Natural bioactive substances in milk and colostrum: effects on the arterial blood pressure system

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High blood pressure is a significant public health problem worldwide which is associated with increased risk of cardiovascular disease, stroke, and renal disease. The development of this disease is influenced by genetic and environmental factors. The results of many studies have linked increased consumption of milk and milk products with lower blood pressure and reduced risk of hypertension. The intake of several minerals found in milk has been demonstrated to have an inverse relationship with blood pressure. Peptides formed during the digestion of milk proteins have also been demonstrated to have a blood pressure lowering effect. Other components in milk that have been examined for their effects on blood pressure have been less promising. More recent data indicate that a dietary pattern that is low in fat, with fruits, vegetables, and low fat dairy products can significantly reduce blood pressure and lower risk of developing high blood pressure.

Milk: Blood pressure: Electrolytes: Minerals: Peptides: Diet: Calcium

Introduction

High blood pressure, which is defined as a systolic blood pressure over 140 mmHg and a diastolic blood pressure over 90 mmHg, remains one of the most significant public health problems in the world (Life Sciences Research Office, 1995). Heterogeneous in origin, the development of this disease is influenced by numerous risk factors, including genetic predisposition, advancing age, a high alcohol intake, overweight, a sedentary life-style, and, for certain people, dietary factors that may include a high sodium intake and/or low calcium intake.

Many studies link higher intakes of milk and milk products with lower blood pressure and reduced risk of hypertension. For example, a study of 5000 men found that men with normal blood pressure reported a higher intake of whole milk than did hypertensive men (Ackley *et al.* 1983). Similarly, the Puerto Rico Heart Study found an inverse association between milk intake and both systolic and diastolic pressure in men (Garcia-Palmieri *et al.* 1984). A Canadian case–control study of pregnant women linked a higher calcium intake from dairy foods during the first 20 weeks of pregnancy with a lower risk of gestational hypertension (Marcoux *et al.* 1991). More recently a multicentre study of more than 450 adults found that a low-fat diet rich in dairy foods (roughly three servings a day), fruits and vegetables (known as the DASH diet) significantly reduced blood pressure within two weeks (Appel *et al.* 1997). A recent reanalysis of this study found that the DASH diet significantly lowers blood pressure in almost all

subgroups of adults studied (e.g. men and women, older and younger adults, obese and lean individuals, African Americans, sedentary and active individuals) (Svetkey *et al.* 1999).

Although both animal and human studies significantly link higher calcium intakes with decreased risk of hypertension, research indicates that the beneficial effects of dairy products on blood pressure regulation involves more than just calcium. The previously mentioned study of 5000 men reported a stronger inverse relationship between whole milk calcium intake and systolic blood pressure (SBP) than between total calcium intake and SBP (Ackley *et al.* 1983). A separate investigation found that providing 600 mg of calcium in the form of yoghurt proved more effective than calcium carbonate supplements in reducing systolic blood pressure and intracellular calcium in black hypertensive adults with non-insulin-dependent-diabetes (Zemel *et al.* 1998). Another study found that milk exerted a greater and more rapid effect than calcium alone in lowering blood pressure in young, normotensive women (Van Berestein *et al.* 1986). Additionally, a recent meta-analysis of 42 studies found that investigations that utilized low-fat dairy foods as the dietary source of calcium produced a greater (although not statistically significant) reduction in blood pressure than studies which employed calcium supplements (Griffith *et al.* 1999). More interesting was the finding that the response to dietary calcium was homogeneous whereas the response to supplemental calcium was heterogeneous.

Milk is a complex mixture of many macro- and

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micronutrients that can influence blood pressure. These biologically active components include not only calcium and other minerals, but also vitamins, protein and potentially lipids. Colostrum contains the same macro- and micronutrients as mature milk, but exhibits a different protein (Montgomery *et al.* 1987) and fatty acid composition (Gibson & Kneebone, 1981) and higher immunoglobulin content (Saravia *et al.* 1983).

Minerals/electrolytes

Milk and colostrum are sources of at least four different minerals/electrolytes that can affect blood pressure (i.e. calcium, sodium, potassium and magnesium).

Calcium

Over 100 animal studies have been conducted on the effect of dietary calcium on blood pressure. The majority of these studies demonstrate an inverse relationship between calcium intake and blood pressure (International Dairy Foods Association, 1995). Similarly, over 100 epidemiological studies have reported an inverse relationship between dietary calcium and blood pressure in humans across a broad range of ethnic and geographic groups.

