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Plasma Renin Activity in Primary and Secondary Depression

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Summary. Plasma renin activity (PRA), both in supine and standing position, was investigated in primary and secondary depressed patients. After orthostatic stimulation (standing position) primary depressed patients showed PRA values significantly lower than did those with secondary depression. The authors stress the importance of the peripheral sympathetic system in the control of renin release and discuss the data obtained in the light of some evidence in the literature indicating a possible impairment of transmitter turnover in central and peripheral noradrenergic synapses in the pathogenesis of primary depression.

Key words: Primary and secondary depression – Plasma renin activity – Noradrenergic system.

Introduction

Primary or endogenous depression is often attributed pathogenetically to an impairment of brain monoaminergic systems (Cazzullo et al., 1966; Baldessarini, 1975), and notably of the noradrenergic system (Schildkraut, 1965). Various pieces of evidence seem to support this view.

The urinary excretion of norepinephrine (NE) and normetanephrine, both derived from NE pools outside the central nervous system (CNS), is said to be reduced in patients with primary affective disorders (PAD) during periods of depression as opposed to periods of normothymia or manic excitation (Schildkraut et al., 1965; Greenspan et al., 1969; Bunney et al., 1970; Jones et al., 1973).

More important are the findings concerning urinary assays of 3-methoxy-4-hydroxyphenylglycol (MHPG), representing the main product of brain NE degradation in a number of mammalian species (Maas and Landis, 1968): this metabolite was reported to be significantly reduced in a group of patients with endogenous depression versus normal controls (Maas et al., 1968).

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As for the study of plasma renin activity (PRA) in depressed patients, its interest stems from published evidence of the influence of the sympatho-adrenergic system on renin release; in fact, it seems that PRA, particularly when stimulated by standing, can be taken as a marker of sympathetic activity (Zanchetti and Stella, 1975).

Furthermore, some preliminary evidence suggests that the sympathetic control of renin incretion is organized centrally, since electrical stimulation of brain areas that are variously involved in the regulation of behavior produces reciprocal influences on renin release (Zanchetti et al., 1976).

Also quite recently, experimental evidence has been offered to show that certain compounds, which increase the endogenous NE content of the brain by blocking its reuptake, at the same time activate the renin-angiotensin system (Pojda and Herman, 1975).

For our part, we found in an earlier study that the reactivity of the renin-angiotensin system under orthostatic stimulation was significantly less in patients with primary depression than in normal controls, and that plasma renin values tended to rise with clinical amelioration induced by treatment (Altamura and Morganti, 1975).

In this present paper we give the results of a study of PRA in patients with primary depression as opposed to patients with reactive-neurotic or secondary depression.

Methods

Our study involved a total of 33 patients of either sex, hospitalized for depression and divided into two groups. The first group consisted of 13 patients with PAD, aged between 27 and 50 (mean: 41.1 ± 1.2); of these, 7 had unipolar depression and the remaining 6 presented bipolar forms with a previous history of manic episodes. The second group consisted of 20 patients between 18 and 45 years of age (mean: 28.8 ± 2.1), suffering from neurotic or reactive (secondary) depression. None of the patients showed evidence of water and electrolyte unbalance or renal, cardiovascular, or liver diseases in preliminary routine examinations. Prior to PRA assays, all patients were taken off all medication for at least one week, with the exception of Valium® when indispensable; they were maintained on a standard hospital diet containing approximately 100 mEq of sodium per day. PRA was assessed after keeping the patient recumbent for 6 h ("supine" PRA), and again after 2 h of upright physical activity ("standing" PRA). Plasma renin was assayed radioimmunologically by the method of Haber et al. (1969), as modified by Leonetti et al. (1975). Reproducibility of the technique was excellent: each sample was regularly analyzed in triplicate with very close results, and the range of repeated measurements of the same plasma, stocked for periods of 4—18 days, was never above 0.4 ng. The depressive situation was evaluated by two independent psychiatrists according to the criteria of Robins and Guze (1973) and using Hamilton's rating scales for depression. The results were analyzed statistically by Student's *t*-test.

Results

The mean PRA measured in patients with primary depression was 0.29 ± 0.06 ng/ml/h in the supine position and 0.93 ± 0.17 ng/ml/h in the standing position; in patients with secondary depression the corresponding values were 0.46 ± 0.06 and 1.64 ± 0.21 ng/ml/h.

Table 1. Plasma renin activity (ng/ml/h) in primary depressed patients

Patients	Age	Sex	Type of depression	"Supine" PRA	"Standing" PRA
R.G.	43	M	unipolar	0.20	1.12
L.G.	43	M	bipolar	0.08	0.62
C.F.	33	M	bipolar	0.18	0.58
M.A.	27	M	unipolar	0.45	0.53
B.G.	50	F	unipolar	0.03	0.15
S.E.	48	M	bipolar	0.80	1.93
C.M.	45	M	unipolar	0.19	0.45
P.C.	27	M	unipolar	0.27	1.03
N.E.	50	F	unipolar	0.27	1.17
M.G.	39	M	bipolar	0.43	2.15
L.G.	37	M	unipolar	0.74	1.16
V.F.	43	F	bipolar	0.04	0.16
M.P.	49	M	bipolar	0.17	1.05
	Mean SE			Mean SE	Mean SE
	41.1 ± 1.2			0.29 ± 0.06	0.93 ± 0.17

Tables 1 and 2 shows the individual values for all patients. Statistical analysis of the PRA values elicited in the two groups of subjects revealed no significant difference between the data obtained in the supine position; conversely, the standing values differed significantly ($P < 0.05$).

