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EFFECT OF PARATHYROIDECTOMY ON CARDIOVASCULAR REACTIVITY IN RATS WITH MINERALOCORTICOID-INDUCED HYPERTENSION

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1 Previous work has shown that parathyroidectomy protected Sprague-Dawley rats against mineralocorticoid hypertension.

2 In order to explain this protection, we studied vascular reactivity to noradrenaline and angiotensin II in several groups of rats with and without their parathyroid and thyroid glands. Work was performed in vagotomized, anaesthetized rats after ganglionic blockade with pentolinium, and atropine sulphate.

3 The reactivity to noradrenaline was significantly lower in parathyroidectomized rats, especially at the beginning of mineralocorticoid treatment.

4 Autotransplantation of parathyroid glands in thyroparathyroidectomized rats re-established normal cardiovascular reactivity and development of hypertension.

5 Cardiovascular reactivity to angiotensin II was not affected in parathyroidectomized rats and was lowered in thyroparathyroidectomized thyroxine-treated rats.

Introduction

The importance of calcium in the contraction of vascular smooth muscle led us to study the evolution of calcium metabolism during mineralocorticoid hypertension in the rat (Stoclet, Miss-Pagès, Berthelot & Gairard, 1975). Participation of calcium in that phenomenon and many cases of hypertension in primary hyperparathyroidism in man (Ory, David & Redmond, 1970; Rosenthal & Roy, 1972; Weil, Lagrue, Fournier & Kazandjian, 1972) caused us to study the influence of the parathyroid gland during mineralocorticoid-induced hypertension. We showed that parathyroidectomy (PTX) protects against mineralocorticoid-induced hypertension (Berthelot & Gairard, 1976). On the other hand, De Champlain & Van Ameringen (1972), Reid, Zivin & Kopin (1975), and De Champlain, Farley, Cousineau & Van Ameringen (1976) observed increased activity of the sympathetic nervous system in rats treated with deoxycorticosterone acetate (DOCA) and 0.9% w/v NaCl solution (saline). In the present study, in order to investigate the anti-hypertensive effect of parathyroidectomy, we compared cardiovascular reactivity to noradrenaline and angiotensin II in normal and DOCA-treated rats with and without parathyroid or thyroparathyroid glands.

Methods

Male Sprague-Dawley rats weighing 120 g at the beginning of the experiment were fed a standard diet containing 0.60% Ca and 0.24% Na. DOCA pellets (total 100 mg in 4 pellets) or placebo pellets (control group) were implanted subcutaneously by the technique of Peterfalvi & Jequier (1960). Starting from the day of operation, DOCA-treated groups drank saline *ad libitum* while control groups drank distilled water.

The rats were randomly divided into several experimental groups: normal DOCA-treated (D) and normal control (C) rats; parathyroidectomized DOCA-treated (PTX-D) and parathyroidectomized control (PTX-C) rats; thyroidectomized and autografted parathyroid DOCA-treated (TXAPT-D) and thyroidectomized and autografted parathyroid control (TXAPT-C) rats; thyroparathyroidectomized DOCA-treated (TXPTX-D) and thyroparathyroidectomized control (TXPTX-C) rats; thyroparathyroidectomized rats treated with DOCA and given a thyroxine (T_4) supplement (TXPTX-DT_4) and thyroparathyroidectomized control rats treated with L-thyroxine alone (T_4) (TXPTX-CT_4).

Surgery was performed under anaesthesia with 30 mg/kg intraperitoneal sodium pentobarbitone 1

week before the start of mineralocorticoid treatment. Parathyroidectomy by cauterization and surgical thyroparathyroidectomy were performed under a binocular lens (×5) to assure complete removal of glands. Parathyroid glands were autografted into the hyoid muscle immediately after thyroidectomy.

The DOCA-treated (D) and control (C) rats were anaesthetized, an incision was made in the skin and the parathyroid glands were exposed, after which the incision was closed.

The TXPTX-T_4 groups received 5 μg of L-thyroxine subcutaneously alternate days after operation. The quantity was adjusted to favour the same rate of growth as in the normal rats. The success of the operations was verified by the level of serum calcium in the case of parathyroidectomy and of autograft, and the change in body weight in the case of thyroidectomy and of thyroparathyroidectomy.

Serum calcium was determined by atomic absorption photometry (Girard & Rousselet, 1967).

