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THE ROLE OF VASOPRESSIN IN BLOOD PRESSURE REGULATION IMMEDIATELY FOLLOWING ACUTE HAEMORRHAGE IN THE RAT

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SUMMARY

1. The possible pressor effect of vasopressin immediately after acute haemorrhage has been studied using anaesthetized Brattleboro rats with diabetes insipidus and rats of the Long Evans parent strain.

2. A blood loss of 0·5% of the body weight caused a significant decrease in mean arterial blood pressure, measured 10 min later, in Brattleboro rats, whereas this degree of haemorrhage was non-hypotensive in the control Long Evans rats. Following subsequent blood losses (each of 0·5% of the body weight), mean arterial blood pressure in Brattleboro rats was always significantly lower than in Long Evans rats.

3. While no antidiuretic activity was at any time found in the plasma of Brattleboro rats, haemorrhages greater than 1% of the body weight were associated with marked increases in plasma arginine vasopressin (AVP) of Long Evans rats.

4. When Brattleboro and Long Evans rats were subjected to a single haemorrhage of 2% of the body weight, the immediate decrease in arterial blood pressure was similar in the two groups. However, 5 and 10 min after the haemorrhage the arterial blood pressure was significantly higher in the Long Evans rats. When vasopressin was infused into Brattleboro rats so that plasma levels of the hormone approached those found in Long Evans rats, the mean arterial blood pressure 0, 5 and 10 min after haemorrhage was similar to that in the Long Evans animals.

5. It is concluded that in the anaesthetized rat, vasopressin plays an important role in the regulation of arterial blood pressure during the period immediately following acute haemorrhage.

INTRODUCTION

It is generally acknowledged that haemorrhage is a potent stimulus for vasopressin release in rats, dogs and cats (Ginsburg & Brown, 1956; Baratz & Ingraham, 1960; Beleslin, Bisset, Haldar & Polak, 1967; Rocha e Silva, Celso de Lima & Castro de Souza, 1978) and that in large doses this hormone causes vasoconstriction (see Saamali, 1968). Whether the vasopressin released in response to haemorrhage affects arterial blood pressure is, however, uncertain (Share & Grosvenor, 1974; Ganong, 1977).

Indirect evidence of a pressor role for vasopressin has been provided by various authors. In 1954, Frieden & Keller showed that neurohypophysectomized dogs had

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a decreased resistance to haemorrhage compared to normal animals, although such studies are subject to criticism in that damage to surrounding hypothalamic tissue and/or disturbance of adenohypophysial function may have affected the findings. Rocha e Silva & Rosenberg (1969) showed that in dogs, infusions of vasopressin which produce plasma concentrations similar to those found after haemorrhage, are pressor, provided that the baroreceptor reflexes are suppressed. Further indirect evidence was produced by the experiments of Szczepanska-Sadowska (1972, 1973) using intact conscious dogs. When vasopressin was infused to bring about plasma levels similar to those measured after a 15 % decrease in blood volume, there was a significant increase in arterial blood pressure. The suggestion that vasopressin may even be involved in normal blood pressure regulation, as indicated by the experiments of Cowley, Monos & Guyton (1974) using baroreceptor-denervated conscious dogs, also implies a pressor role for vasopressin in haemorrhage. Finally, it has been suggested that the pressor effect of this hormone may be a factor in the pathogenesis of malignant hypertension in rats treated with deoxycorticosterone trimethylacetate (Möhring, Möhring, Petri & Haack, 1977), in rats with glycerol-induced acute renal failure (Hofbauer, Konrads, Bauereiss, Möhring, Möhring & Gross, 1977) and in rats with unilateral renal stenosis (Möhring, Möhring, Petri & Haack, 1978).

We have attempted to provide direct evidence for a role of vasopressin in the maintenance of arterial blood pressure after acute haemorrhage by comparing responses in Brattleboro rats with hereditary hypothalamic diabetes insipidus with those of Long Evans rats of the parent strain.