Discussion

The distinction of primary as opposed to secondary depression, currently accepted on the strength of clinical observation (Robins and Guze, 1973), genetic evidence (Winokur, 1975), biochemical considerations (Maas et al., 1974), and pharmacological responses (Angst, 1970), receives further confirmation from the behavior of PRA levels in the two categories of depressed patients. Our own findings indicate that in the supine position patients with primary depression tend to show lower PRA levels than do those with secondary depression, although the difference between the two groups falls short of statistical significance; but in the standing position (where the response constitutes an index of reactivity of the renin-angiotensin system) the same difference increases to the point where it becomes statistically significant. It is unlikely that this significant difference is due to the fact that in our study, patients with primary depression were somewhat older (average: 41.1 years) than those with secondary depression (average: 28.8 years). Although PRA has been found to be inversely related to age (Tuck et al., 1973; Hayduk et al., 1973), subjects in the age range of our patients differ in the PRA levels to a much smaller extent than the two groups of our depressed

Table 2. Plasma renin activity (ng/ml/h) in reactive and neurotic depressed patients

Patients	Age	Sex	Type of depression	"Supine" PRA	"Standing" PRA
I.A.	45	F	neurotic	0.23	0.62
T.A.	27	M	reactive	1.03	1.15
C.N.	30	M	neurotic	0.08	0.05
N.F.	18	F	neurotic	0.55	2.00
M.F.	30	F	neurotic	0.17	2.00
S.C.	30	F	reactive	0.50	2.15
L.F.	33	F	neurotic	0.55	1.45
C.E.	30	F	neurotic	0.37	1.08
S.E.	35	M	neurotic	0.53	2.48
G.A.	33	M	neurotic	0.67	1.42
P.E.	30	F	neurotic	0.50	1.72
I.F.	18	F	reactive	0.27	2.15
C.N.	18	M	reactive	0.60	2.28
V.A.	20	F	reactive	0.58	2.45
R.A.	19	F	reactive	0.33	2.48
T.E.	18	F	reactive	0.13	0.68
D.L.	18	F	reactive	1.10	4.05
L.M.	45	F	neurotic	0.72	1.52
V.F.	35	M	neurotic	0.23	0.57
M.A.	45	M	neurotic	0.10	0.43
	Mean SE			Mean SE	Mean SE
	28.8 ± 2.1			0.46 ± 0.06	1.64 ± 0.21

patients (Tuck et al., 1973). As PRA values, and particularly standing values, are considered to reflect the functional state of the sympatho-adrenergic system (Zanchetti and Stella, 1975), the most reasonable interpretation of our findings is that primary differs from secondary depression in terms of sympathetic activity. In secondary depression, PRA values seem to be closer to the normal range than in the primary form of the disorder (Altamura and Morganti, 1975). So, the low levels of PRA found in primary depression might reflect a reduced function of the peripheral sympathetic system, as indicated by the decreased urinary excretion of catecholamines and their metabolites reported in the literature; this in turn might be due to an impairment of transmitter turnover in central noradrenergic synapses. In other words, the PRA alterations of primarily depressed patients (particularly in the upright position) would be due to some disturbance of noradrenergic pathways in the brain, as apparently corroborated by pharmacologic evidence both in experimental animals and in man.

Thus, for instance, the injection into lateral brain ventricles of NE or of drugs that increment endogenous NE (desmethyl-imipramine and RO 4-1284) activates

the incretion of renin; this can be stopped by the subsequent administration of propranolol (Pojda and Herman, 1975). Conversely, treatment with drugs that deplete NE in the brain and peripheral sympathetic system (e.g., reserpine), or that produce a blockade of β-adrenergic receptors (e.g., propranolol), bring about behavioral depression in the experimental animal (Brodie, 1965; Weinstock and Speiser, 1974) and likewise a depressive state in man (Hollister, 1961; Waal, 1967); at the same time, these treatments also lower PRA levels (Leonetti et al., 1975).

Some data of experimental neurophysiology indicate that the central regulation of renin incretion takes place in the same areas of the hypothalamus that are also active in regard to emotional behavior (Zanchetti et al., 1976).

As for our own findings, one might object that the lower PRA values found in patients with primary depression simply reflect their greater tendency to physical inactivity compared to those with secondary depression; but this is contradicted by the fact that supine and standing PRA values were obtained in identical, standard conditions in the two groups of patients.

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