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Changes in plasma levels of vasopressin and renin in response to haemorrhage in dogs

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Summary

1. The rabbit rectum superfused with blood or Krebs solution was used to assay vasopressin in circulating blood and in plasma extracts respectively.

2. Vasopressin was released by a rapid fall in diastolic pressure of as little as 5 mmHg, and the amount of vasopressin released was proportional to the magnitude of the fall in diastolic pressure in the range studied. These results would indicate that vasopressin release follows the magnitude of the fall in diastolic pressure more closely than the actual decrease in blood volume in haemorrhagic hypotension.

3. It was shown that the time required to induce an increase in circulating vasopressin is inversely proportional to the severity of the fall in diastolic pressure ; this suggested that the stimulation of neurosecretory reflex arc varies with the intensity of the stimulus.

4. The slight changes in plasma renin activity as well as the pattern of renin release suggested the unlikeliness of the influence of renin upon vasopressin secretion under these circumstances. On the contrary, the results suggested that the secretion of large amounts of vasopressin tended to inhibit renin release.

Introduction

Numerous studies have shown that large amounts of vasopressin are released following haemorrhage in the dog, cat and rat (Ginsburg & Brown, 1957 ; Weinstein, Berne & Sachs, 1960 ; Beleslin, Bisset, Haldar & Polak, 1967 ; Rocha e Silva & Rosenberg, 1969 ; Murase & Yoshida, 1971). Increases in peripheral plasma renin activity following haemorrhage have also been reported (Huidobro & Braun-Menendez, 1942 ; Dexter, Frank, Haynes & Altschule, 1943 ; Brown, Davies, Lever, Roberston & Verniory, 1966 ; Johnson, Davis, Baumber & Schneider, 1971).

Recent reports indicate that the renin-angiotensin system plays a role in the regulation of antidiuretic hormone secretion (Malvin, 1971), which may be mediated by a central action of angiotensin (Mouw, Bonjour, Malvin & Vander, 1971). On the other hand, Tagawa, Vander, Bonjour & Malvin (1971) have observed an inhibition of renin secretion by vasopressin in unanaesthetized sodium-deprived dogs. The present work was designed to study the time-courses for vasopressin and renin release and their possible interrelations during acute haemorrhage.

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Methods

Experiments in Krebs solution

As shown by Gilmore & Vane (1970) the rabbit isolated rectum superfused with Krebs solution is suitable for the bio-assay of vasopressin. Rabbits of either sex weighing between 1·5 to 2·5 kg were killed by a stunning blow and bled through the carotid arteries. The terminal portion of the intestine was excised and placed in cool Krebs solution; adherent fascia was trimmed away and the lumen washed carefully. The rectum was then mounted in an organ bath as follows: the oral end of the tissue was occluded and the aboral end tied onto a large polyethylene tube (PE 320) inserted through a side-arm of the organ bath. This tube held the tissue in the proper position. A small piece of tube (PE 50) was then inserted, via the larger tube, into the lumen of the tissue. This system allowed the fluid for intraluminal infusion to enter via the small piece of tube and exit via the large tube without contaminating the superfusing fluid. As soon as it was mounted, the tissue was immediately superfused (Gaddum, 1953) with Krebs solution at 37° C, at a constant rate of 10 ml/minute. The solution was gassed continuously with 95% oxygen and 5% carbon dioxide and its composition was as follows (g/litre): NaCl, 6·9; KCl, 0·35; $CaCl_2$, 0·28; KH_2PO_4, 0·16; $MgSO_4.7H_2O$, 0·29; dextrose, 2; $NaHCO_3$, 2·1.

In some experiments, a chick rectum and a rat colon were also used in parallel assay for their relative specificity to oxytocin and angiotensin respectively. The lumens of the assay organs were routinely perfused (0·1 ml/min) with alprenolol (75 μg/ml), a β-adrenoceptor blocking agent, in order to prevent the inhibitory effects of catecholamines. Lidocaine (50 μg/ml) which was shown to diminish the spontaneous activity and increase the basal tone was used in the perfusion medium to stabilize the base line (Gilmore & Vane, 1970). Tissues were connected to Harvard Heart and Smooth Muscle Transducers model No. 356, counterweighted with 2–3 g, and the movements were recorded on an electronic recording system.