METHODS

The animals used in these experiments were adult male rats of the Brattleboro strain with diabetes insipidus and of the parent Long Evans strain. Rats were of comparable age and weighed 200–300 g.

1. *Sequential acute haemorrhage experiments*

To ensure that Brattleboro rats were adequately hydrated, and remained so during subsequent surgery before infusion, each rat was given a water load (4 ml./100 g body wt.) by intragastric tubing. This volume was based on determinations of water intake in previous metabolism-cage experiments. Long Evans rats were subjected to a similar procedure, but the volume of water administered was only 1–2 ml. per rat. Fifteen minutes after the administration of water, rats were anaesthetized by I.P. injection of Inactin (Promonta, Hamburg) at a dose of 100 mg/kg body wt. (0·4 m-mole/kg). Rectal temperature was maintained at 37 °C by means of a thermostatically controlled heating table. The bladder was cannulated and a tracheostomy performed. The right jugular vein and the right femoral artery were each catheterized. The femoral catheter, containing 10 i.u./ml. of heparin in NaCl solution, was connected to a pressure transducer (Bell & Howell), and the arterial blood pressure measured using a Devices MX2 chart recorder. When the operative procedures were complete, and Brattleboro rats had excreted approximately 80 % of their water load, maintenance infusions of NaCl solution (based on previous observations of NaCl and water excretion in anaesthetized Long Evans and Brattleboro rats) were begun (1·5 ml./hr of NaCl 150 m-mole/l. for Long Evans rats; 4 ml./hr of NaCl 60 m-mol/l. for Brattleboro rats).

After a control period of at least 10 min of stable arterial blood pressure, each rat was bled via the catheterized femoral artery into pots containing trace amounts of heparin. The amount of blood removed was equal to 0·5 % (v/w) of the body weight, the process being completed as rapidly as possible (generally less than 2 min). The catheter was then reconnected to the pressure transducer. After an interval of 10 min, a second 0·5 % haemorrhage was performed and, in

the Brattleboro rats, since urine flow was greatly reduced, the infusion then altered to 1·5 ml./hr of NaCl 150 m-mole/l. The procedure was repeated for subsequent bleeds until the animal died. Each blood sample was rapidly cooled to 4 °C and centrifuged for 5 min. The plasma was stored at −30 °C until bioassayed for antidiuretic activity using the alcohol-anaesthetized Wistar rat preparation of Ames & Van Dyke (1952) modified by Penn (1967). The plasmas from corresponding bleeds in different animals were pooled (usually into groups of three) for assay when necessary, and the antidiuretic activity found was identified as arginine vasopressin on the basis of the shape and duration of the response, and by successful inactivation with thioglycollate. The mean arterial blood pressure for the 2 min period preceding each haemorrhage was determined as the diastolic pressure plus one third of the pulse pressure.

2. *Single acute 2 % haemorrhage experiments*

The animals used in these experiments are considered in three groups: (*a*) Long Evans rats, (*b*) Brattleboro rats and (*c*) Brattleboro rats with vasopressin replacement.

(*a*) *Long Evans rats.* Thirty-seven animals were prepared for haemorrhage as described previously. In this experiment however, after the initial control period, a single haemorrhage of 2 % (v/w) of the body weight was carried out. The blood was collected in two heparinized pots, the first sample of 1·2 ml. being immediately cooled to 4 °C and centrifuged. The plasma was stored at −30 °C until bioassayed for antidiuretic activity. The remainder of the 2 % haemorrhage (in the second pot) was used for the determination of haematocrit and plasma osmolality. This procedure allowed for the estimation of hormone levels before the stimulating effect of the haemorrhage itself on vasopressin release.

After the haemorrhage the femoral catheter was reconnected to the pressure transducer. For ten animals a second blood sample was taken 10 min later and again divided into two, the initial 1·2 ml. sample being used for bio-assay and the remainder for haematocrit and plasma osmolality estimations. The mean arterial blood pressures during the 2 min preceding, immediately after (0 min), 5 and 10 min after the 2 % haemorrhage were determined from the pressure traces. In addition the heart rate was determined before and 6–8 min after the haemorrhage.

