Angiotensinergic Signaling in the Brain Mediates Metabolic Effects of Deoxycorticosterone (DOCA)-Salt in C57 Mice

Justin L. Grobe, Beth A. Buehrer, Aline M. Hilzendeger, Xuebo Liu, Deborah R. Davis, Di Xu, Curt D. Sigmund

Abstract—Low-renin hypertension accounts for ~25% of essential hypertensive patients. It is modeled in animals by chronic delivery of deoxycorticosterone acetate and excess dietary sodium (the DOCA-salt model). Previous studies have demonstrated that DOCA-salt hypertension is mediated through activation of the brain renin-angiotensin system. Here, we demonstrate robust metabolic phenotypes of DOCA-salt treatment. Male C57BL/6J mice (6 to 8 weeks old) received a subcutaneous pellet of DOCA (50 mg for 21 days) and were offered a 0.15 mol/L NaCl drink solution in addition to regular chow and tap water. Treatment resulted in mild hypertension, a blunting of weight gain, gross polydipsia, polyuria, and sodium intake, alterations in urinary sodium and potassium turnover, and serum sodium retention. Most strikingly, DOCA-salt mice exhibited no difference in food intake but did exhibit a large elevation in basal metabolic rate. Normalization of blood pressure by hydralazine (500 mg/L in drink solutions) attenuated the hydromineral phenotypes and renal renin suppression effects of DOCA-salt but had no effect on the elevated metabolic rate. In contrast, intracerebroventricular infusion of the angiotensin II type 1 receptor antagonist losartan (5 μg/h) attenuated the elevation in metabolic rate with DOCA-salt treatment. Together, these data illustrate the necessity of angiotensinergic signaling within the brain, independent of blood pressure alterations, in the metabolic consequences of DOCA-salt treatment. (Hypertension. 2011;57[part 2]:00-00.)

Key Words: hypertension ▪ metabolism ▪ mineralocorticoid ▪ sympathetic nervous activity ▪ salt

In 1971, Laragh1 demonstrated that whereas ~16% of essential hypertensive patients exhibit abnormally high levels of circulating renin, 57% exhibit normal renin levels, and 27% exhibit abnormally low levels of circulating renin. Despite a larger representation in the human population than high-renin hypertension, only a few models of low-renin hypertension are commonly used, such as the deoxycorticosterone acetate (DOCA)-salt model developed in the 1940s and the Dahl salt-sensitive rat developed in the 1950s.2 In 1943, Selye and colleagues3 demonstrated that cotreatment with high dietary sodium.4–6

Chronic DOCA-salt treatment greatly suppresses the peripheral renin-angiotensin system (RAS) but has different effects on the brain RAS. Several groups have demonstrated that although the expression levels for renin are much lower in the brain than in the kidney at baseline, DOCA-salt treatment results in a potent reduction in renal renin mRNA, with no change of renin mRNA in the brain.6,7 Similarly, whereas DOCA-salt causes reductions in renal angiotensin-converting enzyme, this treatment has no effect on brain angiotensin-converting enzyme.7 Angiotensinogen, in contrast, appears to be downregulated by DOCA-salt treatment in both the kidney and brain.8 Further studies have indicated that DOCA-salt hypertension is at least partially mediated through activation of the brain RAS (reviewed in Schenk and McNeill1). Itaya and colleagues9 demonstrated that intracerebroventricular (ICV) delivery of the angiotensin-converting enzyme inhibitor captopril (SQ42225) resulted in both the prevention and the reversal of DOCA-salt hypertension in rats. Similarly, Kubo et al10 and Park and Leenen11 have shown that central delivery of the angiotensin II (Ang II) type 1 receptor antagonist losartan also lowers blood pressure in DOCA-salt rats. Others have demonstrated that DOCA-salt treatment results in increased angiotensin receptor density specifically in cardiovascular control regions of the brain,
including the subfornical organ, median preoptic nucleus, paraventricular nucleus, and area postrema.\textsuperscript{7,12-15}

