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VASOPRESSOR AND OXYTOCIC ACTIVITIES OF THE PITUITARY GLANDS OF RATS, GUINEA-PIGS AND CATS AND OF HUMAN FOETUSES

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It has been shown (Dicker & Tyler, 1953) that the oxytocic activity of pituitary glands of bitches decreased independently of the vasopressor activity after whelping or lactation, and that in dogs' foetuses and puppies both activities developed at different rates. A similar investigation has now been carried out in other domestic animals such as rats, guinea-pigs and cats, and also in human foetuses.

METHODS

Animals

Rats. Normal adult animals of both sexes, females killed after delivery or during lactation, and young rats.

Guinea-pigs. Normal adult animals of both sexes, females killed after delivery or during lactation, and young guinea-pigs.

Cats. Normal adult animals of both sexes, lactatin females, foetuses, and kittens.

Human foetuses.

Preparation and assay of extracts

The whole of the pituitary gland was dissected out and extracted as described by Heller & Zaimis (1949). No attempt was made to separate the posterior lobe from the anterior, as this operation proved to be impracticable in foetuses and very young animals. In certain cases, glands from several animals or foetuses of the same litter were pooled and extracted together. As a control, saline extracts of fresh posterior lobe were also made, according to Heller's (1947) technique. The two methods of extraction yielded comparable results. The extracts were assayed for their vasopressor and oxytocic activities using as standards solutions of vasopressin (Pitressin: Parke Davis and Co.) and of oxytocin (Pitocin: Parke Davis and Co.).

Assay of the oxytocic activity. Holton's (1948) rat's uterus method was adopted. The fiducial limits of error in twelve experiments chosen at random varied between 3·4 and 34·2%; mean: 17·3%.

Assay of the vasopressor activity. Dicker & Tyler's (1953) modification of Landgrebe, Macaulay & Waring's (1946) rat's blood pressure preparation was used. Schild's (1942) four-point assay method was used for the quantitative determination of the vasopressor activity. The fiducial limits of error of the method were between 1·8 and 22·0%; mean: 10·4%.

Calculation of the results

All results were expressed in three ways: mU per gland, mU per 100 g body weight, or mU per 100 cm² body surface.

The following formulae were used for the calculation of body surface:

For the adult rat:

$S = 12{\cdot}54 \times W^{0{\cdot}60}$ (Lee, 1929).

The new-born rat:

$S = 7{\cdot}61 \times W^{0{\cdot}61}$ (Heller, 1952).

The adult cat:

$S = 10{\cdot}0 \times W^{0{\cdot}66}$ (Meeh, 1879).

Adult dog:

$S = 6{\cdot}63 \times W^{0{\cdot}71}$ (Cowgill & Drabkin, 1927; Stewart, 1921).

Human foetuses:

$S = 5{\cdot}188 \times W^{0{\cdot}75}$ (Scammon & Klein, 1929).

Human infants:

$S = 10{\cdot}98 \times W^{0{\cdot}692}$ (Boyd & Scammon, 1929).

No formulae are known for adult and young guinea-pigs, cats' foetuses, and kittens. Their body surface was arbitrarily calculated according to Lee's formula ($S = 12{\cdot}54 \times W^{0{\cdot}60}$).

Statistical treatment. Results are given as means, and their standard errors. 'Student's *t* test' for small sample as described by Fisher (1944) was used for estimating the significance of difference of means. The probability *P* for *t* was obtained from Fisher & Yates's (1943) tables.

RESULTS

Rats

Adult rats. In a series of eighteen rats (eleven females and seven males); body weight ranging from 140 to 350 g; mean: 230 ± 17·3 g (S.E. of eighteen observations), the amounts of vasopressor and of oxytocic activities in the pituitary glands were 350 ± 40·0 (18) and 320 ± 45·0 (18) mU. The ratio of vasopressor activity to oxytocic activity was 1·14 ± 0·052 (18) (Table 1). The amounts of vasopressor and oxytocic activity found in female and male rats were not significantly different.

In female rats killed after they had littered, there was a decrease of the oxytocic activity. The vasopressor activity remained unaffected. Thus the ratio of vasopressor activity to oxytocic activity increased from a mean of 1·14 to 1·73 ($t = 4{\cdot}177$) (Table 1).

In female rats killed after 10–15 days of lactation (mean number of sucklings: 10) there was a further decrease of the amount of oxytocic activity. Changes in the amount of the vasopressor activity were not significant ($t = 1{\cdot}422$, $P < 0{\cdot}2 > 0{\cdot}1$). The ratio of vasopressor activity to oxytocic activity was 1·85 ± 0·21 (6) (Table 1).

