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Fatty Acids and Emotional Behavior

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1. Introduction

Fatty acids are widely distributed in nature. In addition to being found in plants and seeds, these organic compounds are present in other organisms, from unicellular protists to mammals, including humans. The anabolic and catabolic pathways of fatty acids have been identified. They have a well-known function as energy sources in metabolic processes and constitute a fundamental part of cellular membrane structures. Long-chain fatty acids also play a role in inflammatory process. Fatty acids exert their actions by modifying the fluidity of membranes, exerting marked actions on membrane ionic channels, and leading to a reduction in the excitability of cardiac myocytes, thus prompting interest in the study of fatty acids as protectors of cardiac function. Fatty acids exert similar actions on membrane neurons and the modulation of neurotransmission. The role of fatty acids in several psychiatric and neurologic conditions is a topic of current research. Fatty acid deficiency appears to be related to alterations in development, but the results from supplementary diet studies are far from conclusive. Interestingly, fatty acids are present in amniotic fluid, colostrum, and maternal milk in at least two mammalian species (i.e., pigs and humans) and according to both anecdotal and experimental reports appear to produce anxiolytic effects. Additionally, fatty acids exert effects when applied by the olfactory route. Odorant carrier proteins to olfactory receptors are present in maternal fluids and nasal mucosa epithelia. In newborns, fatty acids may also act as olfactory cues for feeding source seeking after exposure during prenatal life, which may constitute an additional function.

2. Overview

Lipids are organic compounds that are insoluble in water but soluble in nonpolar solvents, such as ether and chloroform. Some of these lipids naturally occur in the marine food chain. From an evolutionary ecological perspective, their presence in dinoflagelates, teleosts, amphibians, reptiles, birds, mammalians, and humans is important (Crawford et al., 2009).

In mammals, the highest lipid concentrations occur in adipose tissue, followed by the central nervous system (Carrié et al., 2000). However, lipids are present in all cell types, where they contribute to cell structure and energy storage and participate in many biological processes, such as gene transcription, the regulation of metabolic pathways, and other physiological processes (Gurr et al., 2002).

The biological functions of lipids are as diverse as their chemistry. Fats and oils are the main forms of energy storage in many organisms, and phospholipids and sterols are the major structural elements of biological membranes. Other lipids, although present in relatively small amounts, play a crucial role in the composition of enzymatic cofactors, electron carriers, light pigments, membrane protein folding, digestive tract emulsifiers, hormones, and intracellular messengers (Nelson & Cox, 2005). Fatty acids are the main component of phospholipids, triglycerides, and cholesterol esters (Agostoni & Bruzzese, 1992).

2.1 Definition and classification

Fatty acids are aliphatic carboxylic acids composed of four to 36 carbon chains and a variable degree of unsaturation, ending in a carboxyl group (Berg et al., 2003; Nelson & Cox, 2005). The moiety of carbon chains can be short (2-4 carbons), medium (6-12 carbons), long (14-18 carbons), and very long (derived from 18 carbon molecules; Agostoni & Bruzzese, 1992). The hydrocarbon chain can be saturated or may have one or more double unsaturated bonds (Bézard et al., 1994). Based on the number of unstaurations, the hydrocarbon chain may constitute monounsaturated fatty acids (MUFA) or polyunsaturated fatty acids (PUFA; Agostoni & Bruzzese, 1992; Bézard et al., 1994). The classification of PUFA is based on the location of the last double-bond near the methyl end, yielding the typical location n-3 or n-6. However, mammals cannot introduce double-bonds between C-9 and the methyl end of fatty acids; thus, mammals are not able to synthesize n-3 or n-6 PUFA or convert n-3 PUFAs into n-6 PUFAs or vice versa (Bézard et al., 1994; Colin et al., 2003; Dobryniewski et al., 2007). Instead, n-3 and n-6 PUFA are derived from other fatty acids that act as precursors (Stulnig, 2003). n-3 and n-6 PUFA can be synthesized from the precursors linoleic acid (18:2) and α-linolenic acid (18:3), which in turn may be synthesized from shorter-chain fatty acids, such as palmitic acid (C16:0; Cunnane et al., 1995). Similarly, saturated fatty acids (SFA) and MUFA can be synthesized from acetate precursors (e.g., carbohydrates, glycogenic amino acids) and PUFA (Brenna et al., 2009).

