Changes in Cardiovascular and Renal Functions by Temperature and Epinephrine in the Freshwater Turtle, *Amyda Japonica*

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(Received 15 November, 1987)

=국문초록=

수온변화와 Epinephrine에 의한 자라의 심맥관계 및 신장기능의 변화

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수온변화에 따른 심맥관계 및 신장기능의 변화와 생체실험을 통한 온도에 의한 adrenoceptor의 변형을 알아보기 위해, 무마취 자라에서 18℃에서 25℃로 수온을 증가시 나타나는 혈압, 심박동수 및 신장기능의 변화를 관찰하고, epinephrine 1 ug/kg과 10 ug/kg을 상이한 온도에 노출된 자라의 정맥내 투여하여 나타나는 효과를 비교하였다.

1) 18℃에서 25℃로 수온을 증가시킴에 따라 심박동수는 현저히 증가하여 일정하게 유지되었으나, 혈압 및 혈장 renin 활성도는 변화하지 않았다. 온도증가에 의해 뇨량, 사구체여과율 및 전해질 배설량의 현저한 증가를 보였으나 90분부터는 서서히 감소하기 시작하였다.

2) 수온 18℃에 노출된 자라에서 epinephrine은 dose-dependent한 양상으로 혈압 및 심박동수를 증가시켰으며, 다량의 epinephrine 투여시 작용시간은 현저히 연장되어 있었다. 25℃에 노출된 자라에서는 epinephrine에 의한 혈압상승 효과 및 심박동수 증가는 나타났으나, dose dependency나 작용시간의 차이는 발견할 수 없었다.

3) 동량의 epinephrine에 의한 혈압 및 심박동수의 증가효과는 18℃와 25℃에 노출된 자라에서 유의한 차이를 발견할 수 없었으나, 18℃에 노출된 자라에서 epinephrine의 작용시간 및 반감기가 현저히 연장되어 있었다.

4) Epinephrine 투여에 의해 뇨량, 사구체여과율 및 전해질 배설량의 증가를 관찰하였으며, 이는 dose-dependent 양상이었다. 그러나, 신장효과의 유의한 차이는 상이한 온도에 노출된 두 군에서 발견할 수 없었다.

이상의 결과로, 온도증가에 의한 이뇨 및 sodium 배설효과는 혈관이완에 의한 사구체여과율의 증가에 기인한 것으로 사료되며, 상이한 온도에 노출된 자라에서 epinephrine 효과의 차이를 발견할 수 없었던 것은 본 실험에서 가한 좁은 범위의 온도의 변화 내에서는 adrenoceptor의 변형이 나타나지 않을 것이라고 추론하였다. 그러나 저온에서의 epinephrine의 작용시간의 연장은 아마도 epinephrine의 파괴 효소의 활성도의 감소인 것으로 사료된다.

Key Words: Temperature, Diuresis, Natriuresis, Epinephrine, Blood pressure, Heart rate, Freshwater turtle

*이 논문은 1987년도 문교부 학술 연구 조성비에 의하여 연구되었음.

INTRODUCTION

A poikilotherm encounters a wide range of environmental temperatures through the year and can immediately respond to temperature change for the adaptation of their internal environments. It has been shown that changes in temperature influence blood pressure and heart rate (Lyman and O'Brien, 1960; Ray and Zatzman, 1983; Zatzman and South, 1981), and modify cardiac responsivenss to catecholamines (Benfey, 1979; Herman and Mata, 1985). A few studies have been done on the renal effect of hibernation closely related to changes in cardiovascular function (Hong, 1957; Zatzman and South, 1972; Zatzman, 1984). However, most investigators have used mammalian hibernators and performed under the anesthetized condition as well as a wide range of environmental temperature.

