STUDIES ON AN ANTIDIURETIC SUBSTANCE IN THE BILE

REPORT III. ORIGIN OF THE BILIARY ANTIDIURETIC SUBSTANCE

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It may be surmised that the biliary antidiuretic substance (biliary ADS) is primarily a component of the bile or of blood. In this study, an attempt was made to ascertain the origin of the biliary ADS, whether it is derived from vasopressin or from an antidiuretic substance which is produced in hepatic tissue (hepatic ADS or ferritin).

(I) Consideration of the possibility that the biliary ADS is derived from vasopressin

1) Biliary excretion of Pitressin (vasopressin)

Method: Following an intravenous injection of 2,000 mU of Pitressin (Parke Davis Co.) into a rabbit, the bile was collected through a biliary fistula. The antidiuretic activity (ADS-index) of the bile during two hours after the injection of Pitressin was assayed by the method described in a previous report[1]. The antidiuretic activity of the bile collected for two hours was assayed simultaneously as the control in a rabbit receiving no injection of Pitressin.

Results:

The antidiuretic activity of the rabbit bile was markedly increased following an intravenous injection of Pitressin (Table 1, Fig. 1). This suggests that Pitressin is excreted into the bile and therefore the biliary ADS may be derived from vasopressin.

2) Action of the biliary ADS upon blood pressure

Method: Rabbits were anesthetized by an intramuscular injection of urethane

Table 1. Biliary Excretion of Pitressin

No.	Control group			Pitressin group		
	Body weight (Kg)	Volume of Bile (ml)	ADS-index	Body weight (Kg)	Volume of Bile (ml)	ADS-index
1	1.7	20.0	16.2	1.6	20.0	4.7
2	1.85	12.6	2.0	2.0	11.0	1.5
3	1.8	23.0	22.5	2.1	21.0	12.5
4	1.7	14.0	25.4	1.7	14.0	0.8
5	1.8	14.0	2.3	1.8	12.0	0.0
6	2.5	18.5	1.3	2.2	17.0	0.3
7	2.1	20.0	16.2	2.1	20.0	5.6

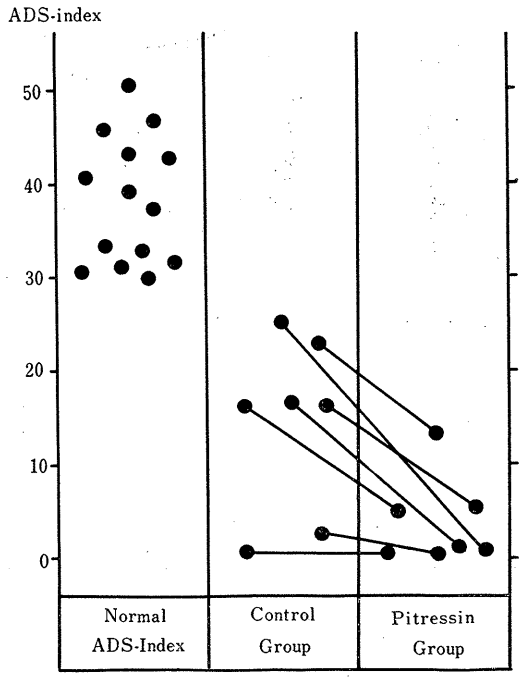

Fig. 1 Biliary Excretion of Pitressin (ADS-index)
The data of the simultaneously undertaken experiments were connected with a line.

(1.0 gm. per Kg. body weight) and cats were anesthetized by ether inhalation, both animals being kept in a continuous deep anesthetic condition by occational intravenous injection of phenobarbital. The blood pressure of the carotic artery was manometrically recorded with a kymograph. Examinations were carried out on the following three specimens: a) *the biliary ADS* which was extracted from 20 ml. of human bile, b) *Pitressin* (200, 500 or 1,000 mU), c) *Extracted Pitressin*; Pitressin was treated with the same procedure as employed for extraction of the biliary ADS. These specimens were diluted with 0.5 ml. of normal saline solution and were in-

jected intravenously in a random order. Each injection was made at the time when the blood pressure had been stabilized.

Results:

In experiments using both cats and rabbits, the "initial" blood pressure (change of blood pressure within one minute after the injection) was generally elevated after an injection of Pitressin. In a few cases, it was depressed momentarily, however. The "main" blood pressure following the initial blood pressure was elevated for more than 10 minutes in all cases (Table 2, Fig. 2).

