



CK levels in unmedicated bipolar patients

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Abstract Various reports have described increased serum creatine kinase (CK) activity in the majority of hospitalized acutely disturbed schizophrenics and patients with affective psychoses. We investigated CK serum levels of 52 unmedicated bipolar inpatients, in manic versus depressive states. Additional 17 patients were evaluated in both states. Hamilton Rating Scale for Depression and Young Mania Rating Scale were used and blood samples were obtained from new admitted patients. Higher CK level was found in the manic patients compared with the depressed ones. Likewise, the CK level was higher in the manic phase than in the depressive one, when tested within the same patient. Our results suggest that the clinical differences between mania and depression states are supported by contrasting levels of CK. The lack of correlations between CK level and motor items suggest that CK level in mania versus depression could emphasize the “thinking speed” and not the motor one.

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1. Introduction

Bipolar disorder (BD) continues to present complex diagnostic and therapeutic challenges. Originally considered two separate diseases (mania and depression), BD is now recognized to be a single disorder characterized by different subtypes and degrees of severity (Moller, 2003).

The neuroendocrine system, which plays an important role in regulation of mood, is dysfunctional in patients suffering from mood disorders (Mazza et al., 2004). Therefore, manic-depressive patients show increased variability in hormonal response from multiple neuroendocrine axes (Amsterdam et al., 1983) but the biological underpinnings of BD is slowly being revealed.

Previous studies tended to focus mainly on serotonin and noradrenaline in relation to the neurobiological mechanism of depression, and there has been a growing belief that the role of dopamine in this pathology is marginal (Brugue and Vieta, 2007). However, traditional accounts stated that hyperfunction of the dopaminergic system led to manic behavior, and that hypofunction induced depressive symptoms

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Table 1 The gender, the mean age ($\pm$ SD), the mean ($\pm$ SD) Hamilton rating scale and Young mania rating scale scores of the patients in the different groups

Patients	N		Age		Hamilton scale		Young scale	
	Female	Male	Mean	S.D.	Mean	S.D.	Mean	S.D.
Depressed	12	7	46.68	13.75	20.15	6.3	–	–
Manic	14	19	39.59	15.37	–	–	22.69	5.35

Table 2 The gender, the mean age ($\pm$ SD), the mean ($\pm$ SD) Hamilton rating scale and Young mania rating scale scores of the patients in the depression state compared with the mania state, when measured within the same subjects

State	N		Age		Hamilton scale		Young scale	
	Female	Male	Mean	S.D.	Mean	S.D.	Mean	S.D.
Depression	13	4	46.94	18.72	18.93	5.18	–	–
Manic			46.35	18.58	–	–	22.37	5.22

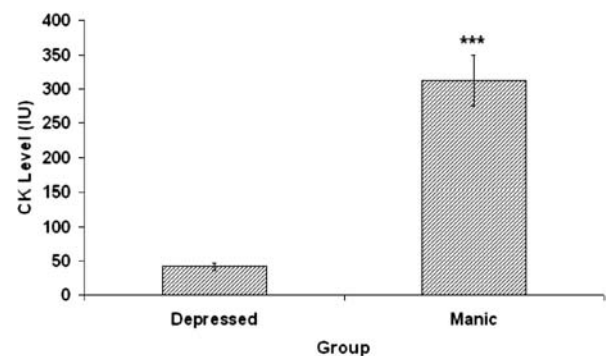
(Randrup et al., 1975). Yet, increased dopaminergic activity may play a primary role in psychotic depression (Wood et al., 2002).

Neural mechanisms mediated by hypothalamic dopamine and by autonomic nervous system may be contributing to the elevation of serum creatine kinase (CK) (Takubo et al., 2003). CK is an enzyme found predominantly in the heart, brain, and skeletal muscles. Its substantial elevation was related to injury, intramuscular injections, use of restraints, intense isometric activity, dystonic reactions or stress (Gabow et al., 1982; Cavanaugh and Finlayson, 1984). Total CK activity and content is lower in brain than in skeletal muscle or the heart. Even though it might be concluded that the CK system plays a less prominent role in brain physiology, there is plethora of evidence for close correlations between creatine metabolism and CK function on one hand and proper brain function on the other (Wyss and Kaddurah-Daouk, 2000). CK isoenzymes are essential for storing, buffering and intracellular transport of “energy-rich” phosphate compounds in tissues with fluctuating high energy demand such as muscle, brain and other tissues and cells where CK is expressed. In brain and many non-muscle cells, ubiquitous cytosolic “brain-type” BB-CK and ubiquitous mitochondrial CK (uMtCK) act as components of a phosphocreatine shuttle to maintain cellular energy pools and allocate energy flux. To date, still relatively little is known about direct coupling of functional dimeric BB-CK with other partner proteins or enzymes that are important for cell function (Burklen et al., 2007). Kinetic (Km) values for similar isoenzymes from two different tissues, i.e., CK MB from heart versus skeletal muscle, were found not different (Schneider et al., 1988). These results show that kinetic analysis of CK isoenzymes cannot differentiate the tissue source of elevated blood CK isoenzymes after the acute stress of long distance running or after acute myocardial infarction.

