CHAPTER VII

RENAL FUNCTION FOLLOWING STEVIOSIDE INFUSION IN RATS TREATED WITH α-ADRENERGIC BLOCKER, NITRIC OXIDE SYNTHESIS INHIBITOR, PROSTAGLANDIN SYNTHESIS INHIBITOR AND CHOLINERGIC BLOCKER

Introduction

Several lines of evidence have revealed that hypotension and natriuresis were apparent during SVS infusion (Melis and Sainati, 1991a,b ; Melis, 1992b). The similar results have been shown in our experiment (chapter IV). From our previous study using lithium clearance method (chapter V) indicated that natriuresis was associated with the reduction of proximal tubular Na^+ reabsorption, renal enzyme Na^+, K^+ ATPase and renal mitochondrial function. In addition, natriuresis induced by SVS infusion was occured along with the elevation of ERBF without a change of GFR (Melis and Sainati, 1991a,b). However it has not yet known whether SVS exerted several actions by its direct or indirect action. It is possible that hypotension and the alterations of renal function induced by SVS infusion was probably dependent on the release of vasodilator and/or inhibition of vasoconstrictor agent. It has been known that various vasodilators and vasoconstrictors such as prostaglandin, angiotensin II (A_{II}) , norepinephrine (NE), arginine vasopressin (AVP) play an important role in renal function and blood pressure (Cogan, 1990 ; Cohen-luria et al., 1993 ; Garg et al., 1993). The effect of SVS infusion has been shown partly dependent on prostaglandin

(Melis and Sainati, 1991a). Thus, the present study was therefore undertaken to determine whether change in blood pressure and renal function during SVS infusion are mediated via mediators by using NE, A_{II}, AVP, atropine (cholinergic bloker), prazosin (∝-adrenergic blocker), L-NAME (nitric oxide synthesis inhibitor), indomethacin (prostaglandin synthesis inhibitor) and L-NAME+ indomethacin.

Materials and Methods

Animal preparation

Male Wistar rats weighing 250-300 g were used in this experiment. The general animal preparations were the same as described in chapter III. After animal preparation, normal saline (NSS) containing 1 gm% of inulin and 0.2 gm% of PAH was infused with the rate of 1 ml/100 gm.BW/hr for 45 min before the begining of experiment. Animals were divided into nine groups, and eight rats in each group was used.

Experimental design

Group I *Animals that received SVS alone.* After animal preparation, the experiment was divided into four 30-min periods, one control, one normal saline (NSS) pretreatment, and two SVS infusion period. Following NSS pretreatment period, animals received an intravenous injection of 200 mg/kg.BW. of SVS (150 mg/ml of NSS), and continued by 200 mg/kg.BW./hr for one hour. Urine and blood sample were collected every periods to determine renal hemodynamics and tubular functions. Blood pressure was continuously recorded throughout the experiment. Arterial blood sample (0.8 ml) was collected in every period to determine renal

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Group VII *Animal pretreated with L-NAME+indomethacin.* The general procedures were the same as group II excepted that L-NAME +indomethacin with the same dose as group V and VI was infused.

Group VIII *Animals pretreated with atropine sulfate* (cholinergic blocker) The same maneuvers as group II were accomplished excepted that 1 mg/kg.BW of atropine sulfate (1 mg/ml) was infused and followed by 1 mg/kg.BW./hr.

Group IX *Animals pretreated with prazosin (α-adrenergic blocker).* The same procedures as group II were performed excepted that prazosin (100 μg/ml) was infused with a priming dose of 100 μg/kg.BW and continued by 200 μg/kg.BW/hr.

Renal hemodynamics and tubular function in both before and during SVS infusion were explained in chapter III.

Statistics

All values are presented as mean±SEM. Statistical analysis was accomplished to compare the difference in the same group using paired t-test. Data was considered to be significant difference from control period at the level of $P<0.05$.

Results

Effect of SVS alone and pretreatment with NE, A_{II} , AVP, prozosin, L-NAME, indomethacin, prazosin and atropine on general circulation.

Figure 7.1 and 7.2 demonstrate the alterations of mean arterial pressure (MAP) and heart rate in rats subjected to SVS infusion alone and pretreated with various substances. In group of SVS infusion alone, MAP was reduced to the minimum level

within 5 min.($P<0.001$). MAP was gradually increased afterward but still lower than the control level ($P<0.05$). Pretreatment with A_{II}, NE, indomethacin, L-NAME and L-NAME+ indomethacin caused the significant increase of MAP. In contrast, prazosin pretreatment depressed MAP ($P<0.01$). No significant change of MAP in rats treated with atropine and AVP. 5 min after SVS infusion, MAP was significantly reduced to the lowest level in all drug pretreatment groups except L-NAME group. After this time, MAP was raised to higher level than that of control period in rats treated with the combination infusion of SVS and A_{II} , L-NAME or L-NAME+indomethacin whereas no significant change in NE or indomethacin pretreatment group. However, the combination infusion of SVS and prazosin still lowed MAP like that of pretreatment period.

NE raised not only MAP but also heart rate . Heart rate was continuously increased throughout the experimental period in this group which was contrast to the prazosin pretreatment. Pretreatment the animals withA_{II} , L-NAME and L-NAME+ indomethacin depressed heart rate which was corresponding to the elevation of MAP. While indomethacin pretreatment raised MAP, there was no significant change of heart rate. Prazosin pretreatment reduced both MAP and heart rate ($P<0.05$). No significant change of heart rate in groups of indomethacin and L-NAME+ indomethacin.

