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THE EFFECT OF ADRENALINE AND NORADRENALINE ON HORMONE SECRETION AND BLOOD FLOW FROM THE THYROID VEIN IN SHEEP WITH EXTERIORIZED THYROIDS

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SUMMARY

1. Emotional stimulus to the sheep has previously been shown to cause increased thyroid hormone secretion; the influence of adrenaline and noradrenaline in this process has been investigated.

2. Sheep bearing exteriorized thyroid glands on carotid artery–jugular vein loops were used. Thyroid vein blood was collected through a cannula in the jugular vein within the loop, and blood flow was measured by a plethysmographic technique.

3. ^{131}I (50 μc) was injected intramuscularly (I.M.) into the sheep, and 4–7 days later the concentration of total and protein bound ^{131}I in thyroid vein blood was measured in samples taken every 10 min for 4 hr. Intra-carotid injections of 1 μg, I.V. injections of 5 μg, or I.V. infusions at 10 μg/min for 10 min, of adrenaline or noradrenaline were administered 1·5 hr after commencement of sampling. Blood flow from the thyroid was measured in similar experiments.

4. No significant changes in thyroid hormone secretion could be attributed to adrenaline or noradrenaline, and it was concluded that circulating catecholamines do not influence the release of thyroid hormone observed after brief emotional stimulus in the sheep.

INTRODUCTION

Interest in the influence of adrenal medullary hormones on the thyroid has been stimulated by two separate lines of research. One is the accumulating evidence of stress causing increased thyroid secretion, both as a consequence of transient stimuli (Falconer & Hetzel, 1964; Amiragova, 1961) and during chronic stimulation (Harrison, Silver & Zuidema, 1966). The other is the evidence for an increased sensitivity to adrenaline and noradrenaline of hyperthyroid animals and patients as indicated by glycolysis (see Harrison, 1964), or increased elevations of blood pressure (Schneckloth, Kurland & Freedberg, 1953). It would appear likely, therefore, that under some conditions of stress thyroid and adrenal medullary hormones may act synergistically. It has been suggested that adrenaline causes an increased output of thyroid hormone (Ackerman & Arons, 1958), so it was of interest to examine the effect of catecholamines on secretion from the exteriorized thyroid of sheep, since this preparation had earlier been shown to respond to stress (Falconer & Hetzel, 1964).

METHODS

Eleven sheep were subjected to thyroid gland exteriorization by the technique described by Falconer (1963). In each sheep one lobe of the thyroid gland was dissected free of all connexions, apart from the thyroid artery and anterior thyroid veins. The carotid artery and jugular vein were freed of all branches apart from the thyroid vessels, for 10–15 cm posteriorly from the angle of the jaw. A skin tube containing the thyroid lobe, carotid artery and jugular vein was constructed on the neck as a permanent loop. One castrate male animal, R6, was included in the group, the others being 3–4 year old ewes. A period of at least 6 months elapsed between surgery of the animals and their experimental use.

The functioning of the exteriorized thyroid glands was demonstrated to be normal by ^{131}I uptake and release measurements. For the experiments described in this paper the animals were given 50 μc ^{131}I in 1·0 ml. 0·9 % NaCl solution I.M., 4–7 days before blood sampling. A polythene or nylon cannula was inserted into the jugular at either the upper or lower end of the carotid artery–jugular vein loop containing the thyroid gland, through a stab incision. To minimize discomfort to the animal 0·5 ml. of 2 % Xylocaine (Astra-Hewlett, Ltd., Watford) was injected intradermally (I.D.) before making the incision. The procedure for collecting blood was carried out as described previously (Falconer & Hetzel, 1964). The animals weighed between 50 and 80 kg at the time of the experiments.

Analytical methods. Total serum or plasma ^{131}I and protein-bound ^{131}I ($PB^{131}I$) were determined in well type scintillation counters (Ekco type N 664 B and Isotope Developments Ltd. type 663C and 722) with automatic scalers (Ekco type 601 and Isotope Developments Ltd. type 1700 F) as previously described (Falconer, 1963). A total of 10,000 counts were recorded for each sample in order to reduce the S.D. of any single measurement to 1 % of the number of counts. Protein-bound iodine (PBI) analyses were carried out by the method of Acland (1957).