Catecholamines have been shown to regulate the cardiovascular system of vertebrates through stimulation of alpha and beta adrenoceptors (Ahlquist, 1948). In birds (Butler et al., 1986), reptiles (Kim, 1985) and amphibians (Erlij et al., 1965; Herman and Mata, 1985; Herman et al., 1986), it is known that the heart rate and blood pressure are regulated by catecholamines via alpha and beta adrenoceptors. The modulation of adrenoceptors by temperature is demonstrated in amphibia (Kunos and Szentivanyi, 1968; Buckley and Jordan, 1970) and mammals (Matheny and Ahlquist, 1974; Corwin et al., 1982). However, few studies on the adrenoceptor alteration of temperature has been done in reptiles and in vivo experiments are very rare. Additionally, the catecholamine effect on renal function is controversal and its modification by temperature is unknown.

The purpose of this study was to evaluate the effect of environmental temperature on the blood pressure, heart rate and renal function in the unanesthetized freshwater turtle. We also determined whether the epinephrine effect on the renal and cardiovascular functions may be modified by the temperature.

MATERIALS AND METHODS

Animals

Both sexes of freshwater turtles, *Amyda japonica*, weighing 250 to 440 gm were obtained from the Sumjin River, Korea. The animals were housed in tanks with access to freshwater (22℃) and a dry sunny area until used for experimentation. They were not fed anything until to be studied and the experiments were performed within 4 days after capture.

General procedure

Turtles were kept in ice-cold water for 1 h. After cold-treatment, they were wrapped in cold cloth, placed their carapace and a silicone tubing filled with heparinized reptilian saline (400 U/ml) was placed in a carotid artery and in an external jugular vein. To catheterize into ureters, turtles were tightly restrained with prone position and operated, as previously described (Cho et al., in press). In brief, two small holes were made on both paravertebral areas of lumbar portion of carapace with trephine. After splitting off small muscles, a perirenal capsule was cut away and ureter was separated carefully from periureteral vein. Silicone catheters were placed into ureters and the holes were sealed. Turtles were kept in a water bath (22℃) and allowed at least 1 day prior to use in an experiment. All experiments were carried out in unanesthetized condition in water bath.

Experimental protocol I; Effect of environmental temperature on the cardiovascular and renal functions in the unanesthetized freshwater turtle.

On the day of experiment, turtles were kept in a water bath (18℃) which is maintained at constant temperature by circulator for 3 h and given an

isotonic saline (0.6%) containing 10 mg/kg inulin as a priming dose followed by infusion of isotonic solution at a rate of 0.05 ml/min. The composition of infusate was 2% glucose, 0.05% inulin and 0.2% NaCl. Following two hours infusion, urine was collected into preweighed tubes from both ureters. Three urine collections were started as a control period and all collection periods lasted 30 min. After that, the bath temperature was rapidly increased from 18℃ to 25℃ within 1 min and maintained constantly at 25℃. Urine samples were continously collected for 150 min. In control group, animals were kept at 18℃ throughout the experiment and urine samples were collected. Arterial blood samples(200 μl) for the measurement of plasma renin activity were collected at 30 min before and, 1 h and 2 h after increasing temperature. Blood (500 μl) for the measurement of inulin was collected at the end of experiment. Arterial blood pressure and heart rate were traced on the physiography throughout the experiments by connecting the carotid arterial catheter to a Statham pressure transducer.

Experimental protocol II; Comparison of epinephrine effect on renal and cardiovascular functions at 18℃ and 25℃

On the day of experiment, turtles were kept in a water bath maintained constantly at 18℃ or 25℃ throughtout the experiment. After 3 h stabilization, turtles were given a priming solution followed by infusion of isotonic solution as described above. Following three collection periods, either EP (1 μg/kg or 10 μg/kg) or saline was injected intravenously and urine was continously collected for 120 min. Arterial blood for the measurement of inulin was collected at the end of experiment. Arterial blood pressure and heart rate were traced on the physiograph throughout the experiment.

