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Biogenic amine turnover and serum cholesterol in suicide attempt

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Abstract The investigation of biological correlates of suicidal behavior is important in searching for possible changes in neuronal systems activity related to that behavior, so that pharmacological interventions may be proposed, especially in high-risk subjects. In a sample of 111 subjects admitted in a general hospital after suicide attempt, we studied the turnover of neurotransmitters by measuring the urinary output of the main metabolites of serotonin, dopamine and noradrenaline (5-HIAA, HVA, MHPG respectively), as well as serum cholesterol, and compared them to those of a group of 62 healthy controls. Venous blood samples and urine samples were collected within 24 hours of admission. Psychiatric diagnosis was made according to DSM-IIIR criteria and assessment of suicide intent with Beck's Suicidal Intent Scale (SIS). Fifty-four (54) subjects received the diagnosis of adjustment disorder, 25 of depression, 16 of schizophrenia and 16 of personality disorder. Fourteen subjects (14) had employed a violent mode of attempt. Urinary MHPG was found significantly higher in all diagnostic groups compared to controls. No difference was found concerning the excretion of HVA and 5-HIAA. Serum total cholesterol was found significantly lower both in violent and non-violent attempters compared to controls after correcting for age. No difference in serum cholesterol or MHPG was found between violent and non-violent attempts. Serum cholesterol and MHPG correlated negatively, while the correlations between cholesterol and 5-HIAA or HVA were not significant. Our results confirm previous reports of lower serum cholesterol in attempted suicide. They are also indicative of an increased noradrenaline turnover in subjects who attempt suicide, at least within 24 hours after the attempt. Whether this activation precedes or follows the attempt because of the specific stress, can not be answered at present.

Key words Suicide attempt · 5-HIAA · HVA · MHPG · serum cholesterol

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Introduction

The investigation of biological correlates of suicidal behavior is important for identifying high-risk subjects and developing strategies of prophylaxis. The prevailing neurochemical theory focuses on the serotonergic system (Asberg et al. 1976), but several data are available about the implication of other neurotransmitter systems. Low concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA), in cerebrospinal fluid (CSF) have been associated with suicidal behavior in patients with depressive illness (Traskman et al. 1981, Roy et al. 1989a) or schizophrenia (Cooper et al. 1992). On the other hand, lower concentrations in CSF and significantly smaller urinary outputs of homovanillic acid (HVA), the metabolite of dopamine, have been reported in patients with depression who had attempted suicide compared to depressed patients without attempt (Roy et al. 1992).

The data concerning the involvement of the noradrenergic system are conflicting. Higher levels of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in CSF have been reported in patients with personality disorder with a history of suicide attempt compared to controls (Brown et al. 1979) and in violent attempters (Traskman-Benz et al. 1993). A negative correlation, though, between measures of suicidal tendencies and CSF MHPG levels has been found in depressed patients (Agren 1980). Smaller growth hormone responses to clonidine, an alpha-2-receptor agonist, have been found in depressed patients with a history of suicide attempt in comparison with nonattempters (Pitchot et al. 1994).

The study of plasma and urinary levels of MHPG has also given conflicting results. Reduced excretion of MHPG has been reported in suicide attempters compared to controls (Agren 1982, Secunda et al. 1986), while in another study no relationship was found between CSF, plasma or urinary indices of noradrenergic function and history of suicide attempt (Roy et al. 1989b). On the other hand, increased norepinephrine output has been found in patients after suicide attempt compared to ideators (Mancini and Brown 1992) and increased urinary excretion of MHPG in patients with adjustment disorder compared to healthy controls (Tripodianakis et al. 2000).

Serum cholesterol has been reported to be lower in subjects who attempt suicide compared to non-attempters and normal controls in several studies (Golier et al. 1995, Kunugi et al. 1997, Papassotiropoulos et al. 1999, Garland et al. 2000). Other studies have failed to confirm this finding (Seneviratne et al. 1999, Almeida-Montes et al. 2000, Huang et al. 2000). A hypothesis that has been proposed for the possible association between cholesterol and suicidality is that low or lowered central nervous system cholesterol reduces 5-HT activity (Boston et al. 1996).