Blood flow measurement. This was done by enclosing the jugular vein-carotid artery loop bearing the thyroid in a Perspex box, acting as an air filled plethysmograph. An elastic cuff was used to occlude the cranial end of the jugular vein, and intermittent manual pressure applied at the caudal end at approximately 10 sec intervals (Falconer, 1965). The air displacement was recorded on a Palmer float recorder of 10 ml. capacity marking a smoked drum.

Adrenaline and noradrenaline were used as tartrate salts. Statistical comparisons were made by means of the t test on groups of observations and paired differences. All the numerical data processing and the statistical analyses were done on a KDF 9 computer (English Electric Co.).

RESULTS

Effect of adrenaline on thyroid secretion and blood flow

Thyroid secretion. Thyroid vein blood samples were collected over a period of approximately 4 hr, at either 10 or 15 min intervals. After the collection of at least five samples, 5 μg of adrenaline was injected into the jugular vein through the blood sampling cannula, and blood sampling was continued as before. A series of four experiments at this dose of adrenaline were carried out, and the results are shown in Table 1.

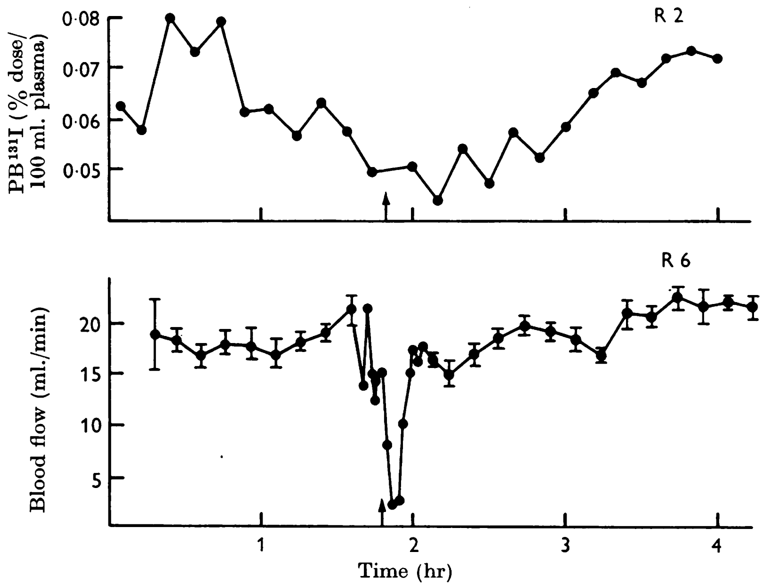

Fig. 1. Effect of 5 μg of intravenous adrenaline (↑) on hormone concentration and blood flow from the thyroid vein. Upper graph: thyroid hormone concentration measured as PB ^{131}I in plasma, obtained from thyroid vein blood from a sheep with an exteriorized thyroid gland (% dose of ^{131}I administered/100 ml. plasma). Lower graph: blood flow into a carotid artery–jugular vein loop containing the thyroid gland, with the jugular vein occluded by pressure at both ends of the loop. Mean flow ± S.E.

In order to examine the effect on the thyroid of a longer treatment with adrenaline, six additional experiments using 100 μg of adrenaline infused at 10 μg/min were carried out, and the results are included in Table 1. The results of one representative experiment at each dose level are shown in Figs. 1 and 2. The effect of intra-carotid administration of 1 μg of adrenaline, close to the thyroid artery, was investigated in two experiments (Table 1).

Blood flow. Measurements of blood flow were carried out over periods of 3–4 hr. A minimum of five consecutive measurements at 10 sec intervals were recorded every 10 min throughout the period. Adrenaline as a single injection of 5 μg or as an infusion of 10 μg/min over 10 min was administered through the jugular cannula at 1–1·5 hr after commencement of the recording. The results of three experiments with 5 μg of adrenaline rapidly injected and three with 10 μg adrenaline/min infused over 10 min are shown in Table 2. The results of two of these experiments are included in Figs. 1 and 2.

