Serum creatine kinase activity differentiates alcohol syndromes of dependence, withdrawal and delirium tremens

Michael Segal\textsuperscript{a,b,⁎}, Avi Avital\textsuperscript{c,d,1}, Alla Rusakova\textsuperscript{a}, Sergio Sandbank\textsuperscript{a}, Abraham Weizman\textsuperscript{e,f}

\textsuperscript{a} Flügelman’s (Mazra) Mental Health Medical Center, Acre, Israel
\textsuperscript{b} Rappaport Faculty of Medicine, Technion Israel Institute of Technology, Haifa, Israel
\textsuperscript{c} Department of Psychology and the Center for Psychobiological Research, The Yezreel Valley College, Israel
\textsuperscript{d} Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel
\textsuperscript{e} Research Unit, Geha Mental Health Center, and Laboratory of Biological Psychiatry, Felsenstein Medical Research Center, Petah Tikva, Israel
\textsuperscript{f} Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

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Abstract

Previous reports described significant differences in serum creatine kinase (CK) activity in bipolar disorder and various forms of depression. The comorbidity of depression and alcohol syndromes was also widely described. We aim to examine potential differences in serum CK level in different alcohol-related syndromes. We assessed morning serum CK activity in 114 inpatients, diagnosed by the Structured Clinical Interview for DSM-IV: Fifty-five subjects with alcohol dependence, 28 with alcohol withdrawal and 31 with delirium tremens (DT’s). We found low normal CK activity for the alcohol dependence, higher for alcohol withdrawal and the highest for DT’s. Peripheral CK activity of four patients that were admitted during each of the three phases showed similar pattern. These findings may be related to enhanced dopamine activity in alcohol dependence and conversely, to a significant decrease in dopamine activity during withdrawal syndromes. We suggest a supplementary simple laboratory tool for the detection of alcohol-related states.

1. Introduction

Alcoholism is a chronic relapsing behavioral disorder characterized by compulsive and excessive drinking.

Ethanol consumption has been demonstrated to induce a dose-dependent release of dopamine (DA) in the nucleus accumbens (NAc) through its effects on opioid or
γ-aminobutyric acid (GABA)-A receptors (Cowen and Lawrence, 1999).

Nevertheless, a decrease in chronic ethanol intake may result from an increase in the tonus of the dopaminergic mesolimbic system (Lanca, 1994). On the other hand, ethanol withdrawal reduces mesolimbic DA release (Diana et al., 1992; Rossetti et al., 1992; Shen and Chiolo, 1993; Weiss et al., 1996). It is currently clear that in addition to the central role of DA transmission (Kalivas, 2001) other neurotransmitters play important roles in reward-related learning and in regulating hedonic states (Hyman et al., 2006).

Moreover, it seems that non-dopaminergic neuroadaptations are involved in the encoding of the behavioral changes that define addiction (Pierce and Kalivas, 1997). The enzyme creatine kinase (CK) could be one of the possible candidate involved in alcohol turmoil related to dopaminergic dysregulation. Creatine and creatine-like compounds are thought to regulate and preserve metabolism in cells with intermittently high and fluctuating energy requirements, including the brain cells (Jost et al., 2002; Chen et al., 1995).

CK is found mainly in the skeletal muscles, heart and brain. Its substantial elevation usually indicates damage or stress in one or more of these organs. Enhanced seru CK activity is found also in a substantial proportion of acutely hospitalized patients suffering from schizophrenia or affective psychosis (Meltzer et al., 1980; Manor et al., 1998; Hermesh et al., 2002a,b). It was suggested that non specific factors such as agitation, trauma, drug treatment, or stress are not only determinants responsible for CK elevation in psychotic patients (Meltzer et al., 1980; Hermesh et al., 2002b). Recently we have reported significantly higher CK levels in unmedicated manic patients compared with depressed ones. The enzyme level correlated with the clinical symptoms but not with the motor activity (Segal et al., 2007a). We found also that CK serum level was significantly higher in nonpsychotic major depression than in other forms of depression. The results suggested a biological disparity between the nonpsychotic major depression and the psychotic cluster of depressive syndrome (Segal et al., 2007b). These alterations in CK levels may be related to changes in dopaminergic activity. According to the neuroadaptations hypothesis of dependence, stimulant withdrawal should be accompanied by neurochemical effects in opposite direction to those seen during acute consumption of the agent (Koob and Bloom, 1988) and probably different from the dependent nonintoxicated states. In order to further determine the possible association between alcohol addiction syndromes and the CK activity, we examined the enzyme serum level on the admission day in patients hospitalized due to dependence, withdrawal or delirium tremens.

2. Materials and methods

The study protocol was approved by the Ethics Local Committee of Flügelman’s (Mazra) Mental Health Center Acre. All subjects gave written informed consent.