2.2 General properties

Fatty acids are esters in natural fats and oils but also exist in non-esterified forms, such as free fatty acids, that circulate in the blood of vertebrates via noncovalent bonds with the carrier protein serum albumin. Typically, the most abundant fatty acids have carbon chains from 14 to 24 atoms, although the most abundant fatty acids contain 16 to 18 atoms. In nature, the most abundant are unsaturated fatty acids, followed by saturated, with double-bonds and a *cis* configuration (Berg et al., 2003; Nelson & Cox, 2005). The *cis* configuration can be converted to the *trans* form by catalytic heating. Saturated fatty acids are very stable, whereas unsaturated acids are susceptible to oxidation (i.e., the more double-bonds, the higher susceptibility to oxidation; Gurr et al., 2002).

2.3 Physical and chemical properties

The physical properties of fatty acids are related to the length of their carbon chain and unsaturation. The nonpolar characteristics of the hydrocarbon chain explain the poor solubility of fatty acids in water. The polar carboxylic acid group (ionized at neutral pH) explains the poor solubility of short-chain fatty acids in water (Berg et al., 2003; Nelson & Cox, 2005). Likewise, longer chains have a higher melting point. Unsaturated fatty acids have a melting point that is lower than that of saturated fatty acids of the same length (Berg et al., 2003; Nelson & Cox, 2005).

2.4 Anabolic processes

The biotransformation process of fatty acids has been summarized by Nelson and Cox (2005). The synthesis of fatty acids may occur by *de novo* synthesis or modification of the carbon chain (Gurr et al., 2002). In *de novo* synthesis, fatty acids are synthesized from pyruvate, the final product of glycolysis, with the participation of a three-carbon intermediary and malonyl-CoA, an irreversible catalytic product of acetyl-CoA (Gurr et al., 2002).

The assembly of the carbon chains of fatty acids occurs through a four-step sequence. A saturated acyl group is the substrate for subsequent condensation with an activated malonyl group. With each step of the cycle, the acyl chain is extended by two carbons. The cycle is completed with the formation of a chain of 16 carbons (i.e., palmitic acid [C16:0], an SFA). Carbons C-16 and C-15 from palmitic acid are derived from the carboxyl and methyl carbons, respectively, of an acetyl-CoA. Other carbons are derived from acetyl-CoA via malonyl-CoA. NADPH acts as a reducing agent, and the two SH groups that are bound to the enzyme are the active group. All reactions in the synthesis are catalyzed by a multienzymatic complex, fatty acid synthase.

Palmitic acid is the terminal product in fatty acid synthesis in animal cells and is the precursor SFA and MUFA through elongation of the carbon chain. Palmitic acid (16:0) can be elongated to form stearate (18:0) or a longer carbon chain through the addition of acetyl groups with the participation of elongase enzymes. The process occurs via two elongation systems located in the mitochondria and smooth endoplasmic reticulum from the liver, brain, and some other tissues (Gurr et al., 2002).

One of the most important functions of elongation is the conversion of essential fatty acids into PUFA (Gurr et al., 2002). However, these fatty acids cannot be synthesized by mammalian cells and must be obtained from the diet as linoleic acid (18:2) and α-linolenic acid (18:3) to be transformed into PUFA, such as dihomo-γ-linolenic acid (18:3), arachidonic acid (20:4), eicosapentaenoic acid (20:5), and docosahexaenoic acid (DHA; 22:6; Haggarty, 2002).