In a previous study, we investigated the urinary excretion of MHPG, HVA, and 5-HIAA, in a group of subjects with adjustment disorder after suicide attempt in relation to platelet MAO activity and plasma cortisol (Tripodianakis et al. 2000). In the present study, we have extended our investigation of neurotransmitter metabolites to a large group of attempters with various psychiatric diagnoses and we then searched for possible associations of the metabolites with serum total cholesterol. We also searched for possible relations of neurochemical measures with clinical variables, such as age, sex, suicidal intent, psychiatric diagnosis and mode of attempt (violent vs nonviolent). The data of the attempters were also compared to those of a group of healthy control subjects.

The rationale for studying urinary neurotransmitter metabolites is that a high proportion of MHPG and HVA originate in the brain rather than the periphery. The actual proportion of MHPG which derives from the brain has been estimated from 20% (Bromley et al. 1980) to 80% (Ebert et al. 1972). Concerning the urinary excretion of HVA, it is estimated that 12% (Lambert et al. 1991) to 25% (Maas et al. 1979) is also derived from the brain. Urinary 5-HIAA expresses to a great extent peripheral serotonin metabolism, but peripheral measures of serotonin activity may also be relevant, and have been assessed in previous studies, such as platelet serotonin and whole blood tryptophan, studied as predictors of suicidal behavior in young psychiatric inpatients (Pfeffer et al. 1998).

Subjects and methods

One hundred and eleven (111) subjects, admitted after a suicide attempt to the medical wards of Evangelismos General Hospital in Athens, were included in the study, 35 males and 76 females. They were all assessed by the psychiatric liaison team. The psychiatric diagnosis was made by two psychiatrists (JT and DS) according to the DSM-IIIR criteria and the severity of the suicidal intent was estimated with the Suicidal Intent Scale (SIS) (Beck et al. 1975). Fifty four (54) patients received the diagnosis of adjustment disorder, 25 of affective disorder, 16 of personality disorder and 16 of schizophrenia. Fourteen (14) patients employed a violent method, 7 males (20% of the male population) and 7 females (9% of the female population). Blood and urine samples were taken within 24 hours of admission from all the patients at 8:00 in the morning. Gastric lavage was performed on the patients who had taken a drug overdose and then they were put on continuous infusion. Further treatment was individualized according to the kind of drugs ingested. Acetylcysteine for the protection of the liver was administered to those who had taken paracetamol and flumazenil to those who had taken high doses of benzodiazepines.

A control group was established from 31 male and 31 female normal volunteers who had no psychiatric history or history of suicide attempt. They were students of a nursing school and hospital staff. The ages of the control subjects were matching the patients' according to sex, i. e., male controls were age matched to male attempters ($F=1.74$, $p=0.19$), and female controls to female attempters ($F=0.42$, $p=0.52$).

Creatinine concentrations were estimated in the urine samples. Patient groups had similar creatinine concentrations, all significantly lower than controls. To compensate for the differences, the concentrations of the metabolites were expressed in nmol/mg creatinine. Urine samples were kept at –35 °C until estimations, which were performed in less than three months. The concentrations of 5-HIAA and HVA in urine were estimated by high pressure liquid chromatography (HPLC) with an electrochemical detector and integrator. Twenty microliters of 1:20 diluted urine samples with and without standards were directly injected into the system. Total urinary MHPG was estimated by gas chromatography (GC): after an overnight hydrolysis with glusulase, MHPG is extracted in ethyl acetate, derivatized with trifluoroacetic anhydride and injected into a GC system with an electron capture detector. Total cholesterol was estimated in plasma samples using commercially available kits.