Analytical methods

Plasma renin concentration (PRC) was measured using excess renin substrate from nephrectomized rabbit, as previously described (Cho et al., 1987). Plasma and urinary inulin was determined by fluor-

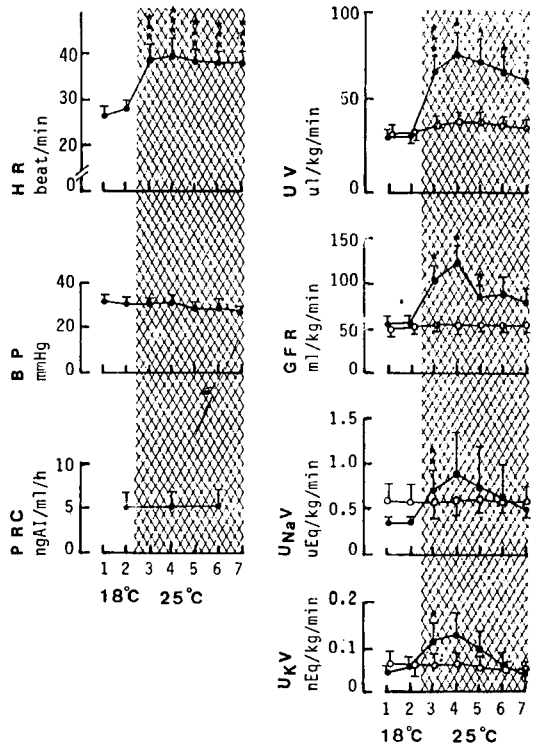

Fig. 1. Effect of temperature on the blood pressure, heart rate, plasma renin concentration, and renal function in the unanesthetized freshwater turtle. HR, heart rate ; BP, blood pressure ; PRC, plasma renin concentration ; UV, urine volume ; GFR, glomerular filtration rate ; UNaV, UKV, excreted amounts of sodium and potassium. 1—7 represents the urine collection periods and each period is 30 min interval. Temperature was changed after two collection period from 18°C (blank area) to 25°C (hatched area). Open dots indicate change in renal function of turtle kept at 18°C (n=6) and closed dots indicates changes in renal function of turtles applied temperature change (n=14). Values are the mean ± SEM. *, Significantly different from control value, *, $P < 0.05$, **, $P < 0.01$, ***, $P < 0.001$.

Table 1. Effects of intravenous administration of epinephrine, 1 μg/kg or 10 μg/kg, on the renal function in the unanesthetized freshwater turtle

		Collection Periods					
		I	II	III	IV	V	VI
UV	Group 1	33.03 ± 5.77	35.98 ± 4.84	38.25 ± 4.42	41.68 ± 5.66	37.25 ± 4.55	34.71 ± 5.4
