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THE ANTIDIURETIC AND OXYTOCIC HORMONES IN THE POSTERIOR PITUITARY GLANDS OF NEWBORN INFANTS AND ADULTS

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Newborn infants pass normally a very dilute urine (McCance & Young, 1941; Heller, 1944) and there is the suggestion that they are unable to concentrate it to the same degree as adults, even when fluid intake is restricted as during the first 3 days after birth. It has been pointed out (Heller, 1944) that glomerular filtrate of the composition elaborated by the kidney of the newborn and flowing at the low velocity resulting from the low glomerular filtration rate, would invariably be highly concentrated when passing through the tubules of a normal adult kidney. It would seem, therefore, that the neurohypophysio-renal mechanism which in the adult is the major determinant of the final concentration of the urine, operates differently in the newborn. The finding (Heller, 1944) that intramuscular doses of posterior pituitary extract which produced a pronounced inhibition of water diuresis in adults, had only a slight effect on newborn infants, agrees with this assumption. However, it still remains to be seen whether lack of antidiuretic hormone is a factor additional to the lower sensitivity of the tubules in preventing the newborn child from concentrating the urine like an adult.

It has been shown in a previous paper (Heller, 1947) that the pituitary gland of newborn rats (in which withdrawal of fluid even for 24 hr. fails to raise the concentration of the urine significantly (Heller, 1949)) contains only about one-tenth of the antidiuretic principle found in the glands of adults of the same strain. However, human beings are more mature at birth than rats and one would therefore expect to find more hormone in the posterior pituitary gland of newborn infants. The work described below gives the results of estimations of the antidiuretic and oxytocic hormones in the posterior pituitary lobes of fifteen newborn infants and fourteen adults.

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METHODS

Age, sex and cause of death of the subjects from which pituitary glands were obtained will be seen from Tables 1 and 2. The bodies were kept in refrigerators up to the time of the post-mortem examination. As soon as possible after the skull had been opened the hypothalamic region including the bones forming the pituitary fossa were removed 'en bloc' and were placed in a large weighing bottle kept in ice in a Dewar flask.

Preparation of extracts. With the help of low magnification the posterior lobe was dissected free from other tissue and immediately weighed in a tared weighing bottle. Five c.c. of acetone were then added which were renewed after 6 hr. After further 18 hr. the acetone was discarded and the gland dried first over calcium chloride and then above phosphorus pentoxide. Extracts were made by macerating the glands in a solution containing 0·9% NaCl and 0·25% acetic acid. For each mg. of dry gland tissue 0·5 c.c. was allowed. The extracts were boiled for 3 min., were then filtered and the residue washed five times with about 0·5 c.c. of 0·9% NaCl or Burn-Dale solution (British Pharmacopoeia, 1932).

Assay of antidiuretic activity. Intravenous injections into unanaesthetized rabbits were employed (Heller, 1941).

Assay of oxytocic activity. Virgin guinea-pig uteri were used. Posterior pituitary extract (British Drug Houses) was used as the standard preparation.

RESULTS

The hormone content of the posterior pituitary lobe of newborn infants and adults. Tables 1 and 2 show the results of hormone estimations in the extract of individual glands. Table 3 gives mean results and their standard errors. No evidence could be obtained from our limited series for a sex difference in either the weight or the hormone content of the adult posterior pituitary lobes. The mean weight of adult posterior lobes (wet) of adult men was $139{\cdot}1 \pm 9{\cdot}9$ mg. (S.E. of eight observations) and that of adult women $131 \pm 7{\cdot}4$ (5) mg. ($t = 0{\cdot}63$, $P > 0{\cdot}5$). The mean content of oxytocic hormone per mg. neurohypophysial tissue was 746 ± 64 (8) mU. in men and 748 ± 69 (5) mU. in women ($t = 0{\cdot}03$, $P > 0{\cdot}9$). The distribution of the sexes did not permit a similar calculation for the glands of newborns.

Influence on hormone content of the delay in removing the pituitary gland after death. The period of delay in removing the glands varied from 7·5 to 40 hr. after death (Tables 1 and 2). However, no significant correlation could be found between the length of time for which the gland remained in the dead body and the amounts of hormone found. For example, 'r' for oxytocic activity per mg. dry posterior lobe tissue of adults $= +0{\cdot}47 \pm 0{\cdot}29$, '$r$' for oxytocic activity per mg. of dry posterior lobe tissue of newborns $= -0{\cdot}33 \pm 0{\cdot}29$. These figures have not been taken to mean that no losses of hormone occur after death, but only as an indication that such losses, if they occur, are within the limits of individual variations and of the errors of the methods of assay.