A second mechanism for the synthesis of fatty acids is desaturation (Gurr et al., 2002). Palmitic acid and stearic acid serve as the precursors of two of the most common MUFA in animal tissues (i.e., palmitoleic acid [16:1] and oleic acid [18:1]), which have a *cis* double-bond between C-9 and C-10. The double-bond is introduced into the fatty acid chain by an oxidative reaction with the participation of O_2, NADH, and three proteins: cytochrome b5, a

flavoprotein (cytochrome b5 reductase), and the enzyme acyl-CoA desaturase, which catalyzes the reaction and acts at specific positions in the fatty acid carbon chain (Sprecher et al., 1995). Mammals have two types of desaturases: stearoyl-CoA desaturase (which catalyzes the synthesis of MUFA) and A5D/A6D desaturases (which participate in the biosynthesis of PUFA; Sampath & Ntambi, 2005).

2.5 Catabolic processes

β-oxidation is the conversion of fatty acids to acetyl-CoA and is the main source of energy for most organisms. Its name derives from the position of the carbon attacked in the acyl chain, and the process occurs in the mitochondria and peroxisomes (Gurr et al., 2002). β-oxidation occurs in three stages. In the first stage, the fatty acids lose two carbon units by oxidative removal, starting from the carboxyl group and ending in the acyl chain. For example, palmitic acid undergoes seven steps in the oxidative sequence and at each step loses two carbons as acetyl-CoA. At the end of seventh cycle, the C-15 and C-16 palmitic acid carbons still remain as acetyl-CoA. The final result is the conversion of the 16-carbon chain of palmitic acid into eight two-carbon acetyl groups in acetyl-CoA molecules. The formation of acetyl-CoA requires the removal of four hydrogen atoms (two pairs of electrons and four H^+) in the middle of the acyl group by dehydrogenases.

In the second stage of oxidation, the acetyl groups of acetyl-CoA are oxidized in the mitochondrial matrix into CO_2 in the citric acid cycle. Thus acetyl-CoA derived from fatty acids enters the final stage of the oxidation of acetyl-CoA derived from glucose via glycolysis and pyruvate oxidation. The first two stages of oxidation produce NADH and FADH2, which in the third stage donate electrons to the respiratory chain, and electrons pass to oxygen, resulting in the phosphorylation of ADP to ATP; thus, the result of the β-oxidation of fatty acids is ATP.

2.6 Physiological role

Fatty acids are involved in energetic, metabolic, and structural processes. Short-chain fatty acids act as growth factors. Long saturated chains are a source of energy, and long-chain unsaturated chains participate in fundamental metabolic processes (Agostoni & Bruzzese, 1992), such as the synthesis of eicosanoids, which are closely related to inflammatory processes (Mesa-García et al., 2006; Zamaria, 2004), the modulation of enzymatic activity, the activation of nuclear transcription factors, and the formation of free radicals in response to oxidative stress (Zamaria, 2004).

Very long-chain molecules constitute biological membranes and participate in development (Agostoni & Bruzzese, 1992). n-3 PUFA (linolenic acid) and n-6 PUFA (linoleic acid; Bézard et al., 1994; Colin et al., 2003; Sardesai, 1992; Sinclair, 1984) are structural components of all tissues and indispensable for the synthesis of the cell membrane (Uauy et al., 2000).

2.7 Mechanism of action on excitable tissues

Fatty acids accumulate in membrane phospholipids near the ion channel, which alters the tension of the membrane, causes conformational changes in the ion channel, and consequently alters its conductance (Leaf et al., 2002). Two forms of Na^+/K^+-ATPase

catalytic subunits are present in the nervous system. The α form is present in astrocytes, glial cells, and other tissues and is seemingly related to K^+ clearance. The α+ subunit is present in neuronal tissue, possesses high affinity for cardiac glycosides, is stimulated by biogenic amines, and participates in Na^+ and K^+ transport. In addition to the well known role of the Na^+/K^+ pump in resting membrane potential, it also participates in the differentiation of nerve cells during neurulation (Stahl, 1986). The modulation of membrane protein function by molecules that possess both hydrophilic and hydrophobic ends has been ascribed to changes in bilayer fluidity and alterations in bilayer stiffness. For example, *N*-type calcium channels may be modulated by a decrease in bilayer stiffness (Lundbaek et al., 1996).

