Ingredient Spotlight

Tetradecyl Thioacetic Acid

What it is?

It is saturated, 16 carbon 3-thia synthetic, structurally modified, non-beta-oxidizable, omega-3 fatty acid.

It shows an enhanced potency in modulating critical steps in lipid metabolism

It has a sulfur atom inserted between the second and the third carbon counted from the carboxyl acid end, and because of this addition it cannot be burnt for energy and thus has no relevant caloric value to humans.

$$CH_3\text{-}(CH_2)_{13}\text{-}S\text{-}CH_2\text{-}COOH$$

How TTA is prepared:

TTA is not a natural occurring fatty acid, but is produced chemically from a Sulphur containing acid and potassium hydroxide dissolved in methanol. Tetraadcylbromide, which is the molecule basis for the TTA is added to the solution and through heating and pH regulation, the necessary reactions, will produce the TTA.

TTA is a dry, white crystalline product that is offered commercially.

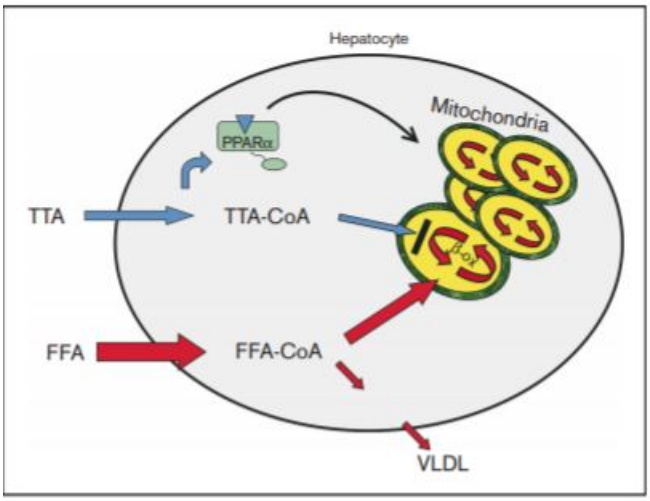
Mechanism of action:

After administration to rats, 3-thia fatty acids have been shown to cause production of megaperoxisomes and micromitochondria , and stimulate the peroxisomal and mitochondrial b-oxidation of fatty acids. Although the 3-thia fatty acids are not b-oxidized, they can be catabolized by sulfur and w-oxidation to dicarboxylic acids that are subsequently excreted by the kidneys.

TTA is metabolized as an ordinary fatty acid and is incorporated into different lipid classes, especially into phospholipid

TTA acts as agonist at all subtypes of PPAR

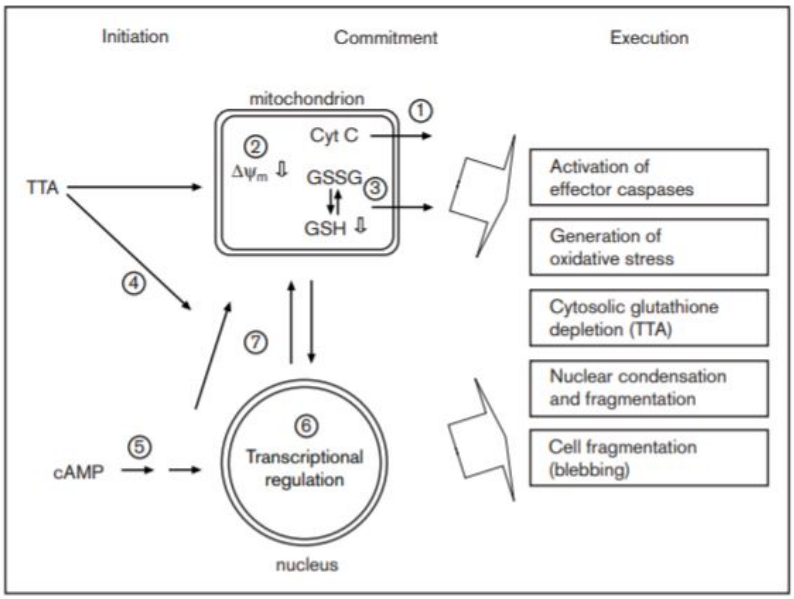
A main determinant of the mechanism of action is the non-β-oxidizable nature of TTA.



Tetradecylthioacetic acid (TTA) is taken up by the hepatocytes and upregulates peroxisome proliferator-activated receptor (PPAR) α target genes and promotes proliferation of mitochondria. TTA is transported into the mitochondria, but it cannot be oxidized (indicated by bold line). There is an increased flux of normal fatty acids to the liver after TTA treatment (thick red arrow). The oxidative capacity is increased, and the degradation of the oxidizable fatty acids leads to a reduced free fatty acid (FFA) availability for triacylglycerol (TAG) synthesis and VLDL formation. β-ox, β-oxidation; CoA, coenzyme A.