After an injection of the biliary ADS, the initial blood pressure was either depressed or unchanged, and the main blood pressure also showed the same change in rab-

Table 2 Influence of Pitressin and Biliary ADS upon the Carotic Blood Pressure

Experiment's Animals	No.	Pitressin			Extracted Pitressin			Biliary ADS		
		ADS-index	Initial blood pressure	Mian blood pressure	ADS-index	Initial blood pressure	Main blood pressure	ADS-index	Initial blood pressure	Main blood pressure
Rabbit	1	5.1	Elevated	Elevated	6.6	Semewhat elevated	Unchanged	—	—	—
	2	—	Somewhat lowered	Elevated	—	Unchanged	Unchanged	—	—	—
	3	27.9	Elevated	Elevated	—	—	—	1.6	Down	Down
	4	—	Down	Elevated	—	—	—	—	Down	Down
	5	6.2	Up and Down	Elevated	9.6	Unchanged	Unchanged	22.6	Unchanged	Unchanged
	6	17.7	Down and up	Elevated	—	—	—	4.5	Unchanged	Unchanged
	7	—	Up and Down	Elevated	—	—	—	—	Unchanged	Unchanged
	8	—	Up and Down	Elevated	—	Unchanged	Unchanged	—	Down momentarily	Unchanged
	9	—	Elevated	Elevated	—	Somewhat elevated	Somewhat elevated	—	—	—
Cat	1	5.3	Elevated	Elevated	15.6	Unchanged	Unchanged	5.9	Down	Somewhat elevated
	2	0.5	Elevated	Elevated	8.9	Unchanged	Unchanged	10.5	Down	Unchanged
	3	16.6	Elevated	Elevated	6.1	Unchanged	Unchanged	22.9	Down	Somewhat elevated
	4	9.3	Elevated	Elevated	14.6	Down momentarily	Unchanged	0.0	Down	Unchanged
	5	—	Elevated	Elevated	—	Unchanged	Unchanged	—	Down	Unchanged

bit's experiments. The initial blood pressure was depressed in all cases of cat experiments and the main blood pressure was either unchanged or rather elevated (Table 2).

These results suggest that the biliary ADS is quite different from Pitressin (vasopressin) in the mode of action on blood pressure.

However, it is premature to conclude from these results that the biliary ADS is entirely different from Pitressin, because Pitressin lost its primary effect on the blood pressure without losing the antidiuretic activity after the extraction by the same procedure as employed for the biliary ADS.

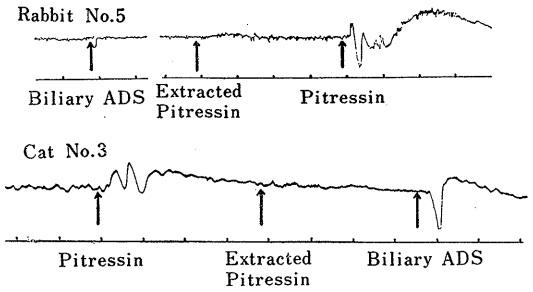

Fig. 2 Influence of ADS upon the Carotic Blood Pressure

3) Action of the biliary ADS upon the mesoappendic test

Method: A rat, weighing about 120 gm. of body weight, was anesthetized with ether inhalation and a subcutaneous injection of urethane. The mesoappendic test was essentially the same as that described by Shorr[2]. The mesenterium of the rat was drawn out and pulled into a chamber containing a normal saline solution (ca. 150 ml.), in which 3 drops of epinephrine (1:500,000) were added every 3 minutes. Then the contraction of the mesoappendic vessels due to epinephrine was observed microscopically.

Results:

In the control experiment a distinct vascular contraction was always noted at each addition of epinephrine, whereas it was supressed by an injection of Pitressin, and also by the biliary ADS (Fig. 3). The more was the injected amount of Pitressin or the higher was the bilirubin concentration of the bile from which the biliary ADS was extracted, the more prolonged was the non-reactive phase. In other words, the biliary ADS as well as Pitressin showed an anti-epinephrinic action as shown by mesoappendic test.

4) Antidiuretic activity and mesoappendic test of the biliary ADS in hypophysectomized rats

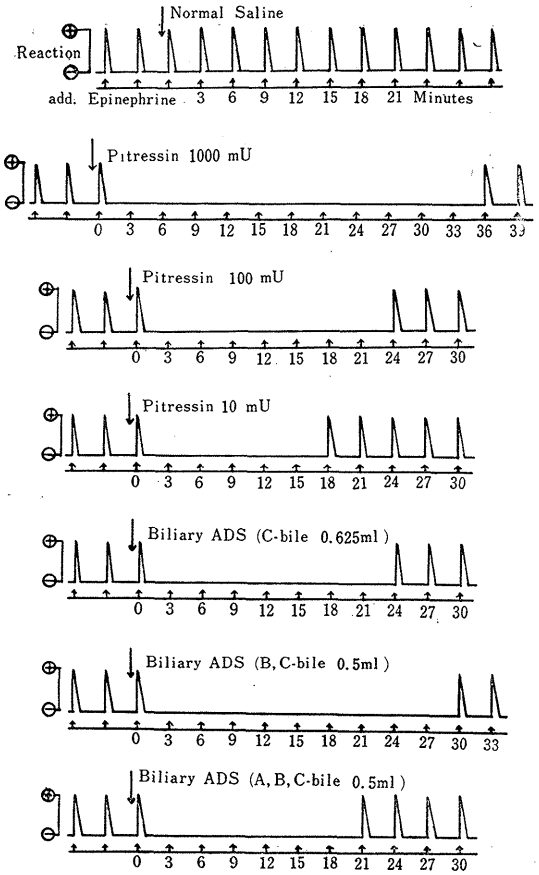

Fig. 3 Mesoappendic Test in Normal Rats

Method: The mesoappendic test for epinephrine (3 cases) and the assay of antidiuretic activity of the biliary ADS (4 cases) were carried out on rats 6 to 10 days after hypophysectomy[3]. The amount of the biliary ADS injected into a group of three rats for the estimation of antidiuretic activity was equivalent to that extracted from 20 ml. of a mixture of human B- and C-bile, and that of Pitressin was 200 mU. The amount of the biliary ADS injected into a rat for the mesoappendic test was equivalent to that extracted from 2.5ml. of human C-bile, and that of Pitressin was 20 mU.

