Regulation of endocannabinoid signalling by dietary fatty acids: implications for brain function, obesity and the metabolic syndrome

Vincenzo Di Marzo
Endocannabinoid Research Group, Istituto di Chimica Biomolecolare, CNR, Pozzuoli (NA), Italy (vdimarzo@icmib.na.cnr.it)

Omega-3 polyunsaturated fatty acids (ω-3-PUFA) are known to affect several brain functions, to ameliorate several metabolic risk factors for cardiovascular disease and, at the same time, to alter the tissue levels of arachidonic acid (AA) esterified to phospholipids. During the last decade, we investigated, in collaboration with several research groups, the effects of dietary ω-3-PUFA supplementation on the tissue levels of the endocannabinoids, anandamide and 2-arachidonoylglycerol, two AA-containing, phospholipid-derived mediators that act mostly by stimulating the activity of two G-protein-coupled receptors, the cannabinoid receptors of type 1 and 2 (CB1 and CB2). Since cannabinoid receptors and endocannabinoids are emerging as key players in the control of synaptic function, on the one hand, and metabolism, on the other hand, we have also investigated if prolonged supplementation of food with dietary ω-3-PUFA affects these functions via alterations of this endocannabinoid system.

Studies on the stress response and on metabolic parameters were carried out, following dietary manipulations in rat dams, by means of behavioral observations in pups, or following milk supplementation with ω-3-PUFA in post-natal mice and piglets. Dietary administration of ω-3-PUFA was also carried out in two animal models of obesity (obese Zucker rats and mice with diet-induced obesity) and in a human clinical study. Finally, experiments were also performed in isolated adipocytes, following addition of AA or long chain ω-3-PUFA to the culture medium for 48 hours. In all cases, the tissue levels of endocannabinoids and their AA-containing biosynthetic precursors were measured by different lipid profiling LC-MS techniques.

In general, brain endocannabinoid levels were much less sensitive to dietary ω-3-PUFA supplementation in adult obese rats than in new-born pups of dams treated during gestation and lactation, or than the levels in peripheral tissues and adipocytes. Pups of dams treated with a high fat diet together with ω-3-PUFA as fish oil (FO) exhibited an enhancement of the stress response that was partly associated with changes in hippocampal and hypothalamic endocannabinoid levels. In rodent models of obesity, a tissue-specific reduction of peripheral endocannabinoid levels was observed, especially if ω-3-PUFA were administered as krill oil *vs*. FO. This reduction in endocannabinoid tone was associated with beneficial effects on several parameters of the metabolic syndrome. Levels of AA-containing endocannabinoid biosynthetic precursors were generally down-regulated following ω-3-PUFA supplementation, suggesting that this type of dietary regimen affects the levels of endocannabinoids in part by reducing their biosynthesis.

Overall, our data suggest that prolonged administration of ω-3-PUFA may both contribute to an enhanced stress response in newborns from treated dams, and promote metabolic benefits in treated obese adults, in part by interfering with endocannabinoid biosynthetic precursor availability. The obese animal metabolic data were supported by findings in a recent human clinical trial in overweight participants.