Differential effects of salt on renal hemodynamics and potential pressure transmission in stroke-prone and stroke-resistant spontaneously hypertensive rats

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Abu-Amarah, Isam, Anil K. Bidani, Rifat Hacioglu, Geoffrey A. Williamson, and Karen A. Griffin. Differential effects of salt on renal hemodynamics and potential pressure transmission in stroke-prone and stroke-resistant spontaneously hypertensive rats. Am J Physiol Renal Physiol 289: F305–F313, 2005. First published April 12, 2005; doi:10.1152/ajprenal.00349.2004.—Salt-supplemented stroke-prone spontaneously hypertensive rats (SHRsp) develop more severe hypertension-induced renal damage (HIRD) compared with their progenitor SHR. The present studies were performed to examine whether in addition to increasing the severity of hypertension salt also enhanced the transmission of such hypertension to the renal vascular bed in the SHRsp. “Step” and “dynamic” renal blood flow (RBF) autoregulation (AR) were examined in ∼12-wk-old SHR and SHRsp after 3–5 days of an 8% NaCl diet. During step AR under anesthesia (n = 8–11), RBF was significantly higher in the SHRsp at all perfusion pressures (P < 0.01), but AR capacity was not different. Similarly, in separate conscious chronically instrumented rats (n = 8 each), both blood pressure (BP) and RBF were modestly but significantly higher at baseline before salt in the SHRsp (P < 0.05). However, transfer function analysis did not show significant differences in the admittance gain parameters. However, after 3–5 days of salt, although average BP was not significantly altered in either strain, RBF increased further in the SHRsp and there was a significantly greater transfer of BP into RBF power in the SHRsp. This was reflected in the significantly higher admittance gain parameters at most frequencies including the heartbeat frequency (P < 0.05 maximum). These differential hemodynamic effects of salt have the potential to enhance BP transmission to the renal vascular bed and also contribute to the more severe HIRD observed in the salt-supplemented SHRsp.

autoregulation; myogenic response; genetics; nephrosclerosis

GENETIC FACTORS ARE BELIEVED to contribute to the considerable variability in the incidence and severity of hypertensive renal injury that is observed in both humans and experimental animals (4, 7, 10, 13, 32, 35, 39). For instance, the spontaneously hypertensive rat (SHR) and the stroke-prone SHR (SHRsp) derived from the SHR progenitor strain display marked differences in the development of severe target organ injury including renal damage; the SHR is relatively resistant, whereas the SHRsp is very susceptible (1, 4, 17, 28, 39, 43). Salt supplementation is widely used to accelerate the hypertension and to demonstrate and investigate this contrasting susceptibility (17, 28, 39). However, the mechanisms by which salt supplementation elicits and accentuates this differential susceptibility to hypertension-induced renal damage (HIRD) have remained controversial (17, 28, 39, 40). The adverse consequences of hypertension on any vascular bed, with or without salt supplementation, are expected to be a function of the degree to which that vascular bed is exposed to the increased pressures (2, 3). Therefore, mechanistically, the differences in the severity of renal damage between SHR and SHRsp after salt supplementation can result from differences in 1) the systemic blood pressure (BP) “load,” 2) the degree to which such load is transmitted to the renal vascular bed, and/or 3) local tissue susceptibility to similar degrees of pressure exposure (2, 3).

Using chronic BP radiotelemetry, we previously showed that the greater severity of HIRD in the salt-supplemented SHRsp is, at least in part, due to greater and more rapid increases in BP after salt supplementation than in the SHR (17). Therefore, a cross transplantation strategy was used to assess the intrinsic genetic susceptibility to HIRD in the two strains independent of the effects of systemic BP profiles (11). The SHRsp kidneys, whether native or transplanted, exhibited twice the severity of HIRD compared with the SHR kidneys when exposed to an identical milieu of systemic BP and metabolic environment of either the salt-supplemented SHR or the SHRsp recipient. This unequivocal demonstration of the greater susceptibility to HIRD in the salt-supplemented SHRsp implies either an enhanced transmission of systemic hypertension to the renal microvasculature and/or an enhanced local tissue susceptibility to the same level of pressure exposure compared with the SHR kidneys. The present investigations were therefore performed to examine whether differences in BP transmission contribute to the increased susceptibility to HIRD in the salt-supplemented SHRsp. As renal autoregulation (AR) is thought to provide the primary protection against an enhanced BP transmission (1–6, 9, 18–20, 24, 26, 30, 42), the effects of 3–5 days of salt supplementation on AR capacity were examined in the SHR and SHRsp strain using both “step” and “dynamic” AR assessment methodologies. This short period of salt supplementation was selected as it has been noted to have minimal BP effects (17) and would thus allow an examination of the BP-independent effects of salt supplementation per se on pressure transmission. It was reasoned that the potential for renal vascular injury associated with rapid increases in BP after the first week in 8% NaCl diet-fed SHRsp (17) might complicate interpretations.