Figure 4. Proposed mechanism behind tetradecylthioacetic acid-induced apoptosis

Tetradecylthioacetic acid (TTA) may interact directly with mitochondrial proteins/receptors, leading to cytochrome c (Cyt C) release (1), membrane depolarization (2) and modulation of mitochondrial glutathione content and redox equilibrium (3). It is not revealed whether the nucleus is involved in the apoptotic induction (4); however, the commitment phase is thought to proceed without directly involving the nucleus. In contrast, apoptosis induced by cyclic adenosine monophosphate (cAMP) propagates through phosphorylation cascades (5) and leads to nuclear regulation of transcription and proteins synthesis (6). The mitochondria are probably involved at several stages in cAMP-induced apoptosis (7). GSH, nonoxidized glutathione; GSSG, oxidized glutathione.



Peroxisome proliferator activated receptors (PPARs):

They are members of the nuclear hormone receptor superfamily of ligand-activated transcription factors, that play an important role in many cellular functions including lipid metabolism, cell proliferation, differentiation, adipogenesis and inflammatory signaling.

There are three distinct PPAR subtypes

PPARα is expressed in tissues exhibiting high rates of β-oxidation such as liver, kidney, heart and muscle. PPARα activation induces hepatomegaly and proliferation of liver peroxisomes. PPARα agonists (fibrates) have shown therapeutic utility as lipid lowering agents. (In simple words, PPARa tends to clear fats from the blood into muscle or liver cells, and encourage them to be burnt for energy in these locations)

PPARδ (also known as PPARβ and NUC1) is ubiquitously expressed in tissues and has been implicated in energy metabolism in both adipose and skeletal muscle.

PPARγ is highly expressed in adipose tissue and is a key transcription factor involved in the terminal differentiation of white and brown adipose tissue. PPARγ agonists such as the glitazones (thiazolidinediones) are marketed as antidiabetic agents. (PPARγ makes new fat cells for fats to reside in which minimizes their potential toxicity).

There is evidence that both PPARα and PPARγ could interfere with atherogenesis, in part by exerting an anti-inflammatory activity.

Name	PPARα	PPARδ	PPARγ
Tissue expression	Liver Kidney Heart Muscle	Placenta Skeletal muscle (ubiquitously expressed)	Adipose tissue Skeletal muscle Heart Lung Ovary
Physiological effects	Fatty acid synthesis Oxidation Ketogenesis	Fatty acid oxidation Cell cycle control	Adipocyte differentiation Glucose homeostasis

Disease relevance	Dyslipidaemia Atherosclerosis Inflammation	Metabolic syndrome Cancer	Diabetes Psoriasis Cancer Inflammation

Actions of TTA:

The biological responses to TTA include

- mitochondrial proliferation in liver, muscles and heart[1]
- increased catabolism of fatty acids,
- anti-adiposity, [2]
- improvement in insulin sensitivity[3]
- antioxidant properties [4]
- reduced proliferation and induction of apoptosis in rapidly proliferating cells [5]
- cell differentiation
- Anti-inflammatory action.

Role of TTA in Weight loss:

Attenuates Dyslipidemia (reduce plasma lipids level): due to increased mitochondrial fatty acid oxidation that is caused by activation of PPAR alpha and delta receptors.[6]

[1] Berge RK, Aarsland A, Kryvi H, et al. Alkylthio acetic acids (3-thia fatty acids)±a new group of non-beta-oxidizable peroxisome-inducing fatty acid analogues: II. Dose-response studies on hepatic peroxisomal and mitochondrial changes and long-chain fatty acid metabolizing enzymes in rats. Biochem Pharmacol 1989; 38:3969±3979.
[2] Madsen M, Guerre-Millo M, Flindt EN, et al. Tetradecylthioacetic acid prevents high fat diet induced adiposity and insulin resistance. J Lipid Res 2002 (in press).
[3] Madsen L, Guerre-Millo M, Flindt EN, et al. Tetradecylthioacetic acid prevents high fat diet induced adiposity and insulin resistance. J Lipid Res. 2002;43(5):742-750.
[4] Muna ZA, Bolann BJ, Chen X, et al. Tetradecylthioacetic acid and tetradecylselenoacetic acid inhibit lipid peroxidation and interact with superoxide radical. Free Radic Biol Med 2000; 28:1068±1078.
[5] Berge K, Tronstad KJ, Flindt EN, et al. Tetradecylthioacetic acid inhibits growth of rat glioma cells ex vivo and in vivo via PPAR-dependent and PPARindependent pathways. Carcinogenesis 2001; 22:1747±1755.
[6] Løvås, K., Røst, T. H., Skorve, J., Ulvik, R. J., Gudbrandsen, O. A., Bohov, P., Wensaas, A. J., Rustan, A. C., Berge, R. K., & Husebye, E. S. (2009). Tetradecylthioacetic acid attenuates dyslipidaemia in male patients with type 2 diabetes mellitus, possibly by dual PPAR-alpha/delta activation and increased mitochondrial fatty acid oxidation. Diabetes, obesity & metabolism, 11(4), 304–314. https://doi.org/10.1111/j.1463-1326.2008.00958.x