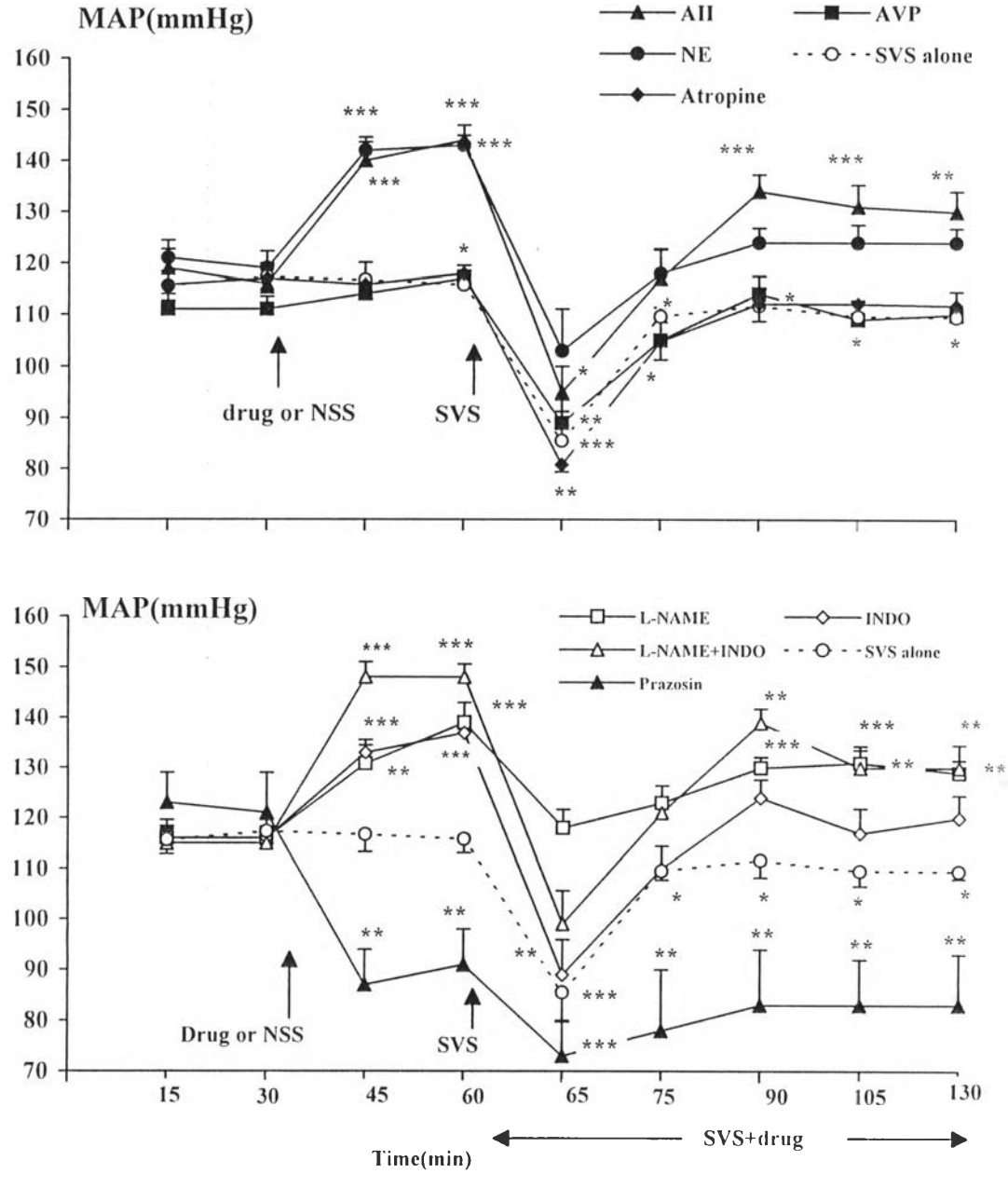

Figure 7.1 Changes of mean arterial pressure(MAP) in rats treated with SVS alone and pretreated with norepinephrine (NE), prazosin, angiotensin II (AII), arginine vasopressin (AVP),atropine,L-NAME, indomethacin(INDO), and L-NAME+ indomethacin (L-NAME+INDO). All values are presented as mean+SEM. The arrow denotes pretreatment the rats with normal saline (NSS) or various drugs. Significant difference is indicated by *P<0.05, **P<0.01, ***P<0.001.