Blood-bathed organ technique

The technique of Gilmore & Vane (1970) was employed to assay directly and continuously the levels of vasopressin in circulating blood. In these experiments, female dogs weighing from 8 to 15 kg were given morphine (1 mg/kg s.c.) followed 20–30 min later by chloralose (50 mg/kg i.v.) and urethane (600 mg/kg i.v.). The trachea was cannulated and the animal ventilated with a Harvard respiratory pump. Polyethylene cannulae were tied into a femoral artery and the contralateral femoral vein for the removal and the replacement of blood. The other femoral artery was also cannulated to record the blood pressure by means of a Harvard recording system connected to a pressure transducer (Harvard No. 375). Following completion of surgical procedures, heparin (1,000 IU/kg) and dextran (M.W. 110,000, 6% in 0·9% w/v NaCl solution, 10 ml/kg) were injected intravenously.

The superfusing Krebs medium was replaced by blood (10 ml/min) withdrawn by way of the femoral arterial cannula. After the blood had superfused the isolated organs, it was collected in a reservoir and returned to the animal through the femoral vein. In these experiments, the animals were usually submitted to three short haemorrhages which were separated into groups A, B and C according to a predetermined fall in diastolic pressure (diastolic ΔP), as described by Rocha e Silva & Rosenberg (1969). The blood was collected in siliconized and heparinized

glass bottles and was returned to the animal as soon as a maximal relaxation of the assay organ was obtained. Under these conditions, the average volumes of blood withdrawn were 56·6 ml, 101 ml and 150 ml for haemorrhages of group A, B and C respectively.

The time-course of vasopressin release was determined by the time interval (seconds) between the beginning of the haemorrhage and the first evidence of a relaxation of the assay organs. This was corrected by the time required for the blood to travel through the cannula between the femoral artery and the assay organs.

Assay of vasopressin and renin activity in plasma extracts

In this series of experiments, the animals were prepared as described above, except that they were anaesthetized with sodium pentobarbitone (25–30 mg/kg i.v.). Both femoral arteries were cannulated, one for the recording of blood pressure and the other for the removal of blood. A femoral vein was also cannulated for the administration of dextran and heparin and to return the blood to the animal. These animals were subjected to only one haemorrhage (15 ml/kg). For this purpose, the blood was withdrawn rapidly into a siliconized and heparinized glass bottle until the calculated volume (15 ml/kg) was obtained. Samples of blood (15 ml) were collected before and 2, 10, 20 and 30 min after haemorrhage in cold (4° C) siliconized polycarbonate tubes. The blood was then returned to the animal, and another sample collected 30 min later. Blood withdrawn for assay was always replaced by an equal volume of dextran.

Vasopressin was extracted according to the method of Bisset, Hilton & Poisner (1967). The method was slightly modified as follows: evaporations were performed with a Buchler Evapo-Mix at 50° C, and all centrifugations were carried out at 3,000 *g* and at 4° C. The extracts were assayed as described above. Vasopressin standards, and extracts were infused along with the superfusing fluid. Recovery studies were performed by adding known amounts of vasopressin to dog plasma which had been allowed to stand at room temperature for 24 hours. In these conditions, 85 to 90% of the added vasopressin was recovered.

Plasma renin activity was determined according to the method of Gagnon, Sirois, Gysling & Regoli (1972). In brief, plasma samples were adjusted to pH 5·5 with 0·5 N HCl. Diisopropylfluorophosphate (DFP, 1×10^{-5} moles in isopropyl alcohol) was added to the plasma which was then incubated (with shaking) for 3 h at 37° C. Following incubation, 2 volumes of absolute ethanol were added and the mixture centrifuged at 12,000 *g*. The supernatant was decanted and evaporated. The residue was dissolved in 2 ml of distilled water and assayed on the rat isolated colon superfused with Krebs solution. The specificity of the assay organ to angiotensin was assured by the use of a mixture of inhibitors in the superfusion fluid (Gagnon & Sirois, 1972), and a specific inhibitor of angiotensin II (Gagnon, Park & Regoli, 1971) was used as a further and absolute index of specificity.

