

AN UPDATE ON THE EFFECTS OF CONJUGATED LINOLEIC ACID (CLA) IN A RODENT MODEL OF POLYCYSTIC KIDNEY DISEASE

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Polycystic kidney disease (PKD) is a genetic disorder that affects millions of people worldwide. In the United States alone, approximately 600,000 people are currently suffering from this disease. Autosomal dominant PKD, which comprises about 90% of the cases of PKD, results from passage of the disease gene from one parent to a child. This form of the disease usually occurs between the ages 30–40, but can also begin at an early age. Morphologically, PKD is characterized by the growth of numerous cysts in the kidney resulting in increased size of the organ. Complications from the disease include pain, urinary tract infections, hypertension and most importantly kidney failure. It is important to note that PKD is the fourth leading cause of end-stage renal disease. In fact, approximately half of the patients with PKD require either hemodialysis or renal transplantation. Unfortunately, other than symptomatic management there is no specific therapeutic agent indicated to treat this debilitating disease.

Conjugated linoleic acid (CLA), a dietary fatty acid, has received widespread attention due to its anti-cancer anti-atherosclerotic, anti-inflammatory and anti-diabetic effects in laboratory animals. CLA collectively refers to a group of linoleic acid (18:2, c9, c12) derivatives with several positional (double bonds in carbon 7 and 9; 8 and 10; 9 and 11; 10 and 12 or 11 and 13) and geometric (*cis*, *Z* and *trans*, *E*) isomers. CLAs are relatively abundant in ruminant meat and heat-processed dairy products. These fatty acids are formed from linoleic acid in the intestine of livestock by bacterial flora and are deposited in tissues and milk.

At the cellular level, CLAs elicit their effects *via* activation of a class of nuclear receptors known as PPARs (peroxisome proliferator-activated recep-

tors). Functionally, PPAR is a ligand-activated transcription factor, which is involved in gene expression in a tissue-, sex- and species-dependent manner (1). Upon activation by CLA, PPAR forms a heterodimer with RXRa and regulates gene expression by binding to PPAR-response elements (PPRE) on responsive genes. Important genes regulated by PPARs include lipid metabolism, cellular proliferation, differentiation and apoptosis. Anti-cancer and metabolic effects have been the main emphasis of CLA research in the laboratory. In recent years however, CLA's effect on polycystic kidney disease has been studied as elucidated below.

Han:SPRD-cy rat model is employed for studying PKD as it resembles several features of the human form of the disease including autosomal dominance, sexual dimorphism, as well as inflammation and fibrosis in the kidney. Feeding CLA (1% w/w, containing different CLA isomers) to male Han:SPRD-cy weanling rats for 8 weeks significantly reduced fibrosis and macrophage infiltration in the kidney (2). While urinary creatinine level was found to be significantly reduced in rats with PKD, CLA feeding on the other hand, resulted in marked increase in urinary creatinine in these animals. Eight weeks of CLA treatment significantly reduced renal prostaglandin E₂ (PGE₂) release in healthy and PKD animals (2). Arachidonic acid, the precursor molecule for prostaglandin biosynthesis in renal tissue was unaffected by CLA treatment. This suggests CLA's direct inhibitory effect on the expression or activity of cyclooxygenase (COX), the rate-limiting enzyme for conversion of arachidonic acid to different prostaglandins.

Similar to weanling rats, CLA feeding to male Hans:SPRD-cy rats with advanced PKD markedly reduced macrophage infiltration and fibrosis in the

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kidney (3). These effects, however, were not accompanied by improvement of renal functions for such as: creatinine clearance, serum creatinine, and proteinuria. In the same study, CLA treatment decreased oxidative damage and renal cell proliferation by 30 and 35%, respectively. These results suggest that reduction of inflammatory process in the kidney alone may not be sufficient to improve renal functions. Interestingly, CLA treatment for 8 weeks in weanling Han:SPRD-cy rats with PKD produced a declining trend in oxidative stress although this effect did not reach statistical significance. The variation in anti-oxidative effect may be due to a difference in the length of CLA treatment (8 weeks *versus* 16 weeks).

In separate studies, effects of CLA on parathyroid hormone (PTH) level were examined. Rats with PKD had a marked increase level of PTH as compared to unaffected animals (4). CLA (1% w/w) treatment for 8 weeks reduced PTH level by 60%. CLA treatment did not significantly change any effect on bone morphology i.e., femur weight, bone area, and bone mineral content. Important plasma biomarkers such as calcitonin and plasma calcitriol (vitamin D₃) was unaffected by CLA feeding (4). Release of PGE₂ from kidney was markedly reduced by CLA. Whether this latter mechanism is directly involved in decreased plasma concentration of PTH remains to be determined.

While attempting to separate the effects of CLA on gender, male and female offspring of Han:SPRD-cy heterozygotes were fed for 12 weeks with 1% and 2% CLA mixture (containing equimolar concentration of 9c 11t CLA and 10t 12c CLA) (5). There was a dose-dependent increase in serum creatinine level in the female rats, whereas in the male animals there was no change in serum creatinine with either doses of CLA. These observations indicate a gender-specific effect of CLA on this biomarker. While 2% CLA treatment markedly reduced renal cystic change in male rats, in female rats the significant reduction was observed with both dosages of CLA. A marked reduction was also observed in renal fibrosis and ox-LDL level in both genders with CLA. However, 2% CLA diminished the antifibrotic effects in male animals suggesting

potential toxic effect. CLA treatment significantly reduced macrophage infiltration and PCNA count in the kidneys of both male and female rats. Statistical analysis reveals a negative correlation with renal 9c 11t CLA concentration and histological damage in the kidney. In the future, a dose-response curve with various doses of CLA may be undertaken to determine the beneficial *versus* harmful effect of the fatty acid in PKD. Interestingly, in this study, CLA did not induce PPAR γ expression in either gender (5). This may be due to a poor detection limit in the experimental procedure. Alternatively, *in vitro* studies with a particular cell line may be utilized for detecting PPAR γ expression.

Based on the findings of the above-mentioned studies, it can be concluded that CLA produces some beneficial effects in a rodent model of PKD. Important effects of CLA include: 1) reduction of inflammation, 2) modulation of oxidative stress, 3) an increase in creatinine excretion and 4) a decrease in plasma PTH level. These effects, although very important, cannot be explained by well-characterized mechanisms. Future, in-depth studies are warranted to further our understanding of CLA effect on PKD.

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