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The distribution and accumulation of fucoxanthin and its metabolites after oral administration in mice

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The pharmacokinetics of dietary fucoxanthin, one of the xanthophylls in brown sea algae, is little understood. In the present study, mice were orally administered fucoxanthin, and the distribution and accumulation of fucoxanthin and its metabolites fucoxanthinol and amarouciaxanthin A were measured in the plasma, erythrocytes, liver, lung, kidney, heart, spleen and adipose tissue. In a single oral administration of 160 nmol fucoxanthin, fucoxanthinol and amarouciaxanthin A were detectable in all specimens tested in the present study, but fucoxanthin was not. The time at maximum concentration (Tmax) of these metabolites in adipose tissue was 24 h, while the Tmax in the others was 4 h. The area under the curve to infinity (AUC1) of fucoxanthinol in the liver was the highest value (4680 nmol/g × h) among the tissues tested in the present study, while the AUC1 of amarouciaxanthin A in adipose tissue was the highest value (4630 nmol/g × h). In daily oral administration of 160 nmol fucoxanthin for 1 week, fucoxanthin was also detectable in the tissues even at a low concentration. The amount of fucoxanthinol was 123 nmol/g in the heart and 85·2 nmol/g in the liver. Amarouciaxanthin A in the adipose tissue was distributed at a concentration of 97·5 nmol/g. These results demonstrate that dietary fucoxanthin accumulates in the heart and liver as fucoxanthinol and in adipose tissue as amarouciaxanthin A.

Fucoxanthin: Fucoxanthinol: Amarouciaxanthin A: Mice

Brown algae are a traditional foodstuff of East Asians, and an epidemiological study(1) has shown that the consumption of brown sea algae is associated with a low risk of breast cancer. Brown alga powders or extracts have been reported to suppress chemical-induced carcinogenesis in animals(2–5). Fucoxanthin is one of the xanthophylls found in brown algae such as kombu (Laminaria japonica), hijiki (Sargassum fusiforme) and wakame (Undaria pinnatifida)(6). The oral administration of fucoxanthin prevented carcinogenesis in several animal models(7,8). Recent studies with cancer cell lines have suggested that the suppressive effect is due to the inhibitory effect of fucoxanthin on cell proliferation through the induction of apoptosis(9,10) and cell cycle arrest(11). In addition to these activities, the compound also has anti-inflammatory and anti-obesity activities(12,13). Interestingly, a recent study showed that dietary fucoxanthin stimulates the expression of uncoupling protein 1 in the mitochondria of white adipose tissue and facilitates the consumption of fats in rats(14). Thus, fucoxanthin has various physiological activities and contributes to the beneficial effects of brown algae.

Many studies(15–20) have reported the metabolism of hydrocarbon carotenoids such as α-carotene and β-carotene; these carotenoids are absorbed in the small intestine and then converted to vitamin A. However, information on the metabolism of non-provitamin A-type carotenoids is insufficient to explain their bioavailability and safety, although some xanthophylls such as astaxanthin and canthaxanthin have had their metabolism and accumulation reported(21–24). Recent studies suggested that dietary fucoxanthin is hydrolysed to fucoxanthinol in the gastrointestinal tract by digestive enzymes such as lipase and cholesterol esterase, absorbed in the intestinal cells(25), and then converted to amarouciaxanthin A in the liver(26) (Fig. 1). Fucoxanthinol was detectable at 0·8 pmol/ml in human plasma after a daily intake of stir-fried wakame (6 g dry weight) including 6·1 mg (9·26 μmol) of fucoxanthin for 1 week(27). These reports showed the mechanisms of absorption and metabolism of dietary fucoxanthin, but did not explain the bioavailability of fucoxanthin.

In the present study, the distribution and accumulation of fucoxanthin and its metabolites were investigated in mice orally administered with fucoxanthin once or daily for 1 week.

Experimental methods

Reagents

Pancreas lipase type II, lysophosphatidylcholine (1-palmitoyl-sn-glycero-3-phosphocholine), mono-olein (glycerol α-mono-
oleate), taurocholic acid sodium salt hydrate and 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyl were purchased from Sigma Chemicals (St Louis, MO, USA). Astaxanthin was purchased from Extrasynthese (Genay, France). All other reagents were of the highest grade commercially available.

