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Human platelet monoamine oxidase activity in health and disease: a review

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SUMMARY The most readily available source of monoamine oxidase in man is the platelet, although only the B form of the enzyme is represented in this site. Platelet activity is higher in women than in men. The enzyme activity is generally stable and is partly under genetic control. There is some evidence that individuals with low activity have a higher psychiatric morbidity than those with high activity.

Despite some negative studies, the consensus of publications dealing with schizophrenia, migraine, and alcoholism find that mean platelet monoamine oxidase activity in the patient group is lower than in the controls. Values are raised in unipolar depression. Technical differences, or patient or control group heterogeneity, might well account for the absence of unanimity in the literature. A considerable degree of overlap between patient and control values, whatever the clinical diagnosis, appears to be the standard finding.

Apart from these neuropsychiatric disturbances, platelet monoamine oxidase activity is raised in megaloblastic anaemia and reduced in iron deficiency anaemia. Although altered enzyme activity values may be linked to abnormal platelet populations in some of the haematological disorders discussed, in general the causes of abnormal platelet monoamine oxidase activity are unknown.

The insoluble mitochondrial enzyme, monoamine oxidase (MAO) (EC.1.4.3.4), is the subject of a voluminous literature (for review, see refs 1-3). Most of the biologically active monoamines it numbers among its substrates are either known neurotransmitters or neurotransmitter candidates. Thus, even though MAO is widely distributed through the body, it is not surprising that its possible role in neuropsychiatric disorders has figured most prominently in these research publications.

One of the major constraints to its direct study in man is the problem of accessibility. Although occasional attempts have been made to quantify enzyme activity in biopsy samples from a variety of different sources, including jejunal mucosa,[4,5] skin fibroblasts,[6] buccal scrapings,[7] and muscle,[8] for most practical purposes the only readily accessible source of the enzyme for routine studies derives from certain formed elements of the blood. Although lymphocytes, which may be difficult to harvest, have on occasion been used as enzyme source,[9] the blood platelet, which is relatively easy to obtain in pure preparation, has been the tissue of choice to an overwhelming extent.

Not that the human platelet enzyme is ideal to provide an insight into the status of central nervous system MAO. A widely accepted working classification of the enzyme into A and B forms exists, based on the differential inhibitory ability of the drug clorgyline;[10] type A is defined as the form sensitive to clorgyline, and this oxidatively deaminates noradrenaline and 5-hydroxytryptamine but not phenylethylamine; type B is preferentially inhibited by deprenyl[11] and selectively deaminates phenylethylamine[12] and *tele*-methylhistamine[13] rather than noradrenaline and 5-hydroxytryptamine. Tyramine and dopamine are substrates for both forms. It is quite clear that the human platelet is a pure source of MAO B,[14] as, for that matter, is human lymphocyte.[9] Although the human brain has a relatively high MAO B content[15] and dopamine is predominantly metabolised by MAO B in striatum and accumbens,[16] substantial MAO A activity is also present. Even so, and as we discuss below, changes in platelet activity have been noted in a variety of human disease states, and, in the few instances where it is possible to make direct comparison, it has been difficult to detect any

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correlation between brain and platelet enzyme status.[17] The absence of an immediate explanation for any of the platelet enzyme changes that we detail does not, however, prevent us from employing them empirically for diagnosis or patient management.

It should be pointed out here that several studies of platelet MAO have also measured a *plasma* amine oxidase[18 19] quite distinct from MAO but with a number of overlapping properties. Like MAO B, it actively oxidises benzylamine but metabolises other monoamines poorly.[20] Whereas MAO is a mitochondrial flavoprotein, benzylamine oxidase,[21] as we must call this enzyme without prejudicing the question of what its true natural substrates are, is soluble and copper-dependent. Apart from plasma, this enzyme is widespread, being concentrated particularly in blood vessel walls but absent from brain and liver parenchyma.[22 23] Benzylamine oxidase and MAO B can be distinguished, where necessary, by the judicious use of selective inhibitors.[22]

