Dietary Mono- and Polyunsaturated Fatty Acids Similarly Increase Plasma Apolipoprotein A-IV Concentrations in Healthy Men and Women

Mario Kratz, Ursel Wahrburg, Arnold von Eckardstein, Benjie Ezeh, Gerd Assmann, and Florian Kronenberg

ABSTRACT We investigated the effect of dietary fatty acid composition on plasma apolipoprotein (apo) A-IV concentrations. Plasma apo A-IV concentrations were measured by ELISA in plasma of 48 healthy men and women in a controlled dietary study. First, all participants consumed a 2-wk baseline diet rich in saturated fatty acids (SFA). Then, they were randomly assigned to one of three dietary treatments, which contained refined olive oil [rich in monounsaturated fatty acids (MUFA), n = 17], rapeseed oil [rich in MUFA and α-linolenic acid [18:3(n-3)], n = 13], or sunflower oil [rich in (n-6) PUFA, n = 18] as the principal source of fat for 4 wk. The plasma concentrations of apo A-IV increased when subjects consumed the diets rich in unsaturated fatty acids, by 16% or 13.0 mg/L [F(2,76) = 12.874, P < 0.001 by repeated-measures ANOVA]. The increase was not affected by diet group affiliation, gender or apo A-IV genotype. In conclusion, diets rich in unsaturated fatty acids, independent of the degree of unsaturation, gender and apo A-IV genotype, increase plasma apo A-IV concentrations compared with a baseline diet rich in SFA in healthy men and women. J. Nutr. 133: 1821–1825, 2003.

KEY WORDS: • monounsaturated fatty acids • polyunsaturated fatty acids • chylomicrons • absorption • humans

Human apolipoprotein (apo) A-IV is a 46-kDa glycoprotein (1,2) that is synthesized in the small intestine in response to the absorption of dietary or biliary fat. Apo A-IV synthesis is likely coupled to the assembly and/or transport of chylomicrons (3). Apo A-IV reaches the bloodstream as part of the chylomicrons via the thoracic duct, and is present in plasma either bound to HDL or in a free form (4,5). Numerous in vitro studies suggest that apo A-IV participates in the reverse cholesterol transport pathway. Apo A-IV promotes cholesterol efflux from cells, and activates the enzymes lecithin:cholesterol acyltransferase, cholesterol ester transfer protein and lipoprotein lipase [reviewed in (6)]. Furthermore, strong evidence from experiments in rats suggests that apo A-IV plays a role in the control of food intake, i.e., intravenous and cerebrovascular administration of apo A-IV strongly suppresses food intake, whereas the administration of apo A-IV antisemum stimulates feeding [reviewed in (7)]. Also, apo A-IV modulates gastric acid secretion and gastric emptying in rats in a dose-dependent manner (8,9). Interestingly, apo A-IV has also been reported to have an antioxidant effect in inhibiting lipid peroxidation processes (10,11). Taken together, these findings suggest that apo A-IV may represent an antiatherogenic factor.

Indeed, Cohen et al. (12) and Duverger et al. (13) showed that genetically modified mice carrying several copies of the human or mouse apo A-IV gene developed markedly less atherosclerosis than control mice (12,13). It was even demonstrated that atherosclerosis-prone apo E knockout mice had considerable protection against atherosclerotic lesions when overexpressing the human apo A-IV gene either in liver or in the intestinal tract (11,13). Observations from these studies suggest that apo A-IV acts by increasing the potential of HDL to promote cholesterol efflux from cholesterol-loaded cells (12) and/or by exerting antioxidative properties within the arterial wall (11). In humans, a cross-sectional study in two different ethnic populations revealed an inverse association between plasma apo A-IV concentrations and coronary artery disease (14). This finding was confirmed in a Chinese population study (15) as well as in patients with kidney impairment (16).