For the statistical evaluation of the data, we employed analysis of variance (ANOVA) using age and sex as covariates when appropriate, and post hoc comparisons. Linear regression analysis and the nonparametric Spearman correlation coefficient test were applied in searching relations between variables.

Results

We first examined the possibility of direct influences of the mode of attempt, i. e. type of drug(s) ingested on the biochemical measures (Table 1). For this purpose, we established four subgroups, one with those patients who used analgesics (n=38), a second with those who used

Table 1 Concentrations of 5-HIAA, HVA and MHPG expressed in nmol/mg creatinine, and serum cholesterol (pCHOL, mg/dl) in subgroups of suicide attempters according to drugs ingested

Subgroup	N	5-HIAA	HVA	MHPG	pCHOL
Analgesics	38	14.0±5.3	14.0±6.1	10.1±5.0	173±40
Benzodiazepines	30	16.2±6.0	16.9±9.2	11.2±7.5	181±36
Other drugs	29	14.3±4.7	14.6±8.8	8.9±4.9	176±37
Violent mode	14	16.5±6.6	15.8±10.1	10.1±5.7	176±41
ANOVA, F/p		1.42/0.24	0.77/0.51	0.81/0.81	0.27/0.85

benzodiazepines (n=30), a third one with those who used other drugs (n=29) and a fourth group with 14 patients who used violent methods or substances not intended for human consumption (poisons, and caustic agents). Analysis of variance (ANOVA) showed no significant differences in the levels of neurotransmitter metabolites or plasma cholesterol between these four subgroups. The lack of differences in the four subgroups indicates no major influence of the drugs ingested by the subjects and of the treatment given to them in the hospital. An additional indication of no influence of the drugs ingested was the lack of correlation between the quantity ingested either for analgesics or for benzodiazepines (Spearman correlation coefficient).

Female attempters were significantly younger (mean age 25.6, SD=9.4) than male attempters (mean age 33.1, SD=12.3, F=12,28, $p < 0.001$) and scored lower in the SIS (F=5.16, p=0.025). However ANOVA with age taken as covariate showed that the difference in suicide intent between the two sexes was not significant (F=0.60, p=0.44). Attempters with schizophrenia and affective disorder had undertaken the most serious attempts, compared to attempters with adjustment disorder (ANOVA, p=0.001 for both comparisons). No significant difference in suicide intent existed between the patients with adjustment and personality disorder (p=0.98).

Attempters who employed a violent method were significantly older (mean age 35.5, SD 11.1) than those who took an overdose (mean age 26.8, SD 10.5, p=0.002) and controls (mean age 31.5, SD 8.1, p=0.003). In Table 2 are shown the concentrations of the metabolites and of cholesterol in the subgroups of violent and nonviolent attempters and controls. Analysis of variance (ANOVA) with age and sex as covariates indicated significant differences for MHPG and cholesterol only. Both violent and nonviolent attempters had significantly higher MHPG excretion than controls (p=0.038 and p=0.0002, respectively) and significantly lower cholesterol (p=0.041 and 0.0002, respectively). No difference existed between violent and nonviolent attempters either for MHPG (p=0.98) or for cholesterol (p=0.94). A weak, but significant negative correlation was found between MHPG and cholesterol in the group of attempters (Pearson r=–0.219, $p < 0.02$).

Table 2 Neurotransmitter metabolite excretion and serum cholesterol in groups of controls and violent and non-violent attempters. Comparison with ANOVA with age and sex as covariates

Group	N	Age	u5HIAA	uHVA	uMHPG	pCHOL
Controls	62	31.5±8.1	15.9±3.7	14.3±5.0	6.98±2.86	196±35
Violent	14	35.8±11.1	16.5±6.6	15.8±10.3	10.1±5.7	175±41
Nonviolent	97	26.8±10.5	14.7±5.4	15.1±8.0	10.1±5.8	176±37
Post hoc comparisons						
Controls vs nonviolent, p			0.17	0.50	0.0002	0.0004
Controls vs violent, p			0.66	0.49	0.038	0.041
Nonviolent vs violent, p			0.21	0.74	0.98	0.94

