Suicidality, impulsivity and aggression—is there a link to 5HIAA concentration in the cerebrospinal fluid?

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Abstract

In biological suicide research, low cerebrospinal fluid–5-hydroxyindolacetic acid (CSF–5HIAA) concentrations have been associated with suicidality, aggression and impulsivity. However, it frequently appears that the interpretation of existing study results is flawed. The analysis of various published findings suggests that contaminating factors like impulsivity or depressive symptoms in suicide attempters are often not taken into consideration at the time of suicide. The seemingly ‘robust’ association of low CSF–5HIAA concentration with ‘suicidality’ and ‘aggression’ is in fact rather weak. Reported associations of subgroups of suicidal behavior (e.g. violent suicide attempts) with low CSF–5HIAA concentrations are likely to represent somewhat premature translations of findings from studies that have flaws in methodology. Furthermore, the perception of ‘suicidal behavior’ as autoaggressive behavior or inwardly directed aggression in the view of the authors may not be useful in biological suicide research. The construct of aggressivity is insufficiently defined, resulting in difficulties to interpret empirical data. Some evidence exists, however, that reduced CSF–5HIAA concentrations might be related to certain depressive symptoms and changes in impulsivity. More carefully designed studies are required to overcome the existing methodological shortcomings.

Keywords: Suicide; Serotonin; Cerebrospinal fluid; 5-HIAA; Violence; Methodology

1. Introduction

During the last 10–20 years, ‘suicidal behavior’ has been mostly conceptualized as related to a deficient serotoninergic system. It has been postulated that reduced serotoninergic neurotransmission is associated with depression, suicidal behavior, aggression and impulsivity.

In this context, it has been suggested that assessment of the serotonin metabolite 5-hydroxyindolacetic acid (5HIAA) in the cerebrospinal fluid (CSF) could be used to assess serotonin turnover in the brain (Moir et al., 1970). Thus, reduced concentrations of 5HIAA in the CSF are thought to reflect central serotoninergic hypoactivity and a deficient serotonin system. However, many authors were unable to find a general association between low CSF–5HIAA concentrations and suicidal behavior. This is not surprising, since suicidality is a relatively inhomogenous behavior occurring...
in a very inhomogenous group of psychiatric patients and other subjects.

Some authors, therefore, suggested that a deficient serotonin system might not be related to suicidality in general but to certain types of suicidal behavior, e.g. violent suicide attempts or planned suicidal acts (Åberg et al., 1976; Träskman-Bendz et al., 1993, 1992; Mann et al., 1992).

Since many studies have shown a relationship between suicide attempts, classified in various ways, and some peripheral markers, these findings were perceived as evidence for a relationship between dysfunction of the serotonin system and suicidal behavior. However, even though many studies found some relations between selected aspects of the serotonin system and some sort of suicidal behavior, very few studies confirmed and, if so, only partially, the findings of previous studies. It seems that many conclusions drawn from these studies may be premature.

Suicidality, suicidal patients and suicidal acts can be broken down in many ways. It is not surprising that a statistically significant relationship between serotoninergic markers and some type of defined suicidal behavior can be found, as long as a broad range of subgroupings of suicidal behavior are tested statistically for associations with one serotoninergic parameter. It is remarkable to what extent this has become a common procedure in psychiatric research. Type 1 error could be one of the reasons why almost any study is able to present some form of evidence of an association between suicidal behavior and some peripheral indicators of a deficient serotonin system. It must be assumed that many of the reported statistically significant findings are simply coincidental.

2. Methods

To illustrate the methodological complexities mentioned in the introduction, several often quoted articles reporting associations between the serotonin system, suicidal behavior, aggression, impulsivity and depression will be reviewed in the following. A critical comparison of these articles will show that many constructs and concepts in biological suicide and aggression research need to be reconsidered.

It is not the aim of this article to review in a systematic and comprehensive way any existing studies in this area. On the contrary, we are selective in finding suitable examples to make our arguments understood.