All substances were freshly prepared in Krebs solution ; ascorbic acid was added to all solutions of catecholamines. The concentration of drugs refers to their final concentration in the superfusing fluid, and where applicable, concentrations of salts are expressed in terms of free base. The following drugs were used: morphine sulphate (Glaxo–Allenburys) ; alprenolol hydrochloride and lidocaine hydrochloride (Astra) ; (−)-adrenaline bitartrate, atropine sulphate, diisopropylfluorophosphate

(DFP) (Sigma Chemicals); vasopressin (Pitressin), oxytocin (Pitocin) (Parke-Davis); chloralose (Baker Chemical Co.); urethane (Matheson, Coleman & Bell); pentobarbitone sodium (May & Baker); dextran (Pharmacia); heparin sodium (Riker); oxprenolol and angiotensin amide (Ciba); methysergide bimaleate (Sandoz); polyphloretin phosphate (PPP) (AB LEO); 8-L-ala-angiotensin II (synthesized by Dr. W. K. Park in our department).

Results are given as mean ± S.E., and significance of differences has been calculated with the *t* test for paired data.

Results

Tissues superfused with Krebs solution

In the first series of experiments the relative sensitivity of the assay organs to vasopressin and oxytocin was measured. Figure 1 shows that vasopressin (4, 8, 16, 32, 65, 125 μU/ml) induces a dose-dependent relaxation of the rabbit rectum. No response was observed at doses lower than 4 μU/ml; doses of 125 μU/ml induced a maximal response. On some occasions, the preparation did not remain relaxed when larger doses of vasopressin (250 to 500 μU/ml) were infused.

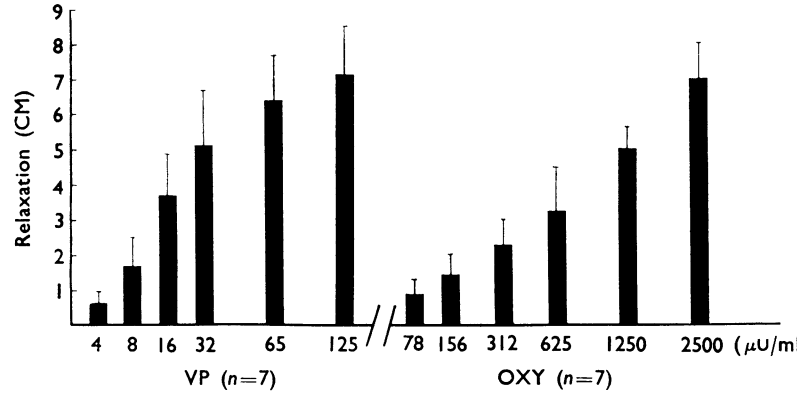

FIG. 1. Dose-dependent relaxations induced by increasing doses of vasopressin (VP) and oxytocin (OXY) in the rabbit rectum superfused with Krebs solution. The tissues were treated intraluminally with alprenolol and lidocaine. *n*=Number of observations.

Figure 1 also shows that the rabbit rectum is relaxed by oxytocin, but it is also evident that the tissue is appreciably less sensitive to oxytocin than to vasopressin. The threshold dose for oxytocin was about 78 μU/ml, i.e. about 20 times higher than that observed for vasopressin. Oxytocin (156, 312, 625, 1,250 and 2,500 μU/ml) induced a dose-dependent relaxation but vasopressin was always 20 to 40 times as active in this respect.

Tissues superfused with blood

In some of these experiments, two rabbit recta and a chick rectum were used. The latter, according to Gaddum (1959), contracts in the presence of concentrations of oxytocin that barely relax the rabbit rectum.

