原　著

PLASMA CATECHOLAMINES IN PULMONARY TUBERCULOSIS

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Fifty pulmonary tuberculous patients (minimal ; moderate and far-advanced), 18 TB-healed persons and 15 healthy control subjects were examined for plasma levels of adrenaline (AD), noradrenaline (NA), dopamine (DA), ACTH and cortisol. The estimated hormones were found to be increased significantly with the severity of the disease suggesting that the stress of infection plays a role in induction of enzymes responsible for catecholamines synthesis with subsequent stimulation of ACTH and cortisol secretion. Noradrenaline appeared the most effective in this respect.

INTRODUCTION

Tuberculosis (TB) is a chronic destructive disease resulting in a state of persistent stress, either exerted by metabolite(s) released by the microorganisms, the products of destroyed tissues, or due to other psychosomatic factors.

We have studied the pituitary hormones : growth hormone (GH), prolactin (PRL) and adrenocorticotrophic hormone (ACTH) as well as cortisol in bronchogenic and haematogenous TB patients and in healed-TB subjects (ex-patients). Those hormones were significantly increased in sera of investigated patients, but no significant changes were observed in ex-patients compared with the control group[1].

Catecholamines, adrenaline (AD), noradrenaline (NA) and dopamine (DP) are enumerated among the stress hormones. Literature concerning the plasma catecholamines are scanty. Some investigators reported high levels in different stressful conditions as myocardial infraction[2], septicaemia, trauma, haemorrhage[3], and exposure to cold[4].

Noradrenaline has the suppressive effect on T-lymphocytes[5] ; the cells that play an essential defensive role against tuberculosis.

This work was planned to evaluate plasma catecholamines by radio-enzyme assay technique, ACTH and cortisol by radioimmunoassay method in TB patients, ex-patients in comparison with healthy subjects.

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SUBJECTS AND METHODS

Three groups of subject were included in this study :

1) Pulmonary TB patients (n=50), 2) ex-patients (healed TB, n=18 ; and 3) healthy controls (n=15).

All the subjects were age-matched, The body weight of the patient groups and ex-patient subjects were 57 ± 6.4 and 60 ± 4.5kg (± SD) respectively ; and that of the control was 62 ± 3.5kg. Based on the classification of the National Tuberculosis Association[6] patients with pulmonary tuberculosis were divided into minimal (group I), moderate (group II) and far-advanced (group III). This classification is still recommended by Seaton et al[7]. Minimal lesion correspond to those with unilateral shadows with moderate density without cavitation confined to above the 2nd condrosternal junction, the 4th spine or the 5th thoracic vertebral body. Moderate lesions are those uni-or bilateral shadows involving one lung volume, or with dense and confluent shadows affecting one-third of a lung, or with cavities less than 4 cm in diameter. Far-advanced lesions are those with more extensive involvements.

At 9.00 a.m., fasting blood samples were taken in EGTA tubes, centrifuged in a cooling centrifuge for 10 min. at 750 xg. Plasma was kept in aliquates at −20℃ till time of assay. Cortisol[8] and ACTH[9] were assayed by double antibody technique of radioimmunoassay using kits manufactured by Diagnostic product Corporation, Los Angeles, CA. Plasma catecholamines were assayed using kits produced by Amersham Plc. UK. This method was based on utilization of catechol-0-methyl transferase (COMT) to transfer (^{3}H) methyl group from adenosyl-L-(methyl-^{3}H) methionine to AD, NA aud DP to obtain tritiated metanephrine, normetanephrine and 3-methoxytyramine respectively. The methylated derivatives were isolated by thin layer chromatography. They were extracted and a scintillation liquid was added, and then the tubes were counted by a liquid scintillation counter[10].

The results were statistically analysed in comparison with the control group and correlation coefficient (r) was calculated.

RESULTS

Plasma ACTH (mean ± SEM) in the control was 147.3 ± 6.3 pg/m*l*, but in the patient groups it was 177 ± 5.56, 188 ± 5.88, and 221 ± 9.14 pg/m*l* in groups I, II and III respectively. Healed

Table 1. Plasma ACTH (pg/m*l*), Cortisol (μg/d*l*) Dopamine (DP), Adrenaline (AD), and Noradrenaline (NA) (pg/m*l*) in Normal, TB, and Healed-TB (ex-patients) Groups