	Group 2	52.55 ± 12.55	55.06 ± 17.56	71.34 ± 18.67**	62.03 ± 18.82	57.52 ± 15.67	48.04 ± 11.07
	Group 3	33.61 ± 5.06	38.22 ± 4.25	53.15 ± 7.92*	46.33 ± 5.57	39.66 ± 4.28	37.74 ± 6.10
	Group 4	51.80 ± 16.81	51.80 ± 16.81	89.22 ± 28.41*	56.60 ± 16.32	52.43 ± 17.88	37.34 ± 13.65
GFR	Group 1	0.052 ± 0.012	0.051 ± 0.010	0.054 ± 0.012	0.053 ± 0.015	0.055 ± 0.016	0.056 ± 0.013
	Group 2	0.099 ± 0.022	0.108 ± 0.037	0.147 ± 0.040*	0.114 ± 0.021	0.107 ± 0.021	0.094 ± 0.017
	Group 3	0.072 ± 0.012	0.087 ± 0.015	0.110 ± 0.021	0.095 ± 0.018	0.081 ± 0.012	0.082 ± 0.017
	Group 4	0.082 ± 0.016	0.082 ± 0.016	0.138 ± 0.032*	0.080 ± 0.014	0.072 ± 0.011	0.049 ± 0.010
UNaV	Group 1	0.62 ± 0.31	0.58 ± 0.31	0.59 ± 0.31	0.61 ± 0.31	0.59 ± 0.30	0.57 ± 0.30
	Group 2	0.29 ± 0.10	0.35 ± 0.15	0.55 ± 0.20**	0.50 ± 0.24	0.39 ± 0.18	0.30 ± 0.13
	Group 3	0.32 ± 0.08	0.31 ± 0.09	0.66 ± 0.33*	0.45 ± 0.15	0.30 ± 0.08	0.29 ± 0.09
	Group 4	0.27 ± 0.10	0.27 ± 0.10	0.97 ± 0.49**	0.34 ± 0.10	0.18 ± 0.06	0.10 ± 0.01
UKV	Group 1	66.95 ± 33.43	66.00 ± 33.00	65.60 ± 30.25	65.60 ± 32.20	58.25 ± 23.50	53.60 ± 29.30
	Group 2	30.52 ± 10.46	27.38 ± 11.87	35.40 ± 11.87	33.39 ± 15.16	24.91 ± 10.07	18.44 ± 5.94
	Group 3	23.79 ± 3.93	27.40 ± 6.14	43.70 ± 16.82	37.47 ± 11.60	25.05 ± 5.97	22.98 ± 6.14
	Group 4	28.41 ± 7.80	28.41 ± 7.80	95.10 ± 41.44*	30.32 ± 3.59	22.48 ± 3.19	20.73 ± 3.23