Assay procedures and variability among studies

One recurring problem throughout the platelet MAO literature is an apparent lack of reproducibility between studies. This is particularly true of work on schizophrenia. Of the variety of explanations put forward to account for these discrepancies,[24] one obvious one is technical: a bewildering variety of approaches to the assay of platelet activity has been recorded. There have been variations in anticoagulant used for collecting the blood sample, in method employed for harvesting the platelets, and in substrate used for assaying the enzyme. Both citrate and EDTA have been employed as anticoagulants. While citrate may be preferable for 'platelet function tests', EDTA has advantages for biochemical work of the type studied in this review as it lowers ionised calcium concentration sufficiently to prevent platelet aggregation.[25] With citrate, platelets tend to clump, which may interfere with their preparation. Nor is it known whether any factors are released on aggregation which affect platelet MAO activity. There is no doubt that the method of platelet preparation employed may be important. White *et al.*[26] have found specific MAO activity to vary fivefold with changes in the platelet harvesting procedure. Such factors as leucocyte contamination, differences in subpopulation of platelets recovered, or contamination of the platelet plug with plasma protein may all be important. Even the employment of siliconised pipettes can affect the eventual answer.[27] Most groups prepare a platelet-rich plasma by slow centrifugation of the whole blood; the separated supernatant is then spun at a faster speed to obtain a platelet button, which is washed and stored frozen. There is good evidence,[28 29] however, that the platelet population is heterogeneous and that large, dense platelets, which sediment more readily, have higher MAO activity per unit protein than the small, lighter ones. Thus, a platelet preparation method that results in large platelets sedimenting with the red cells would seriously distort the specific activity range of the remaining platelets. Although there is individual variation in both platelet and erythrocyte sedimentation rates, the effect on resulting MAO activity has not so far been examined. Murphy *et al.*[30] demonstrated interindividual differences between all platelet fractions in certain subjects. It is possible that some of the recorded pathological changes in platelet MAO activity reflect an altered type of platelet population, and, in such cases, it would be particularly important to harvest as representative a spectrum of the platelets present as possible in their naturally occurring proportions. Control and patient samples should also be collected simultaneously and prepared on the same centrifuge.

Murphy and his colleagues, who have extensive experience in this field, have recently assayed platelet activity in platelet-rich plasma without preparing a platelet button.[19] Although this simplifies the procedure, it introduces a new variable. Yu and Boulton[31] have recently shown that plasma can activate platelet MAO substantially, depending on the substrate employed. If this activation phenomenon were to vary in different clinical states, then the direct assay in plasma could compound two different variables.

A wide range of radioactive substrates has been used for this estimation,[32] but there is no convincing evidence that divergent results between groups derive from this cause, and several studies show a high degree of correlation using different substrates.[19 33] If a molecular variant of MAO were present in a particular individual, its detection might conceivably depend on choice of substrate or on concentration of the particular substrate employed. A low substrate concentration, for example, might detect an enzyme with reduced K_m and unaltered V_{max}, which a higher concentration would fail to pick up.

Apart from technical differences, another likely explanation for variation is group heterogeneity. A statistical analysis which finds no significant difference between the groups does not prove that they are the same. There may be a subgroup of unknown size among patients with, say, schizophrenia or migraine with low activity. If this were the case, then the results of any one study would depend on the proportion of low subgroup patients included. With small samples more variability

would be predicted than with larger ones, and the effect would also be more pronounced if the samples being compared were drawn from a different, including racially different, population base. The composition of 'control groups' is also important (*cf*, the lower activity recorded in hospital professional staff[34] or military personnel[35] compared with random controls).

If many independent studies using various assay procedures on material from different patient populations show a similar trend, then the findings become more convincing, as will be seen below: of the six independent studies[36–41] of migraine, five noted a reduction in platelet activity, significant in four, and in none was there an increase; all five published independent studies, and our unpublished observations on unipolar depression demonstrated an increase in platelet MAO activity.[42–46] Wyatt and his colleagues[24] discuss this point in relation to the investigation of schizophrenia. Nineteen out of 26 studies they reviewed showed a statistically significant decrease at the 0·05 level, and the possibility of this happening by chance alone is less than 1 in 10.[19] Even so, these calculations may be somewhat distorted by the fact that there is a greater tendency to publish positive than negative findings, and, indeed, some more recently published studies have been negative.