3. Results

3.1. CSF–5HIAA in suicidal behavior

Many review articles reported on consistently reduced 5HIAA levels in the CSF of suicidal patients (Åberg, 1997; Mann, 1999; Mann et al., 1999; Brunner and Bronisch, 1999), impulsive and/or violent individuals (e.g. impulsive offenders and arsonists—Roy and Linnoila, 1988; Golden et al., 1991), but not in depressive individuals (Maes and Meltzer, 1995).

Some reviews suggested that a general association of low CSF–5HIAA concentrations with suicidality exists, while others found reduced mean CSF–5HIAA concentrations only in suicidal individuals with violent suicide attempts or highly planned suicide attempts.

Inconsistencies resulting from these conflicting observations deserve further attention since a confusing number of biological suicide studies with apparently contradictory findings contribute to a lack of clarity in biological suicide research.

3.1.1. Positive findings

In some studies, mostly with relatively small sample sizes, CSF–5HIAA was reduced in suicidal patients as compared to nonsuicidal individuals. However, most of these studies cannot be compared directly with each other due to differing definitions of suicidal behavior. As shown below, some studies examined patients immediately after a suicide attempt, while in others a history of suicidal behavior was sufficient for participants to be classified as ‘suicidal’ (Brown et al., 1982). In other studies suicidality was determined by item 3 of the Hamilton Rating Scale for Depression (HAM-D). Thus, because of small sample sizes and more or less arbitrary definitions of suicidality, it cannot be concluded that results of such studies, in fact, confirm other positive findings.
Oreland et al. (1981) found significantly lower CSF–5HIAA levels in 15 nondepressed non-violent suicide attempters compared to depressed patients and healthy volunteers. Jones et al. (1990) reported reduced CSF–5HIAA concentrations in 12 elderly suicide attempters compared to nonsuicidal patients and healthy controls irrespective of the method of the suicide attempt.

Brown et al. (1982) examined 12 patients with a diagnosis of a borderline personality disorder (BPD). Patients with a history of suicidal behavior \( (n=5) \) had lower CSF–5HIAA levels than patients without such a history.

Ninan et al. (1984) observed significantly lower CSF–5HIAA concentrations in eight suicidal schizophrenic patients compared to eight nonsuicidal schizophrenics.

Peabody et al. (1987) reported a negative correlation between 5HIAA and item 3 (suicidality) of the HAM-D in 37 male depressed patients. However, no information was given on the number of patients with a suicide attempt.

These studies are, to some extent, in contrast to other studies in which reduced CSF–5HIAA concentrations were found in violent suicide attempters, but not in non-violent suicide attempters (Träskman-Bendz et al., 1993; Banki et al., 1984).

3.1.2. Partially positive findings

Some studies published during the nineties showed associations between some characteristics of suicidal behavior and CSF monoamine metabolites. However, those studies mostly could not confirm observations of previous studies on correlations of CSF–5HIAA and other aspects of suicidality. These studies cannot simply be taken as further evidence of an association of a deficient serotonin system with suicidality according to the quoted studies of the eighties. In fact the more recent studies are in many aspects in contrast with previous studies even though some relationships between the serotonin system and suicidality could be demonstrated.

Mann et al. (1992) showed that suicidal individuals who had planned their suicide attempts intensively had significantly lower CSF–5HIAA levels than ‘low planners’. Severity of medical damage did not correlate with CSF–5HIAA levels. Mann et al. (1996) and Mann and Malone (1997) reported an association between CSF–5HIAA, degree of planning of a suicide attempt and medical damage. No relationship was found with the use of violent suicide methods, subjective intent of suicide and recency of suicide attempts. Since the suicidal patients were not compared to healthy controls, it remains unclear whether suicide attempters differed in their CSF–5HIAA concentrations from healthy individuals or not.

Cremniter et al. (1999) observed reduced CSF–5HIAA concentrations among 23 suicidal patients compared to 23 control subjects. This difference, however, was only due to the 14 impulsive attempters.

3.1.3. Negative findings

A considerable number of well-designed studies, including a relatively high number of suicidal individuals and a matched healthy and/or nonsuicidal control group, did not observe any difference in CSF–5HIAA concentrations between suicidal and nonsuicidal individuals (Roy-Byrne et al., 1983; Roy et al., 1985, 1990; Secunda et al., 1986; Gardner et al., 1990; Mann et al., 1996). These studies deserve attention, since studies with unequivocal results are scarce.

