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Effects of adrenalectomy and of hypophysectomy on the development of sound-withdrawal hypertension

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Female rats, initially 160–180 g, of a single inbred Wistar strain develop an hypertension reaching peak value at 4 weeks and stabilizing at a slightly lower level by the 6th week after transfer to a sound-proof semi-anechoic room (SPR). Blood corticosterone and deoxycorticosterone levels do not change significantly: urinary catecholamine excretion gradually decreases, and the rates of the urinary excretion of water and of Na^+ in the first hour of water diuresis are depressed throughout the first week in the SPR. Adrenalectomy with salt maintenance, and hypophysectomy, prevent the development of this hypertension. Treatment with methyl prednisolone restores the ability of the adrenalectomized, but not of the hypophysectomized, rats to develop sound-withdrawal hypertension.

Previous work has demonstrated that female rats of a single inbred Wistar strain develop hypertension when deprived of the extraneous sounds encountered in the normal rat room. The hypertension develops to a peak value in 4–5 weeks and then stabilizes at a value slightly below the peak. This hypertension, termed sound-withdrawal hypertension, is associated with histologically demonstrable changes in arterioles and small arteries and is prevented by relay of sounds from the normal rat room into the sound-proofed semi-anechoic room at unchanged intensity (Marwood & Lockett, 1973).

Our purpose has been to determine whether adrenalectomized and hypophysectomized rats also develop sound-withdrawal hypertension.

METHODS

One hundred and fifty-eight female rats of a single inbred Wistar strain, initial weight range 160–180 g, were trained, housed and fed similarly either in the stock (normal) rat room (NRR) or in the semi-anechoic sound-proofed (SPR) room, as previously described (Marwood & Lockett, 1973). All normal and hypophysectomized animals drank tap water, all adrenalectomized rats drank aqueous 0·9% NaCl.

Operations were performed under anaesthesia induced by injection of sodium methohexital (45 mg kg^{-1}, i.p.). The method of Zarrow, Yokim & others (1964) was used for bilateral adrenalectomy. Hypophysectomy was performed by the transpharyngeal route as described by Burn, Finney & Goodwin (1950). Half the number of hypophysectomized and of the salt-maintained adrenalectomized animals received methyl prednisolone (70 μg s.c. per rat) once weekly. Successful hypophysectomy was confirmed by observation of adrenal atrophy, and adrenalectomy, both by

Table 1. *The effects of adrenalectomy and of hypophysectomy with and without methyl prednisolone (MP) 70 μg per rat, per week, on the development of sound-withdrawal hypertension and on organ weights, in rats. All measurements were made in the 5th experimental week.*

Parameter	Intact rats		Adrenalectomized + SPR		Hypophysectomized + SPR	
	Controls	SPR	Salt maintenance	Salt + MP	Without MP	With MP
Mean systemic arterial pressure:						
Before block (mm Hg)	132·9 ± 11·7	185·2 ± 3·6**	116·5 ± 14·4††	190·7 ± 3·6**	127·0 ± 0·9††	147·0 ± 3·2*
After ganglion block (mm Hg)	79·2 ± 7·9	94·4 ± 2·4*	45·3 ± 3·7††	98·0 ± 3·9**	55·3 ± 7·7††	67·2 ± 4·2*
Pressor effects (blocked) in mm Hg:						
Noradrenaline 0·25 g	60·6 ± 6·0	105·1 ± 3·9**	57·3 ± 7·0††	84·2 ± 6·3††	76·8 ± 3·5††	66·8 ± 6·6
Tyramine 25 g	59·8 ± 5·8	107·4 ± 3·3**	37·0 ± 4·0††	77·0 ± 9·3**	59·8 ± 7·9††	72·4 ± 3·0
Angiotensin II-val-amide 1·0 ng	36·7 ± 4·3	49·1 ± 2·5*	23·0 ± 1·5†	53·6 ± 3·7**	44·8 ± 3·8	43·4 ± 3·1
Vasopressin 0·2 mU	31·5 ± 3·1	34·4 ± 2·9	9·3 ± 1·5††	38·6 ± 3·6**	32·5 ± 1·0	35·8 ± 2·9
Body weight, g	195·8 ± 5·3	198·4 ± 3·7	175·5 ± 9·9	140·3 ± 7·0*	156·0 ± 8·2†	107·2 ± 6·6**
Organ weight, mg						
L adrenal	30·1 ± 1·2	34·3 ± 1·0	—	—	8·9 ± 0·8††	9·0 ± 0·2
R adrenal	27·2 ± 2·7	26·7 ± 2·5	—	—	7·4 ± 1·0††	8·1 ± 0·3
Heart	580·7 ± 13·1	650·1 ± 14·5*	489·0 ± 27·5†	565·7 ± 21·0*	398·0 ± 21·9††	377·8 ± 14·3
Thymus	245·3 ± 12·5	292·0 ± 13·3*	342·0 ± 56·5†	19·8 ± 3·2**	165·8 ± 13·8††	11·2 ± 1·7**

The values shown are means ± standard errors, determined on groups of 12 to 29 rats, significant differences attributable, in intact rats, to effects of sound-withdrawal and in operated rats to the action of methyl prednisolone (MP) are indicated by asterisks: significant effects of hypophysectomy and of adrenalectomy are indicated by †: one, $P < 0.05$; two, $P < 0.01$ SPR indicates storage for 4–5 weeks in a semi-anechoic sound-proofed room.

inspection of the abdominal cavity and by observation of an appropriate change in thymus weight (Table 1).