Results:

In hypophysectomized rats, as in normal rats, injection of the biliary ADS showed an antidiuretic activity and also anti-epinephrinic action as measured by mesoappendic test (Fig. 4, 5). Namely, the biliary ADS acted directly on the kidney or mesoappendic vessels. Injection of Pitressin also had an antidiuretic activity in

hypophysectomized rats.

Since ferritin (≒VDM) exerts its antidiuretic action through the pituitary gland[4], it might be reasonable to presume that the biliary ADS is similar to vasopressin rather than to ferritin. But it is unwise to draw any such conclusion, because the difference between the biliary ADS and ferritin is not as yet proved as will be discussed later.

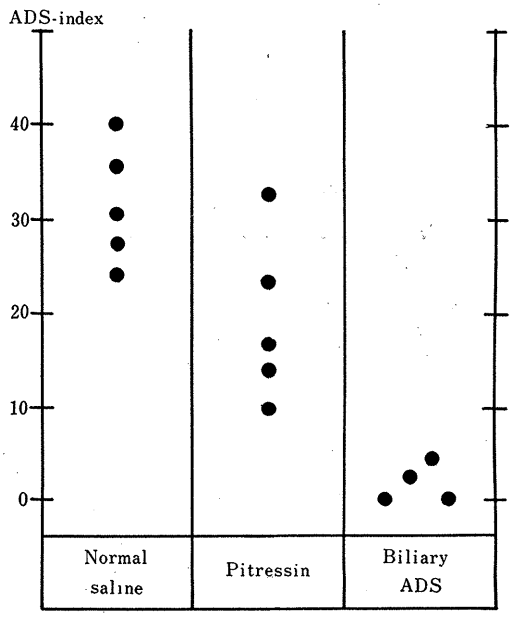

Fig. 4 Antidiuretic Activity of ADS in Hypophysectomized Rats

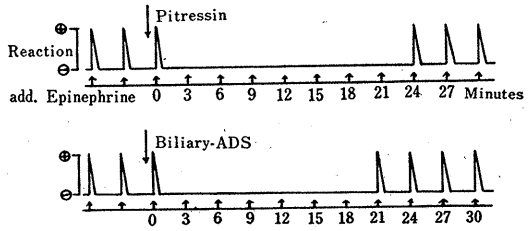

Fig. 5 Mesoappendic Test in Hypophysectomized Rats

5) Influence of the biliary ADS on the urinary excretion of minerals in adrenalectomized rats

Method: Rats were adrenalectomized bilaterally under an intraperitoneal injection of methylhexabital. Immediately after the adrenalectomy 2 ml. of 20 per cent glucose solution and 0.1 mg. of triamcinolone were injected intraperitoneally. During

60 hours following the operation rats were given a pellet diet and normal saline solution ad libitum. From the afternoon of 4th day the rats were kept from the diet and fluid, and in the following morning they were subjected to the experiment.

In these animals the antidiuretic activity of the following three specimens diluted with 0.5 ml. of 5 per cent glucose solutions was examined; a) *the biliary ADS* which was extracted from 5 ml. of human bile, b) *Pitressin* (20 mU), and c) *Extracted Pitressin*; Pitressin (20 mU) was treated with the same procedure as employed for extraction of the biliary ADS.

The urinary concentration of Cl,-Na-and K-ions before and after the injection of the test material was estimated, and the Cl-, Na- and K-index were calculated as follows.

$$\text{Cl-, Na-, or K-index} = \frac{\text{Average urinary concentration of Cl-, Na- or K-ion during 90 minutes after the injection of the test material}}{\text{Average urinary concentration of Cl-, Na, or K-ion during 120 minutes before the injection of the test material}}$$

Results:

In the Pitressin group, the ADS-index was lower than the control, and the Cl-, Na- and K-indices were higher than the control (Table 3). It was thus demonstrated that Pitressin has an antidiuretic activity as well as a concentrating activity for electrolytes in urine in spite of the absence of the adrenal glands.