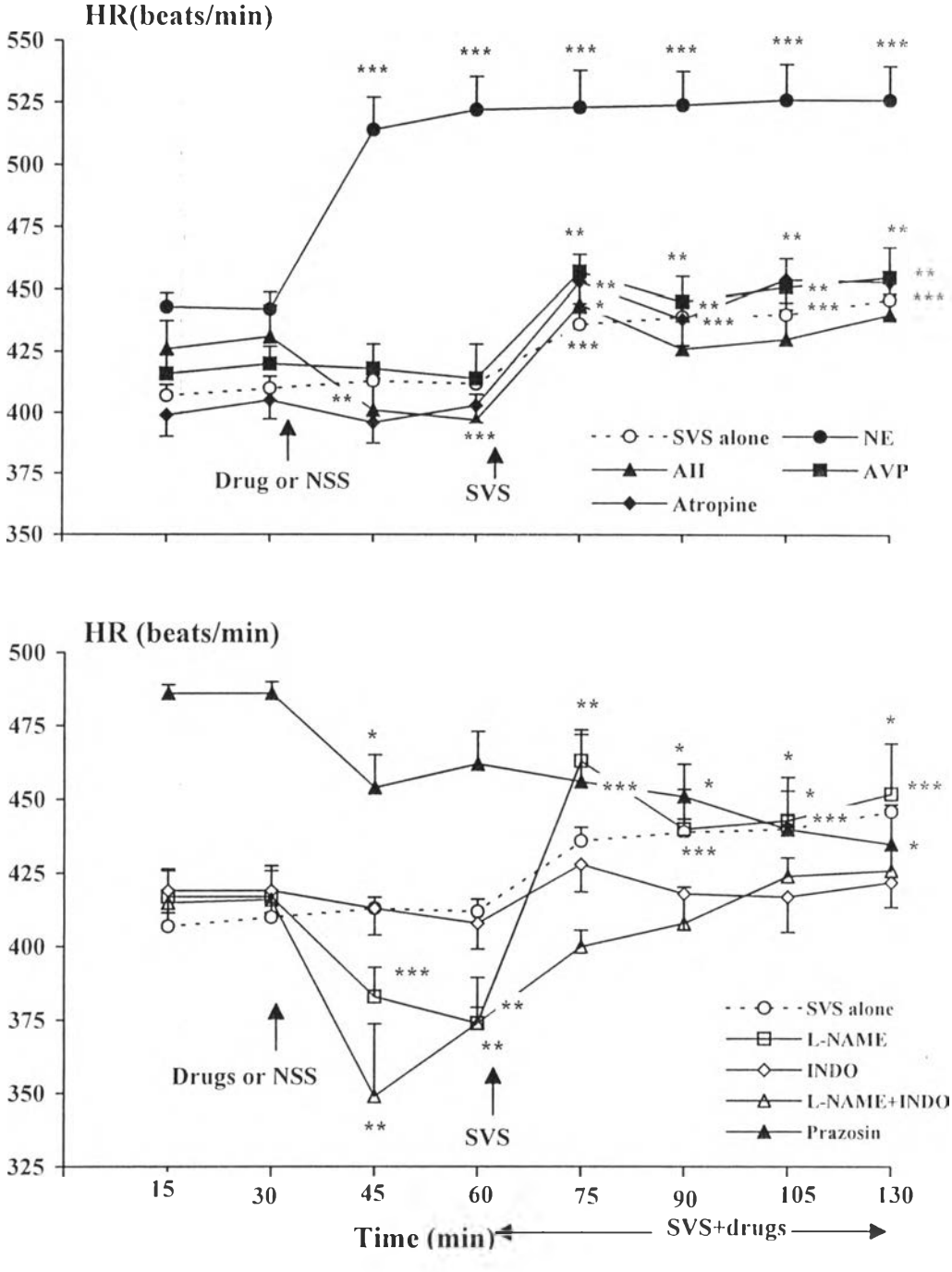

Figure 7.2 Changes of heart rate (HR) in rats treated with SVS infusion alone and pretreated with norepinephrine(NE),prazosin,angiotensin II (A_{II}),arginine vasopressin(AVP), atropine, L-NAME, indomethacin(INDO), and L-NAME+ indomethacin(L-NAME+INDO).All values are presented as mean+SEM.The arrow denotes pretreatment the rats with normal saline(NSS) or various the drugs. Significant difference is indicated by *P<0.05,**P<0.01,***P<0.001.

The effect of SVS infusion alone and pretreatment with NE, A_{II} , AVP, L-NAME, indomethacin and atropine on renal function.

Renal hemodynamics alteration in response to SVS infusion alone and pretreated with NE,A_{II} , AVP,L-NAME and, indomethacin .

The effects of SVS infusion on renal hemodynamics in rat pretreated with or without drugs are shown in table 7.1 and figure 7.1. SVS infusion alone significantly raised effective renal blood flow (ERBF) ($P<0.05$) without a change of GFR during the first 30 min period of SVS infusion. Pretreatment with NE markedly reduced ERBF from 44.72±4.04 to 21.68±3.58 ml/kg.BW, ($P<0.001$) but no significant alteration of GFR was noted. The similar results were shown in rats pretreated with L-NAME and L-NAME+indomethacin.

Pretreatment with A_{II} significantly decreased ERBF ($P<0.001$) and GFR ($P<0.05$). In contrast, pretreatment with AVP and atropine had no effect on both ERBF and GFR. The combination infusion of SVS and NE,A_{II} , L-NAME, L-NAME+indomethacin or atropine significantly decreased both ERBF and GFR. In contrary, pretreatment with AVP or indomethacin normalized both ERBF and GFR during the first but reduced in the second period of SVS infusion.

Effect of SVS infusion on renal tubular function in rat pretreatment with NE,A_{II} , AVP, L-NAME, indomethacin and atropine .

The influences of SVS infusion on renal tubular function are shown in table 7.1-7.4. Urine flow rate (V) was significantly increased from 19.11±2.19 to 26.42±

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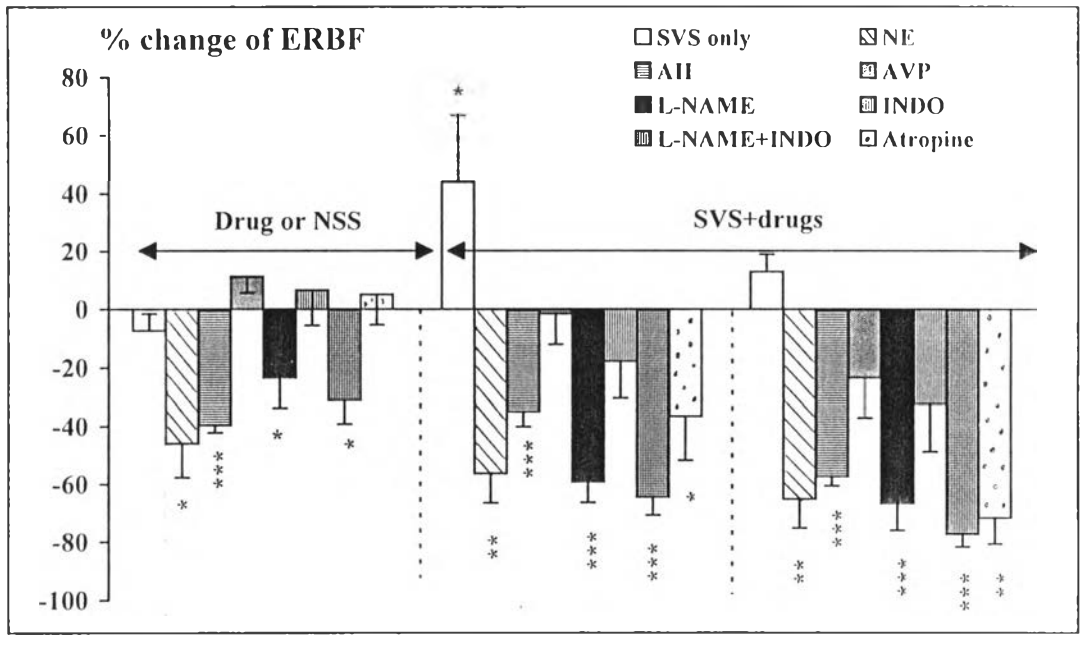
Table 7.1 Change in renal hemodynamics and urine flow rate in response to SVS infusion alone and during pretreated with norepinephrine (NE), angiotensin II (A_{II}), arginine vasopressin (AVP), L-NAME, indomethacin (INDO), L-NAME+indomethacin (L-NAME+INDO), and atropine.

