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Effects of Dietary *Spirulina* on Vascular Reactivity

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ABSTRACT There are several reports suggesting that *Spirulina* (*Arthrospira*) may have a beneficial effect in the prevention of cardiovascular diseases. Here we review the results of studies on the effects of dietary *Spirulina* on the vasomotor reactivity of aortic rings excised from either lean or obese Wistar rats. We also review preliminary results on the effects of *Spirulina* intake on plasma lipids and blood pressure in humans. The results of the former studies strongly suggest that *Spirulina* induces a tone-related increase in the synthesis/release of nitric oxide by the endothelium as well as an increase in the synthesis/release of a vasodilating cyclooxygenase-dependent metabolite of arachidonic acid and/or a decrease in the synthesis/release of a vasoconstricting eicosanoid by the endothelium. In humans, *Spirulina maxima* intake decreases blood pressure and plasma lipid concentrations, especially triacylglycerols and low-density lipoprotein-cholesterol, and indirectly modifies the total cholesterol and high-density lipoprotein-cholesterol values.

KEY WORDS: *• antihypertensive activity • antioxidant activity • lipids • nitric oxide • prostanoids •* **Spirulina maxima**

INTRODUCTION

Spirulina (*Arthrospira*) is a group of blue-green cyanobacteria. For centuries, *Spirulina* has been a traditional food in some cultures. More recently it is used as a nutritional supplement throughout the world, and there are several reports suggesting that *Spirulina* may have a beneficial effect in the prevention of cardiovascular diseases.[1–4]

Cardiovascular diseases, specifically myocardial infarction and stroke, are leading causes of morbidity and mortality in developed countries.[5] Classical risk factors for these diseases include obesity, sedentary lifestyle, smoking, dyslipidemias, postmenopausal estrogen deficiency, type 2 diabetes mellitus, atherosclerosis, and hypertension.[6–9] In recent years, it has been recognized that atherosclerosis is an inflammatory disease,[10] and, hence, elevated serum levels of inflammatory markers (like C-reactive protein) are now considered both risk factors and predictors of future cardiovascular events.[11] Emerging evidence has shown that both in humans and in animal models, the intake, as a food supplement, of the nontoxic nonteratogenic blue-green cyanobacterium *Spirulina* has beneficial effects on most of the above-mentioned risk factors.[1–3,12] Such effects have been related to one or more of the biochemical constituents of *Spirulina*, which include phycocyanin (an cyclooxygenase type 2 inhibitor and antioxidant),[4,13–15] γ-linolenic acid (an essential fatty acid and precursor of arachidonic acid),[12] carotenes, and tocopherol,[16] as well as sodium and calcium spirulan.[17,18] All the above-mentioned risk factors are associated with an altered vascular reactivity, characterized by an increased responsiveness to vasoconstrictor stimuli and decreased vasodilator responses. This altered vascular reactivity is caused, at least in part, by endothelial dysfunction, namely, a decreased release of endothelium-derived vasodilator mediators (mainly nitric oxide and vasodilating prostanoids)[19–21] and an increased release of vasoconstrictor agonists (mainly endothelin and vasoconstricting prostanoids).[22–29]

Based on these antecedents, the studies here reviewed were designed to explore possible effects of dietary *Spirulina* on the vasomotor reactivity of aortic rings excised from either lean or obese Wistar rats. We also summarize here results regarding the effects of *Spirulina* intake on blood pressure and plasma lipids of a group of human volunteers.

MATERIALS AND METHODS

For the experiments in rats an experimental model that allows identifying with certainty if a given vascular response is or is not endothelium-dependent was used. In brief, in this model a pair of rings (one with intact endothelium, the other endothelium-denuded) excised from the same thoracic aorta are continuously superfused in the same miniature organ

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chamber, and the tension developed in response to a given vasoactive agonist is recorded. In these studies only two vasoactive agonists were tested. Vasoconstriction was elicited by the α-adrenoceptor agonist phenylephrine, while vasodilation was explored with carbachol (carbamoylcholine), an endothelium-dependent muscarinic agonist. To identify nitric oxide-mediated vasodilation N^{ω}-nitro-L-arginine methyl ester (L-NAME) was used to inhibit nitric oxide synthesis. To identify responses mediated by arachidonic acid-derived, cyclooxygenase-dependent prostanoids, the cyclooxygenase inhibitor indomethacin was used.