Young rats. Vasopressor assays of pituitary gland extracts of new-born rats were not possible, as intravenous injections of these extracts into rats produced invariably a fall of the blood pressure. In rats aged 5 days, however, the mean amounts of vasopressor and oxytocic activities of the pituitary gland were 22·0 and 2·6 mU/gland and the ratio of vasopressor activity to oxytocic

TABLE 1. Relation between vasopressor (V) and oxytocic (O) activities, body weight and body surface in adult rats, guinea-pigs, cats and dogs

	Body wt. (g)	Surface (cm²)	mU/gland		mU/100 g body wt.		mU/100 cm²			Average no. of litter mates
			V	O	V	O	V	O	V/O	
Adult rats (18)	230	325	350 ± 40·0	320 ± 45·0	150 ± 9·9	130 ± 9·6	100 ± 8·1	95 ± 9·3	1·14 —	— —
Female rats, Delivery (5)	186	288	330 ± 51·4	190 ± 24·9	181 ±29·5	105 ±15·0	116 ±18·3	67 ± 8·9	1·73 —	9 —
Female rats, Lactating (6)	216	314	240 ± 56·6	130 ± 23·8	134 ±50·5	71 ±21·8	85 ±27·5	45 ±11·8	1·85 —	10 —
Adult guinea-pigs (16)	411	461	600 ±122·0	240 ± 70·4	145 ±80·8	61 ±12·7	128 ±23·7	54 ±15·9	2·43 —	— —
Female guinea-pigs, Delivery (4)	538	544	770 ±134·2	460 ±187·2	135 ±28·3	79 ±20·6	135 ±29·4	81 ±22·2	1·88 —	3 —
Female guinea-pigs, Lactating (2)	682	620	470	129	69	19	76	21	3·64	3
Normal cats (4)	3,140	2,302	3,870 ±262·0	3,250 ±460·3	126 ±10·3	108 ±10·9	168 ± 9·6	141 ±18·3	1·19 —	— —
Lactating cats (4)	2,750	2,269	2,440 ±722·9	1,020 ±422·1	90 ±30·1	37 ±14·3	108 ±32·3	45 ±18·4	2·38 —	3 —
Normal dogs (8)	12,313	5,248	7,050 ±420	6,950 ±505	64 ± 1·6	629 ± 8·4	142 ± 9·3	138·0 ±14·7	1·03 —	— —
Female dogs, Delivery (3)	14,500	5,941	6,600 ±1,830	3,500 ±1,021	48·0 —	28·0 —	113 —	65 —	1·93 —	4 —
Female dogs, Lactating (4)	12,000	5,150	6,600 ±1,480	1,220 ± 203	61 ±13·9	13 ± 4·6	131 ±24·4	23 ± 4·9	5·41 —	6 —

Data for dogs have been taken from Dicker & Tyler's (1953) paper.
Number of animals in parentheses.

activity was 8·4. In young rats aged 21 days, the mean amounts of vasopressor and oxytocic activities had increased to 83 and 61 mU/gland; the ratio of vasopressor activity to oxytocic activity had fallen to 1·4, thus resembling that of adult rats.

Guinea-pigs

Adult guinea-pigs. In a series of six animals of both sexes from a heterogeneous stock (body weight ranging from 250 to 534; mean: 411 g), the amounts of vasopressor and oxytocic activities of the pituitary glands were 600 ± 122·0 (6) and 240 ± 70·4 (6) mU. There were wide variations in the amounts of both principles: the vasopressor activity varied from 168 to 879 mU, the oxytocic activity from 83 to 545 mU. The ratio of vasopressor activity to oxytocic activity was, however, in all cases greater than 1; its mean value was 2·43. These findings agree with those of Waring & Landgrebe (1950).

In female guinea-pigs killed either after delivery or during lactation, the same variability in the amounts of both vasopressor and oxytocic activities obtained. The mean ratio of vasopressor activity to oxytocic activity during lactation was 3·64 (Table 1).

Young guinea-pigs. Vasopressor and oxytocic activities were assayed in three litters, one of full-term foetuses, and two of new-born guinea-pigs aged 1 and 6 days. At birth, the mean amount of vasopressor activity was 145 mU/gland and that of oxytocic activity 14·5 mU/gland. In guinea-pigs aged 6 days, the vasopressor and oxytocic principles were 172 and 38·6 mU. Concurrently, the ratio of vasopressor activity to oxytocic activity decreased from 10 at birth, to 8·9 in a 1-day-old, and 4·5 in a 6-day-old guinea-pig.

Cats

Adult cats. The amounts of vasopressor and of oxytocic activity in the pituitary gland of adult cats of both sexes were 3870 ± 262 (4) and 3250 ± 460 (4) mU. This agrees with Phillips & Hare's (1945) results. The ratio of vasopressor activity to oxytocic activity was 1·19 ± 0·111 (4) (Table 1).