In these experiments, 17 dogs were submitted to haemorrhage. Superfused blood invariably contracted the assay organs; 30–60 min thereafter these stabilized

TABLE 1. *Increases in the level of circulating vasopressin (VP) in response to haemorrhage in dogs*

Experiment No.	Group A			Group B			Group C		
	Diastolic* ΔP (mmHg)	Increase circulating VP (μU/ml)	Time-course of VP release (seconds)	Diastolic* ΔP (mmHg)	Increase circulating VP (μU/ml)	Time-course of VP release (seconds)	Diastolic* ΔP (mmHg)	Increase circulating VP (μU/ml)	Time-course of VP release (seconds)
1–A	5·3	34·0	44·0	11·7	71·3	33·0	21·7	136·7	22·6
2–A	5·3	28·0	51·0	13·4	34·0	44·0	26·0	82·0	28·0
3–A	5·0	44·0	57·3	12·4	170·0	38·6	22·0	184·0	25·3
4–A	4·7	26·0	65·3	9·3	70·4	49·3	18·3	112·7	44·0
5–A	4·8	68·0	76·0	10·2	105·0	60·0	18·8	170·0	32·0
6–A	5·4	51·0	80·0	16·7	68·3	68·0	22·7	90·0	37·0
7–A	4·7	14·2	68·0	7·6	68·0	57·3	26·0	102·5	36·0
8–A	5·0	59·0	57·3	16·3	103·5	28·0	22·0	193·3	20·0
9–A	7·6	74·5	52·0	12·7	142·7	33·3	21·7	187·0	22·6
10–A	5·4	25·8	49·3	10·0	59·5	28·0	18·3	117·3	14·6
11–A	4·7	18·5	48·0	10·6	22·0	24·0	20·4	90·0	8·0
12–A	5·3	30·5	44·0	14·2	33·5	36·0	20·6	85·0	28·0
13–A	5·6	23·3	52·0	8·3	30·0	36·0	23·2	175·0	28·0
14–A	8·5	16·5	44·0	14·3	34·0	36·0	26·7	190·0	20·0
15–A	3·3	34·5	60·0	10·0	81·0	36·0	24·3	149·0	20·0
16–A	5·0	19·2	21·3	9·4	62·0	12·0	22·6	82·0	10·6
17–A	4·3	34·3	52·0	13·8	78·3	40·0	22·4	198·3	41·0
Mean	5·3	35·3	54·2	11·8	72·6	38·8	22·2	137·9	25·7

* Maximal fall in diastolic pressure during haemorrhage.

at a new baseline. When infused into the superfusing blood, vasopressin still induced a dose-dependent relaxation of the rabbit rectum; the sensitivity of the tissue was comparable to that in tissues superfused with Krebs solution. In all experiments, the dose-response curve (16 to 250 μU/ml) to vasopressin was always repeated after the third haemorrhage. The response induced by the dose of 250 μU/ml was, in all cases, greater than the largest response induced during haemorrhagic periods, showing that the relaxations produced by circulating vasopressin were sub-maximal. Adrenaline was always infused at a dose of 1 μg/ml to insure that the isolated organs would not respond to any increase in circulating catecholamines.

The effect of haemorrhage on vasopressin release is shown in Table 1. Haemorrhage of group A (mean ΔP diastolic=$5{\cdot}28 \pm 0{\cdot}29$ mmHg), induced increases in circulating vasopressin ranging from 14 to 74 μU/ml (mean, $35{\cdot}34 \pm 4{\cdot}27$ μU/ml). Following the replacement of blood, the level of circulating vasopressin rapidly declined to control values, as shown by the return of the assay tissues to their control baseline. In this group of dogs that had undergone haemorrhage, the time-course of vasopressin release ranged from 21 to 80 seconds (mean, $54{\cdot}21 \pm 3{\cdot}2$ seconds). Although we did not attempt to establish exactly the basal level of vasopressin in the bathing blood, the dose-response curve showed that the minimal effective dose (which should reflect the basal level) ranged between 16 and 32·5 μU/ml.

