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EFFECTS OF POLYUNSATURATED FATS ON BLOOD PRESSURE[1]

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INTRODUCTION

Hypertension is recognized as an important risk factor for cardiovascular disease in industrialized societies. Much effort has been expended during the last 10–15 years pursuing both pharmacological and nonpharmacological approaches to reduce blood pressure. Because the nonpharmacological approach is a reasonable way of dealing with hypertension, serious efforts must be made to establish which environmental factors affect blood pressure. Several have been described; these include diet modification, weight reduction, alcohol control, stress management, and relaxation. When examining the

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influence of diet on hypertension, one must determine which specific nutrients affect blood pressure and how to modify them.

Recent literature relating polyunsaturated fatty acids (PUFAs) to blood pressure regulation has been reviewed (34). This chapter emphasizes the role of linoleic (n-6), γ-linolenic (n-6), α-linolenic (n-3), eicosapentaenoic (EPA, n-3), and docosahexaenoic (DHA, n-3) acids. Focus is placed on the nutritional aspects of these fatty acids, their relationship to prostaglandin (PG) metabolism, and how the PGs may affect blood pressure (62, 74, 77). In this chapter, we also summarize the results of nutritional intervention studies conducted in man and animals consuming n-6 and n-3 PUFAs.

BLOOD PRESSURE IN ANIMALS: n-6 FATTY ACIDS AND PROSTAGLANDINS

Early evidence that a seminal extract lowered blood pressure of man and animals was demonstrated by Goldblatt (28) and von Euler (88). Evidence that a lipid-soluble seminal preparation was involved in regulating blood pressure came from the work of Bergström et al (4), who showed that the administration of prostaglandin E (PGE) to animals reduced blood pressure. Additional examples of this phenomenon were published (21, 83, 84, 94). Larsson & Änggård showed that rabbits infused with arachidonate had a dose-dependent decrease in blood pressure (45), which was associated with an increase in the urinary output of PGE_2. The output of PGs was blocked by indomethacin, a nonsteroidal anti-inflammatory agent that resulted in an increase in blood pressure.

An early study implicating linoleic acid in blood pressure control (63) reported that the deprivation of linoleic acid during a salt-loading study resulted in a significantly elevated blood pressure in the rat and that elevated blood pressure was mediated through an impairment of renal homeostatis, which affected water, sodium, and potassium excretion. Other studies have corroborated these findings (81, 82, 86). ten Hoor & van de Graaf (82) found that the urinary excretion of total PG metabolites was reduced substantially when linoleic acid intake was low. However, total PG metabolites increased in urine of rats after they were fed diets with increasing increments of linoleic acid for four months. Of the PGs analyzed, prostacyclin (PGI_2) metabolites were shown to have increased in isolated pulsation-perfused rat aorta. At about the same time, it was reported (48, 51, 75) that the development of an elevated systolic blood pressure was aggravated in rats by a relatively low level of dietary linoleic acid even when the dietary intake of sodium was low.

Cox et al (14) demonstrated that urinary excretion of PGE_2 was dependent on dietary linoleic acid. In support of these findings, Tobian et al (85) showed in a salt-loading study that feeding high levels of linoleic acid to salt-sensitive

Dahl rats increased PGE_2 levels of renal papilla and reduced blood pressure. The increased PGE_2 at the papilla was thought to facilitate the transport of sodium in both the ascending limb of the loop of Henle and the collecting tubule, thereby increasing capacity for sodium excretion and eventually lowering blood pressure (78, 79).

A study by Düsing et al (16) showed that a rise in arterial pressure in Sprague-Dawley rats fed a low level of linoleic acid was associated with a suppression of the vascular rise in circulating thromboxane A_2 (TxA_2) concentrations. A more recent study (15) showed that renal prostaglandins may play a role in blood pressure regulation by affecting renal excretory function and renal renin secretion. Generation of four metabolites, $PGF_{2\alpha}$, PGE_2, 6-keto-$PGF_{1\alpha}$, and TxB_2, by rat-isolated glomeruli and papillary homogenates decreased with the changes in linoleic acid and NaCl intake. This effect occurred in the absence of changes in renal blood flow, glomerular filtration rate, and urinary excretion of inorganic phosphate, which suggests an effect on tubular sodium reabsorption beyond the proximal tubule. Both "distal delivery" and "distal fractional chloride absorption" were affected by linoleic acid deprivation; this finding suggests that linoleic acid deprivation and subsequent renal prostanoid deficiency in the rat is associated with increased sodium absorption in the thick ascending limb of Henle and the distal portion of the nephron. Furthermore, linoleic acid deprivation was associated with an increase in papillary osmolality by raising tissue concentrations of sodium, chloride, and potassium. Papillary urea concentration was unchanged; thus increased papillary osmolality may be independent of changes in papillary blood flow.