Collection of urine. Rats were placed in individual stainless steel metabolic cages resting above polyethylene funnels designed to separate faeces from urine. In some experiments all urine voided between 9 a.m. and 5 p.m. was collected into 25 ml beakers containing 2 ml of $Na_2S_2O_5$ 1 mg ml^{-1} (aqueous) for estimation of urinary outputs of catecholamines. In other experiments, rates of elimination of water, sodium (Na^+) and potassium (K^+) were measured in the first hour after the administration of an oral water load equivalent to 2·5% body weight, as previously described (Marwood & Lockett, 1972). Concentrations of adrenal corticoids in heart blood were determined as before (Ilett, 1969).

Urinary catecholamines were estimated by the method of Anton & Sayre (1962). Urinary Na^+ and K^+ were determined by flame photometry.

Mean systemic arterial pressure and the responses of the mean arterial pressure to pressor agents were determined as previously (Marwood & Lockett, 1973).

RESULTS

Effects on the mean systemic arterial pressures of the exclusion of adventitious sounds for 4 to 5 weeks, in intact and operated rats. Intact rats exposed to withdrawal of all adventitious sounds for 4–5 weeks developed an hypertension (Table 1) which persisted, although in lesser degree, after induction of ganglionic blockade by injection of pentolinium (1 mg, i.v. or 5 mg, s.c.). After ganglion block, highly significant increases were found in the pressor effects of fixed doses of (−)-noradrenaline and of tyramine and a smaller but significant increase in the responses to angiotensin II-val^5-amide: responses to vasopressin were unaffected.

Salt-maintained adrenalectomized rats did not develop hypertension on exposure to 4–5 weeks of sound-withdrawal. The mean systemic arterial pressures before and after ganglion block and responses to all four pressor agents were subnormal in these animals (Table 1). In contrast, salt maintained adrenalectomized animals which

had regularly received glucocorticoid (methyl prednisolone) developed a sound-withdrawal hypertension which persisted, although lessened, after ganglion block. In these animals effects of vasopressin rose to equal, and of (—)-noradrenaline, tyramine and angiotensin II-val^5-amide, increased to exceed, the levels normal for intact rats unexposed to sound-withdrawal. Hence, the pressor responses shown by salt maintained, glucocorticoid treated, ganglion-blocked, adrenalectomized rats in the 5th week of sound-withdrawal resembled those induced in intact rats by deprivation of sounds.

Hypophysectomized rats did not develop sound-withdrawal hypertension. After 4–5 weeks in the sound-proofed room (SPR) the mean systemic arterial pressures of these animals, before and after ganglion block, were below those of normal intact animals exposed to normal sounds; the responses of the hypophysectomized rats to the various pressor agents resembled those of the normal rats (Table 1). Methyl prednisolone caused a small but significant increase in the mean systemic pressures but did not influence the effects of pressor agents in hypophysectomized animals stored in the SPR.

Effects of withdrawal of adventitious sounds on the urinary excretion of sodium (Na^+) and catecholamines, and on the concentrations of corticosterone and deoxycorticosterone in heart blood. The mean systolic arterial pressures of normal rats exposed to the absence of all adventitious sound rises to a maximum at the end of the 4th or the beginning of the 5th week, then falls slightly to a stable maintained value markedly in excess of normal (Marwood & Lockett, 1973). These two phases can conveniently be classified as the phase of development (weeks 1–4) and the phase of stabilization (weeks 5–8) of a sound-withdrawal hypertension. The effects of sound-withdrawal on the urinary excretion of water and of Na in the first one hour after administration of an oral water load equivalent to 2·5% body weight were measured during the development of sound-withdrawal hypertension. The absence of external noises had no significant effect on water elimination but reduced ($P < 0{\cdot}01$) Na excretion from the 1st to the 7th day (Fig. 1); the ratio, $Na^+ : K^+$ in the urine was, however, unaffected.