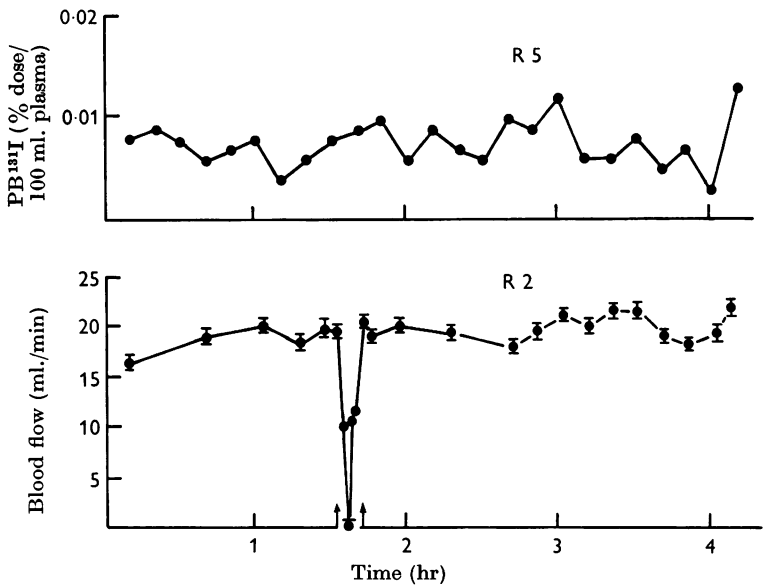

Fig. 2. Effect of an intravenous infusion of adrenaline at 10 μg/min for 10 min (↑—↑) on hormone concentration and blood flow from the thyroid vein. Upper graph: thyroid hormone concentration measured as $PB^{131}I$ in plasma from thyroid vein blood, ewe R5. Lower graph: blood flow into a carotid artery–jugular vein loop containing the thyroid gland, as in Fig. 1. Mean flow ± S.E., ewe R2.

Effect of noradrenaline on thyroid secretion and blood flow

Thyroid secretion. The experimental design was the same as has been described above for adrenaline. The results of a series of three experiments in which 5 μg of noradrenaline was injected, and three experiments in which 10 μg noradrenaline/min was infused for 10 min, are shown in Table 3.

Blood flow. To investigate the short-term changes in blood flow following noradrenaline infusion, three experiments were carried out in which 5 μg of noradrenaline was rapidly injected I.V. Flow recording was done at approximately 10 sec intervals for 10 min. A further three experiments were done similarly, in which a rapid intravenous injection of 100 μg of noradrenaline was given and the results of the experiments are shown in Fig. 3. The 100 μg dose of noradrenaline caused convulsions resembling vomiting in the experimental animal.

ABBLE 1. Effect of adrenaline on the total plasma ^{131}I radioactivity and PB ^{131}I radioactivity of thyroid vein blood obtained from conscious sheep with exteriorized thyroid glands. All measurements are expressed as % of dose of ^{131}I administered/100 ml. plasma. The mean differences in radioactivity ±S.E. of mean differences, comparing the means before treatment with those after, are given in the last two columns

Sheep no.	Duration of experiment (min)	No. of samples before treatment	Mean total ^{131}I (% dose/ 100 ml.)	Mean PB ^{131}I (% dose/ 100 ml.)	No. of samples after treatment	Mean total plasma ^{131}I after treatment (% dose/ 100 ml.)	Mean PB ^{131}I after treatment (% dose/ 100 ml.)
			5 μg of adrenaline intravenously				
17	235	5	0·59	0·38	12	0·50	0·36
17	240	5	0·47	0·33	14	0·42	0·32
71	235	5	0·19	0·16	12	0·18	0·15
R2	250	11	0·10	0·064	15	0·11	0·093
						−0·034 ±0·021*	−0·002 ±0·011*
			10 μg/min of adrenaline for 10 min intravenously				
3	240	5	0·074	0·038	12	0·066	0·032
7	240	7	0·15	0·14	10	0·13	0·12
10	240	7	0·065	0·050	11	0·066	0·049
11	240	7	0·11	0·082	11	0·10	0·077
R3	240	6	0·018	0·022	8	0·015	0·017
R5	240	10	0·037	0·007	15	0·033	0·008
						−0·006 ±0·003*	−0·008 ±0·004*
			1 μg of adrenaline intra-arterially				
R8	240	10	0·079	0·068	15	0·070	0·062
R8	240	10	0·094	0·079	15	0·088	0·068
						−0·0075 ±0·0013*	−0·0084 ±0·0025*

