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Serum CPK and Aldolase Activity in Man Following Controlled Administration of Psychotomimetic Drugs

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Summary. Serum creatine phosphokinase (CPK) and aldolase activities were determined in thirty-six subjects following the administration of LSD-25 or N,N-dipropyltryptamine in varying doses. No significant increase in the mean activity of either enzyme was found at the times blood samples were obtained after drug administration. The results are discussed with reference to the increases in CPK and aldolase activity which occur in the acute psychoses.

Key-Words: Lysergic Acid Diethylamide — N,N-dipropyltryptamine — Psychotomimetic Drugs — Creatine Phosphokinase — Aldolase — Schizophrenia.

In a number of recent studies (Meltzer, 1968, 1969b, c; Meltzer *et al.*, 1969a, b), an increase in the activity of the enzymes creatine phosphokinase (CPK) and aldolase in plasma or serum has been found in fifty to sixty percent of acutely psychotic patients at the onset of a psychotic episode. Non-specific factors such as oral or intramuscular medication, physical activity, diet, stress and hypersecretion of corticosteroids have been considered but do not appear to be related to the elevation of these enzymes in the acutely psychotic patients (Meltzer, 1968, 1969a, b; Meltzer *et al.*, 1969a, b). Isoenzyme studies have shown that the increased CPK activity is of the muscle-type, not the brain-type (Meltzer, 1968, 1969b; Meltzer *et al.*, 1969a, b) which suggests that the CPK is not coming from brain. The absence of increased CPK activity in the spinal

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fluid of acutely psychotic patients also supports the hypothesis that the increased CPK actively is not coming from brain (Meltzer, 1968, 1969b). Large increases in serum CPK activity of the muscle-type have also been found in some patients with acute brain disturbances from such diverse causes as brain trauma, encephalitis, cerebrovascular accidents, etc. (Dubo, 1968; Cao *et al.*, 1969). Despite the fact that the CPK and aldolase appear to be coming from muscle and not brain, and that increased CPK activity may occur in patients with acute brain dysfunction from a wide variety of causes, the serum CPK activity of acutely psychotic patients is highly correlated with global ratings of psychosis and specific dimen-, sions of psychopathology on various psychiatric rating scales (Meltzer 1968; Meltzer, 1969b, c; Meltzer *et al.*, 1969b). Thus, the serum CPK activity in acutely psychotic patients appears to be a biochemical correlate of the acute psychotic process in many, but not all, such patients. The increased activity of the enzyme in serum is probably the result of an increase in muscle cell membrane permeability (Meltzer, 1968). A number of models for relating brain dysfunction and muscle dysfunction have been discussed elsewhere (Meltzer, 1969c).

Since the psychotomimetic drugs have been thought to produce, in man, a "model" psychosis or an altered state of consciousness which must be based altered brain functioning, it is of interest to determine if either serum CPK or aldolase activity, or both, is increased following psychotomimetic drugs in man.

In a preliminary report, we noted that increased activity of CPK or aldolase, or both, did occur in some subjects receiving LSD-25, in high or low doses, or N,N-dipropyltryptamine (DPT) in doses of 30—75 mg (Meltzer, 1968). We now wish to report further results of this study.

Methods

I. Subjects

A. Fifty-six male and female patients with a history of either chronic alcoholism or severe psychoneurotic symptoms were selected from the population at the Spring Grove State Hospital for participation in a study concerning the psychotherapeutic efficacy of a drug-induced psychedelic experience (Kurland *et al.*, 1967). The subjects were given general medical care, including vitamin supplementation, for at least one month prior to their sessions with psychedelic drugs. They were carefully prepared for their drug experience by the therapist who conducted the drug sessions, which was done in a manner designed to enhance the emotional experience of the subjects.

Subjects received 50 μg, 350 μg, or 450 μg LSD-25 orally or 30 mg, 50 mg, or 75 mg DPT intramuscularly. Heparinized blood samples were

collected one week before, approximately twenty-four hours after the termination of the session, and frequently many weeks later. Plasma was separated and coded, so that it was impossible to tell whether a sample was pre-or-post-drug, and delivered the day the sample was drawn to the National Institute of Mental Health where one of us (H.M.) determined CPK and aldolase activity.

