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Platelet Adenylate Cyclase Responses in Depression:

Implications for a Receptor Defect

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Abstract. The dose-dependent stimulatory response of prostaglandin E_1 (PGE_1) on the net synthesis of ^{3}H-adenosine 3′,5′-monophosphate (cyclic AMP) in platelets whose adenine nucleotide pools had been labelled by prior incubation with ^{3}H-adenine was measured. Also, the dose-dependent inhibition produced by norepinephrine (NE) on this stimulatory process was evaluated. Platelets were obtained from eleven moderately depressed male patients and from eight non-depressed normal male control subjects. No difference was noted between the two groups of subjects either in the stimulation produced by PGE_1 or in the inhibition caused by NE. Subdividing the patients into different subgroups (e.g., bipolar or unipolar) did not produce any significant differences. This finding suggests that there is no generalized defect in alpha adrenergic responses in depressed male patients.

Key words: Adenylate Cyclase — Norepinephrine — Prostaglandin E_1 — Platelet — Depression.

It has been hypothesized that affective illnesses are a reflection of some disturbance in biogenic amine function (Prange, 1964; Schildkraut, 1965; Coppen, 1967), depression being associated with an absolute or relative deficiency of biogenic amines at some important functional site in the brain. To evaluate this hypothesis, most investigators have studied amines or their metabolites in blood, urine, or lumbar fluid. The results of many of these studies are contradictory (see Robins and Hartman, 1972; Mendels and Stinnett, 1973; Post *et al.*, 1973) and it has been suggested that "no clinical studies have revealed unequivocal, consistent, and unique physiological abnormalities in depressives which complement the pharmacologically derived monoamine theory" (Carroll, 1971).

An alternative strategy to measuring the concentration of monoamines or their metabolites is to evaluate responses produced by such compounds in depressed patients. Such a strategy might be profitable in

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light of recent suggestions of a monoamine receptor abnormality in certain depressed patients (Ashcroft *et al.*, 1972). The response measured in the present study was the norepinephrine (NE)-induced decrease in radioactive adenosine 3′,5′-monophosphate (cyclic AMP) net synthesis in platelets. This biochemical response to NE was chosen as it appears that adrenergic receptors are closely related to and may even be a part of adenylate cyclase (Robison *et al.*, 1969b), the enzyme which catalyzes the conversion of adenosine triphosphate (ATP) to cyclic AMP (Sutherland and Rall, 1960).

Postulated neurotransmitter agents, such as the catecholamines, can increase the concentration of cyclic AMP in brain (Kakiuchi and Rall, 1968; Kakiuchi *et al.*, 1969), and cyclic AMP has been implicated in synaptic transmission (Siggins *et al.*, 1969). Perhaps as a consequence of this information, the urinary excretion of cyclic AMP has been measured in both depressive and manic patients. Several groups of investigators have found the urinary excretion of cyclic AMP to be low in depression and elevated in mania (Paul *et al.*, 1970; Abdullah and Hamadah, 1970; Paul *et al.*, 1971), but this has not been a consistent observation (Brown *et al.*, 1972; Jenner *et al.*, 1972). Similar controversy exists with regard to the lumbar fluid concentration of cyclic AMP in manic-depressive illness (Robison *et al.*, 1970; Cramer *et al.*, 1972).

Methods and Materials

Patient Characteristics. Eleven male depressed patients who were hospitalized on a clinical research ward were studied. Some of the characteristics of these patients are noted in Table 1. They all had a syndrome of depression, without any history or current clinical features suggestive of any other psychiatric disorder; schizophrenia, drug abuse, alcoholism, organic brain syndrome, etc. Furthermore, the severity of the depression was characterized on both an observer scale (Hamilton, 1960) and on a self-rating scale (Beck *et al.*, 1961). With one exception (CO) all of the patients were moderately-severely depressed. The patients were characterized as being bipolar depressive (recurrent depressive episodes with a history of a clear-cut manic or hypomanic episode in the past); unipolar depressive (recurrent depressive episodes without a history of mania or hypomania); or depressive neurosis (a group of patients with a history of mild-moderate chronic symptomatology usually associated with an "inadequate" personality).

The eight control subjects were healthy male employees of the hospital. Their mean age was 40 $\pm$ 4.5 years ($\bar{X} \pm$ SEM), which is somewhat lower than the average age of the patient population (50 $\pm$ 3), but not significantly so. All patients and subjects were drug-free for at least 2 weeks prior to evaluation of platelet adenylate cyclase activity.

Blood Drawing. After an overnight fast, about 35—40 ml of blood was drawn from the antecubital vein into a polypropylene centrifuge tube containing 0.5 ml of 0.15 M EDTA solution as an anticoagulant. Platelet rich plasma (PRP) was obtained by centrifuging the whole blood at 200 g for 15 min at 4°C. The supernatant fluid (i.e., the PRP) was removed with a plastic pipet and centrifuged again for 5 min at 200 g to remove contaminating leukocytes.