The apparent atheroprotective effects of apo A-IV have stimulated interest in the factors involved in the modulation of plasma apo A-IV concentrations. It has been shown that

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apo A-IV synthesis is stimulated by triacylglycerol-containing diets in rats (17). Weinberg and colleagues (18) observed in humans that serum apo A-IV concentrations are significantly correlated with the percentage of total energy consumed as dietary triacylglycerol. This appears to be true, however, only for fatty acids with >14 carbon atoms. Short- and medium-chain fatty acids do not depend on chylomicron assembly in the intestinal cells, and it has been demonstrated that these fatty acids do not promote the expression of apo A-IV (3). To date, knowledge of the effects of the different longer-chain dietary fatty acids on plasma apo A-IV concentrations is limited and inconsistent. In rats, one group reported similar effects of diets rich in saturated fatty acids (SFA) or PUFA (17), whereas another group observed increased synthesis of apo A-IV in response to oleic acid (18:1) or linoleic acid (18:2) compared with stearic acid (18:0) (3). In the human intestinal Caco-2 cell line, oleic acid and docosahexaenoic acid were more potent than linoleic acid and α-linolenic acid in increasing the gene expression and secretion of apo A-IV (19).

Taken together, the studies conducted to date have not fully delineated the effect of dietary fatty acids on plasma apo A-IV concentrations. Therefore, we investigated this issue in healthy volunteers who participated in a strictly controlled dietary study. This study was designed initially to investigate the effect of refined olive oil [rich in monounsaturated fatty acids (MUFA)], rapeseed oil [rich in MUFA and α-linolenic acid [18:3(n-3)], and sunflower oil rich in (n-6) PUFA] on LDL oxidizability (20).

**SUBJECTS AND METHODS**

**Participants.** Of 700 students living in boarding school-type conditions in a third-level technical college, 115 nonsmoking volunteers were screened for participation. Inclusion criteria were a body mass index < 27 kg/m², serum cholesterol concentrations < 7.76 mmol/L and triacylglycerol concentrations < 3.39 mmol/L. Of the 115 volunteers, 40 were excluded because of diabetes mellitus (n = 1), hyperlipidemia (n = 3), thyroid disease (n = 5), intake of vitamin supplements (n = 2), hyperuricemia (n = 4) and allergy, intolerance or aversion to foodstuffs contained in the study diets (n = 23). Other exclusion criteria were drug or substance abuse and malabsorption syndromes. Of the 75 students who qualified for participation in the study, 69 (35 men, 34 women), aged 18–43 y were chosen for inclusion by drawing lots. Six subjects withdrew during the study because of intermittent illness and five withdrew because they were unwilling or unable to comply with the dietary regimen. Fifty-eight participants (31 men, 27 women) finished the study. The complete set of samples for plasma apo A-IV measurement was available for 48 participants (23 men, 23 women). The baseline characteristics of the participants are shown in Table 1. Nineteen women who were taking oral contraceptives were instructed not to stop taking them and not to change to another brand. The participants were also asked not to change their regular lifestyles and their usual level of physical activity throughout the study. The protocol and the objectives of the study were explained to the subjects in detail. All gave written consent. The study protocol was approved by the Ethics Committee of the University of Münster.

**Design and diets.** The study was conducted in a parallel design and consisted of two consecutive dietary periods for each subject. All participants consumed a baseline high fat diet rich in SFA for 2 wk and were then randomly divided into three groups. This was done using tables of random digits, separate for men and women, which were generated by a professional biostatistician. The study personnel and the participants were aware of group affiliations. Each group consumed a high fat diet containing refined olive oil (8 men, 9 women), rapeseed oil (6 men, 7 women) or sunflower oil (9 men, 9 women), as the principal source of fat for 4 wk. These diets were identical in every respect except for the fatty acid composition (Table 2). The dietary treatments were described in more detail previously (20). Venous blood samples were obtained at the beginning of the study (visit 1), after the baseline period (visit 2), after 2 wk (visit 3) and after 4 wk (visit 4) of the study diets. All samples were drawn after an overnight fast of at least 9 h. The plasma was isolated immediately, and frozen at −70°C before analysis.