Group		ACTH	Cortisol	DA	AD	NA
Control	Mean	147.3	9.9	24.5	61.5	20.7
n=15	SEM	6.3	1.14	5.47	7.6	11.4
Group I	Mean	177	13.4	487	531	648
n=17	SEM	5.56	0.88	38.8	37.8	47.9
	P_1<	NS	NS	0.001	0.001	0.001
Group II	Mean	188	16	689	710	753
n=16	SEM	5.83	1.3	78	89.9	61.6
	P_1<	0.001	0.01	0.001	0.001	0.001
	P_2<	NS	NS	0.05	NS	NS
Group III	Mean	221	20.4	1030	802	967
n=17	SEM	9.14	0.82	99.6	67.4	117.6
	P_1<	0.001	0.001	0.001	0.001	0.001
	P_2<	0.001	0.001	0.001	0.001	0.001
	P_3<	0.001	0.01	0.02	NS	NS
Healed-TB	Mean	132	9.3	29.4	57.9	89.6
n=18	SEM	4.76	0.45	1.9	4.3	6.4
	P_1<	NS	NS	NS	NS	NS

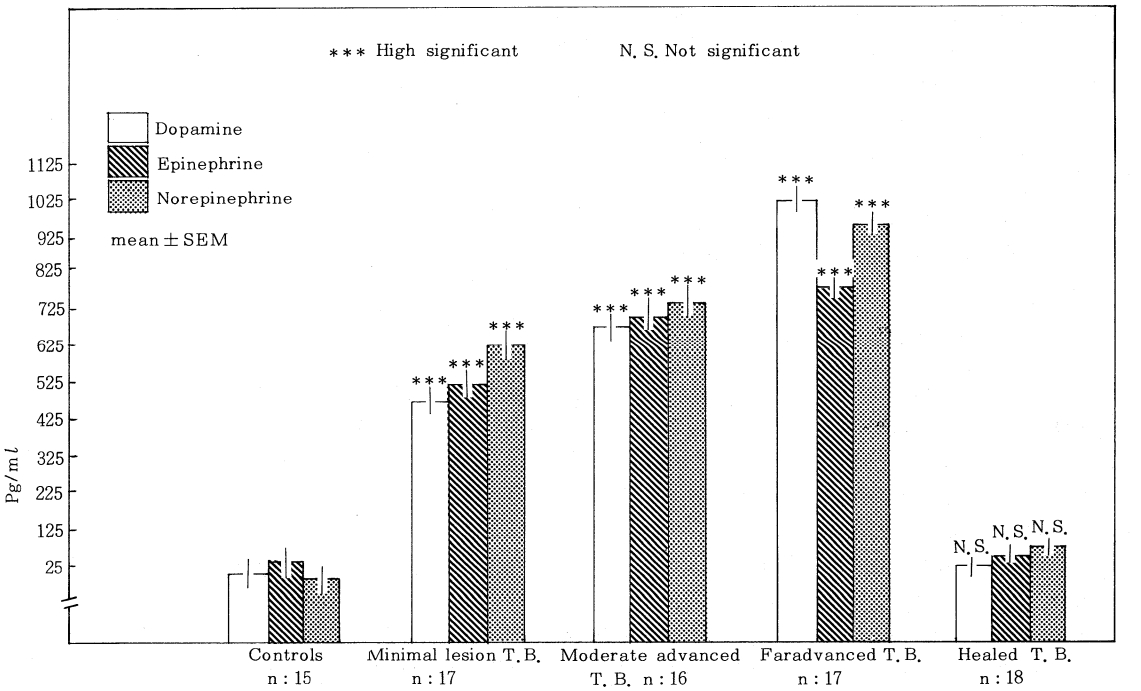

Fig. Plasma Catecholamines Levels(mean ± SEM)in T. B. and Healed T. B. Subgroups VS Control Subgroup

group had plasma ACTH of 132 ± 4.76 pg/m*l*. Only group Ⅲ had significant elevation of ACTH levels compared to other groups (Table 1, Fig.).

Cortisol serum levels were 9.9 ± 1.14, 13.4 ± 0.88, 16 ± 1.3, 20.4 ± 0.82, and 9.3 ± 0.45 μg/d*l* in the control, groups Ⅰ, Ⅱ, Ⅲ and healed −TB subjects successively. Still group Ⅲ had the significant higher level compared to other group levels which had insignificant alterations among themselves.

Plasma DA was 24.5 ± 5.47, 487 ± 38.8, 689 ± 78, 1030 ± 99.6 and 29.4 ± 1.9 pg/m*l* in controls, groups Ⅰ, Ⅱ, Ⅲ and in the healed −TB subjects respectively TB groups had significant higher levels vs the control. Plasma AD in the same groups were 61.5 ± 7.6, 531 ± 37.8, 710 ± 89.9, 802 ± 67.4, and 57.9 ± 4.3 pg/m*l* in the same order.

Plasma NA levels were 20.7 ± 11.4, 648 ± 47.9, 753 ± 61.6, 967 ± 117.6, and 89.6 ± 6.4 pg/m*l* respectively in the control, TB groups Ⅰ, Ⅱ, Ⅲ and the healed−TB group.