Dissection of the posterior pituitary lobe of newborn infants. The small size of the posterior lobe of newborn infants (mean weight $= 15{\cdot}1 \pm 1{\cdot}6$ mg.) made its dissection difficult, and the question arose whether we succeeded in separating

TABLE 1. The antidiuretic and oxytocic hormone content of posterior pituitary glands of adults

No.	Age in years	Sex	Wt. of anterior lobe (wet, mg.)	Wt. of posterior lobe (wet, mg.)	Wt. of posterior lobe as % of whole pituitary gland	Wt. of posterior pituitary lobe (dry, mg.)	Solids in posterior lobe (%)	Antidiuretic activity		Oxytocic activity		Delay in removal of pituitary gland (hr. after death)	Cause of death
								mU./ posterior lobe	mU./mg. dry posterior lobe tissue	mU./ posterior lobe	mU./mg. dry posterior lobe tissue		
1	14	♀	—	122·0	—	17·6	14·4	≃17600	≃1000	≃16000	≃910	13	Severe anaemia
2	15	♂	427·4	94·4	18·1	15·2	16·1	>12500<16700	>830<1100	≃15900	≃1050	22	Tuberculous meningitis
3	24	♂	—	140·7	—	17·0	12·1	> 6800<13600	>400<800	≃9000	≃530	14	Chronic glomerulo-nephritis
4	32	♂	352·5	171·6	32·7	33·8	19·7	≃2000*	≃60*	≃680*	≃20*	7	Meningioma
5	39	♀	505·3†	123·3	19·6	19·1	15·5	> 9600<14300	>500<750	≃9200	≃510	7	Chronic nephritis and hypertension
6	46	♂	276·8	126·2	31·3	17·5	13·9	> 8800<12400	>500<710	≃11700	≃670	30	Lobar pneumonia
7	47	♂	408·4	166·1	28·9	22·0	13·3	>11000<22000	>500<1000	>13900<27500	> 630<1250	24	Brain tumour
8	48	♂	482·6	149·9	23·7	25·2	16·7	>18300<24000	>730<980	≃16400	≃650	18	Shock
9	50	♂	—	111·0	—	17·3	15·7	≃6900	≃400	≃9900	≃570	15	Rectal carcinoma
10	51	♂	540·6	101·0	15·7	12·2	12·1	> 7600<9200	>500<750	≃9800	≃800	25	Gastric ulcer
11	59	♀	548·1	143·3	20·7	20·0	14·0	>19000<29000	>950<1450	≃17000	≃850	24	Pulmonary embolism
12	60	♀	505·8	153·2	23·2	23·5	15·4	>12900<17600	>550<750	≃16400	≃700	20	Cerebral embolism
13	63	♂	197·4	124·2	38·6	18·6	15·0	>14300<18600	>770<1000	≃14100	≃760	26	Pneumonitis
14	64	♀	536·0	113·1	17·4	18·0	15·9	>13500<18000	>750<1000	≃13900	≃770	22	Pulmonary embolism

* Not included in mean (Table 3).
† Content of colloid cyst weighing 88·7 mg. not included.

TABLE 2. The antidiuretic and oxytocic hormone content of posterior pituitary glands of newborn infants

No.	Extra-uterine life (days)	Maturity (weeks)	Sex	Body wt. (kg.)	Wt. of anterior lobe (wet, mg.)	Wt. of posterior lobe (wet, mg.)	Wt. of posterior lobe as percentage of whole pituitary gland	Wt. of posterior lobe (dry, mg.)	Solids in posterior lobe (%)	Antidiuretic activity		Oxytocic activity		Delay in removal of pituitary gland (hr. after death)	Cause of death
										mU./ posterior lobe	mU./mg. dry posterior lobe tissue	mU./ posterior lobe	mU./mg. dry posterior lobe tissue		
1	Stillborn	40/40	♂	4·63	95·6	24·7	20·1	3·0	12·1	<1500*	<500	>990<1850	>330<650	7·5	Intracranial haemorrhage
2	Stillborn	Premature	♂	—	31·6	18·0	36·3	2·5	13·8	≃200	≃80	≃200	≃80	12·0	Prematurity
3	Stillborn	—	♀	—	48·4	22·2	31·4	2·2	10·0	≃400	≃180	≃320	≃150	24·0	Erythroblastosis foetalis
4	0·1	30/40	♀	—	54·2	7·9	12·8	1·8	22·8	>200<330	>100<180	≃210	≃110	9·5	Intracranial haemorrhage
5	0·1	—	♂	—	63·5	11·9	15·8	2·3	19·3	>400<650	>175<280	—	—	26·0	Cystic kidneys
6	1·0	28/40	♂	1·37	51·6	18·7	26·6	2·4	12·9	>240<480	>100<200	≃190	≃80	40·0	Prematurity, atelectasis
7	2·0	33/40	♂	2·31	41·6	14·4	25·7	3·0	20·8	>300<600	>100<200	≃240	≃80	12·0	Atelectasis
8	4·0	36/40	♂	1·98	45·5	15·2	25·0	1·7	11·2	>160*	>95*	≃160	≃95	7·5	Shock (P.M. : N.A.D.)
9	4·0	40/40	♂	2·66	74·2	20·4	21·6	2·0	14·2	>250<500	>125<250	>250<480	>125<240	20·0	Haemorrhagic disease
10	4·0	32/40	♂	1·47	53·4	13·7	20·4	2·8	20·4	≃200	≃70	—	—	14·0	Basal atelectasis. Kern icterus
11	16·0	38/40	♂	—	78·1*	29·5*	27·4*	4·2	14·2	≃500	≃115	>440<580	>110<140	30·0	Intracranial haemorrhage
12	26·0	40/40	♀	—	85·6*	9·0*	10·5*	1·5*	16·5	>400<650	>270<430	≃250	≃165	24·0	Congenital heart disease