Before the study, the participants kept a careful 3-d dietary record. This was used to estimate each subject’s habitual energy and nutrient intake. The records were coded and calculated on the basis of German standard food tables (Bundeslebensmittelschlüssel). The study diets were calculated for 10 levels of energy intake ranging in steps of 0.84 MJ/d (200 kcal/d) from 7.52 to 15.05 MJ/d (1800–3600 kcal/d) by using a computer-based nutrient calculation program (EBIS, Research Center for Nutrition, Eslingen, Germany). All participants were weighed twice a week while wearing light clothing, and energy intake was adjusted when necessary to maintain a stable body weight. During the study, the mean (±SD) body weight decreased by 0.65 ± 1.12 kg.

**Laboratory measurements.** Plasma apo A-IV concentrations were determined using an ELISA that employs affinity-purified rabbit anti-human apo A-IV polyclonal antiserum as the capture antibody and the same antibody coupled to horseradish peroxidase as the tracer antibody-purified rabbit anti-human apo A-IV polyclonal antiserum as the capture antibody and the same antibody coupled to horseradish peroxidase as the tracer. The standards and the samples were incubated for 1 h, then washed and incubated with substrate for 30 min. The absorbance was measured at 450 nm using a microplate reader. The concentration of apo A-IV in the samples was calculated from the standard curve.

**TABLE 1**

Baseline characteristics of participants

<table>
<thead>
<tr>
<th></th>
<th>All subjects</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>48</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>Age, y</td>
<td>25.4 ± 5.5</td>
<td>27.6 ± 5.6</td>
<td>23.4 ± 4.7</td>
</tr>
<tr>
<td>Height, cm</td>
<td>1.75 ± 0.08</td>
<td>1.81 ± 0.05</td>
<td>1.69 ± 0.06</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>70.5 ± 10.7</td>
<td>78.7 ± 7.8</td>
<td>63.0 ± 6.6</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/L</td>
<td>4.95 ± 0.81</td>
<td>4.99 ± 0.64</td>
<td>4.92 ± 0.95</td>
</tr>
<tr>
<td>Serum LDL-cholesterol, mmol/L</td>
<td>3.04 ± 0.75</td>
<td>3.25 ± 0.48</td>
<td>2.84 ± 0.89</td>
</tr>
<tr>
<td>Serum HDL-cholesterol, mmol/L</td>
<td>1.48 ± 0.44</td>
<td>1.35 ± 0.39</td>
<td>1.60 ± 0.45</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
<td>0.87 (2.46)</td>
<td>0.80 (1.10)</td>
<td>0.99 (2.46)</td>
</tr>
<tr>
<td>Plasma apo A-IV, mg/L</td>
<td>97.2 ± 31.2</td>
<td>107.7 ± 31.1</td>
<td>87.5 ± 28.5</td>
</tr>
<tr>
<td>Apo A-IV genotype, n,n,n</td>
<td>38, 10, 0</td>
<td>19, 4, 0</td>
<td>19, 6, 0</td>
</tr>
</tbody>
</table>

1 Value are means ± SD or medians (ranges).
2 To convert to mg/L, multiply by 386.7.
3 To convert to mg/L, multiply by 885.7.
4 Frequency of apo A-IV genotypes 1/1, 1/2 and 2/2.
Dietary fatty acid composition and apo A-IV