The amount of oxytocic activity in the pituitary gland of female cats killed after they had been lactating for 2–3 weeks fell to 1024 ± 422 (4) mU ($t = 2{\cdot}450$, $P = 0{\cdot}05$). Changes in the amount of vasopressor activity were not significant ($t = 1{\cdot}850$, $P < 0{\cdot}2 > 0{\cdot}1$). The ratio of vasopressor activity to oxytocic activity increased to 2·38 (Table 1). The decrease of the oxytocic activity seemed to vary with the number in the litter and the length of lactation. In one cat, however, which reared two kittens, the oxytocic activity of the pituitary gland was normal and the ratio of vasopressor activity to oxytocic activity was 1·13.

Cats' foetuses and kittens. Vasopressor and oxytocic activities were assayed in one litter of foetuses (age: 56 days), two litters of full-term foetuses and two litters of kittens aged 12 and 21 days. In the foetuses, the mean amounts of vasopressor and of oxytocic activities were 53 and 13 mU/gland. The ratio of vasopressor activity to oxytocic activity was 4·1. In kittens at birth, the mean amounts of vasopressor and oxytocic activities were 160 and 34 mU/gland. In kittens aged 21 days, they had increased to a mean of 610 and 190 mU/gland, respectively. Concurrently, the ratio of vasopressor activity to oxytocic activity had fallen from 4·7 at birth to 3·3.

Human foetuses

The vasopressor and oxytocic activities of the pituitary gland of twenty-five human foetuses were estimated. The age of the foetuses calculated according to Huggett & Widdas's (1951) formula ranged from 55 to 195 days of uterine life. In very young foetuses, dissection of the pituitary gland was impossible. A certain amount of tissue found in and around the sella turcica was cut out and extracted. In older foetuses from about 110 days onwards, relatively well-formed pituitary glands were found; they were dissected out and extracted in the usual way.

Neither vasopressor nor oxytocic activities were found in foetuses younger than 70 days; from 70 to about 110 days, both activities could be demonstrated. The amounts present, however, were too small to be assayed quantitatively—even when up to four samples of hypophyseal tissue were pooled. Quantitative assays were possible in more developed foetuses only (from 110 days onwards). The amounts of either activity varied widely in foetuses of comparable age. For instance, in three foetuses aged 150, 152 and 156 days, the values of vasopressor activity were 159, 123 and 182 mU/gland, while those of oxytocic activity were 46, 8 and 53 mU/gland, respectively. In all the foetuses examined, however, the amount of vasopressor activity exceeded markedly that of the oxytocic activity. Both activities increased with age. In a foetus of 112 days the vasopressor activity was 53 mU/gland, the oxytocic activity was 1·9 mU/gland, and the ratio of vasopressor activity to oxytocic activity was 28. In a foetus 40 days older, vasopressor and oxytocic activities were 123 mU and 8·0 mU/gland, and the ratio of vasopressor to oxytocic activity was 15. In a foetus of 195 days the ratio of vasopressor to oxytocic activity had further decreased to 6. It would appear to be about 1 in full-term babies (Heller & Zaimis, 1949).

DISCUSSION

It is clear from these results that the neurohypophysis of adult guinea-pigs, in contrast with that of adult rats and cats as well as that of dogs (Dicker & Tyler, 1953), always contained more vasopressor than oxytocic activity. This agrees entirely with Waring & Landgrebe's (1950) findings; these authors suggested that the fact that the ratio of vasopressor to oxytocic activity found in guinea-pigs of heterogeneous breed was different from that of other species, implied 'either that separate excitants are manufactured by the gland *or* that the one substance is not the same in all vertebrates and can even vary among individuals of the same species'. The latter view is entirely speculative. The former view, on the other hand, finds some support in the following facts: in the domestic animals studied the oxytocic activity decreased during lactation independently of the vasopressor activity; during foetal life and early infancy, the rate of formation of the two activities was markedly different.

The finding that the decrease of the oxytocic activity in rat and cat, as well as in dog (Dicker & Tyler, 1953) was most noticeable during normal lactation would seem to support the hypothesis of a close correlation between the oxytocic activity and the 'let down' process of milk suggested by Turner & Cooper (1941), Ely & Petersen (1941), Petersen (1942), Linzell (1950), Whittleston (1950) and Cross (1951). There would also seem to be some relation between the decrease of oxytocic activity and the number of littermates reared. For the same period of lactation of 15 days, the ratio of vasopressor to oxytocic activity was 1·2 in a female rat which had reared three new-born rats, while it was 2·4 in female rats which had fed ten baby rats. Similar observations had been made in bitches (Dicker & Tyler, 1953). The ratio of vasopressor to oxytocic activity was 3·4 and 4·0 in two bitches which had fed three puppies for 4 weeks, while it was 11·0 in a bitch which had reared eight puppies for 3 weeks. This may explain the discrepancy between the present findings and those found in goats (Folley, 1952) which in general have one or two kids only.

