Selective right, but not left, coronary endothelial dysfunction precedes development of pulmonary hypertension and right heart hypertrophy in rats

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Submitted 15 June 2005; accepted in final form 14 September 2005

Sun, Xiaowei, and David D. Ku. Selective right, but not left, coronary endothelial dysfunction precedes development of pulmonary hypertension and right heart hypertrophy in rats. Am J Physiol Heart Circ Physiol 290: H758–H764, 2006. First published September 19, 2005; doi:10.1152/ajpheart.00647.2005.—We investigated a causal role for coronary endothelial dysfunction in development of monocrotaline (MCT)-induced pulmonary hypertension and right heart hypertrophy in rats. Significant increases in pulmonary pressure and right ventricular weight did not occur until 3 wk after 60 mg/kg MCT injection (34 ± 4 vs. 19 ± 2 mmHg and 37 ± 2 vs. 25 ± 1% septum + left ventricular weight in controls, respectively). Isolated right coronary arteries (RCA) showed significant decreases in acetylcholine-induced NO dilation in both 1-wk (33 ± 3% with 0.3 μM; n = 5) and 3-wk (18 ± 3%; n = 11) MCT rats compared with control rats (71 ± 8%, n = 10). Septal coronary arteries (SCA) showed a smaller decrease in acetylcholine dilation (55 ± 8% and 33 ± 7%, respectively, vs. 73 ± 8% in controls). No significant change was found in the left coronary arteries (LCA; 88 ± 6% and 81 ± 6%, respectively, vs. 87 ± 3% in controls). Nitro-l-arginine methyl ester-induced vasoconstriction, an estimate of spontaneous endothelial NO-mediated dilation, was not significantly altered in MCT-treated SCA or LCA but was increased in RCA after 1 wk of MCT (-41 ± 6%) and decreased after 3 wk (-18 ± 3% vs. -27 ± 3% in controls). A marked enhancement to 30 nM U-46619-induced constriction was also noted in RCA of 3-wk (-28 ± 6% vs. -9 ± 2% in controls) but not 1-wk (-12 ± 7%) MCT rats. Sodium nitroprusside-induced vasodilation was not different between control and MCT rats. Together, our findings show that a selective impairment of right, but not left, coronary endothelial function is associated with and precedes development of MCT-induced pulmonary hypertension and right heart hypertrophy in rats.

The vascular endothelium plays an important role in homeostasis by modulating vascular smooth muscle tone. Healthy endothelium constitutively produces endothelium-derived relaxing factor (EDRF or NO) and contributes to the resting vascular tone by counteracting physiological vasoconstrictor forces such as prostaglandin H2/thromboxane A2, endothelin, and superoxide anion (5, 28). Considerable clinical and experimental animal studies have shown that altered endothelial vasoregulatory function could contribute both to the early onset and to the progression of many cardiovascular diseases including heart hypertrophy (9, 10, 24, 26, 29, 30). For instance, Treasure et al. (26) reported that dilator reserve of the coronary microvasculature was markedly diminished in patients with dilated cardiomyopathy. Chronic pacing-induced heart failure in dogs also impairs endothelium-dependent dilation in epicardial coronary conduit arteries (29) and intramyocardial resistance arteries (24). This altered coronary vasomotion and the resulting changes in myocardial blood flow distribution were postulated to contribute to altered myocardial contractile function and promote the development of heart failure. However, an exact cause-effect relationship between coronary endothelial dysfunction and the development of myocardial hypertrophy/failure remains to be established. Indeed, several published reports showed either no change or increased endothelium-dependent vasodilation in heart failure (1, 11, 19). These conflicting results may be due in part to differences in the models, the time courses, and the severity of the heart failure studied, as well as the vascular tissues used to assess endothelial dysfunction. Furthermore, in most of the published reports indicating a decreased endothelial function in heart hypertrophy, endothelial dysfunction appeared to be a generalized phenomenon and there was no internal control to show that normal endothelial function remained unaffected in noninvolved organs and/or vascular beds.