**Preparation of fucoxanthin, fucoxanthinol and amarouciaxanthin A**

Kombu (*L. japonica*) cultured in Hokkaido, Japan was harvested and extracted with ten volumes of absolute ethanol. After the extract was evaporated to remove the ethanol, the residue was extracted again with ethyl acetate and subjected to a silica gel column chromatography with a Wakogel C-100 (Wako Pure Chemical Industries, Osaka, Japan) eluted with hexane–ethyl acetate (1:1, v/v) as a mobile phase. The orange-coloured phase that was rich in fucoxanthin was collected and dried by an evaporator. The dried matter was dissolved in 95 % methanol and was then subjected to preparative HPLC as well as purification of fucoxanthinol as described above to purify the fucoxanthinol. Fucoxanthinol was eluted at 12 min of the retention time. The fucoxanthinol was >99 % purity as determined by the peak area and molecular extinction coefficient. The $\lambda_{\text{max}}$ of fucoxanthinol in ethanol was 449 nm ($E_{1\text{cm} 1\%} = 1760$).

Amarouciaxanthin A was purified from the tunicate *Amaroucia plicifera* as described previously[29], and identified by NMR and MS analyses.

**Preparation of mixed micelles containing fucoxanthin**

A mixed micelle containing fucoxanthin was prepared as described previously[30]. In brief, 1-58 mg fucoxanthin was dissolved in 300 $\mu$l ethanol with 19-4 mg taurocholic acid sodium salt hydrate and was then dried under a stream of N$_2$ gas. The residue was added to 1 ml 3-75 mM-lysophosphatidylcholine, 300 $\mu$l 25 mM-mono-olein, 300 $\mu$l 75 mM-oleic acid and 1-4 ml distilled water and was agitated by a vortex mixer for 1 min. This mixture was used as the mixed micelle comprising 0-8 mm-fucoxanthin, 12 mm-sodium taurocholate, 2-5 mm-mono-olein, 7-5 mm-oleic acid and 1-25 mm-lysophosphatidylcholine for oral administration to mice.

**Animals**

All animal treatments were approved by the Institutional Animal Care and Use Committee (permission numbers 19-5-17 and 19-5-19) and were carried out according to the Guidelines on Animal Experimentation of Kobe University. Male Imprinting Control Region (ICR) mice (aged 7 weeks; Japan SLC, Shizuoka, Japan) were acclimatised at 23°C with a 12 h light–dark cycle for 1 week and were allowed *ad libitum* access to food (Rodent Lab EQ 5L37; Japan SLC) and drinking water.

In the experiment with a single administration, the mice were fasted for 12 h and then administered with 200 $\mu$l of mixed micelles including 160 nmol (0-105 mg) of fucoxanthin intragastrically. After being anaesthetised with Nembutal (Dainippon Sumitomo Pharma, Osaka, Japan), the animals were killed 1, 2, 3, 4, 6, 9, 12, 24, 48 and 72 h after the administrations. The control mice at the 0 h time point were not orally administered anything but were anaesthetised.

In the experiment with a daily administration for 1 week, the mice were daily administered with 200 $\mu$l mixed micelle including 160 nmol fucoxanthin for 7 d intragastrically, and were anaesthetised 24 h after the final administration. The control mice were orally administered with mixed micelle without fucoxanthin as a vehicle.

The blood was collected by cardiac puncture in a heparinised syringe and was centrifuged at 1000 g for 10 min at 4°C. The supernatant fraction and precipitant are referred to...
as the plasma and erythrocytes, respectively. The liver was removed and immediately perfused with PBS and then frozen by liquid N$_2$. The lung, kidney, heart, spleen and intraperitoneal adipose tissues were removed and immediately frozen by liquid N$_2$. These were stored at $-80^\circ$C until use.