The pituitary glands of new-born animals (rats, cats and guinea-pigs, as well as dogs) always contained more vasopressor activity than oxytocic activity, though the amount of the vasopressor activity was markedly smaller than that found in adult animals. According to Heller & Zaimis (1949) the ratio of vasopressor to oxytocic activity is about 1 in new-born babies as in adults, though the absolute amounts of the vasopressor and oxytocic activities are much smaller in new-born infants than in adults. These findings led Heller & Zaimis (1949) to ask 'whether the apparent inability of new-born infants to concentrate the urine to the same degree as adults' arose from the lack of available hormone. Table 2 shows the mean amounts of both vasopressor and oxytocic activities available per 100 cm^2 body surface. In contrast with what was expected, the amount of vasopressor activity in new-born animals is not very much different from that found in adult animals. It is therefore most unlikely that the inability of new-born animals to concentrate urine can be attributed to a lack of the antidiuretic-vasopressor hormone present in the pituitary gland. It could, however, be due either to an inability of the gland to respond normally to secretory stimuli or to an insensitivity of the kidneys to a normal secretion of neurohypophyseal hormone. It would appear (Heller, 1952) that the kidneys of new-born rats are less responsive to exogenous posterior pituitary antidiuretic hormone than adults.

While the neurohypophyseal tissue of new-born animals has achieved maturity as to its antidiuretic-vasopressor activity, it is still immature as to its oxytocic function. As the main function of the oxytocic activity seems to be linked in adult life with parturition and 'let down' of milk, it may be surprising to find appreciable amounts of it in the pituitary glands of full-term foetuses. It has been suggested that in animals with many foetuses like the pig there was a cumulative effect of the foetus's oxytocic activity which might act as an accessory during parturition (Bell & Robson, 1937). The small amount of the oxytocic activity of each foetus in the species investigated does not, however, support this hypothesis. It is interesting to note that in general the depletion of oxytocic activity found in females after delivery was more pronounced in the case of small than of large litters. For instance, the ratio of vasopressor to oxytocic activity was 1·6 and 1·3 in bitches with five and six puppies; it was 3·0 in a bitch with two puppies only.

TABLE 2. Amounts of vasopressor and oxytocic activities found in the neurohypophysis of animals and man, expressed in terms of body surface

	mU/100 cm² body surface	
	Vasopressor activity	Oxytocic activity
Adult dogs of both sexes	142	138
Adult cats of both sexes	168	141
Adult rats of both sexes	105	95
Adult guinea-pigs of both sexes	128	54
Men*	84	80
New-born:		
Dog	71	4
Cat	98	16
Rat†	88	10
Guinea-pig	76	8
Baby*	17·0	17·6

* The results for man and baby have been taken from Heller & Zaimis's (1949) paper. Those for man were recalculated on the basis of a body surface of 1·73 m². For the baby, Heller & Zaimis's (1949) results were recalculated on the basis of a mean body weight of 2·4 kg, with a corresponding body surface of 2205 cm² (Boyd & Scammon, 1929).

† The rats were 5 days old.

Whatever the merit of these speculations, the fact remains that in adult female rats, cats and guinea-pigs, as well as in bitches (Dicker & Tyler, 1953), the oxytocic activity of the pituitary gland decreases during lactation, independently of the vasopressor activity. This observation and that of a differential rate of development of the two activities during foetal life and early infancy provides some grounds for suspecting that they exist as separate entities in the gland. This hypothesis would be strengthened if it could be shown that one of the two activities could increase independently of the other. This question is now being investigated.

SUMMARY

1. The vasopressor and oxytocic activities present in the pituitary gland have been assayed in adult rats, guinea-pigs and cats of both sexes, in female rats, guinea-pigs and cats killed after delivery and after lactation, in new-born rats and guinea-pigs, in cats' foetuses and kittens as well as in human foetuses.

2. When compared with standard solutions of Pitressin and Pitocin, the ratio of vasopressor activity to oxytocic activity of extracts of the pituitary glands of adult rats and cats was 1; it was greater than 1 in adult guinea-pigs.

3. There was some decrease of the oxytocic activity during parturition; during lactation this decrease was very pronounced. The decrease of the oxytocic activity occurred independently of the vasopressor activity.

4. The ratio of vasopressor activity to oxytocic activity of extracts of the pituitary glands of foetuses (including human foetuses) and of young animals was always greater than 1·0. It was greatest during foetal life; it decreased with age.

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