The above procedure was repeated for the other twenty-seven Long Evans rats, but in these animals the period between the 2 % haemorrhage and the final bleed was either 2·5, 5 or 7·5 min.

(*b*) *Brattleboro rats.* Ten Brattleboro rats were prepared for haemorrhage as described previously, and a 2 % haemorrhage carried out as in (*a*) above. Following the haemorrhage the infusion was immediately reduced to 1·5 ml./hr of NaCl 150 m-mole/l. The mean arterial blood pressure and the heart rate were determined as described in (*a*) above, the period between the 2 % haemorrhage and the final bleed being 10 min.

(*c*) *Brattleboro rats with vasopressin replacement.* Following catheterization of the jugular vein, eighteen Brattleboro rats were infused with NaCl solutions (150 m-mole/l.) containing various vasopressin concentrations such that the resulting plasma hormone levels were comparable with those estimated in the Long Evans rats in (*a*) above, both before the 2 % haemorrhage and during the 10 min period after it. The modifications to the general procedure consisted of the following:

(i) the rats were given a smaller water load (2 ml./100 g body wt.);

(ii) three catheters were placed in the jugular vein, each one containing a different vasopressin solution. The concentration of vasopressin in the first catheter was 10 m-u./ml. (infusion 1); in the second catheter, either 40, 50 or 60 m-u./ml. (infusion 2); and in the third, either 100 or 150 m-u./ml. (infusion 3);

(iii) I.V. infusion was begun immediately after catheterization of the jugular vein;

(iv) the rates of infusion used were: before the 2 % haemorrhage, infusion 1 at a rate of 1·5 ml./hr; from the onset of haemorrhage until 2·5 min after, infusion 2 at 1·5 ml./hr; between 2·5 and 5 min after haemorrhage infusion 3 at 1·5 or 2 ml./hr; between 5 and 10 min after haemorrhage (when appropriate, see (v)), infusion 2 at 1·5 or 2 ml./hr.

(v) eight rats were bled 5 min after the 2 % haemorrhage and the others bled after 10 min.

Statistics

All differences between means were calculated using the unpaired Student *t* test unless otherwise stated. Mean values are given with their standard errors (S.E.).

RESULTS

(1) *Sequential haemorrhage experiments*

The mean arterial blood pressures of Long Evans and Brattleboro rats during the control period and 8–10 min after each of five 0·5% haemorrhages are shown in Fig. 1. The mean arterial blood pressures (± S.E.) during the control period in the

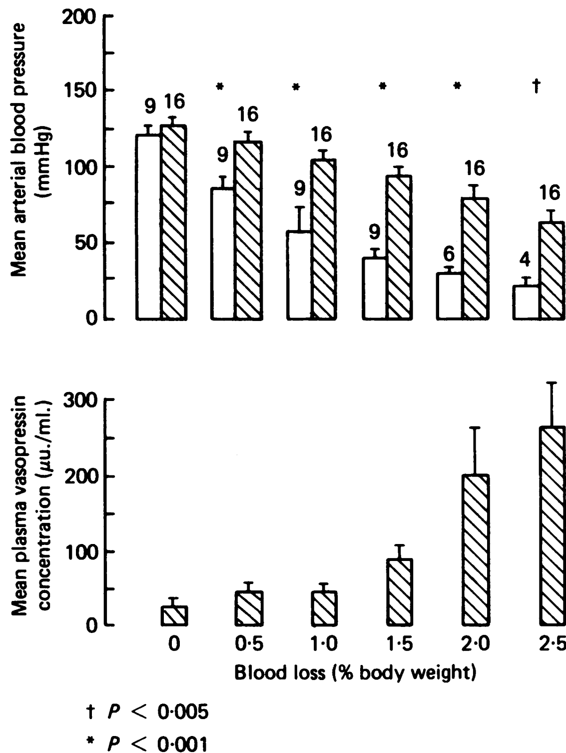

Fig. 1. Mean arterial blood pressures and mean vasopressin concentrations of grouped plasmas measured in Long Evans (▧) and Brattleboro rats (□) subjected to progressive haemorrhage. Numbers above the columns represent the numbers of animals surviving each 0·5% (v/w) blood loss. Vertical bars through the columns represent the ± S.E. of the means.

two groups of animals were 128 ± 2 and 122 ± 5 mmHg respectively, values which are not significantly different from each other. 8–10 min after the first haemorrhage, the mean arterial blood pressure of the Brattleboro rats was significantly lower than the corresponding value in Long Evans rats, and remained so following each successive haemorrhage.

