Inter-organ Relation between Salivary Gland and Kidney in Lithium Excretion. III. Enhanced Salivary and Systemic Clearance of Li^+ by Oral Administration of NaCl in Dogs[1)]

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Effects of oral administration of NaCl on salivary and systemic clearance of Li^+ were investigated following bolus intravenous administration of LiCl in male beagle dogs. Fifty ml of NaCl solution (100 meq/l) was administered orally 7 times at 1 h intervals. Gustatory stimulation of salivation was continued for 390 min using citric acid solution. Saliva was collected by means of permanent fistulae for parotid and mandibular-sublingual glands. Salivary clearance of Li^+ was markedly increased by continuous stimulation of salivation, and was enhanced further after oral administration of NaCl solution. Renal clearance of Li^+ showed a decreasing tendency under continuous salivation compared with the condition without gustatory stimulation; however, this decreasing tendency disappeared after oral administration of NaCl solution. Consequently, systemic clearance of Li^+ was increased due to the contribution of increased salivary clearance. Enhancement of salivary Li^+ clearance after administration of NaCl suggests the salivary excretion mechanism of Li^+ may include a reabsorption process, like its renal excretion. Administration of NaCl solution had similar effects on salivary and systemic clearances of K^+ to those on Li^+ clearances, and a significant correlation was observed between Li^+ and K^+ clearances of both salivary gland and kidney.

Keywords lithium; sodium; potassium; continuous salivation stimulation; NaCl administration; parotid saliva; mandibular-sublingual saliva; salivary clearance; renal clearance; dog

Interest in the salivary excretion of Li^+ is rising from the viewpoint of salivary Li^+ concentrations for therapeutic drug monitoring. Significant correlations between salivary and plasma concentrations of Li^+ were reported in man.[2-5)] However, most of these reports simply describe the ratio of Li^+ concentration in saliva to that in plasma (S/P ratio), and factors influencing the S/P ratio have not yet been clarified. There have been few studies in animals to clarify the characteristics of kinetics and/or the mechanism of the salivary Li^+ excretion.

Our previous study in dogs demonstrated that the S/P ratio and salivary clearance of Li^+ increased with plasma Li^+ concentration,[6)] suggesting the existence of a saturable reabsorption process in the salivary excretion mechanism of this substance. We also investigated the pharmacokinetic characteristics of salivary and renal Li^+ excretions under continuous stimulation of salivation in dogs which had permanent fistulae of the parotid and mandibular-sublingual glands.[7)] Under this condition, an inter-organ relation was observed between the salivary gland and kidney, where a decrease in renal Li^+ clearance took place together with an increase in salivary Li^+ clearance. This was probably caused by the excessive secretion of saliva corresponding to about 4% of body weight of the dogs. In our subsequent study, the inter-organ relation was not influenced by the oral administration of water to compensate for the continuous stimulation of salivation.[8)] It was reported that the renal Li^+ excretion was decreased under the condition of low Na^+ intake in man,[9)] rats[10-12)] and dogs.[13)] Na^+ loss due to excessive salivation was probably the cause of the decrease in renal Li^+ clearance with continuous salivation stimulation in our previous experiment.

The purpose of the present study was to demonstrate the effect of oral administration of NaCl solution on salivary and renal excretion of Li^+, and to obtain clues for understanding the inter-organ relation between salivary gland and kidney. Characteristics of the reabsorption process in the salivary excretion mechanism of Li^+ were discussed from changes in Na^+ and K^+ excretion as well as Li^+ excretion after administration of NaCl solution.

Materials and Methods

Materials All chemicals and reagents including LiCl (Wako Pure Chemical Industries, Ltd., Osaka, Japan) were commercial products of analytical grade.

Animals Studies were performed in three male beagle dogs weighing 11.0—12.0 kg purchased from Fuji Life-science Incorporated (Kitakoma, Japan). They were housed in stainless steel kennels, water was probided *ad libitum*, and a commercial dry food (CLEA CD-5, CLEA Japan Incorporated, Tokyo, Japan) was fed once a day. All dogs had been operated for the formation of permanent fistulae[14)] to collect parotid saliva (Pr) and mandibular-sublingual saliva (MS) separately. One fistula had been made for each pair of these salivary glands. The beagle dogs employed in the present study were the same as those used in previous reports.[7,8)] Creatinine clearance of the dogs was 2.49 ± 0.408 ml/min/kg in the present study.

