THE EFFECT OF DESOXYCORTICOSTERONE ACETATE ON THE THYROID UPTAKE OF IODINE AND ON THE RENAL EXCRETION OF IODINE, CHLORINE, SODIUM AND POTASSIUM

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INTRODUCTION

The supposition that the adrenal glands exert an inhibitory influence on the thyroid gland is not a new one, being first made by Solis - Cohen in 1897 (1). This concept of an inhibitory action was based on the apparent amelioration of the clinical signs and symptoms of Graves' disease following treatment with adrenal extract (2, 3). However spontaneous remissions occur in Graves' disease (4) and the value of these observations is therefore limited.

Marine and others later performed certain experimental works tempting to support this concept, e.g. sublethal injury to the adrenals was claimed to produce a symptomcomplex which resembles Graves' disease in the rabbit and cat (5, 6, 7, 8, 9). On the other hand certain experiments pointed to a synergism between adrenal cortical hormones and thyroid hormone, e.g. the increased oxygen consumption after administration of either adrenal cortical extract or of thyroxin (10, 11) and the action of DOCA on the accelerated metamorphosis of amphibia - larvae (12).

Within recent years there has been renewed interest in the possibility of a thyroid - adrenal interrelationship. Two factors are responsible for this: To - day accurate tests for the assessment of the thyroid function in men are available and pure adrenal cortical hormones are likewise available and used extensively in therapy.

There is good evidence that adrenal cortical hormones depress certain aspects of thyroid function in men and in

animals. The uptake of radioactive iodine and the protein - bound iodine decrease (13, 14, 15, 16, 17), a slight fall of the basal metabolic rate has also been reported (18). These findings have led to the concept of "corticogenic hypothyroidism" (16). A decreased thyroid function has been reported during an alarm - reaction, a state associated with hyperactivity of the adrenal cortex (19), but has not been confirmed (13). Thyroid depression has also been reported after administration of sex hormones, which substances have also been used in the treatment of Graves' disease (20) and shown to be goitrogenic in animals (21).

This paper is concerned with the effect of one particular cortical hormone (Desoxycorticosterone acetate, DOCA) on the thyroid function. Certain aspects of the metabolism of chlorine, sodium and potassium were also investigated in an attempt to correlate them with changes occuring in iodine metabolism during administration of DOCA.

METHOD

The experiments were carried out on 15 persons, 13 of whom were patients on the psychopathic ward of the Winnipeg General Hospital. These latter subjects had no organic diseases being admitted solely for psychiatric reasons. At the time of investigation none had undergone any shock treatment or surgery within the previous year. As far as could be ascertained they had not had an increased iodine intake (in cough medicines, diodrast, etc.). The two remaining patients (T.K. and R.R.) were admitted to other services. Details of all subjects are to be seen in table I. The patients received the ordinary ward diet and performed the usual ward activities.

The same experimental procedure was performed twice on all the patients, once before the administration of DOCA and once afterwards, every patient acting thus as his own control. The findings of the first experimental period were also compared with the values obtained on a normal control group which had been investigated previously in this laboratory (22).

The fasting patient was given 75 - 100 μC of carrier - free radioactive iodine ^{131} orally at 7.30 AM. Approximately 2 hours later he emptied the bladder, a blood sample was taken, the exact time noted and two counts 6 inches over the neck and one count 6 inches over the thigh were taken. These procedures were completed within 4 - 6 minutes. The urine was collected after voluntary voiding since it has been shown that the same clearance values are obtained with this method and with catheterization as long as the subjects are in moderate

diuresis (23, 24). The patients were kept under observation and usually well hydrated. Some of the psychotic patients refused any fluid intake. Approximately 2 hours later the patient again voided, a blood sample was taken, the exact time noted and the counts over neck and thigh repeated. The emptying of the bladder by the psychotic patients was always observed. The whole amount of urine passed during the two hours was exactly measured.

26 hours after the ingestion of the iodine (24 hours after the first examination) the thyroid counts were repeated and a third blood sample was taken. The thyroid counts were again repeated on the following day, 50 hours after the ingestion of iodine.

Following the 50 - hour - count the patients were started on DOCA (Percorten Ciba): 10 mgms daily in two 5 mgms doses approximately 12 hours apart. Beginning with the fourth day after starting DOCA, the procedures described above were repeated, the administration of DOCA being continued during this time. The whole experiment lasted 8 days for each patient.