Several enzymes involved in lipid metabolism are induced after TTA treatment, including carnitine acetyltransferase and palmitoyl-CoA hydrolase, palmitoyl-CoA synthetase, acyl- CoA hydrolase etc.

Stimulation of PPAR-Alpha induce satiety and decrease appetite. This results in decrease oral intake and consequently helps in weight loss.[7]

It has a hypophagic effect which further helps in regulating obesity [8]

Furthermore, activators of PPARγ may increase feed intake and weight gain besides their beneficial effects on plasma lipids and insulin resistance.

TTA feeding promote reduced body weight gain in rats given high-fat diets, in spite of higher feed intake due to increased expression of UCP1 and UCP3.[9]

TTA reduced the total plasma cholesterol and triacylglycerol levels by 17% by increasing the number of mitochondria and by stimulating the mitochondrial β-oxidation of normal fatty acids

[7] Fu, J., Gaetani, S., Oveisi, F., Lo Verme, J., Serrano, A., Rodríguez De Fonseca, F., Rosengarth, A., Luecke, H., Di Giacomo, B., Tarzia, G., & Piomelli, D. (2003). Oleylethanolamide regulates feeding and body weight through activation of the nuclear receptor PPAR-alpha. Nature, 425(6953), 90–93. https://doi.org/10.1038/nature01921

[8] De Vos, P., Lefebvre, A. M., Miller, S. G., Guerre-Millo, M., Wong, K., Saladin, R., Hamann, L. G., Staels, B., Briggs, M. R., & Auwerx, J. (1996). Thiazolidinediones repress ob gene expression in rodents via activation of peroxisome proliferator-activated receptor gamma. The Journal of clinical investigation, 98(4), 1004–1009. https://doi.org/10.1172/JCI118860

[9] Wensaas, A. J., Rustan, A. C., Rokling-Andersen, M. H., Caesar, R., Jensen, J., Kaalhus, O., Graff, B. A., Gudbrandsen, O. A., Berge, R. K., & Drevon, C. A. (2009). Dietary supplementation of tetradecylthioacetic acid increases feed intake but reduces body weight gain and adipose depot sizes in rats fed on high-fat diets. Diabetes, obesity & metabolism, 11(11), 1034–1049. https://doi.org/10.1111/j.1463-1326.2009.01092.x

Summary of related studies:

Title	Year	Results	DOI
Tetradecylthioacetic acid prevents high fat diet induced adiposity and insulin resistance	2002	TTA reduced adiposity, hyperglycemia, and markedly improved insulin sensitivity as determined by the intravenous glucose tolerance test	https://pubmed.ncbi.nlm.nih.gov/11971945/
Hepatic fatty acid metabolism as a determinant of plasma and liver triacylglycerol levels. Studies on tetradecylthioacetic and tetradecylthiopropionic acids	1995	TTA did potently reduce plasma cholesterol levels in rats and dogs and raised the HDL/LDL ratio by 40%	10.1111/j.1432-1033.1995.tb20193.x
Tetradecylthioacetic acid attenuates dyslipidaemia in male patients with type 2 diabetes mellitus, possibly by dual PPAR-α/δ activation and increased mitochondrial fatty acid oxidation	2009	Mean LDL cholesterol level declined from 4.2 to 3.7 mmol/l, accompanied by increased levels of the HDL apolipoproteins A1 and A2, and a decline in LDL/HDL ratio	https://doi.org/10.1111/j.1463-1326.2008.00958.x

		from 4.00 to 3.66 was see. Total fatty acid also declined.	
The PPAR pan-agonist tetradecylthioacetic acid promotes redistribution of plasma cholesterol towards large HDL	2020	TTA promoted a shift in the plasma lipoprotein fractions with an increase in larger HDL particles.	10.1371/journal.pone.0229322
Tetradecylthioacetic acid (a 3-thia fatty acid) decreases triacylglycerol secretion in CaCo-2 cells	1995	TTA absorbed and metabolized as efficiently as oleic acid, tetradecylthioacetic acid was incorporated into cell-associated triacylglycerol to the same extent as normal fatty acids (e.g., oleic acid and palmitic acid), the amount of triacylglycerol secreted from cells incubated with tetradecylthioacetic acid was 8 to 10 times lower than the amount secreted from cells incubated with palmitic acid	https://pubmed.ncbi.nlm.nih.gov/7775865/