In addition to the blood pressure consequences of DOCA-salt, several studies have noted negative body weight effects of this treatment.\textsuperscript{4-5,16,17} These effects appear to be dependent on the phase of DOCA-salt treatment, however, as the body weight effects do not appear until after the onset of hypertension and the suppression of renal renin expression and are confounded by water and sodium loading during the early phases of treatment.\textsuperscript{5} Furthermore, the body weight effects are dependent on dietary sodium, as body weight effects of DOCA are masked on a sodium-free diet.\textsuperscript{4}

Recently, we described a novel double-transgenic mouse model of brain-specific RAS hyperactivity (the “sRA” mouse).\textsuperscript{17} sRA mice exhibit polydipsia, polyuria, elevated sodium intake, hypertension, lean bodies, and a high level of activity-independent thermogenesis. We determined that although the hydromineral phenotypes of the sRA model were completely dependent on elevated adrenal steroids, the metabolic phenotypes were dependent on a combination of elevated sympathetic nervous activity and a suppression of the circulating RAS. Thus, given the similarities in phenotypes between sRA mice and DOCA-salt–treated mice,\textsuperscript{17} the demonstration that hyperactivity of the brain RAS is sufficient to cause these phenotypes,\textsuperscript{17-19} and the involvement of the central RAS in DOCA-salt hypertension,\textsuperscript{8-11} we hypothesized that angiotensinergic signaling within the brain is necessary for the metabolic phenotypes of the DOCA-salt model.

\section*{Methods}

\subsection*{Animals}

All animal work was approved by the University of Iowa animal care and use committee and was performed in accordance with the National Institutes of Health \textit{Guide for the Care and Use of Laboratory Animals}.

Male C57BL/6J mice were obtained from Jackson Laboratories (Bar Harbor, ME) between 6 and 8 weeks of age. Mice were acclimated for 1 week before baseline measurements were taken. Mice were anesthetized by isoflurane inhalation for subcutaneous implantation of a 50-mg pellet of DOCA (21-day release, Innovative Research of America) or a sham implantation. After recovery from anesthesia, animals were singly housed in standard forced-air shoebox cages. Control animals were maintained on standard chow and ad libitum access to tap water. DOCA animals were maintained on standard chow and ad libitum access to both tap water and a 0.15 mol/L (0.9%) NaCl drink solution. One cohort of animals had hydralazine (500 mg/L, Sigma) added to all drink solutions. A second cohort of mice underwent ivc cannulation and subcutaneous implantation of a 50-mg pellet of DOCA (21-day release, Innovative Research of America) or a sham implantation. After recovery from anesthesia, animals were singly housed in standard forced-air shoebox cages. Control animals were maintained on standard chow and ad libitum access to tap water. DOCA animals were maintained on standard chow and ad libitum access to both tap water and a 0.15 mol/L (0.9%) NaCl drink solution. One cohort of animals had hydralazine (500 mg/L, Sigma) added to all drink solutions. A separate cohort of mice underwent ivc cannulation, and subcutaneous osmotic minipumps (Alzet) were used to chronically infuse losartan (5 μg/h, Sigma) or artificial cerebrospinal fluid (vehicle, aCSF) into the lateral cerebral ventricle (~1.0 mm lateral, 0.3 mm dorsal, 3.0 mm ventral to bregma). This cannulation surgery was performed under ketamine/xylazine (87.5 and 12.5 mg/kg IP, respectively) anesthesia. A separate cohort of mice were treated with DOCA-salt plus subcutaneous infusion of saline or Ang II (100 ng/kg per min) by an osmotic minipump (Alzet) implanted simultaneously with the DOCA pellet. Housing rooms were maintained on a 12:12 light/dark cycle, between 21°C and 23°C, and 15% to 40% relative humidity.

\subsection*{Intake Behaviors}

Food, water, and 0.15 mol/L NaCl intakes and urine and fecal outputs were measured with the use of mouse-size metabolism cages (Nalgene). Urine was collected for atomic absorption spectrophotometry (Instrumentation Laboratories) and melting-point (Fiske) determinations of electrolyte and osmolyte load.