Following a period of about 30 min, the animals were again submitted to haemorrhage (group B: mean ΔP diastolic=$11{\cdot}8 \pm 0{\cdot}63$ mmHg), and increases in circulating vasopressin ranging from 34 to 170 μU/ml (mean, $72{\cdot}55 \pm 9{\cdot}43$ μU/ml) were observed. The mean increase in circulating vasopressin following group B haemorrhages was significantly greater ($P<0{\cdot}01$) than that observed after group A haemorrhages. The time-course of vasopressin release in group B had a mean value of $38{\cdot}82 \pm 3{\cdot}2$ s, and was significantly shorter ($P<0{\cdot}01$) than the interval observed after group A haemorrhages. Again the level of circulating vasopressin declined rapidly towards control values when blood was returned to the animals. As seen in Table 1, the third haemorrhagic period (group C: mean ΔP diastolic= $22{\cdot}21 \pm 0{\cdot}59$ mmHg) produced increases in circulating vasopressin ranging from 82 to 198 μU/ml (mean, $137{\cdot}92 \pm 10{\cdot}59$ μU/ml). The mean increase in vasopressin level was significantly greater ($P<0{\cdot}001$) than that observed after group B haemorrhages. In group C haemorrhages, the time-course of vasopressin release had a mean value of $25{\cdot}76 \pm 2{\cdot}37$ s which is significantly shorter ($P<0{\cdot}01$) than the one observed in group B haemorrhages.

In some experiments, an attempt was made to detect concomitant changes in plasma renin activity in order to determine if renin release follows vasopressin release. No change in circulating angiotensin was detected. In four other experiments, the intra-carotid infusion of sub-pressor doses of angiotensin failed to produce detectable changes in circulating vasopressin.

Figure 2 illustrates a typical experiment in which a rabbit and chick rectum were superfused with blood from dogs. Following haemorrhage, the rabbit rectum relaxed while the chick rectum did not respond, thereby indicating that oxytocin was not responsible for relaxation of the rabbit rectum; otherwise a simultaneous contraction of chick rectum would have been observed.

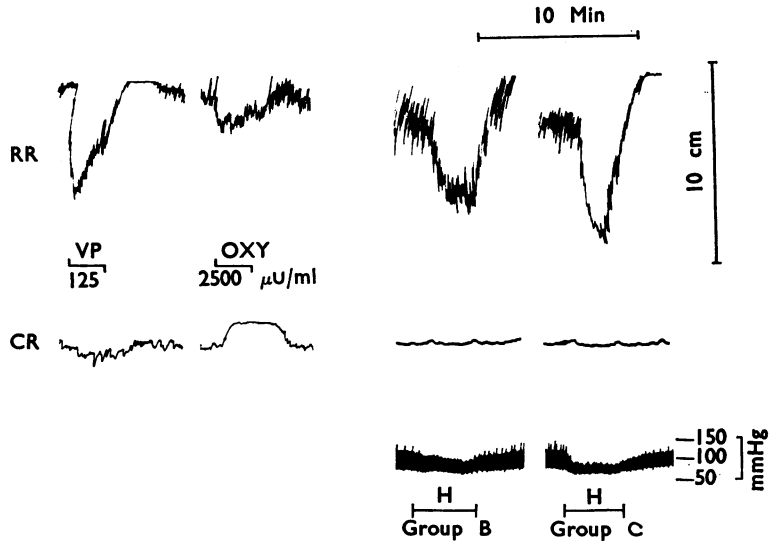

FIG. 2. The left side of the figure shows the effect of exogenous vasopressin (VP) and oxytocin (OXY) upon the rabbit rectum (RR) and the chick rectum (CR) bathed in dog's blood. The right side of the figure shows the effect of endogenous vasopressin released by acute haemorrhages (H) of group B (mean ΔP diastolic 11·8 mmHg) and group C (mean ΔP diastolic=11·8 mmHg) and group C (mean ΔP diastolic=22·2 mmHg). The tissues were treated intraluminally with alprenolol and lidocaine.

In the last series of experiments, ten dogs were submitted to a single haemorrhage of 15 ml/kg of body weight. Blood samples were taken before, after and at different times during haemorrhage, and extracts were assayed separately for vasopressin and angiotensin as described in **Methods**. The values were not corrected for recoveries.