Because of the reputation of PUFA as cardiac protectors, many studies have explored the action of fatty acids on cardiac myocytes. In these cells, n-3 and n-6 PUFA (DHA, α-linolenic acid, arachidonic acid, and linoleic acid) but not *trans* MUFA or SFA reduce Na^+ currents (Xiao et al., 1995). Free PUFA modulate voltage-sensitive Na^+ channels through the inhibition of agonist binding to the Na^+ channel protein in a dose-dependent, saturable, reversible, and allosteric manner (Kang & Leaf, 1996) but do not upregulate cardiac Na^+ channel expression in the long-term (Kang et al., 1997). Although PUFA may produce supraventricular and ventricular arrhythmias, its anti-arrhythmic properties are attributable to inhibition of Na^+ voltage-dependent currents, leading to hyperpolarization and reducing the availability and release of Ca^{2+} and sharing some actions with lidocaine (Lombardi & Terranova, 2007; Xiao et al., 1997, 1998). In other tissues, such as human fetal tracheal cells, *cis* PUFA and MUFA (e.g., arachidonic acid, linoleic acid, and oleic acid) but not SFA (e.g., stearic acid, palmitic acid, and myristic acid) modulate Cl^- channel activity by interrupting the open channel current (Hwang et al., 1990). In smooth muscle cells, arachidonic acid, oleic acid, myristic acid, and linoleic acid but not myristoleic acid, caprylic acid, or palmitic acid activate K^+ currents (Ordway et al., 1989; Robertson & Steinberg, 1990), also producing hyperpolarization.

The motor cortex of the human brain contains primarily long-chain fatty acids, such as arachidonic acid (C20:4n-6) and DHA (C22:6n-3). Other shorter-chain fatty acids are more likely to be involved in vascular blood flow, and eicosanoid activity involved in responses to injury. In animals, through alternative processes of desaturation and elongation, arachidonic acid may be formed from linoleic acid (18:2n-6), and DHA may be formed from α-linolenic acid (18:3n-3) but in a relatively inefficient manner because of the characteristics of being rate limited and very slow. Therefore, its ingestion in the diet seems to be crucial. Double-blind, controlled studies are needed before reaching conclusions about the properties of PUFA as cardiac protectors.

Intriguing results have been found regarding the actions of fatty acids in nervous tissue. Fatty acids regulate ion channels (Ordway et al., 1991) and can be delivered to the cells from extracellular sources, such as albumin and lipoproteins (Ordway et al., 1991). Fatty acids can enter the brain and exert their effects on neurons when administered systemically (Lauritzen et al., 2000). PUFA easily cross the blood-brain barrier and accumulate in neuronal membranes (Robinson & Rapoport, 1986). Arachidonic acid and other fatty acids regulate ion channels themselves through direct action or indirectly through their metabolites (Ordway et al., 1991). Likewise, at least one *cis* MUFA (oleic acid), one n-6 PUFA

(arachidonic acid), and one n-3 PUFA (DHA) increase the binding of [^{3}H]diazepam to the benzodiazepine/γ-aminobutyric acid (GABA) receptor (Nielsen et al., 1988). Long-term ethanol or diazepam administration increases the proportions of plasma SFA and MUFA and decreases PUFA (Ristic et al., 1995). Therefore, some anxiolytic action may be expected.