TABLE 2
Composition of the study diets

<table>
<thead>
<tr>
<th></th>
<th>Habitual diet</th>
<th>Baseline diet</th>
<th>Olive oil diet</th>
<th>Rapeseed oil diet</th>
<th>Sunflower oil diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>48</td>
<td>48</td>
<td>17</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>Energy, MJ/d</td>
<td>11.1 ± 2.5</td>
<td>10.0 ± 2.3</td>
<td>9.7 ± 2.1</td>
<td>10.3 ± 2.0</td>
<td>10.6 ± 2.4</td>
</tr>
<tr>
<td>Carbohydrates, % energy</td>
<td>48.1 ± 6.6</td>
<td>45.2 ± 1.1</td>
<td>46.9 ± 1.1</td>
<td>47.1 ± 0.6</td>
<td>47.7 ± 0.7</td>
</tr>
<tr>
<td>Protein, % energy</td>
<td>14.9 ± 2.7</td>
<td>16.8 ± 0.5</td>
<td>14.4 ± 0.5</td>
<td>14.4 ± 0.3</td>
<td>14.1 ± 0.3</td>
</tr>
<tr>
<td>Fat, % energy</td>
<td>36.1 ± 5.7</td>
<td>38.0 ± 0.8</td>
<td>38.7 ± 0.9</td>
<td>38.5 ± 0.6</td>
<td>38.2 ± 0.6</td>
</tr>
<tr>
<td>Saturated fatty acids, % energy</td>
<td>15.9 ± 2.6</td>
<td>19.0 ± 0.5</td>
<td>10.7 ± 0.3</td>
<td>9.2 ± 0.2</td>
<td>10.0 ± 0.2</td>
</tr>
<tr>
<td>Monounsaturated fatty acids, % energy</td>
<td>11.9 ± 2.7</td>
<td>11.3 ± 0.3</td>
<td>23.2 ± 0.5</td>
<td>19.1 ± 0.3</td>
<td>8.7 ± 0.2</td>
</tr>
<tr>
<td>(n-6) PUFA, % energy</td>
<td>5.0 ± 1.9</td>
<td>5.2 ± 0.23</td>
<td>3.0 ± 0.2</td>
<td>6.5 ± 0.1</td>
<td>18.1 ± 0.3</td>
</tr>
<tr>
<td>(n-3) PUFA, % energy</td>
<td>0.8 ± 0.4</td>
<td>0.4 ± 0.0</td>
<td>0.4 ± 0.0</td>
<td>2.5 ± 0.2</td>
<td>0.3 ± 0.0</td>
</tr>
<tr>
<td>Cholesterol, mg/MJ</td>
<td>30.7 ± 7.8</td>
<td>16.7 ± 1.1</td>
<td>17.6 ± 0.8</td>
<td>16.9 ± 0.9</td>
<td>16.5 ± 1.0</td>
</tr>
<tr>
<td>Dietary fiber, g/MJ</td>
<td>2.37 ± 0.81</td>
<td>3.73 ± 0.24</td>
<td>3.06 ± 0.14</td>
<td>3.13 ± 0.31</td>
<td>3.04 ± 0.17</td>
</tr>
</tbody>
</table>

1 Values are means ± SD.
2 Calculated from 3-d dietary records (0.9% of energy was supplied as alcohol).
3 To convert to kcal/d, multiply by 239.

was performed by isoelectric focusing and immunoblotting (23). The molecular basis for the electrophoretic variants, apo A-IV-1 and apo A-IV-2, is a G→T substitution in the third base of codon 360, resulting in a glutamine for histidine change in the mature protein (24,25). This substitution results in an increase in the positive charge of the apo A-IV-1 protein by one unit, which can be detected by isoelectric focusing. The frequencies of the allele 1 vary between 0.88 and 0.94 and of allele 2 between 0.06 and 0.12 in the various populations investigated. Some recent studies have suggested that this polymorphism is associated with increased postprandial hypertriglyceridemia, reduced LDL cholesterol response to dietary cholesterol, and increased HDL cholesterol response to changes in total dietary fat content [reviewed in (26)]. Serum lipid concentrations were measured as described earlier (20).

Statistical analysis
All statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS, version 10.0, SPSS, Chicago, IL) computer program. Apo A-IV concentrations in plasma appeared to be approximately normally distributed, as confirmed by checking normal plots and histograms of the data and by performing Kolmogorov-Smirnov-tests.

Data were analyzed using repeated-measures ANOVA, with the apo A-IV data of visits 2, 3, 3 and 4 as the three levels of the within-subject factor (time), and apo A-IV genotype, gender, and diet group as between-subject factors. Post-hoc comparisons of visit 2 vs. 3 and 3 vs. 4, respectively, were done by paired t tests. Visits 1 and 2 were also compared by paired t test. These tests were two tailed, and the level of significance for all tests was P < 0.05.