High-performance liquid chromatography analysis of fucoxanthin and its metabolites

The erythrocytes were washed twice with a 3-fold volume of PBS. The plasma and erythrocytes were added to 10 $\mu$l 5 $\mu$M-astaxanthin as an internal standard. The plasma was diluted with a 3-fold volume of PBS. A sample (approximately 300 mg) of the tissue specimens was also mixed with 10 $\mu$l 5 $\mu$M-astaxanthin and homogenised in a 9-fold volume of PBS. A sample (800 $\mu$l) of the diluted plasma, diluted erythrocytes, or tissue homogenate was mixed with 600 $\mu$l distilled water and 1.5 ml dichloromethane–methanol (1:2, v/v). They were extracted with 3.0 ml dichloromethane three times, and the dichloromethane layer was collected after centrifugation at 1500 g for 15 min. After evaporation, the residue from the dichloromethane layers was dissolved in a mixed solvent of dimethyl sulfoxide–methanol (1:1, v/v), and a 50 $\mu$l sample was subjected to HPLC analysis. A HPLC system equipped with an L-7420 detector was employed. The column (250 mm $\times$ 4.6 mm internal diameter) and a guard column (10 $\times$ 4.0 mm internal diameter) were of the Capcell pak C18 UG80 (Shiseido, Tokyo, Japan) and were maintained at 35°C. Gradient elution was performed with solution A, which was composed of methanol–0.3 % (w/v) ammonium acetate (pH 3.0) (7:3, v/v), and solution B, which comprised 100 % methanol delivered at a flow rate of 1.0 ml/min as follows: initially 80 % of solution A, and then 80 to 0 % of A for 25 min. Fucoxanthin, fucoxanthinol and amarouciaxanthin A were monitored at a wavelength of 450 nm and their peak area was determined. The amounts of fucoxanthin, fucoxanthinol and amarouciaxanthin A were calculated using calibration curves constructed with purified fucoxanthin, fucoxanthinol and amarouciaxanthin A.

Pharmacokinetic and statistical analysis

The pharmacokinetic parameters of fucoxanthin and its metabolites were calculated from their concentration time course using a non-compartmental pharmacokinetic analysis program.$^{(5)}$

Results

Time-dependent changes in the levels of fucoxanthin and its metabolites after a single oral administration

To understand the time-dependent changes in the levels of fucoxanthin and its metabolites in tissues, mice were given a single oral administration of mixed micelle containing 160 nmol (0.105 mg) of fucoxanthin. Fucoxanthin and its metabolites were measured in the blood and tissues 1, 2, 3, 4, 6, 9, 12, 24, 48 and 72 h after the administration. Figure 2 showed the representative HPLC chromatogram of the extract from the plasma of mice 4 h after administration. The peaks at 11.9 and 13.8 min completely fitted the peaks corresponding to the standards for fucoxanthinol and amarouciaxanthin A, respectively, when the extract mixed with these standards was injected into the HPLC (data not shown). On the other hand, fucoxanthin was undetectable in any tissues tested in the present study or in the blood. Except for in the adipose tissue, fucoxanthinol and amarouciaxanthin A increased until 4 h after administration and then decreased gradually until 24 h (Fig. 3). They were undetectable 48 h after administration (data not shown). Although the concentration of the metabolites in the adipose tissue also increased until 4 h and then decreased as in the other tissues, the concentration increased again, reached its maximum at 24 h after the administration, and the metabolites were still detectable at 72 h (Fig. 3).

The pharmacokinetic parameters were calculated from these data (Fig. 3) and are shown in Tables 1 and 2. The time at maximum concentration (T$_{max}$) in the adipose tissue was 24 h, while those in the other tissues were all 4 h (Table 2). The liver showed the highest values (584 and 190 nmol/g) for the maximum concentration (C$_{max}$) of fucoxanthinol and amarouciaxanthin A, respectively, among the tissues tested in the present study (Table 2). The adipose tissue showed the lowest values (38.8 and 83.7 nmol/g) for the C$_{max}$ of fucoxanthinol and amarouciaxanthin A, respectively, among the tissues tested in the present study (Table 2). The area under the curve to infinity (AUC$_{\infty}$) of fucoxanthinol in the
Liver was the highest value (4680 nmol/g h) among the tissues tested in the present study (Table 2), while the AUC of amarouciaxanthin A in the adipose tissue was the highest value (4630 nmol/g h). The terminal half-life (t1/2) of fucoxanthinol and amarouciaxanthin A in the adipose tissue were 16·0 and 25·5 h, respectively, although the t1/2 in the other tissues, and the plasma and erythrocytes were 2·5–9·0 and 2·5–10·1 h, respectively. Thus, the t1/2 in the adipose tissue was 2-fold longer than those of the other tissues.