In a sample of 36 volunteers (16 men and 20 women between 18 and 65 years old) the effects of dietary *Spirulina maxima* (4.5 g/day for 6 weeks) on triacylglycerols (TAG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), aspartate aminotransferase (AST), plasma glucose concentration, and blood pressure were evaluated. Fasting blood samples and blood pressure obtained just before starting the *Spirulina* treatment were taken as controls, and afterwards blood pressure and fasting blood samples were obtained weekly. Volunteers did not modify their dietary habits during the experimental period.

RESULTS

Effects of dietary Spirulina *on vasomotor responses of aortic rings from lean rats*

Rings with endothelium from lean rats fed on a diet containing 5% *Spirulina* developed less tension in response to phenylephrine than corresponding rings from rats fed on a control diet (Fig. 1). This decrease was reversed when the cyclooxygenase was inhibited with indomethacin. In the presence of indomethacin, the concentration–response curve to phenylephrine of rings from *Spirulina*-fed rats was significantly shifted to the right of the corresponding curve of rings from rats fed control diet. The effects of inhibition of the cyclooxygenase on the vasoconstrictor effect of phenylephrine observed in rings with endothelium from *Spirulina*-fed rats suggests that dietary *Spirulina* increases the synthesis/release of a vasodilating cyclooxygenase-dependent metabolite of arachidonic acid and/or decreases the synthesis/release of a vasoconstricting eicosanoid by the endothelium.[30,31] These effects may be related to the relatively high linolenic acid content of the cyanobacteria.[12] As expected, in rings with endothelium from *Spirulina* fed rats, L-NAME, added after the inhibition of cyclooxygenase, induced an additional increase in the responses to phenylephrine. In neither the absence or the presence of indomethacin or L-NAME did dietary *Spirulina* have any significant effect on the phenylephrine-induced tension of endothelium-denuded rings (Fig. 2 and Table 1). Rings from *Spirulina*-fed rats showed both a leftward shift of the concentration–response curve to carbachol and a higher percentage of maximal relaxation in response to this agonist than those from rats on control diet (Fig. 3).[12] These latter results indicate that dietary *Spirulina* also increases the receptor-mediated synthesis/release of nitric oxide.

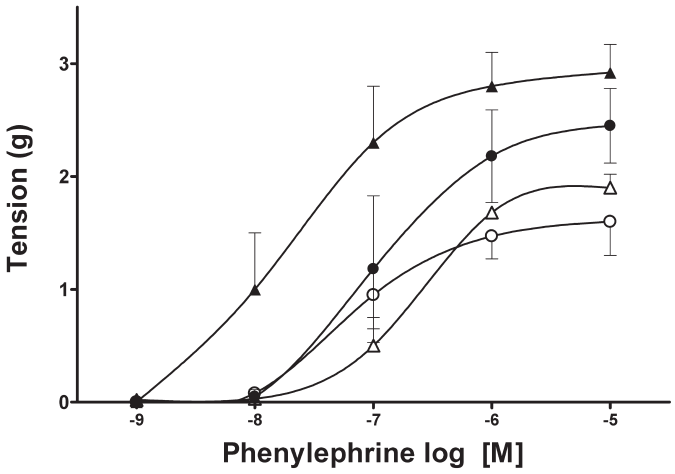

FIG. 1. Effects of dietary *S. maxima* on the concentration–response curves to phenylephrine (10^{-9}–10^{-5} *M*) of aortic rings with endothelium from lean rats (circles) and from rats fed on a fructose-rich diet (triangles). The curves were obtained either in rings from rats fed on a control diet (solid symbols) or in rings from rats fed on a diet supplemented with *S. maxima* (open symbols). Data are mean ± SD values from five rats.