Schoene et al (68) fed spontaneously hypertensive (SHR) and Wistar-Kyoto (WKY) rats semisynthetic diets containing 0, 5, and 10% corn oil for 12 weeks. Blood pressures of both species decreased as the corn oil content of the diet increased, while PGE_2 and $PGF_{2\alpha}$ increased in kidney medullae of these rats.

Weanling male Wistar rats were fed an essential fatty acid (EFA)-deficient diet for 25 weeks followed by an EFA-supplemented diet for 3 weeks (29). Towards the end of the EFA-deficient diet period, water consumption increased about 60%, and urinary output and PGE_2 excretion decreased about 45 and 70%, respectively. Feeding the EFA-deficient rats diets supplemented with EFA for 3 weeks decreased water consumption and raised the urine output to that observed in the controls.

Mills & Ward (54) compared four oils, including evening primrose oil, in borderline hypertensive rats (BHR) whose drinking water was replaced with 1% NaCl solution. They found that evening primrose oil (with 9% γ-linolenic acid) was the most hypotensive. Groups of rats who received MaxEPA and sunflowerseed oil had similar increases in blood pressure that were interme-

diate between the evening primrose oil and safflower oil groups. The olive oil–fed animals had the highest blood pressure. The protective effect of γ-linolenic acid seemed to be greater than that of the other fatty acids tested. The apparent explanation for this effect is that the γ-linolenic acid is more accessible to the cyclooxygenase enzymes since it bypasses the early desaturating enzymes in its conversion to arachidonic acid. Engler et al (19) also demonstrated in male Sprague-Dawley rats the hypotensive effects of dietary γ-linolenic acid from borage oil. They noted that the animals consuming the borage oil had attenuated in vivo pressor responses to norepinephrine and angiotensin II.

In summary, practically all the studies in which diets enriched with n-6 PUFA were consumed showed that blood pressure was decreased regardless of the strain of rat used. In general, the vasodilator PGs, PGI_2, and PGE_2 increased in either kidney, aorta, blood, or urine when linoleic acid was increased. Dietary linoleic acid also reduced blood pressure regardless of whether the rats were salt-loaded. The blood pressure lowering effect appeared to be mediated through the PG changes. The latter were promoted systemically and led to increased water and salt excretion from the kidney.

BLOOD PRESSURE IN ANIMALS: n-3 FATTY ACIDS AND PROSTAGLANDINS

Evidence suggests that n-3 fatty acids may also be important nutrients in regulating blood pressure. n-3 fatty acids are obtained in the diet as α-linolenic acid from plant leaves and seed oils such as linseed, soybean, and canola oils and as EPA and DHA from marine oils.

Schoene et al (66) reported the effect of feeding n-3 fatty acids from menhaden oil (high in EPA and DHA) on the in vitro production of PGs from arachidonic acid. The formation of PGE_2 and $PGF_{2\alpha}$ was impaired in homogenates of kidney medullae and cortices of SHR rats fed the menhaden oil diet. This effect was not observed in the WKY group of animals that served as a control. The reduction in the diene PGs produced in the kidney corresponded to the decreased level of arachidonic acid found in the tissue. Blood pressures in SHR rats and stroke-prone rats consuming diets containing corn oil plus menhaden oil were lower than in the corresponding corn oil–fed animals (67). In contrast to data reported above, Scherhag et al (65) reported elevated blood pressure in Sprague-Dawley rats after six weeks on diets containing either cod-liver oil, which is high in EPA and DHA, or linseed oil, which served as a source of α-linolenic acid. This effect was associated with a suppressed generation of vasodilator PGI_2 by vascular tissue. The authors concluded that the suppression of vascular PGI_2 promoted the hypertensive effect of the cod-liver oil and linseed oil supplements. It has been shown that EPA is readily incorporated into rabbit aorta phospholipids in vitro and that

EPA is a poor substrate for cyclooxygenase enzymes (92). Furthermore, increasing the amount of dietary α-linolenic acid suppressed the levels of arachidonic acid in tissue lipids. This finding suggests that the conversion of linoleic acid to arachidonic acid may be partially inhibited by α-linolenic acid because of its higher affinity to the desaturating enzymes (55).

