A High-Salt Diet Alters Circadian Blood Pressure Rhythm in Dahl Rats

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HASHIMOTO, J., IMAI, Y., MINAMI, N., MUNAKATA, M., SAKUMA, H., SASAKI, S., YOSHINAGA, K. and ABE, K. *A High-Salt Diet Alters Circadian Blood Pressure Rhythm in Dahl Rats.* Tohoku J. Exp. Med., 1994, 173 (3), 345-354 — To determine whether salt loading and salt sensitivity are related to the circadian variation in blood pressure (BP), we studied the circadian rhythm of BP in Dahl rats. Thirteen Dahl salt-sensitive (Dahl-S) and 14 salt-resistant (Dahl-R) rats were fed a high- or low-salt diet after weaning. Mean arterial pressure (MAP) and heart rate (HR) were measured every 4 sec throughout 24 hr in freely moving rats, and the data obtained were analyzed quantitatively by the cosinor method. MAP mesor was significantly elevated in Dahl-S rats on a high-salt diet (SH), as compared with those on a low-salt diet (SL), but there was no difference in the MAP mesor between Dahl-R rats on a high-salt diet (RH) and those on a low-salt diet (RL). MAP amplitude was significantly greater and HR amplitude was smaller in SH rats than in SL rats; the amplitudes of MAP and HR in RH rats were similar to those in RL rats. MAP acrophase was significantly delayed in SH and RH rats as compared with SL and RL rats, respectively; the time delay in the MAP acrophase was not accompanied by a synchronized delay in HR acrophase. The time delay in MAP acrophase was greater in SH rats than in RH rats. These results indicate that salt loading influences the amplitude and acrophase of BP, and that the effect of salt loading on circadian BP rhythm is modulated by salt sensitivity. ——— circadian rhythm; blood pressure; Dahl rats; cosinor analysis

The existence of the circadian rhythm in blood pressure (BP) has been demonstrated in humans (Mancia et al. 1983) and in experimental animals (Smith et al. 1987; Minami et al. 1988; Friberg et al. 1989). Factors postulated as responsible for the regulatory mechanisms involved include the autonomic nervous system (Mann et al. 1983), humoral factors (Imai et al. 1988), and physical activity (Rowlands et al. 1980). Circadian BP rhythm might also be affected by

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Received February 15, 1994; revision accepted for publication June 13, 1994.

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salt loading and salt sensitivity, based on reports of the possible effects of salt loading and salt sensitivity on circadian BP rhythm in patients with essential hypertension (Delea 1979; Bittle et al. 1985).

About 30 years ago, Dahl and coworkers developed two strains of rats, a salt-sensitive (Dahl-S) strain that becomes hypertensive with high-salt intake and a salt-resistant (Dahl-R) strain that remains essentially normotensive despite high-salt intake. The Dahl model has been useful for studying the relationship between salt and hypertension. Previous studies have examined the roles of the nervous system (Takeshita and Mark 1978; Takeshita et al. 1979; Goto et al. 1982), kidney (Dahl and Heine 1975; Roman 1986; Morgan et al. 1990), adrenal cortex (Iwai et al. 1969) and unidentified humoral factors (Hirata et al. 1984) in the development of hypertension in Dahl-S rats. The same factors that are responsible for hypertension in Dahl-S rats might affect circadian BP rhythm as well as BP itself, since some of these factors, particularly the neural factor, are more or less linked to the intrinsic rhythm of BP (Mancia et al. 1983; Mann et al. 1983). A previous study demonstrated a difference between Dahl-S and Dahl-R rats in circadian BP rhythm when both were fed a high-salt diet (Brown et al. 1989).

In the present study, we recorded BP and HR in conscious unrestrained Dahl rats throughout 24 hr; the data were analyzed by the cosinor method. Cosinor analysis is an acknowledged method for quantitative assessment of circadian variation in various physiological parameters (Halberg et al. 1972; Nelson et al. 1979). In our previous studies, cosinor analysis was applied effectively to delineate circadian BP rhythm in patients with essential hypertension (Munakata et al. 1991) as well as in spontaneously hypertensive rats (Munakata et al. 1990).

We employed cosinor analysis in the present study to analyze 24-h BP and HR and to clarify the influence of salt loading and salt sensitivity on circadian BP and HR rhythm in Dahl rats.

