High-Provitamin A Carotenoid (Orange) Maize Increases Hepatic Vitamin A Reserves of Offspring in a Vitamin A-Depleted Sow-Piglet Model during Lactation

Emily K. Heying, Michael Grahn, Kevin V. Pixley, Torbert Rocheford, and Sherry A. Tanumihardjo

Abstract

The relationship of dietary vitamin A transfer from mother to fetus is not well understood. The difference in swine offspring liver reserves was investigated between single-dose vitamin A provided to the mother post-conception compared with continuous provitamin A carotenoid dietary intake from biofortified (enhanced provitamin A) orange maize (OM) fed during gestation and lactation. Vitamin A-deficient sows were fed OM or white maize (WM) + 1.05 mmol retinyl palmitate administered at the beginning of gestation. Piglets from sows fed OM had higher liver retinol concentrations and a combined mean concentration from 10 to 28 of 0.11 ± 0.030 μmol/g. Piglets from sows fed WM had higher serum retinol concentrations (0.56 ± 0.25 μmol/L; P = 0.0098) despite lower liver retinol concentrations of 0.686 ± 0.026 μmol/g from 10 to 28. Milk was collected at 0, 5, 10, 20, and 28 d after birth. Piglets from sows fed OM had a higher milk retinol concentration (1.36 ± 1.30 μmol/L; P = 0.038), than those fed WM (0.93 ± 1.03 μmol/L). Sow livers were collected at the end of the study and had identical retinol concentrations. Consumption of daily provitamin A carotenoids by sows during gestation and lactation increased liver retinol status in weanling piglets, illustrating the potential for provitamin A carotenoid consumption from biofortified staple foods to improve vitamin A reserves. Biofortified OM could have a measurable impact on vitamin A status in deficient populations if widely adopted. J. Nutr. 143: 1141–1146, 2013.

Introduction

Vitamin A deficiency (VAD) affects over 250 million people and contributes to morbidity and mortality in many developing nations. Pregnant and lactating women are especially at risk, because retinol requirements increase during this time. Chronic VAD during pregnancy results in low newborn vitamin A reserves. The most common method to alleviate VAD in countries with high risk is supplementation programs for lactating mothers and children up to 5 y of age. A prior recommendation for lactating mothers in high-risk VAD communities was 2 doses of 200,000 IU vitamin A within 6 wk of delivery, with at least 1 d between doses. However, because evidence is lacking for the impact of this intervention on childhood mortality, the WHO does not currently recommend this regimen as public health policy. Therefore, other sustainable methods are needed to improve population vitamin A status.

In a meta-analysis of 16 supplementation trials in children, vitamin A supplementation was associated with a 24% decrease in all-cause mortality and decreased prevalence of diarrhea, measles, night blindness, and xerophthalmia. Regarding supplementation to postpartum mothers, a study in Ghana, India, and Peru found greater breast milk retinol concentrations through 2 mo, but not 6 mo, indicating nonsustained improvement. Furthermore, supplementation programs, although common, can be expensive and require continuous external resources for their continuity.
diets and a complement or alternative to supplementation in efforts to alleviate VAD (8). Maize (Zea mays) is a biofortification target due to its high consumption, particularly in Africa (9,10). Most provitamin A-enhanced maize contains mainly β-carotene, but some varieties have increased β-cryptoxanthin content (11,12). Provitamin A carotenoids must be cleaved in the intestine by β-carotene monoxygenase, allowing for regulation of carotenoid bioconversion to retinol (13). Thus, biofortification poses no risk of toxicity, due to increasing provitamin A carotenoids instead of preformed retinyl esters used in fortification programs (8). Maize biofortified with provitamin A improved the retinol status of depleted gerbils (9) and efficient bioconversion factors were obtained in 2 small human trials (14,15). However, to date, no studies to our knowledge have determined the carotenoid composition throughout the study (26). Sows were fed 2.5 kg/d during gestation and 5.0 kg/d during lactation.

**Sample collection.** Piglet male–female pairs (n = 102) from sows fed diet were randomly selected to be killed at d 0 (n = 26), 10 (n = 28), 20 (n = 28), and 28 (n = 20) after birth. The birth weights for piglets from sows fed OM and WM feeds were 1.55 ± 0.26 and 1.49 ± 0.31 kg, respectively, which did not differ by sex or treatment. Blood and liver samples were collected from piglets at each time point. Sow livers were collected from randomly selected sows (n = 3/group) at d 28 post-farrowing.