In Table 3 are shown the concentrations of the neurotransmitter metabolites in urine and the serum cholesterol levels in the control and the psychiatric diagnostic groups of patients. Analysis of variance (ANOVA) with age as covariate indicated significant differences between the groups only for MHPG (F=5.56, p=0.0003) and for cholesterol (F=5.30, p=0.0005). Further analysis, with age as covariate, showed that the differences from controls for MHPG were significant for all the diagnostic subgroups, i.e., for adjustment disorder (p=0.022), for affective disorder (p=0.004), for personality disorder (0.002), and for schizophrenia (p=0.005). Serum cholesterol, was significantly lower in the subgroups with adjustment disorder ($p < 0.01$), personality disorder ($p < 0.0001$) and schizophrenia ($p < 0.02$), but not in the group with affective disorder (p=0.99).

We searched further for a possible correlation between biological variables and the score in SIS. Serum cholesterol and Suicidal Intent Scale score gave a significant positive correlation (Spearman R=0.265, p=0.005).

Table 3 Serum cholesterol and urinary MHPG, HVA, and 5-HIAA in the diagnostic groups of attempters and the controls. Mean values and SD. Statistical analysis by ANOVA with age and sex as covariates and post hoc comparisons for serum cholesterol and MHPG, where significant differences between groups were found

Group*	N	Age	CHOL		uMHPG		u5HIAA	uHVA
			x±SD	F/p	x±SD	F/p	x±SD	x±SD
CNTR	62	31.6±8.1	196±35	Ref.	6.98±2.86	Ref.	15.9±3.7	14.3±5.0
AD	54	24.1±9.5	172±35	6.54/0.011	9.03±4.92	5.32/0.022	14.9±5.4	13.8±6.2
MAD	25	37.0±11.5	204±30	0.01/0.99	10.55±6.0	8.51/0.004	14.8±5.9	16.3±9.8
PD	16	24.4±6.2	150±33	16.36/0.0001	12.18±7.45	14.31/0.0002	14.6±6.2	17.0±9.2
SCH	16	30.4±9.9	172±37	5.48/0.02	10.94±5.86	8.10/0.005	15.9±5.2	16.2±9.8
F				5.30		5.56	0.53	1.02
p				0.0005		0.0003	0.71	0.40

* *CNTR* Controls, *AD* Adjustment disorder, *MAD* Major Affective Disorder, *PD* Personality Disorder, *SCH* Schizophrenia

No correlation existed between MHPG and score in SIS.

Discussion

The concentrations of the noradrenaline metabolite MHPG in urine of subjects after suicide attempt were significantly higher in all four diagnostic groups compared to healthy controls. Although the exact significance of urinary MHPG and its origin is questionable, previous studies have shown that it correlates with total body NE production (Linnnoila et al. 1983) and that central and peripheral NE systems are functionally related (Maas et al. 1979). It has been proposed that increases in noradrenergic activity enhance orientation to the environment (Siever and Davies 1985). Moreover, sustained increases in noradrenergic activity may serve an alarm function, as suggested by increased firing of the locus coeruleus in response to threatening stimuli in primates (Redmond 1977). In humans, different stimuli, such as the cold pressor test or stimulation with low-level shocks, increase plasma norepinephrine and urinary MHPG, respectively (Buchsbaum et al. 1981). Another aspect of the role of the noradrenergic system is that it is related to the interpretation construed by the individual to explain environmental events. Higher MHPG output has been reported to be associated with the phenomenon of learned helplessness and more specifically with perceptions of powerlessness (Samson et al. 1992), and lower levels of urinary norepinephrine with positive cognitive reappraisal coping behaviors and perceptions of mastery (Schaeffer and Baum 1989). So we might hypothesize that the suicidal act, as a behavior orienting the person towards the environment in the form of "appeal" or "cry for help", and as the result of perceptions of powerlessness, is characterized by increased noradrenergic activity. Whether this heightened noradrenergic activity precedes or follows the attempt, can not be answered at present.