Fig. 3. Time profiles of fucoxanthinol (●) and amarouciaxanthin A (○) after a single oral administration of fucoxanthin. Mice were orally administered with mixed micelles containing fucoxanthin (160 nmol/mouse). The concentration of fucoxanthinol and amarouciaxanthin A in the plasma (A), erythrocytes (B) and tissues (liver (C), lung (D), kidney (E), heart (F), spleen (G) and adipose tissue (H)) was determined by HPLC as described in Experimental methods. Values are means (n 6), with standard errors represented by vertical bars.

Table 1. Single-dose oral pharmacokinetic parameters for plasma and erythrocytes of fucoxanthinol (FxOH) and amarouciaxanthin A (AxA)*

<table>
<thead>
<tr>
<th></th>
<th>Cmax (nmol/l)</th>
<th>Tmax (h)</th>
<th>t1/2 (h)</th>
<th>AUC∞ (nmol/l × h)</th>
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<tr>
<td></td>
<td>FxOH</td>
<td>AxA</td>
<td>FxOH</td>
<td>AxA</td>
</tr>
<tr>
<td>Plasma</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>132</td>
<td>230</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Erythrocytes</td>
<td>42·6</td>
<td>67·0</td>
<td>4</td>
<td>4</td>
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</table>

Cmax, maximum concentration; Tmax, time at maximum concentration; t1/2, terminal half-life; AUC∞, area under the curve to infinity.

* Imprinting Control Region (ICR) mice were orally administrated with fucoxanthin at the dose of 160 nmol/mouse.
The accumulation of fucoxanthin and its metabolites after daily oral administration for 1 week

To examine the accumulation of fucoxanthin and its metabolites, mice were orally administered a mixed micelle containing 160 nmol fucoxanthin for 1 week. During the experiment, the food intake and body-weight gain did not differ between the fucoxanthin-administered mice and the vehicle-administered mice (data not shown). Fig. 2 shows the HPLC chromatogram of the extract from the liver of mice. The peaks at 11·9, 13·8 and 16·4 min completely fitted the peaks corresponding to the standards for fucoxanthinol, amarouciaxanthin A and fucoxanthin, respectively, when the extract mixed with these standards was injected into the HPLC (data not shown).

Fucoxanthin was detectable in the erythrocytes, liver, lung, kidney, heart, spleen and adipose tissues, but not in the plasma (Fig. 4). The amount of fucoxanthin was 23·1 nmol/g in the adipose tissue, 20·1 nmol/g in the heart and 15·1 nmol/g in the liver (Fig. 4 (B)). Fucoxanthinol and amarouciaxanthin A were distributed in all of the tissues (Fig. 4 (B)), as well as in the plasma and erythrocytes (Fig. 4 (A)). The amount of fucoxanthinol was 123 nmol/g in the heart, 85·2 nmol/g in the lung and 83·2 nmol/g in the liver. Amarouciaxanthin A in the adipose tissue and plasma was distributed at a concentration of 97·5 nmol/g and 82·0 nmol/l, respectively, higher than the equivalent concentrations of fucoxanthin and fucoxanthinol.

