Oleoylethanolamide (OEA)

Much fat is turned into ethanolamides, which act as signaling molecules. For example, converted Arachidonic Acid as a signaling molecule is called AEA (Arachidonoylethanolamide). AEA is an endocannabinoid, triggering cannabinoid receptors in a way that triggers appetite.

Another example is Oleic Acid (as in olive oil), which acts as a signal molecule in the form of OEA (Oleoylethanolamide). OEA activates PPAR-α and can contribute to the initiation of Torpor.

Stearic Acid (as in meat from ruminants (beef, bison, venison, lamb) and some fish), as a signaling molecule (SCA), acts to help break down AEA and OEA by activating FAAH, the enzyme that degrades them (Kasatkina, 2020).

Daniele Piomelli. A Fatty Gut Feeling. Trends Endocrinol Metab. 2013 Jul;24(7):332-41. https://pubmed.ncbi.nlm.nih.gov/23567058/

The ability to sense dietary fat is a critical adaptative function. The high energy density of fat and the essential role of lipids as building blocks of cell membranes, hormones, and many bioactive molecules creates the need to obtain adequate dietary fat, and optimize its storage and utilization. The dietary fat monitoring system begins in the taste buds, where it triggers a potent stimulatory effect on appetite. Simultaneously, the fat in food stimulates subcortical regions of the brain involved in the regulation of reward-oriented behavior, and causes a release of endocannabinoids in the proximal gut. These combined events are important in determining the innate attraction to high-fat foods.

After stimulating appetite, dietary fat also has a contrasting effect in the sense that it has satiety-inducing effects via biosensors in the duodenum and jejunum, which significantly suppress food intake. Both the oral appetite stimulation and the upper intestine satiety response are carried to the subcortical brain and the hypothalamus by Vagal afferents. This series of events involves the gut exocrine hormones cholecystokinin and serotonin, but there is an even more significant role played by fatty acid ethanolamides, particularly the entholamide of Oleic Acid, Oleoylethanolamide (OEA).

When OEA production is maximized, the tendency to continue producing OEA is suppressed as the excess OEA is broken down into its constituent Oleic Acid and Ethanolamine. It is critical to note that excess dietary Oleic Acid, will also suppress the formation of OEA. So paradoxically, even though dietary fat activates OEA production, dietary Oleic Acid (such as from Olive Oil), actually suppresses the beneficial satiety and anti-inflammatory effects of OEA. Oleic Acid thereby induces increased appetite, and increased lipogenesis in the liver and in adipocytes. Excessive intake of any fat, not just OEA, tends to inhibit small intestine FAE production. By that mechanism, an extremely high-fat diet actually promotes further overeating, at least partly by suppressing the satiating effects of gut-derived OEA.

Healthy production of OEA is mediated via the Parasympathetic and Sympathetic nervous systems. Vagal afferents from the upper small intestine sense the OEA activation of PPAR- α, thus transmitting a signal to the brain stem that causes a release of oxytocin (the "feel good hormone" nursing babies stimulate from mother's pituitary) for the satiety reflex, while also activating the memory consolidation in higher brain centers associated with pleasure-reward, and finally, activating the Sympathetic preganglionic nerve, which sends a message back to the GI tract with two purposes. First, to enable the production of more OEA, and second, to decrease GI motility to facilitate the full absorption of the precious fatty acids.

Interestingly, Sympathetic activity alone is sufficient to trigger OEA formation in white adipose tissue. This adipocyte stimulation occurs with no accompanying increased OEA in either the liver or intestine. Sympathetic activation is a classic response to cold exposure, and one of its key bioidentical consequences is the mobilization of free fatty acids from adipocytes. OEA plays a significant role in the mobilization of fats as they are broken down into free fatty acids and glycerol and released into circulation. The essential role of norepinephrine in mobilization and subsequent oxidation of fats for energy is one reason why medicating with beta blockers tends to cause weight gain.