RESULTS
Apo A-IV concentrations decreased during the baseline diet period (visit 1 to visit 2) by 14% or 13.6 mg/L [95% CI, −6.9 to −20.2 mg/L, T(47) = 4.111, P < 0.001, Table 3]. The three diets rich in unsaturated fatty acids (visits 2–4), however, had the opposite effect. Repeated-measures ANOVA revealed a strong increase in apo A-IV [+13.0 mg/L, F(2,76) = 12.874, P < 0.001] in the whole group. Although at first sight this increase appeared to be greater in subjects fed the rapeseed oil and sunflower oil diets than in those fed the olive oil diet, there was no effect of diet group affiliation [F(4,76) = 1.749, P = 0.148 for time × oil group interaction]. Gender and apo A-IV genotype also did not affect the diet-induced increase in plasma apo A-IV levels [F(2,76) = 0.883, P = 0.418 for time × gender interaction; F(2,76) = 0.647, P = 0.527 for time × apo A-IV genotype interaction]. Interestingly, the increase in apo A-IV in subjects consuming the three oil diets was not linear [quadratic within-subject contrast for the time effect: F(1,38) = 19.313, P < 0.001] because apo A-IV concentrations in plasma further decreased in the first 2 wk of diet consumption [visit 2 vs. visit 3: −5.2 mg/L (−6%), 95% CI, −0.5 to −9.9 mg/L, T(47) = 2.210, P = 0.032]. Thus, the increase in plasma apo A-IV concentrations in subjects consuming the three diets rich in unsaturated oils was confined to the last 2 wk of this phase [visit 3 vs. visit 4: +18.2 mg/L (+23%), 95% CI, +12.1 to +24.2 mg/L, T(47) = 6.055, P < 0.001].

DISCUSSION
In the present study, we investigated the effect of diets differing in their fatty acid composition on plasma concentrations of apo A-IV. During the baseline phase, with consump-

TABLE 3
Dietary mono- and polyunsaturated fatty acids similarly increase plasma apolipoprotein A-IV concentrations in healthy humans

<table>
<thead>
<tr>
<th></th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>48</td>
<td>48</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>mg/L All subjects</td>
<td>97.2 ± 31.2</td>
<td>83.6 ± 21.72</td>
<td>78.4 ± 23.9</td>
<td>96.6 ± 30.43</td>
</tr>
<tr>
<td>Olive oil diet</td>
<td>95.8 ± 32.3</td>
<td>84.2 ± 23.0</td>
<td>82.9 ± 30.6</td>
<td>89.8 ± 28.5</td>
</tr>
<tr>
<td>Rapeseed oil diet</td>
<td>100.4 ± 26.7</td>
<td>81.7 ± 23.2</td>
<td>70.8 ± 19.1</td>
<td>101.3 ± 37.4</td>
</tr>
<tr>
<td>Sunflower oil diet</td>
<td>96.1 ± 34.5</td>
<td>84.4 ± 20.5</td>
<td>79.7 ± 19.3</td>
<td>99.5 ± 27.0</td>
</tr>
</tbody>
</table>

1 Values are means ± SD. The baseline diet was consumed between visits 1 and 2, and the respective oil diets were consumed between visits 2 and 4.
2 Visit 1 vs. visit 2: −13.6 mg/L, 95% CI, −6.9 to −20.2 mg/L, T(47) = 4.111, P < 0.001 by paired t test.
3 F(2,76) = 12.874, P < 0.001 for time effect (visit 2 to visit 4); time × diet group, time × gender, and time × apolipoprotein A-IV genotype interactions statistically not significant (repeated-measures ANOVA).
tion of a diet relatively rich in SFA, apo A-IV concentrations decreased consistently in almost all subjects. During the first 2 wk of consuming the oil diets, with refined olive oil, rapeseed oil or sunflower oil as the principal source of fat, this decrease continued in 30 of the 48 subjects. By contrast, plasma concentrations of apo A-IV strongly increased in 43 of the 48 participants during the last 2 wk of consumption of these diets. Neither the oil consumed nor gender or apo A-IV genotype affected this diet-induced increase in plasma apo A-IV concentrations.