Experimental Protocols Dogs were used for the experiment in an unanesthetized condition without fasting. They were hung in a sling and immobilized with a muzzle. A bolus injection of LiCl (0.145 meq/kg body weight) was given to each dog through the cephalic vein as its aqueous solution (0.290 meq/ml).

Collection of blood, saliva and urine was in accordance with the methods described in our preceding paper.[7)] Blood samples were drawn at 2.5, 5, 10, 20, 35, 60, 90, 120, 180, 240 and 360 min after i.v. administration of LiCl into ice-chilled heparinized tubes. The plasma was obtained by centrifugation of the blood at 1600 *g* for 15 min. The two kinds of saliva (Pr and MS) were collected by devices made of polyethylene tubing (i.d. 6 mm) and led to test tubes through Tygon tubing (i.d. 1/16 inch, Norton

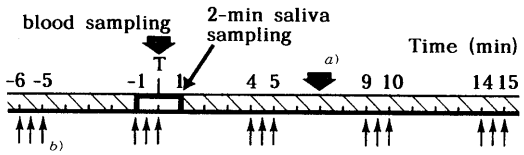

Fig. 1. Protocol of Saliva and Blood Collection

Time *T* on this scale indicates the sampling time of blood and saliva in this experimental schedule. The blood sample was drawn at the midpoint of a 2-min period for saliva sampling. *a*) Saliva was collected throughout the experiment, including the 2-min saliva sampling. *b*) Upward arrows represent a gustatory stimulation of salivation with citric acid.

K.K, Tokyo, Japan).[14] Salivation was gustatorily stimulated by applying 0.4 ml of 10% citric acid solution containing 20% sucrose onto the tongue of each dog. Protocol of saliva and blood collection is shown in Fig. 1 in relation to the stimulation of salivation. Three stimulations at 30 s intervals were repeated every 5 min after the administration of LiCl for 390 min. Saliva was collected throughout the experiment (for 390 min), including 2-min periods for saliva sampling at 5, 10, 20, 35, 60, 90, 120, 180, 240 and 360 min after the administration of LiCl. The 2-min saliva samples were used determine the time course of salivary lithium concentration (Fig. 2). Immediately before the administration of LiCl, the bladder was emptied using a urethral catheter (Argyle Rob-Nel Catheter, 10 Fr, Japan Sharwood Ltd., Tokyo, Japan). Urine was thereafter collected throughout the experiment using this catheter.

NaCl solution (100 meq/l), warmed to approximately 35 °C, was administered orally to the dogs through Tygon tubing (i.d. 1/16 inch). Fifty ml of the solution was given 7 times at 1-h intervals from 25 min before the i.v. administration of LiCl. We previously carried out an experiment without any gustatory stimulation or oral administration of NaCl solution (control) and an experiment with the stimulation of salivation but without oral administration (stimulated),[7] using the same three beagle dogs. The concentration and volume of the administered NaCl solutions were roughly equal to the body fluid loss due to the continuous salivation estimated from these "control" and "stimulated" experiments. We also carried out an experiment with the stimulation of salivation and oral administration of the same volume (50 ml × 7) of plain water instead of NaCl solution (stimulated + water),[8] using the same beagle dogs. Since all experiments in this study were carried out within one year and no significant change was observed in creatinine clearance for any of the dogs during this period, it can be assumed that the effect of time on Li^+ disposition can be neglected.

Analytical Methods salivary flow rate (μl/min/kg) was estimated from the sample weight assuming the specific gravity of saliva to be 1.00.[15] Concentrations of Li^+ and K^+ in the biological fluids were determined with a flame photometer (Shimadzu AA-630-12, Shimadzu Seisakusho Co., Ltd., Kyoto, Japan) after appropriate dilution with NaCl solution (100 meq/l). Concentrations of Na^+ were determined after dilution with KCl solution (100 meq/l). These dilution procedures were performed to compensate for changes in the flame emission owing to the existence of other cations.

