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An Inverse Correlation between Spontaneous Eye-Blink Rate and Platelet Monoamine Oxidase Activity

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Summary: An inverse correlation between platelet monoamine oxidase activity and spontaneous eye-blink rate, a putative measure of central dopaminergic activity, was found in medication-free chronic schizophrenic patients without tardive dyskinesia ($n = 20$, $r_s = -.47$, $P < .025$). A similar correlation was found when patients with tardive dyskinesia were included but was weaker ($n = 27$, $r_s = -.35$, $P < .05$). Normal controls and patients with tardive dyskinesia did not demonstrate this relationship. This report confirms a previous finding of a significant platelet monoamine oxidase-blink rate correlation in chronic schizophrenic patients. Insofar as this relationship is mediated by dopamine, it suggests that dopaminergic relations are more readily demonstrated in schizophrenic subjects than normals. Moreover, tardive dyskinesia appears to obscure this dopaminergic relationship.

Decreased monoamine oxidase (MAO) activity in the platelets of chronic schizophrenic patients suggested the relevance of this enzyme to central nervous system (CNS) function (Murphy and Wyatt, 1972). Two findings argue against this notion. First, decreased MAO activity has not been found in the postmortem brains of schizophrenic patients (Schwartz, Aikens and Wyatt, 1974). Secondly, the decrease in platelet MAO appears, at least in part, to result from neuroleptic treatment (DeLisi *et al*, 1981; Meltzer *et al*, 1981; Owen *et al*, 1981).

An effect of neuroleptics on platelet MAO activity does not rule out the possibility that platelet MAO activity may reflect the state of catecholamine activity in the CNS, perhaps through a relationship with brain MAO activity. For example, Kleinman *et al* (1979), have found a positive correlation between plasma prolactin concentration and platelet MAO activity. Since hypothalamic dopamine inhibits prolactin release from the anterior pituitary (Thorner, 1977), it can be argued that platelet MAO activity may be inversely related to tubero-infundibular dopamine activity.

We sought to examine further the relationship of platelet MAO activity and central dopamine activity using spontaneous eye-blink rates. Eye-blink rates are decreased in Parkinson's disease (Hall, 1945) and increased in schizophrenia (Stevens, 1978; Karson *et al*, 1981a). Since central dopamine activity is decreased in the former (Hornykiewicz, 1974), and postulated to be increased in the latter (Carlsson and Lindqvist, 1963), Stevens (1978) hypothesized that blink rates may be mediated by central dopamine activity. This assertion is strengthened by the finding that in monkeys, apomorphine, a dopamine agonist, increases blink rates in a dose related fashion (Karson *et al*, 1981b).

Interestingly enough, blink rates have also been shown to correlate inversely with platelet MAO activity (Freed *et al*, 1980) although values for both parameters were obtained and combined from the medicated and unmedicated state. Since neuroleptics reduce blink rates (Karson *et al*, 1981a) as well as MAO activity, we sought to retest this relationship in medication-free schizophrenic patients. Because adventitious movements are associated with increased blink rates in monkeys (Karson *et al*, 1981c) as well as patients with Parkinson's disease and levodopa-induced dyskinesia (Karson *et al*, 1982), we also examined this relationship in patients with tardive dyskinesia.

Materials and Methods

Twenty-seven chronic schizophrenic inpatients (Research Diagnostic Criteria) (Spitzer, Endicott and Robbins, 1977), (21 males, 6 females, mean age 31 years, SD±6 years) who were not subjects in the previous study (Freed *et al*, 1980), consented to

participate in this study. In addition, 36 normal volunteers recruited from the clinical and laboratory staff as well as a nearby university served as controls (34 males, 2 females, mean age 25, SD±6 years).

Blinks were counted as previously described (Freed *et al*, 1980; Karson *et al*, 1981a). Since speech increases blinking (Karson *et al*, 1981d), all subjects were counted while they participated in clinical interviews. During medication free periods (mean duration ± SD = 7±3 weeks, range 2–12 weeks) blinks were counted weekly. The medication-free blink rate is the mean of these counts.

