



### n-3 Fatty acids and the endocannabinoid system

Dear Sir:

Carpentier et al (1) mentioned in a recent issue of the Journal that the pleiotrophic effects of n-3 polyunsaturated fatty acids (PUFAs) decrease the burden of the metabolic syndrome, which prevails in Western countries and is related to the epidemic of obesity. In large epidemiologic studies, persons who consume higher amounts of fish also consume higher amounts of total calories but are not more obese, although the levels of exercise are similar in both Western countries (2, 3) and in Japan (4). Previously, I speculated that, at least in part, the beneficial effects of fish oil on obesity and obesity-related metabolic risk factors may be related to long-chain monounsaturated fatty acids (5), which may have relatively high ligand activities on peroxisome proliferator-activated receptor delta (6). Recently, Horvath (7) reviewed the effects of the endocannabinoid system on energy homeostasis and pointed out that the initial anorectic effect of the cannabinoid receptor 1 (CB1) antagonist, rimonabant, is diminished after the first weeks, whereas longer lasting weight loss is achieved. These findings indicate that the peripheral metabolic actions of cannabinoids are very important in body weight regulation. It is possible that n-3 PUFAs may act as competitive inhibitors in the peripheral endocannabinoid system, thereby promoting energy metabolism and exerting antiobesity and anti-inflammatory effects. Two major CB1 agonists—anandamide (arachidonoyl ethanolamine) and 2-arachidonoyl glycerol—are n-6 PUFA derivatives, whereas n-3 and n-6 PUFAs are competitors as components of cell membrane phospholipids and in many biochemical pathways, such as eicosanoids and leukotrienes. At least in the brain of mice, n-3 PUFA deficiency elevates and n-3 PUFA enrichment reduces 2-arachidonoyl glycerol concentrations (8).

The author had no conflict of interest.

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### Reply to E Oda

Dear Sir:

The comments of Oda concerning our article on the role of n-3 polyunsaturated fatty acids (PUFAs) in the metabolic syndrome (1) are well understood. Oda speculates that the beneficial effects of n-3 fatty acids in the metabolic syndrome would result (at least in part) from an inhibition of the peripheral endocannabinoid system, with long-lasting effects on body weight regulation. Indeed, some arachidonoyl derivatives may act as agonists of cannabinoid receptor 1 (CB 1). Changes in n-3 PUFA intakes markedly affect arachidonic acid (20:4n-6) concentrations in different tissues and may alter the activation of the CB 1 system. For instance, the data provided in Table 1 indicate that the relative concentration of C20:4n-6 is significantly increased in the brain, liver, soleus muscle, heart muscle and heart endothelium of second generation n-3-depleted rats, as recently studied in our laboratory. In addition, n-3 and n-6 PUFAs may exert opposing effects on the endocannabinoid system, but this remains to be determined.

Likewise, beneficial effects of n-3 PUFAs on obesity-related metabolic risk factors may result from changes in tissue concentration of specific very long-chain monounsaturated fatty acids, such as 24:1n-9 (nervonic acid). As a matter of fact, we recently observed a decrease in the relative content of C22:1n-9 (the immediate precursor of C24:1n-9) in phospholipids of the brain, soleus muscle, and endocardium (but not liver and cardiomyocytes) of the same second generation n-3-depleted rats, when compared with measurements obtained in control rats of same sex (female) and age (Table 1).

None of the authors had a conflict of interest.