Calculations The area under the curve of Li^+ concentrations corresponding to time 0 to 390 min (AUC_{390}) for plasma was estimated by the trapezoidal rule for each dog. The values obtained from the computer-fitted curve were used for the plasma concentrations at time 0 and 390 min. The AUC_{390} for saliva (Pr and MS) and urine were calculated from the mean Li^+ concentrations in each sample of saliva and urine, respectively, multiplied by 390 min. The mean concentration of Li^+ in each biological fluid was determined from the cumulative recovery of Li^+ over the 390 min divided by the total volume of each fluid. Ratio of Li^+ concentrations in saliva or urine to that in plasma (S/P or U/P ratio) was calculated as the ratio of the AUC_{390}, that is,

S/P ratio for Pr or MS

$$= (AUC_{390} \text{ for Pr or MS})/(AUC_{390} \text{ for plasma})$$

$$= (\text{mean concn. in Pr or MS})/(\text{mean concn. in plasma}) \quad (1)$$

U/P ratio

$$= (AUC_{390} \text{ for urine})/(AUC_{390} \text{ for plasma})$$

$$= (\text{mean concn. in urine})/(\text{mean concn. in plasma}) \quad (2)$$

Salivary and renal clearance of Li^+ was calculated by the following equation,

salivary clearance for Pr or MS

$$= (X_{S,390} \text{ for Pr or MS})/(AUC_{390} \text{ for plasma}) \quad (3)$$

$$\text{renal clearance} = X_{U,390}/(AUC_{390} \text{ for plasma}) \quad (4)$$

where $X_{S,390}$ and $X_{U,390}$ represent the cumulative recovery of Li^+ through the 390 min into saliva and urine, respectively. Clearances (μl/min/kg) were normalized by the body weight of each dog in this report. Systemic clearance of Li^+ was considered to be the sum of salivary and renal clearances, assuming that no Li^+ was excreted *via* any other route than the kidneys and the salivary glands under these experimental conditions; this is because Li^+ elimination is known to take place almost exclusively through the kidneys under normal conditions.[16] Na^+ and K^+ clearances were calculated by dividing the excretion rates of Na^+ and K^+ by their respective mean concentrations in plasma.

Statistical Analysis The same three beagle dogs were used in each experimental condition described in this paper. Inter-individual variations of data were analyzed by means of the analysis of variance. Differences in the mean values of data were analyzed by the paired *t*-test where there were inter-individual variations at $p<0.10$, or by Student's *t*-test where no inter-individual variation was observed ($p \geqq 0.10$). Data were expressed in the mean ± S.D. of the three dogs unless otherwise indicated.

Results

Li^+ Concentration in Biological Fluids Figure 2 shows plasma and saliva Li^+ concentrations following i.v. administration of LiCl under the continuous stimulation of salivation with (stimulated + NaCl solution) or without (stimulated) oral administration of NaCl solution. The plasma concentration-time plots of Li^+ resulted in a slightly more rapid downward curve following administration of the solution. Significant difference was observed in the plasma concentration at 360 min between "stimulated + NaCl solution" and "stimulated." When the same volume of plain water was orally administered instead of NaCl solution (stimulated + water),[8] the plasma concentrations of Li^+ were almost the same as those in the "stimulated" experiment. The ratios of the AUC_{390} for saliva or urine to those for plasma are shown in Table I together with each AUC_{390} value, where "control" represents data in the experiment without any gustatory stimulation. The ratio of AUC_{390} for saliva to plasma (S/P

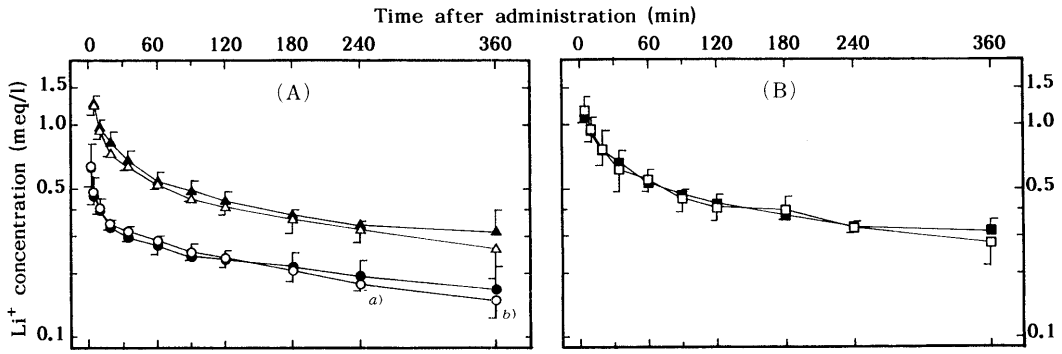

Fig. 2. Plasma and Saliva Li^+ Concentrations under Continuous Stimulation of Salivation with (Stimulated + NaCl Solution) or without (Stimulated) Oral Administration of NaCl Solution in Beagle Dogs (LiCl 0.145 meq/kg, i.v. Bolus)