B. Five subjects, all of whom were frequent users of LSD and other psychotomimetic drugs, were admitted to the National Institute of Mental Health. Each was given a comprehensive medical and psychiatric work-up. The subjects were placed on a constant metabolic diet with a constant fluid intake and restricted to the hospital for the entire study. Each subject was trained to perform a variety of psychophysiologic tasks in a two-day control period. Then, each subject was given either LSD-25, 1 μg/kg or 2 μg/kg, or nicotinic acid, 50 mg, orally, in varying sequences, on three separate days with a drug-free day in-between. Bloods samples were obtained before, one hour after and twenty-four hours after each drug was given. The serum was separated, frozen, coded and analyzed for CPK and aldolase activity by one of us (H.M.) with no knowledge as to whether the samples were obtained before or after the drugs. After the drug was ingested the subjects performed the battery of psychophysiologic tests in which they had previously been trained. Because of the requirement that each subject perform the required tests as well and as possible under each drug condition, no attempt was made to impart any emotional quality to the drug sessions.

II. Chemical Methods

CPK and aldolase activity was determined by spectrophotometric methods which couple the reduction of nicotinamide nucleotides to the enzyme reactions (Rosalki, 1967; Berger, 1968).

Results and Data Analysis

I. Spring Grove State Hospital Patients

Thirty-one subjects had one blood sample taken before and another taken approximately twenty-four hours after the drug session. Twenty-five other subjects were lost to this study because blood samples were not obtained until much longer than twenty-four hours after their drug session. The mean CPK activity of the plasma samples prior to administration of the psychotomimetic drugs was 30.3 I.U./L. ± S.D. 16.9 I.U./L. The mean plasma aldolase activity was 273 mμmol ml^{-1} hr^{-1} ± S.D. 70 mμmol ml^{-1} hr^{-1} (Table 1)[1]. The upper limit of CPK was taken to

1 The aldolase units in the first report of this work were incorrectly given as μmol ml^{-1} hr^{-1} (Meltzer, 1968).

be greater than 64 I.U./L. and of aldolase greater than 413 mμmol ml^{-1} hr^{-1} (mean + 2 S.D.). Two of the thirty-one pre-drug plasma samples exceeded these limits for CPK activity and one for aldolase activity.

Table 1. *Plasma CPK and aldolase activity before and after drugs*

Drug group	CPK (I.U./L.)	Aldolase (mμmol ml^{-1} hr^{-1}
Pre-drug ($N = 31$)	30.3 (16.9)[a,b]	273 (70)[b]
24 hours after all drugs ($N = 31$)	31.4 (15.1)	300 (125)
24 hours after LSD-50 μg ($N = 8$)	28.9 (10.4)	354 (195)
24 hours after LSD-450 μg ($N = 16$)	29.9 (24.3)	285 (93)
24 hours after DTP: 30—75 mg ($N = 7$)	43.2 (24.0)	301 (123)
Samples > 24 hours after drugs ($N = 31$)	28.6 (13.1)	253 (71)

[a] (Standard deviation).

[b] There were no significant differences between the plasma CPK and aldolase activities before the drugs or afterwards using a two-tailed *t*-test.

The mean CPK and aldolase activity for this group of thirty-one patients following LSD or DPT, regardless of dose, was not significantly different from the pre-drug enzyme activity ($p > 0.05$) (Table 1). Nor was there any significant difference when the data for each drug at low or high dose, was tested individually for a significant difference before and after the drug ($p > 0.05$) (Table 1). Six of the thirty-one plasma samples taken approximately twenty-four hours after drug administration had aldolase activity and three had CPK activity that was greater than the pre-drug ninety-five percent confidence limits. The overall incidence of abnormally increased enzyme activity of either enzyme following the drugs is, however, not significantly different from the indidence before the drugs were given (Chi-Square = 2.307, $p > 0.10$). The incidence of abnormal aldolase activity following LSD-25, either low or high dose, was five of twenty-four, which is not significantly different from that before the LSD (one of twenty-four) (Chi-Square = 1.714, $p > 0.10$). The magnitude of the increases in aldolase activity were also relatively minor in comparison with that noted in acutely psychotic patients which frequently exceeded 750 mμmol ml^{-1} hr^{-1} (Table 2). The increase in CPK activity which occurred after DPT administration were very small and could have been the result of local muscle trauma from intramuscular injections (Warnock and Ellman, 1969; Meltzer, 1969a) (Table 2).