Ziemlański et al (93) fed Wistar rats diets containing various fats along with 1.5% NaCl added to the drinking water to induce hypertension. The rise in blood pressure was greatest in the rats on the animal fat diet, and lower in the animals fed sunflowerseed oil or partially hydrogenated marine oil, and lowest in the rats consuming cod-liver oil diets. Elevated blood pressure was also found in salt-loaded SHR rats fed marine oil (MaxEPA) (11). In the absence of dietary NaCl, blood pressure was not affected and the 2-series prostanoids were suppressed in SHR and WKY rats. The hypertensive rats showed diminished excretion of 6-keto-$PGF_{1\alpha}$ and PGE_2 in urine. The ability of SHR rats to excrete a salt load was reduced when they were fed a diet enriched with MaxEPA; they exhibited mild sodium retention and increased vascular sensitivity. This effect was similar to that shown by salt-loaded EFA-deficient rats. In another study, DOCA-salt-loaded, unilaterally nephrectomized Sprague-Dawley rats were fed different fats in semisynthetic diets for 21 days. Webb et al (90) observed that blood pressure was lower in the marine oil-supplemented group than in the group consuming safflower oil. The amount of arachidonate in kidney phospholipid fatty acids was markedly lower in rats fed marine oil compared to levels in rats fed safflower oil. At the same time, an increase in EPA and DHA occurred in kidney phospholipids while only EPA was increased in plasma phospholipids.

Codde et al (12) showed that the suppression of the 2 series PG synthesis by a marine oil diet (MaxEPA) was not accompanied by accelerated DOCA-salt hypertension. Feeding PUFA (safflower oil) diminished DOCA-salt hypertension, but this effect could not be related specifically to PG synthesis. The lower pressures observed in rats that were fed n-3 or n-6 and that had DOCA or 1-kidney, 1-clip hypertension suggest that volume-dependent forms of hypertension are sensitive to increased dietary PUFA intake. Although the mechanism for this attenuation of hypertension is obscure, it did not seem to involve the renin-angiotensin system, which was suppressed in both models, and thus must be due to effects of PUFA on other vasoactive mechanisms. Hui et al (32) showed that linoleic acid and marine oil fatty acids were equally potent in reducing systolic arterial pressure induced by the chronic infusion of angiotensin II in Sprague-Dawley rats. Systemic and renal synthesis of PGI_2 and the renal formation of PGE_2 were unaffected. Indomethacin inhibited the biosynthesis of PGI_2, but not PGE_2, and only partially neutralized the antihypertensive effects of linoleic acid or marine oil fatty acids. Apparently, linoleic acid and marine oil fatty acids exerted equivalent antihypertensive effects in angiotensin II-induced hypertension that appeared to be independent

of the prostaglandin system. When McIntosh et al (52) fed a commercial diet supplemented with various fats to Hooded Wistar rats for eight months, they found that arterial blood pressure was elevated by sheep fat and lowered by sunflowerseed oil and tuna oil.

Sunflowerseed oil, linseed oil, and evening primrose oil were shown to attenuate hypertension in SHR rats (30) when the feeding regimen was started immediately after suckling. During the prehypertensive period, the reduction in blood pressure was most pronounced in the rats treated with α-linolenic acid, and the decreased blood pressures were not explained by changes in prostanoid production. Hoffmann & Förster (31) showed that semisynthetic diets enriched with n-3 and n-6 PUFA reduced the development of hypertension in SHR rats compared to those consuming chow in the third and fourth generations of a four generation feeding period. PGI_2-like production from isolated pulsating perfused aortic preparations was reduced in rats fed linseed oil, but not in those fed sunflowerseed oil. These effects disappeared when regular chow was substituted for the PUFA diets during the fifth and sixth generations.

In summary, the studies generally showed decreases in blood pressure in rats fed either linseed oil containing α-linolenic acid or marine oils containing EPA and DHA. Additional dietary studies are necessary to explain the mechanism for lowering blood pressure by n-3 fatty acids.