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METHODS

The SHRsp were obtained from a colony transferred to Hines VA from the colony that had been maintained at the University of Michigan in Ann Arbor since 1981 (11, 16, 17). The SHR were obtained from Harlan (Indianapolis, IN). Only male rats were used and all were cared for in accordance with the Guide for the Care and Use of Laboratory Animals (Department of Health, Education, and Welfare), and the experimental protocols were approved by the joint Institutional Animal Care and Use Committee of Loyola University Stritch School of Medicine and Edward Hines Veterans Hospital. They were housed in a constant-temperature room with a 12:12-h light-dark cycle and as described below, they had free access to rodent chow (Purina) with a standard 1% NaCl or 8% NaCl content (Purina) and drinking fluid (tapwater). Step and dynamic autoregulatory studies were performed in separate sets of rats.

Step studies. Male SHR and SHRsp (11–12 wk, 250–300 g body wt) were placed on an 8% NaCl diet with free access to drinking water for 4 days before the studies were performed. The rats were anesthetized with inactin (100 mg/kg ip) and surgically prepared as described previously (5, 6, 18, 19). In brief, a tracheostomy was performed using polyethylene (PE-200) tubing, and a carotid and a femoral artery were cannulated with PE-50 tubing and connected to a Windograf recorder (model 40–8474; Gould, Glen Burnie, MD) for continuous recording of renal perfusion pressure (RPP). A femoral vein was cannulated with PE-50 tubing and a 150 mM NaCl bolus equal to 1% of the body weight was administered, followed by a continuous maintenance infusion of 150 mM NaCl at 0.055 ml/min for replacement of surgical and ongoing fluid losses. An ultrasonic transit time (1RB) flow probe was placed around the left renal artery for measurement of renal blood flow (RBF) by a flowmeter and AR studies were performed using aortic miniclamps positioned above and below the left renal artery to lower or raise RPP measured via the femoral or the carotid artery catheter, as previously described (5, 6, 18, 19). The RBF was allowed to stabilize for 1 to 2 min at each pressure before RBF measurements were made. Initial step reductions of RPP in these hypertensive rats were followed by pressure steps in the reverse order. The RBF responses for each pressure step (in both directions) were then averaged for the calculation of autoregulatory indexes (AI). Flow probes were validated as previously described (5, 18). AI were calculated as previously described for each pressure step (fractional change in RBF/fractional change in RPP) (5, 6, 18, 19). An AI of zero indicates perfect AR, whereas an AI of one indicates that the vessels act as passive conduits for blood flow.

Dynamic AR studies. One week before the scheduled studies, additional 11- to 12-wk-old male SHR and SHRsp (n = 8 each strain) underwent placement of radiotransmitters for BP radiotelemetry and chronic renal perivascular transonic flow probes (left renal artery) for RBF measurements, as previously described (5, 18). In brief, under pentobarbital sodium anesthesia, each rat had a BP sensor (model TA11PA-C40; Data Sciences) inserted into the aorta via the right femoral artery and advanced into the aorta to a position below the level of the renal arteries, and the transmitter was fixed to the peritoneum. An ultrasonic transit time flow probe (1RB, Transonic Systems, Ithaca, NY) was placed around the left renal artery and packed in Dacron mesh to ensure proper alignment of the probe and vessel. The probe cable was secured to back muscles, routed subcutaneously, and exteriorized at the back of the neck. After rats were allowed to recover for 1 wk, the flow probes were connected to a transonic flowmeter (T106, Transonic Systems) and simultaneous recordings of BP and RBF were obtained for 1–2 h at a sampling rate of 200 Hz in conscious unrestrained SHR and SHRsp rats between 10 AM and 3 PM. Two recordings were obtained in each rat at intervals of 24 h and the results were averaged for each rat. The rats were then placed on an 8% NaCl diet for 4 days, and the recordings were repeated.