Thus, the effect of the dietary fat composition on plasma apo A-IV concentrations differs considerably from the effect of dietary fatty acids on apo A-I concentrations. Unsaturated fatty acids, particularly PUFA, reduce plasma apo A-I concentrations compared with SFA (27), which was also the case in our study (data not shown). Thus, apo A-IV and apo A-I appear to be differently and independently regulated by dietary fat composition. Because both proteins contribute to the reverse cholesterol transport pathway, the increase in plasma apo A-IV concentrations might compensate in part for the decrease in apo A-I concentrations in subjects consuming these diets. An estimation of the effect of these changes on reverse cholesterol transport or on atherosclerosis risk, however, is rather complicated, particularly because the magnitude of the net cholesterol transport to the liver appears to be determined by cellular processes rather than by plasma concentrations of HDL cholesterol or apolipoproteins (28). On the other hand, the observations that transgenic mice over-expressing mouse or human apo A-IV develop distinctly less atherosclerosis (12,13) suggest that the diet-induced increase observed in plasma apo A-IV concentrations might ameliorate the risk of atherosclerosis.

Which factors might have led to the decrease in apo A-IV concentrations when the baseline diet was consumed? The major differences between the habitual diet of the participants and the baseline diet were that the latter offered a lower cholesterol intake, a higher fiber intake and a smaller amount of mono- and disaccharides. The higher fiber intake, in particular, might explain the decrease in apo A-IV concentrations because fiber can slow down and even suppress fat absorption (29). Furthermore, dietary fiber interacts with bile components in the intestinal tract (30), which might also affect apo A-IV synthesis. In addition, the decrease in apo A-IV concentrations in plasma might be due to the reduced cholesterol intake during this phase. A decreased cholesterol consumption is likely to reduce the rate of chylomicron assembly in the intestinal cells, which in turn could slow down apo A-IV synthesis and secretion (3). Consistent with this hypothesis, it was recently reported that apo A-IV concentrations in plasma and in triacylglycerol-rich lipoproteins decrease with cholesterol consumption of a diet that contained very little cholesterol (31).

The most obvious explanation for the increase in plasma apo A-IV concentrations with consumption of these diets is that the unsaturated fatty acids might have exerted direct effects on the expression and/or secretion of apo A-IV in the intestinal cells. This agrees with findings in the human intestinal Caco-2 cell line, in which isolated fatty acids (oleic, linoleic, α-linolenic and docosahexaenoic acids) increased the synthesis of apo A-IV by switching on its gene (19). The effect of SFA was not evaluated in these experiments. Another possible explanation might be an influence of unsaturated fatty acids on apo A-IV catabolism, i.e., its hepatic clearance rate. This would also provide an explanation for the time lag effect seen in subjects consuming these diets because metabolic changes are likely to require far more time to affect plasma concentrations than direct effects on gene expression. However, because we have not investigated these mechanisms, these hypotheses are tentative.

The major limitation of our study is that apo A-IV concentrations were measured ex post. Thus, the number of subjects may have been inadequate for detecting a difference among the diet groups. Also, the study was not explicitly designed to compare the three oil diets with the SFA diet. To this end it would have been sensible to include a fourth group that consumed a SFA diet over the entire period of time. Therefore, hidden time effects, which might have led to the increase in plasma apo A-IV within the last 2 wk of the study, cannot be ruled out completely.

In conclusion, diets rich in unsaturated fatty acids increase plasma concentrations of apo A-IV compared with a baseline diet rich in SFA in healthy men and women. It remains to be established, however, whether such an increase in plasma apo A-IV concentrations lowers the risk of coronary heart disease. All our observations of a decrease in plasma apo A-IV concentrations during the baseline diet period suggests that a high fiber intake and/or a low cholesterol intake lowers plasma concentrations of apo A-IV.

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LITERATURE CITED

10. Qin, X., Swartzfeld, D. K., Zheng, S., Hui, D. Y. & Tso, P. (1998) A in plasma apo A-IV by switching on its gene (19). The effect of SFA was not evaluated in these experiments. Another possible explanation might be an influence of unsaturated fatty acids on apo A-IV catabolism, i.e., its hepatic clearance rate. This would also provide an explanation for the time lag effect seen in subjects consuming these diets because metabolic changes are likely to require far more time to affect plasma concentrations than direct effects on gene expression. However, because we have not investigated these mechanisms, these hypotheses are tentative.

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