The effect of haemorrhage on the diastolic pressure, vasopressin and renin release is outlined in Table 2. Haemorrhage induced a decrease in diastolic pressure ranging from 9·6 to 41·3 mmHg (mean, 23·02±2·95 mmHg). As compared to earlier experiments (with the blood-bathed organs), some of these

TABLE 2. *Plasma vasopressin (VP) and renin activity (R) in response to haemorrhage (15 ml/kg) in dogs*

		Vasopressin (μU/ml) and renin (ng/ml angiotensin II) in blood											
				Haemorrhage									
Expt. No.	Diastolic ΔP* (mmHg)	Control VP	R	2 min VP	R	10 min VP	R	20 min VP	R	30 min VP	R	60 min† VP	R
1–B	22·3	—	22·9	—	22·4	—	18·3	—	13·1	—	25·1	—	13·9
2–B	22·3	34·0	—	105·0	—	61·0	—	65·0	—	53·0	—	43·0	—
3–B	9·6	30·3	—	92·3	—	74·0	—	80·6	—	33·3	—	56·6	—
4–B	18·0	29·0	10·3	70·0	20·4	40·0	9·1	21·0	5·6	29·0	4·3	32·0	9·0
5–B	14·6	29·0	3·3	79·0	4·0	31·0	4·6	24·0	2·3	38·0	2·5	22·0	10·8
6–B	37·0	47·5	14·7	196·0	15·2	162·5	15·2	135·0	8·3	24·0	15·3	23·7	7·6
7–B	16·7	25·0	1·8	51·0	2·8	28·5	5·7	19·0	2·1	42·0	9·9	35·5	3·2
8–B	27·7	60·0	14·0	175·0	20·7	98·0	10·4	77·0	14·4	80·0	21·7	70·0	5·6
9–B	41·3	86·0	15·1	160·0	15·8	70·0	14·8	40·0	13·2	22·0	23·1	35·0	16·6
10–B	20·7	16·5	19·8	125·0	28·2	40·0	25·1	40·0	16·9	64·0	29·8	30·0	14·7
Mean	23·0	39·7	12·7	117·0	16·2	67·2	12·9	55·7	9·4	42·8	16·4	38·7	10·2
MBP‡	(mmHg)	178·0±14·4		160·0±13·4		166·0±12·0		169·0±11·9		171·0±11·2		180·0±	8·8

* Maximal fall in diastolic blood pressure during haemorrhage. † 30 min after return of blood to the animal. ‡ Mean blood pressure.

decreases in diastolic pressure fell into the range of group B or group C haemorrhages, while others were more severe.

As shown in Table 2, following haemorrhage, the level of circulating vasopressin rose from 39·7 μU/ml to a peak value of 117·0 μU/ml within the first 2 min of haemorrhage. Then it decreased progressively although hypovolemia was still maintained. Thirty minutes after the cessation of haemorrhage, the level of circulating vasopressin had returned to control values. From these results, it is evident that the increase in circulating vasopressin was subjected to rather large variations. This can probably be explained by the fact that haemorrhage induced falls in diastolic pressure which varied greatly among the animals. As seen in Table 2, dogs 6-B, 8-B and 9-B showed the most severe hypotension and also the largest increases in vasopressin levels, confirming our results with the blood-bathed organ technique.

Table 2 also shows that plasma renin activity increased from 12·7 to 16·2 ng/ml within the first 2 min after haemorrhage. After 20 min of haemorrhage renin activity decreased to a value ($9{\cdot}4 \pm 1{\cdot}8$ ng/ml) below control levels. The 30 min blood sample (during haemorrhage) showed a second peak (16·4 ng/ml) followed by a decrease to values slightly below control levels 30 min after blood had been returned to the animal. As in the case of vasopressin levels, and probably for the same reasons, a large variation in plasma renin activity was observed.