A review of 25 epidemiological studies relating the intake of calcium or calcium-rich foods to blood pressure found that the majority of these studies supported an inverse relationship (Cutler & Brittain, 1990). Similarly, a meta-analysis of 23 population samples abstracted from 19 published papers links 1000 mg higher calcium intake with significantly lower systolic and diastolic blood pressure in both men and women (Cappuccio *et al.* 1995).

Epidemiological studies published after these meta-analyses were conducted continue to support a beneficial effect of increasing calcium intake on blood pressure. For example, follow-up data from the first National Health and Nutrition Examination Survey (NHANES I) of more than 6600 adults found that subjects who reported high calcium intakes were less likely to develop hypertension ten years later (Dwyer *et al.* 1996). A recent analysis of data from more than 600 children participating in the Dietary Intervention Study in Children (DISC) also links higher intakes of calcium with lower diastolic blood pressure (Simons-Morton *et al.* 1997). A recent study of 260 children reports that children of mothers who consumed an additional 2 g of supplemental calcium a day during pregnancy exhibit lower blood pressure levels than children of mothers who did not consume the additional calcium (Hatton *et al.* 1998).

Clinical trials demonstrate that certain subsets of the population exhibit greater decreases in blood pressure in response to increased dietary calcium than others. A meta-analysis of 33 randomized controlled intervention trials found that calcium supplementation exerted greater blood pressure-lowering effects in hypertensive adults than in normotensive adults and greater effects in pregnant women than in non-pregnant adults (Witteman *et al.* 1989). Clinical trials also indicate that individuals with the following blood profile: low blood renin, low ionized calcium, and elevated blood 1,25-dihydroxyvitamin D levels experience greater reductions in blood pressure in response to increasing dietary calcium than hypertensive subjects with the opposite blood profile (Resnick *et al.* 1986). Clinical investigations on calcium and blood pressure indicate that population subgroups most likely to benefit from increasing calcium intake include pregnant women, older adults, African Americans, diabetic individuals and individuals with low renin activity, lower blood calcium levels, and higher levels of urine calcium and blood parathyroid and vitamin D hormones (Miller *et al.* 1999). In a recent position statement, the American Heart Association noted that increasing dietary calcium may 'preferentially' reduce blood pressure in individuals with salt-sensitive hypertension and further stated that the beneficial effect of increasing dietary calcium on blood pressure is more evident when initial calcium intakes are low (i.e. 300–600 mg/day) (Kotchen & McCarron, 1998).

Researchers propose that calcium may decrease blood pressure by a variety of mechanisms including: (1) increasing urinary sodium excretion, (2) preventing a sodium chloride-induced decrease in the levels of the neurotransmitter noradrenaline which would otherwise constrict blood vessels, (3) preventing a rise in calcium-regulating hormones (i.e. parathyroid hormone and 1,25-dihydroxyvitamin D3) which would otherwise increase blood vessel resistance, (4) suppressing the renin–angiotensin system which, in turn, relaxes smooth muscle cells lining blood vessels, (5) decreasing intracellular calcium, (6) decreasing smooth muscle hypertrophy, and (7) increasing production of an endothelial relaxing factor.

Sodium

Researchers propose that dietary sodium increases blood pressure by osmotically drawing water into extracellular spaces, such as blood vessels. Although historically dietary sodium has been linked with blood pressure, research conducted over the past three decades indicates that only certain people respond to increasing dietary sodium intake with a rise in blood pressure (i.e. 'salt sensitivity'). Animal as well as human research demonstrates that salt sensitivity is not a universal trait. Whereas spontaneously hypertensive rats (SHR) respond to increases in dietary sodium with an increase in blood pressure, other strains of rats (e.g. Wistar Kyoto) remain relatively refractory to sodium intake (Frohlich *et al.* 1993).