The 114 study subjects were all inpatients: fifty five were diagnosed according to DSM-IV criteria as suffering from alcohol dependence; 28 from alcohol withdrawal and 31 from delirium tremens. Diagnostic procedures were carried out by a trained psychiatrist using the Structured Clinical Interview for DSM-IV (SCID), and re-confirmed also at the discharge time. Exclusion criteria were other Axis I disorder, past or present history of drug dependence according to random urine drug testing in the admission day. The patients were without intramuscular treatment until routine blood samples were received.

They were without antipsychotic or mood stabilizer treatment. Most patients were unmedicated at the admission time (78/114). Those that received medication in the emergency setting were treated by oral doses of Lorazepam 1 mg or Diazepam 5 to 10 mg, Prophethemazine HCl 25 to 50 mg, Vitamin B1 100 mg, Vitamin B6 250 mg and Vitamin B12 250 mcg.

Blood samples for serum CK determination were collected between 8 – 9 AM in the admission day, on a routine blood chemistry screening, prior to the addition of any medication. The fresh serum was separated and assayed immediately in order to avoid the decrease of enzyme’s activity by freezing (Lev et al., 1994–1995). 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 CVs: 2.93, 1.87 and 1.42. The sensitivity was of 2 U/L and the range 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 is 150 U/L for women and 175 U/L for men (CK NAC UV, 1996).

3. Results

The average age (Table 1) of the subjects in the different groups was similar \([F(2,111)=1]\).

A significant effect of CK level was revealed between the groups \([F(2,111)=55.56, P<0.0001]\). Specifically, subjects during delirium tremens had the highest (mean: 1085.58; SD: 281.77 U/L) CK level (P<0.0001) followed by subjects during withdrawal (mean: 354.8; SD: 158.76 U/L; P<0.013). The lowest CK level was found in subjects during dependence (mean: 63.56; SD: 18.15 U/L) (Fig. 1).

In spite of the difficulty to detect the same subject in different phases, we have identified four subjects who had multiple admissions, one in each of all three phases (Table 2), showing a similar pattern of CK level modulation as in the between-subjects design above.

4. Discussion

The clinical entities of alcohol dependence, withdrawal and delirium tremens are rarely confused. However, our results show for the first time that creatine-kinase (CK) seems to differentiate biologically alcohol related syndromes.

Previous reports on serum CK activity and alcohol use disorders are scars. Ikeda (1977) described a positive correlation between high CK serum levels (more than 101 U/L) and psychotic symptoms in the month before and after the hospital admission of alcoholic patients. Moreover, increased serum CK activity levels were found to be common in heavy alcohol use patients without evidence of myocardial damage.
ischemia. CK values decrease over the first 24 h of hospital admission, different from rising and falling as is typical of myocardial infarction (Osborn et al., 1995).

Creatine (Cr) was recently identified as a rather potent natural survival- and neuroprotective-factor for developing nigral dopaminergic neurons (Andres et al., 2005). Cr supplementation improves the function of the creatine kinase/phosphocreatine system by increasing cellular creatine and phosphocreatine levels, the rate of ATP resynthesis and maintaining cellular-energy homeostasis (Jost et al., 2002). Miura et al. (1999) showed that Cr was sharply inhibited by dopa and dopamine in the presence of ferrylmyoglobin. Neural mechanism mediated by hypothalamic DA and by autonomic nervous system may be contributing to the elevation of serum CK (Takubo et al., 2003).

In our current study we found the lowest CK level in the alcohol dependent group, which may be associated with the hyperdopaminergic tone. The results seem to confirm the hypothesis that alcohol dependence is accompanied by increased DA activity. DA levels were found to be increased in rats NAc while anticipating the access to ethanol (Weiss et al., 2003) and this was followed by an intensive release once the animals were able to respond to alcoholic beverage. The reduced DA release and turnover reported in alcohol dependence on alcohol, delirium tremens results from irreversible, cumulative changes in the central nervous system caused by years of heavy alcohol consumption (Hersh et al., 1979; Hemmingsen and Kramp, 1988). It has been hypothesized that whereas withdrawal symptoms such as autonomic hyperactivity are the result of recent physical dependence on alcohol, delirium tremens results from irreversible, cumulative changes in the central nervous system caused by years of heavy alcohol consumption (Hersh et al., 1997). Prolonged heavy alcohol addiction may lead to a progressive impairment of centrally-mediated dopaminergic activity. The epiphenomena of reduced DA neurotransmission may be reflected peripherally by a compensatory increase of serum CK activity levels as a neuroprotective mechanism. This notion is supported by Andres et al. (2005) that suggested creatine neuroprotective role for developing nigral dopaminergic neurons. Jost et al. (2002) have shown that the creatine supplementation improves the function of the creatine kinase/phosphocreatine system by increasing cellular creatine and phosphocreatine levels, the rate of ATP resynthesis and maintaining cellular-energy homeostasis.

