Low HDL cholesterol, aggression and altered central serotonergic activity

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Abstract

Many studies support a significant relation between low cholesterol levels and poor impulse, aggression and mood control. Evidence exists also for a causal link between low brain serotonin (5-HT) activity and these behaviors. Mechanisms linking cholesterol and hostile or self-destructive behavior are unknown, but it has been suggested that low cholesterol influences 5-HT function. This study was designed to explore the relationship between plasma cholesterol, measures of impulsivity and aggression, and indices of 5-HT function in personality disordered cocaine addicts. Thirty-eight hospitalized male patients age 36.8 ± 7.1 were assessed with the DSM-III-R, the Buss–Durkee Hostility Inventory (BDHI), the Barratt Impulsiveness Scale (BIS) and the Brown–Goodwin Assessment for Life History of Aggression. Fasting basal cholesterol (total, LDL and HDL) was determined 2 weeks after cocaine discontinuation. On the same day 5-HT function was assessed by neuroendocrine cortisol and prolactin and psychological (NIMH and ‘high’ self-rating scales) responses following meta-chlorophenylpiperazine (m-CPP) challenges. Reduced neuroendocrine responses, ‘high’ feelings and increased ‘activation-euphoria’ following m-CPP have been interpreted as indicating 5-HT alterations in a variety of psychiatric conditions. Significantly lower levels of HDL cholesterol were found in patients who had a history of aggression (P = 0.005). Lower levels of HDL cholesterol were also found to be significantly associated with more intense ‘high’ and ‘activation-euphoria’ responses as well as with blunted cortisol responses to m-CPP (P = 0.033, P = 0.025 and P = 0.018, respectively). This study gives further support to existing evidence indicating that in some individuals, the probability of exhibiting impulsive...
and violent behaviors may be increased when cholesterol is low. It also suggests that low cholesterol and alterations in 5-HT activity may be causally related. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Recent studies suggest the existence of associations between low or lowered total cholesterol levels and increased mortality from suicide, violence and accidents (Muldoon et al., 1990). Associations have also been found between low cholesterol and symptoms or behaviors that did not result in final outcomes such as depression, suicidal ideation, suicide attempts or violence. Evidence for these associations is derived from prevention trials aimed at lowering cholesterol concentrations by diet, drugs or both, from prospective epidemiological studies in which follow-up was done in individuals with varying levels of plasma cholesterol who did not undergo specific cholesterol lowering interventions, and from clinical studies in which cholesterol and psychopathology were assessed concomitantly (for review, see Muldoon et al., 1993).

Behaviors associated with low cholesterol have also been observed in patients with a deficient serotonergic neurotransmission. This has prompted some investigators to assess the existence of associations between low cholesterol and indices of altered serotonergic function and psychopathology, and to wonder whether low cholesterol and reduced serotonergic activity could be causally related. To date, evidence supporting the existence of a link between reduced cholesterol levels and alterations in 5-HT function is still scant.

In order to examine the existence of relationships between plasma cholesterol, psychopathology and indices of serotonergic neurotransmission in humans, we measured plasma cholesterol in a group of abstinent personality disordered cocaine addicts whose serotonergic function had been assessed with the serotonergic probe meta-chlorophenylpiperazine (m-CPP). Neuroendocrine and psychological changes following m-CPP administration were the topic of a first study (Buydens-Branchey et al., 1997). Because only a limited amount of research has been undertaken to determine the possible role of high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol in psychiatric disorders and in serotonergic neurotransmission, we decided to measure plasma levels of HDL and LDL cholesterol in addition to those of total cholesterol in the patients who participated in this investigation.