Blood was drawn from all subjects using a 19 gauge needle and syringe and placed into plastic tubes containing EDTA-citrate. Platelets prepared by the Corash (1979) method were analyzed for MAO activity by a modification (Wise *et al*, 1979) of the Wurtman and Axelrod method (1963). The drug free platelet MAO activity was the mean activity of the weekly platelet MAO determinations after the second drug free week. For normal controls the procedures were the same except that blink rates and platelet MAO values were usually determined once.

If a patient exhibited persistent dyskinetic movements with a severity of 2+ or more in any of the seven motor groups described in the Abnormal Involuntary Movement Scale (AIMS) and met additional criteria (Jeste and Wyatt, 1982), the diagnosis of tardive dyskinesia was made. There were seven patients with TD, four males and three females (mean age 33±8 years).

Results

Table I shows the mean values of blink rates and MAO activity in each of the subject groups as well as the correlations between platelet MAO activity and blink rate. There is a significant correlation in all patients ($r_s = -.35$, $P < .05$) which is stronger when patients with TD are excluded ($r_s = -.47$, $P < .025$). There is no significant correlation in normal controls and in patients with dyskinesia. While the blink rates of schizophrenic patients are significantly higher than the normal controls ($P < .05$, independent groups T-test, one-tailed assumption), the MAO activity was not different between the groups.

Discussion

We found an inverse correlation between platelet MAO and spontaneous eye blink rate in a second group of chronic schizophrenic patients using a different platelet MAO assay. This study improves on the first because medication-free patients were used. This relationship did not exist in normals or in the admittedly small number of patients with TD that we studied. The presence of only one patient with TD in the original study compared with seven such patients in this study may account, in part, for the lower overall correlation currently found.

Since blink rates are a putative measure of central dopamine activity, the inverse correlation with platelet MAO activity in schizophrenic patients suggests that platelet MAO activity is related to central dopaminergic activity in these patients, possibly by reflecting brain MAO activity. The low correlation coefficient, however, points to the limited nature of this relationship. As normal controls do not demonstrate this relationship it may indicate that schizophrenic patients are more sensitive to variations

TABLE

Mean medication-free blink rate and platelet MAO activity and their correlation

	Blink rate (blinks/minute)	Platelet MAO (nM/mg/hour)	Correlation between blink rate and platelet MAO activity
Controls	22±13	21.6±5.1	−.08
All patients	28±17*[a]	22.8±6.3	−.35*[b]
Subgroups:			
Patients without tardive dyskinesia	27±18	23.5±5.2	−.47**
Patients with tardive dyskinesia	31±12	20.8±8.9	−.07

* $P < .05$.

** $P < .025$.

[a] *T*-test compared to control group. One-tailed assumption.

[b] Spearman's $r(r_s)$, one-tailed assumption (Siegel, 1956).

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in central dopaminergic activity. While it is tempting to speculate that this is related to increased dopamine receptor numbers in schizophrenic patients compared with normals, it is possible that other factors either enhance this relationship in patients and obscure it in normals, or both.

It is difficult, however, to invoke 'other' factors to explain the failure to find the inverse correlation in chronic schizophrenic patients with TD. The TD and non-TD groups are comparable in terms of age, history of chronic institutionalization, and are housed in the same building under identical conditions. Moreover, we have found that neuroleptics may not decrease the blink rate in patients with TD as they do in other schizophrenic patients (Karson and Freed, 1982, in preparation). Since TD occurs only in a certain proportion of patients treated with neuroleptics, it is possible that some of the central neurochemical processes may be different in patients with TD compared with patients without TD. Indeed, one recent study shows that TD may be a relevant dimension for subtyping the schizophrenic syndrome (Jeste *et al*, 1982). At any rate these current findings suggest that either (1) patients with TD are hyposensitive to alterations in CNS dopaminergic activity or (2) non-dopaminergic variables obscure dopamine mediated relationships of patients with TD.

Regardless, this report confirms a previous finding of an inverse correlation between platelet MAO and spontaneous eye-blink rates in chronic schizophrenic patients. Insofar as this relationship is mediated by dopamine, its occurrence in schizophrenic patients and its absence in normals suggests that dopaminergic relationships differ between the two groups.

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