No detectable antidiuretic activity was found in any of the plasma samples from Brattleboro rats. In Long Evans rats, the plasma level of antidiuretic activity assigned to vasopressin (mean ± S.E.) increased from a value of 28 ± 3 μu./ml. during the control period to 266 ± 56 μu./ml. after a total blood loss of 2·5% of the body weight. However, the increase in plasma hormone levels only became significant (paired t test) once the blood loss was 1·5% of the body weight ($P < 0·02$) or more ($P < 0·05$ at 2% and $P < 0·01$ at 2·5%).

While all sixteen Long Evans rats survived the 2·5% blood loss (with two animals surviving a total blood loss of 4% of the body weight), only four of the nine Brattleboro rats survived a 2·5% bleed.

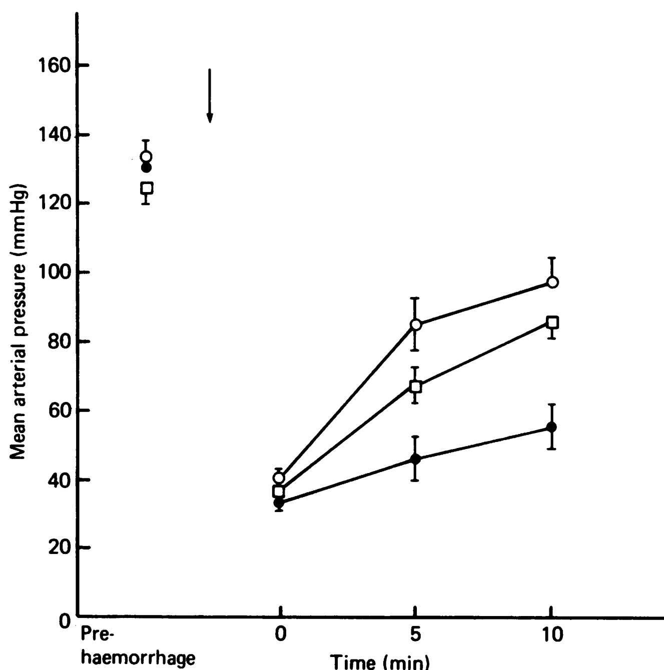

Fig. 2. Mean arterial blood pressures (± S.E. means) in Long Evans rats (□) Brattleboro rats (●) and Brattleboro rats given vasopressin replacement (○) before and after (0, 5 and 10 min) a single 2% (v/w) haemorrhage which is represented by the vertical arrow.

(2) *Single 2% haemorrhage experiments*

(*a*) *Mean arterial blood pressure*

The mean arterial blood pressure was measured before, immediately after (0 min), 5 and 10 min after a 2% haemorrhage in Long Evans rats, and in Brattleboro rats with or without vasopressin replacement. Values are given in Fig. 2. The pre-haemorrhage (control) values in the three groups of rats were not significantly different from each other, and were similar to the control values measured in experiment 1. Immediately after the haemorrhage, the arterial blood pressure decreased significantly (paired t test: $P < 0{\cdot}001$) from the respective prehaemorrhage value in each group of animals. Over the next 10 min the arterial blood pressures in the Long Evans rats and the Brattleboro rats given replacement vasopressin gradually returned towards control values, and were not significantly different from each other 5 and 10 min after the bleed. However, the arterial blood pressure of the Brattleboro rats which did not receive vasopressin replacement remained low, and 5 and 10 min after the bleed was significantly lower than the other two groups (Figs. 2 and 3).