Increased serum CK level is found in the majority of hospitalized acutely disturbed schizophrenics and patients with affective psychoses (Meltzer et al., 1980). It is probable that some of these elevations do not result from nonspecific factors such as activity, trauma or stress, which do cause increases in some cases (Meltzer et al., 1980), but are

related to psychomotor agitation and medication (Manor et al., 1998; Terao et al., 1999). Patients that received injections had significantly raised CK levels over the first few days post-admission; these levels tended to normalize over 72 h (Wilhelm et al., 1994). Another recent postmortem study (MacDonald et al., 2006) found decreased expression of CK mRNA in the hippocampus and dorsolateral prefrontal cortex of bipolar patients, contrary to increased levels of CK protein observed in cerebrospinal fluid and serum of bipolar patients after an acute episode (Vale et al., 1974; Taylor and Abichandani, 1980; Manor et al., 1998).

In our recent study (Segal et al., 2007) we found CK serum levels to be within the normal range (Men <190 UI, Women <165 U.I.) but significantly higher in nonpsychotic major depression than in all other forms of depression, i.e.: psychotic major depression, bipolar depression and schizoaffective depression. Moreover, a significant correlation was found between the severity of the depressive episode (Ham-D score) and the CK level in the nonpsychotic depressed patients. Thus, we presume that neural mechanisms mediated by dopamine or serotonin may influence the levels of serum CK. Therefore, in the present study we set to investigate the CK in bipolar patients in order to assess eventual differences between enzyme levels in mania versus depression states.

**Figure 1** CK serum levels were significantly higher in the manic patients than in the depressed ones (***) $P < 0.0001$.

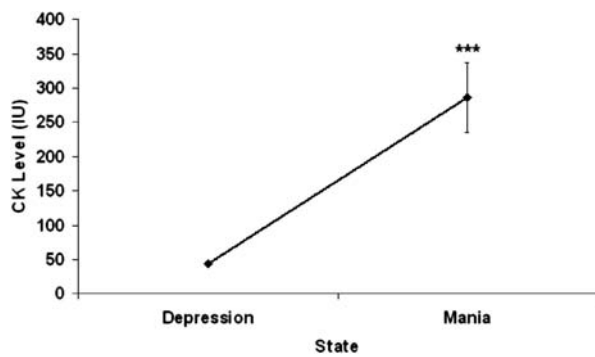


Figure 2 CK serum levels were lower in the depression state compared with the mania state, when measured within the same subjects (** $P < 0.0001$).

We hypothesize that differences in CK levels between the two conditions could suggest different catecholamine activity, mainly of dopamine.

2. Experimental procedures

The study protocol was approved by the Ethical Local Board Committee of Flügelman's (Mazra) Mental Health Center, Acre.

2.1. Subjects

The study comprised 52 male and female inpatients diagnosed as bipolar: 33 with mania and 19 with depression. An additional 17 bipolar patients were evaluated in both states: Manic and depressed. All of them were unmedicated for at least four weeks. Exclusion criteria were physical illness including any cerebral or endocrine pathology, alcohol or drug abuse and pregnancy and no depot antipsychotics for at least six months.

After complete description of the study to the subjects, written informed consent was obtained from all participants.

2.2. Assessment of major depression and mania episodes

The diagnosis of major depression and of mania (severity and subtypes) was made by DSM-IV criteria (APA, 1994). Hamilton rating

scale for depression (Hamilton, 1960) was used in order to evaluate the severity of the syndrome and of various symptoms. Young mania rating scale (Young et al., 1978) was used to assess the manic symptoms. The assessments were performed blindly to the CK level measurements.

Blood samples of CK were obtained in the morning (8–9 AM) as part of a routine battery of tests taken from new admitted patients, prior to any treatment. The fresh serum was separated and assayed immediately in order to avoid the decrease of enzyme's activity by freezing (Lev et al., 1994–5). The intra-assay variability determined on 20 replications of each control for three levels gave coefficients of variation (CV%) of 2.05, 1.82 and 1.44. The inter-assay variability determined for ten days on two replicates of each control for three levels was for CV%: 2.93, 1.87 and 1.42. The sensibility was of 2 U/L and the interval of measure was 2–1000 U/L.

CK serum levels were evaluated by the CK NAC UV liquid (1996) – an UV Kinetic determination of CK in serum and plasma. The upper limit for normal CK was established to less than 150 U/L for women and less than 175 U/L for men (CK NAC UV, 1996).

3. Results

Demographic data as well as the diagnostic results of all subjects are presented in Tables 1 and 2. The CK serum levels were found in the "low-normal" range for the depressed patients and higher than normal for the manic patients [$t(36) = 6.05$, $P < 0.0001$; Fig. 1]. Likewise, CK serum levels were lower in the depression state compared with the mania state, when measured within the same subjects [$t(16) = 5.137$, $P < 0.0001$; Fig. 2].

However, no significant correlations were found between the CK level and the motor items of Young Scale in the manic patients or between the CK level and agitation or motor retardation items for Hamilton Scale in the depressed patients, examined in different groups (Table 3) or within the same subjects (Table 4).