MAO activity in normal subjects

GENETIC INFLUENCE

Platelet MAO activity is to some extent under genetic control. Nies *et al.*[18] compared nine monozygotic twin pairs, 11 dizygotic twin pairs, and 20 age- and sex-matched control pairs and reported that intraclass correlation coefficients followed the order: monozygotic > dizygotic > control. Pandey *et al.*[47] showed that 'between family' variance is greater than that 'within family'. Hussein *et al.*[48] similarly noted that intrapair differences are significantly smaller in monozygotic twins compared with controls. None of these studies sheds any light on the mechanism of the genetic control, or how direct or indirect it might be.

EFFECT OF RACE

A potentially important, but neglected, factor in some of the clinical studies is race. DeLisi[49] found lymphocyte MAO activity to be significantly less in blacks than in whites, while Groshong *et al.*[6] made a similar observation on platelets.

EFFECT OF SEX AND AGE

The single finding that meets with most general agreement is that females have higher platelet MAO activity than males.[19 50] In monkeys, however, activity appears to be similar in both sexes.[50a] In contrast with the earlier claim of Robinson *et al.*[50] of a rise with age, Murphy *et al.*[19] found that enzyme activity does not change significantly between 10 and 70 years; our own group confirms these data.

The distribution of activity is unimodal,[19 47] although Murphy *et al.*[19] noted more high and low activity values than would be expected in a normal distribution. The level of platelet MAO activity in normal subjects seems to be fairly constant.[18 19]

HORMONAL CONTROL

Although Belmaker *et al.*[51] reported that platelet MAO activity fluctuates during the menstrual cycle, we have failed to confirm this finding (unpublished). It would be surprising if any such effect were a direct one on MAO, for all the available evidence, which undoubtedly shows a progestagenic rise in MAO activity in some organs of the body,[52 53] points to this rise occurring solely in MAO A;[54] platelet activity only represents MAO B.[14] Redmond *et al.*[55] showed that in male Rhesus monkeys platelet MAO activity is lower during the mating season than outside it, at the time of peak plasma testosterone concentration. Feldman and Roche[56] found no effect of an oestrogen-progesterone oral contraceptive on platelet MAO activity. They were also unable to find any evidence of abnormal activity in hyperthyroid or hypothyroid patients,[57] despite earlier changes noted by Levine *et al.*[58] in thyrotoxicosis. Adrenaline infusion produces an increase in specific MAO activity.[59 60] Gentil *et al.*[59] suggest that this effect stems from the release of new, more active platelets with higher enzyme activity. We have recently shown that both violent exercise[61] and noradrenaline infusion provoke a rise in platelet count which is highly correlated with specific MAO activity.

PSYCHOLOGICAL CORRELATION OF PLATELET MAO ACTIVITY IN A NORMAL POPULATION

Buchsbaum and coworkers[62] screened a large population of college students for their platelet MAO activity and were able to identify a subgroup of the population with low activity and an increased vulnerability to psychiatric disorder. The most significant findings were in low MAO males, who had an increased incidence of criminal convictions, while their families showed a greater likelihood of suicide attempts. This group have amplified and extended these observations in several subsequent studies in an attempt to demonstrate correlations between a variety of normal states of behaviour and MAO activity.[63–67] For example, they reported that the low MAO group spent more time in sensa-

tion-seeking leisure activities. Although Shaughnessy *et al.*,[68] in an independent study of adult women, also found some correlation between platelet activity and personality, there was disagreement in detail with Buchsbaum's group.

Platelet MAO in human disease

SCHIZOPHRENIA

The initial finding of Murphy and Wyatt[69] of reduced platelet MAO activity in schizophrenic patients generated much interest, as did their follow-up study[70] of reduced activity in both schizophrenic twins and discordant monozygotic co-twins, suggesting that low platelet MAO activity might be a genetic marker for schizophrenia. Not all the large number of subsequent reports confirmed the original findings however, and considerable controversy now surrounds the subject. To date at least 33[6 8 26 33 34 69–100] separate groups of chronic schizophrenics have been reported upon (some in more than one publication). Twenty reported significant decreases with at least one (but not necessarily all) of the substrates investigated while only one described a significant increase,[94] in non-hallucinating chronic schizophrenics. Considering all studies on average, schizophrenic platelet MAO activity was reduced by 27% compared with control. The variability is reduced if schizophrenic patients are separated into those with acute and chronic illness. Eleven of 14 studies[42 69–74 77 90 93 98 101–103] recorded no difference in acute schizophrenics compared with controls, a finding that should not occasion surprise as there is evidence from family studies that acute, remitting schizophrenia is a disease genetically distinct from chronic schizophrenia.[104] Initial studies suggested that the paranoid group of chronic schizophrenics have lower platelet MAO activity than control subjects,[34 91 92] but this has not been confirmed by others.[6 95 100] The presence of verbal auditory hallucinations was reported by Schildkraut *et al.*[83] and Meltzer *et al.*[99] to be associated with statistically significantly low platelet MAO activity, but neither Mann and Thomas[95] nor Bond *et al.*[94] could confirm this finding.