Cardiovascular reactivity (CVR)

Blood pressure was measured on unanaesthetized warm rats, by the tail cuff method, 24 h before study of CVR.

For CVR study, animals were anaesthetized with an intraperitoneal injection of sodium pentobarbitone (30 mg/kg). In order to minimize their spontaneous blood pressure regulation, we pretreated them with pentolinium (25 mg/kg, s.c., May and Baker) and atropine sulphate (0.25 mg/kg, s.c.) according to the method described by Dupont & Sassard (1974). Two small polyethylene cannulae were implanted, one in the carotid artery for direct measurement of mean blood pressure and one in the jugular vein for drug injections. At the same time vagotomy was performed on both sides. Mean blood pressure was measured directly with a Statham 23 D B pressure probe.

Cardiovascular reactivity to noradrenaline was expressed as changes in blood pressure (Δ BP) evoked by injection of noradrenaline, 125, 250 or 500 ng/kg or of angiotensin II 50, 100 or 200 ng/kg. After the three doses of noradrenaline, reproducibility was checked with the smallest dose.

CVR was measured during the early phase of hypertension (2 weeks after the start of treatment with DOCA) and during the sustained phase (10 weeks after the start of treatment), in D, C, PTX-D, and PTX-C rats. In a second part of this work, CVR was measured during the early phase in TXAPT-D, TXAPT-C, TXPTX-D, TXPTX-C, TXPTX-DT_4, and TXPTX-CT_4 groups.

The data are arithmetical means of n individual values ± s.e. mean. Statistical comparisons were made with Student's t test.

Results

Effect of parathyroidectomy

Growth (Table 1) Comparison of rats in the same category (C or D) and at the same period, showed that parathyroidectomy did not significantly lower weight.

Table 1 Effect of parathyroidectomy on serum calcium and blood pressure during mineralocorticoid induced hypertension in Sprague-Dawley rats

Group	Number of rats		Body weight (g)		Serum calcium (mg/l)		Arterial blood pressure: Awake (mmHg)		Pretreated§ (mmHg)		Decrease (%)	
	2nd week	10th week	2nd week	10th week	2nd week	10th week	2nd week	10th week	2nd week	10th week	2nd week	10th week
C	19	6	240 ±4.98	385 ±5.98	99 ±1.57	100 ±1.01	124 ±2.04	150 ±1.80	75 ±2.55	79 ±4.91	39 ±2.12	48 ±2.82
D	14	6	224 ±5.21	380 ±13.2	95 ±1.50	101 ±0.94	148*** ±6.02	170*** ±3.45	70 ±4.01	78 ±4.39	57*** ±2.87	54 ±2.96
PTX-C	17	6	229 ±6.45	370 ±5.21	57 ±1.77	60 ±3.06	116 ±2.86	146 ±4.90	71 ±2.99	86 ±4.21	39 ±4.00	41 ±3.91
PTX-D	17	5	211 ±4.67	371 ±9.15	61 ±1.86	64 ±3.96	124‡‡‡ ±2.43	155‡‡ ±4.71	70 ±4.14	82 ±3.18	43* ±4.80	47 ±1.51

C: control rats; D: normal DOCA-treated rats; PTX-C: parathyroidectomized control rats; PTX-D: parathyroidectomized DOCA-treated rats.

§ Rats anaesthetized with sodium pentobarbitone (30 mg/kg, i.p.) and pretreated with pentolinium (25 mg/kg, s.c.) and atropine sulphate (0.25 mg/kg, s.c.). Mean ± s.e. mean.

* Comparison of D and C; ‡ Comparison of D and PTX-D. One symbol: $P < 0.05$; two symbols: $P < 0.02$; three symbols: $P < 0.001$