Discussion

The results presented confirm the previous findings of Gilmore & Vane (1970) by showing that the sensitivity and the specificity of the rabbit rectum render this tissue suitable for the bio-assay of vasopressin. The assay organ did not respond to catecholamines when their action was prevented by adrenoceptor blockade; hence, the only agents that were still able to relax the tissue were vasopressin and oxytocin. However, the lack of responsiveness of the tissue to oxytocin coupled with the fact that oxytocin could not be detected in the blood, as shown by the absence of contraction of the chick rectum, clearly demonstrated that only changes in circulating vasopressin were measured. These results also confirm previous observations that vasopressin release, in response to haemorrhage, occurs without concomitant oxytocin release in cat and dog (Beleslin *et al.*, 1967; Fabian, Forsling, Jones & Lee, 1968).

The experiments with the blood-bathed organ technique reveal that vasopressin secretion in the dog in response to haemorrhage has a very low threshold. Indeed, a rapid fall of about 5 mmHg in diastolic pressure is associated with the release of large amounts of vasopressin. This is a much lower threshold than that found by Rocha e Silva & Rosenberg (1969). Our experiments also show that the amount of vasopressin released is proportional to the magnitude of the fall in diastolic pressure, not exceeding 22 to 25 mmHg. Maximal vasopressin secretion with greater falls in blood pressure was not determined. The results also indicate that vasopressin is released in a characteristic manner: there is a maximal peak after 2 min, following which the level decreases towards control values although oligaemia and hypotension were maintained, showing that a sudden variation in blood pressure is probably the most important stimulus for vasopressin secretion. The second series of experiments with fixed-volume haemorrhages (15 ml/kg) support this observation. Although blood loss (on a weight basis) was the same in all animals,

the fall in diastolic pressure varied greatly from animal to animal. Under these conditions, the amounts of vasopressin released also varied greatly from one animal to another and were proportional to the fall in diastolic pressure. Therefore, it appears that vasopressin release follows the magnitude of the fall in diastolic pressure more closely than the actual decrease in blood volume.

Since the blood-bathed organ technique permits the direct and continuous measurement of circulating vasopressin, it is obviously the best method for studying the time-course of vasopressin release in response to haemorrhage. The present experiments demonstrate that the time required to produce an increase in circulating vasopressin is inversely proportional to the severity of the fall in diastolic pressure. The secretory process in response to haemorrhage was shown to be fairly rapid (from 25 to 54 seconds). Previous reports by Share (1967) in dogs, and by Clark & Rocha e Silva (1967) in cats suggested that vasopressin release following haemorrhage, is mediated via an afferent pathway in the vagi and sinus nerves, and that the baroreceptors may regulate vasopressin release. It seems possible, therefore, that the time required to stimulate such a neurosecretory reflex arc would vary with the intensity of the stimulus which, in the present case, is the magnitude in the fall in diastolic pressure.

The results also demonstrate that changes in plasma renin activity were of a lower order than those observed with vasopressin. It seems unlikely that such small changes in plasma renin activity can influence the release of vasopressin as has been suggested by other workers (Bonjour & Malvin, 1970; Mouw *et al.*, 1971). However, Claybaugh & Share (1972) recently reported that the renin-angiotensin system seems not to play an important role in stimulating vasopressin release in response to haemorrhage in dogs. The finding that the 30 min blood sample (Table 2) showed a markedly elevated renin activity despite the fact that plasma concentration of vasopressin had returned to control levels would support this conclusion.

Our results indicate that renin is released in a biphasic manner; the first peak corresponded to the maximal release of vasopressin and was probably due to the powerful stimulus evoked by the rapid loss of blood and the consequent fall in diastolic pressure. Plasma renin activity then decreased to values lower than controls and was followed by a secondary increase. The significance of these findings cannot be clearly explained at present. However, Vander (1968) and Tagawa *et al.* (1971) have demonstrated that an elevation of plasma vasopressin by as little as 1 μU/ml was sufficient to inhibit renin release significantly. Hence, both vasopressin and renin could be released simultaneously during rapid haemorrhage; subsequently, the very large amounts of circulating vasopressin would tend to inhibit renin release. The rapid fall in plasma vasopressin would then allow renin release to resume, corresponding to the second peak observed in plasma renin activity.

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