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INSIGHTS INTO THE ANTIHYPERTENSIVE EFFECTS OF CONJUGATED LINOLEIC ACID (CLA) IN DIFFERENT RODENT MODELS

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Conjugated linoleic acid (CLA) consists of isomers of linoleic acid with conjugated double bond system. These isomers are formed in rumen gut by the enzymatic action of bacterial flora and then deposited in milk and tissue. Hence, major sources of CLA in the diet include meat and heat-processed dairy products. Numerous studies have characterized CLA's chemopreventive role in diseases such as cancer, obesity, diabetic and atherosclerosis (1). More recently, CLA's emerging role as an antihypertensive agent has been reported in the literature (2–4). In spite of the availability of numerous therapeutic agents to treat hypertension, there is always a growing need of therapeutic agents with greater efficacy and fewer adverse effects. From this aspect, CLA's antihypertensive role is significant as it is derived from foodstuff with a minimal potential of serious adverse effects. In this communication, some recent findings on CLA's blood pressure lowering effect are presented.

CLA's blood pressure lowering effect has been investigated in different rat models. In spontaneously hypertensive rats (SHRs), four week of CLA feeding significantly suppressed any increase in systolic blood pressure (2). Similar beneficial effects were also observed in Zucker diabetic fa/fa (ZDF) rats (3). In both studies (2, 3), CLA was administered as a mixture, which contained predominantly 9-*cis*, 11-*trans* CLA (9c 11t CLA) and 10-*trans*,12-*cis* CLA (10t 12c CLA) along with trace amounts of other CLA isomers. Interestingly, in a separate study (4), 10t 12c CLA, but not 9c 11t isomer, significantly suppressed the development of hypertension in Otsuka Long-Evans Tokushima Fatty (OTELF) rats. This latter study compared the effects of 9c 11t CLA with 10t 12c CLA on hypertension where 9c 11t CLA's effect on systolic blood pressure was not different from linoleic acid-fed control animals (4). This result suggests that blood pressure lowering effects of CLA in OTELF rats is mediated in part, by the 10t 12c isomer.

To elucidate on CLA's antihypertensive mechanisms, phospholipid content of CLA-fed SHRs was analyzed (2). CLA treatment markedly decreased D-9 desaturation index of phospholipids of erythrocyte membrane, hepatic tissue and plasma. D-9 desaturation index is the determinant of oleic acid (18:1) *versus* stearic acid (18:0) ratio. The expression of stearoyl-CoA desaturase 1 (SCD-1), the rate-limiting enzyme for the conversion of stearoyl CoA to mono-unsaturated oleoyl-CoA, however, was not affected by CLA treatment. The exact mechanism involved in CLA-mediated alteration of membrane characteristics therefore remains elusive. .

10t 12c CLA treatment significantly decreased leptin and angiotensinogen expression in adipose tissue (4). Leptin, a 16-kDa peptide hormone is predominantly secreted by the white adipose tissue and is associated with the development of diabetes, hypertension and atherosclerosis. For example, in hypertension, leptin stimulates sympathetic nervous system (SNS) by increasing the activity of corticotropin releasing factor in the brain (5). Leptin-stimulated increase in sympathetic stimulation (measured by changes in mean arterial pressure and heart rate) was abolished by pretreatment with adrenergic receptor blockers in Sprague-Dawley rats (6).

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Angiotensinogen secreted by adipose tissue is enzymatically cleaved to angiotensin-I by renin. Angiotensin-I is further converted to a potent vasoconstrictor, angiotensin-II by angiotensin converting enzyme. As a vasoconstrictor, angiotensin-II activates angiotensin receptors and increases the release of aldosterone from adrenal gland.

10t 12c CLA treatment decreases white adipose tissue content (4); angiotensinogen expression was concurrently found to be less.

Adiponectin levels in plasma and white adipose tissue were markedly increased in CLA-fed SHRs and ZDF rats (2, 3). In fact, plasma adiponectin increase correlated with the increase in adiponectin mRNA in the white adipose tissues. Adiponectin can decrease elevated blood pressure in rats by 2 mechanisms: 1) induction of nitric oxide (NO) production in the endothelium resulting in vasodilation (7), and 2) marked inhibition of SNS activity and hypertension by a central mechanism (8). The latter effect appears to be antagonistic with leptin's pressor action.

From the mechanisms presented in these studies, it appears that 10t 12c CLA's antihypertensive effect in rats is different than when CLA is administered as a mixture of isomers. It is possible that 9c 11t CLA or a different isomer in the mixture may be reducing SBP in SHRs and ZDF rats, which require additional investigations.

In the above studies, SBP was the only parameter studied in CLA-treated animals. Other hemodynamic parameters that need to be assessed include heart rate, diastolic pressure, cardiac output, stroke volume and changes in the mean arterial pressure. Studies evaluating these parameters in conscious animals may provide a better understanding of CLA-mediated regulation of blood pressure in the rodents. Similarly, quantitative RT-PCR rather than semi-quantitative method (4) may be employed for robust data on gene expression. Finally, since CLA activates peroxisome proliferator-activated receptors (PPARs) (9), it will be interesting to determine whether some of these vasoactive effects of CLA are mediated by this nuclear receptor.

REFERENCES

1. Belury MA.: Annu. Rev. Nutr. 22, 505 (2002).
2. Inoue N., Nagao K., Hirata J., Wang Y.M., Yanagita T.: Biochem. Biophys. Res. Commun. 323, 679 (2004).
3. Nagao K., Inoue N., Wang Y.M., Yanagita T.: Biochem. Biophys. Res. Commun. 310, 562 (2003).
4. Nagao K., Inoue N., Wang Y.M., Hirata J., Shimada Y., Nagao T., Matsui T., Yanagita T.: Biochem. Biophys. Res. Commun. 306, 134 (2003).
5. Correia M.L., Morgan D.A., Mitchell J.L., Sivitz W.I., Mark A.L., Haynes W.G.: Hypertension 38, 384 (2001).
6. Carlyle M., Jones O.B., Kuo J.J., Hall J.E.: Hypertension 39, 496 (2002).
7. Hattori Y., Suzuki M., Hattori S., Kasai K.: Diabetologia 46, 1543 (2003).
8. Tanida M., Shen J, Horii Y, Matsuda M, Kihara S, Funahashi T , Shimumora I, Sawai H., Fukuda Y., Matsuzawa Y., Nagai K.: Exp. Biol. Med. (Maywood) 232, 390 (2007).
9. Moya-Camarena S.Y., Van den Heuvel J.P., Belury M.A.: Biochim. Biophys. Acta. 1436, 331 (1999).

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