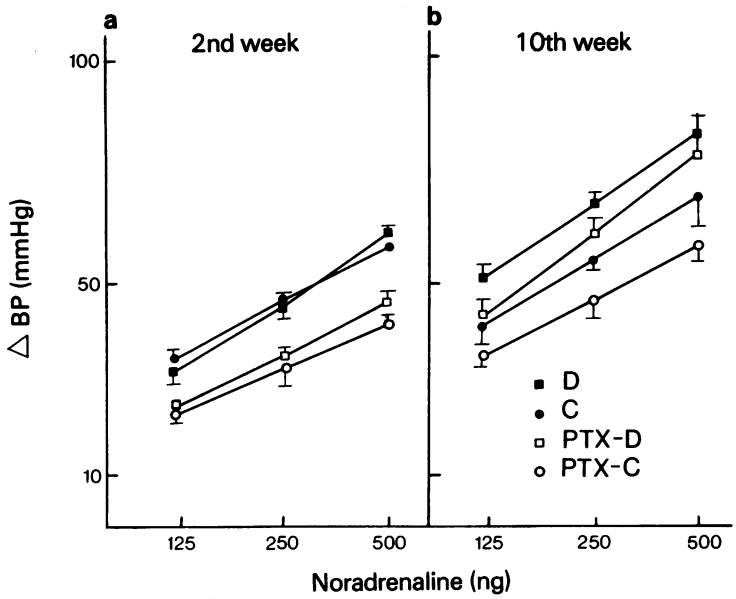

Figure 1 Cardiovascular reactivity to noradrenaline during mineralocorticoid hypertension, expressed as change in blood pressure (Δ BP), after injection of three doses of noradrenaline. The vertical lines show the s.e. mean. (■) Normal DOCA-treated rats (D); (●) normal control rats (C); (□) parathyroidectomized DOCA-treated rats (PTX-D); (○) parathyroidectomized control rats (PTX-C). Significances omitted from the graph for clarity are as follows: 2nd week, comparison of D and PTX-D, $P < 0.001$; of C and PTX-C, $P < 0.01$; 10th week, comparison of C and D, $P < 0.05$; of PTX-C and PTX-D, $P < 0.02$; and of regression curves for D and PTX-D, for C and PTX-C, $P < 0.05$.

Serum calcium (Table 1) As expected, both PTX-C and PTX-D groups had lower levels of serum calcium than the C and D groups. Furthermore, the serum calcium concentrations were the same in PTX-C and PTX-D rats at both 2 weeks and 10 weeks after parathyroidectomy demonstrating that in the two groups tested after 10 weeks, the parathyroid glands had still not regrown.

Blood pressure (Table 1) Two weeks after the start of treatment, D rats were slightly hypertensive. Blood pressure was higher in this group than in the C and PTX-D groups ($P < 0.001$). Ten weeks after mineralocorticoid-treatment, D rats were hypertensive, PTX-D rats were not ($P < 0.001$), and normal control rats had slightly lower arterial blood pressure than PTX-D rats.

Pretreatment with pentolinium and atropine Inhibition of the autonomic nervous system produced a similar arterial blood pressure in PTX-D and D rats during both the early and the sustained phase of mineralocorticoid-induced hypertension. In the early stage, arterial blood pressure fell further in the D than in the C group; after 10 weeks there was no difference. After parathyroidectomy there was no difference between the PTX-D and PTX-C groups.

Cardiovascular reactivity to noradrenaline The CVR was lower in all groups of parathyroidectomized rats than in corresponding non-parathyroidectomized ones, whether they were DOCA-treated or not and regardless of the time elapsed (2 or 10 weeks) after the operation (Figure 1). However, the difference between PTX-D and D rats was more significant after 2 weeks ($P < 0.001$) than after 10 ($P < 0.05$, dose-effect curves). During the onset of hypertension, CVR did not differ between the D and C groups nor between the PTX-D and PTX-C groups. After 10 weeks of mineralocorticoid treatment, the D and PTX-D groups were more reactive than their controls.

Effect of parathyroid autotransplantation and thyroidectomy in the early phase of hypertension

Growth (Table 2) Two weeks after the start of treatment with DOCA, the weight of rats without thyroid hormones (TXPTX and TXAPT groups) was reduced. The weight of thyroxine-supplemented rats (TXPTX-T_4 groups) was nearly as great as that of the C group.

Serum calcium (Table 2) The serum calcium level in autotransplanted rats (TXAPT groups) was signifi-

cantly higher than in thyroparathyroidectomized rats (TXPTX groups). The value of nearly 100 mg/l observed after autotransplantation was normal.

Arterial blood pressure (Table 2) Arterial blood pressure was higher in mineralocorticoid-treated autotransplanted rats (TXAPT-D group) than in controls (TXAPT-C group) ($P < 0.01$). In the other groups arterial blood pressure remained unchanged.

Pretreatment with pentolinium. After pretreatment, blood pressure fell further in the TXAPT-D than in the TXAPT-C group but the difference is not significant.