At the time of the second dose of radioactive iodine (100 - 125 μC) there was of course still a considerable amount of radioactivity left in the thyroid gland. This amount was estimated each day, corrected for biological isotope decay and deducted from the actual counts found. The amount of radioactivity left over in blood and urine is so small as to be negligible.

The amount of radioactive iodine present in the thyroid gland was measured by means of a shielded collimated scintillometer (25) and compared with similar counts taken 6 inches above

a glass bottle containing an aliquot of the dose of radioactive iodine ingested by the patient. In this way the amount of radioactive iodine in the gland could be expressed as a percentage of the given dose. The thyroid counts were corrected by subtracting a background count taken 6 inches over the mid thigh and the counts of the standard by subtracting the background counts of the room.

The blood was collected in heparin or a mixture of potassium and ammonium oxalate, centrifuged, and the erythrocytes discarded. The iodine in plasma and urine was precipitated as palladium iodide as described previously (22). The radioactivity of the dry precipitates was measured with a Geiger - Mueller counter and compared with that of an aliquot of the same radioactive iodine the patient had ingested, prepared in the same manner. The results were expressed as a percentage of the given dose per 100 ml of plasma or urine.

From the amounts of radioactive iodine determined at two known times in the plasma and from the amount of I^{131} taken up by the thyroid gland and excreted in the urine during this known time interval one is able to calculate the rate of clearance of plasma of iodine by the kidneys and the thyroid gland and also the rate of accumulation of iodine by the thyroid gland.

The thyroid clearance was calculated from $\frac{\text{thyroid uptake / minute}}{p}$ = ml / min., where p = plasma concentration of I^{131}. As the I^{131} concentration in the blood falls exponentially a logarithmic mean concentration was determined with the formula $\frac{P_1 - P_2}{\log_e P_1 - \log_e P_2}$ (26, 27).

The renal clearance was calculated with the usual formula $\frac{UV}{P}$, p again being the logarithmic mean plasma concentration. The thyroid accumulation rate equals the amount accumulated during the clearance period divided by the time in hours.

The endogenous creatinine clearance was taken as a measurement of the glomerular filtration rate (28, 29), having been shown to be a fair approximation of this value. The glomerular filtration rate was standardized to 1.73 m^2 body surface, this estimation of the body surface being based on the weight during the first clearance period, any weight gain due to DOCA being disregarded.

The product of the glomerular filtration rate and the mean logarithmic plasma concentration indicates the filtration per minute of I^{131}. The amount excreted per minute was calculated from the urine flow during the clearance period and from the urine concentration of radioactive iodine. The difference of these two figures gives the percentage reabsorption by the tubules. The percentage of excretion was also calculated using the formula of Platt (30) which is independent of the accuracy of the urine collection.

The protein - bound iodine in the plasma was estimated by the method of Barker (31) which was also used for the determination of the stable iodine in the urine.

The kidney does not differentiate between I^{127} and I^{131}. Assuming a complete mixing of I^{127} and I^{131}, the ratio $\frac{I^{131}\text{ concentration}}{I^{127}\text{ concentration}}$ in the urine and plasma must be the same. Thus the I^{127} concentration in the plasma can readily be

calculated when the other three factors are known (32). Based on the same assumption the rate of uptake of I^{127} by the thyroid gland can be calculated; the ratio $\frac{I^{131} \text{ uptake rate}}{I^{127} \text{ uptake rate}}$ must be equal to the ratio in blood or urine because the thyroid gland also does not differentiate between stable iodine and isotope.

Plasma chlorides were estimated according to the method of Schales and Schales (33), urine chlorides by the method of Volhard - Arnold (34). Sodium and potassium in plasma and urine were determined by flame photometry. The percentage reabsorption and renal clearance of these ions was estimated using the same principles as outlined above for iodine. The plasma proteins were measured by the method of Phillips et al. (35).

RESULTS

In table II are shown certain measurements made on the subjects before DOCA administration compared with similar measurements made on normal subjects reported in a previous communication (22). Only the thyroid uptake of stable iodine showed a significant difference between the two groups, as it can be seen in the table.

Three of the 15 patients are reported separately in table IX. H.P. was examined for the second time after having had DOCA injections for only 24 hours, compared with 72 hours for the rest of the group. W.H. proved to be hypothyroid, and E.G. showed an abnormally low creatinine clearance and would not take fluids. The results of these three are not included in the group but considered separately.

I. Thyroid function.

As is shown in table III the hourly uptake of I^{131} and I^{127} is depressed after administration of DOCA. The mean uptake of the radioactive isotope before DOCA was 3.2 % per hour. The same value after DOCA was 1.5 % per hour and this difference was found to be statistically highly significant. Of 12 subjects examined only one (E.L.) was found to have a slightly elevated uptake rate during DOCA administration.