Table 3 Mineral-index of Urine in Bilaterally Adrenalectomized Rats

	ADS-index	Cl-index	Na-index	K-index
Control	32.0	0.55	0.48	0.70
	26.8	1.70	0.58	0.63
	60.0	2.69	0.36	0.74
	62.7	0.66	0.68	0.62
	32.2	0.75	0.74	0.43
	36.4	0.58	1.25	0.80
	37.8	0.50	0.20	0.46
Pitressin	9.3	6.75	1.67	2.63
	21.3	0.53	0.89	2.12
	11.0	0.60	7.35	2.27
	10.6	3.90	4.88	2.30
	0.6	2.00	0.41	2.89
	4.3	1.15	6.86	—
Extracted Pitressin	12.9	0.29	0.32	0.64
	31.2	2.06	1.37	0.97
	17.6	0.66	0.63	0.67
	31.7	1.10	0.74	1.75
	22.9	0.68	0.37	0.77
Biliary ADS	22.1	0.52	0.23	0.93
	7.0	0.75	0.56	1.40
	4.0	0.65	0.94	0.74
	7.6	0.78	1.54	0.93
	6.7	0.80	0.93	1.03

In the biliary ADS group, the ADS-index was lower than the control, but the mineral indices were the same as that of the control (Table 3). In other words, a distinct difference was noted in the urinary excretion of minerals between the biliary ADS and Pitressin.

However, it can not be concluded from these results that the biliary ADS is entirely different from Pitressin (vasopressin), because Pitressin lost the activity to concentrate urinary electrolytes without losing the antidiuretic activity when processed by the same procedure as employed for extraction of biliary ADS (Table 3).

6) Clinical experiment

Method: Potencies of both biliary and urinary ADS were estimated in a case of diabetes insipidus, whose urine output was about 8 liters a day. The biliary ADS was extracted from 15 ml. of C-bile of the patient, and the urinary ADS from 200 ml. of the urine before and after a treatment with Posterin-Rhino-Cream which contains vasopressin. The extracted antidiuretic substances were assayed in 3 rats according to the method by Taylor-Walker[5].

Results:

Potency of the biliary ADS of this case of diabetes insipidus was within normal

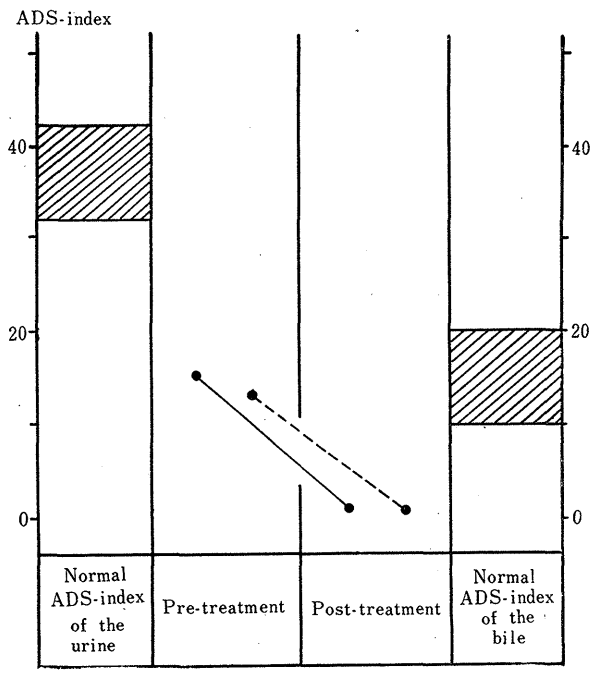

Fig. 6 Antidiuretic Activities of the Bile and Urine of a Case of Diabetes insipidus

Solid line: Urinary ADS-index, Broken line: Biliary ADS-index

limits (Fig. 6). Should the biliary ADS be derived from vasopressin, it would be expected that the antidiuretic potency of the bile in diabetes insipidus is low, because the excretion of vasopressin is imparied in this disease. Because of the limited number of our case, no conclusion could be made. Furthermore, the urine of this patient had an antidiuretic activity.

The potencies of both biliary and urinary ADS increased after a treatment with vasopressin (Fig. 6). The results corroborate clinically that vasopressin may be excreted into the bile.

7) Stability of the biliary ADS– comparison of the chemical properties between the biliary ADS and Pitressin

Methods:

(i) Stability of the biliary ADS in an acid medium: The biliary ADS extracted from about 80 ml. of human bile, or 400 mU of Pitressin was made up to 5 ml. with water. Each solution was divided into two equal portions; one portion was brought to pH 3 with 2N HCI and, after keeping at room temperature, it was neutralized with 2N NaOH for intraperitoneal injection (0.5 ml. per rat) to estimate the ADS-index; the other portion was used for the control.

(ii) Stability of the biliary ADS in an alkaline medium: Preparation of the biliary ADS and Pitressin was the same as above. One of the samples was kept at room temperature after bringing the pH to 13 with 2N NaOH, and another sample was heated in boiled water for 20 minutes at pH 8. These samples were then neutralized with 2N HCI for intraperitoneal injection. Control samples for each assay were prepared also.