2. Methods

2.1. Patients

Patients selected for participation in the study were 38 men whose age (mean ± S.D.) was 36.8 ± 7.1 years. They were studied while hospitalized on a locked inpatient drug rehabilitation unit. They did not receive any medication during their stay in the hospital. Patients were excluded from the study if they had a major physical illness or abnormalities on liver function tests. Patients with a history of intravenous use of any substance and patients who had used opiates in any form during the year preceding admission were also excluded from the study. They were screened with the SCID (Spitzer et al., 1990; First et al., 1997a,b) and were enrolled in the study if they met DSM-III-R criteria for cocaine dependence but did not meet criteria for any other Axis I disorder (including dependence on any substance besides cocaine). The presence of one or more Axis II disorders was not an exclusionary criterion. Patients were also administered the Barratt Impulsiveness Scale (Barratt, 1957) and the Buss–Durkee Hostility Inventory (Buss and Durkee, 1957). The Buss–Durkee score was arrived at by adding the scores on seven hostility subscales and one suspicion subscale. A modified version of the Brown–Goodwin Assessment for Life History
of Aggression was also part of our test battery (Brown et al., 1981). This questionnaire was aimed at eliciting information about the following behavioral categories: problems with discipline in the armed forces; problems with discipline at work; non-specific fighting; specific assaults on other persons; property damage; antisocial behavior involving the police or not; and arrests or incarceration for assaultive or other behaviors. In each category, non-occurrence was scored as 0; one event was scored as 1; two events were scored as 2; three, ‘several,’ or ‘frequent’ events were scored as 3; and four or more, ‘many,’ or ‘numerous’ events were scored as 4. Patients with a score of 8 or more were considered to have a history of aggression.

2.2. m-CPP challenge procedure

After having signed informed consent, each subject participated in two test sessions during which either m-CPP (0.5 mg/kg) or placebo was given orally as identical-looking capsules. The order of m-CPP and placebo administration was random and capsules were given according to a double-blind design. The time interval between the administration of m-CPP and placebo was 72 h. Testing took place from 12 to 19 days after discontinuation of cocaine use. Subjects were instructed to fast after midnight on test days. During the test sessions, they remained in a semirecumbent position, stayed awake, abstained from smoking, and continued to fast until the end of the session. Blood samples were drawn for prolactin and cortisol determinations, 30 and 15 min before and 30, 60, 90, 120, 180, and 210 min after m-CPP and placebo administration. Total, HDL and LDL cholesterol were determined in the sample collected 15 min before m-CPP administration. Psychological changes occurring during the challenge procedures were assessed with a modified version of the National Institute of Mental Health (NIMH) self-rating scale, which comprises 24 items rated on a 4-point scale (non-existent = 0, mild = 1, moderate = 2, marked = 3) (Murphy et al., 1989). This scale is divided into the following six subscales: anxiety, activation-euphoria, depressive affect, dysphoria, altered self-reality, and functional deficit. A ‘high’ scale, which is not part of the NIMH scale but has been utilized by other investigators, was used as well (Charney et al., 1987). The four-point rating system on this scale was the same as that used for the NIMH scale. The NIMH and ‘high’ scales were used 30 min before and 30, 90, 150, and 210 min after m-CPP and placebo administration.

2.3. Biochemical determinations

Plasma prolactin and cortisol levels were measured with radioimmunoassay kits from ‘ICM Biomedical Inc.’ Intraassay and interassay coefficients of variance were 6.1% and 8.3% for prolactin, and 6.7% and 8.9% for cortisol, respectively. Plasma m-CPP levels were measured according to the method of Suckow et al. (1990). Intraassay and interassay coefficients of variance were 6.7% and 8.6%, respectively.

Total cholesterol was measured by an enzymatic method similar to that described by Allain et al. (1974). HDL cholesterol was separated by precipitation of LDL and VLDL lipids, using dextran sulfate and magnesium chloride (Warnick et al., 1983) and measured in the supernatant by the same enzymatic method as total cholesterol. LDL cholesterol was calculated by subtracting HDL cholesterol and triglycerides from total cholesterol.

2.4. Data analysis

The levels of total, HDL and LDL cholesterol of aggressive and non-aggressive patients were compared with analyses of covariance (ANCOVAs), using age and weight as covariates. Associations between continuous variables (such as Barratt and Buss–Durkee scores) and levels of cholesterol were done with partial correlations, controlling for the effects of age and weight.

GLM (general linear model) ANCOVAs, assessing separately the effect of individual continuous predictors (called covariates) on dependent variables, were used to assess the significance of associations between total cholesterol and its subfractions and the neuroendocrine and psychologi-
cal responses to m-CPP (McCullagh and Nelder, 1989). More specifically, GLM repeated measures ANCOVAs were used to test the effect of either total, HDL or LDL cholesterol (covariates) on sequential baseline- and placebo-corrected m-CPP responses with age, weight and peak m-CPP level as additional covariates.