The uptake of stable iodine before DOCA was 2.3 µgms per hour, after DOCA it was 1.2 µgms per hour. This difference was also found to be statistically significant..These results are also presented in table III, along with data on the

thyroid clearance of radioactive iodine which value is believed to be a more accurate estimation of the thyroid function (27). Before the administration of DOCA 17.4 ml of plasma were cleared per minute by the thyroid gland. This fell to 7.5 ml after 72 hours of DOCA, a highly significant difference.

The depressing action of DOCA on the thyroid function is further shown in fig. 1, where the 2, 4, 26 and 50 hour thyroid uptakes of the tracer dose of radioactive iodine are compared in each subject before and after treatment with DOCA. In all 12 patients with one exception, after DOCA therapy the percent uptake was lower at each time interval examined. The one exception D.C., showed a slightly increased 50 hour uptake of I^{131} after 3 days of DOCA.

II. Iodine level in plasma.

The level of I^{131} in the plasma 26 hours after the dose and the plasma level of stable iodine during the clearance periods is shown in table IV. The amount of radioactive iodine present in the blood 26 hours after the ingestion of the tracer dose was not significantly different after the injections of DOCA. The fasting plasma level of I^{127} was somewhat higher after DOCA, the mean value rising from 0.25 µgms% to 0.32 µgms%, but this difference was not significant.

Table V shows the values of protein - bound iodine before and after hormone administration and the changes in plasma proteins in 6 of the group on whom these were observed. Both showed a tendency to fall under the DOCA treatment.

III. Renal function.

In 7 of 11 subjects the glomerular filtration rate was considerably increased by the administration of DOCA. In the other 4 a fall could be observed. When this group as a whole is considered statistically although the mean glomerular filtration rate was higher after DOCA than before, this difference was not significant. These results are to be seen in table VI.

The amount of I^{131} and I^{127} filtered by the glomeruli per minute did not change significantly as shown in table VI.

As seen in table VI there was no change in the rate of excretion of either I^{131} or I^{127} following DOCA. Likewise there were no definite alterations in the tubular reabsorption or in the renal clearance of iodine. There appears to be a tendency to an increase in reabsorption of the tubular load of iodine and to a decrease of the renal clearance rate but both differences were statistically not significant.

Data concerning the plasma level and renal excretion of chlorine, sodium and potassium are shown in tables VII and VIII, of these only the plasma level of potassium showed any significant change. The concentration of potassium in the plasma was markedly decreased after the administration of DOCA. The rest of the data is not reported in detail, only the means, standard deviations and standard errors of the means of the plasma levels, the amount excreted per minute, the percentage reabsorbed, and the renal clearances of chlorine, sodium and potassium are shown in table VIII. As

may be seen DOCA did not bring about any alterations in these values.

Table I.

Clinical Details

Subjects	Sex	Age	Diagnosis
T.K.	M	18	Tb, ankle, arthrodesis
W.O'C.	M	38	Mental deficiency, psychosis
D.C.	M	22	Schizophrenia, affective psychosis
G.S.	M	50	Mental deficiency, psychotic episodes
R.A.	M	27	Schizophrenia, paranoid
H.B.	F	41	Neurotic depress. react.
W.P.	M	17	Schizophrenia
E.I.	F	22	Mental deficiency
A.S.	F	21	Schizophrenia, affective psychosis.
H.A.	F	21	Schizophrenia
T.T.	M	31	Chronic alcoholism*
R.R.	M	35	Parkinsonism, postencephalitic
H.P.	M	18	Schizophrenia, paranoid
E.G.	F	55	Schizophrenia, paranoid
W.H.	M	22	Schizophrenia

* Off alcohol and on medical treatment for 5 weeks prior to experiment, no organic lesions detected.

Table II.

Comparison of normal control group and psychotic patients before DOCA

	No.	Psychotic	No.	Normal	t	p
Thyroid uptake I^{131} % dose per hour	12	3.2 ± 0.4	12	4.2±0.6*	1.4	<0.5 >0.1
Thyroid uptake I^{127} mgm/hour	10	2.27± 0.31	7	1.08±0.23	3.14	<0.01
Plasma I^{127} µgm/100 cc.	9	0.25± 0.03	8	0.17±0.005	2.5	< 0.105 > 0.02
Thyroid clearance I^{131} ml/min.	12	17.4 ± 2.0	12	12.2±2.5	1.6	>0.1 <0.5
Glomerular filtration rate ml/min.	11	130 ± 6.9	11	140 ±1.6	2.2	<0.05 >0.02
Tubular reabsorption of I^{131}, % of filtered load	11	73.3 ± 1.6	11	72.9 ±1.5	1.1	<0.05 >0.1
Renal clearance I^{131} ml/min.	11	29.3 ± 2.7	12	31.4 ± 2.0	0.6	>0.5

* ± s.e.

