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Vasopressin Administration in the First Month of Life: Effects on Growth and Water Metabolism in Hypothalamic Diabetes Insipidus Rats

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WRIGHT, W. A. AND C. L. KUTSCHER. *Vasopressin administration in the first month of life: effects on growth and water metabolism in hypothalamic diabetes insipidus rats.* PHARMAC. BIOCHEM. BEHAV. 6(5) 505–509, 1977. – Rats homozygous for the mutant gene for diabetes insipidus (Brattleboro strain) are stunted in growth compared to rats heterozygous for the mutant gene and normal rats without the mutant gene. The hypothesis was tested that normal growth depends upon the presence of vasopressin. It was expected that replacement therapy of vasopressin to rats homozygous for diabetes insipidus would make possible a normal growth rate similar to that of rats heterozygous for diabetes insipidus. Rats heterozygous and homozygous for diabetes insipidus were treated with 0.25 U (Days 0–9) and 0.5 U (Days 10–29) of vasopressin during the first month of life. During the treatment period, vasopressin significantly increased the urine osmolalities of the homozygous rats demonstrating the renal effectiveness of the vasopressin. The results showed that remedial vasopressin administration could not produce normal growth rates in homozygous rats and may be detrimental. Six weeks following vasopressin treatment, homozygous, diabetes insipidus rats which had received vasopressin had increased 24 hr water intakes and decreased urine osmolalities compared to control, homozygous rats. Heterozygous rats also had decreased urine osmolalities resulting from vasopressin six weeks after the cessation of vasopressin treatment.

Brattleboro strain Diabetes insipidus Growth Vasopressin

RATS WHICH are homozygous for the recessive allele for hypothalamic diabetes insipidus (DI) do not synthesize vasopressin (VP) [12,22]. Rats which are heterozygous (HZ) for the allele have a partial deficiency for VP synthesis and release, compared to normal rats which do not possess the mutant allele [16,22]. Growth rate of DI rats and ultimate body weight attained is significantly less than that of HZ and normal rats [22] and this difference may be seen as early as the second month of life [20]. There are three explanations which have been advanced to account for the retarded growth and evidence can be cited for each. (1) There may be a deficiency of growth hormone synthesis, release, or utilization by the target cells. (2) Normal release of growth hormone may depend upon the presence of vasopressin (in DI rats there is none). (3) The VP deficiency may interfere with growth because the DI rat may have difficulty ingesting and digesting food because it may be in a state of partial dehydration.

Chronic treatment with growth hormone increased growth rate of DI rats [20]. Growth hormone releasing factor was found to be normal in DI rats, but a marked deficiency exists in the growth hormone content of the adenohypophysis [1,17]. There may be a reduction in the amount of releasable growth hormone available to be introduced into general circulation [1].

There is conflicting evidence on the question of whether VP has a releasing effect on growth hormone. Experiments on rats and monkeys provided evidence for such an effect [5,8]; however, some investigators have failed to find any evidence of growth in non-DI rats following administration of VP [3, 7, 19]. In humans, growth hormone was released following VP in some patients, but not in all [4,18].

Sokol and Sise [20] found that daily administration of vasopressin for 13 weeks beginning at weaning (4 weeks) did not increase rate of weight gain in DI rats, but the administration of growth hormone did. At the end of 5 months of postweaning treatment with growth hormone, body weights and tail lengths of DI rats were approximately the same as those of normal rats.

Although the above evidence suggests that growth hormone deficiency plays a critical role in retarding growth of DI rats, it cannot yet be claimed with certainty that vasopressin deficiency is without consequence since Sokol and Sise did not make vasopressin injections during the potentially critical first month of life. During this time the kidney of the normal rat gradually develops levels of

functioning characteristic of the adult in regard to osmotic diuresis, water diuresis, concentration of urine, and response to vasopressin and adrenal hormones [6]. The development of function may parallel anatomical development. At birth, a portion of the renal cortex, the neogenic zone, contains tissue which postnatally becomes differentiated into renal tubules (nephrogenesis) beginning at approximately 12 days of life and ending at approximately 28 days. The number of nephrons at birth is more than doubled after 2 weeks [2].

The consequences of vasopressin deficiency on rate of development in DI rats during the first month of life could be significant because milk is the initial food of the preweaning rat. In human infants with DI, milk exacerbates the symptoms and produces hypocaloric dwarfism due to voluntary food restriction [9]. Although renal function of the normal, neonatal rat is below adult levels, the posterior pituitary is capable of releasing vasopressin by 2–3 days of age and exogenous vasopressin can produce antidiuresis within the first week of life. By 28 days, the normal rat can excrete urine as concentrated as that of the adult [6].

