 large</td>
<td>200 - 800</td>
<td>4 or n.v.</td>
<td>36 - 320</td>
</tr>
<tr>
<td>Fortified Soy Milk</td>
<td>240 ml</td>
<td>200 - 700</td>
<td>n.v.</td>
<td>32 or n.v.</td>
</tr>
<tr>
<td>Fortified Fruit Juice (including orange juice)</td>
<td>240 ml</td>
<td>50 – 600</td>
<td>FO, 100 - 300</td>
<td>FO, 16 - 240</td>
</tr>
<tr>
<td>Fortified Milk</td>
<td>240 ml</td>
<td>n.v.</td>
<td>FO or n.v.</td>
<td>FO or DHA algae oil</td>
</tr>
<tr>
<td>Fortified Yogurts (including baby foods)</td>
<td>100 – 180 g</td>
<td>n.v. or 100</td>
<td>n.v.</td>
<td>n.v. or 32 from DHA algae oil</td>
</tr>
<tr>
<td>Fortified Spreads/ margarine*</td>
<td>1 tablespoon</td>
<td>n.v. or 400 - 1300</td>
<td>FO or n.v.</td>
<td>n.v. or FO or algae oil or 32</td>
</tr>
<tr>
<td>Fortified Breads*</td>
<td>1 slice</td>
<td>n.v.</td>
<td>n.v.</td>
<td>n.v.</td>
</tr>
</tbody>
</table>

supplement the product with DHA only. Soy milk naturally contains some ALA but some brands have been fortified with algae oil to add DHA. Generally, if the food contains ALA the source is usually from plant oil such as flaxseed, one of the highest in ALA. If DHA is on the food label the ingredient will typically be from an algal source of oil. Finally, if the food product contains both EPA and DHA, the ingredient source is commonly fish oil.

Questions often arise about the bioavailability of omega-3 PUFA in these functional food products. The type of omega-3 fatty acids used in these food products is either the triglyceride or ethyl ester forms which are readily bioavailable. Omega-3 fatty acids are usually added as triglycerides after being protected by microencapsulation. Microencapsulation prevents the oil from oxidation during food preparation and storage; this enhances the stability of the omega-3 fatty acids in the food thereby increasing the shelf life of these products. If oxidation of unsaturated fatty acids occurs in the food it may contain oxidation by-products that can lead to undesirable flavors.

Omega-3 PUFA for Health and Reducing Disease Risk

Maternal and Child nutrition

The omega-3 PUFA were recognized to be important in the normal development of the brain and retina in animals and subsequently in the human infant. The National Institute of Nutrition and Food Technology (NINFT) research findings on the benefit of maternal diets that contained omega-3 PUFA on neural and retinal development led to the fortification of infant formula in many countries. Much research has focused on the pregnancy and lactation stages of life and the impact of DHA on the developing fetus since it obtains DHA through the placenta and after birth from breast milk. Once the child advances to solid foods a dietary source of DHA is required. While the current requirements are based on ALA intake, DHA has specific functions in early development and growth. A study of infants fed formula fortified with DHA as 0 (control), 0.32, 0.64, or 0.96% of total fatty acids—all containing 0.64% AA from birth to 12 months found that 0.32% of total fatty acids from DHA improved visual acuity; higher amounts did not result in additional improvements.

A recent study in the Journal of Nutrition examined the amount of ALA, EPA and DHA consumed by Canadian children aged 4-8 years. The researchers found that, on average, the children in this study consumed 1161 mg/day of ALA, 54 mg/day of DHA and 38 mg/day of EPA. Compared to the AI set by the DRI, 61% of children in the study met the recommendations for ALA, while only 22% met the suggested intake for DHA and EPA. Comparisons to other associations’ and countries’ recommendations were similar, reflecting a large gap between recommendations and actual intake of long chain omega-3 PUFAs.

Cardiovascular Disease

The relationship between omega-3 fatty acids and cardiovascular disease risk has been well established. Substantial evidence indicates that the omega-3 fatty acids found in fish, DHA and EPA, decrease the risk of coronary heart disease and ischemic heart disease.
Physician's Health Study reported that consumption of one or more servings of fish per week was associated with a 52% lower risk of sudden cardiac disease compared to less than one fish meal per week. Reduction of sudden cardiac risk was recently estimated by Harris et al. Pool analyses from prospective cohort studies demonstrated that an intake of 250 mg EPA + DHA per day in healthy individuals reduced risk of cardiac death. Another benefit of DHA and EPA related to cardiovascular disease is that these fatty acids aid in lowering heart rate and blood triglyceride levels. It is known that fish oil can reduce serum triglyceride levels by 20 - 50%, similar to the reduction achieved by statins, niacin and fibrates. A prescription form of EPA + DHA, Lovaza (GlaxoSmithKline, UK), is available to treat patients with serum hypertriglyceridemia. Each Lovaza 1 gram capsule contains 465 mg EPA ethyl ester, 375 mg DHA ethyl ester, 80 mg of other omega-3 fatty acids, 30 mg of omega-6 fatty acids, and 50 mg of antioxidants. Based on the cardiovascular protective actions of omega-3 fatty acids in the general population as well as the triglyceride lowering effects, the American Heart Association has recommended that the public consume two fish servings weekly for health and those with documented elevated triglycerides should supplement their diet with 2-4 g/day of EPA and DHA (Table 1).

Mood Disorders

Epidemiological evidence supports the intake of seafood in those with aggressive behavior, depression, and other mood disorders based on an inverse relationship between omega-3 PUFA intake and mood disorders. However, clinical trials have yielded conflicting results with varied sample size, methods, and the mood disorder under investigation. The use of long chain omega-3 PUFA as monotherapy for major depressive disorder (MDD) is not currently recommended use as an adjunctive therapy for MDD treatment is recommended by the American Psychiatry Association (APA) for their general health benefits and the cardiovascular benefits because many with MDD have comorbid cardiac ailments.