The inhibition of GABA neurotransmission by arachidonic acid or its peroxidized metabolites contributes to the pathogenesis of ischemia-perfusion neuronal injury because the accumulation of these n-3 PUFA (but not SFA) inhibits GABA-mediated neuronal inhibition, leading to increased neuronal excitability (Schwartz & Yu, 1992). This may be related to the observation that barbiturates produce a Ca^{2+}-dependent decrease in Cl^- flux through the $GABA_A$ receptor, which is reduced by phospholipase A2 (Schwartz et al., 1988), leading to the increased formation of oxygen free radicals and consequently apoptosis. Interestingly, in the hippocampus, arachidonic acid helps maintain membrane fluidity (Fukaya et al., 2007) and enhances synaptic transmission (Williams et al., 1989). PUFA but not MUFA or SFA inactivate Na^+ currents, reducing neuronal firing and increasing their refractory period in CA1 neurons (Vreugdenhil et al., 1996).

In neuroblastoma/glioma hybrid cell culture studies, PUFA (e.g., linoleic acid, linolenic acid, and arachidonic acid) decrease Na^+ action potentials. One *trans* MUFA (i.e., oleic acid) does not produce such changes, and one SFA (i.e., palmitic acid) and one *trans* MUFA (i.e., elaidic acid) increase the frequency and amplitude of action potentials without influencing resting membrane potentials, Ca^{2+} action potentials, or membrane capacitance (Love et al., 1985).

Arachidonic acid also appears to modulate the activity of cytosolic protein kinase C by selective induction of phosphorylation, modulating transmembrane signaling (Khan et al., 1991). The fluidity of the acyl chains of fatty acids present in the bulk of membrane phospholipids modulates enzymatic activity (Harris, 1985).

In summary, n-3 PUFA modify some membrane functions, such as ion channel modulation, by increasing membrane fluidity (Simopoulos, 1999). The ion channel modulation exerted by fatty acids is very similar to that produced by local anesthetics, such lidocaine (Bean et al., 1983), and some anticonvulsant drugs, such as phenytoin (Rogawski & Porter, 1990; Schwartz & Grigat, 1989). The activation of several neurotransmitter receptors, such as dopamine D_2, 5-hydroxytryptamine-3, and opioids, alters the membrane flux of K^+ (Drukarch et al., 1989; Miyake et al., 1989). Some of the known effects of DHA include changes in membrane fluidity and stability (Litman et al., 2001), changes in dopaminergic and serotonergic transmission (Chalon et al., 2001; Zimmer et al., 2000, 2002), and the regulation of membrane-bound enzymes and cellular signal transduction (McNamara et al., 2006; Vaidyanathan et al., 1994).

2.8 Clinical aspects

The role of essential fatty acids in mammals was long been unknown, but more similarities than discrepancies appear to exist between the general actions of SFA, MUFA, and PUFA on diet pleasantness, visual appearance, smell, taste, aftertaste, and palatability, subjective hunger ratings, and energy intake in healthy males (Strik et al., 2010). Differences can be found with regard to undesirable effects. With regard to cholesterolemia, no differences

were found between diets rich in MUFA and PUFA, but a SFA-rich diet produced the highest cholesterol concentrations (Trautwein et al., 1999). Decades ago, fatty acids were perceived as precursors for the biosynthesis of other substances (e.g., those related to inflammatory processes) and other fatty acids (Friesen & Innis, 2006) that are components of the cell membrane (Carrié et al., 2000) may participate in many functional processes (Kidd, 2007).

2.9 Development

Docosahexaenoic acid is the main n-3 PUFA found in the phospholipid fraction of the brain and has been implicated in the prenatal and postnatal development of the retina and brain (Hamazaki et al., 1996; McCann & Ames, 2005; SanGiovanni et al., 2000). Deficiencies in DHA during development are related to deficits in the structure of the retina, impairing visual acuity and cognitive function (Crawford, 1993; Neuringer et al., 1986; Reisbick et al., 1997).

During pregnancy, dietary *trans* fatty acids (e.g., elaidic acid) produce deleterious effects on health. The most abundant long-chain fatty acids in breast milk are DHA and arachidonic acid. Supplementation with marine oil products does not produce adverse effects and improves sensorial function and other cognitive functions after birth (Brenna & Lapillonne, 2009). Supplementation with DHA in infants that are less than 1 year old improves seeking behavior that later it is related to increased exploratory activity and less distractibility (Colombo et al., 2004). A DNA microarray study of the brain in rats subjected to different diets that contained different amounts of n-3 PUFA found some deficiencies in the expression of several genes, which became up- or downregulated and were related to the expression of cytochrome c and tumor necrosis factor (Kitajka et al., 2004). Maternal dietary SFA may produce persistent alterations in Na^+,K^+-ATPase function in the offspring, which could increase the risk of adulthood disease (Armitage et al., 2008).