Results:

(i) Stability of the biliary ADS in an acid medium:

Both potencies of the biliary ADS and Pitressin were stable after heating for 10 minutes in an acid medium (Table 4, 5). Potency of the biliary ADS was decreased into some extent by 20 minutes' heating, whereas that of Pitressin was preserved

Table 4 Stability of Pitressin in Acid Medium (pH 3)

Treatmet	No.	Pre-Treatment ADS-index	Post-Treatment ADS-index
Room-Temperature for 2 hours	1	19.0	13.3
	2	10.3	6.2
	3	16.2	11.0
Boiling for 10 minutes	1	19.0	18.8
	2	10.3	16.4
	3	16.2	18.6
Boiling for 20 minutes	1	1.0	3.7
	2	1.4	3.4
	3	1.9	1.9

Table 5 Stability of the Biliary ADS in Acid Medium (pH 3)

Treatment	No.	Pre-Treatment ADS-index	Post-Treatment ADS-index
Room-Temperature for 2 houre	1	1.0	1.4
	2	5.5	5.2
	3	6.9	8.1
Boiling for 10 minutes	1	1.0	0.8
	2	5.5	1.2
	3	6.9	11.9
Boiling for 20 minutes	1	1.0	6.8
	2	5.5	13.2
	3	6.9	23.1

(Table 4, 5). However, this does not indicate a complete inactivation, because their ADS-indices were not as low as the normal ADS-index (38.0 ± 6.8) which was obtained by an intraperitoneal injection of a normal saline.

(ii) Stability of the biliary ADS in an alkaline medium:

The biliary ADS, as well as Pitressin, was inactivated both by keeping at room temperature for 2 hours and by heating for 20 minutes (Table 6, 7). These results suggest that the biliary ADS has chemical properties very similar to those of Pitressin.

Table 6 Stability of Pitressin in Alkaline Medium

Treatment	No.	Pre-Treatment ADS-index	Post-Treatment ADS-index
Room-Temperature for 2 hours (pH 13)	1	11.5	28.9
	2	18.3	30.8
	3	11.4	21.4
Boiling for 10 minutes (pH 8)	1	1.8	27.5
	2	6.1	20.0
	3	0.3	25.6
	4	0.7	16.8
	5	4.8	19.7

Table 7 Stability of the Biliary ADS in Alkaline Medium

Treatment	No.	Pre-Treatment ADS-index	Post-Treatment ADS-index
Room-Temperature for 2 hours (pH 13)	1	23.3	26.6
	2	7.9	16.5
	3	0.6	9.0
Boiling for 20 minutes (pH 8)	1	31.9	42.1
	2	0.0	21.1
	3	1.6	10.7
	4	5.8	16.4
	5	14.3	21.1

(II) Consideration of the possibility of the biliary ADS being of hepatic origin

In a previous report[6], it has been shown with isolated rabbit livers that the anti-

diuretic activity of a perfusate is more potent after two hours' perfusion, and that the antidiuretic activity of the perfusate containing Pitressin was inactivated during the first hour of perfusion and the activity was increased during the second hour (Fig. 7). Since inference has been made that this phenomenon resulted from an antidiuretic substance newly produced from the liver tissue, further studies on this "hepatic ADS" are carried out.

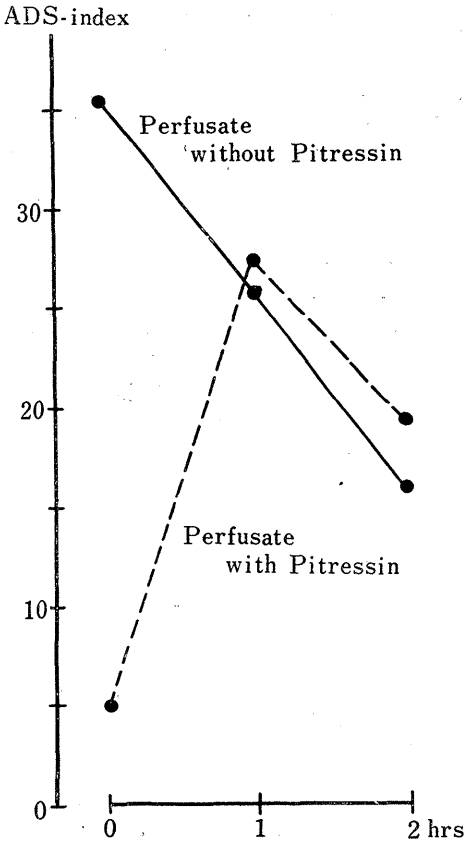

Fig. 7 Perfusion of Normal Rabbits Liver

1) Re-examination of the hepatic ADS—examination with perfusion of an isolated rabbit liver whose function has been accelerated

Methods:

(i) Method to obtain a functionally accelerated liver by an injection of sodium hippurate: It has been observed in our laboratory that following an injection of sodium hippurate two hour excretion of phenolsufonphthalein (PSP) which was

loaded intravenously is increased 2–2.5 times the control[7]. Therefore, 5.0 ml. of 3% sodium hippurate was injected intravenously to a rabbit 30 minutes before the isolation of the liver, and the same dose of sodium hippurate was also added to the perfusing solution.

(ii) Method to obtain a functionally accelerated liver by bilateral nephrectomy: It has been observed in rabbits that the biliary excretion of PSP is increased twice the control if the animal was kept in an anuric state for 24 hours after bilateral nephrectomy[7]. Therefore, the livers of rabbits maintained for 24 hours following bilateral nephrectomy served as the source of functionally accelerated livers for perfusion experiments.