The serum CK activity values that we have found, clearly separated the withdrawal condition from DT’s. If peripheral CK activity reflects alterations in central DA activity, it could be that the changes in serum CK activity are attributable to temporally DA hypofunction in alcohol withdrawal that progresses or not to an acute central DA deficiency in DT’s.

A closer monitoring of CK serum levels and dopaminergic indices (e.g. homovanillic acid levels in the serum and cerebral spinal fluid, prolactin release) in patients admitted during alcohol withdrawal syndromes, especially of those with history of DT’s, may clarify the relationship between changes in sera activity of CK and dopaminergic dysregulation in states of alcoholism, that may be independent of motor activity. It is of note that acute central dopaminergic suppression by DA blockers may lead to neuroleptic malignant syndrome (NMS), associated with high serum CK related to muscle origin (Sakkas et al., 1991; Buckley and Hutchinson 1995; Hermesh et al., 2002a; Spivak et al., 2000). The similarities between depression and alcohol or drug dependence were extensively described (Schuckit, 1986; Roussaville et al., 1987; Kessler et al., 1994; Markou et al., 1998; Sher et al., 2003). Brain dopaminergic, serotonergic, and noradrenergic systems have been implicated in biological mechanisms of both depression and alcoholism (Kapur and Mann, 1992; Nemeroff et al., 1997; Schatzberg et al., 2002).

The CK levels in alcohol dependence and withdrawal in the present study are similar to our previous study of CK level in depression and manic phases of bipolar disorder (Segal et al., 2007a). While the symptoms resemble, the clinical differences manifested in the dysphoric mood of alcohol withdrawal versus the manic euphoria possibly reside in the activity of serotonin-2a (5HT2a) receptor, enhanced in mania, suppressed in alcohol withdrawal. Variation in the density of 5HT2a at the level of gene expression, receptor expression or turnover, may determine the increase in CK activity during acute psychosis (Metzger, 2000), which may resemble psychotic features of DT. Moreover, though we previously (Segal et al., 2007a) did not find a correlation between serum CK activity and motor activity in mania, it is still possible that the elevation in serum CK activity in DT’s results from the extreme agitation, which may cause a metabolic stress/damage to the skeletal muscle cells and subsequently release of large amounts of muscle cell contents into circulation (Qiu et al., 2004).

Table 2 Serum CK activity in four patients, measured across all three alcohol syndromes

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<tr>
<th>Age (years)</th>
<th>CK level (IU)</th>
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<td></td>
<td>Dependence</td>
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<td>90</td>
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<td>42</td>
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<td>79</td>
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Figure 1 Serum CK level is highest in delirium tremens (***P<0.0001) and intermediate level in withdrawal (**P<0.013) patients.
In conclusion, activity of creatine kinase in serum obtained freshly on inpatient admission can distinguish the clinical states of alcohol dependence, alcohol withdrawal and delirium tremens. It may be speculated that state-dependent changes in dopamine and serotonin centrally-mediated neurotransmission influence by an unknown mechanism(s) the activity of creatine kinase peripheral blood. It is unclear whether the changes in serum CK activity are merely markers or epiph-
omena of state-dependent changes in centrally-mediated neurotransmission, or are changes in peripheral CK activity part of pathophysiology of these states of alcoholism. Serum activity of CK may reflect centrally-mediated effects by neurotransmitters on energy metabolism in brain. It seems likely that, as in NMS, the predominant source of increased CK activity in serum is the skeletal muscles (Osborn et al., 1995; Qiu et al., 2004). Further investigation should compare the serum CK activity in dependence and withdrawal syndromes to alcohol intoxication states and to look for gender and age differences, as well as alterations in central and peripheral DA indices. On the clinical level, it seems that a simple and rapid routine evaluation of serum CK activity in the admission setting may provide a reliable supplementary diagnostic tool of the various states of alcoholism. Thus, it could also support immediate treatment decisions.

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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; Participated with important contribu-
tion to the discussion. He managed the preparation of the manuscript.

Alia Rusakov: Participated in the recruitment of the participants, the clinical evaluation, in the preparation of serum samples, 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
All the authors disclosed any actual or potential conflict of interest with other people or organizations.

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References

Buckley, P.F., Hutchinson, M., 1995. Neuroleptic malignant syn-


CK, NAC, UV, 1996. Liquid Determinazione cinetica UV secondo le recomendazione D6Kc nel siero e nel plasma. Sentinel CH, Milano, Italy.


Hemmingsen, R., Kramp, P., 1988. Delirium tremens and related clinical states: psychopathology, cerebral pathophysiology and psychochemistry: a two-component hypothesis concerning etiol-