(b) Antidiuretic activity

For each of the thirty-seven Long Evans rats, the plasma antidiuretic activity was determined in the first 1·2 ml. of the blood samples obtained both in the initial haemorrhage (control values) and either 2·5, 5, 7·5 or 10 min later. The concentrations

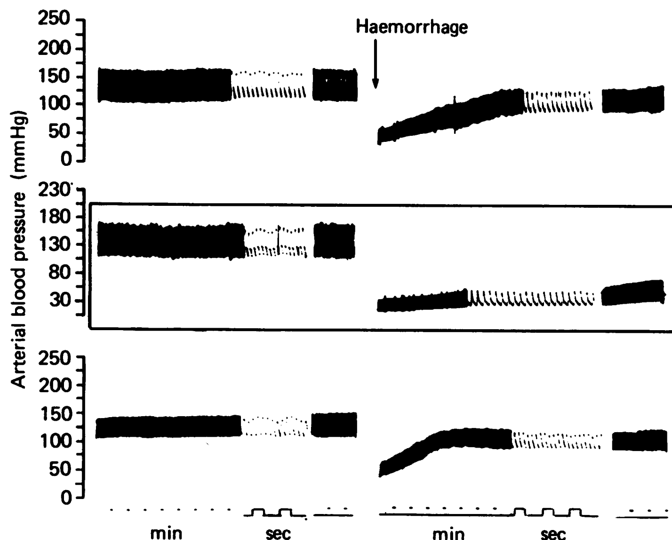

Fig. 3. Typical arterial blood pressure records of a Long Evans rat (upper trace), a Brattleboro rat (middle trace) and a Brattleboro rat given vasopressin replacement, for the 10 min periods before and after a single 2 % (v/w) haemorrhage.

TABLE 1. Mean plasma arginine vasopressin (AVP) concentrations (± S.E.) measured 2·5, 5, 7·5 and 10 min after a single 2 % (v/w) haemorrhage in Long Evans rats, and 5 and 10 min after a similar blood loss in Brattleboro rats with vasopressin replacement (n = numbers of rats)

Time after haemorrhage (min) ...		2·5	5	7·5	10
Long Evans rats	n	10	8	10	9
	AVP (μu./ml.)	112 ± 18	252 ± 44	189 ± 32	85 ± 7
Brattleboro rats	n	–	8	–	10
(with vasopressin replacement)	AVP (μu./ml.)	–	190 ± 46	–	98 ± 13

of hormone in the control samples were similar to those measured in experiment 1 (see above). Mean values for the antidiuretic activity assigned to vasopressin, determined in the other plasma samples, are given in Table 1. The plasma hormone concentrations rose rapidly after the haemorrhage to reach a peak after 5 min. Mean values for plasma vasopressin levels 5 and 10 min after the haemorrhage in the Brattleboro rats infused with vasopressin are also given in Table 1. These values were not significantly different from those of the Long Evans rats at corresponding times. No antidiuretic activity was found in the plasma of any of the Brattleboro rats not receiving vasopressin replacement.

(*c*) *Heart rate*

The mean ($\pm$ S.E.) prehaemorrhage values for heart rate were 339 ± 10, 386 ± 11 and 376 ± 14 beats/min for the Long Evans rats, the Brattleboro rats and the Brattleboro rats with vasopressin replacement, respectively. The mean for the Long Evans rats was significantly lower than the values for Brattleboro rats ($P < 0.01$) and Brattleboro rats with vasopressin ($P < 0.05$). Six to eight minutes after the haemorrhage, heart rates (means $\pm$ S.E.) for these three groups of rats were 310 ± 12, 328 ± 10 and 368 ± 16 beats/min, respectively. The decreases in heart rate after the 2 % haemorrhage were significant only for the Long Evans rats ($P < 0.02$) and the Brattleboro rats without vasopressin replacement ($P < 0.005$), using the paired Student *t* test.

(*d*) *Haematocrit and plasma osmolality*

Haematocrits and plasma osmolalities were comparable in all three groups of rats, both before and after the 2 % haemorrhage.