METHODS

Thirteen male Dahl-Iwai salt-sensitive (Dahl-S) and 14 salt-resistant (Dahl-R) rats already weaned were obtained from Tsukuba Research Laboratories, Eizai Co., Ltd. (Tokyo). The rats had originally been obtained from Brookhaven Laboratories (Upton, NY, USA). Soon after being transported to the laboratory, the rats were assigned to four groups, namely, Dahl-S rats given a high-salt (8% NaCl) diet (SH, $n=6$); and Dahl-S rats given a low-salt (0.3% NaCl) diet (SL, $n=7$); Dahl-R rats given a high-salt diet (RH, $n=7$); and Dahl-R rats given a low-salt diet (RL, $n=7$).

Preparatory operative procedures

Experiments were begun when the rats were between 8 and 12 weeks old. Under ether anesthesia, the left femoral artery was cannulated with tapered PE-100 polyethylene tubing for recording of arterial pressure. The catheter was

tunneled subcutaneously to exit between the scapulae, and penicillin-G (50,000 U) was injected intramuscularly after its implantation. The arterial catheter was connected to a hydraulic swivel-tethering system. Rats were individually housed in metabolic cages in a room kept at constant temperature (23°C) and humidity (60%) on a 12-hr light-dark cycle (light: 8:00 a.m. to 8:00 p.m.; dark: 8:00 p.m. to 8:00 a.m.). To keep the arterial catheter patent, heparinized saline solution (50 U/ml) was infused continuously at a rate of 80 μ l/hr. The animals had free access to food and water, and were allowed at least one day for recovery before experiments began.

Recording procedure

After the recovery period, BP and HR in freely moving rats were recorded from the arterial catheter via a P23Ib Statham pressure transducer (Oxford, CA, USA) and strain-gauge amplifier (Model 1257; NEC-San-ei, Tokyo). The analogue signals of phasic pressure, mean arterial pressure (MAP), and HR were digitalized through an analogue/digital converter (Mark 1; N.C.C., Tokyo). Digital signals of MAP and HR were fed to a microcomputer (Model HP-9816; Hewlett-Packard, Fort Collins, CO, USA) every 4 sec for 24 hr, and the values were averaged every hour.

Cosinor analysis

An off-line computer calculated cosinor parameters from 24 sequential data points for hourly mean MAP and HR. Details of the cosinor analysis have been reported elsewhere (Halberg et al. 1972; Nelson et al. 1979; Munakata et al. 1991). Briefly, the cosinor analysis was used to fit a cosine curve with a period of 24 hr to the 24 time series data. Three cosinor parameters, i.e., mesor (the value about which oscillation occurs: MAP mesor, HR mesor), amplitude (half the difference between the highest and the lowest values: MAP amplitude, HR amplitude), and acrophase (the timing of high point, in degrees: MAP acrophase, HR acrophase), were determined by the method of least squares. The zero-amplitude test was used to estimate the significance of a fitted cosine curve. A probability of more than 95% was accepted as significant.

Statistical analysis

Data are expressed as mean $\pm$ s.e. unless otherwise stated. Statistical significance of differences between groups was evaluated by one-way analysis of variance followed by multiple comparisons using Scheffé's F-test. Differences were considered to be significant at a level of $p < 0.05$.

RESULTS

In a zero-amplitude test, a significant HR rhythm was detected in all 27 rats (100%), and a significant MAP rhythm in 25 rats (92.6%), but not in the remain-

ing two (one SL and one RL rat).

The MAP mesor was remarkably higher in SH rats than in SL rats, but there was no significant difference between the values for RH and RL rats (Fig. 1). The MAP mesor in SL rats was not different from that in RL rats.

Fig. 1. Mesor of circadian rhythm for mean arterial pressure (MAP) and heart rate (HR) in Dahl salt-sensitive (DS) and salt-resistant (DR) rats. Data are expressed as mean $\pm$ s.e. Dotted columns, a high-salt (8% NaCl) diet; open columns, a low-salt (0.3% NaCl) diet. * $p < 0.05$.

Fig. 2. Distribution of the amplitude of circadian rhythm for mean arterial pressure (MAP) and heart rate (HR) in Dahl rats. Horizontal bars represent means of the amplitude. SH, Dahl salt-sensitive rats on a high-salt diet; SL, Dahl salt-sensitive rats on a low-salt diet; RH, Dahl salt-resistant rats on a high-salt diet; RL, Dahl salt-resistant rats on a low-salt diet. Open circles, with significant circadian rhythm ($p < 0.05$); closed circles, without significant circadian rhythm. * $p < 0.05$.