Cardiovascular reactivity to noradrenaline. TXAPT-D and TXAPT-C rats showed a greater vasopressive response than TXPTX-D and TXPTX-C rats ($P < 0.02$) (Figure 2a and b). Thus, parathyroid autotransplantation in thyroidectomized rats enhanced CVR to noradrenaline. Nevertheless, the CVR of autotransplanted rats was slightly lower than that of C rats (Figure 1a). Thyroxine administration produced a higher noradrenaline response in thyroparathyroidectomized rats of both C and D groups. Dose-effect curves are significantly different ($P < 0.05$) (Figure 2b).

Cardiovascular reactivity to angiotensin II (Figure 3) After 2 weeks of treatment there was no significant difference between PTX and C rats (with or without DOCA); only thyroparathyroidectomized rats given a thyroxine supplement (TXPTX-T_4 groups) had lowered reactivity.

Discussion

Parathyroidectomy and cardiovascular reactivity

Our most interesting result is the diminution of CVR to noradrenaline that parathyroidectomy produced in PTX-D and PTX-C rats. During both the early and the late phase of mineralocorticoid hypertension, PTX-D rats were less reactive than D rats. Moreover, changes in reactivity were independent of mineralocorticoid treatment, since PTX-C rats were less responsive than C rats to noradrenaline.

In DOCA-treated rats, parathyroidectomy decreased activity of the autonomic nervous system: after pretreatment with pentolinium, blood pressure fell more in D than in PTX-D rats 2 weeks after DOCA administration. The difference between these two groups of rats was less at 10 weeks. The activity of the autonomic nervous system increased during

Table 2 Serum calcium and arterial blood pressure of parathyroid autotransplanted and thyroparathyroidectomized Sprague-Dawley rats 2 weeks after start of mineralocorticoid treatment

Group	Number of rats	Body weight (g)	Serum calcium (mg/l)	Arterial blood pressure		
				Awake (mmHg)	Pretreated§ (mmHg)	Decrease (%)
TXAPT-C	7	185 ±4.33	101 ±1.43	113 ±4.21	64 ±5.99	43 ±5.01
TXAPT-D	9	182 ±3.75	100 ±1.20	131** ±2.95	62 ±5.11	52 ±4.00
TXPTX-C	6	169 ±5.28	48 ±1.83	104 ±3.49	62 ±3.59	40 ±2.71
TXPTX-D	5	174 ±1.67	64 ±5.92	112 ±4.52	57 ±2.87	49 ±3.12
TXPTX-CT_4	6	238 ±5.50	63 ±4.15	109 ±3.64	68 ±6.35	—
TXPTX-DT_4	6	217 ±7.22	60 ±2.12	120 ±3.09	68 ±4.63	—

TXAPT-C: thyroidectomized and autografted parathyroid control rats; TXAPT-D: thyroidectomized and autografted parathyroid DOCA-treated rats; TXPTX-C: thyroparathyroidectomized control rats; TXPTX-D: thyroparathyroidectomized DOCA-treated rats; TXPTX-CT_4; thyroparathyroidectomized control rats treated with L-thyroxine alone; TXPTX-DT_4; thyroparathyroidectomized rats DOCA-treated rats given a thyroxine supplement.

§ Rats anaesthetized with sodium pentobarbitone (30 mg/kg, i.p.) and pretreated with pentolinium (25 mg/kg, s.c.) and atropine sulphate (0.25 mg/kg, s.c.). Mean ± s.e. mean.