If low MAO activity were a genetic marker for vulnerability to schizophrenia, this might be due to a mutant form of the MAO molecule itself. Belmaker *et al.*[104a] found electrophoretic mobility to be unchanged in platelet enzyme from schizophrenics but the samples tested had normal activity; it seems likely that an aberrant molecule would be present only in individuals with low activity. Belmaker *et al.*[86] did note an increased K_m. Murphy *et al.*[105] described normal heat stability at 50°C and a normal K_m in chronic schizophrenics with low MAO activity, although two other papers reported a decrease in K_m.[87 106] Because of such discrepancies, it would be of great interest if these experiments could be repeated in other laboratories. Studies showing different substrate preferences by platelet MAO in schizophrenics compared with controls[73 91] also point to the presence of an aberrant enzyme; here, too, it seems important to obtain further data. Berrettini *et al.*[107] noted the presence of an endogenous plasma inhibitor of MAO in their low-activity schizophrenics, but Wise *et al.*[108] were unable to replicate these findings.

As most schizophrenic patients in the published studies were undergoing treatment or had in the past been treated with neuroleptics, while controls were drug-free, any possible effect of neuroleptics on platelet MAO activity becomes important to identify. Murphy and Wyatt[69] found no significant change in activity in untreated patients compared with those treated for two weeks with phenothiazines. Wyatt *et al.*[70] showed platelet MAO activity in the drug-free co-twins to be as low as that in drug-treated schizophrenic twins, both being below control value, suggesting an absence of drug effect. Chlorpromazine treatment failed to change activity in schizophrenics after two weeks[95] or over six months.[33] Before we dismiss the possibility of any drug effect completely, however, it is as well to remember that concentrations of chlorpromazine, of the order of those found in brains of treated subjects, will produce a greater than 40% inhibition *in vitro* when tested on both MAO A and MAO B of human brain.[109] Moreover, two groups of investigators have claimed to find lower platelet MAO activity in neuroleptic-treated patients, but Takahashi[77] expressed his results in terms of oxidation of 5-hydroxytryptamine, a poor substrate for MAO B, while Friedhoff[93] prepared his drug-free and drug-treated patients' platelets differently, thus vitiating the results.

INFANTILE AUTISM

Cohen *et al.*,[110] using tyramine as substrate, found that platelet MAO activity in autistic children is not significantly different from that of normal children or adults; Takahashi *et al.*,[111] using 5-hydroxytryptamine, confirmed these findings.

HUNTINGTON'S CHOREA

Significantly raised platelet MAO activity has been found in two studies of Huntington's chorea.[112 113] In the former, a 20% increase in activity for the whole group was observed, although the values were significantly different from controls only in male patients. In two subjects, improvement in clinical condition was paralleled by a fall in enzyme activity.

In the second study, 'offspring at risk' also had significantly raised activity, and the authors suggested that the finding might have useful predictive value as a marker of the disease. However, a mean rise of 20% would suggest a considerable overlap between patients and controls.

AFFECTIVE DISORDERS

There are good clinical and genetic reasons for dividing affective disorder into bipolar and unipolar subgroups, depending on the presence or absence of a history of mania.[114] Platelet MAO activity in unipolar patients has consistently been shown to be significantly elevated compared with controls.[42–45] High values have also been noted in depressed schizophrenics.[115] Murphy and Weiss[46] found a 10% increase, which did not reach statistical significance, in unipolar patients. In no case has a decrease of platelet MAO activity been described in unipolar depression.