Discussion

In the present study, the metabolism, distribution and accumulation of dietary fucoxanthin and its metabolites were investigated. When mice were given daily administrations, amarouciaxanthin A accumulated in the adipose tissue (Fig. 4), while fucoxanthinol accumulated in the other tissues. The percentage of fucoxanthin, fucoxanthinol and amarouciaxanthin A to the sum of all of these in the adipose tissue was estimated from the data shown in Fig. 4 as 13, 32 and 55 %, respectively, while the percentage in the other tissues was 1–11, 63–76 and 20–26 %, respectively. Thus, the accumulation ratios of fucoxanthinol and amarouciaxanthin A in the adipose tissue were different from those in the other tissues. The present study demonstrated that dietary fucoxanthin preferentially accumulates as amarouciaxanthin A in the adipose tissue and as fucoxanthinol in the other tissues tested in the study.

A previous study demonstrated that fucoxanthin was undetectable because it is metabolised in the gastrointestinal tract and is absorbed into the body as its metabolite, fucoxanthinol(25). However, the daily oral administration of

Table 2. Single-dose oral pharmacokinetic parameters for tissues levels of fucoxanthinol (FxOH) and amarouciaxanthin A (AxA)*

<table>
<thead>
<tr>
<th>Tissue</th>
<th>C_{max} (nmol/g)</th>
<th>T_{max} (h)</th>
<th>t_{1/2} (h)</th>
<th>AUC_{0} (nmol/g × h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FxOH</td>
<td>AxA</td>
<td>FxOH</td>
<td>AxA</td>
</tr>
<tr>
<td>Liver</td>
<td>584</td>
<td>190</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Lung</td>
<td>428</td>
<td>180</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Kidney</td>
<td>224</td>
<td>102</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Heart</td>
<td>229</td>
<td>126</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Spleen</td>
<td>249</td>
<td>95·5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>38·8</td>
<td>83·7</td>
<td>24</td>
<td>24</td>
</tr>
</tbody>
</table>

C_{max}, maximum concentration; T_{max}, time at maximum concentration; t_{1/2}, terminal half-life; AUC_{0}, area under the curve to infinity.

* Imprinting Control Region (ICR) mice were orally administrated with fucoxanthin at the dose of 160 nmol/mouse.
Dietary fucoxanthin and its metabolites 247

fucoxanthin showed that fucoxanthin was detectable in mice, though the concentration was lower than that of its metabolites (Fig. 4). According to the study using mice or Caco-2 cell monolayers as an intestinal epithelial cell model \(^{25}\), the appearance of fucoxanthinol in mouse plasma was more rapid compared with Caco-2 cell monolayers, and this was considered to be due to the presence of pancreatic juice containing lipase, phospholipase and cholesterol esterase. Furthermore, fucoxanthin was detected in the basolateral medium cultured Caco-2 cell monolayers. These results indicate that fucoxanthin will be absorbed without conversion to fucoxanthinol when the capacity of intestinal hydrolytic activity is over the concentration of dietary fucoxanthin. In the present study, the amount of ingested fucoxanthin would be over the capacity by the daily administrations. A small amount of fucoxanthin seems to be absorbed without being metabolised and degraded, although most of this compound was metabolised and absorbed into the body. This is the first report describing the detection of dietary fucoxanthin accumulation in mammalian tissues. Additionally, when mice were orally given a single administration (160 nmol), the \( T_{\text{max}} \) of fucoxanthin in the plasma, liver, kidney, heart, lung and spleen was 4 h (Table 2). On the other hand, the previous study demonstrated that the \( T_{\text{max}} \) was 2 h in the plasma and liver after a single administration of fucoxanthin (40 nmol). The difference in \( T_{\text{max}} \) might be due to the effects of different doses of fucoxanthin on the capacity of intestinal hydrolytic activity.