In 2009 Hibbeln and Davis assessed maternal needs for DHA as it relates to neurological outcomes including decreased maternal depression at 32 weeks and adverse neurodevelopment. They calculated that long chain omega-3 PUFA intake of 0.40% of energy or 900 mg/d/2000 calories during pregnancy from seafood is likely to meet requirements for 97.5% of the population of mothers and offspring. Inflammation and Anti-inflammatory Actions

As a defense mechanism against infection and other insults, inflammation is an indispensable weapon in host protection. However, pathological inflammation leads to irreparable damage to host tissues which can contribute to disease. Long chain PUFAs are precursor prostanoids, pivotal mediators of inflammation. AA is a primary substrate of a series of pro-inflammatory eicosanoids as previously discussed. The omega-3 PUFAs, EPA and DHA, have anti-inflammatory and pro-resolving actions in the inflammatory process, effectively counterbalancing the actions of AA. Omega-3 PUFA have been effectively utilized to mitigate diseases with an inflammatory component, such as rheumatoid arthritis, inflammatory bowel diseases, and asthma. Its use potentially could be applied to other health conditions where inflammation is involved.

Gastrointestinal Diseases

Inflammatory bowel disease (IBD), Crohn’s disease and ulcerative colitis (UC) have both genetic and environmental etiologies. Nutrition is a cornerstone of IBD management for acute “flare-ups” and maintenance of disease remission. The inflammatory nature of IBD led to research on the effects of omega-3 PUFA for its management. Fish oil supplementation results in the incorporation of the EPA and DHA into the colonic mucosal lipids of IBD patients, which potentially decreases inflammatory mediators. This data provided proof of concept that omega-3 PUFA intake has the potential to decrease inflammation in the colonic mucosa. However, the data for omega-3 PUFA as a specific treatment for IBD is weak. The current literature is inconclusive because of the use of different treatments including duration, dosage, and source of long chain omega-3 PUFA as well as differences in study populations, i.e., adult vs. pediatric and active vs. remission state of disease. The mechanistic possibilities for an effect of omega-3 PUFA on IBD is strong, yet published clinical outcomes are inconclusive.

The data on omega-3 PUFA in managing Crohn’s disease is slightly more favorable. A one-year, double-blind, placebo-controlled study compared the effects of enteric-coated fish oil (1.8 g EPA, 0.9 g DHA/day) with triglyceride placebo (Miglyol 812, a mixed triglyceride of fractionated fatty acids that is 60% caprylic and 40% capric acids) oil in 78 subjects with Crohn’s disease in remission. Significantly more patients in the fish oil group remained in remission compared to the placebo—59% compared to 26%, respectively. However, two more recent, multicenter, randomized, double-blind, placebo-controlled trials (Epanova Program in Crohn’s Study [EPIC]-1 and EPIC-2) found no effect of omega-3 PUFA for the maintenance of remission in Crohn’s disease patients. At one year, EPIC-1 reported 31.6% of patients in the omega-3 group (2 - 2.4 g EPA, 0.6 - 1 g DHA as free fatty acids/day) compared to 35.7% in the placebo group relapsed to active disease. EPIC-2 at one year found 47.8% compared to 48.8% in the...
omega-3 PUFA and placebo groups, respectively, in relapse. Omega-3 PUFAs as a treatment for UC has also been examined. In this model of distal disease, sigmoidoscopy can be used to assess the changes in colonic tissue. In a randomized, double-blind, placebo-controlled investigation, patients with active distal proctocolitis, given fish oil (3.2 g EPA, 2.4 g DHA) demonstrated improved clinical activity, sigmoidoscopic and histological scores, and decreased inflammatory and cytotoxic activity compared to a placebo group (sunflower oil). The effects of omega-3 PUFA on relapse and remission were not examined.

The Cochrane group has published meta-analysis reviews on omega-3 PUFA for maintenance of remission in Crohn’s disease and UC. For the maintenance of Crohn’s disease remission, six studies (including the most recent EPIC trials) were included; a marginal benefit was observed for omega-3 PUFA therapy. However, the authors caution that the studies were clinically and statistically heterogeneous. The meta-analysis review of omega-3 PUFA therapy for UC remission included three small studies and found no benefit. Each study used different formulations and dosages of omega-3 PUFAs and none of the studies evaluated the effects of an enteric-coated fish oil capsule. Since the publication of this review in 2007, there have been no subsequent studies in humans on the effects of omega-3 PUFA on UC.

Emerging Research for Omega-3 PUFA

Aging

Assessment of the aging process is difficult and expensive. Farzaneh-Far et al. used a novel marker of biological age—telomere length—to examine an association between long chain omega-3 PUFA levels and aging in patients with coronary heart disease (CHD). Telomeres are repeat DNA sequences at the ends of chromosomes. Shorter telomere length is associated with morbidity and mortality making telomere length a useful marker of biological age. In this study, both telomere length as well as tissue EPA and DHA levels were assessed in a prospective cohort study of stable CHD patients (average age of 66 years) at baseline and after 5 years. Patients with the lowest EPA and DHA level had the fastest rate of telomere shortening. Alternatively, increasing EPA and DHA levels by 1 standard deviation was associated with reduced risk of telomere shortening. In a sample of 234 adults aged 36 - 88 years, the older adults had greater EPA and DHA plasma phospholipid concentrations compared to young adults. This finding was partly explained by the greater fish intake in older adults and a possible interaction with lower LA levels observed in the older adults. This data suggests that in vivo long chain omega-3 levels can be maintained or increased by dietary sources and may have an impact on the aging process. Although these new findings for omega-3 PUFA are exciting, they are preliminary; further research is needed.

Obesity and the Endocannabinoid Signaling System

Obesity and its associated health consequences have been identified with dysregulation of the endocannabinoid (EC) system. The discovery of the cannabinoid receptors in the brain (called CB1) and periphery (called CB2) and the link that endogenous cannabinoids (anandamide or AEA and 2-arachidonoylglycerol or 2-AG) activate these receptors prompted numerous investigations. Of particular interest is the area of obesity management, as it was found that CB1 antagonism could decrease food intake. This action is a result of blocking the activation of the CB1 receptor in the brain, thus impairing the agonist AEA from binding and stimulating food intake (Figure 6). The specific CB1 antagonist SR141716A (Rimonabant®) has been found to be effective for the treatment of obesity. However, recent reports of depression and suicidal idealties have led to the discontinuation of its use both in Europe and clinical trials in the United States. CB1 is also expressed in peripheral tissues including adipose, liver, pancreas, muscle and bone (Figure 6). Endogenous cannabinoids, like AEA and 2-AG, are synthesized on demand from AA, found in glycerolipids (Figure 6). Since AA is a principle substrate for the endogenous agonists, the competition between long chain omega-3 PUFA (EPA and DHA) and AA potentially may reverse the activation of CB receptors and alter EC signaling to promote health and, in the case of obesity, possibly altering appetite. This is just one example of where new applications of omega-3 PUFA research may improve the human condition.