\subsection*{Indirect Calorimetry}

Metabolic rate was estimated by indirect calorimetry, as previously described.\textsuperscript{17} In brief, room air was drawn through a water-jacketed, 2-L chamber (Ace Glass, Vineland, NJ) maintained at 30°C, and oxygen (S-3A/II, AEI Technologies) and carbon dioxide (CD-31, AEI Technologies) concentrations were determined in effluent air. Data were recorded and analyzed with a PowerLab (ADInstruments) with associated Chart software on a personal computer. One cohort of animals was anesthetized with ketamine/xylazine for metabolic rate determinations at thermoneutrality, after acute injections of saline (10 μL/g body weight) and propranolol (10 mg/kg IP in 10 μL/g body weight).

\subsection*{Blood Pressure}

Blood pressure was determined by radiotelemetry as previously described.\textsuperscript{17} In brief, animals were anesthetized with ketamine/xylazine, and an indwelling catheter was implanted into a common carotid artery. The body of the radiotelemetric probe (TA11PA-C10, Data Sciences International) was implanted in the subcutaneous space of the abdomen, and a DOCA pellet was implanted in the subcutaneous space between the scapulae. After 3 weeks of treatment, blood pressures were recorded for 30 seconds every 5 minutes for 5 consecutive days. Data from each animal were averaged hourly, and corresponding times across the 5 days were averaged for each animal to create a single composite 24-hour tracing for each animal.

\subsection*{Gene Expression}

Total RNA was isolated from kidney samples with the use of Tri-Reagent (Molecular Research Center, Cincinnati, OH). Renin mRNA was measured by real-time polymerase chain reaction with a Taqman primer/probe set (Mm02342888_Gh, Applied Biosystems).

\subsection*{Statistics}

Data were analyzed by 1- and 2-way ANOVA, with repeated measures as appropriate. Fisher least-significant-difference multiple-comparison procedures were used for post hoc comparisons. Data sets failing either normality or equal variance tests were subjected to nonparametric analyses, including ANOVA on ranks (Friedman ANOVA) and post hoc rank-sum (Mann-Whitney) tests. Differences were considered significant at $P<0.05$. All data are presented as mean±SEM.

\section*{Results}

DOCA-salt treatment resulted in an increased serum sodium concentration (sham 150.9±0.2 vs DOCA-salt 160.0±2.0 mmol/L; n=4 each, $P=0.03$). Three weeks of DOCA-salt treatment also resulted in a moderate, nocturnal hypertension (Figure 1, A and B) and bradycardia (Figure 1C). Cotreatment with the direct vasodilator hydralazine resulted in the normalization of blood pressures with no effect on the bradycardia. DOCA-salt treatment also resulted in a slight suppression of physical activity during the early portion of the dark phase (Figure 1D), which was largely unaffected by hydralazine treatment.

Chronic DOCA-salt treatment had no effect on food intake but resulted in robust changes in hydromineral turnover (Table 1). Total fluid intake was grossly elevated with DOCA-salt (roughly 8-fold), such that DOCA-salt–treated mice consumed more than their individual body weights in...
fluids per day. Total sodium intake (from both food and NaCl drink sources combined) was also greatly elevated with DOCA-salt treatment (roughly 2.5-fold), although this was not attributable to altered intake preferences for the 0.15 mol/L NaCl solution versus tap water. Urine volume paralleled total fluid intake, showing a large elevation with DOCA-salt treatment. Cotreatment with hydralazine attenuated many of the hydromineral turnover phenotypes but also had no significant effect on food intake. We cannot rule out contributions of possible taste effects of hydralazine on fluid intake behaviors in the DOCA-salt animals, although no alterations in fluid intake were noted in the sham + hydralazine group (Table 1).

Urine electrolytes were affected by DOCA-salt but were largely unchanged by hydralazine. Urine sodium and potassium concentrations were greatly suppressed with DOCA-salt (Table 1). Hydralazine cotreatment had no significant effect. Total daily sodium loss in the urine was elevated with DOCA-salt, which was partially reversed by hydralazine. Total daily potassium loss in the urine was significantly increased with hydralazine cotreatment.