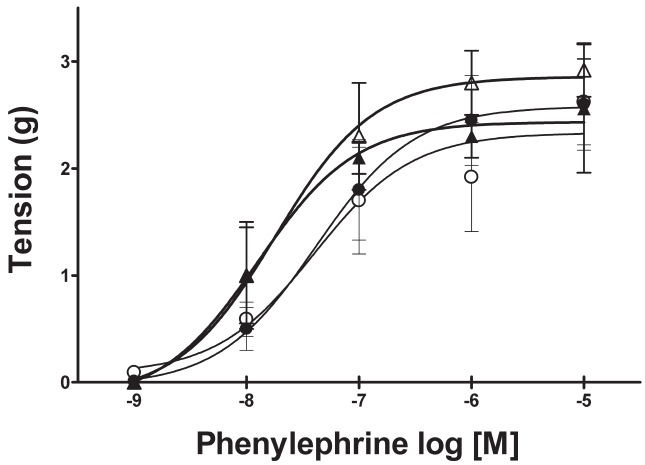

FIG. 2. Effects of dietary *S. maxima* on the concentration–response curves to phenylephrine (10^{-9}–10^{-5} *M*) of aortic rings without endothelium from lean rats (circles) and from rats fed on a fructose-rich diet (triangles). The curves were obtained either in rings from rats fed on a control diet (solid symbols) or in rings from rats fed on a diet supplemented with *S. maxima* (open symbols). Data are mean ± SD values from five rats.

Effects of dietary Spirulina *on vasomotor responses of aorta rings from obese rats*

The above-described experiments showed that dietary *Spirulina* increases, in rat aortic rings, the synthesis/release of both nitric oxide- and vasodilator cyclooxygenase-de-

TABLE 1. EFFECTS OF DIETARY *SPIRULINA* ON THE CONCENTRATION–RESPONSE CURVE TO PHENYLEPHRINE (10^{-9}–10^{-5} *M*) OF AORTIC RINGS FROM LEAN AND FRUCTOSE-FED RATS

	With endothelium		*Without endothelium*	
Group	*PD_2*	*Maximum tension (g)*	*PD_2*	*Maximum tension (g)*
Normal diet (group A)				
− indomethacin	6.98 ± 0.08*	2.45 ± 0.17	7.34 ± 0.01*	2.60 ± 0.22
+ indomethacin	6.34 ± 0.03*	2.40 ± 0.23	6.93 ± 0.01*	2.32 ± 0.30
+ L-NAME	6.24 ± 0.01*	2.62 ± 0.28	6.39 ± 0.01*	2.45 ± 0.45
Normal diet + *Spirulina* (group B)				
− indomethacin	6.96 ± 0.02*	1.44 ± 0.08*^{A}	7.76 ± 0.24*	2.65 ± 0.25
+ indomethacin	7.09 ± 0.01*^{A}	1.91 ± 0.22	7.28 ± 0.01*^{A}	2.43 ± 0.18
+ L-NAME	6.36 ± 0.01*^{A}	2.13 ± 0.26*	6.64 ± 0.01*^{A}	2.94 ± 0.38
Fructose diet (group C)				
− indomethacin	6.86 ± 0.12*	2.80 ± 0.18*$^{\dagger B}$	7.85 ± 0.11*^{A}	2.98 ± 0.09
+ indomethacin	6.77 ± 0.27	1.68 ± 0.28*	7.34 ± 0.05*	2.57 ± 0.37
+ L-NAME	6.33 ± 0.01*^{A}	1.82 ± 0.16$^{\dagger A}$	6.85 ± 0.06*^{B}	2.57 ± 0.32
Fructose diet + *Spirulina* (group D)				
− indomethacin	6.65 ± 0.02*^{AB}	1.99 ± 0.11^{ABC}	7.87 ± 0.24*^{A}	2.67 ± 0.14
+ indomethacin	6.01 ± 0.01*^{ABC}	1.68 ± 0.16^{A}	6.96 ± 0.06*^{BC}	2.52 ± 0.25
+ L-NAME	6.55 ± 0.01*^{BC}	2.08 ± 0.25	6.77 ± 0.02*^{ABC}	2.20 ± 0.14

PD_2, -log of mean molar concentration causing 50% of maximum response to phenylephrine (10^{-5} *M*); maximal tension, that developed in response to phenylephrine (10^{-5} *M*). Where indicated, indomethacin was used at 10^{-6} *M*, and L-NAME was used at 300 μM. Data are mean ± SEM values ($n = 6$ for each group). Within a given group and column, values marked with the same symbol (* or †) are significantly different ($P < .05$) from each other. Values marked A, B, or C are significantly different ($P < .05$) from the corresponding value of group A, group B, or group C, respectively.

pendent metabolites of arachidonic acid and also decreases in those rings the release of vasoconstrictor eicosanoids. Since it has been shown that in obesity nitric oxide synthesis/release is decreased and release of vasoconstrictor eicosanoids is increased,[7,20–22,25–29] it was considered of interest to evaluate the effects of dietary *Spirulina* on the vascular reactivity of aortic rings excised from rats in which obesity had been induced after a 6-week period of replacing glucose with fructose in the purified diet.