4. Discussion

The results of the present study clearly suggest a different CK activity in unmedicated bipolar patients illustrated on the

Table 3 The mean serum CK levels ($\pm$ SD) and the mean ($\pm$ SD) motor items of the Hamilton rating scale and Young mania rating scale scores of the patients in the different groups

Patients	N	CK		Ham–D score		Ham–D retard.		Ham–D agit.		Young score		Y Incr Mot act.	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Depressed	19	48.29	27.29	20.9	7	1.31	0.74	0.73	1.04	–	–	–	–
Manic	33	295.11	20.75	–	–	–	–	–	–	22.81	5.5	2.54	0.86

Table 4 The mean serum CK levels ($\pm$ S.D.) and the mean ($\pm$ S.D.) motor items of the Hamilton rating scale and Young mania rating scale scores of the patients in the depression state compared with the mania state, when measured within the same subjects

State	N	CK		Ham–D score		Ham–D retard.		Ham–D agit.		Young score		Y Incr Mot act.	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Depressed	17	42.45	13.67	19.57	423	1.16	0.51	0.38	0.77	–	–	–	–
Manic		297.67	18.72	–	–	–	–	–	–	22.15	5.24	2.52	0.84

admission day by low enzyme levels in depression and significantly higher levels in mania. Importantly, we were able to show a significant difference of CK values in 17 patients that were evaluated in different phases of mania or depression.

However, we found no relationship between the CK levels and motor activity (enhanced in mania, retarded in depression) illustrated by the relevant Hamilton and Young items. In the past, increased serum CK levels have been reported to be present during acute exacerbations of major "functional" psychoses (Meltzer et al., 1980) with no evidence of muscle trauma or hyperactivity (Meltzer et al., 1996). Retarded and Withdrawn patients and those with psychomotor retardation had normal serum CK (Soni, 1976) but on their return to normal psychomotor activity the CK levels tended to rise. This alteration in CK levels between acutely psychotic versus withdrawn patients may correspond to the polarity of CK level we have observed in BD patients.

In the past, increased serum levels of CK protein taught to indicate muscle damage (Meltzer, 1969; Meltzer and Moline, 1970). However, other studies have shown that isometric muscle tension cannot account for the large spike in serum CK protein levels following an elevated state in bipolar disorder and schizophrenia (Goode and Meltzer, 1976). Only few studies addressed to CK levels and bipolar affective disorder. Taylor and Abichandani, 1980 reported that 25 acutely psychotic patients were found to have unexplained elevations of serum CK; 56% had diagnosis of primary affective disorder, bipolar type mania. In a recent article (Melkersson, 2006) checked serum CK level in chronic psychosis patients treated by atypical and typical antipsychotics. Paradoxically, significant higher median CK level was found for patients receiving Clozapine and Olanzapine compared to patients treated by conventional antipsychotics.

Creatine that is converted by CK to phosphocreatine (PCr) was recently identified as a potent natural survival- and neuroprotective factor for developing nigral dopaminergic neurons (Andres et al., 2005). The creatine shuttle plays a critical role in cellular energy storage and regulation, thus it has suggested that bipolar disorder might be accompanied by reduced PCr levels and altered mitochondrial function (Wallimann et al., 1992; Neumann et al., 2003). Indeed, spectroscopic imaging studies have shown reductions of PCr in bipolar disorder and depression (Kato et al., 1993; Kato et al., 1994; Dager et al., 2004). Moreover, a recent review (Yildiz-Yesiloglu and Ankerst, 2006) on neurochemical alterations in bipolar disorder stressed the importance of creatine magnetic resonance, but questioned its validity because of its suggested alteration by disease or medication state. Automated measures of activity (such as an actigraph worn like a wristwatch) would be of interest in future controlled studies of possible associations between serum CK activity and motor activity in patients with bipolar disorder.

Our findings on unmedicated patients raise the possibility of different interaction between catecholamines and CK in bipolar disorder with a regionally imbalance between the dopamine and serotonin systems. So far, it is unclear if the state-dependent differences observed in serum CK activity during the manic and depressed phases of bipolar disorder reflect parallel changes in the enzyme expression, protein

content or catalytic efficiency in the brain. Furthermore, it may be premature to speculate about the precise role of neuroprotection conferred by phosphocreatine or the mediating function of specific neurotransmitters on CK activity. Our results obtained in unmedicated BD patients need further validation and replication

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Contributors

Michael Segal and Avi Avital are equal contributors to the study. Michael Segal designed and supervised the study, wrote the protocol and the first draft of the manuscript. Avi Avital managed the writing of the first draft, the writing of the results, the statistical analysis, and participated with important contribution to the discussion. He managed the preparation of the manuscript. Marina Drobot participated in the recruitment of the participants, the clinical evaluation, the preparation of serum samples, and managed part of the literature. Aida Lukanin participated in the recruitment of the participants, the clinical evaluation, the preparation of serum samples, and managed part of the literature. Sergio Sandbank contributed to the study design and to the discussion. Abraham Weizman participated in the design of the study and the interpretation of the results. All the authors contributed to and approved the final manuscript.

Conflict of interest

There is no conflict of interest.

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