Subsegments of 30 min in duration from each recording that were free of noise or other artifacts were selected from each data record. These 30-min signals were resampled to a sampling rate of 20 Hz using a low-pass anti-aliasing filter to remove variations in the signals at greater than 10 Hz. Each time sequence of 36,000 data points was then subjected to linear trend removal. The transfer functions of the dynamic relationship between BP (input) and RBF (output) were analyzed using standard methods (5, 12, 14, 18, 20, 23, 24, 30). The BP and RBF power spectra estimates were determined using the Fast Fourier Transformation-based Welch’s averaged periodogram method (50% overlap of 7 segments of 8,192 samples) and a Hanning window was applied (31). Input and output autopower spectra and cross power spectra were calculated for each segment and then averaged. The admittance function was computed as the ratio of cross spectrum to BP power spectrum. The coherence function was also computed from the cross and auto power spectra. Fractional gain in admittance (FGA) was obtained by normalizing admittance gain by the conductance computed over the entire 30-min record. The natural frequencies of the myogenic and the tubuloglomerular feedback mechanisms (TGF) were determined from their characteristic signature resonance peaks in fractional gains between 0.1 and 0.3 Hz and between 0.025 and 0.05 Hz, respectively, by inspection of individual records, and then averaged across each record (18). The heartbeat frequency (HB) range was determined from the BP power spectral density as the frequency at which maximal BP power is reached in the 4- to 8-Hz frequency range. For quantitative analysis of the effects of salt supplementation on BP and RBF spectra, the BP and RBF power content was computed for the frequency bins, 0.0025–0.025 Hz, 0.025 to 0.25 Hz and the HB frequency, as collectively these bins account for almost all of the power in the BP spectra.

Statistical analysis. ANOVA followed by a Student-Newman-Keuls test and paired and unpaired Student’s t-tests were used as appropriate. For data that did not exhibit a Gaussian distribution, the nonparametric Mann-Whitney U-test or Wilcoxon matched pair signed ranks test was used. A P > 0.05 was considered not significant. Results are means ± SE (15).

RESULTS

Step AR studies. Figure 1 shows the results of the step AR studies. As can be noted, RBF was significantly higher in the SHRsp compared with the SHR at all RPPs. However, the capacity to autoregulate the steady-state RBF in response to
step changes was not different between the two strains as indicated by the lack of significant difference in calculated AI for each of the pressure steps. However, in both strains, the AR capacity was maximal at pressures >150 mmHg and the least at pressures <125 mmHg.

Fig. 2. Mean values of blood pressure (BP; A), RBF (B), and conductance (C) during control measurements (basal) and after 3–5 days of 8% NaCl diet during dynamic AR studies in conscious SHR and SHRsp strains. *P < 0.05, n = 8 each.

Fig. 3. BP and RBF power spectra computed over 30 min in conscious SHR and SHRsp rats (n = 8 each) at baseline and after 3–5 days of an 8% NaCl diet.
Dynamic AR studies. Figure 2 shows the basal values of BP (A), RBF (B), and conductance (C) and the effects of 8% NaCl dietary supplementation on these parameters during the dynamic AR studies in conscious SHR and SHRsp. At baseline before salt supplementation, the average BP in the SHRsp was modestly but significantly higher than in SHR. Salt supplementation resulted in small but nonsignificant BP increases in both strains (Fig. 2A). RBF was also significantly higher at baseline in the SHRsp and increased further after salt, while there was no change in the SHR (Fig. 2B). The differences in renal vascular resistance (RVR) at baseline and in response to salt supplementation in the two strains are reflected in the calculated conductance (1/RVR) values. At baseline, conductance was not significantly different despite the significantly higher BP in the SHRsp and salt supplementation further increased the conductance in the SHRsp but did not alter it in the SHR (Fig. 2C).