Plasma ACTH, cortisol and dopamine were higher in groups Ⅱ and Ⅲ vs group Ⅰ. Adrenaline and noradrenaline showed insignificant elevation in group Ⅱ vs group Ⅰ, and in group Ⅲ vs group Ⅱ.

Healed−TB group had insignificant values of ACTH, cortisol and catecholamines compared to the healthy controls.

Table 2. The Expiratory Flow Rate (L/min) in Normal, Tuberculous, and Healed Groups

Parameter	Control	group Ⅰ	group Ⅱ	group Ⅲ	Healed
Mean	466	468	406	313	414
SEM	22.15	10.77	13.9	13.8	13.22
P_1<		NS	0.05	0.001	NS

Group Ⅰ :minimal TB, Group Ⅱ :moderate TB, Group Ⅲ far−advanced TB
P_1=*vs* control, P_2=*vs* group Ⅰ, P_3=*vs* group Ⅱ.
NS=insignificant.

The expiratory flow rate was 466 ± 22.15, 468 ± 10.77, 406 ± 13.9, 313 ± 13.8, and 414 ± 13.22 L/min. in the control, TB groups (I through Ⅲ), and healed-TB respectively. Only groups Ⅱ and Ⅲ had significant lower values versus the control group.

No significant correlation had been found between AD and cortisol or ACTH in the investigated groups, nor between cortisol and ACTH.

DISCUSSION

Plasma catecholamines are progressively increasing with the advance of tuberculous lesion. Their values agree with that of ACTH and cortisol. Common aetiology contributing for elevation of these hormones could be suggested : one of them may precede and herald the others.

Adrenaline, noradrenaline and dopamine increase in plasma in response to stress[11]. Dopamine serves chiefly as a precursor of AD and NA[12]. Chronic stress is reported to induce tyrosine hydroxylase, dopamine-B-hydroxylase and phenylethanolamine-N-methyl transferase enzymes[13]. The latter author stated that no exact feedback loop has been described controlling catecholamines secretion, but the inducible stimulus for the pre-mentioned enzymes might come through the preganglionic fibres of the splanchnic nerve supplying the adrenal medulla, from the hypothalamus, brain stem and the cervical segment of the spinal cord. One may suggest that catecholamines, noradrenaline in particular, may stimulate ACTH secretion with secondary release of cortisol. Our observation that NA was the highest of the three catecholamines studied in each of the TB groups may support this suggestion.

Noradrenaline and glucocorticoids inhibit the defensive mechanisms of T-lymphocytes against microorganisms[5]. This raises the question that which of them contribute for the other ; viz, the destructive effect of TB bacilli on lung tissue or the elevation of these hormones. It seems that both are interacting factors.

Intravenous infusion of methoxamine, a highly selective α-adrenoceptor agonist, stimulates ACTH and cortisol secretion. This response is abolished by administration of thymoxamine, the corresponding α-antagonist[14]. This type of adrenoceptors are located in the hypothalamus and its central connections rather than in the pituitary, suggested that adrenergic stimulation of ACTH secretion is mediated through CRF released from the paraventricular nucleus of the hypothalamus[15]. Experimental animal studies revealed that corticosteroid secretion is stimulated by implanation of NA into the hypothalamus but not into the pituitary[16)~18]. Controversial findings are obtained by Weiner and Ganong[19]. The hypothalamic NA is almost all extrinsic[20].

On the other hand, intravenous infusion of AD in supraphysiological doses has no effect on ACTH or cortisol secretion basally or after CRF injection[21], suggesting that circulating AD has no physiological role in stimulating ACTH secretion. In support with this finding, insulin-induced hypoglycaemia is not associated with AD secretion in spite of stimulated cortisol secretion[22].

Dopamine has no important effect on ACTH secretion whether basal[23] or insulin-induced hypoglycaemia[24] or following CRF injection[15]. Bromocryptin, DA agonist, and metoclopramide, DA antagnoist, have no effect on basal plasma cortisol[25].

Mammalian adenohypophysis does not receive catecholinergic innervation[26], the hypothalamic DA is almost all intrinsic[20]. The systemic circulating DA cannot pass the blood-brain barrier[27]. Al-Damluji and Rees[15] claimed no evidence for B-adrenergic or dopaminergic effect on ACTH secretion in man.

It can be concluded from our work that the progressive increase of basal catecholamines that rise in parallel with the severity of the disease is due to the stress caused by the damage occurred in the lung tissue. Also, NA rather than AD and DA., may mediate the increase in ACTH and cortisol plasma levels. Healed tuberculous subjects show insignificant differences in the estimated hormones compared to normals ; probably due to relief of the stress condition caused by TB infection.

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