Figure 6. The endocannabinoid signaling system is shown for its actions on the brain and peripheral organs where the receptors reside. The endogenous agonists AEA and 2-AG for these receptors are derived from AA and antagonists prevent the activation of the receptor, as the example for the CB1 antagonist SR141716A, which prevents the mediation of stimulation of food intake.
Omega-3 PUFA Implications for the Future of Dietetics

The future of dietetics lies in our hands, as stated by Judith Gilbride, past president of ADA, “from the molecular level through clinical practice, owning the science—meaning full participation in the conduct of biomedical research coupled with full understanding of the results and implications for practice—is critical for our future”. It is essential that dietitians keep abreast of and participate in current research, understand and interpret the results and their implications for practice, and communicate the information with the public, clients and patients. The use of standardized language in medical records and resources such as the Evidence Analysis Library (EAL) will enable the execution of more clinic-based research that will propel the profession forward. Many of the replies to questions under the omega-3 category in the EAL are concluded with the statement ‘future research is needed; suggesting possible initiatives for dietitians. As mentioned, one resource to help dietitians stay abreast of current findings and locate patient education materials is the Omega-3 Learning website. The site lists publications by topic areas as well as outlines recommendations for omega-3 PUFA intake set forth by expert scientific organizations and authoritative bodies from around the world.

There is no doubt that the media and Internet provide a myriad of messages about omega-3 PUFAs and their potential benefits. A recent Google search uncovered over 3.5 million web links for “omega-3 fatty acids”. This is an overwhelming amount of information that can be either credible or misleading. Thus, a non-biased, fact-based and accurate source of information for nutrition and health about omega-3 PUFAs is needed to educate professionals and consumers alike. Because education is a core mission of the Omega-3 Learning Consortium, alignment with ADA is a way to achieve the mission and vision of both groups. This is the rationale behind the networking relationship between Omega-3 Learning and DIFM. ADA’s strategic plan for 2009 was directed at how the organization positions itself for the future; and omega-3 PUFA education fits into a number of ADA’s strategies. One of ADA’s goals is to improve the health of Americans. One strategy to meet this goal is to inform the public about ways to improve its health; another is to equip ADA members to use research in their work (ADA Strategic Plan 2009). The Consortium and Omega-3 Learning website is a place for dietitians to gather and share research on omega-3 PUFAs. The new networking relationship between Omega-3 Learning and DIFM members is an exciting opportunity for DIFM members to utilize scientifically relevant and accurate information from the Consortium to strengthen their professional status. The Consortium and DIFM will work cooperatively to develop and implement continuing education to their members.

Conclusion

Omega-3 PUFAs are part of primary and secondary prevention for cardiovascular disease. These nutrients are essential across the lifespan playing a vital role in maternal and infant nutrition as well as potentially playing a role in aging. Similarly, omega-3 PUFAs are potential adjunctive agents in behavioral and psychiatric treatment and gastrointestinal illnesses. Recommended omega-3 PUFA intakes have been set by the 2002 DRIs, and will be included in the 2010 Dietary Guidelines for Americans. Because the amounts and types of omega-3 PUFAs vary in food products and each has a unique metabolism and biological function, understanding the chemistry, biochemistry, and metabolism of these nutrients is paramount. Groups such as ADA, DIFM, and Omega-3 Learning provide an avenue by which to learn about and disseminate information on omega-3 PUFAs.

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Heather L. Hutchins (Hutchins-Wiese) PhD, RD, Post Doctoral Fellow, Center on Aging, University of Connecticut Health Center, studies the effects of PUFA on bone and frailty in older adults. She obtained MS and BS degrees from the University of Connecticut and her PhD from Purdue University in 2010 where she investigated the effects of PUFA on the endocannabinoid system in bone and skeletal muscle under the direction of Dr. Watkins. Contact Heather at the Center on Aging University of Connecticut Health Center, Hutchins-Wiese@uchc.edu, or 860-679-8935.
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Two long-chain omega-3 fatty acids, namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have garnered considerable attention in the scientific community over the past several decades. Numerous investigations have explored the potential health benefits of consuming these fatty acids, with a particular emphasis on their roles in the management of a variety of health conditions. This review will focus on the current state of knowledge regarding the therapeutic efficacy of omega-3 fatty acids in various medical contexts, including inflammatory bowel disease, psychological disorders, and cardiovascular health.

Inflammatory Bowel Disease


Psychological Disorders


Cardiovascular Health

Numerous studies have highlighted the potential cardioprotective effects of omega-3 fatty acids. These effects are thought to be mediated through the reduction of inflammation, modulation of thrombosis, and improvement of lipid profiles. A randomized controlled trial by Dallaire C, Ponich TP, McDonald JW, Hebuntere X, Pare P, Klvana P, Niv Y, Ardizzzone S, Alexeeva O, Rostom A, Kuidelis G, Spielberg J, Gilgen D, Vandervoot MK, Wong CJ, Zou GY, Donner A, Rutgeerts P. Omega-3 free fatty acids for the maintenance of remission in Crohn disease: the EPIC Randomized Controlled Trials. JAMA. 2008;299:1690-1697.

Conclusion

In conclusion, the evidence supporting the efficacy of omega-3 fatty acids in various medical contexts is substantial. However, more research is needed to fully elucidate the mechanisms underlying these effects and to identify optimal dosages and formulations. As we continue to develop our understanding of the role of omega-3 fatty acids in health and disease, it is clear that these nutrients have the potential to play a significant role in promoting overall well-being.
Objective, Learning Codes, and CPE Questions for Fall 2010 CPE—
Omega-3 Fatty Acids: Past, Present, and Future

This article is approved for 1.0 hours of continuing professional education by the Commission on Dietetic Registration. Possible Learning Codes: 2000, 2020, 2100, 4030, 5000, 5160, 9020

Objectives for Omega 3 Article

After reading this review, the food and nutrition professional will be able to:

1. State the Dietary Reference Intake (DRI) and/or Adequate Intake (AI) for alpha linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid.
2. Identify at least three professional and patient resources available on omega-3 fatty acids.
3. List at least three disease processes in which humans may benefit from an increased dietary intake of omega-3 fatty acids.
4. Identify at least one area of emerging research and clinical application of Omega-3 PUFAs.
5. List two omega-6 and two omega 3 PUFAs.
6. List at least three dietary sources of omega-3 PUFAs.