Periods / Parameters	control	drug or NSS	SVS + drug	
	30 min	60 min	90 min	120 min
ERBF (ml/min/kg.BW.)				
SVS group	32.55±1.73	30.23±2.54	45.08±4.64*	34.21±1.61
NE group	44.72±4.04	21.68±3.58**	18.01±3.77**	14.34±4.31**
A_{II} group	39.17±1.85	23.37±0.83***	25.47±2.27***	16.69±1.43***
AVP group	33.76±2.52	36.01±2.17	32.06±2.82	24.47±4.24
L-NAME group	35.54±2.92	25.61±1.82*	13.13±1.58***	10.52±2.15***
INDO group	43.11±4.33	42.88±3.19	34.52±5.19	27.66±5.55*
L-NAME+INDO group	38.56±4.04	24.63±2.82*	13.00±2.30***	9.08±2.08***
Atropine group	37.33±1.83	35.54±3.95	24.81±6.44*	11.11±3.64**
GFR (ml/min/kg.BW.)				
SVS group	5.45±0.28	5.32±0.17	5.21±0.16	5.04±0.26
NE group	7.43±0.13	6.83±0.47	3.76±0.77**	2.57±0.82***
A_{II} group	7.11±0.26	6.16±0.19*	5.90±0.49*	3.63±0.34***
AVP group	6.58±0.52	6.64±0.50	5.52±0.45	3.91±0.63*
L-NAME group	5.86±0.40	5.06±0.33	2.99±0.61**	1.55±0.43***
INDO group	6.16±0.60	6.78±0.82	5.57±0.91	3.86±0.87*
L-NAME+INDO group	5.89±0.32	5.19±0.61	2.64±0.26***	1.45±0.30***
Atropine group	6.62±0.48	5.67±0.62	3.80±1.11*	1.76±0.61**
V (μL/min)				
SVS group	19.11±2.19	19.68±1.32	26.42±2.45*	21.65±1.97
NE group	17.75±0.43	21.01±5.78	18.25±4.39	16.42±2.28
A_{II} group	29.32±5.00	21.07±2.95*	47.59±7.25**	23.33±1.64
AVP group	36.05±5.16	33.90±6.73	45.00±7.57	23.88±4.79
L-NAME group	24.28±3.04	18.26±2.68*	48.97±5.15***	25.06±4.53
INDO group	32.29±4.84	41.49±5.22**	29.16±2.34	15.11±1.59**
L-NAME+INDO group	26.03±3.64	21.74±4.45	30.23±4.58	12.38±3.23*
Atropine group	19.25±2.43	21.86±3.26	25.94±6.45	12.58±4.18

All values are presented into mean±SEM. Abbreviations : ERBF = effective renal blood flow, GFR = glomerular filtration rate, V = urine flow rate, NSS = normal saline. Significant differences comparing to control period using paired t-test are indicated by *P<0.05, **P<0.01,***P< 0.001. The number of rats in each group is 8.

A



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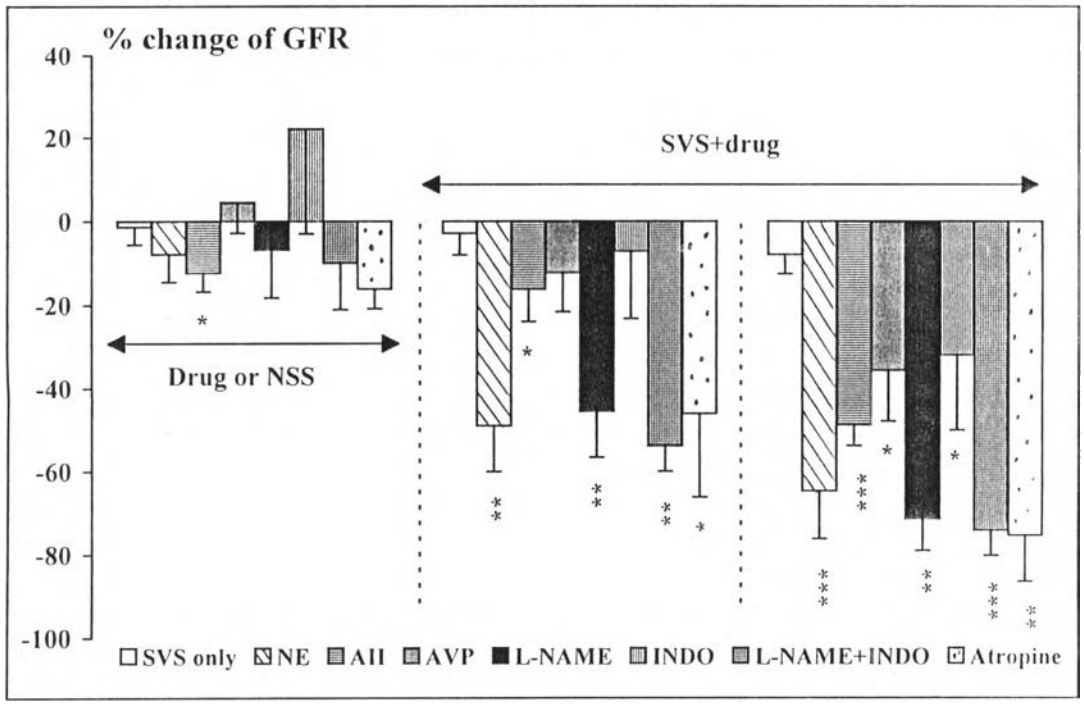

Figure7.3 Percent change of effective renal blood flow(ERBF) and glomerular filtration rate(GFR) (B) in rats given of SVS infusion alone and pretreated with norepinephrine (NE),angoitensin II (A_{II}), arginine vasopressin (AVP), L-NAME, indomethacin (INDO), L-NAME+indomethacin (L-NAME+INDO) and atropine.The number of rats in each group is 8. Significant differences are denoted by *P<0.05,**P<0.01,***P<0.001.

The alterations of fractional excretion of Na^+ (FE_{Na}), K^+ (FE_K) and Cl^- (FE_{Cl}) are illustrated in table 7.3 and figure 7.4. SVS infusion alone raised FE_{Na} ($P<0.01$). Pretreatment with various drugs had no significant influence on FE_{Na} except increased in indomethacin group ($P<0.05$). FE_{Na} was raised throughout the period of SVS infusion in all drugs pretreatment except the last period of AVP and indomethacin group. FE_K was slightly but significantly raised from 33.23±1.89 to 38.39±2.37% ($P<0.05$) during the first period of SVS infusion. Drugs pretreatment were without effect on FE_K except decreased in A_{II} group ($P<0.05$). The first period of SVS infusion had no influence on FE_K in all groups except increased ($P<0.05$) in L-NAME and L-NAME + indomethacin group. No significant alteration of FE_K was produced during the second period of SVS infusion in all groups. The alteration of FE_{Cl} was the same that of FE_{Na}

The fractional excretion of glucose (FE_G) is demonstrated in table 7.4 and figure 7.5. Signficant elevation of FE_G was taken place throughout the period of SVS infusion in SVS group ($P<0.01$). Pretreatment with various drugs had no effect on FE_G. In contrast, FE_G was significantly increased throughout the period of SVS infusion in rat pretreated with all drugs.