The situation is more complex with bipolar depression. Platelet MAO activity in this group has respectively been reported to be significantly decreased,[43 45 46 116] increased,[42 85] or not significantly different[44 117] from control values. Variations in activity seem to have altered with substrate employed, clinical state,[43] and even, perhaps, with lithium responsiveness;[118] thus, lithium-responsive subjects are reported to have normal platelet MAO activity, and lithium-refractory bipolar patients low activity.

In these studies, many of the patients, unlike controls, were under treatment with lithium or tricyclic antidepressant drugs. None was receiving MAO-inhibiting drugs. Tricyclics have been alleged to depress platelet MAO activity,[119] but three subsequent papers failed to provide confirmation of this.[120–122] Although *in vitro* studies clearly show that this group of drugs produces reversible inhibition,[123 124] it appears that circulating levels are too low during treatment to produce this effect to any clinically significant degree *in vivo*,[121] unless there were a high degree of tissue concentration.

There have been reports that therapeutic blood levels of lithium increase platelet MAO activity.[45 125] Berrettini *et al.*[117] and Reveley *et al.* (submitted for publication) however, found no change in platelet activity during treatment, and Pandey[126] found a decrease.

ALCOHOLISM

Sullivan *et al.*[127] noted that platelet MAO activity, using tryptamine as substrate, is lower in chronic alcoholics than in controls. This was observed on each of three abstinent intervals over a 12-month time period, suggesting that such low activity is a stable characteristic of this illness, regardless of alcohol consumption. However, both Takahashi[128] and Brown [129] found that activity returns to normal as the acute episode of alcoholism subsides. Wiberg[130] observed a more complex biphasic pattern. Major and Murphy[35] reported that 99 healthy male alcoholics, in varying stages of abstinence, had significantly lower mean activity than controls; there was no correlation with severity or chronicity of drinking or with duration of abstinence, nor was there a rise to normal values during abstinence, as Wiberg[130] had found. Alcoholics having a first-degree relative with this disease had lower activity than those with a negative family history.[35] Alcohol itself, in the rat at least, does not appear to affect tissue MAO activity in blood concentrations of the order found in human alcoholics.[131] Nor does acetaldehyde cause a change in platelet MAO activity *in vitro* in the highest concentrations reported to occur *in vivo*.[131]

On balance, the evidence thus far suggests that low platelet MAO activity occurs in at least some alcoholics as a stable trait and is not an artefact of ethanol consumption or withdrawal.

MIGRAINE

Hanington[132] proposed that there might be a genetic deficiency of MAO in some migrainous patients and that this might account for the reputed ability of tyramine-containing foods such as cheese to initiate attacks.[133] The tissues of individuals with less oxidative-deaminating activity than normal might allow more tyramine or other amine substrate of MAO into the circulation, to release 5-hydroxytryptamine or noradrenaline from their binding sites. Certainly patients taking MAO-inhibiting drugs may suffer a hypertensive response after eating cheese or other amine-containing food,[134] although there may be other explanations for this phenomenon.[135 136] Several independent studies, using different methods, have shown that migrainous patients have a significantly reduced platelet MAO activity of about 50% compared with controls.[36–38] Bussone *et al.*,[38] as foreshadowed by Hanington,[137] found an even greater reduction in patients with cluster headache. Glover *et al.*[39] noted a small but statistically insignificant decrease in activity in migrainous patients outside an attack, while Thomas[40] found no difference between 17 patients with classical migraine and a control group.

In a large new study of over 120 headache patients[41] we have found a significant decrease in activity in men with classical migraine, tension headache, and cluster headache, but no significant change in men with common migraine or in females with any manifestation of the disease compared with

control. In this study[41] we also showed that MAO activity is relatively stable with repeated assays on the same individual, some over four-year intervals. This was particularly striking in certain subjects with permanently low activity. There was no difference in mean activity of patients taking drugs commonly used in migraine treatment, aspirin, ergotamine, diazepam or clonidine, compared with untreated patients.[39]

Three studies have compared platelet activity in patients with a history of dietary migraine and in those without;[37 39 41] the mean was similar in each. Thus, although more migrainous patients do seem to have lower platelet MAO activity than controls, it is unlikely that any genetic enzymatic deficit can account for most reports of dietary migraine.