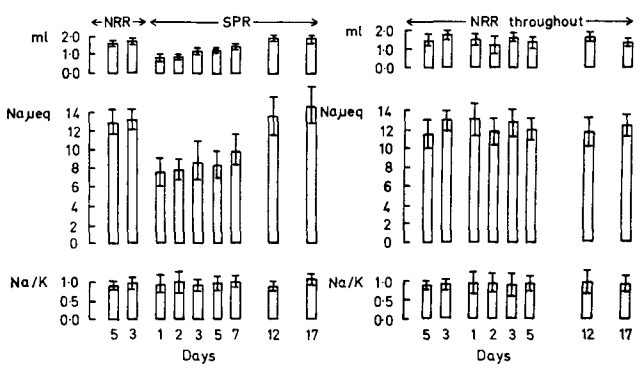

FIG. 1. Rates of elimination of an oral water load equivalent to 2·5% body weight are depressed throughout the first week after transfer of rats to a sound-proof room (SPR) from the normal rat room (NRR). The rate of Na^+ excretion is also depressed during this period, without change in the Na^+/K^+ in the urine. The heights of the rectangles show mean values for a group of 24 rats (left) and a group of 16 rats (right). The inset verticals show the standard errors of these means.

The excretion of catecholamines by rats transferred to the SPR did not differ significantly from that of animals remaining in the NRR for the first 4 weeks, although the rate of excretion of noradrenaline by rats in the SPR tended to fall (Table 2). From the 5th to the 8th week, however, the excretion of both noradrenaline and of adrenaline by rats in the SPR was significantly less than that of rats in the NRR.

Concentrations of corticosterone and of deoxycorticosterone in the heart blood of rats from the SPR tended to fall slowly with time, but these changes did not attain significance (Table 2).

Table 2. *The effect of sound-withdrawal on the urinary outputs of catecholamines and on blood levels of corticosterone and desoxycorticosterone in rats.*

Parameter measured	Control levels (NRR)	Times after entering sound-proof room: Hypertension developing	Hypertension establishing
		weeks 2–4	*end of* 8 *weeks*
Mean systemic pressure mm Hg ..	145 ± 2·7 (32)	172 ± 9·4 (24)**	185 ± 4·8 (32)**
Urinary outputs		*weeks* 1–4	*weeks* 5–8
Adrenaline ng kg^{-1} rat h^{-1} ..	53·6 ± 5·21 (32)	55·3 ± 3·0 (46)	39·2 ± 1·8 (48)**
Noradrenaline ng kg^{-1} rat h^{-1} ..	58·2 ± 4·18 (32)	51·0 ± 1·9 (46)	49·2 ± 1·7 (48)*
Blood corticoids μg 100 ml^{-1}		*in week* 2	*in week* 6
Corticosterone	29·8 ± 6·8 (6)	28·3 ± 4·1 (8)	21·5 ± 2·0 (9)
Desoxycorticosterone	15·9 ± 4·2 (6)	14·1 ± 3·4 (8)	13·6 ± 2·0 (9)

The values shown are means ± s.e., followed by the number of observations in parentheses. The significance of differences between control and experimental means has been determined by variance analysis and is indicated by asterisks: one, $P < 0{\cdot}05$; two, $P < 0{\cdot}01$.

DISCUSSION

Glucocorticoids undoubtedly play a rôle in the development of sound-withdrawal hypertension (SWH) since salt maintained adrenalectomized rats cannot develop SWH, but do so if glucocorticoid is provided. It is possible, however, that the rôle of glucocorticoid in the genesis of SWH is solely permissive since the blood levels of corticosterone found for intact rats during development and stabilization of SWH were not raised. SWH resembles genetic hypertension in requiring glucocorticoid for its development (Iwai, Knudsen & others, 1969) and contrasts with both renal hypertension (Fregly, 1957; de Jong, Frankhuzen & Witter, 1969) and DOCA-salt hypertension (Friedman, Friedman & Campbell, 1949; Finch & Leach, 1970a,b) in this respect.

Hypophysectomized rats do not develop SWH even when supplied with glucocorticoid (6-methylprednisolone) in quantities sufficient to cause typical weight loss and involution of the thymus. Hence, one or more pituitary hormones, additional to ACTH, may play an essential rôle in the genesis of SWH. It is of interest that hypophysectomy also prevents the development of DOCA-salt hypertension (Hall & Hall, 1961).

The appearance of SWH in salt-maintained glucocorticoid-treated adrenalectomized animals strongly indicates that the adrenal medullary hormones themselves play no essential part in the development of SWH. The absence of significant changes in the urinary excretion of adrenaline and noradrenaline during the development of SWH, and reduction in the urinary excretion of these catecholamines during the establishment of SWH in intact rats is also indicative that the sympatho-adrenal axis plays no more

than a minor rôle, if any, in the production of SWH. Previous workers, using rats, have concluded that catecholamines are certainly of no primary significance in the development of renal hypertension (Dorr & Brody, 1966; Lefer & Ayres, 1969; De Champlain, Mueller & Axelrod, 1969; Clarke, Smookler & Barry, 1970) or of spontaneous hypertension (Louis, Krauss & others, 1970).

CONCLUSION

Thus, sound-withdrawal hypertension cannot develop in the absence of glucocorticoid. Since hypophysectomized rats do not develop sound-withdrawal hypertension even when liberally supplied with glucocorticoid, it is possible that the rôle of glucocorticoid is permissive to that of an hypophysial hormone (other than ACTH) in the aetiology of sound-withdrawal hypertension.

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