We recently reported (13) that significant endothelial dysfunction occurred in the pulmonary arteries of monocrotaline (MCT)-induced pulmonary hypertensive rats, whereas endothelial function in the thoracic aorta was not altered. This is consistent with the observation that the aortic blood pressure of MCT rats is not altered (22). MCT is an inactive alkaloid obtained from seeds of Crotalaria sp. and is biotransformed to the toxic metabolite MCT pyrrole (MCTP) in the liver (7, 14). Numerous reports have shown that this active and toxic MCT metabolite causes deleterious injury to the pulmonary vasculature and subsequently results in pulmonary hypertension and right heart hypertrophy/failure (6, 8, 17, 18). Indeed, the lesions induced by MCTP administration in rat pulmonary vasculatures are similar to those observed in humans with primary pulmonary hypertension (PPH; Ref. 20), suggesting that MCT-induced pulmonary hypertension may represent a unique animal model to investigate the interrelationship between endothelial dysfunction and right heart hypertrophy and failure. More importantly, the unaffected left ventricular function and aortic pressure in these MCT-treated rats, with presumably normal endothelial function, would provide an excellent internal negative control for the investigation of the interrelationship between coronary endothelial dysfunction and the development of myocardial hypertrophy and failure. Thus in the present study we compared the vasoactivity of the right, septal, and left coronary arteries (RCA, SCA, and LCA, respectively) of control and MCT-treated rats both before (1 wk

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after MCT injection) and after (3 wk after MCT injection) pulmonary hypertension and right heart hypertrophy were established. Our results show that MCT injection results in a selective impairment of right, but not left, coronary endothelial function and that altered right coronary endothelial function is associated with and precedes the development of MCT-induced pulmonary hypertension and right heart hypertrophy in rats.

**MATERIALS AND METHODS**

The study was approved by the Institutional Animal Care and Use Committee of the University of Alabama at Birmingham and conforms to National Institutes of Health guidelines on the care and use of laboratory animals.

**MCT treatment.** Male Sprague-Dawley rats (180–200 g body wt) were randomly divided into control and MCT-treated groups and maintained in a temperature-controlled room with a 12:12-h light-dark cycle. All rats had access to standard rat chow and water ad libitum. For the MCT-treated group, rats received a single intraperitoneal injection of 60 mg/kg MCT. Control rats received an equal volume of isotonic saline injection. MCT (Sigma-Aldrich, St. Louis, MO) was dissolved in 1 N HCl, and the pH was adjusted to 7.4 with 1 N NaOH according to a method previously described (8, 18). The 1-wk MCT rats were killed 7–11 days after injection, and the 3-wk MCT rats were killed 21–25 days after injection.

**Pulmonary arterial pressure measurements.** Pulmonary arterial pressure measurements were performed as previously described (2, 21). In brief, rats were anesthetized with an intraperitoneal injection of ketamine (100 mg/kg) and xylazine (15 mg/kg) and placed on a Deltaphase isothermal pad (BrainTree Scientific, Braintree, MA) to maintain normal body temperature during surgical procedures and hemodynamic measurements. Catheters were inserted into the carotid artery and advanced to the aortic arch for measurements of aortic blood pressure and into the jugular vein for fluids and drug administration. For pulmonary arterial pressure measurements, a small incision was made in the proximal right external jugular vein through which an introducer and a Silastic catheter (PE-10) were passed. This catheter was filled with a heparin-saline solution, attached by a 25-gauge blunted needle to a pressure transducer (Statham P23Gb) which an introducer and a Silastic catheter (PE-10) were passed. This catheter was filled with a heparin-saline solution, attached by a 25-gauge blunted needle to a pressure transducer (Statham P23Gb) and coupled to a polygraph (model 7, Grass instruments, Quincy, MA), and advanced through the introducer into the pulmonary artery. Catheter position was identified by the change in pressure tracings that arose from the right ventricle. The introducer was then removed. All animals were allowed to stabilize for 20 min before the final readings of the aortic pressure, pulmonary pressure, and heart rate were recorded.

