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Lower CSF Homovanillic Acid Levels in Depressed Patients with a History of Alcoholism

Leo Sher*[,1], Maria A Oquendo[1], Shuhua Li[1], Yung-yu Huang[1], Michael F Grunebaum[1], Ainsley K Burke[1], Kevin M Malone[1] and J John Mann[1]

[1]*Division of Neuroscience, Department of Psychiatry, Columbia University, New York, NY, USA*

Major depression and alcoholism are often comorbid, resulting in more impairment and more suicidal behavior compared with either diagnosis alone. This study compared clinical features and cerebrospinal fluid (CSF) monoamine metabolites in depressed subjects with and without a history of alcoholism and healthy volunteers. We hypothesized that depressed subjects with a history of alcoholism would be more aggressive, impulsive, and suicidal than depressed subjects without a history of alcoholism, and would have lower CSF monoamine metabolite levels. We compared 63 subjects with a current major depressive episode (MDE) and a history of alcoholism, 72 subjects with a current MDE but without a history of alcoholism, and 22 healthy volunteers. Participants with a history of alcoholism were in remission for at least 6 months. All subjects were free from prescribed medications known to affect brain serotonin, dopamine, or norepinephrine systems for a minimum of 14 days. Depressive symptoms, lifetime aggression, impulsivity, Axis II disorders, and suicidal behavior were assessed. CSF was sampled and homovanillic acid (HVA), 5-hydroxyindolacetic acid (5-HIAA), and 3-methoxy-4-hydroxyphenylglycol (MHPG) were assayed by high-performance lipid chromatography with electrochemical detection. Depressed subjects with a history of alcoholism did not differ from depressed subjects without a history of alcoholism in current severity of depressive symptoms, or in past suicidal behavior. Depressed subjects with a history of alcoholism had lower CSF HVA levels, and higher lifetime aggression and current suicide ideation scale scores and were more likely to be tobacco smokers compared with depressed subjects without a history of alcoholism. Low HVA was present after adjustment for sex, aggression and depression scores, cigarette smoking, antisocial and borderline personality disorders, psychomotor retardation, and delusions. Controls had CSF HVA levels intermediate between the two depressed groups. We found no group difference in CSF 5-HIAA and MHPG levels. In individuals with current MDE, those with a history of comorbid alcoholism had lower CSF HVA levels compared with those without a history of alcoholism. Low CSF HVA suggests that impaired dopaminergic activity is associated with a history of alcoholism in persons with current MDE.

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INTRODUCTION

Alcohol abuse and dependence (alcoholism) with their high morbidity and mortality are a major public health problem in the US and worldwide (Nelson and Stussman, 1994; Greenfield and Weisner, 1995; Grant, 1997). A total of 13% of the adult population in the United States has a history of alcohol abuse or alcohol dependence (Grant, 1997). Major depressive disorder is also a significant health issue. The lifetime prevalence of major depression is 5–12% for men and 10–25% for women (American Psychiatric Association, 1994; Blazer *et al*, 1994; Gruenberg and Goldstein, 1997). The National Comorbidity Survey estimates overall lifetime prevalence of major depressive disorder as 17.1% (Blazer *et al*, 1994). Major depression often results in impaired interpersonal, social, and occupational functioning. Recent findings identify both major depression- and alcohol-related disorders in the top diseases that are associated with disability and costs (Murray and Lopez, 1997).

Major depression and alcoholism are often comorbid (Schuckit, 1986; O'Sullivan *et al*, 1988; Herz *et al*, 1990; Buydens-Branchey *et al*, 1989; Roy *et al*, 1991a, b; Cornelius *et al*, 1995, 1996; Davidson and Blackburn, 1998; Spak *et al*, 2000; McGrath *et al*, 2000; Gilman and Abraham, 2001; Thase *et al*, 2001). Schuckit (1986), suggests that between one-quarter and two-thirds of subjects with alcoholism have had depressive symptoms severe enough to interfere with functioning. Depressed subjects with alcoholism have more

*Correspondence: Dr L Sher, Division of Neuroscience, Department of Psychiatry, Columbia University, 1051 Riverside Drive, Suite 2917, Box 42, New York, NY 10032, Tel: +1 212 543 6240, Fax: +1 212 543 6017, E-mail: leosher@neuron.cpmc.columbia.edu
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chronic impairment and suicidal behavior than individuals with either diagnosis alone (O'Sullivan *et al*, 1988; Cornelius *et al*, 1995, 1996; Thase *et al*, 2001).