Table III.

The thyroid uptake of I^{131} and I^{127} and the thyroid clearance of I^{131}.

	I^{131} uptake: % dose/hr.		I^{127} uptake: µgm/hr.		Thyroid clearance I^{131} ml/min.	
	Before DOCA	After DOCA	Before DOCA	After DOCA	Before DOCA	After DOCA
T.K.	1.71	0.89	1.81	0.49	10.6	2.0
W.O'C.	3.60	0.94	1.11	0.60	21.8	6.0
D.C.	5.54	2.26	3.32	2.51	30.5	11.5
G.S.	4.35	2.24	1.47	0.63	23.4	10.5
R.A.	1.74	0.71	2.68	1.78	7.1	3.4
H.B.	5.66	1.23	2.66	1.19	24.2	6.5
W.P.	1.80	1.60	0.86	0.64	9.5	8.9
E.L.	2.04	2.16			14.9	16.5
A.S.	2.49	2.11	2.43	2.33	16.1	12.3
H.M.	4.05	1.34	4.05	1.34	17.9	6.8
T.T.	2.27	0.37	2.27	0.37	11.5	2.7
R.R.	3.46	2.10			20.6	2.6
Mean $\pm$s.d.	3.23 ± 1.38	1.49 ± 0.67	2.27 ± 0.98	1.18 ± 0.79	17.4 ± 7.1	7.5 ± 4.6
$\pm$s.e.	± 0.4	± 0.19	± 0.31	± 0.25	± 2.0	± 1.3
t	3.86		2.74		4.1	
p	< 0.01		> 0.01 < 0.02		< 0.01	

Table IV.

The 26-Hour Blood Level I^{131} and Fasting Blood Level I^{127}

	I^{131}: % dose/100 ml.		I^{127}: µgm/100 ml.	
	before DOCA	after DOCA	before DOCA	after DOCA
I.K.	0.023		0.28	0.39
D.C.	0.040	0.065	0.09	0.17
D.C.	0.042	0.073	0.18	0.36
G.S.	0.032	0.031	0.10	0.10
R.A.	0.169	0.075	0.63	0.87
H.B.	0.042	0.036	0.18	0.34
W.P.	0.032	0.049	0.15	0.12
E.L.	0.022	0.074		
A.S.	0.039	0.098	0.25	0.31
H.M.	0.052	0.039	0.36	0.21
T.T.	0.048	0.031	0.25	0.32
R.R.	0.035	0.016		
Mean	0.049	0.053	0.25 ± 0.11 S.E. ± 0.03	0.32 ± 0.22 S.E. ± 0.07
				t = 0.92
				p > 0.10

Table V.

Body weight, protein-bound iodine and plasma proteins

	Weight: lbs		PBI: µgm/100 ml.		Plasma proteins: gm/100 ml.	
	Before DOCA	After DOCA	Before DOCA	After DOCA	Before DOCA	After DOCA
T.K.	129	129	4.9			
W.O'C	131	150	3.5			
D.C.	135	134				
G.S.	131	136	6.7			
R.A.	136	147	3.2			
H.B.	97	100	4.8	2.7	6.4	5.7
W.P.	150	155	5.3	4.0	7.2	6.3
E.L.	111	110	8.8	5.7	6.3	5.8
A.S.	152	152	5.5	6.0	6.9	6.7
H.M.	118	123	8.3	7.5	6.8	6.2
T.T.	170	175	7.0	7.0	6.6	5.5

Table VII.

Plasma Level of Potassium (mgm./100 ml.)

	Before DOCA	After DOCA
R.A.	16.6	12.2
H.B.	20.4	19.3
W.P.	18.0	18.3
E.L.	14.9	14.1
A.S.	15.9	14.8
H.M.	16.6	12.2
T.T.	22.1	14.5
Mean	17.8 ± 2.6 S.E. ± 1.0	15.1 ± 2.8 S.E. ± 1.0
		t = 2.6
		p < 0.02 > 0.01

Table VIII

Mean values of plasma level and renal excretion of chlorine, sodium, potassium.