Chronic DOCA-salt treatment resulted in a robust (20%) elevation in basal metabolic rate, whether analyzed as raw oxygen consumed (Figure 2A) or oxygen consumption normalized to body weight (Figure 2B). DOCA-salt treatment had no effect on respiratory quotient (Figure 2C). Heat production (Figure 2D), or heat production normalized to body weight (Figure 2E), was greatly elevated (26%) with DOCA-salt treatment. Despite effective blood pressure lowering, hydralazine treatment had no significant effect on oxygen consumption, respiratory quotient, or total heat production in DOCA-salt mice. Hydralazine treatment significantly exaggerated total heat production (44% increase versus sham, 14% increase versus DOCA-salt alone) when normalized to body weight (Figure 2E).

Access to 0.15 mol/L NaCl drink solution alone, without cotreatment with DOCA (n=4), had no effect on body weight (P=0.24 versus sham), oxygen consumed (0.84±0.04 mL/min, P=0.14 versus sham), oxygen consumed per unit body weight (3.14±0.23 mL/100 g per min, P=0.46 versus sham), respiratory quotient (0.81±0.05, P=0.28 versus sham), heat production (0.24±0.01 kcal/h, P=0.17 versus sham), or heat production normalized to body weight (9.06±0.60 kcal/kg per h, P=0.54 versus sham).

Increased energy expenditure by DOCA-salt was accompanied by a possible divergence in weight gain (Table 1). Three weeks of DOCA-salt treatment also resulted in a significant increase in interscapular brown adipose tissue, liver, and kidney weights, but it had no effect on perigenital white adipose or heart. Hydralazine cotreatment appeared to exaggerate heat production and weight suppression, although no significant effects were observed. Hydralazine cotreatment also resulted in suppressed brown and white adipose tissue weights, consistent with an exaggeration of energy expenditure despite the normalization of blood pressure.

As expected, DOCA-salt treatment resulted in a major suppression of renal renin mRNA (Figure 3). Hydralazine treatment resulted in a significant increase in renal renin mRNA in sham animals and prevented the decrease in renin mRNA caused by DOCA-salt treatment. Consequently, renin mRNA levels in the DOCA-salt + hydralazine group were indistinguishable from those of sham animals, despite the large differences in metabolic rate (Figure 2). Furthermore, chronic subcutaneous infusion of Ang II had no significant effect on the elevated basal metabolic rate during DOCA-salt treatment (DOCA-salt, 3.38±0.16 mL O2/100 g per min, n=4; DOCA-salt + Ang II, 3.35±0.18 mL O2/100 g per min, n=4; P=0.88).

To examine the involvement of angiotensinergic signaling within the brain in the development of the metabolic phenotypes of the DOCA-salt model, sham and DOCA-salt mice were chronically treated for 3 weeks with ICV infusion of either aCSF or the Ang II type 1 receptor antagonist losartan. Compared with chronic infusion of aCSF, losartan resulted in the attenuation of the increase in metabolic rate in DOCA-salt mice, without effect in sham mice (Figure 4). As in the hydralazine study (Figure 2C), DOCA-salt treatment again had

![Image](http://hyper.ahajournals.org/)
no significant effect on respiratory quotient, and chronic infusion of losartan also had no effect on energy source (Figure 4C). Losartan treatment resulted in the attenuation of white adipose loss during DOCA-salt treatment, consistent with a losartan-mediated reduction in metabolic rate (Table 2). Renal renin expression was again suppressed by DOCA-salt treatment, which was partially attenuated by chronic ICV losartan (Figure 5). Metabolic effects of ICV losartan treatment in the DOCA-salt group, but not in the sham group, underscores the involvement of angiotensinergic signaling within the brain, specifically in the phenotypes induced by DOCA-salt.