In the following experiment, we attempted to determine if administration of vasopressin in amounts sufficient to be of functional significance, can increase rate of weight gain. Secondly, we wished to determine if any normalization of growth produced by vasopressin injection endured beyond the treatment period. If VP administration increases growth rate, support is provided for either the hypothesis that VP releases growth hormone or that VP overcomes a dehydration state of the DI animal [14]. If a deficiency in growth hormone synthesis or release (by factors other than VP) is the limiting factor in growth of the DI rats, then VP injection, even in the first weeks of life should have little consequence.

METHOD

Animals

Ten female Hz rats and two male DI rats were selected for breeding; ages ranged from 120–150 days old. The litters from these breeders were the experimental subjects (n = 55 males; n = 60 females). A total of 19 litters were used with no female breeder contributing more than two litters. The breeding stock was obtained from the Brattleboro strain maintained at the Syracuse Veterans Administration Hospital (courtesy of Myron Miller, M.D.).

Apparatus

Before weaning at 25 days of age, pups were housed with their mothers in wire mesh cages (28.8 × 43.2 × 24.0 cm) with wood shavings for bedding. After weaning, animals were housed by sex in groups of two to five in the same wire mesh cages without the wood shavings. Animals were maintained on Purina Lab Chow and tap water throughout the experiment. Lights were on for 12 hr/day, temperature maintained at 22 ± 2°C and the air was humidified during the winter months.

Twenty-four hr water intakes were measured by individually housing the animals in steel test cages (24.0 × 16.8 × 14.4 cm) with hardware cloth tops and bottoms. Two, 100 ml drinking tubes graduated in 0.2 ml units were attached to each cage with steel drinking spouts.

Urine samples were collected by suspending the individual cages over aluminum foil. A 0.2 ml sample of urine was analyzed for osmolality on a Precision Osmette osmometer.

Procedure

On the day of birth (Day 0), litters were alternately assigned to either the vasopressin or the control (Oil) condition. Each litter was culled so that litter size was between 6 and 10 pups inclusively. The pups were identified by clipping the nails of the digits. When the ears developed, rats were ear-punched to facilitate identification.

Beginning with Day 0, the pups received vasopressin or control injections. From Day 0 through Day 9, VP animals received daily injections of 0.25 U of lysine vasopressin (Sigma) suspended in 0.025 cc of peanut oil. The Oil animals received the oil injection alone. On Day 10 through Day 29, VP animals received 0.5 U of lysine vasopressin once daily in 0.1 cc of peanut oil while the Oil animals received only the oil injections. VP dosage selection was made with the objective to normalize water turn-over in DI rats [10, 15, 20]. Injections were made subcutaneously in the nape of the neck. Day 29 was the last day of VP or Oil treatments to the subjects.

Day 0, 7, 14, 21, 28, 42, and 70, animals were weighed and their body length (not including the tail) was measured. Through Day 21, body weights were measured to the nearest 0.1 g. Thereafter, measures were made to the nearest g. All body length measures were made to the nearest mm. The Day 70 measure was taken while the animal was ether anaesthetized.

Water intakes were measured for a 24 hr period between Days 27–28, 41–42, and 69–70. On Day 27, the recording period began immediately after the treatment injections had been made. Measures were taken to the nearest 0.1 ml. Food was ad lib during this test.

Urine samples were collected for measuring urine osmolalities on Days 28, 42 and 70, 1 hr following injection on Day 28. If a sample of adequate volume had not been collected in one hr, the urine collecting procedure was repeated the following day. Food and water were not present during the urine collecting session.

The procedure of breeding a HZ with a DI rat of the Brattleboro strain yields offsprings which are either DI or HZ [21]. All the pups of a litter were assigned to either the VP or the Oil group. Therefore, including sex, there were eight groups in the study (2 genotypes × 2 sexes × 2 treatments). Table 1 shows the sample size of each group.

Water intakes and urine osmolalities were taken so that the HZ and DI rats could be distinguished. The Day 70 data for these two measures was subjected to a log transform and then scatterplotted. The 115 animals fell into one of two distinct distributions, except for three animals which were discarded from the data analysis. Animals with urine osmolalities less than 350 m Osm/Kg and 24 hr water intakes over 50 ml were classified as DI and the other animals were classified as HZ. The urine osmolality criteria is the same as what has been used previously [16]. The second criteria was added here since 24 hr water intake and urine osmolality were highly correlated (males, $r = -.91$; females, $r = -.88$).

