Diminished Activity of Platelet Monoamine Oxidase in Down's Syndrome

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INTRODUCTION

Subjects with primary trisomic Down's syndrome (DS) have low concentrations of blood 5-hydroxytryptamine (5-HT) [1, 2]; the cause is unknown. The greater proportion of circulating 5-HT is probably derived from the enterochromaffin cells of the gastrointestinal tract and is bound to platelets [3, 4]. In DS such binding has been found to be normal [5]. A low concentration of platelet 5-HT is therefore presumably due either to a diminished rate of synthesis or an accelerated breakdown.

The main pathway for breakdown of 5-HT is via oxidative deamination catalyzed by monoamine oxidase (MAO, EC 1.4.3.4.) to form the corresponding aldehyde, which is then further oxidized to 5-hydroxyindoleacetic acid (5-HIAA) (fig. 1). It seemed of interest, therefore, to measure the activity of MAO in patients with Down's syndrome. Platelets were selected for study, since there is evidence that the platelet MAO is similar to the liver enzyme with respect to substrate specificity. Moreover, the level of platelet MAO activity appears to be a valuable indicator of total MAO activity [6].

SUBJECTS AND METHODS

Platelets were obtained from 22 children with primary trisomic Down's syndrome in whom the diagnosis had been confirmed by karyotype analysis and from 22 controls who were matched for age (mean: 3.9 years; range: 1.0–7.8 years), domicile, and sex (equal numbers of males and females). All subjects appeared to be free from infection at the time of the investigation. Platelets were isolated by differential centrifugation from 5 ml of blood (anticoagulant 10 mg EDTA) and suspended in 1.0 ml distilled water. Then, 0.1-ml aliquots of the suspension were assayed in duplicate for MAO activity by the spectrophotofluorometric method of Krajl [7]. Protein was assayed by the method of Lowry et al. [8]. A unit is defined as grams 4-hydroxyquinoline formed per milligram platelet protein per 30 min. Duplicate results were always within 10% of each other.

RESULTS AND DISCUSSION

The results are shown in figure 2 and summarized in table 1. Platelet MAO activity was significantly lower in subjects with DS (0.81 units) than in controls (1.24 units)

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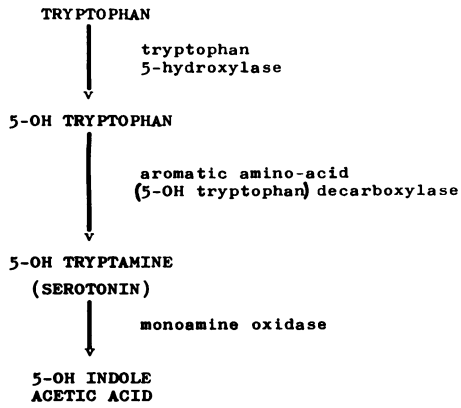

FIG. 1.—The 5-hydroxyindole pathway

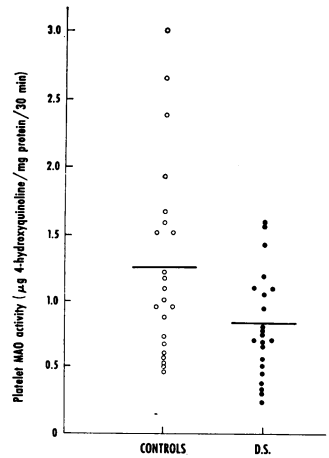

FIG. 2.—Platelet MAO activity in 22 subjects and 22 controls

TABLE 1

PLATELET MAO ACTIVITY*

	Number Studied	Mean	SD	*P*
Controls.....	22	1.24	0.70	.01–.02
Down's syndrome.....	22	0.81	0.38	

* Grams 4-hydroxyquinoline per milligram protein per 30 min.

(P = .01–.02). Control values are similar to those previously reported in longitudinal studies [9].

These findings suggest that accelerated degradation of 5-HT is unlikely to be the cause of low blood 5-HT in DS; it is reasonable to suggest, therefore, that there may be a diminished rate of 5-HT synthesis. However, experimental support for this view

is lacking. Indeed, the observations that administration of L-tryptophan or 5-hydroxytryptophan (5-HTP) [10, 11] to subjects with DS produces a rise of urinary 5-HIAA to normal levels have been interpreted as evidence for the integrity of the enzymes catalyzing the pathway for 5-HT synthesis [12]. However, it is possible that in DS there may be a relative deficiency of L-tryptophan. Thus, it has been found that after oral administration of L-tryptophan, intestinal absorption is less efficient in subjects with DS than in controls [10, 11], and blood tryptophan concentrations tend to be lower [13]. An explanation for low blood 5-HT in DS which is compatible with our findings of low platelet MAO activity and failure of tryptophan [2] or 5-HTP to raise this concentration to normal levels [14] might be that, owing to a relative deficiency of tryptophan, there is repression of the enzymes catalyzing the 5-hydroxyindole pathway (fig. 1). This explanation is also in accord with the observation that the urinary excretion of 5-HIAA is lower in DS than in normal subjects [10, 11].

Another possibility is that trisomic chromosome 21 might carry a regulatory gene for MAO. Redundancy of such a gene might lead to increased synthesis of repressor, and therefore to a decreased rate of MAO synthesis. Such inhibition of enzyme activity resulting from an extra dose of regulator gene has been demonstrated in microbial systems [15]. It is noteworthy that where enzyme activity has been found to be abnormal in DS (for summaries of abnormal activity in DS, see [16, 17]), the direction of change has nearly always been enhancement. The activity of phosphofructokinase, the only other enzyme which appears to have been assayed in DS platelets, was found to be normal [18].

In view of our findings, it is noteworthy that administration of nialamide (a monoamine oxidase inhibitor) has been reported to produce increased motor activity [19] and quickened mental and physical reactions [20], but no convincing improvement in intellectual performance [21].

SUMMARY

Platelet monoamine oxidase (MAO) activity was significantly lower in 22 children with Down's syndrome (DS) than in 22 controls matched for sex, age, and domicile. Since the main pathway for breakdown of 5-hydroxytryptamine (5-HT) is catalyzed by MAO, the data suggest that low concentration of blood 5-HT in DS is not due to an enhanced rate of 5-HT breakdown.

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