2.10 Cognitive impairment

Decreased plasma levels of n-6 PUFA have been associated with physical rather than cognitive or behavioral ailments (Richardson, 2006). Deficiencies in DHA and eicosapentaenoic acid are involved in behavioral problems, such as attention deficit hyperactivity disorder, autism, dyspraxia, dyslexia, and aggression (Richardson, 2006; Stevens et al., 1996), and affective disorders, such as major depressive disorder, bipolar disorder, schizophrenia, and personality disorder. Evidence of altered PUFA status in mental illness, however, is weak. Reports of symptom improvement after PUFA consumption included patients with previous generalized dietary deficiencies of fatty acids (Liperoti et al., 2009; Milte et al., 2009) or other deleterious lifestyle habits (Suominen-Taipale et al., 2010), thus contaminating the interpretation of the data. n-3 PUFA supplementation appears to be effective only in depressive or Alzheimer's carriers of non-apolipoprotein E epsilon4 (Solfrizzi et al., 2010). In animal models of Alzheimer's disease, SFA and n-3 PUFA, including arachidonic acid, produced higher secretion of both Aβ-40 and -42 peptides compared with long-chain downstream omega-3 and MUFA. Lower levels of Aβ and amyloid plaques in the brain were observed when the subjects were fed a low-fat diet enriched with DHA (Amtul et al., 2011).

Some promising reports of the beneficial effects of n-3 PUFA on Alzheimer's disease and Huntington's disease showed that fatty acids appear to be devoid of any effect on cognition, aggression, hostility, and social behavior (Crawford et al., 2009).

2.11 Depression

Reports of the effects of fatty acids on depression have been controversial. For example, in an open-label study, juvenile bipolar disorder patients received supplementary eicosapentaenoic acid and DHA in their diet and exhibited a reduction in their clinical symptoms (Clayton et al., 2009). However, diets enriched with DHA failed to prevent postpartum depression in a randomized controlled trial (Makrides et al., 2010).

However, some intriguing results have been found. Membrane viscosity plays a role in the molecular bases of depression and other disorders and mediates the pharmacology of serotonin. Depression has been associated with low lipid raft viscosity (Cocchi et al., 2010a). The hydroxytrytophan transporter responsible for serotonin reuptake may be the functional locus for depression (Rosen, 2009), and an inverse relationship has been found between arachidonic acid content in neural tissue and the accessibility of serotonin to its receptors. However, an increase in arachidonic acid in brain tissue reduced membrane viscosity (i.e., increased fluidity; Cocchi et al., 2010b), reducing the accessibility of serotonin to its receptors (Heron et al., 1980). The brains of Flinders Sensitive rats, an animal model of depression, contain high concentrations of arachidonic acid (Green et al., 2005).

2.12 Calming effects of maternal biological fluids

Some odors can elicit a sense of family and home safety in adult mammals. Schapiro and Salas (1970) demonstrated that exposure to maternal odors in rat pups before weaning reduced the movements of pups. Oswalt and Meier (1975) found that infant rats reduce their emission of ultrasonic vocalizations when exposed to maternal odors. Therefore, maternal litter or home odors produce signs of calm. In contrast, kittens, pups, and human babies exhibit increased agitation and vocalizations when placed in an unfamiliar environment, but when they return to their nest or close proximity to their mother, both familiar odors, they calm down (Christensson et al., 1995; Michelsson et al., 1996; Schaal, 1988). The application of amniotic fluid odor to the nose significantly reduced crying in human babies when they were separated from their mothers (Varendi et al., 1998). Sullivan and Toubas (1998) suggested that maternal odors could be used to calm and reduce crying in babies. These fluids may be used to promote the acceptance of nipple feeding (Sullivan & Toubas, 1998) because breast milk odors (Rattaz et al., 2005) and milk odor (Nishitani et al., 2009) produce signs of calm. Olfactory exposure to maternal biological fluids (i.e., amniotic fluid, colostrum, and breast milk) appears to promote breastfeeding (Winberg & Porter, 1998).