**Coronary artery studies.** Rat coronary arteries were isolated and prepared according to methods previously described (12). In brief, on the day of the experiment rats were anesthetized with intraperitoneal injection of pentobarbital sodium (60 mg/kg), their thoracic cavities were opened, and their hearts were quickly excised. Under a stereomicroscope, right and left anterior descending coronary arteries were carefully dissected from their corresponding right and left ventricular free walls, while intramyocardial septal arteries were dissected from the septum facing the right ventricular cavity. Each coronary artery, with an average length of 400 μm, was double-cannulated between two 75-μm-tip glass micropipettes and visualized with a Nikon inverted microscope coupled to a video camera and monitor. Changes in luminal diameter and wall thickness were continuously monitored with a Video Dimension Analyzer (Living System Instrumentations, Burlington, VT) and recorded on a Western Graphitec recorder and a computerized data acquisition system. The anatomy of the coronary circulation was similar in all rats, allowing the same section of coronary arteries to be isolated from each rat. The physical characteristics of the three coronary arteries studied for the different experimental animal groups as well as their preconstricting tones and their luminal diameters before the vasoreactivity studies are shown in Table 1. Oxygenated (21% O₂-5% CO₂, balanced with N₂) Krebs-Henseleit solution was maintained at 37°C and continuously circulated through the tissue bath at a rate of 21 ml/min. The Krebs-Henseleit solution consisted of (in mM) 118 NaCl, 4.6 KCl, 27.2 NaHCO₃, 1.2 MgSO₄, 1.2 KH₂PO₄, 1.75 CaCl₂, 0.03 Na₂-EDTA, and 11.1 glucose. The lumen of the vessel was not perfused but was filled with Krebs Henseleit solution.

After 15–20 min of perfusion, the intraluminal pressure of vessels was raised to 40 mmHg and allowed to equilibrate for an additional 30–40 min. Nearly all vessels used in the present study developed spontaneous contractions when the intraluminal pressure was maintained at 40 mmHg. For those that developed fewer or no spontaneous contractions, the thromboxane A₂ analog U-46619 was given to induce a similar constricting tone before vasodilatory testing (see Table 1). The averaged luminal diameters before vasoreactivity studies for the RCA, SCA, and LCA were 182 ± 10, 136 ± 10, and 148 ± 18 μm, respectively. To determine vasodilatory responses, vessel preparations were exposed to either acetylcholine (0.01–3 μM) or sodium nitroprusside (0.1 μM). For vasoconstriction studies we tested vessel response to either 30 nM U-46619 (a thromboxane mimetic) or 70 mM KCl. We also performed cumulative acetylcholine concentration-response studies in the presence of 0.3 mM nitro-L-arginine methyl ester (L-NAME, a specific inhibitor of nitric oxide synthase) to determine the contribution of endothelial NO production to vasodilatation in our preparations. For each concentration of the drug studied, the artery was incubated for a minimum of 3–5 min or until a maximum effect was obtained.

**Drugs.** Acetylcholine, L-NAME, and sodium nitroprusside were purchased from Sigma-Aldrich. U-46619 was a gift from Upjohn/Pharmacia (Kalamazoo, MI). Laboratory reagents and chemicals used for the preparation of Krebs-Henseleit solution were purchased from Fisher Chemicals (Pittsburgh, PA). All drug solutions were prepared just before use.

**Data analysis.** All values are presented and graphed as means ± SE. Statistical analysis was performed by unpaired t-test with Graphpad Prism version 4.0 software. To compare dose-response data, an ANOVA with repeated-measures method was used. A difference was accepted as significant if the probability (P) value was <0.05.

**RESULTS**

MCT-induced pulmonary hypertension and right heart hypertrophy is a well-established animal model (6, 8, 17, 18). As shown in Table 2, during the developmental phase (1 wk after MCT administration) no major change in pulmonary pressure was observed. However, significant increases in pulmonary arterial pressure were observed in both 1-wk and 3-wk MCT rats. These increases were accompanied by increases in pulmonary vascular resistance, as expected. In contrast, there was no significant change in mean pulmonary vascular resistance in control rats. The results summarized in Table 2 indicate that the 3-wk MCT rats exhibit a higher pulmonary arterial pressure and pulmonary vascular resistance compared to the 1-wk MCT rats and control rats. These findings suggest that MCT-induced pulmonary hypertension and right heart hypertrophy is a progressive process.