Roy-Byrne et al. (1983) did not find a significant difference in CSF–5HIAA concentrations of suicidal patients and nonsuicidal patients suffering from an affective disorder. They also did not find any relation between CSF–5HIAA concentrations and severity of the attempt, a possible explanation being the high proportion of bipolar patients among the patients that were examined.

Roy et al. (1985) could not demonstrate any statistical difference in CSF–5HIAA concentrations when comparing chronic schizophrenic patients with violent/non-violent suicide attempts and without suicidal behavior. This was confirmed by Lemus et al. (1990) in a smaller study. In 1986, Roy et al. were unable to find any difference in CSF–5HIAA concentrations between depressed patients with suicidal behavior, depressed patients without suicidal behavior and healthy controls. Similar results were obtained by Secunda et al. (1986) and once more by Roy et al. (1989) and Roy and Pollack (1994). In 1990, Roy et al.,
comparing alcoholics who had or had not attempted suicide with healthy volunteers, found no difference in CSF–5HIAA levels between the three groups. Alcoholics with violent suicide attempts did not differ in their CSF–5HIAA concentrations from alcoholics with non-violent attempts.

3.2. CSF–5HIAA and violent suicide attempts

Low levels of CSF–5HIAA have been associated with violent suicide attempts by a number of authors (Åsberg et al., 1976; Träskman et al., 1981; Träskman-Bendz et al., 1992; Banki et al., 1984). Beyond the fact that these observations could not be consistently reproduced by many others (Mann et al., 1992, 1996; Mann and Malone, 1997; Roy et al., 1985, 1990; Cremniter et al., 1999), it appears unlikely that any reliable conclusion about an association between low CSF–5HIAA concentrations and violent suicide attempts can be drawn based on the present data. First of all, most of the studies reporting an association between violent suicide attempts and low CSF–5HIAA concentrations had very small sample sizes (Table 1). Secondly, methodological problems (e.g. comorbidity of other psychiatric diagnosis) in many studies hinder attempts to draw valid conclusions as to an association of violent suicide attempts with low CSF–5HIAA concentrations. Thirdly, most authors fail to reproduce their observations consistently.

Åsberg et al. (1976) were the first to describe a bimodal distribution in CSF–5HIAA levels among depressed patients. Those depressed patients with a suicide attempt, especially those with violent attempts, were found significantly more often in the group with low CSF–5HIAA concentrations. It has been shown that CSF–5HIAA concentrations are negatively correlated with body height (Roy et al., 1990): men are usually taller than women and there was a very high proportion of males among violent suicide attempters in Åsberg’s sample. In their study (Åsberg et al., 1976) the impact of body height on the results was not controlled; thus the results could be explained by the high proportion of men among violent suicide attempters. The bimodal distribution reported by Åsberg et al. (1976) was not found in the other studies quoted below.

Banki et al. (1984) observed significantly reduced CSF–5HIAA concentrations in violent suicide attempters compared to nonsuicidal individuals. Non-violent attempters did not differ in their CSF–5HIAA concentrations from nonsuicidal patients in contrast to other studies in which a general relationship between suicidality and lower CSF–5HIAA concentrations was reported (Oreland et al., 1981; Jones et al., 1990).

Träskman-Bendz et al. (1992) studied CSF–5HIAA concentrations in 61 suicide attempters. They showed that the 18 violent suicide attempters significantly more often had CSF–5HIAA levels below the median.