Any odorant molecule requires a binding carrier protein with high affinity for membrane olfactory receptor neurons (Pelosi, 2001). Guiraudie-Capraz et al. (2005) used gas chromatography-mass spectrometry (GC-MS) to identify seven fatty acids (i.e., linoleic acid, palmitic acid, lauric acid, capric acid, myristic acid, palmitoleic acid, and oleic acids) in breast milk, colostrum, and amniotic fluid in pigs. Three carrier proteins were found not only in amniotic fluid, colostrum, and milk, but also in nasal mucosa and the vomeronasal organ, which seemingly mediate the fatty acid-induced initiation of perception (Guiraudie-

Capraz et al., 2003; Tegoni et al., 2000) with different affinities (Guiraudie-Capraz et al., 2003). Therefore, these proteins participate in the detection of chemical and biochemical signals, at least in pigs (Guiraudie-Capraz et al., 2005). Notably, these proteins have also been found in human amniotic fluid (Liberatori et al., 1997) and colostrum (Murakami et al., 1998), suggesting the stimulation of olfactory receptors very early in life, even during intrauterine life.

2.13 Fatty acids and anxiety

Few studies have compared the effects of n-3 and n-6 fatty acids on behavior. Although better results have been found in animals that received n-3 fatty acids than n-6 fatty acids (Wainwright, 1992), the absence of control groups prevents the acceptance of the results. Another study sought to find a relationship between essential fatty acids and behavior. Nakashima et al. (1993) used the elevated plus maze to assess anxiolytic-like behavior in rodents. In this study, linoleic acid produced a trend toward anxiolysis compared with α-linolenic acid, but this study also lacked a control group.

In humans, Mamalakis et al. (1998) did not find any relationship between linoleic acid and myristic acid and anxiety measured with the Spielberg scale or trait anxiety measured and Zung scales. However, they detected a positive relationship between trait anxiety scores and the linoleic acid + α-linolenic acid / DHA + arachidonic acid ratio (Mills et al., 1994). However, a mixture of PUFA may reduce anxiety scores, reflected by increased appetite, increased sense of humor, increased strength, decreased fatigue, increased academic performance, decreased lack of sleep, and decreased plasma cortisol (Yehuda et al., 2005).

Pageat (2001) patented a product whose active ingredient is a mixture of fatty acids that has been used to decrease stress, anxiety, and aggression in mammals, such as pigs, dogs, cats, and even children, and reduce anxiety signs when the animals are separated from their mother or in an unfamiliar place. The same formulation was tested by McGlone and Anderson (2002) on weight gain, feeding efficiency, and agonistic behavior in piglets.

We recently used GC-MS to demonstrate that human amniotic fluid, colostrum, and maternal milk consistently contain eight fatty acids (Mendoza-López et al., 2010). Both human amniotic fluid and an artificial mixture of the same proportion of fatty acids produced anxiolytic effects comparable to diazepam in Wistar rats subjected to validated tests that measure anxiety, including the defensive burying test and elevated plus maze. We concluded that amniotic fluid and its fatty acids have anxiolytic effects (Contreras et al., 2011).

2.14 Fatty acids as feeding cues

Newborns are attracted to odors that come from their mother's breast (Porter & Winberg, 1999), milk, colostrum (Nowak et al., 2000), and amniotic fluid (Porter & Winberg, 1999; Schaal et al., 1998). This behavior could be related to the fact that during the last trimester, the odorants in amniotic fluid are in close contact with nasal chemoreceptors. Newborn infants may retain an olfactory memory of these odors and later respond to these signals during the early postnatal period (Hepper, 1995).