Brain dopaminergic, serotonergic, and noradrenergic systems have been implicated in biological mechanisms of both depression and alcoholism (for reviews, see Nemeroff *et al*, 1997; Fromme and D'Amico, 1999; Geracioti, 1997; Koob, 1992; Kapur and Mann, 1992; Nevo and Hamon, 1995; Oquendo and Mann, 2000; Valenzuela and Harris, 1997; Schatzberg *et al*, 2002). The cerebrospinal fluid (CSF) concentrations of the dopamine, serotonin, and to a lesser degree norepinephrine metabolites, homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA), and 3-methoxy-4-hydroxyphenylglycol (MHPG), respectively, are presumed to reflect the turnover of parent neurotransmitters in the central nervous system (Moir *et al*, 1970; Bowers, 1972; Stanley *et al*, 1985; Sharma *et al*, 1994; Reuster *et al*, 2002). Accordingly, measurements of these compounds in lumbar CSF have been employed in studies of brain function *in vivo*.

Roy *et al* (1991a) found lower CSF levels of the dopamine metabolite HVA in depressed compared with never depressed subjects with alcohol dependence. Although multiple studies have shown changes in CSF monoamine metabolites in subjects with alcoholism (Roos and Silfverskiöld, 1973; Kato *et al*, 1979; Goldman *et al*, 1992; Takahashi *et al*, 1974; Major *et al*, 1977; Fujimoto *et al*, 1983; Virkkunen *et al*, 1996; Fils-Aime *et al*, 1996; Petrakis *et al*, 1999; Adinoff *et al*, 1996, 1995, 1991; Geracioti *et al*, 1994, 1993; Virkkunen *et al*, 1994; Kaakkola *et al*, 1993; Roy *et al*, 1990; Roy and Linnoila, 1989; Hawley *et al*, 1988; Borg *et al*, 1982; Geracioti, 1997), the study by Roy *et al* (1991a), to our knowledge, is the only study that measured CSF HVA in depressed individuals with alcoholism. Most studies do not distinguish possible biological effects of related psychopathology such as depression, psychosis, suicidal behavior, or smoking.

This is the first study to compare CSF monoamine metabolites and clinical features in depressed subjects with and without a history of alcoholism and healthy controls. We hypothesized that depressed subjects with a history of alcoholism would be more suicidal, aggressive, and impulsive than depressed subjects without a history of alcoholism and healthy controls and that CSF monoamine levels would be lower in depressed subjects with a history of alcoholism. We also evaluated the effects of psychosis, psychomotor change, and cigarette smoking.

MATERIAL AND METHODS

Subjects

Participants were recruited through advertising and referrals and admitted to a university hospital for participation in mood disorders research. All subjects gave written informed consent as required by the Institutional Review Board for Biomedical Research. In all, 72 depressed subjects without a history of any alcohol or substance abuse/dependence (19 males and 53 females), 63 depressed subjects with a history of alcoholism (35 males and 28 females), and 22 healthy volunteers (10 males and 12 females) participated in the study. In all, 58 depressed subjects without a history of alcoholism and 55 depressed subjects with a history of alcoholism were inpatients. A total of 14 depressed subjects without a history of alcoholism and eight depressed subjects with a history of alcoholism were treated as outpatients. All met DSM-IV (American Psychiatric Association, 1994) criteria for a current major depressive episode (MDE). Participants had to be free from prescribed medications known to affect brain serotonin, dopamine, or norepinephrine systems for a minimum of 14 days. The drug-free interval was longer for drugs with a long half-life (6 weeks for fluoxetine and 4 weeks for oral antipsychotics). Among psychotropics, only small doses of short-acting benzodiazepines were permitted but not 72 h before the lumbar puncture. Individuals with a history of alcoholism were free from alcohol dependence for at least 6 months, therefore the current episode of major depression was independent, that is, not alcohol induced. Subjects were free from any substance abuse for at least 2 months. The duration of the drug-free status of the subjects was established by a combination of urine and blood toxicological screenings, observation in hospital, and a history obtained from the participant, the participant's family, and the referring physician. Subjects with current symptoms of alcohol/drug withdrawal states were not accepted in the study. Subjects were not allowed to smoke for 12 h before the lumbar puncture.