The mean activities of serum CPK or aldolase in the same group of subjects after the drug sessions, at intervals of one week to several

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months, were not significantly different from those before or twenty-four hours after the drug sessions (Table 1). Two of the samples had aldolase activity which exceeded the pre-drug upper limits for these patients but none of the plasma samples had increased activity of CPK.

Table 2. *Increases in plasma CPK and aldolase activity in 8 subjects following psychotomimetic drugs*

Drug	CPK (I.U./L.)		Aldolase (mμmol ml^{-1} hr^{-1}	
	Pre	Post	Pre	Post
LSD-450 μg	1	39	149	483
LSD-450 μg	20	20	240	780
LSD-450 μg	11	33	219	450
LSD-50 μg	21	51	254	749
LSD-50 μg	27	10	365	465
DPT-30 mg	18	72	238	257
DPT-30 mg	27	51	399	548
DPT-30 mg	29	78	290	251

II. N.I.M.H. In-Patients

In the N.I.M.H. in-patient study, there was not significant change in serum CPK or aldolase activity following LSD-25 or nicotinic acid. CPK activity ranged between 8 and 25 I.U./L. and aldolase between 157 and 281 mμmol ml^{-1} hr^{-1} in the five subjects. One of the subjects developed an adverse response following the high dose of LSD-25. His behavior was characterized by muteness and withdrawal and lasted forty-eight hours. No increase in serum CPK or aldolase activity developed within twenty-four hours, but unfortunately no serum samples were obtained thereafter.

Discussion

The administration of LSD-25 or DPT, in low or high doses, under controlled clinical conditions had no statistically significant effect on serum CPK or aldolase activity. This was true regardless whether an intense emotional experience or control of ego functioning was encouraged. In the preliminary report of these studies (Meltzer, 1968) a tendency for aldolase activity to increase following LSD-25 or DPT was noted, but in the current extension of these studies to a larger series of patients, this tendency failed to attain statistical significance. The Spring Grove patients were mainly alcoholics, and lingering liver ansd mucle damage could have been a major factor in the increased aldolase activity following LSD-25.

Two factors should be considered further before concluding that serum CPK and aldolase activity is not increased by psychotomimetic drugs: the frequency of obtaining blood samples after drug administration and the numerous factors which influence serum enzyme activity. Enzyme activity could have been increased for brief periods before, in between, or only after these times. However, in the acutely psychotic patients studied, serum CPK activity is normally increased five to ten days after the onset of a psychotic episode but may rarely be present for as brief as a day (Meltzer, 1968; Meltzer, 1969b). Since the serum activity of any enzyme is the net result of influx into and removal of the enzyme from the circulation, and is further modified by any enzyme inhibitors or activators present, it is quite possible that measuring the enzyme activity, particularly as long as twenty-four hours after drug administration, could miss changes in two compensating parts of the system which would set the equilibrium at a different level of enzyme turnover. Our measures of enzyme activity would not detect such changes in turnover.

Increased activity of CPK or aldolase, or both, has been found in four patients believed to have ingested illicit LSD or mescaline, three of whom had prolonged schizophreniform psychoses (Meltzer, 1969d). The results of the study reported here make it likely that the increased serum enzyme activities noted in these patients were concomitants of the psychotic process rather than a direct effect of the psychotomimetic drugs.

The altered state of consciousness produced by LSD-25 and DPT is rarely accompanied by serum enzyme changes comparable to those found in acute psychosis. We will not be able to drawn any conclusions from the data as to whether they are fundamentally different mental states until much more is known about the relationship between central nervous system dysfunction and serum enzyme changes in acutely psychotic patients.

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