CPE Questions:

1. Which of the following are omega-3 PUFAs?
   a. Cyclooxygenase and delta-6 desaturase
   b. Arachidonic acid (AA) and linoleic acid (LA)
   c. cis and trans fatty acids
   d. apha linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosapentaenoic acid (DHA)
2. The DRI for alpha linolenic acid in adults:
   a. is 10% of AMDR
   b. is 250 mg/day of EPA & DHA
   c. is 1.1 g/day for women and 1.6 g/day for men
   d. has not been determined, the guidelines will be published within the year
3. Aside from fish, omega-3 PUFAs are naturally found in which foods?
   a. Safflower oil
   b. Sunflower oil
   c. Fortified beverages (milk and juice)
   d. Flaxseeds & oil
4. Which omega-3 PUFA is most important to fetal and neonatal development?
   a. EPA
   b. DHA
   c. AA
   d. LA
5. Omega-3 PUFAs have demonstrated statistically significant clinical efficacy in all of the following except:
   a. Attenuating the aging process by inhibiting oxidation
   b. Reducing triglycerides
   c. Promoting fetal and neonatal neural and retinal development
   d. Modulating inflammation
6. All of the following are resources available on the Omega-3 Learning website except:
   a. Food product database
   b. Evidence Analysis Library
   c. Patient and professional newsletters
   d. References and research articles

CPE Reporting Form • Fall 2010 • Omega-3 Fatty Acids: past present, and future. Expiration Date 10-31-2011

Please print or type

Name: ____________________________________________________________
Address: __________________________________________________________
ADA Membership #: ____________________________________________Phone: ____________________________
Email Address: __________________________________________________
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This activity had been approved for one hour of CPE credit. You will be notified if hour is not approved.

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   DIFM DPG c/o Amy Jarck,
   P.O. Box 3624, Pittsfield, MA 01202
   phone: 800-279-6880 or info@integrativerd.org.
   Please include the following information: title of the article; newsletter issue and date (example: Fall 2010); your name, address, telephone number, email address, and ADA member registration number.
3) Once this information has been received, Amy Jarck DIFM Executive Assistant, will email verification of completion for the CPE credit. Complete and retain the Certificate of Completion for your records along with the verification you receive in case you are audited by ADA.

ANSWER KEYS: 1-D; 2-C; 3-D; 4-B; 5-A; 6-B
Highly Palatable Foods: The Brain Reward Pathways and Connections to Overeating

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Food, Reward and Obesity

For decades we have been taught that the key to losing weight is a matter of energy balance; eat less and exercise more. Yet more and more people continue to gain weight. In fact, in the United States two thirds of adults are overweight and more than 72 million of them are obese. The global picture of overweight and obesity is sobering and the number of overweight people now surpasses the number of undernourished by several hundred million. In 2005 over 20 million children under five years of age were overweight and the World Health Organization has predicted that by 2015, approximately 2.3 billion adults will be overweight and over 700 million will be obese.

Obesity rates have climbed in unison with the availability of inexpensive highly palatable foods, i.e., processed foods rich in fat, salt, and refined sugars. Eating behaviors characterized by food cravings and binging have increased concomitantly with the increased exposure to these highly palatable foods. Research in both animal models and human imaging studies shows that high calorie, highly palatable foods are directly associated with addiction and loss of control.

Emerging science has revealed that excessive food consumption involves the brain’s pleasure centers. Neuroimaging studies have shown that food, like substances of abuse, leads to increased dopamine release in the pleasure center of the brain. Positron emission tomographic (PET) imaging studies have shown that obese individuals, like drug abusers, have lower levels of dopamine D2 receptors. Lower dopamine D2 receptors make the obese individual less sensitive to reward stimuli. This, in turn, may make the obese individual more vulnerable to excessive food intake as a way to satisfy a reduced reward signal.

This new research is important because it helps explain the reason why obese individuals either fail to succeed with weight loss efforts or regain lost weight. Few diet products or programs address the reward pathways that drive eating behaviors. A truly effective approach to weight management should encourage strategies aimed at improving dopamine functioning in the brain’s reward circuitry. This article will review emerging science that describes a direct link between the activation of the reward/pleasure pathways in the brain and eating behaviors.

The Brain is Reward Driven

In order to better understand the drive to overeat and food addiction we must first understand the basics of the brain’s “pleasure or reward center”. The nucleus accumbens (a collection of neurons found in the striatum) was first identified as the brain’s pleasure center in the 1950s. A reward circuit (figure 1), which includes the ventral tegmental area (VTA), nucleus accumbens, septum, amygdala (involved in emotion), and prefrontal cortex (thinking part of the brain), was later identified. When the brain receives a sensory stimulus that is positive (i.e., highly palatable food), signals are sent to the VTA. The VTA, in turn, releases dopamine into the nucleus accumbens, septum, amygdala, and prefrontal cortex. Dopamine leads to feelings of exuberance, desire, and positive emotions. The pleasure associated with dopamine’s release reinforces eating.

Obesity & Reduced Food Reward:

The dopamine reward pathways influence the fundamental drive to eat. Dopamine is required to initiate each meal and it is associated with the duration and quantity of a meal. Weak activation of dopamine-based reward circuitry may increase overeating.

Recent research has found lower dopamine D2 receptors in obese subjects. In some of these individuals a genetic variation may be the cause. An association between the Taq 1 A allele and lower levels of dopamine D2 receptors has been found by some researchers. It may be that individuals with reduced dopamine D2 receptors use food to increase dopamine stimulation to a more satisfying level.

Figure 1. Reward Pathway


pleasure pathways, habits, & addiction:

The brain is plastic, meaning it can change. If an individual repeatedly engages in an eating behavior (i.e., binging) the nervous system will actually become wired for that behavior. It will strengthen the neural (synaptic) connections for that behavior. This is known as experience-dependent plasticity. Changes occur at brain synapses as we make choices, exhibit certain behaviors, store memories, and learn. It is thought that most learning
Highly Palatable Foods

occur in the brain through the process of strengthening or weakening synapses. Therefore, the brain will actually be modified by the repeated act of overeating.15

The brain creates memories about eating behaviors. Glutamate, an excitatory neurotransmitter, plays a role in synaptic plasticity. It is involved in cognitive functions such as learning and memory.16 It is, therefore, important in storing information about eating experiences, such as pleasure felt when eating. Later cues in the environment, such as a person, a smell (i.e. French fries), or a location, can “trigger” memories of the pleasurable experience. These pleasurable memories can lead to cravings and relapse.17

When addiction occurs the pleasure circuits are in a sense “hijacked”. The addiction basically takes over the pleasure and motivational centers of the brain, creating intense cravings. When the craving is satisfied there is a cascade of pleasure neurotransmitters, including serotonin, dopamine, enkephalin, and GABA. With repeated abuse (i.e., binging) the amount of neurotransmitter released in response to normal stimuli is reduced.18 Therefore, more substance (i.e., food) is needed to get the same sense of pleasure. In other words, the food addict will need more food to get the same effect.