* Not included in mean (Table 3).

it quantitatively from the rest of the gland. The antidiuretic and oxytocic activities of extracts from three whole pituitary glands were therefore estimated. Results of animal experiments (Heller, 1941, 1947) had shown that the presence of pars glandularis tissue did not interfere with the assay for the antidiuretic principle. The pituitary gland of the 1st infant of this series (age in days = 0·1, maturity = 28/40) contained $\simeq$ 250 mU. in terms of antidiuretic activity and $\simeq$ 300 mU. in terms of oxytocic activity, that of the second infant (age in days = 0·7, maturity = 36/40) contained $\simeq$ 330 mU. and > 250 < 275 mU., and that of the third infant (age in days = 7·0, maturity = 28/40) > 200 < 300 mU. and > 250 < 375 mU. These figures compare well with the results obtained from separated posterior lobes (Table 2). They suggest that the dissection of the posterior lobe of newborn infants was successful.

TABLE 3. The antidiuretic and oxytocic hormone content of human posterior pituitary glands (means and their standard errors)

	Adults	Newborn infants
Wt. of anterior lobe (wet, mg.)	435±33·8	60±5·9
Wt. of posterior lobe (wet, mg.)	131±6·5	15±1·6
Wt. of posterior lobe as percentage of whole pituitary gland	24·5±1·82	23·6±2·22
Wt. of posterior lobe (dry, mg.)	19·8±1·4	2·4±0·2
Solids in posterior lobe (%)	14·9±0·53	15·8±1·38
Antidiuretic activity:		
(*a*) (mU./posterior lobe)	14570±1580	375±40
(*b*) (mU./mg. dry posterior lobe tissue)	761±58	166±25
Oxytocic activity:		
(*a*) (mU./posterior lobe)	13850±1085	387±20
(*b*) (mU./mg. dry posterior lobe tissue)	747±45	150±38

Proportion of antidiuretic to oxytocic activity in the posterior pituitary lobe extracts. No significant difference between the mean amounts of antidiuretic and oxytocic hormone was found in either the glands of adults (t between mU. antidiuretic and mU. oxytocic principle per mg. dry neurohypophysial tissue = 0·19, $P > 0·8$) or those of newborn infants ($t = 0·37$, $P > 0·7$). It seems, therefore, that in human posterior pituitary glands the two activities occur in the same proportion as in the international standard powder which is prepared from pituitaries of cattle or pigs.

Comparison of the hormone content of the posterior pituitary lobe of newborn infants with that of glands of adolescents and adults. The number of 'adult' glands (Table 1) investigated was too small to permit a subdivision into age groups. The mean hormone content of the pituitary lobes of two adolescents, aged 14 and 15, was slightly higher (antidiuretic activity per mg. dry tissue = 985 mU., oxytocic activity = 980 mU.) than the mean of adult subjects but this may have been accidental ($t = 2·12$, $P > 0·05$). When figures for all subjects between the ages of 14 and 64 (Table 1) were pooled, the following means and

standard errors were obtained: antidiuretic activity per mg. dry neurohypophysial tissue = 761 ± 58 mU., oxytocic activity per mg. tissue = 747 ± 45 mU. The corresponding figures per mg. of dry neurohypophysial tissue of newborn infants were 166 ± 25 and 150 ± 38 mU. Per mg. dry tissue the posterior pituitary lobe of the newborns contained, therefore, approximately one-fifth of the active principles found in the glands of adults. Since the percentage of solids of the posterior lobe was found to be much the same in adults (14·9 ± 0·53 g./100 g.) and in newborn infants (15·8 ± 1·38, $t = 0{\cdot}69$, $P > 0{\cdot}5$), the ratio remains the same if hormone content is calculated per mg. *wet* neurohypophysial tissue.