* Not significant $P > 0{\cdot}1$ by t test.

TABLE 2. Effect of adrenaline on the blood flow from the exteriorized thyroid glands of conscious undisturbed sheep. The mean differences in blood flow ±S.E. of mean differences, comparing the means before treatment with those after, are given in the last column

Sheep no.	Duration of experiment (min)	No. of mean rates of flow recorded before treatment	Over-all mean flow rate before treatment (ml./min)	No. of mean rates of flow recorded after treatment	Overall mean flow rate after treatment (ml./min)
		5 μg of adrenaline intravenously			
R2	107	4	15·8	7	14·6
R2	112	5	19·9	5	19·2
R6	240	9	22·1	14	22·8
					−0·4±1·23*
		10 μg/min of adrenaline for 10 min intravenously			
R2	240	6	22·6	14	27·4
R6	180	4	33·6	12	29·5
R6	270	10	22·5	16	23·7
					+0·62±4·56*

* Not significant $P > 0{\cdot}5$.

TABLE 3. Effect of noradrenaline on the total plasma ^{131}I radioactivity and PB ^{131}I radioactivity of thyroid vein blood obtained from conscious sheep with exteriorized thyroid glands. All measurements are expressed as % of dose of ^{131}I administered/100 ml. plasma. The mean differences in radioactivity ± S.E. of mean differences, comparing the means before treatment with those after, are given in the last two columns

Sheep no.	Duration of experiment (min)	No. of samples before treatment	Mean total ^{131}I (% dose/ 100 ml.)	Mean PB ^{131}I (% dose/ 100 ml.)	No. of samples after treatment	Mean total plasma ^{131}I after treatment (% dose/ 100 ml.)	Mean PB ^{131}I after treatment (% dose/ 100 ml.)
			5 μg of noradrenaline intravenously				
R6	260	11	0·068	0·051	16	0·057	0·048
R6	240	10	0·087	0·060	15	0·079	0·050
R8	240	10	0·042	0·032	15	0·041	0·034
						−0·007 ±0·003*	−0·003 ±0·004*
			10 μg/min noradrenaline for 10 min intravenously				
R2	250	10	0·096	0·059	16	0·082	0·049
R8	250	10	0·044	0·031	16	0·039	0·028
R8	240	10	0·048	0·030	15	0·044	0·029
						−0·007 ±0·003*	−0·005 ±0·003*

* Not significant $P > 0·1$ by t test.

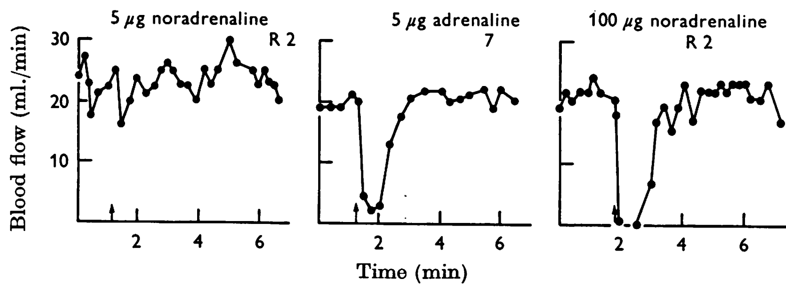

Fig. 3. Comparison of the effect of a rapidly injected dose (↑) of 5 μg or 100 μg I.V. noradrenaline, or 5 μg I.V. adrenaline, on blood flow from the thyroid vein, measured as in Fig. 1.