Both epidemiological and clinical human trials indicate that only 30–60 % of people with hypertension and 15–45 % of normotensive individuals are saltsensitive (Sullivan, 1991). This research supports the finding that African Americans with family history of hypertension, obese individuals, adults over 55 years of age, and people with low blood renin levels are more likely than other individuals to be salt-sensitive (Sowers *et al.* 1988). One of the largest cross-sectional studies conducted to study the impact of dietary sodium on blood pressure, the International Study of Electrolyte Excretion and Blood (INTERSALT) examined adults in 52 different communities (The INTERSALT Cooperative Research Group, 1988). Although this study linked increasing sodium intake (reflected by urine sodium levels) with an increase in blood

pressure with increasing age, this investigation found no significant association between sodium intake and either mean blood pressure or the prevalence of hypertension. A subsequent analysis of INTERSALT data that were corrected for initial blood pressure levels, found no significant relationship between sodium intake and the rate of age-related increases in blood pressure (Hanneman, 1996; Davey Smith & Phillips, 1996).

A recent review of 56 randomized, controlled clinical trials concluded that dietary sodium restriction lowers blood pressure levels more in older, hypertensive adults than in younger, hypertensive individuals (Midgley *et al.* 1996). This meta-analysis found little or no blood pressure benefit of reducing sodium intake in adults with normal blood pressure levels. Since the publication of this meta-analysis, a three-year intervention study called the 'Trials of Hypertension Prevention' found that sodium restriction exerted no significant effect on blood pressure in both hypertensive and non-hypertensive adults (The Trials of Hypertension Prevention Collaborative Research Group, 1997). This study of 2400 adults with 'high normal' blood pressure linked a 4 g reduction in daily salt intake with only a 2·9 and 1·6 mm Hg drop in systolic and diastolic blood pressure, respectively, after 6 months. The researchers also found that this benefit in blood pressure lowering 'mostly vanished by 36 months' (Taubes, 1998).

Potassium

A number of animal studies, epidemiological investigations, and clinical trials support that dietary potassium can reduce blood pressure (Haddy, 1991; Linas, 1991). It has been suggested that high intakes of dietary potassium may protect against the development of hypertension and improve blood pressure control in those who have high blood pressure (National Institutes of Health, 1997).

A recent meta-analysis of 32 randomized, controlled trials found that potassium supplementation reduces both systolic and diastolic blood pressure, particularly among hypertensive individuals and people who consume high levels of sodium (Whelton *et al.* 1997). The investigators conclude that increasing potassium intake may prove beneficial to prevention and treatment of hypertension, especially among individuals who experience difficulty in lowering their sodium intake. The Nurses Health Study of 300 women with normal blood pressure and habitually low intakes of calcium, potassium, and magnesium, linked supplemental intakes of potassium, but not calcium or magnesium, with lower blood pressure (Sacks *et al.* 1998). Similar to research findings on calcium, studies also indicate that increasing potassium intake may lower blood pressure more in African-American individuals than in white subjects (Brancati *et al.* 1996). A recent study reports that increasing potassium intake can suppress salt sensitivity in African-American adults (Morris *et al.* 1999).

Researchers have proposed several mechanisms for the blood pressure-lowering effects of potassium. These mechanisms include increased urinary sodium excretion and reduced urinary excretion of calcium and magnesium (Reusser & McCarron, 1994).

Magnesium

Research on the effect of magnesium on blood pressure is limited. However, a significant number of animal, epidemiological and clinical trials support a beneficial effect of magnesium on blood pressure. Research studies report that experimental animals exhibit a rise in blood pressure when fed a magnesium-deficient diet (Berthelot & Esposito, 1983; Altura *et al.* 1984). Similarly, prospective human studies offer evidence for a beneficial effect of dietary magnesium on blood pressure regulation. The Honolulu Heart Study of more than 600 men reported a strong inverse relationship between magnesium intake and both systolic and diastolic blood pressure (Joffres *et al.* 1987). The Nurses Health Study reports that women who consumed at least 280 mg of magnesium a day exhibited one-third less chance of developing hypertension than women who consumed less than 200 mg of magnesium per day (Witteman *et al.* 1989).

Despite the positive findings of both animal and epidemiological studies on magnesium and blood pressure, clinical trials have, for the most part, yielded no or only slightly beneficial effects of magnesium supplementation on blood pressure (Witteman *et al.* 1989). Researchers note that magnesium appears to exert a beneficial effect a on blood pressure primarily in individuals who are deficient in this nutrient (Zemel *et al.* 1997). Paolisso & Barbagallo (1997) propose that magnesium can reduce blood pressure by promoting vascular smooth muscle relaxation.