** $P < 0.01$ Comparison of TXAPT-D and TXAPT-C.

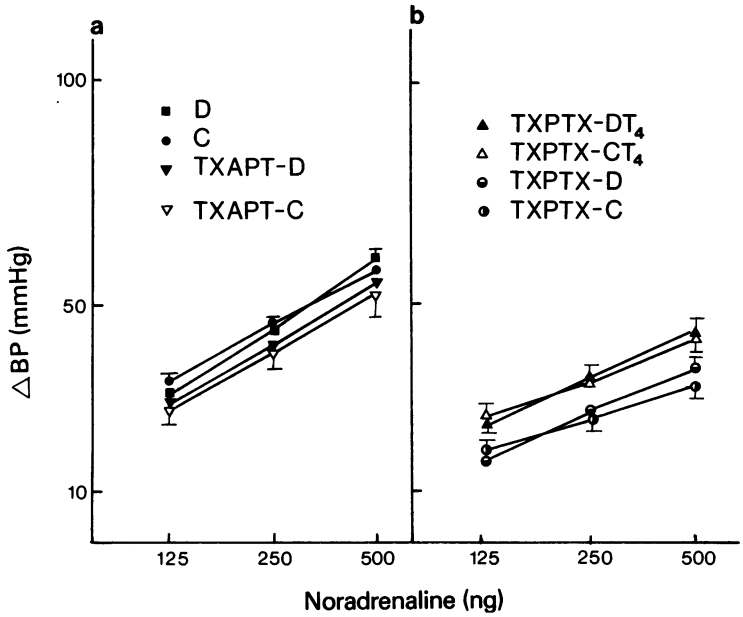

Figure 2 Cardiovascular reactivity to noradrenaline, 2 weeks after the start of mineralocorticoid-treatment, expressed as change in blood pressure (Δ BP), after injection of three doses of noradrenaline. The vertical lines show the s.e. mean. (a) (●) DOCA-treated normal rats (D); (■) normal control rats (C); (▼) Thyroidectomized and autografted parathyroid DOCA-treated rats (TXAPT-D); (▽) thyroidectomized and autografted parathyroid control rats (TXAPT-C). (b) (▲) Thyroparathyroidectomized DOCA-treated rats given thyroxine (TXPTX-DT_4); (△) thyroparathyroidectomized control rats given thyroxine (TXPTX-CT_4); (◑) thyroparathyroidectomized control rats (TXPTX-C); (⊖) thyroparathyroidectomized DOCA-treated rats (TXPTX-D). Significances omitted from the graph for clarity are as follows: (a) comparison of C and TXAPT-C, NS, of D and TXAPT-D, NS; (b) comparison of TXPTX-D and TXPTX-DT_4, $P < 0.05$ of TXPTX-C and TXPTX-CT_4, $P < 0.05$; (a and b) comparison of TXAPT-D and TXPTX-D, $P < 0.02$, of TXAPT-C and TXPTX-C, $P < 0.02$.

DOCA-induced hypertension. De Champlain *et al.* (1976) and Reid *et al.* (1975) have reported increased serum catecholamines in DOCA-treated rats. Hypocalcemia after parathyroid removal probably diminished noradrenaline release from sympathetic nerves, since variations in calcium concentration produced this phenomenon (Johnson, Thoa, Weinshilboum, Axelrod & Kopin, 1971; George & Leach, 1975). Parathyroidectomy may protect against development of hypertension by partially inactivating the autonomic nervous system. Study of catecholamine turnover in PTX-D rats would be of great interest.

CVR changes with the phase of hypertension: Sturtevant (1956) observed hyper-reactivity in rats 34 weeks after the start of treatment with DOCA, but other workers found no difference 4 weeks after the start of treatment (Shibayama, Mizogami & Sokabe, 1971). In rabbits, increased cardiovascular reactivity with renal hypertension was described by Conway (1955). Our present work confirms that there was no change in CVR in rats with or without parathyroid glands 2 weeks after treatment with DOCA; later, during the sustained phase of hypertension (10 weeks after the start of treatment with DOCA), D and PTX-D rats were more reactive than their controls.

Parathyroid autotransplantation, thyroparathyroidectomy, and cardiovascular reactivity

Surgery and L-*thyroxine supplementation* Parathyroid autotransplanted and thyroparathyroidectomized rats weighed less than control rats ($P < 0.001$). Thyroid ablation was correctly performed. Nevertheless rats in the TXAPT-C group weighed slightly more than those in the TXPTX-C group ($P < 0.01$), which suggests that a few thyroid cells may have been autotransplanted with the parathyroid glands. Supplementation of thyroparathyroidectomized rats with L-thyroxine was sufficient to re-establish the same growth rate as in normal rats with intact thyroid glands. Calcemia of parathyroid autotransplanted rats reached normal values, a finding that supports the validity of our autotransplantation procedure. Within a week after surgery, parathyroid glands transplanted