We next tested whether sympathetic nervous activity contributes to the elevated metabolic rate in DOCA-salt–treated mice. To accomplish this, we examined the effect of an acute peripheral injection of propranolol on metabolic rate in anesthetized mice at thermoneutrality, as previously reported. The difference in baseline heat production under anesthesia was blunted in DOCA-salt compared with sham mice (Figure 6A), such that the statistical difference between sham and DOCA-salt mice observed in our 2 previous experiments (Figures 2D and 4D) was lost (P=0.08). Propranolol caused a reduction in heat production in sham and DOCA-salt mice that was greater than vehicle (P<0.01). A significant interaction between groups was uncovered with propranolol treatment (2-way repeated-measures ANOVA DOCA-salt×propranolol interaction P<0.05). DOCA-salt animals exhibited a small but statistically significant increase in sensitivity of basal metabolic rate to low-dose propranolol compared with sham animals (Figure 6B). These data support a potential role for sympathetic nervous activity but certainly do not rule out other mechanisms.

**Discussion**

The main findings of the current study are as follows: (1) DOCA-salt, in addition to causing hypertension, causes an
increase in basal metabolic rate without an effect on food intake; (2) the increase in metabolic rate occurs independent of the blood pressure elevation and alteration in hydromineral turnover; and (3) the increase in metabolic rate is due in part to AT1 receptor signaling within the brain. This study therefore advances the concept that angiotensinergic signaling in the brain may, in addition to regulating cardiovascular and renal function, also regulate metabolism.

We chose to examine the DOCA-salt model to complement previous studies in a transgenic mouse model (the sRA model) of brain RAS hyperactivity. The DOCA-salt model depends on elevated brain RAS signaling to elicit and maintain hypertension. In sRA mice, increases in central Ang II resulted in hypertension and robust hydromineral phenotypes. In addition, sRA mice exhibited a marked elevation in activity-independent, thermogenic energy expenditure. Thus, both sRA mice and DOCA-salt–treated mice exhibit similar elevations in basal metabolic rate.

We examined whether the metabolic phenotypes were secondary to the hypertension in DOCA-salt mice. Hydralazine normalized blood pressure and largely attenuated hydromineral turnover. On the contrary, lowering blood pressure had no effect on the metabolic rate. We therefore conclude that the metabolic increases with DOCA-salt are mediated through a mechanism that is distinct from and not secondary to the hypertension.

We next assessed whether the increase in metabolic rate required activity of the brain RAS. Unlike hydralazine, central infusion of losartan resulted in a blunting of the increase in metabolic rate caused by DOCA-salt treatment. Previous studies have shown that the hypertension elicited by DOCA-salt is mediated, at least in part, by activity of the central RAS. Consequently, this supports the conclusion that activity of the brain RAS is necessary for both the hypertension and the elevated metabolic rate in response to DOCA-salt, although the efferent mechanisms may be distinct.

We previously demonstrated that increased sympathetic nervous system will also play a role in regulating metabolic rate. This suggests that elevated adrenal steroids per se are not sufficient to elicit changes in metabolic rate. Using a parallel argument, we hypothesize that in the DOCA-salt model, elevated steroids induce activity of the brain RAS and thereby...
the sympathetic nervous system, which subsequently modulates metabolic rate.

We also showed that sRA mice exhibit suppressed circulating RAS activity as measured by decreased renal renin mRNA and circulating angiotensin peptides. Suppression of the circulating RAS is a hallmark of the DOCA-salt model, and indeed, we showed that DOCA-salt treatment suppressed renal renin mRNA. Many pharmacologic and genetic studies have shown that interference with the RAS results in body weight loss, resistance to weight gain, and/or altered adipose development. Ang II replacement in renin-knockout mice normalized body weight and adiposity back to that of wild-type mice. Similarly, an 8-week infusion of a nonpressor dose of Ang II in sRA mice normalized metabolic rate. We therefore hypothesized that suppressed peripheral RAS activity in DOCA-salt mice may contribute to the increased metabolic rate. The first challenge to this hypothesis came from the observation that hydralazine, which lowered blood pressure and restored renal renin mRNA levels, did not restore metabolic rate. It is possible that although renal renin mRNA was normalized by hydralazine, renin release or activity may still remain suppressed. Nevertheless, to test this hypothesis directly, we treated DOCA-salt mice with a nonpressor dose of Ang II simultaneously by using the same 3-week treatment paradigm. Similar to hydralazine, Ang II had no effect on the elevated metabolic rate induced by