Vitamin D

Limited research conducted in both animals and humans indicates that vitamin D may play a role in blood pressure regulation. Researchers have reported differences in vitamin D metabolism between spontaneously hypertensive and Wistar–Kyoto rats (Merke *et al.* 1987). These studies also link higher blood vitamin D levels with lower blood pressure in spontaneously hypertensive rats (Kurtz *et al.* 1986).

Similarly, investigations on humans have linked higher blood vitamin D levels with lower blood pressure levels in several population subgroups, including hypertensive adults (Young *et al.* 1990), men with impaired glucose tolerance (Lind *et al.* 1989) and postmenopausal women (Sowers *et al.* 1988). More recently, a study of 100 men with normal blood pressure levels links higher blood vitamin D levels with lower blood pressure (Kristal-Boneh *et al.* 1997).

The following possible mechanisms by which vitamin D may affect blood pressure have been proposed.

(1) Vitamin D enhances the absorption of calcium which, in turn, can decrease blood pressure.
(2) Vitamin D decreases blood levels of parathyroid hormone which, when elevated, can increase blood pressure (McCarron *et al.* 1980; Grobbee *et al.* 1988).
(3) Calcitriol may suppress plasma renin activity (Resnick & Laragh, 1984).
(4) Vitamin D binds to specific receptors in tissues involved in blood pressure regulation, including

heart muscle (Stumpf, 1990) and vascular smooth muscle (Merke *et al.* 1987).

Future studies are needed to further elucidate the role of vitamin D in blood pressure regulation.

Protein/peptides

Milk protein is composed of two major fractions, a micellar (casein) and soluble (whey) fraction. The content and composition of casein and whey proteins in milk differs among species. For example, cow's milk contains a higher proportion of casein to whey than human milk and is composed of four components α_{S1}-casein, α_{S2}-casein, β-casein, and κ-casein, whereas human casein consists mainly of α-casein and a small fraction of κ-casein.

Milk proteins (or more specifically, their peptides derived during digestion or food processing) can influence blood pressure both indirectly and directly. The phospho-peptides of casein, especially α-casein, indirectly affect blood pressure by binding to and enhancing the absorption of calcium in the intestine (Schlimme & Meissel, 1995). In addition to this indirect influence, a number of milk-derived peptides directly influence blood pressure (Tesche-macher & Koch, 1991). Researchers have discovered that a number of peptides derived from casein inhibit angiotensin I-converting enzyme (ACE), an enzyme that is integrally involved in the renin–angiotensin system (Meisel, 1997).

ACE catalyses the formation of the potent vasoconstric-tor angiotensin II from angiotensin I and also inactivates the vasodilator, bradykinin (Maruyama *et al.* 1987; Nakamura *et al.* 1996). By decreasing the formation of angiotensin II and bradykinin through the inhibition of ACE, casein peptides can increase blood flow and consequently reduce the risk of hypertension.

Fiat *et al.* (1993) identified three peptides in bovine Sl-casein (residues 23–34, 23–27 and 194–199) and one in bovine casein (residues 177–183) that inhibit ACE and increase bradykinin levels. It is presumed that these peptides physically compete for ACE where the inhibitory activity depends on a specific peptide structure – specifically a proline, lysine, or arginine at the C-terminus.

The antihypertensive effect of milk protein and casein peptides has been demonstrated in numerous studies in laboratory animals (Yamamoto *et al.* 1994). In 1987, researchers found that both a casein-rich diet and a whey-rich diet decreased blood pressure and attenuated the development of severe hypertension in stroke-prone spontaneously hypertensive rats (SHRSP) (Ikeda *et al.* 1987). Noting that research links certain amino acids with decreased risk of stroke, the researchers ascribed the observed antihypertensive effects, in part, to 'the amino acid compositions in casein and whey' (Ikeda *et al.* 1987).

Yamamoto *et al.* (1994) reported that skim milk fermented by several strains of *Lactobacillus helveticus* exhibited antihypertensive activity in spontaneously hyper-tensive rats (SHR). This study also found that administering either Val-Pro-Pro or Ile-Pro-Pro at levels which approxi-mated the ACE inhibitory activity of the sour milk dosage also significantly decreased SBP in the SHR rats. In contrast, oral administration of either the sour milk or tripeptides had no effect on the SBP of normotensive Wistar–Kyoto rats (WKY). It was concluded that the antihypertensive effect of Calpis sour milk and the tripeptides, Val-Pro-Pro and Ile-Pro-Pro are specific to the hypertensive state. Subsequent research found that feeding sour milk (called Calpis) fermented by a starter containing *Lactobacillus helveticus* and *Saccharomyces cerevisiae* to spontaneously hypertensive rats, decreases the activity of ACE in the aorta (Nakamura *et al.* 1995). This study isolated and identified two kinds of ACE inhibitory peptides, Val-Pro-Pro and Ile-Pro-Pro from Calpis sour milk that accounted for most of the ACE inhibitory activity in this milk.