Highly Palatable Foods:

People don’t binge on broccoli and spinach, they binge on highly palatable foods loaded with refined sugars, fat, and salt. This is at least partly driven by the brain’s pleasure center. Using functional magnetic resonance (fMRI) imaging technology Killgore, et al.19 examined the brains of subjects showing them images of low-calorie and high-calorie foods. When subjects were shown the pictures of low-calorie foods, they had very little activation in the reward centers of the brain compared to controls.

However, when shown pictures of high calorie food with high reward, subjects had significant activation of the reward circuitry.20 Excessive consumption of highly palatable foods actually alters the brain circuitry involved in sensory processing of food, particularly the lips, tongue, and mouth. Obese individuals have been found to have enhanced sensitivity in brain regions involved in sensory processing. This heightened sensitivity makes the eating experience of these foods more rewarding and might contribute to overeating.19 These highly palatable foods share certain neural pathways. One such pathway is the mesolimbic dopamine system.19 Binging on these highly processed calorically dense foods can release excessive amounts of dopamine in the brain which high sugar22,23

Processed foods can have dozens of ingredients, so it is not an easy task to determine which constituents in foods might trigger reward pathways and the addictive process. Much of the research thus far has focused on sugar.

Are We Addicted to Sugar?

Professor Bart Hoebel and his research team in the Department of Psychology at the Princeton Neuroscience Institute have studied sugar addiction in rats for many years. Their early research demonstrated behavioral patterns similar to those seen in addicts—sugar-binging followed by withdrawal when sugar was removed. Hoebel’s more recent research found that rats showed signs of craving and relapse, a critical component of addiction. The rats, after learning

Table 1. Neurotransmitters Involved in Food Intake Regulation

| Stimulate Feeding (usually decrease energy expenditure) | • Anandamide • ß-endorphin • Dynorphin • GABA • Galanin • Ghrelin • Growth hormone releasing hormone • Neuropeptide Y • Norepinephrine |
| Inhibit Feeding (usually increase energy expenditure) | • Cholecystokinin (CCK) • Corticotropin-releasing factor (CRF) • Dopamine • Insulin • Leptin • Glucagon • Neurotensin • Thyrotropin-releasing hormone • Melanocyte-stimulating hormone |

Table 1. Neurotransmitters Involved in Food Intake Regulation

can override satiety signals.21 In addition, certain neurotransmitters (Table 1) that stabilize appetite long term, such as leptin, insulin, and ghrelin, become less effective when the diet is laden with processed foods containing high fat and to binge, worked harder to get sugar when it was reintroduced and they also consumed more sugar than before.24 In their experiments, binging on sugar triggered a surge of dopamine in the nucleus accumbens. There were
fewer dopamine receptors than before and more opioid receptors, suggesting an adaptive response. The dopamine and opioid systems are involved in reward and motivation and are important in controlling wanting and liking something.25

Animal research suggests that sugar and drugs of abuse act on the brain in similar ways. Behavioral and neurochemical changes in the brain following a sugar-binge resemble those produced when an individual takes a drug such as nicotine, cocaine, or morphine. Because sugar releases opioids and dopamine it is expected to have addictive potential.26

The pleasure from the sweet taste of sugar-dense foods and beverages initially motivates over-consumption. In fact, research is finding that sweet taste may be more rewarding and possibly more addictive than cocaine. Researchers at the University of Bordeaux in France found that when rats were allowed to choose between water sweetened with saccharin and intravenous cocaine, 94% of the animals preferred the saccharin. This same sweet preference was also seen with sucrose. The researchers speculated that supra-normal stimulation of sweet receptors by sugar-rich diets, such as those seen in modern society, could create a supra-normal reward signal in the brain that could potentially override self-control mechanisms and lead to addiction.27

**Does Eating High Fat Stimulate Eating?**

According to data from the United Nations Food and Agricultural Organization, the dramatic increase in consumption of fatty foods over the last thirty years may be partly responsible for the growing obesity epidemic.28

Eating high-fat (HF) may increase drives to eat more fat. A study conducted by Gaysinskaya et al.29 found that caloric intake was increased throughout the day in animals fed a small HF meal early in the day compared to those fed a low-fat meal. Triglyceride levels increased 2-3 times in the HF group, but there were no changes in leptin or insulin levels. Leptin and insulin are known to inhibit feeding. The expression of orexigenic (appetite stimulating) peptides, galanin in the paraventricular nucleus and orexin in the perifornical lateral hypothalamus, were increased.29 The findings of this research suggest a potential mechanism involving circulating lipids and orexigenic peptides. Hence, eating a HF diet might in turn stimulate eating.

It is not only short term eating patterns that are affected by fat intake. Long-term eating patterns can actually be predicted by early life experiences. Chang et al.30 found that maternal HF diet exposure lead to changes in rodent offspring following weaning. In as little as two weeks of exposure to a HF diet, both female and male offspring showed increased intake of calories, body weight, a stronger drive for fat intake, and a rise in brain peptides that are stimulated by fat.30

There appears to be a positive feedback loop in which a fat rich meal stimulates certain brain systems that further drive fat intake. In fact, the brain systems involved in reward and palatability can each stimulate and be stimulated by the intake of diets rich in fat. It may be that this vicious cycle actually starts in utero and continues through adulthood.30

**Stress, Reward Pathways and Eating**

It is well known that stress affects eating behaviors. Brain reward circuitry appears to play a key role in stress related food intake. A theoretical model of Reward Based Stress Eating has been proposed by researchers at the University of California, San Francisco Department of Psychiatry.31 According to this model, cortisol and the reward circuitry affect motivation for calorically dense food intake. The reward value of food may be influenced by cortisol via neuroendocrine/peptide mediators such as insulin, leptin, and neuropeptide Y (NPY). Hence, the model also emphasizes the relationship between stress, eating, and potential neuroendocrine mediators.31

Stress, in addition to highly palatable food, can stimulate endogenous release of opioids. Opioid release appears to be part of the organism’s defense mechanism designed to protect from detrimental stress effects. This is done by reducing hypothalamic-pituitary-adrenal (HPA) axis activity and thereby attenuating the stress response. Stimulation of the reward circuits via the intake of highly palatable foods, stress induced stimulation of the HPA axis, or both, may lead to neurobiological adaptations that encourage overeating.31

**Treating Obesity by Changing the Brain**

Most weight loss programs are not successful long-term. One reason may be due to the lack of attention given to the brain’s very powerful reward pathways. To improve success it may be necessary to change reward circuitry that trigger cravings and drives to overeat highly palatable foods. Behavioral interventions that enhance dopamine function hold potential in the treatment of obesity. Breakthroughs in neuroscience show us that we can change our brain’s circuitry. We can literally choose to increase certain neural networks and reduce others. A comprehensive behaviorally based program designed to “re-wire” the brain’s reward pathways can be an effective way to reduce food cravings and overeating. Although detailed program design is beyond the scope of this article, a few suggestions will be made.