![Image](image-url)

**Figure 4.** Metabolic effects of central AT1 receptor blockade during DOCA-salt hypertension. A, Oxygen consumed per minute by mice at thermoneutrality (30°C). B, Oxygen consumed per minute, normalized to body weight. C, Respiratory quotient. D, Heat produced. E, Heat produced, normalized to body weight. Sham + aCSF n = 5, sham + losartan n = 4, DOCA-salt + aCSF n = 8, and DOCA-salt + losartan n = 8. *P < 0.05 sham + aCSF; †P < 0.05 vs DOCA-salt + aCSF and P < 0.05 vs sham + aCSF; ‡P = 0.061 vs DOCA-salt + aCSF and P < 0.05 vs sham + aCSF. All data are mean ± SEM.

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<th>Parameter</th>
<th>Sham + aCSF (n = 5)</th>
<th>Sham + Losartan (n = 4)</th>
<th>DOCA-Salt + aCSF (n = 8)</th>
<th>DOCA-Salt + Losartan (n = 8)</th>
</tr>
</thead>
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<tr>
<td><strong>Body mass, g</strong></td>
<td>25.3 ± 0.4</td>
<td>25.5 ± 0.9</td>
<td>23.4 ± 0.4*</td>
<td>23.8 ± 0.4*</td>
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<td>Interscapular brown, mg</td>
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<td>62.8 ± 5.2</td>
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<td>2.71 ± 0.14*</td>
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<td>294 ± 32*</td>
<td>222 ± 18*</td>
<td>269 ± 28*</td>
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<td>Perigenital white, mg/g</td>
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<td>8.8 ± 0.6*</td>
<td>10.5 ± 1.2*†</td>
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<td>Liver, g</td>
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<td>Kidney, mg/g</td>
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<td>Sodium, mmol/L</td>
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<td>157.1 ± 2.2*</td>
<td>161.3 ± 0.7*</td>
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"mg/g" and "g/g" indicate normalization to body weight, in grams.
*P < 0.05 vs sham + aCSF.
†P < 0.05 vs DOCA-salt + aCSF.
DOCA-salt. It remains possible that a 3-week treatment period is insufficient to restore the metabolic rate to control values, as a 3-week Ang II infusion in sRA mice was similarly ineffective. An increase in the duration of the Ang II treatment would require a similar increase in the duration of the DOCA-salt. This was not performed in the current study because of the well-known shift in the mechanism controlling hypertension over time with DOCA-salt. The sympathetic nervous system is the driving force during the “developed” phase (2 to 6 weeks) of hypertension in DOCA-salt rats, whereas humoral mechanisms play a greater role in the “malignant” phase (>6 weeks). Future studies will establish whether the increase in metabolic rate is retained during the malignant phase of DOCA-salt hypertension and whether circulating Ang II is important during this phase.

Perspectives
Our data, first in sRA mice, and herein with DOCA-salt mice, advance the novel concept that the brain RAS may play a role in the control of energy expenditure. Here we have documented robust metabolic consequences of DOCA-salt treatment in C57BL/6J mice that are dependent on activity of the RAS in the brain. We propose a working model whereby DOCA-salt induces angiotensinergic signaling within the brain to increase metabolic rate through the sympathetic nervous system (Figure 7). The mechanism regulating metabolic rate by the brain RAS occurs in parallel with the mechanism elevating arterial pressure, but the increased pressure per se does not play a causative role. The role of other factors known to participate in DOCA-salt hypertension (that is, vasopressin and endothelin) in the regulation of metabolic rate remains unclear, as does the importance of circulating Ang II. Importantly, the differential mechanisms regulating metabolic rate and blood pressure by the brain RAS may implicate angiotensinergic signaling within discrete and distinct regions of the brain. Identification of these pathways may increase our understanding of the broader actions of the RAS in blood pressure and metabolic regulation, which could have implications for the understanding and treatment of metabolic disorders such as obesity.

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Disclosures

None.

References

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