When related to body weight the posterior lobe of newborns was found to weigh about four times more than that of adults (8·3 ± 1·2 mg./kg. body weight as against 2·0 mg./kg., assuming a mean body weight of 65 kg. for adults), while the ratio weight of posterior lobe/weight of anterior lobe was very similar in both instances (Table 3). Since, per mg. neurohypophysial tissue, the posterior lobe of newborn infants was shown to contain about one-fifth of the hormones found in that of adults, it follows that the hormone content of the posterior pituitaries of newborns, when calculated per kg. body weight, is only a little lower than that of adults. The following mean values were obtained for antidiuretic activity (oxytocic activity in parentheses): newborn infants = 185 ± 21 (175 ± 31) mU./kg. body weight, adults = 224 (213) mU./kg. body weight. It may be doubted whether much significance should be attributed to this relationship, which basically only expresses the high relative weight of the brain and its appendages in the human newborn.

DISCUSSION

While the active principles in the posterior pituitary gland of newborn infants seem to have been estimated only in isolated cases, several authors have reported on the hormone content of large series of adult human glands: Unfortunately, Lampe's (1926) careful work was done before the adoption of the international standard, which makes his results difficult to interpret. More recent is the work of Simon & Nagy (1934) who assayed the pressor and oxytocic principles, and that of Jores & Zschimmer (1934) who estimated the oxytocic principle only. The results of Simon & Nagy are in good agreement with ours. Their series of twenty adult pituitaries, for instance, contained a mean of 10750 ± 1721 mU. oxytocic hormone/gland; the mean of our estimations (derived from a comparable series) is 13850 ± 1085 mU./gland. The figures of Jores & Zschimmer are unaccountably lower.

The posterior lobe of newborn infants contained only about one-fifth of the antidiuretic and oxytocic principles found in the adult glands (per mg. dry tissue). This low hormone content is unlikely to have been due to an increase of secretory activity immediately before or during parturition: the hormone con-

centration (=mU./mg. neurohypophysial tissue) was much the same in newborn infants as in children who died 7 and 16 days after birth. It seems reasonable to assume that this interval would allow for replenishment of the gland. However, we may regard the neurohypophysis as modified hypothalamic tissue (see, e.g., Griffith, 1940), i.e. as bearing a similar relationship to the hypothalamus as does the adrenal medulla to the sympathetic nervous system. The low hormone content of the posterior pituitary lobe of newborn infants would thus be well in harmony with the immaturity of the human hypothalamus at birth (Le Gros Clark, 1938; Papez, 1940).

The demonstration, in the newborn child, of a low concentration of antidiuretic hormone in the posterior pituitary gland, leads to the question whether the apparent inability of newborn infants to concentrate the urine to the same degree as adults arises from a lower sensitivity of their renal tubules to the antidiuretic hormone (Heller, 1944) or whether lack of hormone production contributes to this inadequacy of the neurohypophysio-renal mechanism at birth. It was shown (Table 3) that the content of antidiuretic hormone of the neurohypophysial tissue of newborns was about 20% of that of adults. The hormone content of the posterior lobe of a boy of 10 suffering from diabetes insipidus, which we recently had occasion to investigate (details of this case will be given in a later publication) was less than 1% of the normal, a finding which is in good agreement with estimations of the antidiuretic hormone in the gland of experimental animals whose pituitary stalks had been severed (Fisher & Ingram, 1936; Hickey, Hare & Hare, 1941; Hare, Hickey & Hare, 1941). Conversely, it has been shown by O'Connor & Verney (1942) in dogs that a residuum of about 5% of the antidiuretic function of the neurohypophysis suffices to constrain the output of urine within normal limits. While the hormone content of the neurohypophysial tissue of the newborn infant is undoubtedly much lower than in the adult, it is thus hardly low enough to attribute the low concentrations of urine in newborn infants to a deficiency of the antidiuretic pituitary principle.

SUMMARY

1. Antidiuretic and oxytocic hormones were estimated in the posterior pituitary lobes of fourteen adults (Table 1) and fifteen newborn infants (Table 2).

2. The following mean figures were obtained in adults: antidiuretic activity $= 14570 \pm 1580$ mU./gland (761 ± 58 mU./mg. dry neurohypophysial tissue); oxytocic activity $= 13850 \pm 1085$ mU./gland (747 ± 45 mU./gm. dry neurohypophysial tissue).

3. Mean figures obtained in newborn infants were as follows: antidiuretic activity $= 375 \pm 40$ mU./gland (166 ± 25 mU./mg. dry neurohypophysial tissue); oxytocic activity $= 387 \pm 20$ mU./gland (150 ± 38 mU./mg. dry neurohypophysial tissue).

4. Calculated per mg. dry tissue the posterior pituitary lobes of newborn infants contained therefore only about one-fifth of the antidiuretic and oxytocic hormones found in the glands of adults. The significance of this finding is discussed with reference to the renal function of the newborn.

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