DSM-IV Axis I and Axis II disorders were diagnosed using the Structured Clinical Interview I (SCID-I) and the Structured Clinical Interview II (SCID-II), respectively, for DSM-IV (American Psychiatric Association, 1994). Healthy controls were recruited through advertising and were free of psychiatric disorder based on the SCID-NP (nonpatient version). All subjects had a physical examination and routine laboratory screening tests, including urine and blood toxicological screenings, to rule out neurological or medical illness that could affect their mental status or CSF monoamine metabolites.

The current severity of depression was assessed by the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and the Beck Depression Inventory (BDI) (Beck *et al*, 1961). Lifetime aggression and impulsivity were assessed with the Aggression History Scale (Brown–Goodwin, revised) (Brown and Goodwin, 1986) and the Barratt Impulsivity Scale (Barratt, 1965), respectively. Current hopelessness was measured with the Beck Hopelessness Scale (Beck *et al*, 1974b). Current suicidal ideation was measured by the Scale for Suicidal Ideation (SSI) (Beck *et al*, 1979). Details of lifetime suicide attempts were recorded on the Columbia Suicide History Form, which records all suicide attempts chronologically, including documentation of the method and degree of medical damage (Medical Damage Scale) and suicidal intent by the Beck Suicide Intent Scale (SIS) (Beck *et al*, 1974a). Symptoms were measured within 14 days from the lumbar puncture.

The Lumbar Puncture and CSF Monoamine Metabolites Assay

The lumbar puncture was performed at about 08:00 h, after the subject had been kept at bed rest and fasting from midnight. The CSF was withdrawn from the L4–L5 interspace, with the subject in the left decubitus position. After

the removal of 1 ml of CSF into the first sample tube, a further 15 ml of CSF was collected in the second and third tubes. These tubes were then immediately transferred on ice water to be centrifuged at 4°C, and the supernatant pooled from the second and third tubes. The 15 ml of supernatant was divided into 1-ml aliquots for storage at −70°C until assay. CSF amine metabolites were assayed in one of the 1-ml aliquots of the 15-ml sample.

CSF HVA, 5-HIAA, and MHPG were assayed by high-performance liquid chromatography with electrochemical detection (Scheinin *et al*, 1983). The within- and between-run coefficients of variance of the assay were less than 10%. The sensitivity of the assay was 0.5 pmol/injection. All samples were kept frozen until assay. Storage effects were not detected.

Statistical Analyses

Gender distribution of subjects was evaluated with the χ^2 test. Demographic and clinical characteristics and CSF monoamine metabolites in depressed subjects with and without a history of alcoholism and healthy volunteers were compared using a general linear model. We compared CSF HVA in the two depressed groups controlling for sex, aggression, and depression (HDRS) scores, tobacco smoking, antisocial and borderline personality disorders, psychomotor retardation, and delusions because studies have suggested that these parameters may affect the CSF HVA content (Raleigh *et al*, 1992; Nordin *et al*, 1995; Seegal, 1985; Campanella *et al*, 1977; Lindstrom, 1985; Aberg-Wistedt *et al*, 1985; Houston *et al*, 1986; Almay *et al*, 1987; Jones *et al*, 1990; Faustman *et al*, 1991; Limson *et al*, 1991; Spiegel and King, 1992; Johnson *et al*, 1994; Soderstrom *et al*, 2001; Kapur and Mann, 1992; Brown and Gershon, 1993; Lykouras *et al*, 1994; van Praag *et al*, 1975; Post *et al*, 1973; Chotai *et al*, 1998; Daderman and Lidberg, 2002; Geracioti *et al*, 1999). Suicide attempt status was evaluated using the chi-squared test. All tests were two-tailed and significance required $P<0.05$.