DISCUSSION

It has been the aim of the experiments described in this paper to investigate the effect of physiological doses of adrenaline and noradrenaline on thyroid hormone secretion. To assess the correct dose of adrenaline, a comparison has been made between the thyroid vasoconstriction induced by fear, and by intravenous adrenaline (Falconer, 1965). A single intravenous injection of 5 μg of adrenaline, or an intravenous infusion at the rate of 10 μg/min, caused an almost complete cessation of thyroid blood flow in these experiments (Figs. 1 and 2).

The data presented in Table 1 show that the administration of these intravenous doses of adrenaline have had no significant effect on the concentration of hormone in the blood leaving the thyroid vein. There is, however, a general tendency for a fall in the concentration of radioactive iodine in thyroid vein blood throughout the experiments, which can be attributed to the early elevation of concentration due to the stimulus of cannulation (Fig. 1) (Falconer & Hetzel, 1964). It is also likely that the decrease in concentration shown in the arterial infusion experiments is due to the same effect, as a marked early rise in concentration of radioactive iodine in both fractions of plasma was followed by a steady decline for the remainder of the period of the experiments.

A second statistical analysis was carried out on the $PB^{131}I$ concentrations in plasma for 1 hr before, and 1 hr after, intravenous adrenaline. No significant change was observed after 5 μg of adrenaline ($P > 0{\cdot}1$), and after 10 μg/min of adrenaline, a decreased concentration occurred of marginal statistical significance ($0{\cdot}1 > P > 0{\cdot}05$).

In Fig. 1 a marked rise in hormone concentration is seen during the last 2 hr of the experiment. This is observed in animals when they become increasingly irritable due to the restraint of the experimental procedure, and tends to be eliminated after sufficient exposure to experimentation.

Chemical analyses of protein-bound iodine were done on a proportion of thyroid vein blood samples, and showed no major alterations in hormone concentration following adrenaline administration. The blood samples were taken after the acute vasoconstrictor effects of adrenaline had disappeared, and therefore do not show concentration changes caused by the reduction or temporary cessation in blood flow. The lack of any significant longer term alteration in thyroid blood flow following adrenaline is apparent from Table 2. Previous measurements of blood flow from the thyroid gland of sheep stimulated by a barking dog have shown an increase in both blood flow (Falconer, 1965) and thyroid hormone concentration (Falconer & Hetzel, 1964). This substantial increase in actual thyroid hormone secretion elicited by emotional stimulus (Fig. 4) could not be induced by adrenaline administration. These observations are in agreement with studies on the rat (D'Angelo, 1956), rabbit (Brown-Grant & Gibson, 1956) and dog (Mowbray & Peart, 1960) in which no effect of adrenaline on thyroid secretion could be demonstrated.

In the dog Ackerman & Arons (1958) reported an increase in thyroid hormone concentration in thyroid vein blood during adrenaline infusion, but did not measure thyroid blood flow. It appears likely that these changes were therefore a consequence of decreased blood flow through the gland. The effects of very large doses of adrenaline (150–170 μg/kg) on thyroid ^{131}I release in the dog have been studied by Amiragova (1960), who reported an increased ^{131}I release in seventeen out of fifty-five experiments. In other experiments electrical and reflex stimulation of dogs was shown to increase the release of ^{131}I from the thyroid; this was concluded to be due to the release of adrenal medullary hormones (Amiragova, 1961). In both of these studies in the dog, further experimentation is needed to clarify the results.