	Before DOCA			After DOCA		
	Mean	± S.D.	± S.E.	Mean	± S.D.	± S.E.
Plasma Na mgm.%	327.8	± 15.6	± 4.5	331.9	± 13.2	± 3.8
Na excreted per min/mgm.	2.3			2.5		
Na reabsorbed %	99.4			99.5		
Na clearance ml/min.	0.72			0.72		
Plasma Cl, mgm.%	373			372		
Cl excreted per min., mgm.	6.0			6.7		
Cl reabsorbed %	98.6			98.7		
Cl clearance ml/min.	1.62			1.80		
Plasma K mgm.%	17.8	± 2.6	± 1.0	15.1	± 2.8	± 1.0
K excreted per min. mgm.	2.6			2.6		
K reabsorbed %	88.3	± 2.3	± 0.9	85.8	± 7.3	± 2.7
K clearance ml/min.	13.9			14.0		

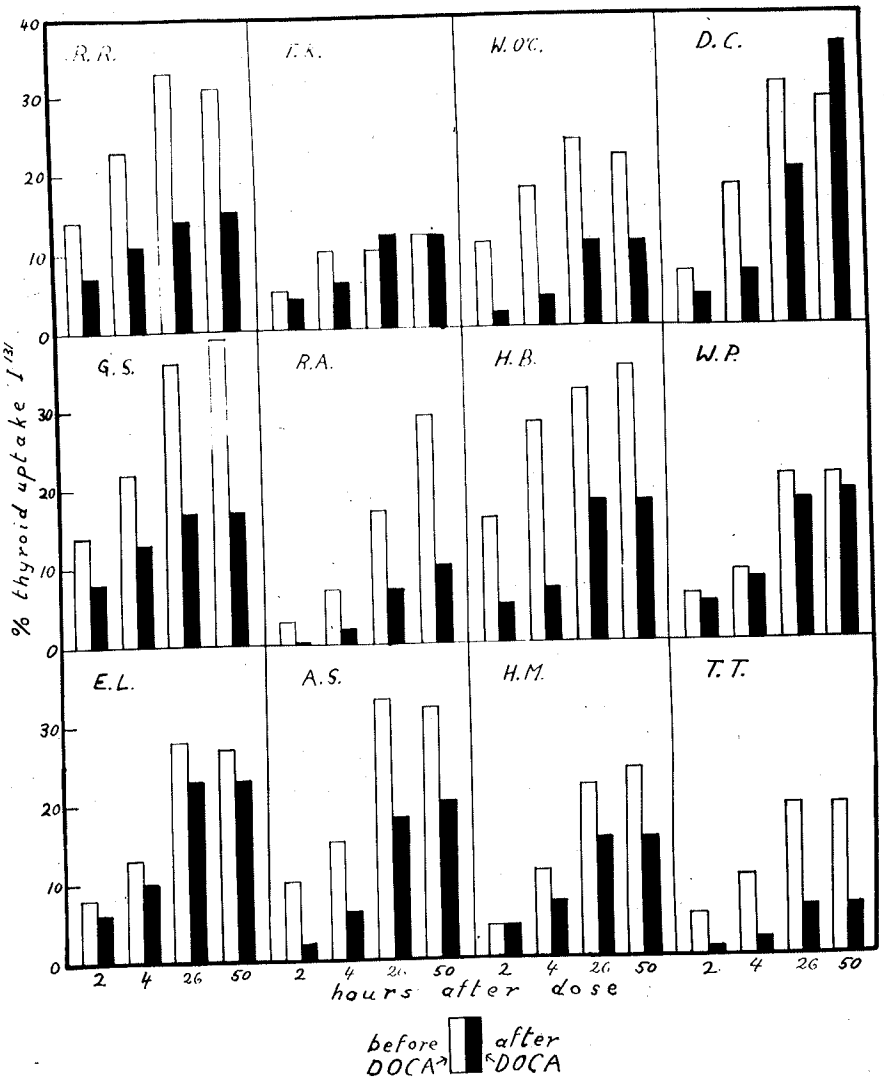

Fig. 1. The thyroid uptakes of I^{131} in 12 subjects before and after treatment with DOCA for 3 days.