**Serum and liver analyses.** Piglet serum (500 µL) was analyzed for retinol using a standardized method with minor modifications (9). Retinyl acetate was the internal standard, 500 µL cold ethanol with 1% butylated hydroxytoluene was added and the sample was extracted 3 times with 1 mL hexanes. The Waters HPLC has been described (9). Solvent A was 95.5 (v/v) acetonitrile:water and Solvent B was 85:10:5 (v/v/v) acetonitrile: methanol: dichloroethane. Solvent A (100%) started at 2.0 mL/min from 0 to 3 min, with a change to 50% A and 50% B from 3 to 5 min and held until 6 min before reequilibrating with 100% A from 6 to 10 min. Livers were analyzed using previously published methods (16). Three sections of liver (−1.5 g total) were randomly taken, homogenized by mortar and pestle with 2–3 g anhydrous sodium sulfate, and repeatedly extracted with dichloromethane to 30 mL. Five mL was dried under nitrogen and reconstituted in 100 µL 75:25 (v/v) methanol:dichloroethane; 50 µL was injected onto the same HPLC (9). Two mobile phases were used with modification (18): solvent A was 92.5:7.5 acetonitrile:water (v:v) and solvent B was 85:10:5 acetonitrile:methanol:dichloroethane (v:v:v); both with 0.365 g triethylamine/L as modifier. Retinol and retinyl ester values were summed to obtain the total vitamin A concentration (µmol/g liver) or corrected for liver weight for total liver reserves (µmol/liver) (18). Sow livers were also separately analyzed for carotenoids using the same extraction procedure and the carotenoid HPLC analysis (26). Sow milk collection. Milk was analyzed for retinol by using a modification to a previously described method (12). Synthesized C23-apo-carotenal was used as an internal standard. After saponification and extraction, the residue was reconstituted in 100 µL 50:50 (v/v) methanol:dichloroethane and 25 µL was injected onto a Resolve C18 5-µm, 3.9-× 300-mm reversed-phase column (Waters) equipped with a guard column. Milk fat was assayed using a published gravimetric method (27). Milk (1 mL) was analyzed for carotenol concentration by using modifications to a published method (26). Then β-apo carotenal as internal standard, 2 mL ethanol with 0.1% butylated hydroxytoluene, and 800 µL 50:50 (w/vw) potassium hydroxide:water were added, mixed, and saponified for 8 min at 45°C, mixing at 4 min. Following saponification, 1.5 mL cold water was added and the sample was extracted 3 times with 1.5 mL hexanes. Organic layers were pooled, dried under nitrogen, and resuspended in 100 µL 50:50 (v/v) methanol: dichloroethane; 80 µL was injected onto Waters carotenoid 3-µm, 4.6-× 250-mm reversed-phase column (Milford) equipped with a guard column. The HPLC system was described (9).

**Statistical analysis.** Values are means ± SDs. A repeated-measures ANOVA with mixed effects was used with SAS PROC MIXED software (version 9.2, SAS Institute) for the sow milk. An AUC analysis was performed on sow milk using a 2-tailed t test. A likelihood ratio test was used to test for unequal variance. The influence of treatment, day, and sex were evaluated by using a 3-factor ANOVA model in the piglet data. Tukey’s adjustments were used to make comparisons between groups for piglets and sows. Treatment effects and interaction terms were considered significant at P ≤ 0.05. Slopes were determined for liver retinol accrual over time and considered significant if different from zero.