BLOOD PRESSURE IN HUMANS: n-6 FATTY ACIDS AND PROSTAGLANDINS

Dietary Intervention Studies

FREE-LIVING STUDIES A series of studies reviewed in this section attempt to define the effect of diets enriched with n-6 fatty acids (primarily linoleic acid) on blood pressure in human subjects. The effects of linoleic acid feeding on PG levels of tissue or on urinary excretion products in relation to blood pressure are discussed.

A dietary intervention study in which all foods were weighed or measured was conducted with 10 men and 11 women (normo- to high-normotensive), 40-60 years old (39). During the first 40 days the diets contained 25% of total calories (en%) from fat with a polyunsaturated to saturated fatty acid ratio (P:S) of 1.0. The linoleic acid content of the diet rose from 3.8 en% during the pre-study period to 6.5 en% during the 25-en% period. The saturated fatty acids decreased from 17 en% to 6.7 en% during these periods. A significant decrease of 13 mm Hg systolic and 7 mm Hg diastolic blood pressure was observed for all subjects. No further change was observed in blood pressure when the fat content of the diet was increased to 35 en% during the second 40 days.

In studying 8 mild hypertensives over a 4-week period, Comberg et al (13) also observed a decrease of 8 mm Hg diastolic blood pressure when the volunteers consumed linoleic acid-enriched diets containing sunflowerseed oil and soybean oil. Systolic blood pressure also decreased, but not significantly.

In a crossover study (37), 10 hypertensive males were compared to 10 normotensive males. All foods were prepared in a metabolic kitchen and were weighed. The intervention diet contained 25 en% total fat of which 6.6 en% was n-6 PUFA. Systolic and diastolic blood pressure was significantly lower in the hypertensives during the low-fat, higher P:S intervention period than during ingestion of a typical USA diet. The normotensives showed no significant changes during either dietary period. Sodium and potassium excretion and urine volume in the hypertensives showed a progressive increase during the low-fat, higher P:S dietary period. When the diets were reversed, sodium excretion and urine volume decreased progressively to initial levels, but potassium changes were variable (38).

Four groups of males selected on the basis of their blood pressures, i.e. normal to slightly elevated, participated in a study where they consumed natural diets containing 2 levels of fat, 44 and 25 en%, at P:S of 0.3 and 1.0 (41). All of the foods consumed were weighed. Regardless of the level of fat, systolic and diastolic blood pressures decreased when the subjects consumed the P:S 1.0 diets. When the subjects consumed the higher fat P:S 1.0 diet, systolic blood pressure decreased by 8 mm Hg and diastolic pressure decreased by 7 mm Hg. On the low fat, high P:S diet, systolic and diastolic blood pressure decreased by 6 mm Hg. These data suggested that linoleic acid was the nutrient that reduced blood pressure.

Rao et al (61) supplemented PUFA in the diets of normotensive and hypertensive subjects for 6 weeks. When safflower oil was added to the diet, a significant decrease of 5 mm Hg in both systolic and diastolic blood pressure occurred. Groundnut oil (peanut oil) produced a decrease of 8 mm Hg in diastolic blood pressure only. A third group of subjects, unresponsive to antihypertensive therapy, had a reduction of 7 mm Hg in systolic and diastolic blood pressure when they were supplemented with safflower oil for 6 weeks.

When Margetts et al (49) placed normotensive subjects on either high or low P:S diets, no change in blood pressure was observed. Data obtained from this study appeared to agree with the lack of dietary effect of linoleic acid on blood pressure for normotensives in other studies (9, 27, 37, 53, 60, 64). However, Mutanen et al (57) investigated the effects of sunflowerseed-oil and rapeseed-oil enriched diets on blood pressures of normotensive males and females and found a significant decrease of 1.3 mm Hg in diastolic pressure when the 59 subjects consumed the sunflowerseed-oil diet. No effect on blood pressure was observed when the subjects consumed the high α-linolenic acid (rapeseed-oil) diet.

In an attempt to define which fatty acid influenced the reduction in blood pressure, a study was conducted on a metabolic research unit (33, 35) in which mildly hypertensive men consumed a diet containing ~ 10 en% of each saturated and monounsaturated fatty acid. In addition, 3 en% linoleic acid was fed for 6 weeks and then was increased to ~ 10 en% for an additional 6 weeks. A significant decrease in systolic and diastolic blood pressure of 7 mm Hg and 5 mm Hg, respectively, was observed during the 10-en% linoleic acid feeding period.