The following indices of the intensity of psychological and neuroendocrine responses to m-CPP were also calculated: delta max (maximum change from baseline following m-CPP) and double delta (difference between delta max and the change from baseline at the corresponding time following placebo).

3. Results

3.1. Pre-challenge assessments

3.1.1. History of Aggression / Barratt and Buss-Durkee scales

Eleven patients were determined to have had a life history of aggression on the basis of their answers to the modified version of the Brown-Goodwin questionnaire. Patients who had a positive score in one of the aggression categories usually had positive scores in other categories. Of the 11 patients determined to be aggressive, 10 had a history of assaultive behavior. These behaviors included murder (one patient), attempted murder (one patient), shooting and injuring others (three patients), stabbing (two patients), threatening drug dealers with a gun to obtain cocaine (one patient), and repeated physical fights without weapons (nine patients). Other behaviors included armed robbery (six patients) and repeated episodes of property damage (eight patients). Three patients had been jailed for crimes involving violence. Patients who did not meet criteria for a life history of aggression had not engaged in the behaviors described above with the exception of assaults and property damage, but far fewer patients in this group had exhibited these behaviors and, when they did, they reported fewer episodes than did individuals categorized as having had a history of aggression. As could be expected, the majority of patients in both groups had committed crimes that did not involve violence, such as burglaries, thefts without confrontation of the victim, and receiving stolen property.

The mean Buss-Durkee inventory and Barratt scale scores for the entire population were 34.2 ± 11.3 and 81.0 ± 13.6, respectively. Aggressive patients had significantly higher Buss-Durkee scores than non-aggressive patients 43.4 ± 9.7 vs. 30.5 ± 9.8; P = 0.001. They also had significantly higher Barratt scale scores 92.5 ± 14.9 vs. 76.3 ± 9.8; P = 0.001). These data are shown in Table 1.

Table 1
Characteristics of patients with and without a history of aggression*

<table>
<thead>
<tr>
<th></th>
<th>Aggression history</th>
<th>Between-group comparisons (significance level)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive (n = 11)</td>
<td>Negative (n = 27)</td>
</tr>
<tr>
<td>Age</td>
<td>36.45 ± 6.56</td>
<td>36.96 ± 7.39</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.45 ± 14.62</td>
<td>78.70 ± 11.66</td>
</tr>
<tr>
<td>Borderline personality disorder</td>
<td>6 (54.5%)</td>
<td>2 (7.4%)</td>
</tr>
<tr>
<td>Nr. of patients (%)</td>
<td>11 (100%)</td>
<td>9 (33.3%)</td>
</tr>
<tr>
<td>Antisocial personality disorder</td>
<td>92.55 ± 14.93</td>
<td>76.26 ± 9.82</td>
</tr>
<tr>
<td>Buss-Durkee scale score</td>
<td>43.45 ± 9.73</td>
<td>30.48 ± 9.76</td>
</tr>
</tbody>
</table>

*The age, weight and Barratt and Buss-Durkee scores of aggressive and non-aggressive patients were compared with Student’s t-tests. The numbers of patients meeting criteria for personality disorders were compared with Fisher’s exact tests.
3.1.2. Personality disorders

Cocaine addicts selected for this study did not meet DSM-III-R criteria for any Axis I disorder with the exception of psychoactive substance use disorder but were not excluded if they met criteria for Axis II disorders. A sizable percentage (65.8%) of patients met DSM-III-R criteria for at least one of these Axis II disorders. The percentages of patients meeting criteria for the various personality disorders were as follows: antisocial, 52.6%; passive-aggressive, 28.9%; borderline, 21.1%; narcissistic, 15.8%; paranoid, 13.2%; avoidant, 10.6%; histrionic, 5.3%; self-defeating, 5.3%; schizotypal, 2.6%. No one met criteria for dependent, obsessive–compulsive, or schizoid personality disorders. Thirty-four percent of the patient population (13 patients) met criteria for two or more personality disorder diagnoses.