RESULTS

Demographic and Clinical Characteristics

We compared demographic and clinical characteristics and CSF monoamine metabolites in the three groups (Tables 1 and 2). There were fewer females (44.4%) than males in the group with a history of alcoholism compared with the group without a history of alcoholism (73.6% females) and healthy controls (54.5% females) ($df=2$, $\chi^2=12.1$, $P=0.002$). The group with a history of alcoholism had fewer years of education than controls (Table 1). The two depressed groups did not differ in the percentage of inpatients/outpatients ($df=1$, $\chi^2=1.1$, $P=0.3$) or suicide attempters ($df=1$, $\chi^2=1.7$, $P=0.2$).

Table 1 Demographic and Clinical Characteristics of Depressed Subjects and Healthy Volunteers

	Controls ($n=22$)		Subjects without a history of alcohol dependence ($n=72$)		Subjects with a history of alcohol dependence ($n=63$)		Analysis		
Measure	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**df**	***F/t***	***P***
Age (years)	39.1	13.9	38.9	12.8	35.8	11.1	2154	1.2	0.3
Total years of education	16.9	1.6	15.4	3.0	14.6	2.7	2140	4.7	0.01[a]
Number of previous depressive episodes	N/A	N/A	4.6	7.1	6.0	13.6	120	0.7	0.4
Age of onset of the first depressive episode	N/A	N/A	25.7	13.7	23.6	11.7	125	−1.0	0.3
HDRS	0.7	0.9	19.8	6.0	19.9	6.5	2152	94.5	<0.0001[a,b]
BDI	2.0	2.9	28.5	11.2	28.7	10.7	2140	57.7	<0.0001[a,b]
Aggression History Scale	14.2	3.7	16.7	5.0	21.5	6.0	2147	20.1	<0.0001[a,c]
Barrat Impulsivity Scale (BIS)	34.0	10.8	50.9	15.5	57.9	19.2	2125	15.1	<0.0001[a,b]
Beck Hopelessness Scale	1.7	2.4	13.5	5.3	11.8	5.3	2143	43.5	<0.0001[a,b]
Age at first suicide attempt	N/A	N/A	27.6	13.1	25.4	13.5	1	0.5	0.5
Suicidal Ideation Scale	N/A	N/A	13.2	10.3	16.8	10.7	132	2.0	<0.05
SIS	N/A	N/A	16.8	5.5	17.2	5.5	80	0.4	0.7
Number of suicide attempts in attempters	N/A	N/A	3.1	3.2	3.0	2.1	77	−0.3	0.8
Maximum lethality of suicide attempts	N/A	N/A	3.8	2.2	3.7	1.8	77	−0.1	0.9

[a]Controls are different from depressed subjects with a history of alcohol dependence at 0.05.
[b]Controls are different from depressed subjects without a history of alcohol dependence at 0.05.
[c]Depressed subjects with a history of alcohol dependence are different from depressed subjects without a history of alcohol dependence at 0.05.

Table 2 CSF Monoamine Metabolites in Depressed Subjects with and without a History of Alcohol Dependence and Healthy Volunteers

	Controls ($n=22$)		Subjects without a history of alcohol dependence ($n=72$)		Subjects with a history of alcohol dependence ($n=63$)		Analysis		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**df**	***F***	***P***
HVA (pmol/ml)	187.1	71.5	214.6	81.4	176.2	67.9	2154	4.6	0.01[a]
5-HIAA (pmol/ml)	94.0	35.3	103.9	34.1	95.9	33.6	2154	1.2	0.3
MHPG (pmol/ml)	39.2	22.1	43.4	16.9	38.6	13.5	2154	1.5	0.2

[a]Depressed subjects with a history of alcohol dependence are different from depressed subjects without a history of alcohol dependence at 0.05.