**Results**

Carotenoid content of feed and total retinol intake. The following carotenoids were quantified in the OM feed (µg/g):
lutein and zeaxanthin (11.7 ± 2.35); all-trans, 9-cis, and 13-cis β-carotene (10.6 ± 1.6); β-cryptoxanthin (0.34 ± 0.09); and α-carotene (0.58 ± 0.19). Only trace amounts of carotenoids were found in the WM feed. The weekly OM theoretical retinol concentration was 41.8 ± 2.3 and 41.9 ± 2.7 nmol/g feed (12 µg/g feed) for the OM from Indiana and Wisconsin, respectively. The overall WM feed theoretical retinol concentration was 0.35 ± 0.24 nmol/g (0.14 µg/g feed). Using the IOM bioconversion factor of 12 µg retinol activity equivalents (RAEs) (2), the total RAE in the feed for sows fed WM was 28.6 and 57.2 µg RAE/d, respectively. The total RAE throughout gestation and lactation was 43.9 and 4.9 mg for OM and WM, respectively. Thus, in theory, OM provided more vitamin A to the sows than the retinyl palmitate supplement (i.e., 300 mg retinol equivalents) during the entire study duration.

**Piglet weights.** Piglet weights did not differ between treatment groups or sexes. Piglet weights at 0, 10, 20, and 28 d were (pooled means ± SDs) 1.52 ± 0.29, 3.58 ± 0.74, 5.40 ± 0.72, and 5.71 ± 1.37 kg, respectively.

**Serum retinol.** Serum retinol concentrations were higher in piglets from mothers fed WM than those fed OM (P = 0.0098) and differed by time (P < 0.0001). Across treatments, serum retinol increased from d 0 to 10 and then remained unchanged or decreased between d 10 and 28 for piglets in both treatment groups (Table 1). Piglets at d 0 had significantly lower serum retinol values than at later time points, regardless of diet. The WHO defines serum retinol concentrations <0.7 µmol/L to be indicative of VAD in humans (28). Using this indicator, only the mean value for the 10-d-old piglets from the WM-fed sows was an adequate serum retinol concentration, i.e., >0.7 µmol/L (Table 1).

**Liver retinol and carotenoid reserves.** Piglet liver weights were higher in piglets from the OM group (P = 0.033) and increased with time (P < 0.0001), but no interaction between treatment and time was detected. Piglet liver weights were 46 ± 12, 111 ± 15, 131 ± 15, and 148 ± 48 g for the OM group and 42 ± 12, 96 ± 20, 121 ± 16, and 139 ± 23 g for the WM group at 0, 10, 20, and 28 d, respectively. OM resulted in higher (P < 0.0001) hepatic retinol concentrations (µmol/g) in piglets than in those from sows fed WM (Fig. 1), which were calculated by summing retinol and all identifiable retinyl esters with photodiode array detection. Hepatic retinol concentrations differed with time (P < 0.0001) but not between sexes. The interaction between treatment and time was significant (P = 0.0013), whereas there was no interaction for treatment or sex and time. Although piglets from sows fed WM had the same liver vitamin A concentration at d 0 as piglets from sows fed OM, the liver retinol concentrations of piglets from mothers fed OM were higher at d 10, 20, and 28 (Fig. 1A). In piglets from sows fed OM, the liver retinol concentration increased from 0 to 20 d, although d 10 through 28 did not differ. In both groups, the liver retinol concentration increased above the current human deficiency cutoff of 0.07 µmol retinol/g liver on d 10 (24), emphasizing the importance of colostrum; however, this was not maintained in the piglets whose mothers were fed WM. Using

### Table 1

<table>
<thead>
<tr>
<th>Time after birth</th>
<th>n</th>
<th>All µmol/L</th>
<th>OM µmol/L</th>
<th>WM + retinyl palmitate µmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 d</td>
<td>26</td>
<td>0.25 ± 0.08</td>
<td>0.23 ± 0.07</td>
<td>0.26 ± 0.08</td>
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<tr>
<td>10 d</td>
<td>28</td>
<td>0.69 ± 0.19</td>
<td>0.60 ± 0.16</td>
<td>0.76 ± 0.19</td>
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<tr>
<td>20 d</td>
<td>28</td>
<td>0.62 ± 0.15</td>
<td>0.57 ± 0.13</td>
<td>0.66 ± 0.16</td>
</tr>
<tr>
<td>28 d</td>
<td>20</td>
<td>0.55 ± 0.17</td>
<td>0.53 ± 0.16</td>
<td>0.56 ± 0.17</td>
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</table>

Values are means ± SD. A 3-way ANOVA showed a difference by time (P < 0.0001) and piglets by treatment group where serum retinol of WM piglets (0.57 ± 0.25 µmol/L, n = 54) was higher than OM (0.48 ± 0.20 µmol/L, n = 48) (P = 0.0098) and a trend existed for sex difference (P < 0.053), where females (0.56 ± 0.24 µmol/L) had a higher mean value than the males (0.50 ± 0.21 µmol/L). Interactions were not significant. Individual time points without a common superscript letter differ. OM, orange maize; WM, white maize.