Research indicates that long-term feeding (7–23 weeks of age) of Calpis sour milk to SHR rats significantly reduces blood pressure and depresses ACE activity in the aorta, but not in the plasma, heart, lung, liver, kidney, testes and brain (Nakamura *et al.* 1996). This study also found that the antihypertensive activity of the sour milk was dose-dependent and remained evident in SHR rats even 48 hours after replacing the sour milk diet with a control diet. A recent study conducted in SHR found that the tripeptide Ile-Pro-Ala derived from β-lactoglobulin in cheese whey exhibits strong antihypertensive activity (Abubakar *et al.* 1998). Animal research also indicates that an octapeptide derived from casein potentiates bradykinin and other casein-derived peptides may relax arteries by increasing production of nitric oxide (NO) (Lebrun *et al.* 1995).

Research is lacking on the effect of milk proteins on human blood pressure levels. Further research is needed to ascertain whether or not casein and/or whey peptides affect blood pressure regulation in humans, particularly in individuals with hypertension (Yamamoto, 1997).

Lipids

Animal research indicates that a variety of fatty acids ranging from eicosapentaenoic acid to oleic acid may affect blood pressure. Research conducted in pigs indicates that linoleic acid can reduce blood pressure by relaxing the coronary artery potentially by affecting the sodium–potassium ATPase pump (Chiang *et al.* 1989). In contrast, investigators have found that oleic acid may inhibit vasodilation by reducing the activity of the enzyme, nitric oxide synthase. One study documented that oleic acid decreased nitric oxide synthase activity in cultured bovine pulmonary artery endothelial cells (Davda, 1995). This study also reported that oleic acid inhibited the endo-thelium-dependent vasodilator response to acetylcholine in rabbit femoral artery rings preconstricted with phenyl-ephrine. Similar to oleic acid, palmitic acid has also been found to inhibit the production of the endothelium-derived relaxing factor nitric oxide. A study of human umbilical vein endothelial cells incubated with palmitic acid in culture for five hours found a dose-dependent inhibition of nitric oxide release by the endothelial cells. In contrast, this study found no effect of stearic acid on nitric oxide production (Moers & Schrezenmeir, 1996).

Despite the effects of individual fatty acids on blood pressure levels, research indicates no significant effect of either total fat or milk fat on blood pressure. A human study

that varied fat intake from 22 to 40 % of calories and polyunsaturated fat content of the diet from 3 to 19 % of calories found no effect of these dietary manipulations on blood pressure levels in young adults with normal blood pressure levels (Brussard *et al.* 1981). Similarly, a research study that found a beneficial effect of casein and whey on blood pressure in stroke-prone spontaneously hypertensive rats (SHRSP) found no effect of a 20 % milk fat diet on these animals (Ikeda *et al.* 1987).

The lack of evidence for an effect of milk fat on blood pressure may be attributable to the fact that milk fat is composed of more than 12 individual fatty acids, in addition to several other lipid components, including sphingolipids, squalene, cholesterol and free sterols all of which may have differing effects on blood pressure regulation. Collectively, the composite of these lipids that exist in milk fat may exert no net effect on blood pressure.

Conclusion

Milk and milk products are foods rich in many nutrients that may be helpful in lowering blood pressure and reducing risk of high blood pressure, particularly when included as part of a dietary pattern that is low in fat and rich in fruit and vegetables. A recent review on the Dietary Approaches to Stop Hypertension (DASH) diet concluded that health professionals should focus on dietary patterns rather than individual nutrients that can effectively lower blood pressure (Zemel, 1997). Research strongly supports that the DASH diet (a diet high in dairy foods, fruits, and vegetables) is an 'effective strategy for preventing and treating hypertension in a broad cross-section of the population, including segments of the population at highest risk for blood pressure-related cardiovascular disease' (Zemel, 1997). Milk and milk products should be an integral part of dietary efforts to lower the risk of hypertension in the world's populations (Miller *et al.* 2000).

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