All patients with a life-long history of aggression met criteria for at least one personality disorder. The criteria they met most frequently were those of Borderline Personality Disorder and Antisocial Personality Disorder. Six of the eight Borderline Personality Disorder patients and 11 of the 20 Antisocial Personality Disorder patients fell into the aggressive patients category (see Table 1).

3.1.3. Cholesterol and behavioral characteristics

An ANCOVA, with age and weight as covariates, comparing the HDL values of aggressive and non-aggressive patients revealed that the aggressive patients had significantly lower levels of HDL cholesterol than patients without such a history (30.6 ± 5.5 mg/dl vs. 40.3 ± 10.2 mg/dl; \( P = 0.005 \)). These data are shown in Fig. 1.

Although total and LDL cholesterol were lower in patients with a history of aggression, differences assessed with ANCOVAs did not reach conventional levels of significance (141.6 ± 34.4 mg/dl vs. 158.0 ± 32.2 mg/dl for total cholesterol, \( P = 0.086 \); and 84.8 ± 27.0 mg/dl vs. 100.2 ± 30.8 mg/dl for LDL cholesterol, N.S.).

Partial correlations controlling for the effects of age and weight revealed a significant association between HDL cholesterol and the Buss–Durkee score (\( r = -0.35; P = 0.038 \)) and a non-significant association between HDL cholesterol and the Barratt score (\( r = -0.24; P = 0.153 \)). Associations between total and LDL cholesterol and psychological scale scores were not significant.

3.2. Cholesterol and indices of serotonergic function

The statistical associations between HDL cholesterol levels and the neuroendocrine and psychological responses to \( m \)-CPP were tested with GLM repeated measures ANCOVAs, using HDL cholesterol, age, weight and \( m \)-CPP peak levels as covariates.

Low HDL cholesterol levels were associated with blunted cortisol responses. A GLM repeated measures ANCOVA revealed a significant association between HDL cholesterol and the intensity of the cortisol response (\( F_{1,32} = 6.18, P = 0.018 \)) but not between HDL cholesterol and the prolactin response. The trivariate relationship between the cortisol response double deltas, HDL cholesterol levels and presence or absence of aggressive tendencies is depicted in Fig. 2. This figure was divided into four quadrants by two lines intercepting the abscissa and ordinate at points representing the mean cortisol response and HDL cholesterol values. The figure shows that eight of the 11 aggressive patients (72.7%) and the Barratt score (\( r = -0.24; P = 0.153 \)). Associations between total and LDL cholesterol and psychological scale scores were not significant.
fell into the lower left quadrant whereas only six of the 27 non-aggressive patients (22.2%) did.

Lower HDL cholesterol levels were associated with more intense ‘activation-euphoria’ and ‘high’ responses. GLM repeated measures ANCOVAs revealed a significant association between HDL cholesterol and the ‘activation-euphoria’ response ($F_{1,33} = 5.52, P = 0.025$) as well as between HDL cholesterol and the ‘high’ response ($F_{1,33} = 4.93, P = 0.033$). The relationship between HDL cholesterol and the ‘high’ double deltas is illustrated in Fig. 3. This figure also indicates that aggressive patients experienced a moderate or marked ‘high’ more frequently than non-aggressive patients (6/11 or 54.5% vs. 6/27 or 22.2%).

Using the same statistical analyses, total and LDL cholesterol were not found to be associated with any of the neuroendocrine and psychological responses to $m$-CPP.

4. Discussion

4.1. Cholesterol and psychopathology

This study, conducted in personality disordered cocaine addicts withdrawn from cocaine for 12–19 days, revealed that patients who had a past history of aggression had significantly lower levels of HDL cholesterol. Our data confirm the previously reported association between low cholesterol levels and violence. In several meta-analyses of cholesterol-lowering trials, more violent deaths were found among patients whose cholesterol had been reduced (Golomb, 1998). An association between low cholesterol levels and violence was also found in individuals who did not undergo cholesterol-lowering interventions but had low cholesterol values such as forensic patients (Spitz et al., 1994), criminals with an antisocial personality disorder (Vikkunen, 1979) and adolescent boys with aggressive conduct disorder (Vikkunen and Pentinnen, 1984). In addition, low cholesterol was found in groups of patients whose aggression was...
directed against the self instead of others (Lindberg et al., 1992; Modai et al., 1994; Sullivan et al., 1994; Golier et al., 1995; Kunugi et al., 1997).