- A variety of professionals might be involved (i.e., dietitian, physician, exercise physiologist, psychologist) and a variety of formats (online and phone support, individual consultations, group classes, etc.) might be incorporated.
- Treatment should be individualized and incorporate a variety of
Cognitive and behavioral tools. These tools should help the individual: 1) decrease the reward value of the food or behavior; 2) increase the reward of the new positive behaviors; 3) reduce the power of triggers; and 4) strengthen new neural circuits by learning new habits. Stress management tools should be incorporated daily to weaken neural circuits that promote stress. Increasing natural pleasures can help reduce stress and may improve dopamine function. Exercise is a well known natural pleasure, stress reducer, and mood enhancer. This may be due to changes in neurotransmitter concentrations and alterations in central neural activity. Techniques such as mindfulness meditation have been found to increase activity in the left prefrontal cortex, which is associated with joy and peace.

Analysis of stimuli, situations, and cues that trigger out-of-control-eating is critical. This information can help the patient become aware of the unconscious cues or settings that drive overeating behaviors. Avoidance of certain triggers or foods (i.e., refined sugar) may be necessary at least initially. Ingrained behaviors will not likely change without a significant amount of repetition. Cognitive and behavioral tools must be practiced repeatedly if they are going to weaken the strong neural circuits that favor overeating.

It is clear that to better treat the obesity epidemic we must unravel the neural mechanisms that process the hedonic effects of highly palatable foods, but also those that govern reward-learning, reward-value, and decision making in the context of our current economic and social climate.

References


Highly Palatable Foods

Congratulations to 2010 DIFM Award Winners

**Diana Noland – Excellence in Practice Award**

Diana Noland, MPH RD CCN owns a busy Integrative & Functional Medicine Nutrition Therapy (IFMNT) private practice in Northridge, CA. As a Registered Dietitian and Board Certified Clinical Nutritionist her primary clients are those with chronic disease seeking restoration of wellness and physician referrals for nutrition support of critically ill patients. Her special interests include fatty acid metabolism, women’s health, nutritional oral health, cancer adjunctive support, nutrition physical exam skills for chronic disease, and detoxification.

Recognized for her expertise in the clinical application of IFMNT Diana frequently lectures health professionals and lay public on various Functional Medicine and Integrative nutrition-related topics. She has been a featured speaker for the American Dietetic Association Food & Nutrition Conference & Expo (FNCE) as well as faculty for the Institute for Functional Medicine, member of the Nutrition Advisory Board of the Institute of Functional Medicine (IFM), international speaker, and contributing author of several books on integrative nutrition. Diana is also a member of the ADA DIFM DPG SOP/SOPP Committee currently developing the Standards of Practice for DIFM Medicine to be published in the Journal early 2011.

**Annie Hsu Griffin – Excellence in Service Award**

Annie Hsu Griffin, RD LD graduated from The Ohio State University in 1988 with a degree in Nutrition. She completed her internship at Good Samaritan Hospital in Cincinnati, Ohio in 1990 where she was awarded the Sister Romuald Award for leadership. She has worked in Outpatient Diabetes care at Saginaw General Hospital in Saginaw, Michigan, as the Nutrition Coordinator for The Family Practice Residency Program in Midland, Michigan and is currently the Vice President of HSU & Co. Natural Foods in Columbus, Ohio. Annie served as the CPE Certificate Chair for the Dietitians in Functional Medicine DPG from 1998 to 2010. She also is involved with The Pickerington Food Pantry and the Pickerington Local School District where she was awarded the Friends of Pickerington Outstanding Volunteer Award in 2010. Annie is married and has three children.

**Laura Palazzolo – Student Stipend Award**

Laura holds a Master’s Degree from Bastyr University and recently completed her dietetic internship. She has started working as a clinical dietitian in a long term care/rehabilitation facility and is studying for the RD exam. She plans to bring functional medicine into her future endeavors. In her free time you will find her experimenting in the kitchen or exploring the great outdoors.
or mitigating the burden of obesity may involve maintaining an active lifestyle, improving diet quality, and potentially utilizing interventions such as pharmacotherapy. Preventing obesity may be possible by altering thermogenic mechanisms.

Professor Helga Refsum PhD from the University of Oslo, Norway presented intriguing results on the relationship between elevated cysteine, a sulfur containing amino acid, and obesity. The association also occurs in the presence of glutathione, the amino acid to which cysteine is converted by the body, and appears to be specific to cysteine—no association between obesity and other sulfur containing amino acids or their metabolites was found. Once cysteine levels become elevated, they remain high. For example, obese individuals who have undergone bariatric surgery maintain high cysteine levels. One of the possible negative outcomes of high protein diets may be the induction and continued elevation of high cysteine levels. Elevated cysteine levels could contribute to and explain why certain weight loss diets, such as Atkins, fail the test of long term weight loss maintenance.