RESULTS

All data were computer analyzed by a 3-factor (Genotype, Treatment and Sex) analysis of variance program

which handles unequal cell sizes (BMD05V). Post hoc, pairwise comparisons of means were made using the Tukey (a) procedure [11].

Body Weight

The only difference in body weights on Day 0 was a significant Genotype main effect, $F = 4.83$, $p<0.05$. The HZ animals weighed more than the DI animals (Table 1).

On Day 28, all three main effects were significant. HZ animals weighed more than DI animals ($F = 70.06$, $p<0.001$) and males weighed more than females ($F = 7.73$, $p<0.01$). The Treatment effect ($F = 5.24$, $p<0.05$) must be examined by taking into account the Genotype x Treatment interaction ($F = 21.15$, $p<0.001$). VP had the effect of lowering the HZ's body weight ($p<0.05$) but VP did not significantly increase the DI's body weight ($p>0.05$).

At Day 70, HZ animals weighed more than DI animals ($F = 133.13$, $p<0.001$), males weighed more than females ($F = 176.32$, $p<0.001$), but the treatment effect was not significant.

Body Length

There were no significant differences in body length on Day 0. At Day 28, HZ animals were longer than DI animals ($F = 45.55$, $p<0.001$) and males were longer than females ($F = 10.28$, $p<0.01$). Again, the treatment effects ($F = 5.57$, $p<0.05$) had to be interpreted by the Genotype x Treatment interaction ($F = 10.17$, $p<0.01$). VP decreased the body length of the HZ animals ($p<0.05$) while the DI animals' body length was not significantly increased (Table 2).

On Day 70, body length was greater in HZ animals than DI animals ($F = 161.87$, $p<0.001$) and males greater than females ($F = 113.34$, $p<0.001$). The Genotype x Treatment interaction was significant ($F = 4.37$, $p<0.05$) but post hoc tests failed to find VP differentially affecting Genotype.

Water Intake

Twenty-four hr water intakes taken on Day 28 showed a significant Genotype effect ($F = 139.72$, $p<0.001$); DI animals drank more than HZ animals. The Genotype x Treatment interaction was significant ($F = 6.97$, $p<0.01$), but post hoc tests failed to find any significant differences

TABLE 1

BODY WEIGHT (g) IN HZ AND DI RATS TREATED WITH VASOPRESSIN OR OIL

Group	N	Day 0	Day 7	Day 14	Day 21	Day 28	Day 42	Day 70
DI-VP-Male	12	5.7 ± 0.5*	12.8 ± 1.1	24.0 ± 2.9	33.7 ± 5.6	56.7 ± 7.5	109.0 ± 11.1	182.7 ± 20.9
DI-Oil-Male	9	5.6 ± 0.5	13.2 ± 1.6	19.9 ± 4.0	31.6 ± 5.5	52.4 ± 10.0	97.6 ± 7.6	179.7 ± 15.4
HZ-VP-Male	13	6.0 ± 0.7	14.0 ± 1.8	25.6 ± 2.0	35.0 ± 3.8	59.1 ± 5.1	127.6 ± 9.4	225.9 ± 21.7
HZ-Oil-Male	19	6.1 ± 0.6	16.1 ± 2.7	28.8 ± 4.6	42.3 ± 6.0	72.1 ± 10.5	138.9 ± 14.8	251.4 ± 31.5
DI-VP-Female	9	5.4 ± 0.7	12.8 ± 2.1	24.1 ± 4.7	31.8 ± 6.6	51.9 ± 10.2	84.0 ± 9.7	138.9 ± 20.1
DI-Oil-Female	15	5.7 ± 0.5	12.8 ± 2.7	20.3 ± 5.2	29.2 ± 5.6	45.8 ± 7.7	81.1 ± 15.6	138.1 ± 18.5
HZ-VP-Female	19	5.7 ± 0.5	13.0 ± 1.4	24.7 ± 2.5	35.7 ± 3.9	60.1 ± 5.5	113.6 ± 8.2	177.8 ± 13.4
HZ-Oil-Female	16	5.8 ± 0.7	15.0 ± 2.6	28.0 ± 4.0	42.0 ± 5.4	68.0 ± 8.7	123.4 ± 10.3	177.2 ± 18.6

*Mean ± Standard Deviation.