DISCUSSION

In order to analyse data statistically it is necessary that the group be as homogeneous as possible. Three of the 15 patients could therefore not be included in the statistical calculations. H.P. was not submitted to the same procedure as the rest of the group. He was on DOCA for only one day prior to the second clearance period, whereas the rest of the group received DOCA for three days. His data are reported as a single experiment which has to be interpreted cautiously. W.H. was admitted to the psychopathic ward in a psychotic state. Based on our results a diagnosis of hypothyroidism was eventually made and the patient was subsequently treated with thyroid hormone with a marked improvement. These results are reported as a single observation of a case of hypothyroidism treated for three days with DOCA. Part of E.G.'s mental illness took the form of refusing to drink and she could not be persuaded to increase her fluid intake. Her glomerular filtration rate was well below the normal range (67.7 ml or 77.0 ml per 1.73 m^2 body surface area before DOCA and 55.1 ml or 62.7 ml per 1.73 m^2 after DOCA). A moderate decrease in the glomerular filtration rate after water deprivation in the adult man has been described (36, 37, 38). Endogenous creatinine clearances are depressed when the urine flow falls to a low level (0.41 ml / min and 0.21 ml / min in this instance) (29, 39). These three subjects have been reported separately in table IX. It is of interest that W.H.'s hypofunctioning thyroid gland was also further depressed by DOCA.

In four other patients a few data are lacking. The urine collection of R.R. was incomplete. The urine I^{127} of E.L. and T.T. and the 26 hour plasma level I^{131} of T.K. was found to be so high that a contamination probably occured.

The comparison between the previously reported control group and the psychotic group before DOCA shows that the psychotic patients had a higher mean blood level of I^{127} and a higher thyroid uptake rate of I^{127}. This difference could be ascribed to different dietary regimes. The psychotic patients were recent admissions whose previous dietary history was unknown whereas in the normal control group were persons hospitalized for some time for various reasons. All the other investigations revealed no significant difference between the two groups and it is concluded that as far as thyroid and renal function is concerned there is no appreciable difference between psychotic and non psychotic patients with no organic lesions. This is in accordance with Bowman et al. (40) who found a normal thyroid function in patients with mental diseases. Reiss et al. (41) postulated a possible thyroid hyperfunction in schizophrenia but our data on the schizophrenics in the group do not support this claim.

The rate of uptake of radioactive iodine slowed down markedly after the administration of DOCA and the maximum uptake was lower. Such a decrease in the uptake of radioactive iodine may be an artefact. As pointed out above the thyroid gland does not differentiate between stable iodine and radioactive iodine. If only a small amount of iodine is present in the bloodstream and a tracerdose of radioactive iodine is added, a considerable portion of the total iodine which

the thyroid gland picks up, will be radioactive, whereas if the iodine content of the bloodstream is increased the portion of radioactive ions picked up will be smaller. The radioactive iodine has been diluted by the stable iodine.

The possibility of an error through a dilution effect can be excluded by simultaneous studies of the stable iodine. The plasma level of I^{127} is slightly higher after DOCA but the difference is not significant (Vide infra). The thyroid uptake of I^{127} however is significantly decreased. The decreased uptake of I^{131} is therefore not a dilution effect; DOCA depresses the iodine uptake by the thyroid gland in normal subjects. The decreased thyroid activity is further seen in the marked depression of the thyroid clearance rate of I^{131}.

The hypothyroid patient W.H. showed low values to start with. After DOCA the uptake of radioactive and of stable iodine and the thyroid clearance of I^{131} were found to be even more decreased. This indicates that a hypofunctioning thyroid gland can also be depressed by DOCA.

The effect of DOCA on the thyroid gland has not been investigated extensively. Paschkis et al. (19) while investigating the thyroid function of rats in the alarm reaction, administered high doses of DOCA for 2 days, but found no change in the thyroid uptake of I^{131}. Franke et al. (42) reported an increased thyroid I^{131} concentration in adrenalectomized rats maintained on DOCA and normal saline for 8 weeks. Boatman et al. (43) gave small doses of DOCA to rats for 30 days and found an increased concentration of I^{131} in the thyroid gland and other tissues which they considered to

be a manifestation of a retention of I^{131} induced by DOCA.

These studies can not be readily compared with the results reported here. They were carried out on rats and both the dose of DOCA and the duration of the experiment were different.

