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CSF monoamine metabolites and lethality of suicide attempts in depressed patients with alcohol dependence

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Abstract

Background: Alcohol dependence (alcoholism) and major depressive disorder are frequently comorbid and are risk factors for suicidal behavior. Monoaminergic abnormalities have been implicated in the pathophysiology of depression, alcohol dependence, and suicidal behavior. Lower cerebrospinal fluid (CSF) 5-hydroxyindolacetic acid (5-HIAA) levels are associated with higher lethality of suicide attempts in major depression and predict a higher rate of future suicide. We sought to study the relationship of CSF monoamine metabolites to lethality of suicidal acts in depressed subjects with comorbid alcoholism.

Methods: We compared 16 high-and 16 low-lethality drug-free depressed suicide attempters with comorbid alcoholism. Subjects were free from any substance use disorder for at least two months. Demographic and clinical parameters, and CSF 5-HIAA, homovanillic acid (HVA), and 3-methoxy-4-hydroxyphenylglycol (MHPG) levels were examined.

Results: The two groups did not differ with regard to the demographic characteristics. CSF 5-HIAA levels were lower in high-lethality attempters compared to low-lethality attempters. There were no group difference in CSF HVA or MHPG levels.

Conclusion: Higher lethality of suicidal behavior in depressed patients with alcoholism is related to lower serotonergic activity.

Keywords

CSF monoamine metabolites; Suicide attempts; Alcohol dependence; Major depressive disorder; Low serotonergic activity

1. Introduction

Alcohol dependence (alcoholism) and major depressive disorder are frequently comorbid and both are risk factors for suicidal behavior (Roy and Linnoila, 1986; Murphy and Wetzel, 1990; Mann et al., 1999; Harwitz and Ravizza, 2000; Sher et al., 2005; Sher, 2006). Lifetime mortality due to suicide in alcoholism is reported as high as 18% (Roy and Linnoila, 1986) but other estimates (Murphy and Wetzel, 1990) find that the lifetime risk of suicide among individuals with alcohol dependence treated in outpatient and inpatient settings is 2.2% and 3.4%, respectively. The lifetime risk of suicide in major depression is about 15% (Oquendo et al., 2004). Forty percent of a sample of depressed subjects with alcoholism who were

hospitalized had attempted suicide in the prior week and 70% had attempted suicide at some point in their lives (Cornelius et al., 1996).

Monoaminergic abnormalities have been implicated in the pathophysiology of depression, alcoholism, and suicidal behavior (for reviews, see Ratsma et al., 2002; Sher and Mann, 2003a,b). Lower cerebrospinal fluid (CSF) 5-hydro-xyindolacetic acid (5-HIAA) levels are associated with higher lethality of suicide attempts in major depression and predict a higher rate of future suicide (Nordstrom et al., 1994; Mann and Malone, 1997).

Alcoholism is associated with altered CSF monoamine metabolite levels (Ballenger et al., 1979; Banki and Molnar, 1981; Borg et al., 1985; Ratsma et al., 2002; Sher et al., 2003). For example, we have demonstrated that in individuals with major depression, those with comorbid alcoholism had lower CSF homovanillic acid (HVA) levels compared with those without comorbid alcoholism (Sher et al., 2003). However, our study did not focus on suicidal behavior. CSF 5-HIAA is lower in abstinent alcoholics (Ballenger et al., 1979; Banki and Molnar, 1981; Borg et al., 1985). Comorbidity of major depression with alcoholism could mean lower CSF 5-HIAA and underlie greater risk of higher lethality suicide attempts. We examined the relationship of CSF 5-HIAA, HVA, and 3-methoxy-4-hydroxyphenylglycol (MHPG) to lethality of suicide attempts in drug free patients with alcoholism and major depression.

2. Methods

Subjects presented for evaluation and treatment of major depression or 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. All subjects ($N=32$) met DSM-IV (American Psychiatric Association, 1994) criteria for a current major depressive episode, alcohol dependence and had made a previous suicide attempt. Participants were free from 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 within 72 h of the lumbar puncture. 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 were free from any substance use disorder including alcohol use disorders for at least 2 months. Patients with alcohol dependence were in early or sustained full remission. Subjects with psychotic or eating disorders were excluded.

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), (for DSM-IV, American Psychiatric Association, 1994), respectively. All subjects had a physical examination and routine laboratory screening tests, including urine and blood toxicological screenings to rule out neurological or medical illness, or illicit drugs that could affect their mental status or CSF monoamine metabolites.

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., 1974a). 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) (Oquendo et al., 2003) and suicide intent by the Beck Suicide Intent Scale (SIS) (Beck et al., 1974b). Patients with medical lethality scores ≥ 4 were classified as high-lethality suicide attempters, subjects with medical lethality scores <4 were regarded as low-lethality attempters. The classification between low-lethality and high-lethality attempters was based on lifetime history.

The lumbar puncture was performed at about 8:00 AM, after the subject had been kept at bed rest and fasting from midnight. 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. Cerebrospinal fluid amine metabolites were assayed in one of the 1-mL aliquots of the 15-mL sample.

Cerebrospinal fluid 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 at -70°C until assay. Storage effects were not detected.

Demographic and clinical characteristics and CSF monoamine metabolites levels were compared using *t*-test. Correlations between CSF metabolites levels and behavioral measures were computed. A general linear model evaluated effects of age and gender on CSF monoamine metabolites. All tests were two-tailed and significance required $p < 0.05$.