Discussion

SVS has been shown to induce hypotension and natriuresis as indicated in chapter IV and other experiments (Melis, 1992b,1995). However, its actions are somehow directly or mediated through the various mediators. Melis and Sainati (1991a) proposed that the action of SVS infusion was probably dependent on

Table7.2 The alterations of plasma electrolytes in rats subjected to SVS infusion alone and pretreated with norepinephrine (NE), angiotensin II (A_{II}), arginine vasopressin (AVP), L-NAME, indomethacin (INDO), L-NAME + indomethacin (L-NAME+INDO) and atropine.

Periods / Parameters	control	drug or NSS	SVS + drug	
	30 min	60 min	90 min	120 min
P_{Na} (mEq/L)				
SVS group	135.00±0.46	135.13±0.23	135.63±0.42	135.88±0.55
NE group	135.25±0.45	134.50±0.57	135.25±1.19	134.75±0.62
A_{II} group	133.33±0.87	132.78±0.57	135.89±1.11*	133.33±0.65
AVP group	135.88±0.58	135.50±0.65	136.38±0.73	140.25±2.32
L-NAME group	139.13±1.49	138.00±1.22	140.50±2.20	141.38±2.09
INDO group	138.44±0.87	140.11±1.03	139.56±1.67	139.89±1.32
L-NAME+INDO group	138.88±1.30	137.75±1.13	141.50±1.25	142.63±2.11
Atropine group	134.00±1.15	135.75±249	136.00±3.03	135.00±2.00
P_K (mEq/L)				
SVS group	3.58±0.05	3.59±0.03	3.61±0.04	3.64±0.05
NE group	3.82±0.21	3.84±0.19	3.94±0.11	4.40±0.16**
A_{II} group	3.40±0.11	3.57±0.06	3.83±0.08*	3.53±0.08
AVP group	3.60±0.12	3.46±0.06	3.59±0.05	3.71±0.10
L-NAME group	3.53±0.11	3.86±0.19*	3.84±0.15*	4.13±0.19**
INDO group	3.37±0.08	3.39±0.10	3.47±0.06	3.53±0.08
L-NAME+INDO group	3.49±0.15	3.39±0.07	3.89±0.10*	3.84±0.07*
Atropine group	3.60±0.16	3.48±0.06	3.68±0.11	3.73±0.14
P_{Cl} (mEq/L)				
SVS group	103.13±1.14	102.13±0.79	103.50±0.63	104.50±1.16
NE group	103.63±1.31	103.75±0.67	104.13±1.04	104.38±0.92
A_{II} group	103.11±0.75	105.89±1.06*	105.67±1.34*	106.11±1.52*
AVP group	105.63±1.49	104.38±1.03	104.63±1.51	105.38±1.03
L-NAME group	103.75±1.27	103.50±1.79	105.25±2.76	105.25±1.58
INDO group	103.00±1.21	104.00±1.44	103.67±0.87	103.00±0.96
L-NAME+INDO	102.50±0.57	104.75±1.56	105.50±1.87	102.50±0.50
Atropine group	105.75±1.44	103.50±2.10	105.75±5.01	111.50±3.66

Datas are presented as mean±SEM. Abbreviations : P_{Na}, P_K, P_{Cl} = Plasma concentration of sodium, potassium and chloride respectively. Significant differences comparing to control period using paired t-test are indicated by *P<0.05, **P<0.01, ***P<0.001. the number of rats in each group is 8.

Table 7.3 Fractional urinary excretion of sodium (FE_{Na}), potassium (FE_K) and chloride (FE_{Cl}) in rats subjected with SVS infusion alone and pretreated with norepinephrine (NE), angiotensin II (A_{II}), arginine vasopressin (AVP), L-NAME, indomethacin (INDO) , L-NAME + indomethacin (L-NAME +INDO) and atropine.

Periods / Parameters	control	drug or NSS	SVS + drug	
	30 min	60 min	90 min	120 min
FE_{Na} (%)				
SVS group	0.96±0.63	1.11±0.94	1.37±0.13**	1.28±0.11**
NE group	0.53±0.17	0.70±0.24	1.37±0.36*	4.14±2.56*
A_{II} group	0.99±0.24	0.99±0.18	2.26±0.29***	1.93±0.23*
AVP group	1.39±0.18	1.58±0.26	2.53±0.40**	1.83±0.29
L-NAME group	1.38±0.27	1.15±0.19	6.50±1.40**	9.14±2.68*
INDO group	1.24±0.22	2.68±0.35***	2.74±0.32**	3.10±1.06
L-NAME+INDO group	1.32±0.23	1.57±0.24	4.61±0.62***	3.88±0.57**
Atropine group	0.70±0.27	1.13±0.35	2.16±0.37*	3.23±1.08*
FE_K (%)				
SVS group	33.23±1.89	35.55±2.08	38.39±2.37*	34.94±4.29
NE group	27.59±3.08	22.02±1.60	29.61±0.51	35.08±6.30
A_{II} group	37.41±2.40	31.58±2.03*	33.23±2.47	40.06±3.90
AVP group	41.34±1.67	39.35±2.28	43.26±1.59	40.18±2.77
L-NAME group	39.98±2.43	30.99±3.95	61.33±8.44*	62.24±13.60
INDO group	46.74±4.08	46.05±3.63	41.81±6.43	32.91±7.37
L-NAME+INDO group	41.46±6.01	40.04±3.09	57.96±5.36*	49.51±6.38
Atropine group	37.68±6.92	46.49±12.10	58.80±16.02	45.01±11.33
FE_{Cl} (%)				
SVS group	1.25±0.11	1.38±0.09	1.72±0.09**	1.69±0.14**
NE group	1.28±0.30	1.24±0.33	2.28±0.51*	5.32±2.92*
A_{II} group	1.87±0.36	1.80±0.30	3.63±0.43***	3.12±0.33*
AVP group	2.59±0.26	2.59±0.32	4.02±0.51**	3.21±0.45
L-NAME group	2.52±0.39	2.10±0.40	9.72±1.72**	13.20±3.75*
INDO group	2.37±0.33	3.54±0.47*	3.66±0.34*	3.68±1.22
L-NAME+INDO group	2.16±0.30	2.23±0.31	6.27±0.86**	4.38±0.73*
Atropine group	1.86±041	2.44±0.63	4.20±0.92*	4.62±1.28*

The results are indicated as mean±SEM. Significant differences comparing to control period using paired t-test are indicated by *P<0.05, **P<0.01, ***P<0.001.

