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[Lipids, depression and suicide]

[Article in French]

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Polyunsatured fatty acids are made out of a hydrocarbonated chain of variable length with several double bonds. The position of the first double bond (omega) differentiates polyunsatured omega 3 fatty acids (for example: alpha-linolenic acid or alpha-LNA) and polyunsatured omega 6 fatty acids (for example: linoleic acid or LA). These two classes of fatty acids are said to be essential because they cannot be synthetised by the organism and have to be taken from alimentation. The omega 3 are present in linseed oil, nuts, soya beans, wheat and cold water fish whereas omega 6 are present in maize, sunflower and sesame oil. Fatty acids are part of phospholipids and, consequently, of all biological membranes. The membrane fluidity, of crucial importance for its functioning, depends on its lipidic components. Phospholipids composed of chains of polyunsatured fatty acids increase the membrane fluidity because, by bending some chains, double bonds prevent them from compacting themselves perfectly. Membrane fluidity is also determined by the phospholipids/free cholesterol ratio, as cholesterol increases membrane viscosity. A diet based on a high proportion of essential polyunsatured fatty acids (fluid) would allow a higher incorporation of cholesterol (rigid) in the membranes to balance their fluidity, which would contribute to lower blood cholesterol levels. Brain membranes have a very high content in essential polyunsatured fatty acids for which they depend on alimentation. Any dietary lack of essential polyunsatured fatty acids has consequences on cerebral development, modifying the activity of enzymes of the cerebral membranes and decreasing efficiency in learning tasks. EPIDEMIOLOGICAL DATA: The prevalence of depression seems to increase continuously since the beginning of the century. Though different factors most probably contribute to this evolution, it has been suggested that it could be related to an evolution of alimentary patterns in the Western world, in which polyunsatured omega 3 fatty acids contained in fish, game and vegetables have been largely replaced by polyunsatured omega 6 fatty acids of cereal oils. Some epidemiological data support the hypothesis of a relation between lower depression and/or suicide rates and a higher consumption of fish. These data do not however prove a relation of causality. CHOLESTEROL AND DEPRESSION: Several cohort studies (on

nondepressed subjects) have assessed the relationship between plasma cholesterol and depressive symptoms with contradictory results. Though some results found a significant relationship between a decrease of total cholesterol and high scores of depression, some other did not. Studies among patients suffering from major depression signalled more constantly an association between low cholesterol and major depression. Besides, some trials showed that clinical recovery may be associated with a significant increase of total cholesterol. CHOLESTEROL AND SUICIDAL BEHAVIOR: The hypothesis that a low cholesterol level may represent a suicidal risk factor was discovered accidentally following a series of epidemiological studies which revealed an increase of the suicidal risk among subjects with a low cholesterol level. Though some contradictory studies do exist, this relationship has been confirmed by several subsequent cohort studies. These findings have challenged the vast public health programs aimed at promoting the decrease of cholesterol, and even suggested to suspend the administration of lipid lowering drugs. Recent clinical studies on populations treated with lipid lowering drugs showed nevertheless a lack of significant increase of mortality, either by suicide or accident. In addition, several controlled studies among psychiatric patients revealed a decrease of the concentrations of plasma cholesterol among patients who had attempted suicide in comparison with other patients. POLYUNSATURATED FATTY ACID AND DEPRESSION: In major depression, all studies revealed a significant decrease of the polyunsaturated omega 3 fatty acids and/or an increase of the omega 6/omega 3 ratio in plasma and/or in the membranes of the red cells. In addition, two studies found a higher severity of depression when the level of polyunsaturated omega 3 fatty acids or the ratio omega 3/omega 6 was low. Parallel to these modifications, other biochemical perturbations have been reported in major depression, particularly an activation of the inflammatory response system, resulting in an increase of the pro-inflammatory cytokines (interleukins: IL-1b, IL-6 and interferon g) and eicosanoids (among others, prostaglandin E2) in the blood and the CSF of depressed patients. These substances cause a peroxidation and, consequently a catabolism of membrane phospholipids, among others those containing polyunsaturated fatty acids. The cytokines and eicosanoids derive from polyunsaturated fatty acids and have opposite physiological functions according to their omega 3 or omega 6 precursor. Arachidonic acid (omega 6) is, among others, precursor of pro-inflammatory prostaglandin E2 (PGE2), whereas polyunsaturated omega 3 fatty acids inhibit the formation of PGE2. It has been shown that a dietary increase of polyunsaturated omega 3 fatty acids reduced strongly the production of IL-1 beta, IL-2, IL-6 and TNF-alpha (tumor necrosis factor-alpha). In contrast, diets with a higher supply of linoleic acid (omega 6) increased significantly the production of pro-inflammatory cytokines, like TNF-alpha. Therefore, polyunsaturated omega 3 fatty acids could be associated at different levels in the pathophysiology of major depression, on the one hand through their role in the membrane fluidity which influences diverse steps of neurotransmission and, on the other hand, through their function as precursor of pro-inflammatory cytokines and eicosanoids disturbing neurotransmission. In addition, antidepressants could exhibit an immunoregulating effect by reducing the release of pro-inflammatory cytokines, by increasing the release of endogenous antagonists of pro-inflammatory cytokines like IL-10 and, finally, by acting like inhibitors of cyclo-oxygenase. THERAPEUTIC USE OF FATTY ACIDS: Data available concerning the administration of supplements of DHA (docosahexanoic acid) or other polyunsaturated

fatty acids omega 3 are limited. In a double blind placebo-controlled study on 30 patients with bipolar disorder, the addition of polyunsaturated omega 3 fatty acids was associated with a longer period of remission. Moreover, nearly all the other prognosis measures were better in the omega 3 group. Very recently, a controlled trial showed the benefits of adding an omega 3 fatty acid, eicosopentanoic acid, among depressed patients. After 4 weeks, six of the 10 patients receiving the fatty acid were considered as responders in comparison with only one of the ten patients receiving placebo. CONCLUSIONS: Some epidemiological, experimental and clinical data favour the hypothesis that polyunsaturated fatty acids could play a role in the pathogenesis and/or the treatment of depression. More studies however are needed in order to better precise the actual implication of those biochemical factors among the various aspects of depressive illness.

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