Several independent studies have also found significant transitory decreases in platelet MAO activity during a single migraine attack.[36 39 138] However, the transitory reduction in platelet activity may well be a localised platelet effect, deriving perhaps from some circulating non-specific platelet-damaging agent. Platelets from migrainous patients aggregate more readily *in vitro* than control preparations, even outside an attack.[139 140] Whether any connection exists between low MAO activity and increased aggregability is unknown.

EPILEPSY

Kruk *et al.*[141] found platelet MAO activity in epileptic patients (mostly idiopathic temporal lobe epilepsy in this particular group) to be significantly higher than in 'neurological' or normal controls; in contrast, Shohnori *et al.*[142] observed reduced activity in a small sample of epileptics. Neither study found the enzyme change to be related to EEG abnormality, seizure intensity or frequency, or type and dosage of anticonvulsant drugs.

ESSENTIAL HYPERTENSION

Anselmi *et al.*[143] reported that a group of 31 hypertensive patients had platelet MAO activity values about 40% lower than those of a control group.

HAEMATOLOGICAL DISEASE

Iron deficiency anaemia

Mean platelet MAO activity in patients with iron deficiency anaemia appears to be about 30% lower than that of normal controls.[144 145] A reduction in binding of the irreversible MAO inhibitor, (−)-deprenyl, suggests that there is an associated reduction in the number of MAO molecules present.

Megaloblastic anaemia

Platelet MAO activity is substantially raised in megaloblastic anaemia,[146] the mean activity in a group of 17 patients being double that of a control group.[147] Glover *et al.*[147] showed MAO activity to be significantly correlated with degree of abnormality as assessed by the dU suppression test or marrow morphology; it fell to normal with treatment and the patients' recovery. The increase was observed both in patients with folate deficiency or vitamin B_{12} deficiency. Its mechanism, which may be concerned with abnormal platelet size and maturity, remains obscure.

Autoimmune thrombocytopenic purpura and reactive thrombocytosis

The changes in specific MAO activity described in these two diseases similarly seem likely to be linked with altered platelet population.[29] In autoimmune thrombocytopenic purpura, platelet count and platelet protein density are both reduced by more than 50%. Specific MAO activity is also reduced by about half. In reactive thrombocytosis, platelet count and platelet protein density are both doubled, and specific MAO activity is also considerably increased. Such correlations between platelet density and MAO activity per unit protein in these diseases are similar to those found for normal platelets.

Discussion

As we implied in the introduction, most of the literature on this subject is concerned merely with measuring platelet MAO activity in different disease states rather than with more basic research into the causes of any variations discovered. In low MAO activity schizophrenics, there is some evidence that the deficiency is present in other formed elements of the blood such as lymphocytes.[90] However, no reduction of MAO activity has yet been found in the brain.[148 149] Some possible alterations in K_m[87 106] have been noted in schizophrenics but, in general, systematic study of the underlying causes of altered MAO activity has hardly begun. The possibilities are many. Genetically variant forms of the enzyme molecule itself may exist. Different numbers of MAO molecules may be present, perhaps reflecting some primary change in MAO molecules throughout the body or, equally, an abnormal platelet population. It may be that MAO molecules are directly activated or inhibited by small molecule activators or inhibitors. Plasma contains an MAO-activating factor;[31] an MAO inhibitor or inhibitors has been demonstrated in human urine,[150] which may also have some tissue role.

Are the data we have reviewed of any diagnostic or prognostic significance? Even if a mean change in activity is eventually proven unequivocally in any

disease group, there is such a degree of overlap between patient and control that platelet activity measurements alone are unlikely to be of practical usefulness. Certain outstandingly low values which have emerged in some larger patient surveys[39 62] may turn out to form a separate cluster of patients for which particular clinical stigmata may yet be identified. Low MAO activity may be associated with a vulnerability to psychiatric disorder in general (with the exception of unipolar depression), and to schizophrenia, alcoholism, and migraine in particular. Even statistical differences between groups can be employed for multifactorial analyses, which may be helpful in demarcating disease categories, the physical bases of which are not understood. If decreases in MAO activity occur solely in the platelet, we need to know what initiates them. If generalised, then we have to determine whether the degree of deficit is sufficient to play a causative role. Nor do we know of any adverse effect of high MAO activity. Our knowledge of the chemical pathology of platelet MAO is still in its infancy.

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