In most studies levels of total cholesterol were examined and not those of the HDL and LDL fractions. A few studies assessed HDL and LDL cholesterol levels in addition to total cholesterol. Glueck et al. (1994), who studied patients with affective disorders and controls, found that the patients had lower plasma total, HDL and LDL cholesterol levels than controls. Maes et al. (1997) also examined total, HDL and LDL cholesterol in patients with major depression and control subjects and found significantly lower serum HDL cholesterol in the depressed subjects. They also observed that total cholesterol was lower in the patients but that the difference between patients and controls was less significant. HDL cholesterol was significantly lower in depressed patients who had made serious suicide attempts than in those who had not. These data led Maes et al. to speculate that the most important change in serum lipid composition in depressed subjects could occur in HDL cholesterol rather than in total or LDL cholesterol. In the present study, we made similar observations in patients who exhibited problems in aggression and impulse control.

4.2. Cholesterol and 5-HT activity

Our second finding is that of a significant association between low HDL cholesterol and indices of reduced 5-HT function. We observed that low HDL cholesterol was significantly associated with an increased intensity of some psychological responses to m-CPP, namely the ‘high’ and ‘activation-euphoria’ responses. m-CPP is considered to be a predominantly post-synaptic agonist and the increase in 5-HT activity that follows its administration leads to post-synaptically mediated events which include acute psychological and neuroendocrine changes. Several investigators who studied the effects of m-CPP in groups of psychiatric patients with hypothesized serotonin deficits reported psychological effects similar to those we observed. Following the administration of m-CPP, patients diagnosed as having a Borderline Personality Disorder were found to have increased ‘high, happy and depersonalization’ ratings (Hollander et al., 1994), alcoholics were observed to experience ‘ethanol-like’ feelings (Benkelfat et al., 1991; by Krystal et al., 1994) and patients with a seasonal affective disorder were reported to experience an increase in ‘activation-euphoria’ (Jacobsen et al., 1993). In these studies psychological changes produced by m-CPP were interpreted as being indicative of alterations in 5-HT function.

We observed a significant association between low HDL cholesterol and a blunted cortisol response to m-CPP. Blunted neuroendocrine responses to m-CPP have been observed in various psychiatric conditions and interpreted as indicative of 5-HT alterations. A decreased neuroendocrine responsivity to m-CPP has been found by ourselves (Buydens-Branchey et al., 1997) and others (Hollander et al., 1994) to coexist with an increased psychological responsivity and points to the existence of variations in the nature of 5-HT alterations in different brain regions. A recent study using positron emission tomography to explore whether a reduced serotonergic function occurs in brain regions that may play a role in the modulation of aggression (such as the orbital, frontal and cingulate cortex) was conducted in impulsive-aggressive patients and healthy volunteers (Siever et al., 1999). In this study, regional glucose metabolism was assessed following the administration of the 5-HT releaser/reuptake inhibitor, d,l-fenfluramine (60 mg p.o.). Compared with controls, patients showed significantly blunted metabolic responses in the orbital, frontal and adjacent ventral medial and cingulate cortex but not in the inferior parietal lobe. This study provides direct evidence that differences in the metabolic responsivity of healthy subjects and impulsive-aggressive patients to a serotonergic probe can be found in some but not in all brain regions.