Helda Tutunchi, et al. A Systematic Review of the Effects of Oleoylethanolamide, a High-Affinity Endogenous Ligand of PPAR- α, on the Management and Prevention of Obesity. Clin Exp Pharmacol Physiol. 2020 Apr;47(4):543-552. https://pubmed.ncbi.nlm.nih.gov/31868943/

OEA, a high-affinity Endogenous Ligand of nuclear receptor peroxisome proliferator-activated receptor alpha (PPAR- α), plays important roles in various metabolic functions. It has beneficial effects on:

- body composition
- regional fat distribution
- control of food consumption
- effective weight management

OEA leads to satiation and meal termination through PPAR- α -activation and fatty acid translocase CD36. OEA stimulates fatty acid uptake, lipolysis, and Beta-Oxidation, and also promotes food intake control. Its satiety-inducing effects are mediated via activation of hedonic dopamine receptors in the brain, while also increasing oxytocin and brain histamine.

Elahe Pouryousefi, et al. Improved Glycemic Status, Insulin Resistance and Inflammation after Receiving Oral Oleoylethanolamide Supplement with Pre-diabetes; a Randomized Controlled Trial. Diabetol Metab Syndr. 2022 Jun 3;14(1):77. https://pubmed.ncbi.nlm.nih.gov/35659064/

Pre-diabetic subjects, when supplemented with 125 mg OEA daily for 8 weeks, show significant improvements in:

- blood sugar
- insulin
- insulin resistance
- HbA1c
- C-reactive Protein (CRP)

This study confirms the association between Insulin Resistance and Oxidative Stress. In non-diabetic individuals, this connection becomes stronger in those who are overweight or have impaired fasting glucose tolerance.

The increase in Reactive Oxygen Species (ROS) leads to impaired glucose uptake by muscle and adipose tissue and reduces insulin secretion from pancreatic β cells. Oxidative Stress is associated with increased inflammatory cytokines, and one of the causes of inflammation is the accumulation of Triglycerides in non-adipose tissues.

This study also emphasizes that Metformin, the most common drug used to control and treat pre-diabetes, is less effective at improving Insulin Resistance than are lifestyle interventions, including reduced calorie intake and vigorous physical activity, and especially when the physical activity includes strength training.

The small amount of OEA naturally occurring in the upper intestinal tract has several roles:

- improving inflammatory process
- boosting the immune system
- stimulating lipolysis
- efficient lipid oxidation
- reducing all the risk factors for Metabolic Associated Fatty Liver Disease

After 8 weeks of OEA supplementation, and with no change in dietary intake:

- the fasting blood sugar in diabetic individuals decreased from 116 to 102, a decrease of 12%
- blood sugar two hours after the main meal, decreased from 162 to 137, a decrease of 16%
- HbA1c dropped from 6.5 to 5.6.; Insulin dropped from 12.36 to 10.12
- the HOMA measure of Insulin Resistance dropped from 3.55 to 2.54
- CRP dropped by 11% in 8 weeks.

This study reports that there is also significant decrease in the inflammatory cytokines IL-6 and TNF-α after 8 weeks of OEA supplementation. It is noted that inflammatory markers such as CRP, IL-6, and TNF-α involve a vicious cycle in diabetic individuals, such that the inflammatory process is causative in Insulin Resistance, but the diabetic condition increases the inflammatory state, which in turn accelerates the pathology.

Fatemeh Taghizadeh Shivyari, et al. Examining the OEA Supplement Effects on Glycemic Status, Oxidative Stress, Inflammation, and Anti-Mullerian Hormone in Polycystic Ovary Syndrome. J Ovarian Res. 2024 May 22;17(1):111. https://pubmed.ncbi.nlm.nih.gov/38778429/

This study shows the improvement in Fasting Blood Sugar, Insulin Resistance, Total Antioxidant Capacity, MDA as an indicator of Oxidative Stress, C-reactive Protein, TNF-a, and Anti-Mullerian Hormone. In particular, the improvements in Total Antioxidant Capacity and Anti-Mullerian Hormone were "quite remarkable".