(A) Parotid saliva (Pr) and plasma concentrations: ▲ Pr, ● plasma in "stimulated"[7]; △ Pr, ○ plasma in "stimulated + NaCl solution". Mean ± S.D. ($n=3$).
(B) Mandibular-sublingual saliva (MS) concentrations: ■ MS in "stimulated"[7]; □ MS in "stimulated + NaCl solution". Mean ± S.D. ($n=3$). *a*) Different at $0.05<p<0.10$, or *b*) significantly different at $p<0.05$ from the "stimulated" by the paired *t*-test.

TABLE I. Area under the Curve of Li^+ Concentration within 390 min (AUC_{390}), and Ratio of the AUC_{390} for Saliva or Urine to Plasma (S/P or U/P Ratio) under Various Conditions of Stimulated Salivation in Beagle Dogs (LiCl 0.145 meq/kg, i.v. Bolus)

	AUC_{390} (meq·min/l)				S/P ratio		U/P ratio
	Plasma	Pr	MS	Urine	Pr	MS	
Control[7]	91.2±10.3	385±70.7 [a]	249±16.8 [a]	4950±1920 [c]	4.21±0.732 [a]	2.75±0.473 [b]	55.5±23.9 [c]
Stimulated[7]	88.0±4.14	182±1.67 [a]	178±14.3 [a]	5250±2730 [c]	2.07±0.0844 [a]	2.03±0.241	60.0±31.1 [d]
Stimulated+water[8]	97.3±9.34	191±13.6 [a]	208±10.5 [a] [b]	3990±2340	1.97±0.168	2.15±0.221	40.0±19.9
Stimulated +NaCl solution	86.1±3.71	183±19.8	188±12.1	4440±1790	2.12±0.145 [a]	2.17±0.129	52.0±21.8

Mean±S.D. ($n=3$). Pr: parotid, MS: mandibular-sublingual saliva. See text for each experimental condition. *a*) Significantly different at $p<0.05$, or *b*) different at $0.05<p<0.10$ by Student's *t*-test. *c*) Different at $0.05<p<0.10$, or *d*) significantly different at $p<0.05$ by the paired *t*-test.

TABLE II. Salivary and Urinary Flow Rate under Various Conditions of Stimulated Salivation in Beagle Dogs (LiCl 0.145 meq/kg, i.v. Bolus)

	Salivary flow rate (μl/min/kg)			Urinary flow rate (μl/min/kg)
	Pr	MS	Pr+MS	
Control[7]	0.987±0.315 [a]	18.4±10.9 [a]	19.4±11.1 [a]	7.42±2.88
Stimulated[7]	35.6±8.84 [a] [b]	58.3±5.84 [a] [b]	92.9±5.45 [a] [b]	5.72±1.72 [c]
Stimulated+water[8]	41.7±12.9 [a]	68.3±4.59 [a]	110±9.33 [a]	7.65±1.68 [c]
Stimulated+NaCl solution	54.6±12.3	68.9±6.61	123±15.3	7.91±1.00

Mean±S.D. ($n=3$). Pr: parotid, MS: mandibular-sublingual saliva. See text for each experimental condition. *a*) Significantly different at $p<0.05$, or *b*) different at $0.05<p<0.10$ by Student's *t*-test. *c*) Different at $0.05<p<0.10$ by the paired *t*-test.

TABLE III. Li^+ Clearances under Various Conditions of Stimulated Salivation in Beagle Dogs (LiCl 0.145 meq/kg, i.v. Bolus)

Li^+ clearance (μl/min/kg)	Salivary			Renal (CL_R)	Systemic (CL_S+CL_R)
	Pr	MS	Pr+MS (CL_S)		
Control[7]	4.04±0.822 [a]	51.0±30.7 [b]	55.0±31.2 [a]	472±279 [c]	527±270 [b]
Stimulated[7]	73.3±16.3 [a] [a]	119±26.0 [b] [c]	192±10.7 [a] [a]	383±236 [b]	575±243 [b]
Stimulated+water[8]	83.2±33.1 [a]	147±16.6 [b]	230±39.3	324±152	554±115
Stimulated+NaCl solution	114±18.8	150±10.5	264±27.1	464±241	727±254