Few studies have investigated relationships between cholesterol concentrations and 5-HT activity. In an in vitro study, Heron et al. (1980) demonstrated that the incubation of mouse brain membrane preparations with cholesterol hemisuccinate increased their viscosity and was accompanied by an increase in the binding of 5-HT. Steegmans et al. (1996) found that plasma sero-
tonin concentrations were lower in men found to have persistently low serum cholesterol concentrations. Muldoon et al. (1992) observed that the prolactin response of monkeys fed a low-fat and low-cholesterol diet to the serotonergic probe fenfluramine was significantly lower than the response of animals fed a high-fat and high-cholesterol diet. In a study of relationships between hormonal responses to m-CPP and serum cholesterol conducted in 10 healthy Japanese subjects, Terao et al. (1997) observed a significant correlation between low cholesterol and blunted cortisol and prolactin responses. The authors interpreted their findings as indicating that cholesterol levels may be associated with serotonergic receptor function. In the present study, an association was found between low HDL cholesterol and a blunted cortisol response to m-CPP. This was not the case for the prolactin response. One can only speculate about the reasons for this discrepancy. Whereas some of the mechanisms mediating the secretion of prolactin and cortisol following m-CPP administration are similar, other mechanisms contribute more specifically to the release of each hormone separately. In a previous study, involving 31 of the 38 patients who are the topic of the present report, we reported that there was no difference between the prolactin responses to m-CPP of aggressive and non-aggressive patients, although the responses of the two patient groups were blunted by comparison with those of controls (Buydens-Branchey et al., 1997). By contrast, the aggressive patients’ cortisol response was significantly blunted by comparison with that of both non-aggressive patients and controls. Thus, a significant association between low HDL cholesterol and a blunted hormonal response was found only for cortisol whose responsiveness to m-CPP differentiated aggressive from non-aggressive patients.

4.3. Cholesterol, psychopathology and 5-HT activity

Although a number of studies have reported associations between low cholesterol and problems in anger, mood and impulse control as well as between low cholesterol and 5-HT function, there is still a dearth of evidence concerning the existence of links between low cholesterol, reduced 5-HT activity and psychopathology. The most compelling evidence for the possible existence of such links can be derived from a study performed by Kaplan et al. (1994) in monkeys. These investigators artificially manipulated the amounts of cholesterol consumed by cynomolgus macaques. The animals were given diets high in fat and either rich or low in cholesterol. After they had consumed these diets for an average of 4 months, behavioral observations started and continued for 8 months. Plasma cholesterol and cerebrospinal fluid (CSF) metabolites of 5-HT, norepinephrine and dopamine were assessed 4 and 5.5 months after the initiation of behavioral observations. Monkeys fed the low-cholesterol diet were found to have a significantly lower plasma cholesterol level and to be more aggressive and less affiliative. They also had lower CSF concentrations of the 5-HT metabolite, 5-hydroxyindol acetic acid. No relationship was found between cholesterol and the norepinephrine and dopamine metabolites. These data show that the use of a low-cholesterol diet affects simultaneously plasma cholesterol levels, behavior and serotonergic activity. Our finding of simultaneous associations between low HDL cholesterol and indices of altered serotonergic function could be understood in the context of Kaplan et al.’s study.

Mechanisms underlying the association among cholesterol, behavior and 5-HT activity have not yet been elucidated. It has been suggested that reduced plasma cholesterol could depress the cholesterol/phospholipid ratio in neuronal membranes with consequent alterations in membrane fluidity, viscosity and function, including the function of 5-HT receptors and of the 5-HT transporter. It has also been suggested that low cholesterol may be accompanied by a decrease in plasma levels of the 5-HT precursor tryptophan (Engelberg, 1992; Salter, 1992).

In light of the large number of individuals who attempt to lower their blood cholesterol by diet, drugs or both, additional studies are needed to confirm preliminary findings of a functional association between hostile or self-destructive behavior, cholesterol and serotonin. If existing findings were confirmed, a number of questions would
need to be answered. For example, one could wonder whether it is the total cholesterol or one of its subfractions that plays the most important role in behavioral problems. More importantly, one could also wonder whether individuals who exhibit aggression, impulsiveness or suicidal tendencies following cholesterol-lowering interventions present characteristics antedating these treatments that might predict adverse outcomes.

In the present study, some subjects classified as non-aggressive had cholesterol levels as low as those of the aggressive patients. Moreover, normal HDL cholesterol values range from 27 mg/dl to 67 mg/dl. Patients classified as aggressive had mean HDL cholesterol values in the lower range of values found in normal subjects. Low cholesterol values are thus not necessarily associated with an increase in aggression or impulsiveness. On the other hand, evidence reviewed above indicates that in some individuals, low or lowered cholesterol and behavioral problems might be causally related. In these individuals, the suffering due to adverse psychological effects may outweigh the beneficial effects of lowered cholesterol on heart disease. Although it is not presently known who might be at risk for developing behavioral problems in the context of cholesterol-lowering interventions, caution might have to be exercised in the treatment of individuals who have a history of psychiatric disorders.

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References