Experiments designed to explore the effects of fructose-induced obesity on the responsiveness of aortic rings to phenylephrine showed that fructose feeding promotes the synthesis/release of cyclooxygenase-dependent vasoconstricting metabolites of arachidonic acid in rings with intact endothelium (Fig. 1) and that in such rings the basal release of nitric oxide plays a negligible role during phenylephrine-induced tension development (Table 1).

On the other hand, no significant differences were observed in the phenylephrine responsiveness of endothelium-denuded rings excised from either lean or fructose-fed rats (Fig. 2). These latter data confirm the role played by the endothelium, the so-called endothelial dysfunction, in the altered vascular reactivity observed in obesity.

Rings with endothelium from rats fed on a fructose-rich diet supplemented with *Spirulina* developed significantly less tension in response to phenylephrine than corresponding rings from either fructose-fed or lean rats (Fig. 1). A plausible explanation of this result is that in these rings the increased release of vasodilator eicosanoids, described above for lean rats, opposes the fructose-induced vasoconstrictor effects.

Relaxation in response to carbachol was markedly less in rings excised from obese fructose-fed rats than in those from lean rats (Fig. 3). This observation indicates that fructose-

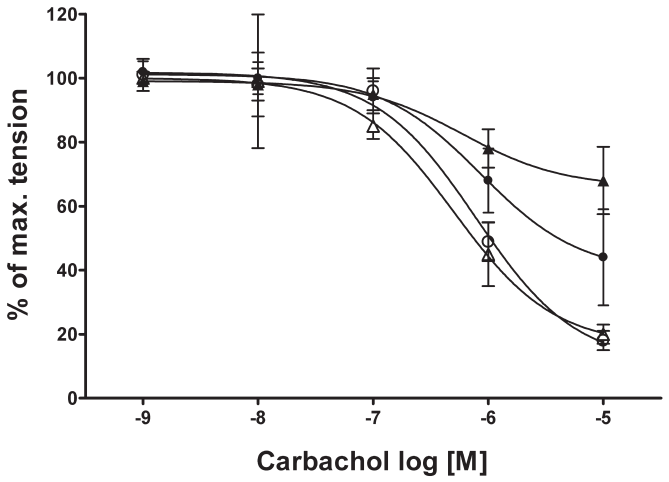

FIG. 3. Effects of dietary *S. maxima* on the concentration–response curves to carbachol (10^{-9}–10^{-5} *M*) on aortic rings with endothelium from lean rats (circles) and obese rats (triangles), precontracted with phenylephrine (10^{-5} *M*). The curves were obtained either in rings from rats fed on a control diet (solid symbols) or in rings from rats fed on a diet supplemented with *S. maxima* (open symbols). Data are mean ± SD values from five rats.

Table 2. Initial and Final High Blood Pressure Prevalences

	Blood pressure			
	Normal	*Prehypertension*	*Hypertension stage 1*	*Hypertension stage 2*
Initial	11	44	31	14
Final	36	50	11	3

Data are percentage prevalences from $n = 36$. $P = .01$ for initial versus final values by χ^2 test.

induced obesity decreases the receptor-mediated synthesis/release of nitric oxide by the endothelium. Inhibition of cyclooxygenase enhanced the carbachol-induced relaxation of these rings markedly more than in rings from lean rats, suggesting that the decreased relaxation in response to carbachol in rings from obese rats may be caused, at least partly, by an increased synthesis/release of a cyclooxygenase-dependent vasoconstricting metabolite of arachidonic acid.[25–27,30]

In aortic rings excised from rats fed fructose-rich diet supplemented with *S. maxima*, carbachol-induced relaxation was similar to that observed in rings from lean rats (Fig. 3). This observation suggest that dietary *Spirulina* either inhibits the increased muscarinic receptor-mediated synthesis/release of cyclooxygenase-dependent vasoconstrictor metabolites of arachidonic acid,[31,32] which may be responsible for the decreased carbachol-induced relaxation in rings from obese fructose-fed rats, or increases the synthesis/release of nitric oxide or even induces both of these effects.