Mean±S.D. ($n=3$). Pr: parotid, MS: mandibular-sublingual saliva. See text for each experimental condition. *a*) Significantly different at $p<0.05$ by Student's *t*-test. *b*) Significantly different at $p<0.05$, or *c*) different at $0.05<p<0.10$ by the paired *t*-test.

ratio) for Pr was lower under the conditions of stimulated salivation than in the "control" experiment. The ratio of the AUC_{390} for urine to plasma (U/P) was extremely high (over 40) due to the difference in the fraction of reabsorbed Li^+ and water to glomerular filtration.[16] Under normal conditions, 70—80% of Li^+ filtered by glomeruli is reabsorbed in renal tubules,[16,17] while more than 99% of water is reabsorbed.

Salivary and Renal Excretion of Li^+, Na^+ and K^+ Salivary flow rate is the major determining factor of salivary Li^+ clearance under the condition of almost constant S/P ratio,[6] as shown by Eq. 3. Table II shows the salivary flow rates in this study together with the urinary flow rate. The continuous stimulation of salivation markedly increased the salivary flow rates for both Pr and MS. Consequently, salivary clearance of Li^+ was also enhanced under the stimulated conditions compared with "control," as shown in Table III, although the S/P ratios for Pr were lower (Table I). From the comparison between "stimulated" and "stimulated+NaCl solution" in the Table III, it was found that the salivary clearance of Li^+ was increased after the oral administration of NaCl solution. When the same volume of plain water was administered instead of NaCl solution (stimulated+water)[8] larger mean values were observed, but they did not represent a statistically significant increase.

In our previous study,[7] renal clearance of Li^+ had a decreasing tendency under the continuous stimulation of salivation (Table III, "control" and "stimulated"). This canceled out the increase in salivary clearance, and systemic clearance of Li^+ did not increase. In this study, the oral administration of NaCl solution restored the renal clearance of Li^+ to a comparable level with that of the "control" experiment (Table III). Consequently, systemic clearance of Li^+ was increased compared with "control" due to the contribution of enhanced salivary clearance. Under the condition of water administration (stimulated+water),[8] no increase in systemic clearance was observed because of the

TABLE IV. Na^+ Clearances under Various Conditions of Stimulated Salivation in Beagle Dogs (LiCl 0.145 meq/kg, i.v. Bolus)

Na^+ clearance (μl/min/kg)	Salivary			Renal (CL_R)	Systemic (CL_S+CL_R)
	Pr	MS	Pr+MS (CL_S)		
Control[7]	0.474±0.0382	10.9±6.39	11.4±6.37	2.31±1.11	13.7±6.29
Stimulated[7]	20.8±8.72	32.6±5.05	53.4±9.83	1.63±0.202	55.0±9.63
Stimulated+water[8]	23.8±6.81	35.6±4.37	59.5±3.60	1.96±0.624	61.4±3.45
Stimulated+NaCl solution	30.8±6.76	40.7±6.16	71.5±12.9	3.44±0.579	74.9±13.1

Mean±S.D. ($n=3$). Pr: parotid, MS: mandibular-sublingual saliva. See text for each experimental condition. *a)* Significantly different at $p<0.05$ by Student's t-test.

TABLE V. K^+ Clearances under Various Conditions of Stimulated Salivation in Beagle Dogs (LiCl 0.145 meq/kg, i.v. Bolus)

K^+ clearance (μl/min/kg)	Salivary			Renal (CL_R)	Systemic (CL_S+CL_R)
	Pr	MS	Pr+MS (CL_S)		
Control[7]	2.40±0.673	49.7±33.9	52.1±34.2	556±272	608±263
Stimulated[7]	113±18.4	190±11.6	302±14.7	376±155	678±159
Stimulated+water[8]	133±14.6	232±23.9	365±34.7	281±137	646±120
Stimulated+NaCl solution	151±31.5	219±23.4	370±52.4	514±201	884±253

Mean±S.D. ($n=3$). Pr: parotid, MS: mandibular-sublingual saliva. See text for each experimental condition. *a)* Significantly different at $p<0.05$, or *b)* different at $0.05<p<0.10$ by Student's t-test. *c)* Significantly different at $p<0.05$, *d)* different at $0.05<p<0.10$ by the paired t-test.