**Table 1. Physical characteristics of coronary arteries used in study of effects of mononitratetan on rat coronary vasoreactivity**

<table>
<thead>
<tr>
<th>Artery</th>
<th>n</th>
<th>Passive Diameter, μm</th>
<th>Constricting Tone, %</th>
<th>Diameter Before Study, μm</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCA-Control</td>
<td>10</td>
<td>276±9</td>
<td>-35±3</td>
<td>182±10</td>
</tr>
<tr>
<td>RCA-MCT 1 wk</td>
<td>5</td>
<td>228±25</td>
<td>-40±5</td>
<td>141±24</td>
</tr>
<tr>
<td>RCA-MCT 3 wk</td>
<td>11</td>
<td>273±14</td>
<td>-38±3</td>
<td>170±14</td>
</tr>
<tr>
<td>SCA-Control</td>
<td>11</td>
<td>220±6</td>
<td>-38±4</td>
<td>136±10</td>
</tr>
<tr>
<td>SCA-MCT 1 wk</td>
<td>4</td>
<td>184±16</td>
<td>-42±5</td>
<td>105±13</td>
</tr>
<tr>
<td>SCA-MCT 3 wk</td>
<td>8</td>
<td>215±10</td>
<td>-42±3</td>
<td>129±12</td>
</tr>
<tr>
<td>LCA-Control</td>
<td>8</td>
<td>216±22</td>
<td>-32±3</td>
<td>148±18</td>
</tr>
<tr>
<td>LCA-MCT 1 wk</td>
<td>5</td>
<td>123±10</td>
<td>-34±3</td>
<td>81±9</td>
</tr>
<tr>
<td>LCA-MCT 3 wk</td>
<td>7</td>
<td>200±19</td>
<td>-35±5</td>
<td>132±18</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE. Constricting tone, % change from the maximum passive luminal diameter before the vasoreactivity studies; RCA, right coronary arteries; SCA, septal coronary arteries; LCA, left coronary arteries.
Table 2. Effects of monocrotaline treatment on rat body weight, right heart-to left-heart weight ratio, and pulmonary pressure

<table>
<thead>
<tr>
<th></th>
<th>Body wt, g</th>
<th>RV/LV+S, %</th>
<th>Pulmonary Pressure, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6</td>
<td>369±13</td>
<td>24.7±0.8</td>
</tr>
<tr>
<td>MCT (60 mg/kg; 1 wk)</td>
<td>5</td>
<td>244±5*</td>
<td>27.2±1.8</td>
</tr>
<tr>
<td>MCT (60 mg/kg; 3 wk)</td>
<td>8</td>
<td>322±10*</td>
<td>36.5±1.6*</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE. MCT, monocrotaline; RV/LV+S, ratio of right ventricular weight to combined left ventricle and septum weight; ND, not determined. *Significantly different from control rats.

and right heart weight was noted. Significant pulmonary hypertension (increased by as much as 85%) and right heart hypertrophy (48%), compared with the isotonic saline-treated controls, were observed 3–4 wk after MCT administration (Table 2). Thus in the present study, 1- to 1.5-wk (1-wk) MCT-treated rats are designated as being in the pre-pulmonary hypertensive state and 3- to 3.5-wk (3-wk) MCT-treated rats are designated as being in the established pulmonary hypertension and right heart hypertrophy state.

Figure 1 shows the acetylcholine-induced dilatory response of RCA among the control and 1-wk and 3-wk MCT-treated rats. In the control RCA, addition of 0.01–3 μM acetylcholine resulted in a potent concentration-dependent vasodilation that reached a maximum of 94 ± 4% (n = 10 rats). The observed acetylcholine dilation was completely abolished by either pretreating these preparations with 0.3 mM L-NAME (a specific inhibitor of endothelial nitric oxide synthase; Fig. 1) or disrupting intimal endothelium (1.2 ± 0.4% with 3 μM acetylcholine; n = 4 rats), demonstrating its complete dependence on the endothelial production of NO. MCT treatment resulted in a time-dependent decrease in acetylcholine dilation. Comparing the middle acetylcholine dose of 0.3 μM, vasodilation was significantly decreased from 71 ± 8% in control rats to 33 ± 3% (n = 5 rats) in the 1-wk and 18 ± 3% (n = 11 rats) in the 3-wk MCT-treated rats. Similar acetylcholine-induced endothelium (NO)-dependent vasodilation was also noted in rat intramyocardial SCA (Fig. 2). MCT-induced depression in SCA vasodilation, however, was less prominent. The SCA acetylcholine-induced dilation was decreased from 73 ± 8% in control rats to 55 ± 8% and 33 ± 7% in 1-wk and 3-wk MCT-treated rats, respectively. No significant change in acetylcholine vasodilation was observed in LCA among control and 1-wk and 3-wk MCT-treated rats (Fig. 3).