Values are the mean ± S.E. Group 1 (n=6) indicates turtles received isotonic saline at 18°C and Group 2 (n=8) and 3 (n=10) indicates turtles received 1 μg/kg of epinephrine at 25°C or 18°C, respectively. Group 4 (n=7) indicates turtles received 10 μg/kg of epinephrine at 18°C. Epinephrine was injected after the second collection period. UV, urine volume expressed in μl/kg/min ; GFR, glomerular filtration rate in ml/kg/min ; UNaV, excreted amount of sodium in μEq/kg/min ; UKV, excreted amount of potassium in nEq/kg/min. *, Significantly different from control value, * $P < 0.05$, **, $P < 0.01$.

ospectrophotometry using the method of Vurek and Pegram (1966). Sodium and potassium were measured by flamephotometry. Results were expressed as means±S.E. Student's t-test were used and the level of significance accepted was less than 0.05.

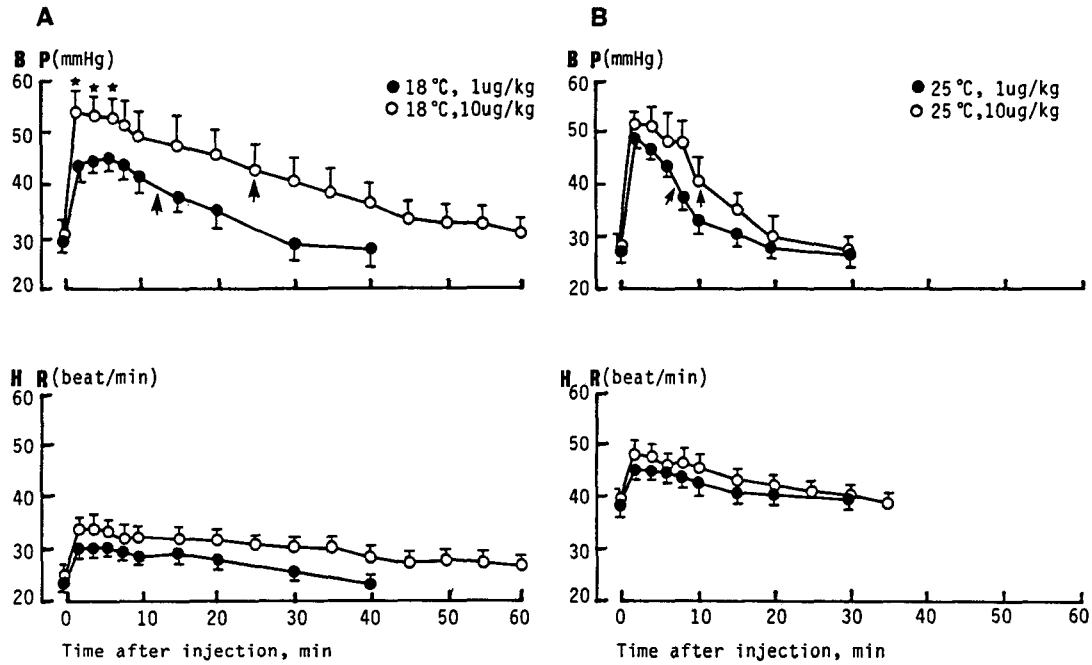

Fig. 2. A. Effect of epinephrine, 1 or 10 ug/kg, on the blood pressure and heart rate of the freshwater turtle kept at 18°C.
B. Effect of epinephrine, 1 or 10 ug/kg, on the blood pressure and heart rate of the freshwater turtle kept at 25°C. Arrows indicate the half-life of vasopressor effect of epinephrine. BP, blood pressure ; HR, heart rate. *, Significantly different from turtles received low-dose of epinephrine. $P < 0.05$.

RESULTS

Effect of temperature on the cardiovascular and renal functions in the unanesthetized freshwater turtle

With increasing water temperature from 18℃ to 25℃, heart rate was immediately increased from 28.2±2.1 to 39.0±3.0 beat/min and maintained constantly throughout the experiment (Fig. 1). However, blood pressure and PRC did not change significantly throughout the experiment. Increase in temperature also caused significant increases in urine flow, glomerular filtration rate and electrolytes excretion at first 30 min, which began to decrease at 90 min after temperature change (Fig. 1). In control group, renal function did not change significantly.

Comparison of epinephrine effect on cardiovascular function at low and high temperature

Figure 2 represents the epinephrine effect on blood pressure and heart rate. At 18℃, either 1 μg/kg or 10 μg/kg of epinephrine caused increase in blood pressure from 29.2±1.5 to 43.8±3.6 mmHg or from 30.6±3.3 to 53.8±3.8 mmHg, respectively (Fig. 2), and it appeared to be dose-dependent. It took 13 min to arrive at the half-life of vasopressor effect of 1 μg/kg epinephrine and 25 min by 10 μg/kg epinephrine. EP caused tachycardia in dose-dependent manner and the duration of cardiovascular responses to high dose of epinephrine was significantly longer than that to low dose of epinephrine. At 25℃, increases in blood pressure and heart rate caused by EP appear-