(iii) Perfusion experiment: According to the technique described in a previous paper[6], a perfusion experiment was undertaken on livers whose function was accelerated.

Results:

With the liver of a rabbit which had been treated with sodium hippurate, the ADS-index of the perfusate in which Pitressin had been added was increased with the lapse of perfusion time, in contrast to the perfusate obtained with a normal liver in which the ADS-index was first increased and then reduced (Fig. 8).

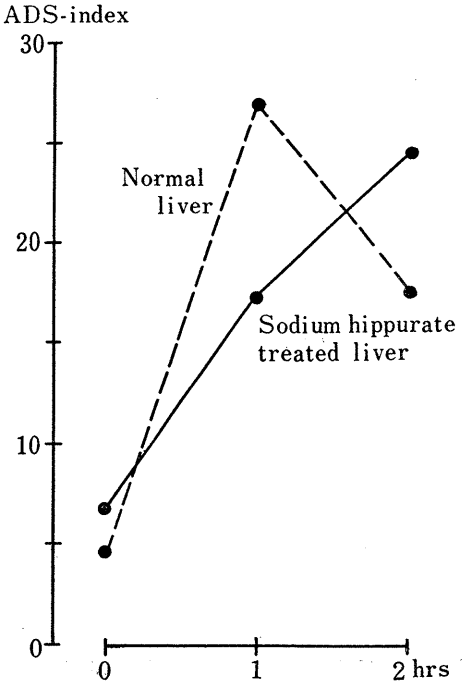

Fig. 8 Perfusion Experiment on the Liver treated with Sodium hippurate (Perfusion with Pitressin)

When studied with livers of rabbits in whom bilateral nephrectomy was performed, the ADS-index of the perfusate without Pitressin was unchanged throughout the experiment, whereas it was decreased with the lapse of perfusion time with normal livers (Fig. 9).

The ADS-index of the perfusate to which Pitressin had been added was increased both during the first and the second hour of perfusion (Fig. 9), whereas it was first increased and then reduced to the normal level in the experiments with normal liver (Fig. 8).

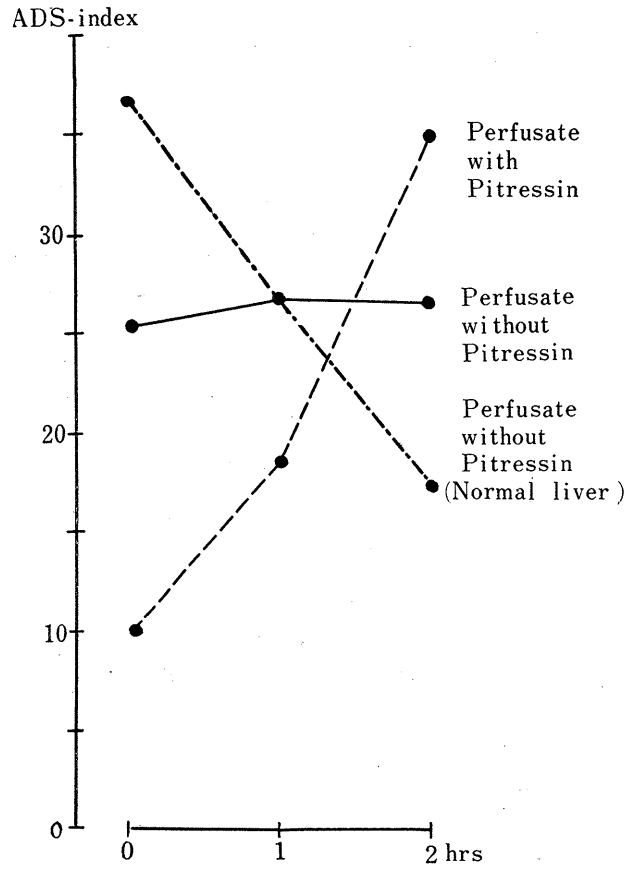

Fig. 9 Perfusion Experiment on the Liver following Bilateral Nephrectomy

These results confirm our hypothesis that a newly produced hepatic antidiuretic substance does not appear in the perfusate of functionally accelerated livers upon prolonged perfusion. This further suggests that the antidiuretic substance in the perfusate may have some relation to exhaustion of liver function. Therefore, it

may be plausible also to presume that an antidiuretic substance is produced from an impaired liver in a form of "hepatic ADS".

(2) Relationship between the hepatic ADS and ferritin

Methods:

(i) Before and after two hour perfusion of the liver, a small lobule of the liver was excised. Fibrous tissue and blood were removed. Two grams of the tissue was then homogenized with 20 ml. of distilled water containing no Fe ion and heated for 8 minutes at 80°C. The homogenate was immediately cooled and centrifuged. The supernant was filtered. The filtrate was boiled for 30 minutes at 100 C°. After immediate cooling, it was centrifused and the precipitate was made up to 1.5 ml. with a normal saline solution. This solution was subjected to an assay for antidiuretic activity.