TABLE 2

BODY LENGTH (mm) IN HZ AND DI RATS TREATED WITH VASOPRESSIN OR OIL

Group	Day 0	Day 7	Day 14	Day 21	Day 28	Day 42	Day 70
DI-VP-Male	48.4 ± 1.7*	69.0 ± 2.8	87.6 ± 4.4	103.7 ± 6.6	126.1 ± 5.6	153.4 ± 6.5	192.8 ± 4.9
DI-Oil-Male	48.4 ± 1.4	68.1 ± 2.7	79.0 ± 9.6	104.1 ± 7.8	124.8 ± 10.2	148.7 ± 3.3	187.9 ± 4.9
HZ-VP-Male	48.8 ± 2.3	71.5 ± 3.9	91.2 ± 4.2	106.5 ± 5.5	128.5 ± 4.0	163.3 ± 5.4	206.6 ± 8.1
HZ-Oil-Male	49.2 ± 1.6	73.9 ± 4.6	94.1 ± 5.3	115.1 ± 7.9	138.4 ± 10.0	164.0 ± 6.5	211.5 ± 8.6
DI-VP-Female	47.6 ± 2.2	63.2 ± 7.6	87.4 ± 5.4	102.4 ± 8.6	122.0 ± 6.9	140.4 ± 6.6	178.4 ± 9.0
DI-Oil-Female	48.8 ± 1.3	67.3 ± 4.5	82.7 ± 8.6	101.3 ± 8.0	118.6 ± 7.5	140.4 ± 9.1	177.4 ± 7.2
HZ-VP-Female	48.5 ± 1.5	69.1 ± 4.0	89.3 ± 3.2	106.3 ± 4.6	128.4 ± 5.3	154.9 ± 4.5	193.6 ± 5.7
HZ-Oil-Female	48.2 ± 2.2	70.9 ± 6.0	91.1 ± 7.4	112.3 ± 6.6	133.6 ± 6.3	156.8 ± 6.6	194.8 ± 5.4

*Mean ± Standard Deviation.

in water intake caused by VP, testing within each genotype (Table 3).

Water intakes on Day 70 demonstrated that DI animals drank more than HZ animals ($F = 587.55$, $p<0.001$). Significant Treatment ($F = 98.79$, $p<0.001$) and Genotype x Treatment ($F = 82.34$, $p<0.001$) effects showed that VP did not have a uniform action on the two genotypes. VP had no effect on water intakes in the HZ animals but it greatly increased water intakes in DI animals ($p<0.01$).

Urine Osmolality

On Day 28 urine osmolalities were greater in HZ animals than DI animals ($F = 106.38$, $p<0.001$) and the Genotype x Treatment interaction was significant ($F = 51.53$, $p<0.001$). Inspection of the data (Table 3) showed that VP greatly increased the urine osmolalities of the DI animals ($p<0.01$); whereas, VP decreased the urine osmolalities of the HZ animals ($p<0.05$).

For urine osmolalities on Day 70, HZ animals were greater than DI animals ($F = 204.03$, $p<0.001$), VP animals less than Oil animals ($F = 19.49$, $p<0.001$), and males greater than females ($F = 7.66$, $p<0.01$). A significant Genotype x Treatment interaction indicated that urine osmolalities in HZ animals were lowered by VP to a greater extent than they were in DI animals ($p<0.05$).

DISCUSSION

Administration of VP during the first month of life did not correct the deficiency in growth rate seen in the DI rats. At least two interpretations are possible. Either growth hormone deficiency, not VP deficiency with the attendent interactions with growth hormone release or with food utilization, is the real cause of the retarded growth, or the dosage of VP used here was inadequate to completely relieve the VP deficiency. The latter conclusion seems unlikely for several reasons. First, the dosages used (0.25 and 0.5 U/day) far exceed the daily output of normal Long-Evans rats whose mean daily urinary excretion of VP was found to be 4.5 mU/day [13]. The 0.5 U/day dosage exceeds the mean VP content of the posterior pituitary of normal rats [16]. Secondly, the VP dosages used produced urine osmolalities in DI rats which were three times as high as those observed in oil-treated DI rats (Table 3). This dosage was found adequate to lower 24 hr ad lib water intakes in adult DI rats [10, 15, 20]; however, in our 28-day old rats only a nonsignificant trend toward reduction of water intake was noted following VP treatment.