3. Results

Demographic and clinical data are provided in Table 1. There were 16 low- and 16 high-lethality suicide attempters. There was no difference between the two groups with regard to the demographic characteristics or psychiatric measures. Notably, severity of depression, suicidal ideation, number of previous major depressive episodes, and aggressive-impulsive traits did not differ between groups. High-lethality suicide attempters had a history of more psychiatric hospitalizations compared with low-lethality attempters ($t = -2.78$, $df = 26$, $p = 0.01$).

CSF monoamine metabolites levels are presented in Tables 2 and 3. Mean CSF 5-HIAA was 23.5% lower in high-lethality attempters compared to low-lethality attempters ($t = 2.1$, $df = 30$, $p = 0.04$). There was no difference in CSF HVA and CSF MHPG levels between the two groups ($t = -0.1$, $df = 30$, $p = 0.9$, and $t = -1.4$, $df = 30$, $p = 0.2$, respectively). Controlling for age and gender did not alter the results for CSF 5-HIAA ($df = 1, 28$, $F = 4.4$, $p = 0.045$). The difference in the CSF HVA and CSF MHPG levels remained non-significant after the adjustment for age and gender ($df = 1, 28$, $F = 0.01$, $p = 0.9$; and $df = 1, 28$, $F = 2.3$, $p = 0.1$, respectively). We found no correlation between depression or suicidal ideation scores and CSF monoamine metabolites levels in each group or in the both groups, combined (data not shown).

4. Discussion

Our finding is consistent with previous reports on the relation between the serotonergic system and lethality of suicide attempts. Low CSF 5-HIAA predicts future suicide attempts

and suicide completions (Nordstrom et al., 1994; Samuelsson et al., 2006) and is consistent with low post mortem brainstem levels of serotonin or 5-HIAA in suicide victims, independent of psychiatric diagnosis (Arango et al., 1995; Sher and Mann, 2003b). The relationship between low serotonergic function and suicidal behavior is also indicated by a blunted prolactin response to serotonin that is released by fenfluramine in suicide attempters with major depression or personality disorders compared with controls (Coccaro et al., 1989; Mann et al., 1995). It has been reported that the more lethal the suicide attempt, the lower the CSF 5-HIAA and the more blunted the prolactin response to fenfluramine (Mann et al., 1995; Mann and Malone, 1997).

The fact that we did not find a difference in behavioral parameters between the two groups or correlations between behavioral measures and monoamine metabolite levels could be related to a small sample size which is a limitation of this study.

Lethality of suicidal behavior in depressed patients with alcoholism is related to lower serotonergic activity. Future studies should determine whether comorbid alcoholism and major depression can predict lethality of future suicide attempts. Future investigations should include the comparison between subjects with comorbid alcoholism and depression and subjects with alcoholism alone.

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Table 1

Demographic and clinical characteristics of high- and low-lethality depressed suicide attempters with comorbid alcoholism

Variable	Low-lethality suicide attempters		High-lethality suicide attempters		Analysis		
	Mean (N)	SD (%)	Mean (N)	SD (%)	<i>t</i> / χ^2	<i>df</i>	<i>p</i>
Age (years)	34.0	11.7	35.5	11.4	−0.4	30	0.7
Gender (% male)	(9)	(56.3)	(7)	(46.7)	0.1	1	0.7
Hamilton Depression Rating Scale	19.2	8.4	19.9	7.0	−0.3	30	0.8
Beck Depression Inventory	29.0	10.9	28.7	11.3	0.7	27	0.9
Beck Hopelessness Inventory	10.0	5.7	12.9	5.7	−1.4	27	0.2
Brown-Goodwin Aggression Scale	23.8	5.5	21.1	6.1	1.3	29	0.2
Barratt Impulsivity Scale	60.3	14.4	57.1	18.9	0.5	23	0.7
Buss-Durkee Hostility Inventory	40.3	16.7	40.1	9.9	0.4	23	0.97
Number of previous hospitalizations	2.2	3.0	6.4	4.9	−2.8	26	0.01
Number of previous depressive episodes	2.1	1.6	5.5	5.6	−1.6	18	0.1
Age at first hospitalization	29.4	13.5	25.1	10.6	0.9	25	0.4
Suicide ideation scale	20.6	11.6	17.9	10.7	0.7	30	0.5
Number of previous suicide attempts	2.8	1.7	4.3	3.1	−1.8	30	0.2
Suicide intent at the time of the most lethal attempt	17.7	5.8	18.3	4.4	−0.3	29	0.8
Maximum lethality of suicide attempts	2.5	1.0	5.3	1.2	−7.3	30	<0.0001

Table 2

CSF monoamine metabolites of high- and low-lethality depressed suicide attempters with comorbid alcoholism

Variable	Low-lethality suicide attempters		High-lethality suicide attempters		Analysis		
	Mean (N)	SD (%)	Mean (N)	SD (%)	<i>t</i>	df	<i>p</i>
5-HIAA (pmol/ml)	119.7	47.1	91.5	23.8	2.1	30	0.04
HVA (pmol/ml)	177.5	69.7	180.1	50.6	-0.1	30	0.9
MHPG (pmol/ml)	37.2	13.1	43.6	12.2	-1.4	30	0.2

Table 3

CSF 5-HIAA of high- and low-lethality depressed suicide attempters with comorbid alcoholism (pmol/ml)

Low-lethality suicide attempters	High-lethality suicide attempters	Analysis		
		<i>t</i>	df	<i>p</i>
87.9	50.1			
71.4	89.7			
119.4	83.8			
98.3	81.2			
99.3	40.9			
72.9	98.3			
71.7	118.6			
142.0	102.0	2.1	30	0.04
62.4	108.1			
155.3	100.0			
181.3	80.0			
145.4	101.0			
177.5	75.3			
91.6	135.3			
116.1	87.0			
223.8	112.1			