(ii) The same precipitate was subjected to an assay for ferritin by the technique used by Yoneyama-Konno[8]. Three milliliters of 10% trichloroacetic acid and 3 ml. of 4% pyrophosphate were added to the precipitate. The solution was heated for 5 to 7 minutes at 100°C, cooled immediately and filtered. Two milliliters of this filtrate was neutralized with 35% KOH with phenolphthalein as indicator, to this were added 10 ml. of acetate buffer of pH 4.6, 0.2 gm. of hydroquinone and them 5 drops of 0.2% α, α'-dipyridyl for color development. The amount of ferritin was estimated colorimetrically.

(iii) Procedure for perfusion experiment was the same as above.

Results:

The production of the new antidiuretic substance in the perfusate was accompanied by an increase of the antidiuretic substance as well as of ferritin in the liver tissue (Fig. 10, Table 8).

It has been generally thought that ferritin is identical with the vasodepressor material (VDM) which may inhibit diuresis by enhancing excretion of vasopressin from the pituitary gland[4], and that ferritin is usually increased in the serum of hepatic disease[9]. Since ferritin was also demonstrated qualitatively in the bile, it may be that the biliary ADS is identical with or closely related to ferritin. However, no conclusion should be made, since the results of the experiments in hypophysectomized rats were contradictory.

(3) The biliary ADS in hepatic diseases

Method: The biliary ADS which was extracted from 10 ml. of C-bile of cases of acute hepatitis and liver cirrhosis was injected into a group of three rats and its antidiuretic potency was assayed. Antidiuretic potency of 100 ml. of the urine of

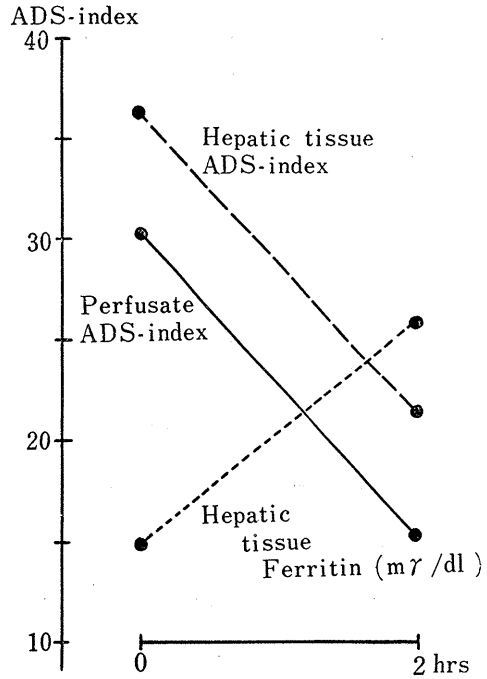

Fig. 10 Relationship between Ferritin and Antidiuretic Activity of the Perfused Liver Tissue

Table 8 Relationship between Ferritin and Antidiuretic Activity of the Perfused Liver Tissue

No.	Pre-Perfusion			Post-Perfusion		
	ADS-index of Liver tissue	Ferritin of Liver tissue (mγ/g)	ADS-index of Perfusate	ADS-index of Liver tissue	Ferritin of Liver tissue (mγ/g)	ADS-index of Perfusate
1	27.6	18	32.5	21.0	38	16.6
2	33.8	31	28.8	26.8	59	18.3
3	39.3	8	29.1	19.2	21	12.5
4	31.9	11	29.3	21.5	14	11.6
5	33.2	25	27.5	18.4	35	12.8
6	40.2	8	28.9	28.0	12	22.1
7	38.1	4	38.6	14.1	12	14.3
Average	36.3	15	30.7	21.3	27	15.5

the same patient was also assayed according to the technique by Taylor-Walker[4].

Results:

The antidiuretic activity of the bile was more potent in patients with liver diseases than in normals, and that of acute hepatitis returned to the normal range with the recovery from the acute phase (Fig. 11).

Urinary antidiuretic activity of patients with liver diseases was equal to or stronger