Amniotic fluid is a complex mixture of fetal and maternal fluid (Lev & Orlic, 1972). Its composition varies according to gestational age and the evolution of maternal-fetal

exchange. During early pregnancy, amniotic fluid is predominantly an ultrafiltrate of maternal serum. During late pregnancy, fetal urine is the main constituent of amniotic fluid (Loughhead et al., 2006).

Newborns oriented longer time to the odor of their own amniotic fluid compared with an unscented control (Schaal et al., 1995; Varendi et al., 1996). Recently, Contreras et al. (2011) analyzed the amniotic fluid, colostrum, and breast milk of 15 volunteer women. Eight fatty acids were consistently found in measurable amounts in the three biological fluids, including lauric acid, myristic acid, palmitic acid, palmitoleic acid, stearic acid, oleic acid, elaidic acid, and linoleic acid. The total amounts of fatty acids were different in each fluid, with the lowest amount found in amniotic fluid, followed by colostrum and milk. These results suggest that similar to other mammalian species (Guiraudie-Capraz et al., 2005; Pageat, 2001), some fatty acids present in biological fluids could serve as sensory cues of maternal and child identification. Additionally, newborns younger than 24 h preferentially orientated toward their own amniotic fluid and an artificial mixture of similar fatty acids (Díaz-Marte et al., 2010). This suggests that the first recognition of odors occurs during intrauterine life. Some of the fatty acids present in amniotic fluid could be a source of prenatal sensory stimulation, and colostrum odor is a bridge between amniotic fluid and milk (Contreras et al., 2011), thus leading to feeding behavior. Therefore, fatty acids could act as feeding cues, leading to appetitive behavior.

3. Conclusions

1. The functions of fatty acids as energy sources and their structural role in cellular membranes and as precursors of inflammatory processes are well known.
2. Fatty acids may modify the fluidity of the lipid membrane of cardiac and neuronal cells, impinging on ion channel permeability and decreasing cellular excitability. These conformational changes in the membrane may also modulate some neurotransmitter functions.
3. Decreased excitability produced by long-chain PUFA is related to some beneficial effects on cardiac function.
4. Similar actions on cardiac cell membranes appear to occur in neurons, in addition to neurotransmitter modulation. Some clinical studies of the therapeutic effects of fatty acids on neurological and psychiatric diseases have been conducted, but most of these studies need to be replicated using double-blind controlled designs before definitive conclusions can be made.
5. Fatty acids are components of amniotic fluid, colostrum, and milk and produce some anxiolytic effects.
6. The sensorial process of odor recognition related to fatty acids has been identified.
7. Fatty acids in maternal-fetal fluids appear to act as feeding cues that guide newborns to the maternal breast.

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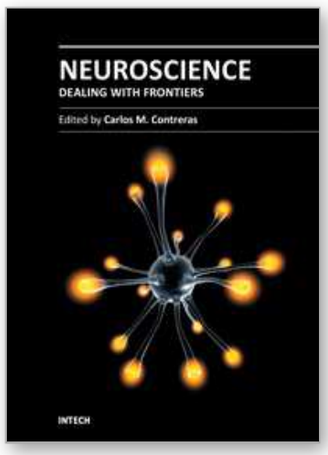

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The Neuronal Doctrine recently reached its 100th year and together with the development of psychopharmacology by the middle of 20th century promoted spectacular developments in the knowledge of the biological bases of behavior. The overwhelming amount of data accumulated, forced the division of neuroscience into several subdisciplines, but this division needs to dissolve in the 21st century and focus on specific processes that involve diverse methodological and theoretical approaches. The chapters contained in this book illustrate that neuroscience converges in the search for sound answers to several questions, including the pathways followed by cells, how individuals communicate with each other, inflammation, learning and memory, the development of drug dependence, and approaches to explaining the processes that underlie two highly incapacitating chronic degenerative illnesses.

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