A total of 59.7% of depressed subjects with a history of alcoholism and 21.1% of depressed subjects without a history of alcoholism were tobacco smokers ($df = 1$, $\chi^2 = 20.7$, $P < 0.0001$). There were no tobacco smokers among normal controls.

In all, 28 (44.4%) depressed subjects with a history of alcoholism and 23 (31.9%) depressed subjects without a history of alcoholism had borderline personality disorder; 10 (15.9%) depressed subjects with a history of alcoholism had antisocial personality disorder, including 6 (9.5%) subjects who had both antisocial and borderline personality disorders. There were no subjects with antisocial personality disorder among depressed subjects without a history of alcoholism.

The depressed groups had comparable HDRS and BDI scores but higher than controls. Age of onset of the first depressive episode, number of previous depressive episodes, and suicidal behavior did not differ between the two depressed groups (Table 1). The depressed group with a history of alcoholism had higher lifetime aggression compared with the depressed group without a history of alcoholism and controls (Table 1). The depressed group with a history of alcoholism had higher aggression scores than the depressed group without a history of alcoholism after adjustment for antisocial ($F = 14.8$, $P < 0.001$) or borderline ($F = 22.2$, $P < 0.0001$) personality disorders. Subjects with a history of alcoholism had higher current suicidal ideation scale score than subjects without a history of alcoholism (Table 1).

CSF Monoamine Levels

CSF HVA levels were lower in depressed subjects with a history of alcoholism compared with depressed subjects without a history of alcoholism ($df = 2,154$, $F = 4.6$, $P = 0.01$) (Table 2). The difference in the CSF HVA levels between the two groups remains statistically significant after adjustment for sex, aggression and depression (HDRS) scores, cigarette smoking, antisocial and borderline personality disorders, psychomotor retardation, and delusions ($df = 1$, $F = 7.4$, $P = 0.008$). CSF HVA was correlated with CSF 5-HIAA ($r = 0.6$, $P < 0.0001$) and CSF MHPG ($r = 0.3$, $P = 0.001$). We did not find any correlations between the CSF monoamine metabolite concentrations and severity of the behavioral measures. Healthy volunteers had HVA levels intermediate between the two depressed groups and there were no statistically significant differences in the CSF 5-HIAA, CSF HVA, and CSF MHPG levels between controls and either of the two depressed groups (Table 2).

DISCUSSION

Clinical Features

The results of our study indicate that depressed subjects with a history of alcoholism are more aggressive than depressed subjects without a history of alcoholism and healthy volunteers. This was the case even when antisocial and borderline personality disorders were taken into account. In addition, depressed subjects with a history of alcoholism reported more current suicidal ideation than depressed subjects without a history of alcoholism. These findings are consistent with reports that subjects with alcoholism are more aggressive and impulsive, and have more suicidal ideation than controls or psychiatric subjects without a history of alcoholism (Nicholls *et al*, 1974; Hesselbrock *et al*, 1985; Zucker and Gomberg, 1986; Cloninger *et al*, 1988; Cornelius *et al*, 1995, 2001; Bates and Labouvie, 1995; Caspi *et al*, 1997; Badawy, 1998; Pihl and LeMarquand, 1998; Sher *et al*, 1999). Prospective studies have demonstrated that impulsive individuals are at elevated risk for the development of alcohol-related problems (Bates and Labouvie, 1995; Caspi *et al*, 1997; Cloninger *et al*, 1988; Zucker and Gomberg, 1986; Sher *et al*, 1999). Aggressive and impulsive behaviors may be a manifestation of underlying personality pathology, or signs of a developmental disorder, or both, that contribute to the development of alcoholism (Sher *et al*, 1999).