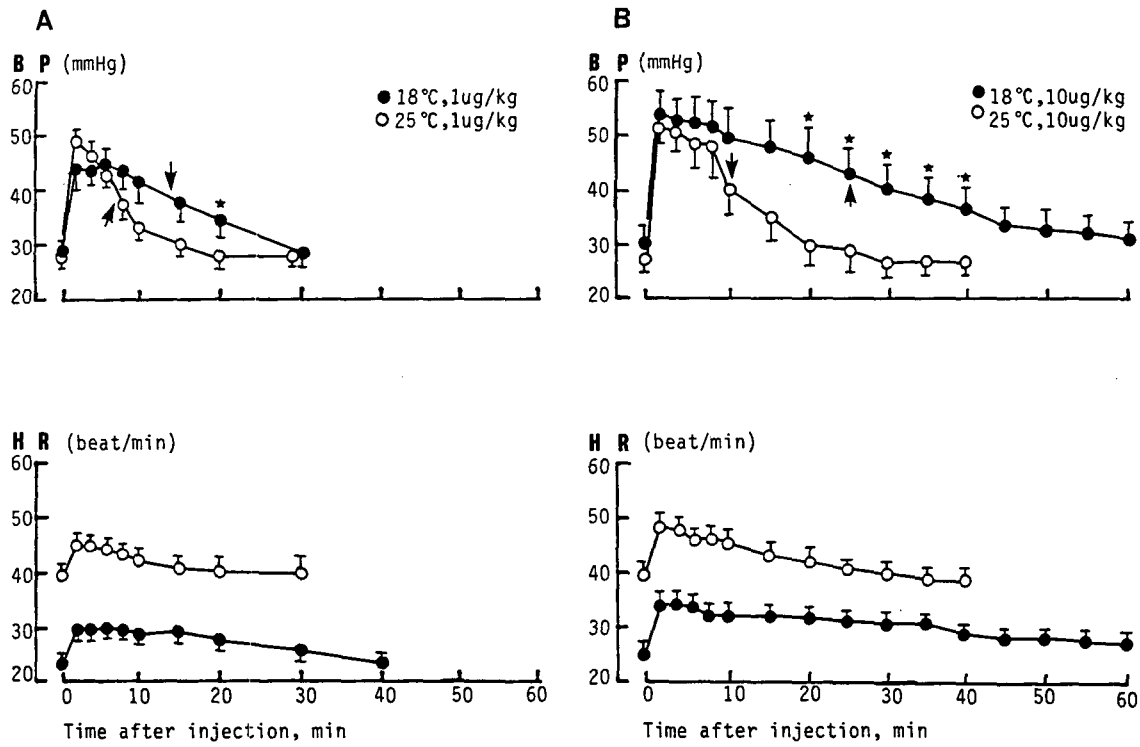

Fig. 3. A. Comparison of epinephrine (1 ug/kg) effect on the blood pressure and heart rate in turtles kept at either 18° C or 25°C.
B. Comparison of epinephrine (10 ug/kg) effect on the blood pressure and heart rate in turtles kept at either 18°C or 25°C. Open dots indicate turtles kept at 18°C and closed dots turtles kept at 25°C. Other legends are the same as in Fig. 2.

ed not to be dose-dependent and no difference in the duration of their responses between two doses of epinephrine was observed (Fig. 2).

The blood pressure of turtle kept at 18℃ did not differ from that kept at 25℃ but the heart rate was significantly different (Fig. 3). Increase in blood pressure caused by either 1 μg/kg or 10 μg/kg, epinephrine at 18℃ was similar to that at 25℃. However, the half-life and duration of vasopressor effect by either dose of epinephrine at 18℃ were longer than those at 25℃ (Fig. 3). Responsiveness of heart rate to EP at low and high temperature was smilar to that in blood pressure.

Comparison of epinephrine effect on renal function at low and high temperature

Table 1 shows the effect of epinephrine on the filtration rate and electrolytes excretion at 18℃, which was dose-dependent manner (Fig. 4). Changes in renal function by 1 μg/kg epinephrine at 18℃ was not significantly different from those at 25℃ (Fig. 4).

DISCUSSION

Most studies on the relation between temperature, cardiovascular and renal functions have been done using nonhibernators and mammalian hibernator under the wide range of temperature from 5℃ to 35℃. We have performed a couple of experiments in the unanesthetized freshwater turtle by changing temperature from 18℃ to 25℃. The present study has been shown that an increase in environmental temperature caused significant increases in heart