It seems reasonable to conclude that the retarded growth rate as seen in DI rats is due to a deficiency in growth hormone which may be caused by a metabolic deficiency other than lack of VP. Since VP injection did not produce significant growth, there is no evidence to support either the hypothesis that VP is needed for growth hormone release or that DI rats cannot utilize food because of dehydrational status. If renal development in DI rats proceeds at the same rate as in normal rats, then the kidneys should have been responsive to exogenous dosages of VP within the first week of life [6]. This probability, coupled with the large dosage given, makes it likely that the renal deficiencies of the DI rats were probably relieved for at least a portion of each day, thus making it unlikely that the retarded growth is hypocaloric dwarfism resulting from an inability of the DI rat pup to ingest and metabolize milk without becoming dehydrated. It should be pointed out, however, that the urine osmolalities were determined one hr after injection when impact of the daily VP injection may have been particularly strong.

Another indication of the efficacy of the VP injections comes from an unexpected finding. The VP injections made during the first 30 days of life produced deleterious changes in water metabolism which endured until at least Day 70. VP-injected DI rats showed higher water intakes and lower urine osmolalities. A similar trend was seen in HZ rats (Table 3).

Thus, VP injections in the first month of life not only failed to eliminate the deficiency in the growth rate, but may have, in some unexplained way, exacerbated the deficiencies in water metabolism of the DI rat. For VP-treated DI rats (males and females combined), mean water intake was 199% more than intake of oil-injected DI rats and mean urine osmolality of the former was 63% of the latter. Furthermore, mean urine osmolalities for VP-treated HZ rats were lower than those of oil-injected HZ at Days 28 and 70 even though water intakes were not different. We have no explanation for the observed deleterious effect of VP.

This study provides the first indication that the DI rat is smaller than the HZ rat at birth, showing that the characteristics of postnatal nutrition cannot be completely

TABLE 3

24-HR WATER INTAKE (WI) IN MILLILITERS AND URINE OSMOLALITY (OSM) IN mOSM/Kg IN HZ AND DI RATS TREATED WITH VASOPRESSIN OR OIL

Group	Day 28		Day 42		Day 70	
	WI	OSM	WI	OSM	WI	OSM
DI-VP-Male	46.3 ± 22.3*	1104.6 ± 364.1	148.6 ± 31.4	144.7 ± 27.7	209.4 ± 43.5	151.9 ± 37.8
DI-Oil-Male	53.8 ± 13.6	271.8 ± 69.9	59.0 ± 16.9	287.2 ± 55.8	97.7 ± 28.9	227.6 ± 59.9
HZ-VP-Male	20.8 ± 3.5	1354.3 ± 602.8	33.7 ± 9.0	1055.3 ± 370.9	35.4 ± 10.3	1219.5 ± 455.2
HZ-Oil-Male	20.3 ± 3.2	1776.7 ± 489.0	27.3 ± 7.6	1471.3 ± 506.3	30.6 ± 9.8	1598.6 ± 444.2
DI-VP-Female	36.0 ± 15.1	1081.3 ± 308.4	124.9 ± 22.0	140.2 ± 26.9	198.8 ± 51.6	143.2 ± 26.0
DI-Oil-Female	49.9 ± 14.2	292.7 ± 69.5	62.1 ± 24.3	328.3 ± 111.0	105.5 ± 20.1	242.0 ± 55.0
HZ-VP-Female	21.6 ± 4.7	1290.2 ± 468.9	29.8 ± 9.2	1041.8 ± 344.5	39.8 ± 10.8	864.3 ± 371.7
HZ-Oil-Female	19.0 ± 3.4	1729.8 ± 527.6	23.8 ± 3.1	1330.0 ± 293.2	22.1 ± 7.3	1363.3 ± 635.6

*Mean ± Standard Deviation.

responsible for the retarded growth. Perhaps the deficiency of growth hormone seen in the adult [1,17] is also present in the fetus.

The two measures of body size, weight and length, yielded approximately the same relationship in this study. This indicates that growth differences in DI rats compared to HZ rats were not due to the amount of body fat accumulated, but were due to proportional differences in rate of growth of the body, including the bones. Tail lengths were also measured. These data were not presented. The same significanct differences and relationships were found with all three measures – weight, body length, tail length – further supporting the notion that growth hormone deficiency is the key to retarded growth in DI rats.

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