Our finding is at variance with some previous studies in which MHPG excretion has been found lower in depressed patients after suicide attempt compared to depressed patients without attempt (Agren 1982, Secunda et al. 1986). In CSF studies it has been reported high in attempters with personality disorder (Brown et al. 1979) and in violent attempters (Traskman-Benz et al. 1993). A difference between our study and previous studies is that we performed clinical and neurochemical assessments within 24 hours following the attempt. In the study of Mancini and Brown (1992) in which urine samples were also collected within 24 hours following the suicide attempt, the authors found increased norepinephrine excretion. Based on this and other studies (Van Praag and Plutchic 1985) we can assume that the timing of neurochemical assessments after a suicide attempt is important. Some biological measures may be trait markers, but some others are related to the state of the subject and probably change over time after the attempt. Future studies should take these changes into account by examining biologic measures and clinical ratings immediately after the attempt and at repeated intervals at a later time.

In line with previous studies, our group of attempters had lower cholesterol levels than the controls (Golier et al. 1995, Kunugi et al. 1997, Papassotiropoulos et al. 1999, Garland et al. 2000). We found no difference in cholesterol between attempters who overdosed and those who employed a violent method. In some studies (Alvarez et al. 1999, 2000) lower cholesterol was found only in violent attempters. In most studies though, low cholesterol is independent of the violence of the act. When diagnostic groups were examined separately, we found that the affective disorder group had cholesterol levels no different from controls. Our result is in agreement with the results of previous studies (Yates and Wallace 1987, Almeida-Montes et al. 2000) where no difference was found between patients with major depression and the normal population. In our study the subjects with affective disorder (n=25) constituted 22% of the total sample and were significantly older than the controls ($p=0.02$). So one can suspect an age effect. We believe though that he have minimized the possibility of such an effect by performing the analysis with age as a covariate. An explanation why we could not find lower cholesterol in the affective disorder group is probably because, in that seriously ill group of patients, psychopathology is a more important factor for suicide attempt than cholesterol.

We found a weak negative correlation between serum cholesterol and MHPG (Pearson $r = -0.219$, $p < 0.02$). It is hard to explain this finding. It has been proposed that activation of the noradrenergic system increases the activity of lipoprotein lipase, which results in an increase of free fatty acids in serum (Hayward et al. 1989). This hypothesis is supported by the results of studies in which high cholesterol levels have been found in patients with panic disorder compared to controls (Agargun et al. 1996).

We found that the 5-HIAA excretion in our group of attempters was not different from controls and did not correlate with serum cholesterol. The data for a possible link of cholesterol with serotonin are inconclusive. Erikson et al. (1996) could not find that cholesterol lowering after simvastatin administration in healthy volunteers has any effect on CSF 5-HIAA. Similarly, Ringo et al. (1994) found only an insignificant correlation between total serum cholesterol and CSF 5-HIAA. However, in an animal study, Kaplan et al. (1994) found lower 5-HIAA concentrations and more aggressive behavior in 17 cynomolgus monkeys fed a low cholesterol diet compared with animals fed normally.

The study of peripheral indices of serotonin activity has also given conflicting results. Delva et al. (1996) found no relationship between cholesterol, plasma tryptophan and d-fenfluramine induced prolactin release, while Steegmans et al. (1996) found a significant correlation between plasma serotonin and cholesterol in sub-

jects with low cholesterol compared to controls with normal cholesterol.

In summary, studying 111 subjects who attempted suicide, we found lower serum total cholesterol levels compared to a group of healthy controls matched for age by sex. We also found increased noradrenaline turnover (high urinary MHPG excretion) compared to controls.

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