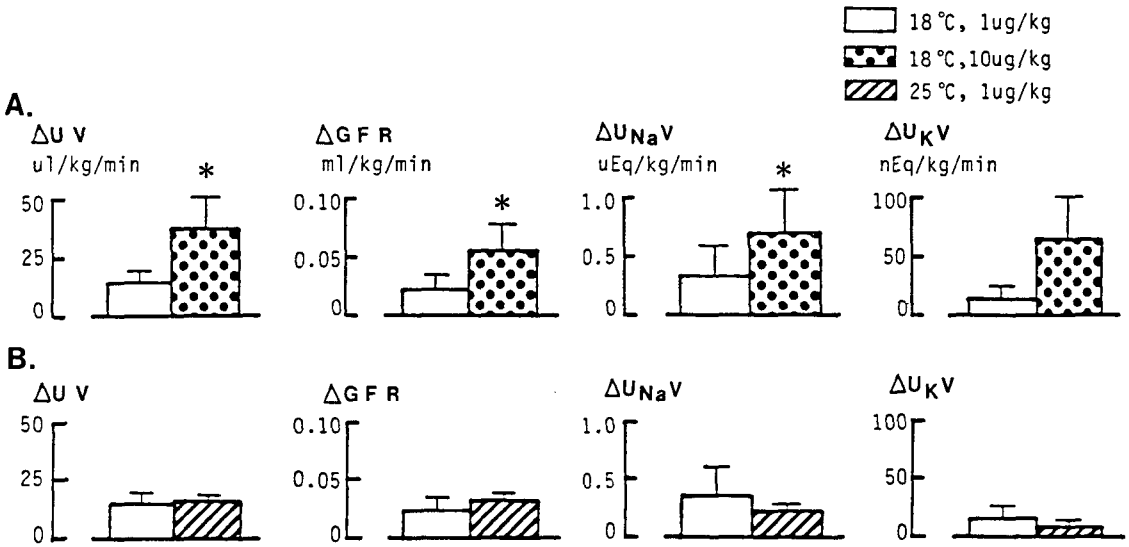

Fig. 4. A. Comparison of renal functions caused by either dose of epinephrine in turtles kept at 18°C.
B. Comparison of renal functions caused by 1 ug/kg epinephrine in turtles kept at either 18°C or 25°C. Other legends are the same as in Fig. 1.

renal function in the unanesthetized freshwater turtle. In control group received saline, renal function was without effect. Epinephrine, either 1 μg/kg or 10 μg/kg, caused increases in urine flow, glomerular rate, urine flow, glomerular filtration rate and electrolytes excretion, and also modified the cardiovascular effect of epinephrine.

The relation between temperature and heart rate, blood pressure and total peripheral resistance has been well known. The results showing a marked increase in heart rate and no change in blood pressure with slight increasing temperature is consistent with other reports (Lyman and O'Brien, 1960; Ray and Zatzman, 1983). The reason for no change of blood pressure despite increase in heart rate may be due to decrease in peripheral resistance caused by either decrease in blood viscosity (Kirkebo, 1968) or vasomotor tone (Albert and Panuska, 1978). Cho et al (1987) have reported a marked increase in PRC in turtles kept at 4℃ and Kim et al, (1987) suggest that renin-angiotensin system may play an important role in hibernation. However, we did not observe a significant change in PRC with incresing temperature from 18℃ to 25℃. This may be due to a slight change in temperture.

The change in cardiovascular function by temperature is closely related to that in renal function. Several studies have been done using non-hibernators and mammalian hibernators during hibernation or deep hypothermia. It is demonstrated that during hibernation, the glomerular filtration rate (GFR) ceased (Moy, 1971) in assoication with thickening of the glomerular epithelial basement membranes (Zimmey, 1968), but renal blood flow continued and greatly reduced. Simultaneously, both urine flow and electrolytes excretion have decreased to conserve water and electrolytes during hibernation (Zatzman, 1984). We observed changes in renal function with the temperature range naturally occuring on Spring and Summer. This study showing that a slight increase in temperature caused significant increases in urine flow, glomerular filtration rate and electrolytes excretion is in agreement with the report (Hong, 1957). The changes in renal function by temperature began to recover at 90 min despite persistent increases in heart rate and temperature. Diuresis and natriuresis by increasing temperature may be due to increased GFR caused by vasodilata-

tion. However, the reason for the restoration of changes in renal function is not clear but may be due to the adaptation of peripheral vessels to new environment. Zatzman and South (1981) have reported about the circannual rhythm of renal function in marmot. Our data do not agree with the report showing that renal plasma flow and GFR on Spring are highest and those on summer and Fall are lowest throught the year (Zatzman and South, 1981). Although the reason for this discrepancy is not clear, it may be due to gradual change in water temperature of river which animals keep alive in. Other reasons may be due to differences in species, anesthetics used or experimental protocol.