In all endothelium-intact rat coronary arteries, addition of 0.3 mM L-NAME resulted in a slow, time-dependent constriction, reaching a maximum in ~15 min. No L-NAME constriction effect was observed in the endothelium-disrupted coronary arteries (~0.4 ± 0.2%; n = 4 rats), suggesting that the observed constriction was due mainly to the inhibition of spontaneous endothelial NO production. The 1-wk MCT RCA showed a significant increase in L-NAME constriction (~41 ± 6%, n = 5 rats; Fig. 4) compared with the control RCA (~27 ± 3%, n = 10 rats), whereas in the 3-wk MCT RCA constriction was significantly decreased (~18 ± 3%, n = 11 rats). No significant difference was noted in the SCA and LCA among control
or 1-wk and 3-wk MCT rats (Fig. 4). A decrease in spontaneous endothelial NO-mediated dilation in RCA may also lead to enhanced vasoconstriction response to known coronary vasoconstrictors. This is shown in Fig. 5, where we found that the responsiveness of 3-wk MCT RCA, but not those from 1-wk MCT rats, was significantly increased to 30 nM U-46619 (a thromboxane mimetic)-induced vasoconstriction (Fig. 5). No significant difference in responsiveness to U-46619 constriction, however, was observed among the control and MCT-treated LCA and SCA (Fig. 5), which is consistent with their similar spontaneous endothelial NO-mediated dilation as shown above.

In contrast, responses of the RCA to 0.1 mM sodium nitroprusside (a NO donor)-induced dilation were not significantly different among control and 1-wk and 3-wk MCT-treated rats (Fig. 6) nor among SCA (93 ± 3% and 90 ± 3%, respectively, vs. 92 ± 4% in control rats) and LCA (95 ± 2% and 98 ± 1%, respectively, vs. 96 ± 3% in control rats). Similarly, the constriction responsiveness of the rat RCA to 70 mM potassium chloride, which was not influenced by spontaneous endothelial NO production, was also not altered in the 1-wk and 3-wk MCT rats (−34 ± 5% and −36 ± 4%, respectively, vs. −34 ± 5% in control rats). These findings suggest that at these stages of MCT-induced pulmonary hypertension and right heart hypertrophy, no significant alteration has extended into the vascular smooth muscle cell function.

**DISCUSSION**

Our results show that MCT treatment resulted in a time-dependent and selective decrease in acetylcholine-induced endothelium- and NO-dependent dilation of rat coronary arteries. The most prominent decrease was in the RCA. Intermediate change occurred in the intramyocardial SCA, whereas no change occurred in the LCA in MCT-treated rats. The decrease in right coronary endothelial response to acetylcholine was...
significant depression of acetylcholine-induced endothelium bioassays of rat intralobar pulmonary arteries (13) found progressively more severe in 1 wk. Our recent functional changes appeared as soon as 24 h after MCT and became significant pulmonary endothelial and alveolar structural alterations, such as cell swelling, decrease in microfilaments, and increase in ground substance, occurred 4 days after MCT administration (70 ± 6% with 0.3 μM acetylcholine compared with 85 ± 4% in control rats) and further decreased to 48 ± 5% 3 wk after MCT. Similar alterations in pulmonary endothelial vasoregulatory function have also been reported (8, 17). Interestingly, in these same MCT-treated animals we found (13) that the thoracic aorta did not show any alteration in the endothelium-mediated dilation response (69 ± 6% in 3-wk MCT rats compared with 72 ± 5% in control rats), suggesting that the MCT-induced changes in pulmonary vasculature are unlikely to be a nonselective toxic effect of MCTP. The present finding of a lack of effect of MCT on LCA supports this contention and further demonstrates that this is likely a result of pathophysiological effects of the MCT treatment, rather than a nonselective chemical injury to the coronary endothelium.