The effect of noradrenaline on thyroid blood flow in the sheep was much less than that of adrenaline (Fig. 3). This observation is in agreement with earlier workers who also reported the relative ineffectiveness of noradrenaline as a constrictor of the thyroid blood vessels (Brown-Grant & Gibson, 1956; Söderberg, 1958; Mowbray & Peart, 1960). A single injection of 5 μg, or an infusion at 10 μg/min of noradrenaline, had only slight

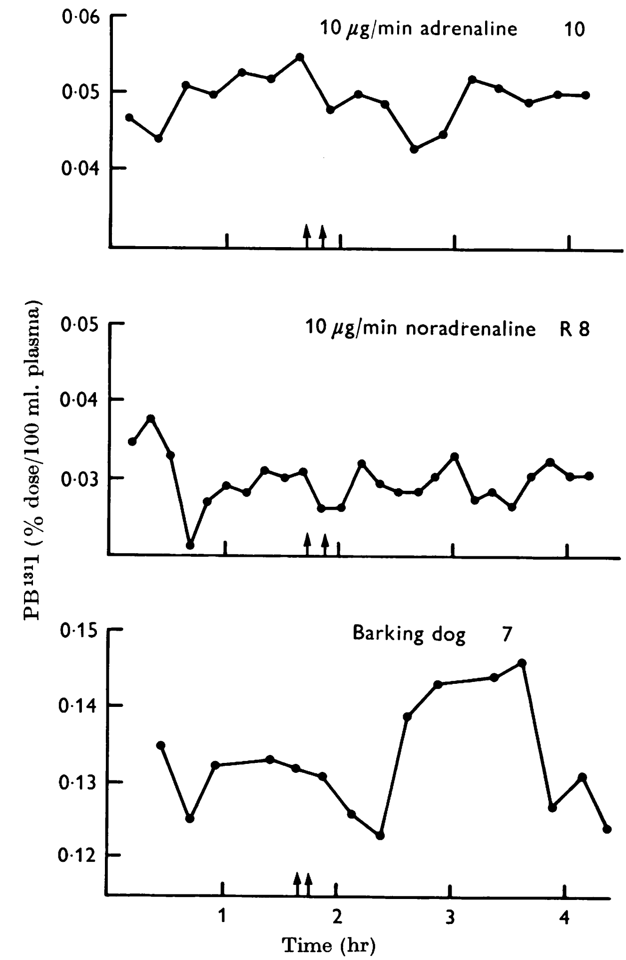

Fig. 4. Comparison of the effect of an I.V. infusion of adrenaline or noradrenaline at 10 μg/min for 10 min (↑—↑) with a barking dog present with the sheep for 5 min, on hormone concentration in thyroid vein blood. Thyroid hormone concentration was measured as in Fig. 1.

vasoconstrictory effects. A single intravenous injection of 100 μg of noradrenaline resulted in complete cessation of thyroid blood flow, accompanied by convulsions resembling vomiting.

TABLE 4. Effect of noradrenaline on the blood flow from the exteriorized thyroid glands of conscious undisturbed sheep. The mean differences in blood flow ± S.E. of mean differences, comparing the means before treatment with those after, are given in the last column

Sheep no.	Duration of experiment (min)	No. of mean rates of flow recorded before treatment	Over-all mean flow rate before treatment (ml./min)	No. of mean rates of flow recorded after treatment	Over-all mean flow rate after treatment (ml./min)
5 μg of noradrenaline intravenously					
R 2	210	9	22·2	11	27·2
R 2	210	7	34·0	14	28·1
R 6	235	9	21·1	14	24·0
					+0·65 ± 3·06*
10 μg/min of noradrenaline for 10 min intravenously					
R 2	240	9	27·6	11	33·2
R 6	190	7	20·1	11	25·2
R 6	240	6	16·2	18	17·4
					+3·96 ± 1·49*

* Not significant $P > 0·1$.

The study on the effect of noradrenaline on thyroid hormone secretion was carried out at the same dose levels as had been used for adrenaline. As can be observed from Table 3, no significant changes in the concentration of hormone in thyroid vein blood occurred although a general decrease with time is again apparent. Similarly, the intravenous injection of 5 μg or 10 μg/min of noradrenaline for 10 min had no significant effect on thyroid blood flow during the 2 hr after administration (Table 4).

From the results presented in this paper it appears that the administration of physiological doses of adrenaline and noradrenaline has no effect on thyroid secretion either in stimulating hormone release, or inhibiting release caused by other factors. It would therefore seem unlikely that the increases in thyroid secretion following emotional stimuli, that have been observed in the sheep, are due to the action of circulating catecholamines.

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