**FIGURE 1** Liver retinol concentrations (A) and total liver retinol (B) in piglets from sows fed OM or WM + retinyl palmitate dose. Values are means ± SD, n = 10–16. Means without a common letter differ, P < 0.05. A 3-way ANOVA showed that time and diet were significant (P < 0.0001) for both concentration and total retinol and an interaction existed between time and diet (P = 0.0017). Sex did not influence the results. OM, orange maize; WM, white maize.
the more conservative cutoff of 0.1 μmol/g (24), only the piglets whose mothers were fed OM reached and maintained that concentration. We also calculated total liver reserves (μmol/liver) (Fig. 1B). Similar to liver retinol concentrations, there were main effects of treatment (P < 0.0001) and time (P < 0.0001) as well as an interaction between treatment and time (P = 0.0017), but sex had no effect. No interaction existed between treatment and sex or sex and time. Total liver reserves were significantly higher at 10, 20, and 28 d in piglets from sows fed OM than in piglets from sows fed WM. However, within the respective treatment groups, the later time points were only significantly higher than d 0 piglets and did not differ between 10, 20, and 28 d. Nonetheless, after evaluating the slope over this time period (Fig. 1B), the total hepatic vitamin A for piglets whose mothers were fed WM remained constant between d 10 and 28, whereas the OM piglet concentrations indicated continued accrual of total liver vitamin A reserves (P = 0.007).

Sow liver vitamin A concentrations were determined at kill (28 d after giving birth) and were 0.22 ± 0.05 μmol/g liver for sows fed OM and 0.22 ± 0.06 μmol/g liver for sows fed WM. This value is >100% higher than the conservative cutoff for adequate liver reserves, i.e., >0.1 μmol/g liver. Thus, OM during gestation and lactation performed as well as a single high-dose supplement in rescuing the mothers from their prior vitamin A-depleted status. Sow liver β-carotene concentrations (all isomers) were 0.25 ± 0.07 nmol/g liver in the OM group and undetectable in the WM group.

Sow milk. Sows had significantly higher colostrum retinol concentrations at birth than milk at any other time point, and sows had significantly higher colostrum retinol isomers) were 0.25–2.5 mol/g (10). The OM used in this study and typical yellow maize used in swine feed are similar (13). Biofortified maize is bred to contain higher amounts of provitamin A carotenoids (i.e., β-carotene and β-cryptoxanthin) compared with conventional yellow maize varieties, which have 0.25–2.5 μg provitamin A/g (10). The OM provitamin A concentrations before and after mixing with the diet were 14 and 12 μg/g, respectively. As a total comparison of RAEs in the feed, sows fed the OM received ~40% more than the sows from the WM and retinyl ester dose. Considering the identical liver reserves in the sows at the end of the study, the extra vitamin A from the β-carotene cleaved in the intestine from OM was shunted to the milk and into the livers of the nursing piglets, demonstrating the importance of continuous dietary vitamin A or provitamin A consumption during lactation. Milk from sows fed the WM diet was not able to prevent VAD as measured by hepatic retinol concentrations, even though these sows had a better vitamin A status during gestation and lactation considering the timing of the supplement. The sows fed WM would have been in negative vitamin A balance during the study, whereas those fed OM were in positive vitamin A balance. One could assume that at any one time in the study, the sows fed WM had a better vitamin A status based on liver retinol reserves, because the groups had identical final retinol concentrations.

The serum retinol concentrations of piglets from mothers fed WM were higher than those in piglets from mothers fed OM, although total liver reserves after baseline were consistently lower for the WM than the OM group. Piglets from both diet treatments had an increase in serum retinol between d 0 and 10, but only the value at 10 d for piglets on the WM diet reached an “adequate” mean retinol concentration (≥0.7 μmol/L). Determining vitamin A status by serum retinol concentration is common but not ideal, because it is homeostatically controlled and may not change in response to an intervention (24). The piglets from sows fed OM had adequate liver reserves (i.e., ≥0.1 μmol/g liver) but did not maintain adequate serum retinol concentration.