COMMUNITY-BASED STUDIES The effects on blood pressure of reducing the amount of fat and increasing the P:S of the dietary fat were reported in a dietary intervention study of a rural Finnish population (40). Fifty-nine high normotensive subjects, 30 men and 29 women, aged 40 to 50 years, participated. A significant decrease in both systolic (7.7 mm Hg) and diastolic (6.3 mm Hg) blood pressure was observed for all subjects on the lower fat (24 en%)-higher P:S diet. The intervention diet contained 8.5 en% linoleic acid, 7.6% saturated, and 6.3 en% monounsaturated fatty acids. Blood pressures returned to initial levels when the subjects reverted to their customary diets.

A follow-up intervention study in 2 other communities in North Karelia, Finland was conducted (59) with 57 normal to moderately hypertensive couples, aged 20 to 50 years. The low-fat diet (6.4 en% n-6 PUFA) group had a reduction in both systolic and diastolic blood pressure. During the switchback period their blood pressures rose progressively to the initial levels. Only small differences were observed in systolic and diastolic blood pressures in the control (4.3 en% n-6 PUFA) and low-salt (3.4 en% n-6 PUFA) groups throughout the study.

In a community-based study in Italy, Strazzullo et al (80) investigated the effects of modifying the typical Mediterranean diet to mimic the typical Western diet in a healthy, rural population in Southern Italy. Fifty-seven normotensive volunteers (29 males and 28 females, aged 30–50 years) were studied. Systolic and diastolic blood pressure increased significantly in males (2.7 mm Hg and 3.6 mm Hg) and females (3.3 mm Hg and 4.0 mm Hg). After a return to their customary diet for another 5 weeks, the blood pressures of the participants returned to baseline levels.

Adolescents (15–18 years) were the focus of a community-based study conducted by Stern et al (76) in North Carolina. Within 6 weeks, the students receiving the dietary supplements (mainly from corn oil) had an 11-mm Hg decrease in systolic blood pressure, while the control group had a decrease of 6 mm Hg. A slight decrease was observed in diastolic blood pressure in both groups. In another community-based intervention study, Vartiainen et al (87) reported that systolic and diastolic blood pressures were decreased by 4

mm Hg and 3 mm Hg, respectively, in children and adolescents (8–18 years) when dietary fat was decreased and P:S levels were increased to either 0.4 or 0.9 (60).

In summary, in all studies where hypertensive subjects were fed n-6 fatty acids, significant reductions in blood pressure were observed. This occurred in free-living and community-based intervention studies and in a metabolic unit study. When normotensive subjects were studied, most authors reported no significant reductions in blood pressure related to dietary linoleic acid.

Epidemiological Studies

Additional supporting evidence relating dietary fat to blood pressure comes from epidemiological studies. A pilot epidemiological study was conducted (36) in farmers, aged 40 to 50 years, in Italy, Finland, and the USA. The Finns, who consumed a diet high in saturated fat and very low in linoleic acid, had significantly higher systolic and diastolic blood pressures than the Italian and USA farmers.

In an epidemiological survey of 650 healthy men, Oster et al (58) found a highly significant negative correlation between the linoleic acid composition of adipose tissue and blood pressure. Dietary linoleic acid intake was positively correlated with urinary sodium concentration and urine volume and negatively correlated with serum sodium concentration. Berry & Hirsch (5) studied the long-term effects of dietary fat on blood pressure by analyzing adipose tissue fatty acid composition of 399 free-living male subjects (average age, 47 years). Stepwise-regression analysis revealed that α-linolenic acid in adipose tissue was associated with a decrease in systolic and diastolic blood pressure and that a 1% increase of α-linolenic acid in adipose tissue was associated with a 5-mm Hg decrease in mean arterial blood pressure.

Prostaglandin Studies

A number of studies have dealt with precursors of PGs and their effects on kidney function, on levels of PGs in plasma, and excretion of PGs, but only a few have taken into account blood pressure regulation. PGs are not stored in the body but are synthesized as needed and degraded in minutes. It is thought that the major end products of circulating PGs are excreted in the urine in the form of polar metabolites. The pharmacological effects of PGs have been studied extensively in the last decade, yet their clinical and nutritional importance is still far from clear. Little is known about the daily synthesis and turnover of PGs or the daily production of PGs in the body as they are affected by n-6 or n-3 fatty acid intake and the degree to which they are related to a variety of physiological functions. The mechanisms of the vasodilatory effect of fatty acids on renal circulation in man remains unclear. Changes in renal eicosanoid metabolism with alterations in the balance of the

vasodilatory eicosanoids PGE_2 and PGI_2 and the vasconstrictor TxB_2 remain a likely explanation.