In the HR mesor, no difference was found between SH rats and SL rats or RH rats. The HR mesor in RH rats was significantly lower than that in RL rats (Fig. 1).

Some differences in relation to strain and diet were also noted in the MAP amplitude (Fig. 2). SH rats had a significantly greater MAP amplitude than did SL or RH rats. However, when assessed as percent amplitude (the amplitude divided by the mesor and multiplied by 100), the difference was insignificant. MAP amplitude in RH rats was similar to that in RL rats. A predicted MAP amplitude was relatively small in the two rats that did not have any significant circadian MAP rhythm.

The absolute and percent HR amplitudes were significantly decreased in SH rats, as compared with SL rats. The percent HR amplitude in SH rats was also significantly smaller than that in RH rats. No difference between RH and RL

Fig. 3. Acrophase of circadian rhythm for mean arterial pressure (MAP) and heart rate (HR). Data are expressed as mean $\pm$ s.d. Rats were housed in a room under a constant light/dark cycle (light, 8:00 a.m. to 8:00 p.m.; dark, 8:00 p.m. to 8:00 a.m.). Closed circles, Dahl salt-sensitive rats on a high-salt diet (SH, $n=6$); open circles, Dahl salt-sensitive rats on a low-salt diet (SL, $n=7$); closed triangles, Dahl salt-resistant rats on a high-salt diet (RH, $n=7$); open triangles, Dahl salt-resistant rats on a low-salt diet (RL, $n=7$). * $p < 0.05$.

rats was observed in HR amplitude (Fig. 2).

SH rats possessed a significantly greater MAP acrophase than did SL rats (Fig. 3). Similarly, RH rats had a greater MAP acrophase than did RL rats. When a comparison was made between SH rats and RH rats, the MAP acrophase shifted significantly later in SH rats.

The HR acrophase in SH rats was similar to that in SL rats or RH rats. The HR acrophase in RH rats was observed at a significantly earlier time of day, as compared with that in RL rats, although the time difference was small (Fig. 3).

DISCUSSION

We demonstrated that the circadian rhythm of BP in Dahl rats was altered by salt loading. MAP amplitude, as well as MAP mesor, was significantly increased by salt loading. Salt loading induced a time delay in the MAP acrophase in both Dahl-S and Dahl-R rats.

This study also showed that the alteration of circadian BP rhythm induced by salt-loading was modulated by salt sensitivity. Dahl-S rats fed a high-salt diet exhibited an increased MAP mesor and amplitude, which was not seen in Dahl-R rats. Additionally, the time delay in MAP acrophase induced by salt loading was more marked in the Dahl-S than in the Dahl-R rats.

We used cosinor analysis for the quantitative evaluation of the circadian rhythm of BP and HR. MAP and HR were collected every 4 sec for 24 hr, and the 24 sequential data points of hourly mean values were calculated to determine cosinor parameters. The zero-amplitude test, used to evaluate the significance of rhythm detection, revealed that the rats studied did not necessarily have a statistically significant circadian BP rhythm (92.6%), even though all of them have a significant circadian HR rhythm (100%). In the two rats that did not exhibit a significant circadian BP rhythm (one SL and one RL rat), the MAP amplitude predicted from the least-squares method was relatively small. Similar results were obtained from human subjects in our recent study (Munakata et al. 1991), suggesting that the magnitude of circadian variation is related to the significance of rhythm detection. In the present study, we focused on the circadian rhythm with a period of 24 hr. The circadian rhythm of BP and HR in rats may include rhythms with periods shorter than 24 hr. To evaluate these rhythms, other analytical methods such as spectral analysis may be useful (Imai et al. 1993).

The MAP mesor was markedly higher in the Dahl-S rats fed a high-salt diet (SH rats) than in Dahl-R rats fed the same diet (RH rats). The present finding is consistent with that in previous studies (Dahl et al. 1968; Rapp 1982; Rapp and Dene 1985).