The effects of salt supplementation on BP and RBF power spectra in the SHR and SHRsp are shown in Fig. 3, A and B, and the quantitative data are presented in Table 1. Although salt supplementation did not have significant effects on the average BP in either strain, it resulted in significant increases in the BP power at the HB frequency in both strains. Additionally, BP power was also increased significantly at the lower frequencies in the SHRsp but not in the SHR. Differences were also observed between the strains for the effects of salt supplementation on RBF power spectra. RBF power was increased significantly at most frequencies in the SHRsp but was essentially unaltered in the SHR. These differential effects are clearly illustrated when the BP and RBF power spectra of the salt-supplemented SHR and SHRsp are directly compared (Fig. 3C and Table 1). Significantly greater RBF power is present in the salt-supplemented SHRsp compared with the salt-supplemented SHR at most frequencies including the HB frequency (Table 1). The differences in the responses to salt supplementation between the SHR and SHRsp with respect to the transfer of BP power into RBF power are best shown in Fig. 4, A–C, which compares the calculated admittance gain parameters for these major BP power frequency bins. As can be seen, admittance gains were significantly higher in the SHRsp for all three frequency bins. This difference is particularly notable at the HB frequency, the largest contributor of pressure power in the BP power spectra, with the admittance gain significantly decreasing in the SHR and increasing in the SHRsp.

The results of conventional transfer function analysis illustrating the effects of salt supplementation on the two strains are presented in Figs. 5, 6, and 7. FGA at the lower frequencies (<0.025 Hz) that has been considered to be an indicator of dynamic AR capacity (ability to buffer BP fluctuations occurring...
ring at <0.25 Hz) averaged ~0.5 at its nadir in both strains and was not significantly or consistently altered by salt supplementation in either strain (Fig. 5, A–C). Similarly, no consistent or significant differences were observed at baseline or after salt on the phase angle that was confined between ±90 degrees (Fig. 6, A–C) despite the pronounced effects of salt on the myogenic resonance peak (see below). Similarly, coherence was similar between the two groups and was not affected by salt, remaining higher than 0.5 at frequencies >0.3 Hz and not unexpectedly reaching unity at the HB frequency band (~6 Hz) (Fig. 7, A–C). The magnitude of the resonance peak at ~0.25 Hz, considered to be the signature of the myogenic mechanism, was significantly attenuated after salt in both SHR and SHRsp but its natural frequency was not altered (~0.3 Hz) (Figs. 5, A–C, and 8). The TGF resonance peak, which is typically observed at ~0.04 Hz, exhibited some variability in its precise location, but no significant consistent differences between SHR and SHRsp were observed at baseline or after salt (0.037 ± 0.003 and 0.038 ± 0.003 Hz in the SHR vs. 0.037 ± 0.002 and 0.036 ± 0.002 in the SHRsp). Similarly, no consistent effects or differences were observed for the magnitude of the TGF peak (FGA) at baseline or after salt in either strain (0.91 ± 0.1 and 0.95 ± 0.1 in the SHR vs. 0.83 ± 0.15 and 0.94 ± 0.2 in the SHRsp). An additional resonance peak of uncertain genesis and/or significance and usually not seen in normotensive rats (18) was observed at 0.6 to 0.8 Hz in both strains. This peak was enhanced by salt in the SHR but not in the SHRsp (Figs. 5 and 8).

DISCUSSION

Superimposed salt supplementation has been widely used to accelerate and accentuate hypertensive renal damage and facilitate the investigation of the responsible pathogenetic mechanisms in both genetic and nongenetic experimental models (11, 16, 17, 24, 28, 32, 33, 37–40). Such investigations have, in part, been stimulated by the fact that certain racial/ethnic groups, such as African-Americans, which display an enhanced susceptibility to hypertensive renal damage, are also reported to be more salt sensitive in their BP responses (4, 8, 13, 25, 29, 35, 41, 45). Nevertheless, the pathways through which the deleterious effects of salt supplementation are produced remain controversial (8, 17, 24, 25, 27–29, 32–34, 37–41, 44, 45, 48). Given the parallelism between the sensitivity to salt-induced increases in BP and the observed enhancement of the severity of renal damage in most of these models, there is little question that an increased severity of hypertension plays a major role in mediating the adverse effects of salt supplementation on renal damage. Therefore, much of the genetic differences in the susceptibility to salt-induced exacerbation of renal damage may be attributable to genetic differences in BP salt sensitivity. Nevertheless, there are data to suggest that such BP-dependent effects of salt supplementation may not entirely account for its deleterious effects on renal damage, even though some of the interpretations of BP independence of such effects are possibly compromised by the limitations of tail-cuff BP measurements.