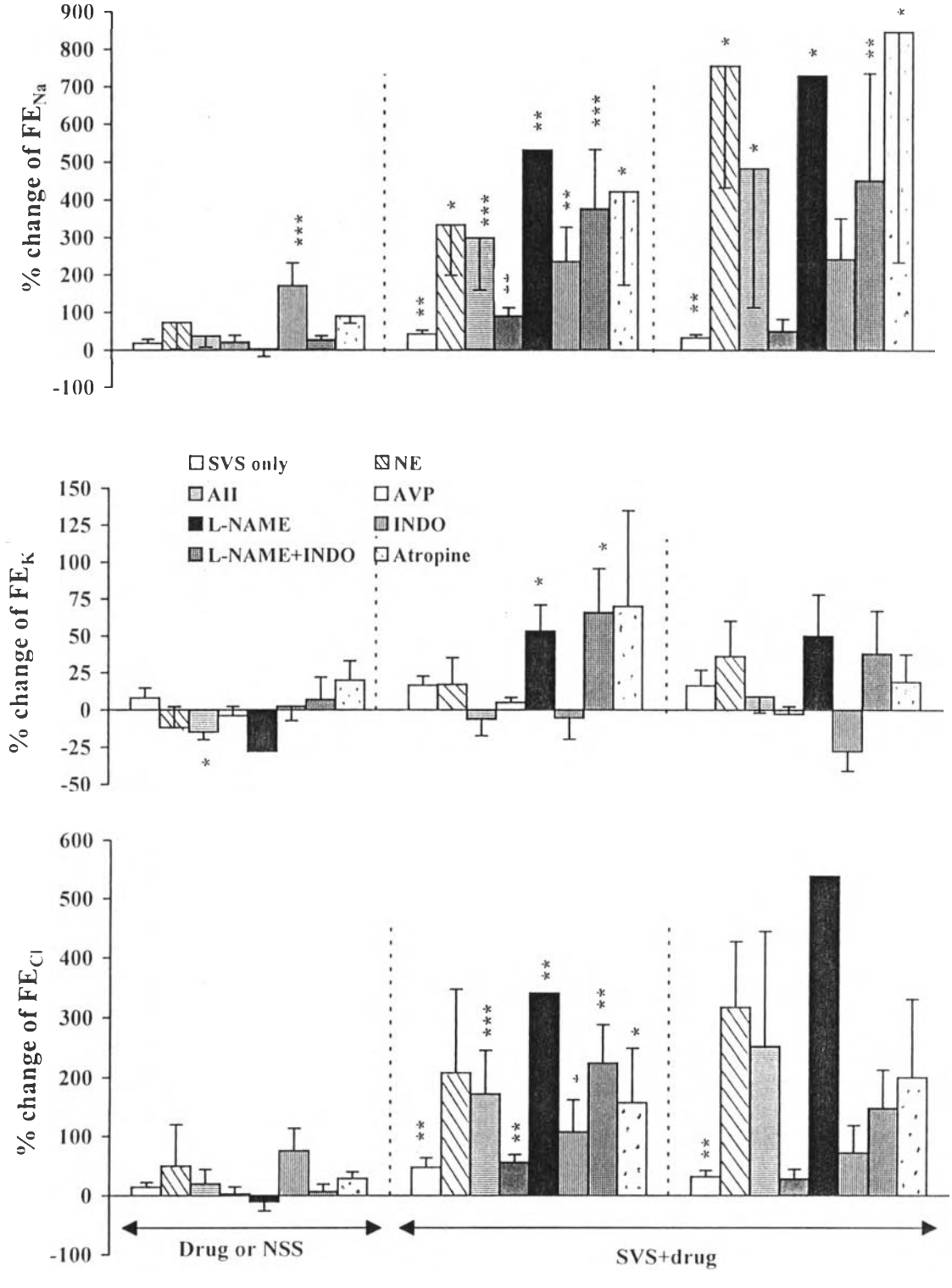

Figure 7.4 Percent change of fractional excretion of Na^+, K^+ and Cl- (FE_{Na},FE_K, FE_{Cl}) in rats given of SVS infusion alone and pretreated with norepinephrine (NE) angoitensin II (A_{II}), arginine vasopressin (AVP), L-NAME, indomethacin (INDO), L-NAME+indomethacin (L-NAME+INDO) and atropine.The number of rats in each group is 8. Significant differences are denoted by *P<0.05, **P<0.0,***P<0.001.

Table 7.4 Effect of SVS infusion on fractional excretion of glucose (FE_G) in rats with or without pretreated with norepinephrine (NE), angiotensin II (A_{II}), arginine vasopressin (AVP), L-NAME, indomethacin (INDO) , L-NAME + indomethacin (L-NAME+INDO) and atropine.

Periods / Parameters	control	drug or NSS	SVS + drug	
	30 min	60 min	90 min	120 min
FE_G (%)				
SVS group	0.10±0.02	0.10±0.01	0.29±0.05**	0.36±0.06**
NE group	0.83±0.18	0.78±0.13	4.78±0.85**	4.26±2.92*
A_{II} group	0.62±0.12	0.71±0.01	1.61±0.14**	3.07±0.75**
AVP group	0.74±0.01	0.76±0.17	1.43±0.31*	2.31±0.68*
L-NAME group	0.89±0.15	0.77±0.18	2.34±0.54*	6.38±2.90*
INDO group	1.02±0.01	1.26±0.19	2.88±0.44**	20.85±9.44*
L-NAME+INDO group	0.89±0.21	0.82±0.14	3.99±1.10*	12.94±5.37*
Atropine group	0.07±0.02	0.09±0.03	0.12±0.04*	2.46±2.03*

Values are expressed as mean±SEM. Significant differences comparing to control period using paired t-test are indicated by *P<0.05, **P<0.01, ***P<0.001. The number of rats in each group is 8.