An epidemiological study \(^{1(1)} \) has shown that the consumption of brown sea algae is associated with a low risk of breast cancer. Administration of fucoxanthin derived from brown sea algae also showed anti-carcinogenic activity \(^{7(8)} \); for example, our previous study \(^{8(9)} \) demonstrated that \( ad \ l\)ib\(i\)tum administration of 0·5 % fucoxanthin-containing drinking water for 4 weeks suppressed azoxymethane-induced aberrant crypt foci, which is a pre-neoplastic marker for colon cancer. The inhibitory mechanism was considered to cause the induction of apoptosis and cell cycle arrest \(^{9(11)} \), and their effective concentrations were more than 20 \( \mu \)M. The present study demonstrated that fucoxanthin accumulated after daily oral administration (Fig. 4). However, this concentration seems to be insufficient to exert physiological activities such as the induction of apoptosis and cell cycle arrest. Asai et al. \(^{26(26)} \) demonstrated the antiproliferative effect of fucoxanthin and amarouciaxanthin A in prostate cancer PC-3 cells; these half-maximal inhibitory concentration (IC\(_{50}\)) values were 3·0 and 4·6 \( \mu \)M, respectively. In the present study, the concentrations of fucoxanthinol and amarouciaxanthin A in plasma were 47 (SE 10) and 82 (SE 22) nmol/l, respectively (Fig. 4), and they were lower than the IC\(_{50}\) values. However, these metabolites may exert their antiproliferative effects additively or synergistically in vivo. Thus, the fucoxanthin metabolites fucoxanthinol and amarouciaxanthin A could be associated with the anti-carcinogenic activity of fucoxanthin.

The AUC\(_{\text{inf}}\) of fucoxanthinol and amarouciaxanthin A in the plasma was 1430 and 2040 nmol/l h, respectively, after an oral administration of 160 nmol fucoxanthin (Table 1). The previous study demonstrated that the AUC\(_{\text{inf}}\) of astaxanthin, one of the xanthophylls, in plasma was 2260 nmol/l h after an oral administration of astaxanthin (approximately 67 \( \mu \)mol) \(^{22(22)} \). The AUC\(_{\text{inf}}\) represented the absorbed amounts of fucoxanthin and astaxanthin, suggesting that the ratio of absorbed fucoxanthin metabolites to the dose was greater than that of astaxanthin. The present study demonstrated that the accumulating tissues for fucoxanthinol were the liver and heart, and that for amarouciaxanthin A was the adipose tissue. On the other hand, astaxanthin was accumulated in the spleen, kidney and adrenal gland in animals greater than in the liver, lung and heart after \( ad \ l\)ib\(i\)tum intake of a diet containing 3 % (w/w) astaxanthin for 14 d in rats \(^{21(21)} \). In addition, this study also showed that the amount of astaxanthin in the spleen was 10-fold higher than that in the liver. Thus, the accumulating tissue and concentration seem to depend on the type of xanthophyll. This indicates that the bioavailability of fucoxanthin (and its metabolites) may be higher than that of other xanthophylls, at least of astaxanthin.

It was reported that fucoxanthinol is converted to amarouciaxanthin A by short-chain dehydrogenase/reductase in the liver \(^{26(26)} \). After daily oral administration of fucoxanthin, the ratio of amarouciaxanthin A in the liver was almost similar to that in other tissues except for the adipose tissue, in which the ratio was the highest among all the tissues tested (Fig. 4). Fucoxanthinol would be converted to amarouciaxanthin A by short-chain dehydrogenase/reductase in the liver and rapidly transported to the other tissues. On the other hand, fucoxanthinol and amarouciaxanthin A were detectable in the adipose tissue but not in the other tissues 24–72 h after the single oral administration of fucoxanthin (Fig. 3). Fucoxanthinol accumulated in the adipose tissues might be slowly converted to amarouciaxanthin A in this tissue. These results indicated that most of the fucoxanthinol was metabolised to amarouciaxanthin A in the liver within 24 h after the administration, and some of the fucoxanthinol was accumulated and slowly metabolised to amarouciaxanthin A in the adipose tissue. To verify this assumption, further studies are needed.

In conclusion, dietary fucoxanthin was mainly converted to fucoxanthinol. Fucoxanthin metabolites were accumulated in the body at a higher ratio than astaxanthin, and were preferentially accumulated in the liver, heart and adipose tissues, suggesting that these tissues are targets of fucoxanthin metabolites.

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T. H., M. M. and K. K. contributed to the design of the study and prepared the paper. Y. O., M. T. and K. Y. performed the animal experiments and analytical work. Y. O., M. T., S. K. D. and T. M. purified fucoxanthin, fucoxanthinol and amarouciaxanthin A.

The authors declare no conflict of interest.

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