		and oleic acid, respectively	
Tetradecylthioacetic acid increases fat metabolism and improves cardiac function in experimental heart failure	2013	TTA decreased free fatty acid levels and had a protective effect on myocardium when given combined with high fat diet	10.1007/s11745-012-3749-z
Cardioprotective effect of the PPAR ligand tetradecylthioacetic acid in type 2 diabetic mice	2011	TTA increased myocardial fatty acid (FA) oxidation and improved ischemic tolerance in diabetic mice	10.1152/ajpheart.00357.2010
Prevention of hypertension and organ damage in 2-kidney, 1-clip rats by tetradecylthioacetic acid	2006	TTA attenuated the development of hypertension, reduced established hypertension, and prevented the development of organ damage in 2K1C rats,	10.1161/01.HYP.0000233018.60736.70
Dietary supplementation of tetradecylthioacetic acid increases feed intake but reduces body weight gain and adipose depot sizes	2009	Rats fed on TTA gained less body weight than lard-fed rats and had markedly decreased subcutaneous, epididymal,	10.1111/j.1463-1326.2009.01092.x

in rats fed on high-fat diets		perirenal and mesenteric adipose depots.	
Lipid-lowering effects of tetradecylthioacetic acid in antipsychotic-exposed, female rats: challenges with long-term treatment	2012	TTA had a protective role in antipsychotic-induced dyslipidemia	10.1371/journal.pone.0050853
Comparative effects of oxygen and sulfur-substituted fatty acids on serum lipids and mitochondrial and peroxisomal fatty acid oxidation in rat	1992	TTA stimulated the mitochondrial fatty acid oxidation, decreased serum cholesterol and decreased serum triacylglycerol	10.1016/0006-2952(92)90248-h
Inhibition of rat lipoprotein oxidation after tetradecylthioacetic acid feeding	2002	Oral administration of TTA inhibited lipoprotein oxidase and prevented atherosclerosis	10.1016/s0006-2952(01)00934-0
The hypocholesterolemic effect of sulfur-substituted fatty acid analogues in rats fed a high carbohydrate diet	1993	TTA reduced the activity of acyl-CoA:cholesterol acyltransferase (ACAT) and resulted in reduced cholesterol synthesis	10.1016/0005-2760(93)90159-7
Dual acting and pan-PPAR activators as	2011	PPAR-α activator drugs decrease plasma	10.1007/978-3-642-17214-4_2

potential anti-diabetic therapies		triglycerides and increase HDL-cholesterol levels. PPAR-δ activators increase the capacity for fat oxidation in skeletal muscle.	
An immunomodulating fatty acid analogue targeting mitochondria exerts anti-atherosclerotic effect beyond plasma cholesterol-lowering activity in apoe(-/-) mice	2013	TTA administration reduce triglyceride levels in plasma and liver. It reduce arachidonic acid and increase EPA level in the heart.	10.1371/journal.pone.0081963
Lipid-lowering and anti-inflammatory effects of tetradecylthioacetic acid in HIV-infected patients on highly active antiretroviral therapy	2004	TTA in combination with dietary intervention reduces total cholesterol, LDL cholesterol, triglycerides and LDL/HDL cholesterol in HIV infected ptients on HAART	10.1111/j.1365-2362.2004.01410.x
Differences in fat accumulation between immature male and female Atlantic salmon Salmo salar after dietary	2016	The fat content during the first spring after dietary TTA was lowered by a greater amount in females than in	10.1111/jfb.13113

administration of tetradecylthioacetic acid		males, In second spring fat was reduced more in males	
In contrast with docosahexaenoic acid, eicosapentaenoic acid and hypolipidaemic derivatives decrease hepatic synthesis and secretion of triacylglycerol by decreased diacylglycerol acyltransferase activity and stimulation of fatty acid oxidation.	1999	TTA decreased triacylglycerol formation caused by inhibition of diacylglycerol acyltransferase and decreased availability of fatty acids for triacylglycerol synthesis by increased mitochondrial beta-oxidation	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1220541/
The effect of tetradecylthioacetic acid (TTA) on body weight management in growing silver foxes (Vulpes vulpes) as a model for dogs (Canis familiaris)	2018	High dose reduced intake while low dose TTA reduced serum TGA, LDL cholesterol in foxes	https://nmbu.brage.unit.no/nmbu-xmlui/bitstream/handle/11250/2570197/Chen-2018.pdf?sequence=1&isAllowed=y