Biological Findings

We found that CSF HVA was lower in depressed subjects with a history of alcoholism than in subjects without a history of alcoholism, even after adjustment for sex, aggression and depression (HDRS) scores, cigarette smoking, antisocial and borderline personality disorders, psychomotor retardation, and delusions. Our findings are consistent with previous reports that alcoholism affects CSF HVA levels (Roos and Silfverskiöld, 1973; Kato *et al*, 1979; Goldman *et al*, 1992; Takahashi *et al*, 1974; Major *et al*, 1977; Fujimoto *et al*, 1983; Roy *et al*, 1991a; Virkkunen *et al*, 1996; Fils-Aime *et al*, 1996; Petrakis *et al*, 1999). Roy *et al* (1991a) reported that depressed subjects with alcoholism had significantly lower concentrations of HVA than never depressed subjects with alcoholism. We did not have a never depressed group with a history of alcoholism, however, we found that depressed subjects with alcoholism had significantly lower levels of HVA than depressed subjects who had never had alcoholism. CSF HVA reflects CNS dopamine turnover (Bowers, 1972; Stanley *et al*, 1985) and our finding suggests that less dopaminergic activity is associated with alcoholism among depressed persons.

The CSF HVA levels in our control group are consistent with values reported in healthy volunteers (Takahashi *et al*, 1974; Kato *et al*, 1979; Roos and Silfverskiöld, 1973; Roy *et al*, 1990; Hibbeln *et al*, 1998; Westenberg and Verhoeven, 1988; Koslow *et al*, 1983; Kanemaru *et al*, 1998; Engstrom *et al*, 1999). Some studies have found lower CSF HVA level in subjects with depression (for reviews, see Kapur and Mann, 1992; Brown and Gershon, 1993; Nemeroff *et al*, 1997). However, the mean CSF HVA level of depressed subjects without a history of alcoholism in our study is higher than reported by other researchers who studied depressed subjects (Takahashi *et al*, 1974; Kato *et al*, 1979; Placidi *et al*, 2001; Åsberg *et al*, 1984; Reddy *et al*, 1992; Westenberg and Verhoeven, 1988; Koslow *et al*, 1983). This difference may be related to the fact that we used a sample of depressed subjects without a history of alcoholism. Our finding appears to be consistent with the study by Vestergaard *et al* (1978), who reported significantly higher CSF HVA levels in depressed subjects than in healthy controls. It is possible that the variability in the rates of comorbid alcoholism and/or other comorbid disorders in different depressed populations plays an important role in

the inconsistency of findings regarding CSF HVA levels in depressed subjects. Low CSF HVA may have more to do with psychopathology related to alcoholism as opposed to mood disorder biology. Our finding is consistent with studies that suggest that dopaminergic mechanisms play a part in the biology of alcohol use disorders, including mechanisms of alcohol dependence and withdrawal (Diana *et al*, 1993; Weiss *et al*, 1996; Weiss and Koob, 1991; Koob, 1992; Noble, 1996; Wiesbeck *et al*, 2000; Fromme and D'Amico, 1999; Nevo and Hamon, 1995; Roos and Silfverskiöld, 1973; Kato *et al*, 1979; Goldman *et al*, 1992; Takahashi *et al*, 1974; Major *et al*, 1977; Fujimoto *et al*, 1983; Roy *et al*, 1991a; Virkkunen *et al*, 1996; Fils-Aime *et al*, 1996; Petrakis *et al*, 1999; Samson *et al*, 1990; Valenzuela and Harris, 1997; Robinson and Berridge, 1993; Vavrousek-Jakuba *et al*, 1992; Quarfordt *et al*, 1991; Modell *et al*, 1993; Grace, 2000).

The absence of data on age-at-onset of alcoholism and subjects' quantity and frequency of alcohol use are limitations of our study. There is also a possibility of a selection bias because only subjects who volunteered to participate in a research program and were able to tolerate a medication washout were included in the study. In addition, the subjects were mostly inpatients.

The results of our study demonstrate that depressed subjects with a history of alcoholism are more aggressive, have more suicidal ideation and lower CSF HVA levels than depressed subjects who do not have a history of alcoholism. The differences in aggression and suicidality may partially explain higher morbidity and mortality among depressed subjects with alcoholism. Future studies are needed to explore the neurobiology of alcoholism, including relationships between CSF monoaminergic metabolites, depression with and without comorbid alcoholism.

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