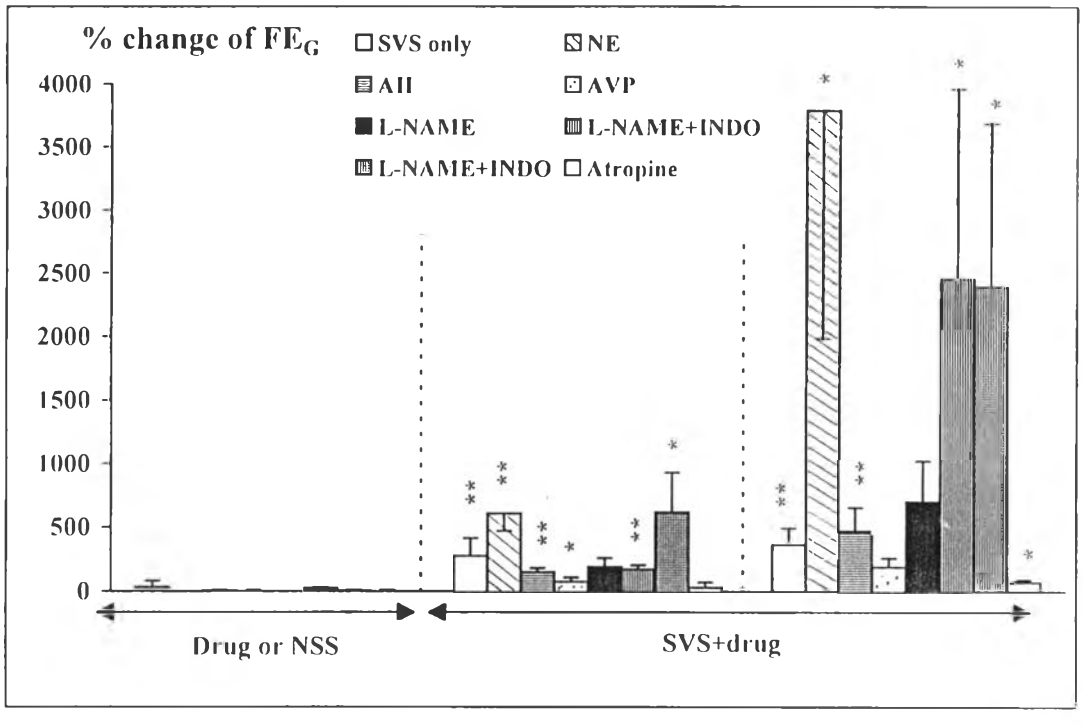

Figure 7.5 Percent change of fractional excretion of glucose(FE_G) in response to SVS infusion alone and pretreated with norepinephrine(NE), angiotensin II (A_{II}), arginine vasopressin (AVP), L-NAME, indomethacin (INDO), L-NAME+indomethacin (L-(NAME+INDO) and atropine. Significant differences are compared to control period are indicated by *P<0.05, **P<0.01, ***P<0.001. The numberof rats in each group

prostaglandin. From the present results, SVS infusion induced hypotension to the lowest level within 5 min after administration. Blood pressure was gradually elevated afterward but still lower than that of base line value whereas heart rate increased throughout the period of SVS infusion. Pretreatment the animals with NE, A_{II}, AVP, indomethacin, L-NAME +indomethacin and atropine could not reverse the lowest level of hypotension induced by SVS infusion. This indicates that hypotensive effect of SVS infusion during this time does not under the stimulation of cholinergic nerve, prostaglandin release and/or inhibition of α-adrenergic receptor, renin-angiotensin system and AVP release. L-NAME pretreatment to abolish NO synthesis obviously reversed the lowest level of blood pressure , implying the participation of NO on hypotensive action of SVS infusion during this time.

After the lowest value of blood pressure induced by SVS, it was gradually elevated afterward but still lower than that of base line value whereas heart rate continuously increased throughout the period of SVS infusion. NE pretreatment could prevent the reduction of blood pressure during this period of SVS infusion but heart rate was extremely high throughout experiment. Also, the simultaneous infusion of prazosin and SVS infusion lowered blood pressure and heart rate with similar magnitude as prazosin pretreatment period. From these results, it seems likely that sympathetic adrenergic activity participates in cardiovascular action of SVS infusion. It is possible that SVS-induced extremely hypotension during the early 5 min stimulates sympathetic nerve to compensate hypotension. However, the compensatory response was not accomplished. NE was found to stimulate prostaglandin synthesis (Dibona, 1986). In addition, prostaglandin released in response to sympathetic

stimulation reduced vasopressor response to sympathetic stimulation and pressor hormone (Lippton et al,1988). From the present experiment, only pretreatment with indomethacin could reverse the hypotension and tachycardia induced by SVS. Thus, the failure of blood pressure recovery may be the result from prostaglandin synthesis produced by sympathetic activation and/or SVS infusion per se. to overcome the sympathetic activity.

The effect of SVS infusion on renal hemodynamics was similar to systemic hemodynamics. The first 30 min of SVS infusion resulted the elevation of ERBF without significant change of GFR, indicating vasodilatation in both afferent and efferent arterioles. Similar result was also observed by Melis and Sainati (1991a,1992b). Only pretreatment with indomethacin and AVP reversed the vasodilator effect of SVS infusion. This implies that prostaglandin and AVP participate in renal vasodilator action of SVS infusion. However, it is uncertain which agent plays a role on renal hemodynamics effect of SVS. It has been reported that prostaglandin synthesis inhibitor has no influence on renal hemodynamics in normal condition whereas prostaglandin raised renal blood flow (Hart and Lifschitz,1987; Zambraski, 1995) which is agreed with the present experiment. Thus renal vasodilator action of SVS infusion during the first 30 min period should be the result from prostaglandin synthesis and/or action.

It has been shown that inhibition of endogenous AVP or exogenous infusion of AVP has no significant influence on renal hemodynamics as well as blood pressure (Rose et al,1991; Söndeen and Claybaugh, 1989) which was quite similar to the

present result. AVP together with SVS infusion reversed renal vasodilator action of SVS. Nevertheless, the recovery of ERBF should not due to the action of vasopressin itself on renal vasculature or inhibition of AVP release. This suggestion can be supported by no changes of renal hemodynamics in both before and during the first period of SVS infusion in AVP group. It should be that AVP administration abolishes the action of SVS on renal vasodilatation. As stated above, the rise of ERBF produced by SVS was mediated via prostaglandin. The possibility that infused AVP inhibits prostaglandin synthesis is unlikely since AVP has been found to activate prostaglandin systhesis (Walker et al, 1978). The recovery of ERBF induced by AVP pretreatment might be the result from its inhibition on SVS-induced prostaglandin synthesis.