There is an extensive literature available on the effect of ACTH and cortisone on thyroid function and on the effect of various stress situations, a state accompanied by elevated titers of adrenal cortical hormones in the body. In general, under such circumstances there appears to be a depression of thyroid function. For example Selye (44, 45) mentioned signs of atrophy and involution in the thyroid gland during the early stages of the general adaptation syndrome and Antopol (46) described the histological picture of thyroid hypofunction after large doses of cortisone in mice. Paschkis et al. (19) found a diminished uptake of I^{131} per mgm of thyroid tissue in rats after giving formalin injections as an alarming stimulus. Soffer et al. (14) concluded from experiments on rats that the normal adrenal cortex and administration of cortisone inhibit the thyrotropin stimulating effect of epinephrine. Money et al. (13) found a depression of I^{131} uptake of the thyroid gland after ACTH and cortisone in rats and Hill et al. (17) induced a depressed I^{131} accumulation gradient and a lower PBI in normal men with ACTH and cortisone. Wolfson et al. (16) made the same observation on patients who had received ACTH or cortisone over several weeks. On the other hand Reiss et al. (47) reported an increased thyroid function in normal men, 3 - 4 hours after stimulation of the adrenal cortex by epinephrine via the pituitary. It may be that initially

there is a stimulation of the thyroid gland for these same workers (48) reported that depression of the iodine uptake by ACTH occurs only after at least 48 hours treatment and in Addison's disease treated with cortisone an initial increased uptake rate was followed by a depression.

A similar response of the thyroid gland to DOCA is possible. After three days the depressed state would be reached. The only subject who was examined earlier (H.P.) did not show a depression of thyroid function but he also showed no evidence of a stimulation.

The reported experiments suggest strongly that a depression of the thyroid gland takes place when DOCA has been given for three days. They do not give any indication of the mechanisms which induce the depression. Soffer et al. (14) assume that the pituitary gland is involved, cortisone inducing a decrease in the production of thyroid stimulating hormone. This assumption is in contradiction to the observation of Oehme (49) that adrenal cortical extract does not prevent the response of the thyroid gland to endogenous thyroid stimulating hormone in guinea pigs. Perry (50) showed recently in rats that the thyroid depressing action of cortisone is a direct action on the gland and not mediated via a depression of the pituitary thyroid stimulating hormone. Similar unpublished experiments (51) with DOCA indicate thatbthis substance also acts directly on the thyroid gland, depressing its activity.

The diminished concentration of the plasma proteins of all subjects examined in the second clearance period suggests that a dilution of the plasma occurred. An increased plasma volume

has been found after DOCA in dogs (52) and in men (53). The drop in the concentration of the protein - bound iodine observed in some subjects is therefore not necessarily an expression of a decrease in the total amount of circulating PBI. A decrease of the PBI after administration of ACTH or cortisone has been reported (17, 15, 18) and assumed to reflect a decreased output of hormone by the thyroid gland. A dilution of the blood has also been found after ACTH or Cortisone (54) and it was thought to be due to a shift of water from the intracellular into the extracellular space (55, 56), in accordance with the observation of an increased amount of intracellular water in adrenal insufficiency (57, 58).

The plasma level of stable iodine appeared to be increased after DOCA but the difference proved to be insignificant on statistical analysis of the data. The beforementioned plasma dilution which per se could cause a lowering of the iodine concentration has to be taken into account. The dilution can not be accurately assessed quantitatively, the possibility of a significant increase of the total circulating iodine however can not be ruled out. The plasma level of I^{131} 26 hours after the ingestion of the tracer dose did not change under the influence of DOCA. The same argument as above can of course be applied to the radioactive iodine.

The endogenous creatinine clearance has been used as an estimation of the glomerular filtration rate, having been shown to give values similar to those obtained with the inulin clearance in normal subjects (28, 29). Brod an Sirota mentioned that a difference might appear under conditions

of an increased protein intake or an increased protein breakdown. This possibility has to be kept in mind when the test is used in connection with ACTH and cortisone. A decrease of the average C_{Cr} / C_{In} ratio under treatment with ACTH or cortisone has been reported (54, 59). A change of this ratio under treatment with DOCA is improbable on this ground as DOCA has no protein - catabolic action.

The endogenous creatinine clearance values in our psychotic patients were unusually widespread, even after standardization: the lowest value was 99 ml per min, the highest 172 ml per min. The reason for the variation is unknown. In 7 patients the endogenous creatinine clearance increased considerably under the DOCA treatment and in 5 patients it decreased. Thus although in a given individual there can be marked changes in the glomerular filtration rate after DOCA, when the group was considered as a whole, the mean was only slightly increased and the difference was not significant.

It has been shown that DOCA increases the low filtration rate in patients with Addison's disease (60). The findings in normals are less clear. Various observers report that DOCA caused an increased glomerular filtration rate in the dog (55, 61, 62, 63). No change has been found in cats (63), in rats (64) and in men (65). ACTH and cortisone have been found usually to cause an increase in glomerular filtration rate in men (56, 54, 66, 67, 68, 69). Levitt and Bader (56, 70) report a gradual increase and later decrease under ACTH or cortisone therapy.