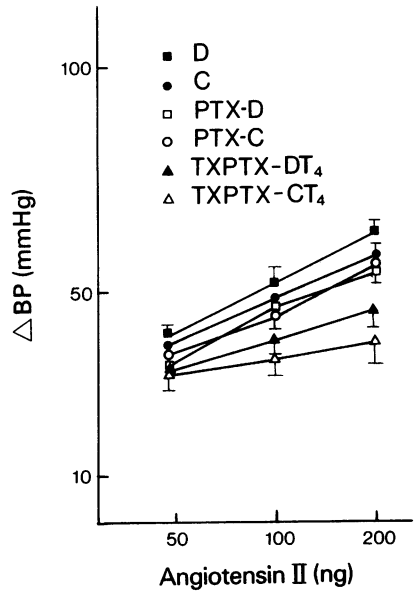

Figure 3 Cardiovascular reactivity to angiotensin II 2 weeks after the start of mineralocorticoid treatment, expressed as change in blood pressure (Δ BP), after injection of three doses of angiotensin II. The vertical lines show the s.e. mean. (■) Normal DOCA-treated rats (D); (●) normal control rats (C); (□) parathyroidectomized DOCA-treated rats (PTX-D); (○) parathyroidectomized control rats (PTX-C); (▲) thyroparathyroidectomized DOCA-treated rats given thyroxine supplement (TXPTX-DT_4); (△) thyroparathyroidectomized control rats given thyroxine (TXPTX-CT_4). Significances omitted for clarity are as follows: comparison of C and D, PTX-D and PTX-C, TXPTX-DT_4 and TXPTX-CT_4, NS; of D and TXPTX-DT_4, $P < 0.05$; and of C and TXPTX-CT_4, $P < 0.02$.

into the hyoid muscle brought serum calcium up to a normal level.

Cardiovascular reactivity to noradrenaline CVR was very low in thyroparathyroidectomized rats and clearly higher in parathyroid autotransplanted rats ($P < 0.02$), where it was nearly normal. This reactivity probably accounts for development of hypertension in such rats without endogenous thyroid hormone (Berthelot & Gairard, 1976). Thus, we conclude that endogenous parathyroid hormone alone increased cardiovascular reactivity to noradrenaline and permitted development of hypertension in the mineralocorticoid-treated rat.

Thyroxine-supplemented thyroparathyroidectomized rats had higher CVR than non-supplemented rats but not as much CVR as the control rats. These results confirm our previous work showing the necessity of the parathyroid glands for the development of hypertension during mineralocorticoid treatment.

Cardiovascular reactivity to angiotensin II In agreement with Nicholas (1971) and Scholtysik & Unda (1971), we did not find any difference between D and C rats in CVR to angiotensin II. Moreover, there was no difference between PTX and normal rats. Parathyroid glands are probably of little importance in the expression of rat CVR to this drug. On the other hand, we have shown indirectly that absence of parathyroid hormone and thyrocalcitonin lessens CVR to angiotensin II, since thyroxine supplemented thyroidectomized rats were less responsive than control rats to this agent ($P < 0.02$).

Mechanism of parathyroid intervention in DOCA-induced hypertension Parathyroid hormone enhances calcemia and cell calcium exchanges. In these experiments, we did not find any correlation between the level of serum calcium and the level of CVR in parathyroidectomized rats. A decrease in serum calcium and in ionized calcium (not measured) probably does not significantly lower the vasopressive action of noradrenaline, since *in vitro* experiments performed on rat isolated aortae showed that very large changes in extracellular calcium concentration are necessary to change the reactivity of arteries (Demesy-Waeldele & Stoclet, 1975). Therefore it seems unlikely that contraction of vascular smooth muscle is influenced by the decreased extracellular calcium concentration in parathyroidectomized rats. In other experiments we have found that hypertension was prevented by parathyroidectomy in D rats even when serum calcium was artificially increased to normal levels in the absence of parathyroid hormone (unpublished observations). In mineralocorticoid-induced hypertension, previous work described an acute vascular effect of parathyroid hormone: vasodilatation of mesenteric arteries in the dog with pharmacological doses (Charbon, 1968). Our previous work in rats showed that parathyroid hormone inhibited an isolated arterial contraction in response to phenylephrine (Berthelot & Gairard, 1975). Parathormone enhanced the influx of calcium into various cells (Borle, 1971), and chronic administration of parathyroid hormone increased calcifications in rats (Selye, Gabbiani & Tuchweber, 1964). We suggest that calcium storage in vascular smooth muscle cells is lessened in parathyroidectomized rats and that noradrenaline stimulation lessens cardiovascular response in mineralocorticoid-treated rats.

Our conclusions may be summarized as follows: in DOCA-treated and control rats, parathyroidectomy lessened cardiovascular reactivity to noradrenaline. Parathyroid glands in autotransplanted

thyroidectomized rats restored normal response in the absence of thyrocalcitonin and thyroid hormones. Parathyroid hormone makes possible the physiological effect of noradrenaline on the cardiovascular system.

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