Dr. Lorraine Brennan BA(Mod) PhD from the University College of Dublin presented a new metabolomics (looking at markers of metabolism that are proteins created from complex gene expression) research approach that employs nutrityping (or metabotyping—a way of defining groups based on metabolic characteristics) and phenotyping to create clusters of dietary intake and metabolite patterns that can define distinct metabolic groups within a study population. These groups can then be analyzed separately to identify intervention effectiveness. Separating individuals into groups based on quantitative measures of metabolism reduces the chances of missing a metabolic effect by averaging the response of all individuals within a study – that is, subgroups exist within any large group. One can analyze how each subgroup responds to a dietary intervention. Dietitians understand this concept, since not all patients respond to the same dietary advice. For example, Dr. Brennan and her colleagues identified three clusters of dietary patterns in their Irish population as: 1. high vegetable intake; 2. high egg, milk, and yogurt intake; or 3. high fat and alcohol intake. Next, they looked at the urine metabolites using nuclear magnetic resonance (NMR) in all individuals within each of the three groups and compared average profiles of individuals within the group against average profiles of individuals in the other two groups. Using this approach, they observed urinary phenylacetylglutamine increased in concentration as vegetable intake increased in group 1, while O-acetylcarnitine increased with increasing red meat intake in group 3. While it is difficult to draw any definitive conclusions for the dietetic practice from these observations, this research approach may eventually yield a better understanding of unique and individualized metabolic programming of humans in relation to habitual dietary intake. Analyzing gene – nutrient, or phenotype, or genotype of individuals first and then separating into similar response groups had been proposed at past NuGO weeks in Montecatini and published.6

Other discussions centered around—
• the use of challenge tests to evaluate individual deviation from a homeostatic state
• using calculus to show how energy expenditure changes in accordance with energy intake
• the association between methylation and gene function
• computational biology in gene association research
• optimal functioning of the human microbiome (gut bacteria), and its association with obesity
• complex protein interactions that form circadian rhythms (per Professor Oren Froy’s presentation on the circadian locomotor outputs cycle kaput (CLOCK) gene, “you are when you eat”)
• the association between individual gene patterns and predictions for weight loss

The most lively discussion was held Thursday night with a debate on whether personalized nutrition can meet its expectations, or whether it is another in

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Colleen Fogarty
Draper MS RD; Nutritional Genomics Chair, Dietitians in Integrative and Functional Medicine (DIFM DPG)

The following is a summary of the most recent NuGO Week scientific conference held in Glasgow, Scotland that focused on the broad topic of metabolic health. NuGO week is an annual, international conference lead by NuGO, formerly the European Nutrigenomics Organization, but now the (global) Nutrigenomics Organization. The European NuGO consists of 24 academic and research organizations. As a non-profit entity, NuGO has been promoting the science of nutritional genomics worldwide and stimulating the exploitation of scientific discovery in the field of nutrition and genomics for the last seven years. More information about NuGO can be located at www.nugo.org and information specific to dietetics at http://www.nugo.org/everyone/28182.

The conference opened with a plenary discussion on the influence of brown fat on body weight control. Although it was once thought brown fat was only found in infants, researchers have recently identified the presence of brown fat in adults. According to Professor Barbara Cannon Bsc PhD Dsc, from Stockholm University, the body increases brown fat production in a cold environment which in turn allows for an increase in thermogenesis. UCP-1, uncoupling protein 1 (OMIM – 113730), is a key mediator of thermogenesis and has also been linked to obesity risk.1-3 Insufficient thermogenesis may therefore be a phenotype associated with obesity risk. Individuals with UCP SNP -3726 A/A have higher UCP-1 expression—which correlates inversely with BMI.1 The alternate, G/G genotypes have lower UCP-1 expression and higher BMIs. Since brown fat is regulated by cortisol and sex hormones, aging, and stress in combination with certain UCP-1 variants and expression, genetic susceptibility may play a key role in body fat regulation. Preventing or mitigating the burden of obesity may

1 Dr. Brennan’sNutriGenetics study of Irish population
a long line of fads in nutritional science. Check out www.nugo.org for more detailed information on the topics discussed at the conference.

Next year, NuGO Week will be held in Wageningen, Netherlands (5–9 September 2011). Although NuGO conferences are designed to share research results, many individuals within the organization believe and encourage the translation of laboratory data to real life. Hence, exchanges between food and nutrition professionals with a background in genomics and an interest in research are welcome to attend. In the meantime, to stay on top of the latest topics in nutritional genomics and nutritional systems biology, join the NutriAlerts listserve created by Jim Kaput, PhD, Director of FDA’s Division of Personalized Nutrition and Medicine at http://www.nugo.org/nutrialerts. Finally, don’t forget to email NGX@integrativeRD.org with your questions!

In Good Health, Colleen

References

Many thanks to Jim Kaput for his thorough review of this article.
By Kathie Madonna Swift, MS, RD, LDN, Past Chair

Strategic Plan and Program of Work (POW): Updated strategic plan and reviewed POW 2009-2010 at Hood River in May 2009

New Staff: DIFM welcomed new staff member, Amy Jarck, website content editor and Executive Assistant.

ADA Honorary Membership: Awarded to Gerard E. Mullin, MD, MS, CNSP and internationally renowned Gastroenterologist from Johns Hopkins Medical Center, for his strong support of Registered Dietitians

Name Change: Formalized name change from Nutrition in Complementary Care DPG to Dietitians in Integrative and Functional Medicine DPG with a new PO mailing address, email address, info@integrativeRD.org, while maintaining the same 800 number for member communication.

Website: Extensive updates to the website were made including a new domain name, www.IntegrativeRD.org. New categories including research updates, genomics information (SNIP updates), Find A DIFM RD, were added. The Natural Standard Database continues to be provided as a member benefit with easier access through www.IntegrativeRD.org.

Student Involvement: Expanded students role in DIFM by having two representatives, Erica Kasuli and Kelly Moltzen who
- participated in monthly conference calls
- initiated Student Speaks column in DIFM Newsletter
- attended and represented DIFM at conferences
- enrolled DIFM on Facebook and Twitter
- authored Student Speaks column in DIFM Newsletter.

Eblasts – Eblasts were sent to members throughout the year to keep members informed of DIFM events and membership benefits.

Newsletters - Four newsletters were published including two with continuing education (CPE) articles and new columns were created including SNIP updates and Students Speak. This was the first year electronic editions were provided.

Banner and Brochure – A state of the art table banner, stand-up banner and brochure were created to market DIFM DPG at meetings including ADA’s Food & Nutrition Conference & Expo (FNCE), state meetings and integrative health care/medicine meetings.

Pre-FNCE Conference – The 2nd Annual Pre-FNCE conference was held, the topic was Detoxification and workshop included DIFM’s Professional Advancement Director, Sheila Dean DSc, RD, LDN, CCN, CDE; Robert Rountree MD, owner and founder of Boulder Wellcare and Medical Director of Xymogen; Belinda Jenks, PhD RD FACN, Director of Scientific Affairs and Nutrition Education at Pharmavite LLC; and Katherine M. Newton PhD, Associate Director of Research, Group Health Research Institute and Affiliate Associate Professor of Epidemiology, University of Washington, Seattle, WA.