A study showing that cortex and medulla have differing roles in the synthesis of PGs through the cyclooxyengenase pathway was conducted by Frölich & Walker (26). They described results in hypertensive subjects in which PGI_2 was shown to be the compound most characteristic of the cortex and the one that promoted renin release from the kidney. They found that PGE_2 was characteristic of the kidney medulla and that it was involved in water and salt regulation. In vivo and in vitro studies by Weber et al (91) demonstrated that renal formation of PGs in the vasculature of the cortex, PGI_2 and $PGF_{1\alpha}$, represented an important step in describing the mechanism of renin secretion, which is influential in controlling electrolyte and volume balance.

Friedman et al (25) reported decreased turnover of PGE_2 levels in infants on a linoleic acid–deficient diet. The influence of linoleic acid intake on PG formation has been studied (1–3, 95) in healthy volunteers, mainly females. The subjects consumed liquid formula diets containing 0, 3, 3.5, 4, 6, 8, 13, 18, or 20 en% of linoleic acid for 2-week periods. Tetranorprostanedioic acid (TNPDA) levels in urine increased with increasing amounts of linoleic acid. TNPDA in urine represents the sum total of the end products of PG metabolism and includes PGE_1, PGE_2, 6-keto-$PGF_{1\alpha}$, and $PGF_{2\alpha}$. In one of these studies (1), systolic blood pressure decreased by 10 mm Hg during the corpus luteum phase of the subjects' menstrual cycles. Although these were short-term dietary intervention studies, the authors demonstrated that linoleic acid stimulated levels of PGs in urine and influenced blood pressure.

The effects of acute administration of linoleic acid on the production of urinary PGE_2 and 6-keto-$PGF_{1\alpha}$ were monitored by Epstein et al (20). Six normal subjects were infused with 1.5 g/kg body weight of safflower oil (Liposyn®) containing approximately 77% linoleic acid over an 8-h period. The Liposyn induced a profound increase in 6-keto-$PGF_{1\alpha}$ while PGE_2 excretion increased modestly.

Ferretti et al (23) investigated the effects of marine oil supplementation on the level of the urinary metabolite of PGE-M (PGE_2 + PGE_1). They found a 14% reduction in PGE-M after 10 weeks of marine oil supplementation, which suggests an inhibition of PG synthesis by marine oil. The occurrence of the trienoic derivatives of PGs, PGI_3, and PGE_3 in humans as a result of marine oil intake has been demonstrated by GC-mass spectroscopy. These PGs were found in urine when marine oils were fed. The mechanism for the reduction in blood pressure appears to be the vasodilatory effect of n-3 fatty acid supplements within the renal circulation (17, 18, 22, 24). Results of a study by Judd et al (42) suggest that the amount of dietary linoleic acid is important in the regulation of PG synthesis. These authors observed significant reductions in the excretion of $PGF_{2\alpha}$ and 6-keto $PGF_{1\alpha}$ when linoleic acid intake was reduced from 6.5 en% to 3.2 en%. Systolic and diastolic blood pressures

were lowered by 9 mm Hg and 4 mm Hg when the total fat was reduced from 37 en% to 25 en%. These changes were not related to the level of linoleic acid. The authors show that $PGF_{2\alpha}$ and 6-keto-$PGF_{1\alpha}$ were positively correlated with the blood pressure changes.

Blair et al (7) studied the levels of PGs in urine after subjects consumed 3 or 10 en% linoleic acid. All foods consumed in this study were weighed. At 10 en% linoleic acid, the female subjects excreted significantly higher levels of PGE_2 while the excretion of 2,3-dinor TxB_2 decreased.