Effects of dietary S. maxima *in humans*

Throughout the experimental period plasma AST and glucose levels did not change significantly. *Spirulina* intake induced significant changes in plasma lipids. Plasma TAG, TC, and LDL-C concentrations decreased ($P < .01$), whereas HDL-C values increased ($P < .05$). However, univariate analysis showed that changes in HDL-C and TC concentrations were dependent on TAG concentration ($P = .247$ and $P = .108$, respectively), while the change in LDL-C concentration was independent of TAG values ($P = .044$).[33]

Blood pressure decreased significantly ($P < .001$) at the end of the *Spirulina* treatment, and a significant decrease of systolic blood pressure was observed after the fourth week of treatment ($P < .01$) (Tables 2 and 3).[33] In another study, a reduction in TAG and TC levels and in the atherogenic indices TC/HDL-C and LDL-C/HDL-C was observed in 25 type 2 diabetic subjects after 2 months of *Spirulina* supplementation.[34] Similar effects had been observed in patients with hyperlipidemic nephrotic syndrome after a similar period of *Spirulina* intake.[35]

The mechanisms involved in the beneficial effects of *Spirulina* on lipid metabolism in humans have not been explored; however, in some studies in rats it was found that a concentrate of *Spirulina platensis* inhibited jejunal cholesterol absorption and ileal bile acid reabsorption, and it was proposed that C-phycocyanin is the responsible for these effects.[36] In another study in rats, a glycolipid, designated as glycolipid H-b2, isolated from *Spirulina* was shown to inhibit pancreatic lipase activity in a dose-dependent manner, and it reduces postprandial TAG levels. In the same study it was found that phycocyanin also inhibits pancreatic lipase.[37]

DISCUSSION

The results of the reviewed studies strongly suggest that *Spirulina* induces in the vascular endothelium an increase in both the tone-related synthesis/release of nitric oxide and the release of a vasodilating cyclooxigenase-dependent product of arachidonic acid and a decrease in the synthesis and release of a vasoconstricting eicosanoid. Dietary *Spirulina* thus supports efficient endothelial nitric oxide synthase

Table 3. High Blood Pressure Prevalences by Gender

	Blood pressure			
	Normal	*Prehypertension*	*Stage 1 hypertension*	*Stage 2 hypertension*
Male				
Initial	1 (6%)	9 (57%)	5 (31%)	1 (6%)
Final	6 (38%)	9 (56%)	1 (6%)	0 (0%)
Female				
Initial	3 (15%)	7 (35%)	6 (30%)	4 (20%)
Final	7 (35%)	9 (45%)	3 (15%)	1 (5%)

Data are number of volunteers (% cases of the total $n = 36$ in the sample). Initial represents values obtained before treatment with *Spirulina*, and final represents values obtained after treatment with *Spirulina*.

activity, while altering the balance of cyclooxygenase products such that prostacyclin is favored over thromboxane/prostaglandin H_2. In rings from obese rats, these effects of dietary *Spirulina* were even more marked, suggesting that dietary *Spirulina* is able to prevent the effects of fructose-induced obesity. In this regard, it is plausible that dietary *Spirulina*, by inhibiting NADPH oxidase[38] and hence suppressing peroxynitrite production, not only has a favorable impact on NO bioactivity, but also favors the production of prostacyclin over that of prostaglandin H_2 and thromboxane.[39]

We are not aware of any other study analyzing the effects of *Spirulina* as a food supplement on vascular reactivity. The validation of these results and conclusions must, therefore, await their confirmation by further studies. Meanwhile, the results, although they should be taken with caution, confirm the reported beneficial effects of *Spirulina* intake on known risk factors for cardiovascular diseases. However, large-scale, well-controlled, clinical trials are needed to validate if *Spirulina* plays a role in the prevention of cardiovascular diseases in humans. In this regard, the results of the studies performed to date in humans, confirming, in small groups, the beneficial effects of oral *Spirulina* on plasma lipids and blood pressure, should encourage clinical researchers to initiate such trials.

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AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

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