The amount of iodine, both stable and radioactive, which

is filtered through the glomeruli per minute did not change significantly under the influence of DOCA. This result is expected because blood level and glomerular filtration rate did not change. The values concerning excretion per minute and percentage tubular reabsorption of iodine show considerable individual variations but the means are not significantly different. The same thing can be said about the renal clearance of iodine. 5 patients had increased renal clearances of iodine after administration of DOCA, 5 patients lowered clearances and in one instance it remained unchanged. The excretion of I^{127} can be markedly changed by DOCA in a given individual but not consistently in any direction. The group as a whole did not show any significant changes in I^{127} excretion and no explanation for the different reaction in various individuals has been found. It is possible that the examination of a larger group would reveal a change in the kidney function after DOCA as far as iodine is concerned, for both excretion and reabsorption show a tendency to rise. This is of course only possible if the glomerular filtration rate tends to rise also.

The plasma level and the renal excretion of chlorine, sodium and potassium can be discussed together. The plasma potassium was significantly lower after administration of DOCA, whereas the potassium excretion and the renal clearance did not show a parallel increase. There are two possible explanations of this discrepancy. The patients received DOCA for 3 days and only on the fourth day the blood and urine were examined. It is not known what happened before and it is possible that

the excretion was elevated at first, to be followed later by a lower plasma level and subsequently by a secondary lowering of the excretion. The other possibility would be a shift of potassium into the cells.

The action of DOCA on the electrolyte balance is qualitatively the same as the action of the glucocorticoids (71, 72). A transient increase of the potassium excretion during the first days of ACTH or cortisone administration has been described by Seldin et al. (73) and by Levitt and Bader (56). An increased intracellular potassium concentration after DOCA has also been reported (55, 56). The increased concentration was accompanied by a loss of intracellular water and thus s shift of potassium into the cells need not have occurred. The relative amount of intracellular potassium is increased in adrenalectomized animals (57) and adrenocortical tumors can cause a depletion of intracellular potassium (74, 75). Thus a shift of potassium into the cells after administration of DOCA seems rather unlikely.

In adrenal insufficiency DOCA restores the sodium and chloride balance and diminishes the potassium retention. The effect of a hormone used as replacement therapy may be quite different from the effect the same hormone exerts when given to a normal subject. Another important factor determining the electrolyte excretion is the electrolyte intake during the experiment. In this investigation the diet was uncontrolled and blood levels and excretion were only examined twice.

A considerable number of papers deals with the influence of adrenal cortical hormones on the electrolyte balance.

This problem has been recently reviewed (76). In general an increased reabsorption of sodium and chloride has been found (54, 66, 77). No changes have been observed by Welt et al. (78) and Zierler and Lilienthal (79) reported a case of actual sodium loss after administration of DOCA. The observation that the effect of ACTH on the tubular reabsorption of sodium is a function of the glomerular filtration rate (80) has not been confirmed in these experiments with DOCA. The effect of adrenal cortical hormones on the excretion of potassium might be indirect: increased potassium excretion when the sodium excretion is decreased (81) or it might be a direct effect on the tubular reabsorption (80).

Not only the electrolyte intake, the blood level and the excretion have to be considered but also the possible shift of water and electrolyte from the intracellular space in the extracellular space under the influence of adrenocortical hormones, as suggested by Levitt and Bader (56).

It is generally assumed that the organism does not distinguish sharply between the halide ions (82, 83, 84, 85, 86, 87). Our investigations confirmed the observation that the kidneys excrete iodide more readily than chloride (82). After administration of DOCA the excretion, reabsorption and renal clearance of chloride and iodide may show a change, but the change does not always occur in the same direction for the two halogens. The significance of this finding is not understood.

No definite conclusions concerning the electrolyte metabolism can be drawn from our investigations. It is obvious

that better controlled experiments, carried out on a metabolic ward, are necessary to throw more light into this difficult problem.

SUMMARY AND CONCLUSIONS

The thyroid function has been investigated in 15 subjects before and after receiving 10 mgms Desoxycorticosteroneacetate daily for 3 days. The thyroid gland is markedly depressed after administration of DOCA as evidenced by low uptake of both radioactive and stable iodine and by a low thyroid clearance of I^{131}. A dilution of the plasma takes place which leads to a decrease of the plasma proteins and of the protein - bound iodine concentration. The plasma levels of iodide, chloride and sodium do not change, the plasma potassium is significantly lower after DOCA. The renal electrolyte excretion is not significantly altered.

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