BLOOD PRESSURE IN HUMANS: n-3 FATTY ACIDS AND PROSTAGLANDINS

One of the earliest reports on the effect of marine oils on blood pressure was by Mortensen et al (56). In studies of marine oil supplementation to Western diets, they administered either 10 g of vegetable oil (a mixture of corn oil and olive oil) or 10 g of marine oil (MaxEPA) to healthy volunteers for 10 weeks. Each oil contained approximately 40% of either n-6 or n-3 PUFA. During the n-3 PUFA feeding period, systolic blood pressure decreased. The intake of the n-3 or n-6 fatty acid supplements represented less than 1 en% of the daily intake. No dietary control was exerted, but the subjects were asked not to change their dietary habits.

Lorenz et al (47) added 40 ml/day of cod-liver oil to the diets of 8 volunteers for 25 days. This amount of cod-liver oil provided about 10 g of n-3 fatty acids per day and represented about 4.5 en% of the total calories. The n-3 PUFA was incorporated into platelet and erythrocyte membrane phospholipids at the expense of n-6 PUFA. Systolic blood pressure decreased by $\sim$ 10 mm Hg and blood pressure response to norepinephrine fell by $\sim$ 11 mm Hg. This reaction was reversed 4 weeks after the cod-liver oil supplementation was stopped. Formation of PGs derived from EPA, and the interference of EPA with formation and action of PGs derived from arachidonic acid, were evident in vitro.

A series of short-term (2 weeks) studies were conducted by Singer et al (69–73) in which mackerel or herring was added to the diets of normotensive and hypertensive subjects. Lower systolic and diastolic blood pressures were usually observed in the subjects consuming the mackerel supplements. von Houwelingen et al (89) attempted to determine the effect of the intake of fish on specific cardiovascular risk factors in the Netherlands and Norway. Healthy male normotensive volunteers, ranging in age from 28 to 45 years, were given a dietary supplement of $\sim$ 135 g/day of either mackerel or meat for 6 weeks. Systolic blood pressure dropped slightly in both groups to a comparable degree; therefore, no specific effect of the fish supplement was observed. The fish-supplemented group had prolonged bleeding times (8.43 min vs 7.72 min

for the control group) along with decreased platelet counts (218×10^9 per liter vs 231×10^9 per liter).

Knapp & Fitzgerald (44) studied blood pressure and eicosanoid production during supplementation with n-3 or n-6 dietary fats for 4 weeks. Thirty two men with mild essential hypertension participated in this study. They reported a reduction in systolic and diastolic blood pressure in subjects who took a supplement of 50 ml/day of MaxEPA, but no changes in the groups consuming 50 ml/day of safflower oil or a mixture of oils similar to that consumed in the USA diet. A significant reduction in TxB_2 metabolites was observed at the end of the high marine oil period. Significant increases in PGE_2 metabolites were found in the group receiving safflower oil, suggesting improved kidney function. Biermann & Herrmann (6) reported that when 125 male subjects consumed either 2 or 6 g/day of marine oil or equivalent amounts of n-6 PUFA, the marine oil contributed to a decrease in blood pressure whereas the n-6 fatty acids did not. In a double-blind study conducted by Kestin et al (43), 33 normotensive men were randomly assigned to diets containing supplements of oil high in either linoleic acid, α-linolenic acid, or EPA + DHA. After 6 weeks of supplementation, the group consuming the high EPA + DHA showed a significant decrease in systolic blood pressure. No effect was shown on diastolic blood pressure.

Margolin et al (50) compared the blood pressure lowering effects of either 9 g of marine oil or 9 g of corn oil. Forty-six elderly hypertensive subjects were randomized into dietary groups in a double-blind crossover study. During the first treatment period, both marine oil and corn oil lowered blood pressure. After a washout period, blood pressures were not lowered any further during the second period. An interesting part of this study was that many of the subjects took the fat supplements in addition to one or more antihypertensive drugs. Apparently, an interaction between the dietary fats and the antihypertensive drugs effectively lowered blood pressure. Bønaa et al (8) demonstrated in hypertensive subjects that dietary supplementation with 6 g/day of marine oil EPA and DHA lowered blood pressure more than did supplementation with 6 g/day corn oil in a control group. The blood pressure response correlated to changes in plasma levels of phospholipid n-3 fatty acids.

Levinson et al (46) studied male and female hypertensives, 18–75 years of age, supplemented with either MaxEPA or palm oil + corn oil. Diastolic blood pressure decreased during treatment in the marine oil group. The amount of n-3 fatty acids used in this study added up to about 21 g/day. This would be equivalent to consuming about 14 kg of fatty fish per day. In this study, serum aldosterone, plasma renin activity, and plasma catecholamine levels did not change with either n-3 or n-6 fatty acid supplementation. Overall, these findings suggest that the renin-angiotensin-aldosterone system, the sympathetic nervous system, and fluidity of cell membranes were not primary mediators of the hypotensive effect of the marine oil.