Alireza Ostadrahimi, et al. The Effect of OEA Supplementation on Lipid Profile, Fasting Blood Sugar and Dietary Habits in Obese People: a Randomized Double-blind Placebo-Control Trial. BMC Endocr Disord. 2024 Oct 8;24(1):210. https://pubmed.ncbi.nlm.nih.gov/39379951/

OEA is expressed in tissues such as neurons, the small intestine, and adipose tissue. OEA occurs naturally in food but in only very small quantities. The most significant sources are cocoa powder and oatmeal. The study confirms the protective role of OEA in inflammation and in neurodegenerative disease such as Parkinsons Disease, and also it has benefits in pain relief, apoptosis induction, weight loss, lipolysis stimulation, and fatty acid oxidation enhancement.

This study shows that supplementation with 125 mg of OEA twice daily for 8 weeks in obese subjects decreased Triglycerides by 14%.

Maja Grabacka, et al. The PPAR-α Regulation of the Gut Physiology in Regard to Interaction with Microbiota, Intestinal Immunity, Metabolism, and Permeability. Int J Mol Sci. 2022 Nov 16;23(22):14156. https://pubmed.ncbi.nlm.nih.gov/36430628/

OEA increases microbiota diversity and shifts the colonic microbiota composition toward higher levels of Bacteroidetes and lower levels of Firmicutes. On the Genus level, OEA decreases Bacillus and certain Lactobacillus (firmicutes) counts. The decrease in Firmicutes/Bacteroidetes ratio from OEA mimics the effect of a high-carbohydrate, low-fat diet.

The altered microbiota composition has implications for the mucosal immune system. Peyer's patches are less prone to induction of proinflammatory responses to Endotoxin (LPS). They are significantly less IL-6, IL-17, IFN-γ, and shift the T-cell polarization from TH1 to TH2.

Evidence from many studies show that the low F/B ratio is associated with lean body proportions with smaller percentage of body fat, and correlates with weight loss in obese individuals. OEA supplementation to obese subjects significantly increases the probiotic A muciniphila abundantly, while reducing caloric intake.

J Sihage, et al. OEA: The Role of Bioactive Lipid Amide in Modulating Eating Behavior. Obes Rev. 2018 Feb;19(2):178-197. https://pubmed.ncbi.nlm.nih.gov/29124885/

This study emphasizes the role of dietary fat Oleic Acid in activating taste receptors in the mouth and in the upper small intestine leading to the formation of OEA. OEA then combines with PPAR-α to enable fat oxidation in the liver, resulting in enhanced energy production.

However, the critical point is that a high-fat meal or a high-fat diet sustained over time, abolishes signaling from OEA. The result is the reverse of OEA benefits, namely, reduced satiety and increased appetite and obesity.

Kalina Duszka, et al. Peroxisome Proliferator-activated Receptors and Caloric Restriction — Common Pathways Affecting Metabolism, Health, and Longevity. Cells. 2020 Jul 16;9(7):1708 https://pubmed.ncbi.nlm.nih.gov/32708786/

While OEA reduces meal size and prolongs eating latency, thereby leading to body weight loss, it has the negative effect of upon intraperitoneal administration, acutely decreases energy expenditure as well as ambulatory and spontaneous locomotor activity. OEA stimulates lipolysis and decreases lipid content in hepatocytes, as well as decreasing serum cholesterol and triglycerides.

Saturated fat ethanolamides and OEA exert powerful cytoprotective effects. They attenuate peripheral inflammation and neuronal toxicity. Particularly, they protect against the toxic effects of endotoxin/lipopolysaccharide (LPS) produced by unhealthy microbiota. Endotoxin toxicity from an unhealthy microbiota downregulates OEA expression in macrophages as part of their pro-inflammatory damage. Maintaining adequate OEA and saturated fatty acid ethanolamide signaling molecule production in macrophages prevents inappropriate inflammatory response to harmful stimuli such as endotoxin.