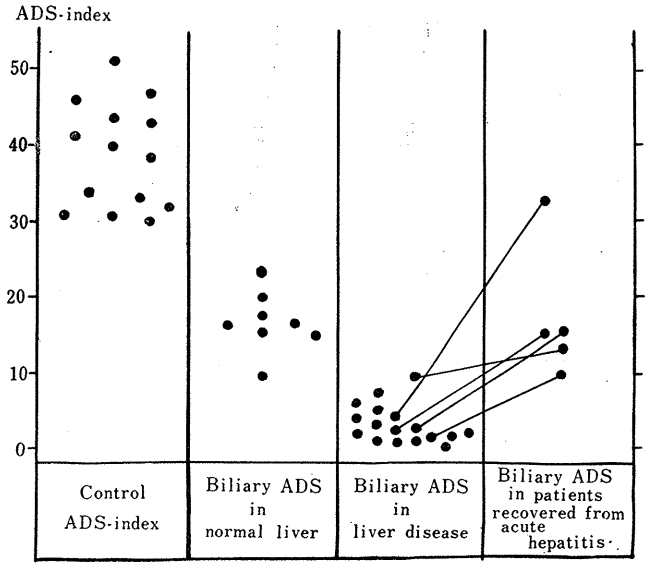

Fig. 11 Antidiuretic Activity of the Bile in Liver Diseases

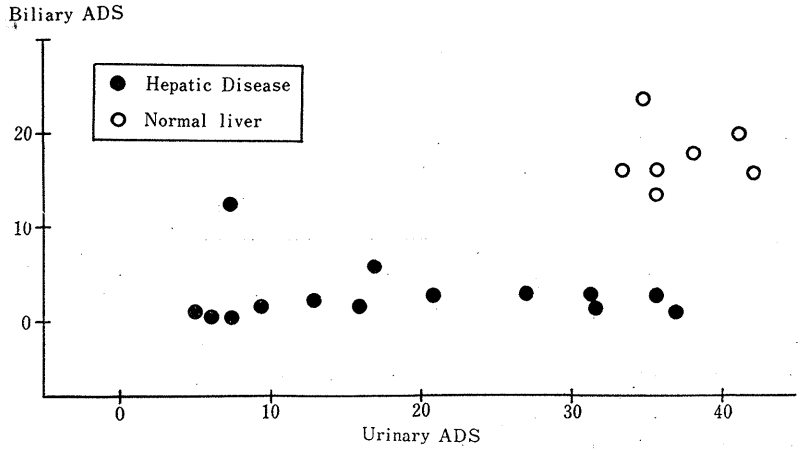

Fig. 12 Correlation between Biliary ADS and Urinary ADS

than that of the normal subjects. However, no correlation was demonstrated between the potency of the biliary ADS and that of the urinary ADS (Fig. 12).

If the biliary ADS was derived from the blood, it might be expected that an antidiuretic substance of the bile is increased in patients with hepatic diseases, because destruction of an antidiuretic substance in blood is decreased in an impaired liver. However, the liver and the pituitary gland must be regarded as the site of production of the antidiuretic substance in blood.

SUMMARY

(I) Relationship between the biliary ADS and vasopressin

1) Intravenously injected Pitressin (vasopressin) was excreted into the bile, suggesting that the biliary ADS may be derived from vasopressin,

2) In contrast to Pitressin, the biliary ADS caused neither elevation of blood pressure in normal cats and rabbits nor increase in urinary concentration of Na, Cl and K ions in bilaterally adrenalectomized rats. However, this does not necessarily mean that the biliary ADS is entirely different from Pitressin, since Pitressin loses these activities without losing the antidiuretic activity, when subjected to the same procedure employed for extraction of the biliary ADS.

3) The biliary ADS as well as Pitressin showed an anti-epinephrinic action when tested by mesoappendic test.

4) Potency of the biliary ADS in a case of diabetes insipidus ranged within normal limits. If the biliary ADS were derived from vasopressin, the antidiuretic potency of the bile of such a patient should be expected to be diminished, because the etiology of this disease involves a lack of vasopressin excretion. The results proved to be otherwise. Nevertheless, this does not necessarily indicate that biliary ADS is not derived from vasopressin, because of the limited observation. Furthermore, the urine of the patient had an antidiuretic activity.

The potencies of both biliary and urinary ADS were increased in this case after a treatment with vasopressin.

5) The biliary ADS as well as Pitressin was found to be considerably resistant to heating in an acid medium (pH 3), but they were readily inactivated by incubation for 2 hours at room temperature in an alkaline medium (pH 13).

6) In hypophysectomized rats, as in normal rats, an injection of the biliary ADS showed an antidiuretic and anti-epinephrinic action as tested by mesoappendic test. Thus, the biliary ADS acts directly on the kidney or mesoappendic vessels.

Because of the fact that ferritin exerts its antidiuretic action through the pituitary gland, it might be reasonable to assume that the biliary ADS is similar to vasopressin rather than to ferritin. However, this is far from a conclusion, because unidentity of the biliary ADS with ferritin is as yet established.

(II) Studies on the origin of the biliary ADS

7) When the perfusion experiments were carried out with rabbit livers whose function was accelerated by an injection of sodium hippurate, a hepatotonica, or by maintaining the animal under an anuric condition for 24 hours by bilateral nephrectomy, no new antidiuretic substance was appeared in the perfusate upon prolonged perfusion. The production of the new antidiuretic substance in the perfusate was

accompanied by an increase of the antidiuretic substance and ferritin in the liver tissue. These facts suggest that the antidiuretic substance in the perfusate may have some relation to hepatic exhaustion.

8) The antidiuretic activity of the bile was more potent in patients with liver diseases than in normals. The activity in cases of acute hepatitis returned to the normal range with the recovery from the acute phase. Urinary antidiuretic activity of patients with liver diseases was equal to or greater than that of the normal subjects. However, no correlation was obtained between the potency of the biliary ADS and that of the urinary ADS.

CONCLUSION

No definite conclusion can be drawn from the results of these experiments as to the origin of the antidiuretic substance in the bile. However, it is very likely that the liver as well as the pituitary gland is the site of production of the biliary ADS.

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