Control heart rate in turtles kept at 25℃ was significantly higher than that in turtles at 18℃ but no significant difference in blood pressure in the two groups was observed. These data are consistent with the report (Herman and Sandoral, 1983). Epinephrine caused an increase in blood pressure with dose-dependent manner at 18℃. The vasopressor effect of epinephrine is more potent in the freshwater turtle than that in bullfrogs and its duration is similar (Herman et al, 1986). The duration of blood pressure response to 10 μg/kg epinephrine at 18℃ was longer than that to 1 μg/kg. However, at 25℃, no differences in duration of vasopressor effect of between two doses of epinephrine was observed. It may be caused by increased enzyme activity at high temperature These data are consistent with studies on catecholamine effect on blood pressure in warm- and cold-acclimated bullfrogs (Herman and Mata, 1985).

The cardiovascular response to epinephrine in the freshwater turtle kept at different temperature was not significantly different. Although the cardiac responsiveness to catecholamine has been reported to be enhanced at high temperature (Sham et al, 1987; Ask, 1983; Morris, 1982), most studies have been done in isolated hearts and under the wide range of temperature. This discrepancy may be caused by different range of temperature, in vivo or in vitro experiment or different species. However, turtles kept at 18℃ have prolonged cardiovascular responses to epinephrine. These date are consistent with studies on catecholamine effects on blood pressure in bullfrog (Herman and Mata, 1985). This may be due to decreased metabolism by catechol-o-methyl transferase, which has been shown to be inhibited 61% in guinea atria at 26℃ as compared to 37℃ (Oppermann et al, 1972).

Epinephrine increased heart rate in turles kept at 18℃ and 25℃. These data agree with studies using toad ventricular strips (Penefsky et al, 1981) or isolated frog heart (Kunos and Nickerson, 1976; Erlij et al, 1985) which all show that catecholamines stimulate heart rate in both warm and cold animals. However, the results disagree with the data showing bradycaria (Herman and Mata, 1985) but Herman and Sandoral (1983) have reported that in frog atropinized, heart rate is increased by epinephrine.

Effects of catecholamines which would tend to increase GFR include constriction of the efferent glomerular arterioles, increased cardiac output and increased blood pressure. However, constriction of the preglomerular vasculature would tend to decrease GFR. Therefore, the effect of adrenaline on renal function seems to be complex and variable. In the unanesthetized freshwater turtle, epinephrine caused increase in urine flow, glomerular filtration rate and electrolytes excretion with dose-dependent manner. The renal effect of epinephrine may be due to constriction of efferent glomerular arterioles or increased cardiac output not due to increased arterial blood pressure because an intravenous injection of angiotensin II caused an epuivalent increase in blood pressure to that of epinephrine did not cause diuresis and natriuresis in turtles (unpublished data). The results are consistent with the data in isolated toad kidneys (Morris, 1984). Morris (1982) has been reported a seasonal change in the magnitude of the renal vasoconstrictor responses to perfused adrenaline. However, no differences in renal function

caused by epinephrine in the two groups was observed.

The present study suggests that diuresis and natriuresis by increasing temperature may be due to increase GFR caused by vasodilatation and the prolongation of duration of vasopressor effect of epinephrine at low temperature may be due to decrease a degradation rate of epinephrine. Diuresis and natriuresis by epinephrine may be due to increase in GFR though the constriction of efferent arterioles or increased cardiac output, and the renal effect of epinephrine may not be modified by changing temperature from 18℃ to 25℃.

ACKNOWLEDGMENT

The author thanks greatly Miss Hyun Sook Kim, Eun Jin Na and Kyung Hwa Nam for their excellent assistance. This work was supported by a grant-in-aid from the Ministry of Education, Korea.

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