DISCUSSION

In the present investigation we have shown that, before haemorrhage, anaesthetized Brattleboro rats devoid of vasopressin are able to maintain their arterial blood pressure at a level that does not differ significantly from that of Long Evans rats. These results accord with clinical observations in patients with diabetes insipidus and suggest that vasopressin is not required for normal blood pressure regulation. However, after even a mild haemorrhage (0·5 % of the body weight, corresponding to approximately 8 % of the total blood volume), which in both Long Evans rats and Wistar rats (Laycock, Penn, Shirley & Walter, 1977) does not lead to any sustained hypotension, there was a significant fall in arterial blood pressure in Brattleboro rats unable to synthesize vasopressin. After subsequent bleeds this disparity between Brattleboro rats and Long Evans rats was even more marked. This finding, together with the higher mortality rate of Brattleboro rats, indicates that vasopressin may help limit hypotension following progressive blood loss, and that it may therefore be of considerable survival value in this situation.

It was observed by Errington & Rocha e Silva (1972) that during chronic sustained haemorrhage, hypophysectomized dogs had a greater survival rate than intact animals. These authors concluded that the non-hypophysectomized dogs had developed haemorrhagic shock, possibly caused by prolonged mesenteric vasoconstriction induced at least partly by vasopressin. They suggested that in the absence of vasopressin such vasoconstriction is absent or attenuated, thus preventing the development of the ischaemic lesions associated with haemorrhagic shock. However, the results of chronic experiments such as these are obviously not directly comparable with those of the present investigation in which the period studied after haemorrhage was of relatively short duration.

The mean prehaemorrhage plasma vasopressin concentration in the Long Evans rats was relatively high, presumably because of anaesthesia and the stress of surgery (Bonjour & Malvin, 1970). In these rats, the plasma level of vasopressin rose rapidly

from control values once the blood loss was 1·5 % of the body weight (corresponding to some 25 % of the blood volume) or more. No antidiuretic activity was detected in any of the grouped plasma samples from Brattleboro rats at any time. Since the neurohypophysis of the Brattleboro rat has appreciable quantities of oxytocin (Valtin, Sawyer & Sokol, 1965; Jones & Lee, 1967; Lee & Williams, 1972), and since oxytocin has measurable antidiuretic activity if released in sufficient quantity (Bisset & Lewis, 1962), the present finding supports the view that haemorrhage stimulates the independent release of vasopressin (Chaudhury & Walker, 1958; Ginsburg & Smith, 1959; Beleslin *et al.* 1967; Schrier, Verroust, Jones, Fabian, Lee & de Wardener, 1968).

In the second part of the present study, we found that 5 and 10 min after a single 2 % haemorrhage the mean arterial blood pressure in Brattleboro rats without vasopressin replacement was significantly less than that of Long Evans rats. However, when vasopressin was infused into Brattleboro rats so that plasma levels of the hormone were similar to those of the Long Evans animals, the difference between the blood pressure responses of the two strains was abolished. This provides strong evidence for a pressor role of vasopressin under these experimental conditions. The mechanism by which vasopressin exerts its pressor action was not studied in the present investigation. It is possible, however, that the sustained hypotension observed after haemorrhage in Brattleboro rats with diabetes insipidus may be due, in part, to the absence of any potentiating effect of vasopressin on the pressor activity of catecholamines (Bartelstone & Nasmyth, 1965) in these animals.

It is of interest that the heart rate decreased after a 2 % haemorrhage in all three groups of rats. This decrease, which was significant in Long Evans rats and in Brattleboro rats without vasopressin replacement, must at present remain unexplained. In this respect, however, it is of interest to note that although Rocha e Silva & Rosenberg (1969) in experiments on anaesthetized dogs found no significant overall change in heart rate as a result of haemorrhage, in traces from the one representative experiment shown in their paper, heart rate did appear to decrease quite markedly with the onset of haemorrhage.

In conclusion, the present findings, although confined to anaesthetized animals, provide strong, direct evidence for an immediate role of vasopressin in arterial blood pressure regulation after haemorrhage.

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