Fig. 5. Transfer function analysis of the fractional gain in admittance between BP (input) and RBF (output) computed over 30 min in conscious SHR and SHRsp rats at baseline and after salt supplementation during dynamic AR studies.
Fig. 6. Transfer function analysis of phase angle (degrees) between BP (input) and RBF (output) computed over 30 min in conscious SHR and SHRsp rats at baseline and after salt supplementation during dynamic AR studies.

Fig. 7. Transfer function analysis of coherence between BP (input) and RBF (output) computed over 30 min in conscious SHR and SHRsp rats at baseline and after salt supplementation during dynamic AR studies.
in the rat models (17, 27, 28, 37–40, 44, 48). This is particularly relevant in view of the present results, which show that even 3–5 days of salt supplementation had significant effects on BP power spectra despite an absence of significant changes in average (mean) BP.

The results of the present studies additionally show that genetic differences in the renal hemodynamic responses to salt supplementation may also have the potential to contribute to a differential susceptibility to renal damage in salt-supplemented animals. Although neither step (AI) nor dynamic AR capacity (FGA at frequencies <0.02 Hz) was differentially altered by salt in the present studies, nevertheless, the obtained data are consistent with a potential enhancement of BP transmission in the salt-supplemented SHRsp. We recently suggested that the ability of the renal vasculature to protect against BP transmission can be assessed in terms of its ability to buffer the different individual components of BP power (energy/unit time) that it is potentially exposed to (2, 3, 5, 18, 26). In biophysical terms, BP power can be considered to consist of two major components; that due to its average (mean) value, the DC BP power, the largest component, and that due to its fluctuations from the average value due to the heart beat (HB) as well as other slower mechanisms (AC BP power) (31). Of the AC BP power, the largest fraction is that due to the HB (2, 5, 18, 26). We also suggested that step and dynamic AR methodologies, at least as currently performed, provide complementary data as they assess the ability to protect against enhanced transmission of different individual components of BP power (5, 18). The step AR methodology assesses the ability of the preglomerular vasculature to respond to large changes in mean BP (DC BP power). However, during conventional step AR studies, only the potential magnitude of the AR response is assessed by the steady-state RBF responses but not its kinetic aspects (5, 12, 18, 20, 22–24, 30, 36). The dynamic AR methodology, on the other hand, provides an index of the kinetics of the AR responses (natural frequencies of the myogenic and TGF control mechanisms) and the potential buffering of AC BP power, including the large component that is present at the HB frequency (18). However, recent data suggest a need for caution in the interpretations of FGA at frequencies <0.025 Hz that have been used to assess the dynamic AR capacity of renal AR mechanisms to buffer the BP power due to slower fluctuations (<0.25 Hz) (5, 12, 18, 22–24, 30). Such assessments have yielded estimates of AR capacity that are at variance with the results of step AR studies, at least in some experimental states (5, 18). This may be a function of the fact that the coherence function is usually <0.5 at frequencies <0.1 Hz during dynamic AR in rats (5, 12, 18, 20, 24, 30), as was also the case in the present studies. This lower coherence likely stems from the nonlinear character of AR dynamics in the frequency ranges where the AR mechanisms are active (although lowered coherence can also arise from noise effects or time variations in linear dynamics) (20). Despite these limitations, a superior alternative to assess the dynamic AR capacity to buffer BP fluctuations in vivo in conscious animals remains to be established, although recent work exploring the use of nonstationary time-frequency analysis techniques shows promise in this regard (49). It also needs to be acknowledged that other alternative methods to assess dynamic AR capacity such as white noise arterial pressure forcing under anesthesia (20, 24) or an analysis of the RBF oscillations after step changes in RPP (47) might have revealed differences in AR behavior between SHR and SHRsp that were not detected by our methods. Nevertheless, it is of note that from the quantitative BP transmission perspective, the pressure power present at frequencies <0.25 Hz is substantially smaller than that at the HB frequency and the DC BP power.