A study by Cobiac et al (10), found that a combination of 8 g marine oil (Himega®) and sodium restriction reduced blood pressure in elderly normotensive subjects. The phenomenon of reducing salt intake while administering marine oil has not been studied to a great extent.

In summary, the results of the studies reported here show that n-3 fatty acids of marine origin generally reduced blood pressure. Of concern in most n-3 fatty acid studies on blood pressure is that capsules of oil were given as supplements at pharmacological levels. Furthermore, when n-6 fatty acids were given as supplements in capsule form to serve as the control fat in a number of n-3 fatty acid studies reported here, the group taking the n-6 fatty acid supplement showed no changes in blood pressure. The lack of effect of the n-6 fatty acids on blood pressure could be due to the low levels of n-6 fatty acids given as supplements and, hence, to low levels of total n-6 fatty acids in the diet. The feeding of high levels of compounds with unsaturated double bonds from marine or plant sources to control blood pressure may be harmful to the degree to which lipid peroxidation occurs under these conditions.

CONCLUSIONS

Dietary n-6 and n-3 fatty acids play a role in blood pressure regulation. Both classes of fatty acids have been shown to reduce blood pressure in rats and hypertensive subjects. Until studies are conducted in which these fatty acids as well as other dietary components are controlled, their role in blood pressure regulation will remain unclear.

Only a few well-designed nutritional studies on the effect of n-3 fatty acids on blood pressure have utilized fish as the primary source of the n-3 fatty acids. These studies were conducted in normotensive individuals and the results were negative, i.e. they did not lower blood pressure. In the case of n-6 fatty acids, a number of studies have been conducted on the metabolic unit, as free-living studies, or as community-based dietary intervention studies in which food intake was carefully controlled. These studies have demonstrated the lowering of blood pressure in hypertensives by dietary means.

The studies where n-3 and n-6 fatty acids were given as supplements (usually in the form of capsules) can be described as pharmacological trials, because the levels of the n-3 fatty acids administered were well beyond what could possibly be eaten as fish. Hence, any interpretation of the data must take into account the fact that these are drug trials. When n-6 fatty acids were given as the so-called control placebo for the n-3 fatty acid studies, the amount of n-6 fatty acid given was usually below the quantity required in the usual diet, i.e. 5 to 10 en%. Moreover, there generally was no attempt to assess the amount of n-6 fatty acids in the diet. Interpretation of the data of n-6 fatty acids supplements to lower blood pressure is difficult if not impossible. On

the other hand, the data for the n-3 fatty acid supplement intake suggests a lowering of blood pressure in hypertensive subjects.

PG production in kidney and other tissue from dietary PUFA is also involved in the regulation of blood pressure. At the present time, it is not possible to relate how n-6 or n-3 fatty acids affect PG production, owing to the lack of adequate techiques for assessing PG output in urine. Clearly, only a sophisticated chemical approach will yield the information needed to arrive at reasonable conclusions. The methods currently being adapted to give this type of information include extraction, chromatography, and mass spectrographic analysis of the urinary metabolites of PGs. Most of the data presently cited in the literature are based on radioimmunoassay techniques for determining the level of PGs in tissue and urine. These techniques, although sensitive, lack specificity. As the spectrographic techniques become available for routine usage, we should be better able to assess the relative roles of n-6 and n-3 fatty acids in controlling blood pressure as well as in other physiological functions.

Further research is needed to understand the relationship between dietary n-6 and n-3 PUFAs and PG metabolism as well as their interaction with other metabolic processes in the regulation of blood pressure.

The level of dietary n-6 fatty acids required to reduce blood pressure in hypertensives appears to be in the range of 5 to 10 en%. This amount of n-6 fatty acids agrees with the recommendations of most health groups for the reduction of blood lipids. The level of n-3 fatty acids required in order to lower blood pressure is not clear, but levels ranging from <3 to about 21 g/day have been reported to reduce blood pressure in hypertensives.

The study of diet and hypertension is still in its infancy and will require a far greater effort to elucidate the role of fat and fatty acids on blood pressure.

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