Urine flow rate was significantly increased during SVS infusion particulary the first 30 min period whereas no change of GFR and plasma Na^+ concentration. Similar results were obtained by Melis and Sainati (1991a). Fractional excretion of electrolyte was also increased. This indicates that there is the depression of tubular reabsorption. Proximal tubule may be the major site for SVS's action since there was an elevation of urinary glucose excretion. The alteration of renal hemodynamics were not the cause of the depression of tubular reabsorption during SVS infusion. This suggestion is supported by the significant increase of FE_{Na} and FE_{Cl} in associated with renal vasoconstiction such as L-NAME, NE and A_{II} group, or without change of renal vascular resistance like indomethacin and AVP group. This indicates that the enhance of Na^+ and Cl^- excretion in response to SVS infusion does not solely depend on renal

hemodynamics. Direct tubular reabsorptive capacity elicited by SVS might account for urinary Na^+ and Cl^- excretion.

During the second period of SVS infusion alone, FE_{Na} and FE_{Cl} were remained high whereas slightly change of renal hemodynamics, suggesting that renal hemodynamics play a minor role on natriuretic effect of SVS infusion. Proximal tubule should be the main site for its natriuretic action because urinary glucose excretion was still high during this period. Both FE_{Na} and FE_{Cl} were remained increased during this period in all drugs pretreatment groups excepted that of AVP and indomethacin group in which they seemed to be recovered. The mechanisms underlying the recovery of FE_{Na} and FE_{Cl} in both indomethacin and AVP group are explained. It has been reported by Rose and his co-workers (1991) that simultaneous intravenous infusion of AVP and V_1 /V_2 - receptor antagonist remained enhanced FE_{Na} during the first 40 min, and then returned to normal level afterward. This result implies that AVP is not able to reverse natriuresis-induced by AVP receptor antagonist until, at least, 40 min which is quite similar to present results. It was interesting to note that FE_G was still elevated whereas Na^+ excretion was normal during this period, indicating that proximal tubular Na^+ reabsorption should still be depressed. Moreover, the predominant site of AVP on Na^+ and H_2O reabsorption locates at thick ascending limb of loop of Henle and collecting tubule not proximal tubule (Hamlyn and Ludens, 1992; Rouffignac et al, 1983). Thus, the recovery of FE_{Na} and FE_{Cl} during SVS infusion in this group should not due to the action of AVP itself on proximal tubular Na^+ reabsorption. Hence, SVS still suppressed proximal tubular

Na^+ reabsorption, and AVP reversed this action by the action on the other site not proximal tubule.

Prostaglandins, especially E series, have been demonstrated to produce natriuresis and diuresis in both vivo and vitro experiment (Hamlyn et al, 1992; Raymond and Lifschitz, 1986; Wald et al,1990). During the first 30 min of SVS infusion, SVS is still able to inhibit tubular Na^+ and Cl^- reabsorption, and prostaglandin does not participate to its diuretic influence during this period. However, FE_{Na} and FE_{Cl} were recovered in the latter period. Like AVP group, the depression of proximal tubular reabsorption produced by SVS infusion was remained occured since the elevation of FE_G was still appeared. In addition, the primary site of prostaglandin action on tubular Na^+ and Cl^- reabsorption is the same as AVP (Hamlyn and Ludens, 1992; Roman and Kauker, 1978). However, it was reported that prostaglandin E_2 infusion enhanced proximal Na^+ reabsorption, at least in part, via the stimulation of A_{II} production in Sprague-Dawley rats (Kinoshita and Knox,1990). From the present experiment, A_{II} infusion had no any effect on natriuretic action of SVS. Thus, the inhibition of prostaglandin synthesis that reversed natriuretic action of SVS, should not be the result from its action on proximal tubule. In conclusion, the reversibility of Na^+ andCl^- excretion after pretreatment with indomethacin or AVP is not due to their actions to interfere the effect of SVS on proximal tubular reabsorption of Na^+ and Cl^-.

It is interesting to note that SVS infusion alone or combination to the various drugs elicited slightly increase in K^+ excretion which was different from Na^+ and Cl^-

excretion. Approximately 50% of filtered K^+ has been reabsorbed by diffusion at proximal tubule (Vander, 1995). However, net result of all transport processes is that most of the K^+ appearing in urine is K^+ that is secreted by the connecting tubule and cortical collecting tubule. The reduction of proximal Na^+ reabsorption decreases proximal K^+ and HCO_3^- reabsorption (Vander, 1995). Around 80-90% of filtered HCO_3^- is reabsorbed at proximal tubule. Therefore, peritubular capillary blood might become acidosis during the reduction of proximal tubular Na^+ reabsorption, and then Na^+ reabsorption at distal nephron might favor an exchange with H^+ rather than K^+. Finally, the reduction of proximal K^+ reabsorption together with the reduction of K^+ secretion, results no or slightly change of K^+ excretion.

FE_K was quite undisturbed during SVS infusion in most animals pretreated with various drugs excepted that of L-NAME and L-NAME+indomethacin. FE_K was significantly enhanced during the first 30 min of SVS infusion in both group. This may be due to the reduction of K^+ reabsorption and/or the facilitation of K^+ secretion. The former should be likely since plasma K^+ level was increased (table 7.2) along with the reduction of urinary K^+ excretion. In this group, SVS depressed tubular Na^+ and Cl^- reabsorption much more the other groups (table 7.3), indicating the markedly reduction of electrolytes reabsorption. By these experimental results it seems to be that nitric oxide synthesis inhibition enhances the effect of SVS on tubular reabsorption.

In conclusion, SVS infusion produced hypotension, renal vasodilation and electrolyte excretion. Its action on blood pressure is indicated to involve nitric oxide,

α-adrenergic receptor and prostaglandin. Renal vasodilator effect of SVS infusion was mediated via prostaglandin. The depression of proximal tubular Na^+ and Cl^- reabsorption induced by SVS infusion is not mediated by any drugs employed in the present experiment.