Navarro et al. (2010) on effects of CLA in mice

“Trans-10,cis-12-CLA dysregulate lipid and glucose metabolism and induce hepatic NR4A receptors,”

On January 1st, a research group around Maria A. Navarro published a paper in Frontiers in Bioscience dealing with effects of dietary CLA in mice. Their conclusion was that trans-10,cis-12-CLA (t10,c12-CLA) enriched diets lead to an accumulation of fat in the liver accompanied by an up-regulation of the hepatic NR4A receptors in ApoE deficient mice.

In a subsequent press release (9/2/2010), the principal investigator stated that CLA leads to an “increase in oxidative stress, inflammation, hyperglycaemia, insulin resistance, lipodystrophy, atherosclerosis and an abnormal accumulation of fat in the liver” and she issued a warning against the use of CLA in foods. It must be noted that the study of Navarro et al. did not investigate the effects of CLA treatment on oxidative stress, inflammation, hyperglycaemia, or atherosclerosis. The effect on plasma insulin observed by Navarro et al. was related to the c9,t11-CLA isomer only and it showed no insulin resistance but an increased insulin sensitivity – which is a beneficial and not an adverse effect.

Furthermore, the described adverse effects observed by Navarro et al. in mice have previously been described and based on comprehensive and numerous clinical studies none of these effects has turned out to occur in humans.

In spite of the absence of any finding on inflammation, glucose metabolism or atherosclerosis in Navarro et al.’s study we shortly summarize the existing evidence on these endpoints.
1) Lipodystrophy and hepatic steatosis

Hepatic steatosis is a well known effect of CLA observed in rodents (Belury 1997, West et al 1998, deDeckere et al 1999, O’Hagan 2003, BASF 2002) and it has been attributed to the high metabolic rate of small animals. Concurrently, rodents also show a remarkably faster and stronger weight loss effect upon CLA treatment than e.g. humans. Since the human metabolic rate is lower and the dose applied in humans relative to body weight is much lower than the dose tested in rodents, the effects on liver integrity are not observed in humans.

At least 13 human clinical studies have been published that reported measurements of the liver itself (by echography) or of liver biomarkers (ALT, AST, GGT, AP) (Blankson 2000, Berven 2000, Smedman 2001, Albers 2003, Noone 2002, Gaullier 2004, Gaullier 2005, Whigham 2004, Taylor 2004, Larsen 2006, Malpeuch-Brugere 2004, Lowery 1998, Kreider 2002). In sum, more than 900 patients participated in these studies conducted under clinical observation and yet there was no observable adverse effect on the liver in any study.

CLA has been used as a food ingredient for more than 10 years and only one isolated case report is known that involved a product that contained CLA and which was related to a liver effect (Ramos 2009). A reversible inflammatory hepatitis (no hepatosteatosis) was observed in one patient receiving a CLA combination product with an unknown composition. Cognis contacted the author in order to clarify the scientific relevance of this case report but the nature, purity and composition of the product in question could not be identified. The case was therefore considered to be inconclusive. A relation of the observed effect to CLA could not be established because the product might have been contaminated or the effect was due to an unknown botanical co-ingredient. CLA products are often blended with plant extracts that claim to have a weight loss effect. Inflammatory effects on the liver are very often related to the plant extracts themselves or to contaminants (e.g. aflatoxins).

2) Glucose metabolism

While hyperglycaemia and insulin resistance is reported by a limited number of researchers (Risérus et al. (2002a, 2004a), Syvertsen et al. (2007) and Moloney et al. (2004)) the observed effects were only slight and close to baseline in these studies. In some cases the effect was only statistically relevant because plasma glucose levels decreased in the control group during
the study. In contrast to these isolated observations more than 20 clinical studies investigated parameters of insulin resistance and no effect on the glucose metabolism was reported. In order to verify this observation, Herrmann et al. (2009) performed a meta-analysis on all existing studies (until end 2009) that investigated any parameter of glucose metabolism, concluding that CLA does not adversely affect parameters of blood glucose homeostasis, including insulin sensitivity/resistance, in overweight male subjects and type-2 diabetic, obese postmenopausal women.

3) Endothelial function

Only Taylor et al. (2006) observed an adverse effect of CLA (1:1 isomer mix) on the endothelial function of healthy but overweight male volunteers.

In contrast to these findings Raff et al. (2006) showed that Tonalin CLA does not adversely affect the arterial elasticity in young men, and in Pfeuffer et al.’s study (2009) endothelial function was unaffected by CLA treatment. The method applied is approved by the US-FDA for use as a diagnostic aid in patients with signs of ischemic heart disease (Barac et al., 2007). Furthermore, aortic stiffness was not affected by a six months CLA treatment (Sluijs et al., 2010).

It must be noted that care should be taken with judging on the endothelial function based on a single data point only. Endothelial function can react acutely upon short term nutritional stimuli and therefore a final conclusion should always be based on the entirety of evidence and on a representative number of data points.

With regard to the risk of atherosclerosis, it is noteworthy that the formation of aortic lipid deposition and atherosclerotic lesions was reduced in hamsters and rabbits fed an atherogenic diet with added CLA (1:1 mix) (Kritchevsky et al., 2000; 2004; Wilson et al., 2006; Mitchell et al., 2005; Nicolosi et al., 1997).

4) Oxidative stress

An increase in urinary 8-iso-PGF2α isoprostane, a potential marker of lipid peroxidation, is reproducibly observed in subjects after treatment with CLA (Basu et al. 2000). Iannone et al
(2009) recently proved that the increased isoprostane levels are not the result of an increased production but of a reduced elimination (Iannone et al., 2009). Other markers of oxidative stress are not affected upon CLA treatment (Etzdorf 2008, Basu et al 2000, 2004). Consequently, there is no evidence that CLA might induce oxidative stress in humans.

5) Conclusion

Navarro et al. investigated the effect of CLA on the hepatic lipid metabolism in mice. Adverse effects were restricted to lipodystrophy and hepatic steatosis which are known for rodents for more than a decade and which have been shown to be of no relevance to humans. Despite Navarro’s statement in her press release, CLA does not adversely affect glucose metabolism, endothelial function, and oxidative stress in humans.

Düsseldorf, February 10, 2009

Dr. Horst Messinger
Chemist, UK/ Eurotox registered Toxicologist
Product Safety & Regulations

Dr. Annette Mehling
Biologist, UK/ Eurotox registered Toxicologist
Product Safety & Regulations
References


BASF AG. (2002a) CLA methyl ester and CLA ethyl ester prenatal developmental toxicity study in Sprague Dawley rats (gavage). OECD 474. Confidential internal study report no 30R0746/009048


Maria A. Navarro, Lina Badimon, Cristina Rodriguez, Maurizio Gentile, Carmen Arnal, Enda J. Noone, Helen M. Roche, Jesus Osada, Jose Martinez-Gonzalez. Trans-10,cis-12-CLA dysregulate lipid and glucose metabolism and induce hepatic NR4A receptors. Frontiers in Bioscience E2, 87-97, January 1, 2010


O'Hagan S; Menzel A. (2003). "A subchronic 90-day oral rat toxicity study and in vitro genotoxicity studies with a conjugated linoleic acid product." Food and Chemical Toxicology 41(12): 1749-1760