In any event, AR efficiency is generally assessed only in terms of fractional changes and differences in the absolute values of ambient BP and RVR (conductance) are factored out. Such normalization is not inappropriate, given the fact that the ambient RVR not only reflects the AR response to the ambient BP but is also importantly modulated by BP-independent factors (neurohormonal, metabolic) (5, 18). Nevertheless, the ambient basal preglomerular resistance is expected to be an important determinant of the ambient fractional transmission of systemic BP; the greater the vasodilation, the more will be the pressure and flow delivered distally. The observed differential effects of salt supplementation on conductance with the associated increases in the admittance gains at both the HB and lower frequencies in the SHRsp, which are less apparent when the data are examined as FGA, are consistent with such interpretations. We have suggested that a similar ambient vasodilation, despite a preserved step AR ability, may account for the increased susceptibility to hypertensive injury after uninephrectomy in several models (3, 5). If these interpretations of the hemodynamic effects of salt supplementation on BP transmission are valid, then the increasing severity of hypertension with time in the SHRsp due to its increased BP salt sensitivity (16, 17) is likely to magnify the adverse effects of salt supplementation on renal damage. In models of malignant nephrosclerosis, such as the SHRsp, renal damage develops when BP exceeds a certain threshold (16, 17). Although renal AR capacity seems to be preserved through much of the AR range in the SHRsp, such enhanced BP transmission may result in a lower BP threshold for renal damage compared with SHR (16, 17). However, it should be acknowledged that we were unable to raise the BP high enough during step AR studies to demonstrate such differences in the upper limit of AR. The relatively reduced AR capacity in both strains to autoregulate RBF at perfusion pressures of 100–125 mmHg compared with that seen in normotensive rats is similar to that
described previously in hypertensive rats and is consistent with the interpretations of an elevation of the lower limit of AR and a shift of the AR range to the right (2, 21).

Of interest, salt supplementation was noted to similarly attenuate the myogenic resonance peak in both the SHR and SHRsP despite the differential effects on conductance and other admittance parameters gains. Although the precise genesis of this resonance peak remains to be established, it has been postulated to represent an interaction between the myogenic mechanisms and the passive elastic properties of the blood vessel (12, 20, 24, 26, 30). We previously suggested that a decrease in the magnitude may serve as an indicator of the strength of the myogenic mechanism based on its attenuation in models of renal mass reduction and after administration of calcium channel blockers (5, 18). Although the present data do not necessarily exclude such interpretations, they are difficult to reconcile with the relative resistance of the SHR strain to renal damage even after salt supplementation. Alternatively, this resistance might be a reflection of the preserved ability of the SHR to better buffer the largest components of the total BP power (DC power and the AC power at the HB frequency). Also of interest, no significant differences at baseline or consistent effects were observed on the resonance peak believed to be generated by an intrinsic oscillation of the TGF system (12, 20, 24, 30). However, it is possible that such effects or the contribution of the TGF system may be masked by the low coherence in this frequency range and the nonstationarity of these signals (5, 12, 18, 20, 49).

In conclusion, the present studies show that salt supplementation may enhance renal damage not only through its effects on systemic BP, but also through its potential effects on BP transmission. These data also show that the sensitivity to such hemodynamic effects of salt may be determined by genetic factors as has also been noted in some human studies, although considerable heterogeneity is observed in those responses (8, 25, 29, 41, 45, 46). Moreover, it is of note that although both SHRsP and the Dahl salt-sensitive (S) strains exhibit similar BP salt sensitivity, the renal hemodynamic responses differ with RBF, tending to decrease in Dahl S rats (38) and increase in the SHRsP. Differences between models might also exist for the effects of salt on local tissue susceptibility to injury in the pathogenesis of HIRD. Several such mechanisms have been postulated (24, 27, 33, 34, 37, 39, 44, 45, 48). Although the BP independence of some of these potential pathways such as the local tissue damage-promoting effects of the renin-angiotensin-aldosterone system (33, 39, 40) has not been sustained when BP radiotelemetry has been used (16), nevertheless other mechanisms such as increased oxidative stress associated with salt supplementation have the potential to enhance tissue susceptibility and damage (27, 34, 48). Such genetic or acquired differences in the range of responses to salt supplementation may account for the considerable diversity in the observed sensitivity to the adverse effects of salt on hypertensive target organ damage.

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