**Discussion**

This study used piglets born to vitamin A-depleted sows that had been “rescued” from VAD after being fed vitamin A-free diets for at least 2 prior parities. Although retinyl palmitate doses are usually given to postpartum women, the sows were given a high dose at the beginning of gestation to compare the maternal-fetal transfer of retinol from retinol binding protein (RBP) during gestation and lactation with that from continuous transfer as retinol and retinyl esters from small daily intakes of β-carotene from high-provitamin A OM. Prior studies have predicted and confirmed the influence of high-dose supplements to lactating sows on nursing piglet vitamin A status (16,18). Although swine do not absorb and store appreciable amounts of β-carotene intact (29), they are recommended as a model for lactation (25) and vitamin A studies for translational studies in humans (25,29). Sows continued being fed their respective diets throughout lactation, allowing for comparison between the 2 treatment groups on retinol transfer through maternal milk and nursing piglet and sow vitamin A status. Piglets weigh approximately the same as human infants at <6 mo of age (30,31), which made them a better model than rodents for this time-sensitive study.

The xanthophyll profile (i.e., lutein and zeaxanthin) of the OM used in this study and typical yellow maize used in swine feed are similar (13). Biofortified maize is bred to contain higher amounts of provitamin A carotenoids (i.e., β-carotene and β-cryptoxanthin) compared with conventional yellow maize varieties, which have 0.25–2.5 μg provitamin A/g (10). The OM provitamin A concentrations before and after mixing with the diet were 14 and 12 μg/g, respectively. As a total comparison of RAEs in the feed, sows fed the OM received ~40% more than the sows from the WM and retinyl ester dose. Considering the identical liver reserves in the sows at the end of the study, the extra vitamin A from the β-carotene cleaved in the intestine from OM was shunted to the milk and into the livers of the nursing piglets, demonstrating the importance of continuous dietary vitamin A or provitamin A consumption during lactation. Milk from sows fed the WM diet was not able to prevent VAD as measured by hepatic retinol concentrations, even though these sows had a better vitamin A status during gestation and lactation considering the timing of the supplement. The sows fed WM would have been in negative vitamin A balance during the study, whereas those fed OM were in positive vitamin A balance. One could assume that at any one time in the study, the sows fed WM had a better vitamin A status based on liver retinol reserves, because the groups had identical final retinol concentrations.