The HR mesor in SH rats resembled that in SL rats, while the mesor in RH rats was significantly lower than that in RL rats. Although the mechanism by which a high-salt diet induced a decrease in HR in the Dahl-R, but not in the

Dahl-S rats, has not been elucidated by the present study, it has been suggested that cardiopulmonary and arterial baroreflexes are impaired in Dahl-S rats (Gordon et al. 1981; Gordon and Mark 1983; Ferrari et al. 1984; Mark et al. 1987; Miyajima and Bunag 1987), and that a high-sodium diet enhances the gain of cardiac baroreflex inhibition of sympathetic nerve activity in Dahl-R rats, but not in Dahl-S rats (Mark et al. 1987). These neural factors may be associated with a strain difference in the response of the HR mesor to salt loading, although it remains to be determined whether the baroreflex could be persistently active.

MAP amplitude in SH rats was significantly greater than that in SL rats, but the MAP amplitude in RH rats was similar to that in RL rats. Thus, salt loading increased circadian BP variation in the Dahl-S but not in the Dahl-R rats. This observation suggests that salt loading and the responsiveness to it are related to the magnitude of circadian BP variation. However, it is possible that the enhancement of MAP amplitude in SH rats was secondary to an elevated MAP mesor, since the percent MAP amplitude was similar in all groups.

Dahl-S rats fed a high-salt diet (SH rats) had a decreased HR amplitude, as compared with Dahl-S rats fed on a low-salt diet (SL rats). In contrast, the HR amplitude in RH rats did not differ from that in RL rats. Although the underlying mechanism has not been clarified, the decrease in HR amplitude in SH rats occurred simultaneously with an increase in MAP amplitude. It has been reported that the circadian HR rhythm is regulated mainly by parasympathetic nervous activity (Guazzi et al. 1968; Zemaityte et al. 1984). It is known that the parasympathetic control of HR is impaired in Dahl-S rats (Whitescarver et al. 1990), so the alteration of HR amplitude in SH rats may be related to that impairment.

MAP acrophase in SH and RH rats was significantly delayed, as compared with that in the SL and RL rats, respectively. This finding indicates that MAP amplitude is delayed by salt loading, whether the rats are salt sensitive or salt resistant. Since the MAP mesor in RH rats was not different from that in RL rats, it is unlikely, at least in Dahl-R rats, that the time delay of MAP acrophase in response to salt loading was associated with an elevation of the MAP mesor. Accordingly, these results suggest that salt-induced change in the acrophase is independent of a change in the mesor. The possibility remains that the time delay of MAP acrophase in response to salt loading observed in the present study was due to behavioral alterations caused by a high-salt intake (e.g., drinking and urination). However, such a possibility seems unlikely, since the HR acrophase was not delayed by a high-salt intake. MAP acrophase was significantly delayed in SH rats, as compared with that in RH rats, indicating that it is affected by salt sensitivity as well as by salt loading. This finding is very similar to the finding in hypertensive subjects that there was a 2-hr difference in BP acrophase between salt-sensitive subjects and non-salt-sensitive subjects when they were ingesting 249 mEq of sodium each day (Delea 1979).

Our results differed from those of a previous study of the circadian variation in BP in Dahl rats (Brown et al. 1989). In the previous study, when the circadian BP variation was assessed by the day-night difference in BP, a significant difference was found only in SH rats, but not in the SL, RH, or RL rats. However, we found a significant circadian BP rhythm in 25 of 27 rats (except for one SL and one RL rat) in our study. As observed in our study, the MAP acrophase might be delayed in rats fed a high-salt diet. When a marked time delay in the acrophase is observed, circadian rhythm may not be assessed precisely by the day-night difference.

The mechanism by which salt loading alters the circadian BP rhythm was not resolved by the present study. It has been suggested that neural (Mann et al. 1983) and hormonal (Imai et al. 1988) factors, as well as physical activity (Rowlands et al. 1980), are variously involved in the regulation of circadian BP rhythm. It is also reported that impairments of neural (Takeshita and Mark 1978; Takeshita et al. 1979; Goto et al. 1982) and humoral (Iwai et al. 1969; Hirata et al. 1984) factors are related to the development of hypertension in Dahl-S rats. Therefore, it is possible that the impairments are associated with the alteration of circadian BP rhythm.

In conclusion, the present study demonstrated that circadian BP rhythm in Dahl rats was significantly altered by high-salt intake and salt sensitivity. The underlying mechanisms remain to be elucidated.

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