CD recordings of the Pre-FNCE Conferences-Pre-FNCE CDs including the 1st annual conference on Gut Health and the 2nd annual conference on Detoxification are available for purchase by members with CPEUs provided.

FNCE Events: DIFM DPG participated in numerous FNCE activities including:
- Integrative and Functional Medicine: Are you Ready?
- Functional Food Tasting co-sponsored with the Vegetarian Resource Group
- Membership Networking Breakfast sponsored by The Lipton Institute of Tea
- Yoga sessions

DIFM Delegate – DIFM DPG Executive Committee supported and appointed DIFM Development Director, Ane Marie Kis MS RD, to represent DIFM RD as the HOD Delegate beginning June 1, 2010.

Networks: New network relationships were established to provide members educational opportunities: American Botanical Council and The International Omega 3 Learning and Education Consortium for Health and Medicine. Other networks were maintained including The Center for Mind Body Medicine (with discounts provided to Food As Medicine) and Institute for Functional Medicine - IFM (discounts provided to IFM Annual Symposium & Applying Functional Medicine in Clinical Practice – AFMCP).

Awards & Stipends - DIFM Annual Awards and Stipends were provided to Rick Hall MS, RD for Excellence in Service, Kathleen Mahan RD, MS, CDE for Excellence in Practice, Laura Palazzolo MS – Student Stipend and Susan A Nichols MS RD CDE CDN – Professional Stipend.

Electronic Mailing Lists (EML) – A DIFM DPG Executive Committee Yahoo EML was formed as a communication forum for the executive committee and the DIFM DPG Integrative RD Yahoo EML was formed as a discussion forum for members and both continue to be in operation.

Mid-Year Meeting and Integrative Healthcare Symposium (IHCS) – A mid-year meeting with focus on DIFM’s Strategic Plan was held in New York City at the same time as the Integrative Healthcare Symposium. DIFM DPG had a booth at and was represented by DIFM DPG EC and members. Strategic contacts and relationships were initiated with external stakeholders in integrative healthcare.

Webinars – Four DIFM DPG webinars were provided to members including three co-sponsored with the Institute for Functional Medicine:
- July 2009- Functional Medicine Approach for Food Intolerances and Allergies by Diana Noland, MPH, RD
- Sept 2009- Functional Nutrition Therapy for Type 2 Diabetes by Sheila Dean DSc, RD, LDN, CCN, CDE (DIFM Professional Advancement Director)
- November 2009- Functional Nutrition Therapy for Fibromyalgia and Other Pain and Fatigue Syndromes by Kathleen L. Mahan, MS, RD, CDE and Coco Newton, MS, RD.
- Nutritional Testing for Integrative and Functional Medicine Clinicians by Elizabeth H Redmond PhD MS RD LD (Incoming DIFM Professional Advancement Chair) co-sponsored by Metametrix was provided in March 2010.

Member Survey – An annual member survey was provided and results were summarized and discussed at the Spring Leadership Retreat in April 2010.

EC Website – An EC only website was established to serve as a library of all DIFM policies, procedures and historical information.

Standards of Practice (SOP) and Standards of Professional Performance Committee (SOPP) - DIFM DPG appointed representatives to a SOP/SOPP committee and have started a framework to develop and continue to work on developing SOP/SOPPs.

Spring Leadership Retreat – The annual Spring Leadership Retreat, held in Buena Vista, CA, was sponsored by the Nutrilite Health Institute. The meeting was attended by Executive and SOP/SOPP committee members, DIFM strategic planning and SOP/SOPP work was conducted.
Stepping it up a notch for DIFM

This year, the theme for Dietitians in Integrative and Functional Medicine seems to have been “stepping it up a notch.” Our fabulous executive committee has worked hard building influential and powerful networks with respected non-profit organizations that have allowed us some wonderful opportunities to advance our education and bring advanced skills to our practice. They have also been working on the ADA Food & Nutrition Conference & Expo (FNCE) events; but not least, we have been involved in composing Standards of Practice (SOP) and Standards of Professional Performance (SOPP). Dietitians can be extremely proud to be a member of DIFM and look forward to the role that the integrative and functional dietitian will be playing in the health and nutrition of America in the future.

The networks that Alicia Trocker, MS RD our network chair, has been developing include, 1) Center for Mind Body Medicine: http://www.cmbm.org/family/ 2) Institute for Functional Medicine: http://www.functionalmedicine.org; 3) American Botanical Council: www.herbalgram.org; 4) Omega 3 Consortium for Education and Learning: http://omega3learning.purdue.edu; and 5) University of Arizona Integrative Medicine http://integrativemedicine.arizona.edu/. With each of these networks, members get incredible discounts for the organizations educational programs. I personally have signed up for several seminars (and enjoying the discounts in registration that the networks allow DIFM members) and I look forward to advancing my skills and knowledge and include them in my practice.

Dr. Elizabeth Redmond PhD MS RD LD, our professional advancement chair, has been coordinating FNCE events and other educational projects. She has been working on the Pre-FNCE workshop 2010 – Cognitive Function Throughout the Life Cycle, Saturday November 6th in Boston. Don’t forget… be sure to register today for the Pre-FNCE Symposium workshop by going to our website: www.integrativeRD.org and when you register, you get a chance to win a free iPad! Hey, encourage your friends to register too! Dr. Redmond has also been developing webinars that are outlined on our website.

Standards of Practice and Professional Performance (SOP/SOPP) is a major accomplishment of our group that will be published in the Journal in the spring. It outlines the skills that DIFM dietitians need to know in an integrative and functional dietitian. As with any skill set, there is responsibility of action and this is a fundamental piece that serves to provide the framework of future certification. Integrative and Functional Medical Nutrition Therapy (IFMNT) is discussed in detail in the SOP/SOPP. Look forward to the Journal publication and ask an EC member about it and the potential certification at Pre-FNCE.

As you can see, we are “stepping it up a notch” and I encourage everyone of you to enjoy all the professional benefits that DIFM is working to bring to you, our members.

Best to you and see you in Boston! Deb.

DIFM Annual Budget Report for 2009-2010
Submitted by Leslie Kay, Treasurer

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Those of you who would like to contribute an article or have topics that you would like to see in future issues, please feel free to drop me an email or give me a call – peaknut@cascadeaccess.com or 702-346-7968 – or contact any one of the capable DIFM leaders listed on the back of the newsletter.