TABLE VI. Correlation Coefficient between Clearances of Li^+ *vs.* Na^+, or Li^+ *vs.* K^+ through Salivary Gland or Kidney in Beagle Dogs (LiCl 0.145 meq/kg, i.v.)

		Equation[a]	Number of data[b]	Correlation coefficient (r)	Significance
Li^+ *vs.* Na^+	CL_{Pr}	$Y=3.57X$	12	0.982	$p<0.01$
	CL_{MS}	$Y=3.81X$	12	0.934	$p<0.01$
	CL_R	($Y=162X$)	12	0.310	Not significant
Li^+ *vs.* K^+	CL_{Pr}	$Y=0.688X$	12	0.945	$p<0.01$
	CL_{MS}	$Y=0.655X$	12	0.943	$p<0.01$
	CL_R	$Y=0.942X$	12	0.881	$p<0.01$

a) Y: Li^+ clearance, X: Na^+ or K^+ clearance. *b)* Number of data was 12 because these analyses were performed with pooled data from four kinds of experimental conditions described in this paper. Each experiment was carried out in three animals.

renal clearance showing a lower mean value.

Tables IV and V show salivary, renal and systemic clearances of Na^+ and K^+, respectively. The continuous stimulation of salivation also enhanced salivary clearances of Na^+ and K^+ as it did that of Li^+. After oral administration of NaCl solution (stimulated+NaCl solution), renal clearance of Na^+ was greater than "stimulated" or "stimulated+water" (Table IV), although plasma concentrations of Na^+ did not differ among these conditions (control: 156.0±2.78 meq/l, stimulated: 157.9±6.55, stimulated+water: 155.0±3.20, stimulated+NaCl solution: 157.4±5.47). Salivary clearance of Na^+ was much larger than its renal clearance under this experimental condition; therefore, changes in the systemic clearance of Na^+ corresponded to those in its salivary clearance. As for K^+, changes in the systemic clearance were similar to those in systemic clearance of Li^+ (Tables III and V). Under the condition of "stimulated+NaCl solution," systemic clearance of K^+ was increased compared with "control" due to the enhancement of salivary clearance. In "stimulated"[7] or "stimulated+water,"[8] however, the systemic clearance did not differ from "control" significantly, since the lower mean value of renal K^+ clearance canceled out the enhancement of salivary clearance. Plasma concentrations of K^+ were 4.78±0.154 meq/l in "control," 4.53±0.398 in "stimulated," 4.38±0.161 in "stimulated+water," 4.09±0.0839 in "stimulated+NaCl solution."

Correlation between Li^+ Clearance and Na^+ or K^+ Clearance Relationship between Li^+ clearance and Na^+ or K^+ clearance was investigated in order to compare the mechanism of Li^+ excretion through the salivary gland and kidney to that of Na^+ or K^+ excretion. The results are summarized in Table VI, where analyses were performed for salivary (Pr and MS) and renal clearances with pooled data from four experimental conditions: "control,"[7] "stimulated,"[7] "stimulated+water"[8] and "stimulated+NaCl solution" in the present study. Significant correlations ($p<0.01$) were observed for all analyses made except for the relationship between renal clearance of Li^+ and Na^+.

Discussion

At the beginning of this series of studies on continuous salivation, we attempted to increase the systemic clearance of Li^+ by increasing the salivary excretion. However, an inter-organ relation in Li^+ excretion was observed with the continuous stimulation of salivation,[7] where a decreasing tendency in renal clearance of Li^+ took place together with an enhancement of salivary clearance (Table III, "control" and "stimulated"). Consequently, the systemic clearance was not increased significantly. One purpose of this study was to elucidate the mechanism responsible for this inter-organ relation. When NaCl solution was administered orally to compensate the body fluid loss due to the vigorous salivation, renal clearance of Li^+ took a comparable value to that in the "control" experiment (Table III, "stimulated + NaCl solution"). That is, the inter-organ relationship disappeared and systemic clearance of Li^+ increased by 38% owing to the contribution of enhanced salivary clearance. The relationship therefore appeared to be caused by the loss of Na^+ and/or water due to the salivation.