The serum retinol concentrations of piglets from mothers fed WM were higher than those in piglets from mothers fed OM, although total liver reserves after baseline were consistently lower for the WM than the OM group. Piglets from both diet treatments had an increase in serum retinol between d 0 and 10, but only the value at 10 d for piglets on the WM diet reached an “adequate” mean retinol concentration (≥0.7 μmol/L). Determining vitamin A status by serum retinol concentration is common but not ideal, because it is homeostatically controlled and may not change in response to an intervention (24). The piglets from sows fed OM had adequate liver reserves (i.e., ≥0.1 μmol/g liver) but did not maintain adequate serum retinol concentration.
concentrations considering the widely used standard cutoff. This
cutoff has utility as a population indicator but does not always
reflect differences in liver retinol reserves (24), which is one
reason why WHO recommends that 2 indicators be used to best
define vitamin A status (28). Furthermore, the modified relative
dose response test, which reliably indicates liver reserves <0.1
μmol/g liver (24), is in good agreement with serum retinol
concentrations <0.5 and >1.6 μmol/L (32). Thus, serum retinol
concentrations between 0.5 and 1.6 μmol/L are inconclusive.
The higher serum retinol concentrations in the piglets from the
WM fed sows may be due to a decrease in degradation
utilization in an effort to maintain function (33), which could result in a
higher concentration due to enhanced recycling (34). In a
prior study, piglet serum retinol concentrations decreased with time
after birth but did not differ between vitamin A treatments (18).
In a recent study in Senegalese infants, serum retinol concentra-
tions predicted only 15% VAD, whereas liver reserves measured by
the modified relative dose response test indicated that 73.5%
were VAD and identified those infants whose mothers had
received postpartum supplementation (35). Liver reserves, which
were measured in both the piglets and sows, are the gold standard
for determining vitamin A status, because they reflect vitamin A
storage that can be drawn upon during times of low intake. The
piglets from mothers fed WM had critically low liver retinol
reserves, even though their mothers had more than double the
adequate liver concentration. This reinforces the importance of
continued vitamin A dietary sources during lactation to support
milk retinol concentrations (27,31,36,37).
The piglet liver results at d 0 indicated that fetal transfer of
vitamin A during gestation was similar for treatments; however,
the OM treatment was clearly more efficacious as a source of
retinol during lactation. OM feeding during gestation led to a
biologically important enhancement of colostrum values leading to
a rapid increase in retinol stores of the nursing piglets, which
was maintained and much higher than the liver stores of the
piglets whose mothers were fed WM. The retinol concentration
in the liver during this time was well above the deficiency cutoff
of 0.07 μmol/g liver and met the 0.1-μmol/g cutoff for adequacy
(24), whereas the mean liver concentration in piglets from sows
fed the WM + retinyl ester dose was >0.07 μmol/g liver only at d
10. The smaller, consistent intake of provitamin A carotenoids
provided additional vitamin A directly to the milk during
lactation via retinyl esters in the chylomicra, whereas piglets
from sows fed the WM diet were still relying on mobilization of
stored liver reserves through plasma retinol delivered to the milk
from RBP as their sole source of vitamin A.
The frequent intake of provitamin A carotenoids from
biofortified maize may sustain adequate vitamin A status in
deficient populations if widely adopted as their staple food. A
study in India found a 54% reduction in childhood mortality in
children who were given small weekly doses of preformed vitamin
A, which represented achievable daily consumption amounts
from foods (38). This is a much higher reduction in mortality than
a meta-analysis performed on routine supplementation trials, i.e.,
24% (5). This may be due to the fact that lung and spleen, two
organs essential for immune function, take up vitamin A mainly
from chylomicra, which has a shorter residence time in the serum
than retinol bound to RBP (39). More frequent doses of vitamin A
or daily provitamin A-containing food would consistently main-
tain vitamin A concentrations in these key organs through
chylomicron delivery.
In this study, the bioconversion of provitamin A carotenoids
to retinol was estimated using the Institute of Medicine biocon-
version factors of 12 μg β-carotene and 24 μg β-cryptoxanthin
to 1 μg retinol (2). Point values of bioconversion factors from
single test meals made with biofortified maize were calculated as
6.5 ± 3.5 in young U.S. women (14) and 3.2 ± 1.5 μg β-carotene
to 1 μg retinol in Zimbabwean men (15). Bioconversion factors
are influenced by several factors (13) and vitamin A status plays a
major role in how much retinol is made from provitamin A
carotenoids (8). Larger, long-term feeding studies are needed in
target populations to tease out the appropriate bioconversion
factors to use for biofortified crops.
Although biofortified maize has many advantages relative to
supplementation strategies, including potential agricultural and
economic growth (40,41), questions still remain about how
effective it will be in reducing VAD prevalence (42). One of
the biggest challenges regarding the future of biofortified maize is
getting the producers and consumers to accept and demand
the biofortified crops so that consumption is sufficient for
VAD populations to reach adequate vitamin A status (8,43).
WM is generally preferred over yellow maize for food in most
African countries (10). However, in a Zambian feeding study of
preschool-age children using high-provitamin A maize, children
adapted to consuming OM meals (i.e., porridge and nsima)
within the first week of the study and intakes of OM were the
same as WM throughout the study (44). Several studies have
reported willingness to consume OM by African consumers
traditionally accustomed to eating WM (45–48) and Low et al.
(49) demonstrated the effectiveness of an appropriate nutrition
education strategy in creating demand for orange sweet potato
by consumers traditionally accustomed to eating white sweet
potatoes. Using biofortification as a tool to combat VAD may
require 2 or more generations to achieve its potential impact on
improved population vitamin A status (8,13). Further, ongoing
work is needed to extend these findings from the swine model to
gain a better understanding of the efficacy and effectiveness of
high-provitamin A carotenoid maize consumption to improve
vitamin A status at the population level.

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the manuscript. All authors read and approved the final manu-
script.

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