It has been extensively reported that MCT treatment in rats consistently results in pulmonary hypertension and right ventricular hypertrophy. These pathological changes, however, generally do not develop until 2–3 wk after MCT treatment and become prominent 3–5 wk after MCT (6, 8, 17). Indeed, in our study we noted that 1 wk after MCT treatment neither the pulmonary pressure nor the right heart weight changed significantly in rats. In contrast, 3 wk after MCT treatment a marked right heart hypertrophy and increased pulmonary pressure were readily evidenced. Thus the present finding of a significant decrease in acetylcholine-induced NO-dependent dilation as well as a decreased spontaneous endothelial NO-mediated dilation seen in the 3-wk MCT-treated RCA is likely associated with the development of pulmonary hypertension and right heart hypertrophy. This is consistent with other reports showing marked endothelial dysfunction in several clinical and experimental hypertensive and heart failure models (9, 10, 24, 26, 29, 30). This endothelial dysfunction can be demonstrated from decreased expression of mRNA and protein of endothelial nitric oxide synthase, decreased NO production, as well as increased oxidative inactivation of NO (3, 15, 23). Our data further show that in conjunction with a decrease in endothelial vasodilatory function there was a corresponding enhanced responsiveness to vasoconstrictive agents such as the thromboxane mimetic U-46619, suggesting that these altered coronary vasomotor responses could lead to altered myocardial blood flow and distribution in the hypertrophied myocardium and further exacerbate the pathological changes in MCT-treated hearts.

However, a cause-effect relationship between coronary endothelial dysfunction and development of myocardial hypertrophy/failure remains controversial. Although in most published reports endothelial dysfunction has been reported, others reported either no change or even an increased endothelium-dependent vasodilation in heart failure (1, 11, 19). One likely cause of these discrepancies may be related to the differences in the experimental animal models studied, the duration and extent of the pathological changes, and the different experimental estimates of the endothelial changes. Indeed, in our studies of 1-wk MCT rats there was significant depression of acetylcholine-induced dilation, whereas spontaneous endothelial NO-mediated dilation was actually increased. It was only when there was clear evidence of pulmonary hypertension and right heart hypertrophy (3-wk MCT rats) that we found both
acetylcholine-induced and endogenous NO-mediated vasodilation to be depressed. These findings of early endothelial changes before pathological changes in the right heart suggest that these endothelial changes may represent an important adaptive response to maintain normal or near-normal cardiac function in MCT-challenged rats.

The trigger and the exact mechanism for this adaptive endothelial response during the developmental phase of pulmonary hypertension and cardiac hypertrophy have not been extensively studied. It is plausible that shortly after MCT administration and MCTP-induced pulmonary injury there may be adaptive changes in sympathetic activity and/or cardiac metabolism. A key link between the neuronal vasoconstrictor mechanism and cardiac metabolism has been reported recently (4, 16, 25). Specifically, Merkus et al. (16) showed that the cardiac myocyte, via its α1-adrenoceptor activation, controls the coronary vascular production of endothelin-1 and vasomotion, and, with endothelin’s multiple sites of action, these authors proposed that this may represent an important protective mechanism to minimize protracted alterations in coronary perfusion during the developmental stages of cardiovascular disease. It is only when these compensatory coronary endothelial changes can no longer provide adequate coronary blood flow to the hypertrophying or hypertrophied ventricular muscles that heart failure develops. The exact molecular relationship between alterations in endothelial function and the development of ventricular hypertrophy/failure is currently under investigation. Furthermore, the possibility that interventions designed to preserve coronary endothelial vasodilatory function in MCT-treated rats may prevent the subsequent development of right heart hypertrophy and failure is also being explored. In conclusion, our results show that selective right coronary endothelial dysfunction occurs before the development of right heart hypertrophy and failure in MCT-treated rats. This suggests that preservation of coronary endothelial function may represent a new and novel therapeutic target for the management of heart hypertrophy and failure.

ACKNOWLEDGMENTS

The authors thank Hsien Chin Wu for excellent technical assistance during the course of this study.

GRANTS

The study described in this article was supported by National Center for Complementary and Alternative Medicine (NCCAM) Grant RO1-AT-001235. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NCCAM or the National Institutes of Health.

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