When the same amount of water was administered in place of NaCl solution (stimulated + water),[8] systemic clearance of Li^+ was not increased because of the renal clearance which had a lower mean value (Table III). As is evident from the salivary and urinary flow rates in Table II, almost the same amount of water was excreted under the conditions of "stimulated + water" and "stimulated + NaCl solution." Even if there were changes in the extracellular fluid (ECF) volume after oral administration of water or NaCl solution, the changes would be the same in these two conditions. Therefore, the disappearance of the inter-organ relation was caused by the compensation of Na^+, not by ECF volume expansion. It is yet unknown what mechanisms operate between the loss of Na^+ through salivary glands and the reduced excretion of Li^+ through kidneys. It seems possible that antidiuretic action, which may be the renin-angiotensin system, is activated by the continuous salivation. This is a subject for future study.

The salivary clearance of Li^+ for Pr + MS corresponded to 36% of the systemic clearance under the condition of "stimulated + NaCl solution," suggesting the possibility that these salivary glands (making a pair on either side) are another route of Li^+ excretion. It should be noted that salivary excretion of drugs can influence the drug elimination from the body in some cases. This possibility was previously suggested for urea and phenobarbital.[18] The salivary clearance values of these drugs determined during a 2 min period with stimulation of salivation corresponded to 18% for urea and 247% for phenobarbital of the systemic clearances determined from the plasma concentration-time curve following bolus injection.

Little is known about the mechanism of salivary Li^+ excretion in spite of the potential usefulness of salivary Li^+ concentration for therapeutic monitoring. It has been suggested that an active secretion mechanism may be involved because of the fact that the saliva/plasma concentration ratio (S/P ratio) of Li^+ is larger than unity in man[2-5] and that the S/P ratio decreased at higher salivary flow rate in dogs.[6,19] This study also showed that the ratios of the AUC_{390} for saliva to plasma, *i.e.* S/P ratios, were larger than unity in Pr and MS and dropped with the continuous stimulation of salivation in Pr (Table I). However, it is yet unknown what characteristics the transport mechanism has and where the transport takes place. Furthermore, positive correlations were observed between S/P ratio and plasma concentration of Li^+ in our previous study.[6] This phenomenon cannot be explained by the active secretion alone, since the S/P ratio is thought to decrease with the increase in plasma concentration where only the saturable secretion operates.

Renal excretion of Li^+ depends on the glomerular filtration and the tubular reabsorption.[16] Higher renal excretion of Li^+ was reported at higher Na^+ intake[9,10,20,21] or under saline loading.[22,23] It was also reported that renal Li^+ excretion related directly to renal Na^+ excretion.[10,21] These findings support that tubular reabsorption of Li^+ takes place through the same mechanism that is responsible for reabsorption of Na^+.[17] In this study, although statistically significant correlation was not observed between renal clearance of Li^+ and Na^+ (Table VI), both were raised after the oral administration of NaCl solution compared with "stimulated" (Tables III and IV).

Salivary clearance of Li^+ was also enhanced after the oral administration of NaCl solution compared with "stimulated" (Table III). Furthermore, the salivary clearance of Li^+ was highly correlated to the salivary clearance of Na^+ in both Pr and MS (Table VI). These results suggest the existence of a reabsorption process of Li^+ in the salivary glands similar to that in the renal tubule. Active reabsorption of Na^+ has been known to take place in striated ducts of salivary glands.[24,25] Parotid and mandibular glands of dog have these striated ducts, and it is supposed that Li^+ may be also reabsorbed in this segment. The positive correlation between S/P ratio and plasma concentration of Li^+[6] can be explained assuming the saturable reabsorption process.

The relationship between renal excretion of Li^+ and K^+ is not yet clear. It was reported that renal excretion of K^+ was significantly greater in lithium-treated rats,[26] and that renal excretion of Li^+ was diminished under extremely low dietary K^+ contents in rats.[27] On the other hand, no significant correlation was observed between the fraction of the filtered Li^+ which was reabsorbed by the renal tubule and the similar fraction for K^+ in dogs.[20] Our results showed a significant correlation between renal clearances of Li^+ and K^+ (Table VI). Furthermore, some common phenomena were observed for Li^+ and K^+ clearances: even when salivary clearance was increased by continuous stimulation, systemic clearance was not increased because renal clearance showed a lower mean value, and the systemic clearance was increased after the oral administration of NaCl solution (Tables III and V). This suggested that renal excretion of Li^+ was related directly or indirectly to that of K^+. A significant correlation was also observed between salivary clearances of Li^+ and K^+ (Table VI). Investigations on the excretory mechanisms of Li^+ should continue with attention given to K^+ excretion as well as Na^+ excretion.

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