In summary, the reported association between low CSF–5HIAA concentrations and violent suicide attempts is not robust. Published associations between low CSF–5HIAA concentrations and violent suicide attempts have been reproduced inconsistently. Furthermore, van Praag and Plutchik (1984) observed an association between violent suicide attempts and certain types of depressions irrespective of the severity of depression. Thus, it appears almost impossible to draw a valid conclusion whether reduced CSF–5HIAA concentrations in violent suicide attempters are related to violent suicide attempts or linked to certain types of depression. Also the impact of environmental factors (e.g. cultural background, availability of violent suicide methods) has to be considered. A valid statement on how many factors contribute to the setting of a suicide attempt appears hardly to be feasible. Thus, confounding factors make the association of violent suicide attempts with reduced CSF–5HIAA levels capricious. In addition, constructs such as ‘suicidality’ or ‘violent suicide attempt’ should be considered as endpoints of various different psychological and biological dysfunctions accompanied by various disturbances in neurotransmitter balance. From a logical point of view, it must be questioned whether an inhomogeneous group, i.e. suicidal individuals, with various psychological dysfunctions would share the same neurobiological changes.
<table>
<thead>
<tr>
<th>Author</th>
<th>Examined individuals</th>
<th>CSF–5HIAA/results</th>
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<tbody>
<tr>
<td>Åberg et al. (1976)</td>
<td>15 Depressed suicidal patients (6 violent/9 non-violent attempters)</td>
<td>In a bimodal distribution all violent attempters were found in the low level group (&lt;15 ng/ml)</td>
</tr>
<tr>
<td>Träskman-Bendz et al. (1993)</td>
<td>30 Suicidal patients; of these 8 violent attempters; 45 controls</td>
<td>Only violent attempters differed in CSF–5HIAA from controls (65.5 ± 11.2 vs. 103.6 ± 38.3 mmol/l)</td>
</tr>
<tr>
<td>Roy-Byrne et al. (1983)</td>
<td>45 Patients with affective disorder; of these 14 suicidal (7 with violent attempts)</td>
<td>No difference in CSF–5HIAA between nonsuicidal patients, violent and non-violent attempters</td>
</tr>
<tr>
<td>Banki et al. (1984)</td>
<td>52 Non-violent, 18 violent suicide attempters and 65 nonsuicidal psychiatric inpatients as controls (all female with different psychiatric diagnoses)</td>
<td>Lower CSF–5HIAA in violent attempters vs. non-violent attempters and nonsuicidal inpatients</td>
</tr>
<tr>
<td>Roy et al. (1985)</td>
<td>27 Suicidal schizophrenic individuals (7 violent attempters) vs. 27 schizophrenic nonsuicidal individuals</td>
<td>No difference in CSF–5HIAA between violent and non-violent suicide attempters and nonsuicidal controls (95.5 ± 18.1/112.8 ± 10.4/112.0 ± 9.1 pmol/ml)</td>
</tr>
<tr>
<td>Roy et al. (1990)</td>
<td>15 Non-violent/5 violent suicide attempters and 108 nonsuicidal controls (all alcoholics) and 30 healthy volunteers</td>
<td>No difference in CSF–5HIAA between violent and non-violent suicide attempters and nonsuicidal alcoholics and volunteers (111.9 ± 45.4/111.4 ± 48.2/9.5 ± 34.3/99.0 ± 40.0 pmol/ml)</td>
</tr>
<tr>
<td>Gardner et al. (1990)</td>
<td>17 Suicidal patients with borderline PD (3 violent attempts) and 17 normal controls</td>
<td>No difference between suicide attempters and controls irrespective of degree of violence (103.6 ± 32.0 vs. 88.1 ± 33.8 pmol/ml)</td>
</tr>
<tr>
<td>Träskman-Bendz et al. (1992)</td>
<td>18 Violent suicide attempters vs. 43 non-violent attempters; all with various psychiatric diagnoses</td>
<td>Patients with violent suicide attempts more often had CSF–5HIAA levels below the median than non-violent attempters</td>
</tr>
<tr>
<td>Mann et al. (1996)</td>
<td>30 Non-violent-, 16 violent suicide attempters and 21 nonsuicidal psychiatric inpatients</td>
<td>No difference in CSF–5HIAA between nonattempters and suicide attempters (103.3 ± 33.3 vs. 112.0 ± 35.7 pmol/l); no difference between violent and non-violent/non-attempters (data not shown)</td>
</tr>
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Table 1 (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Examined individuals</th>
<th>CSF–5HIAA/results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mann and Malone (1997)</td>
<td>16 Non-violent and 6 violent suicide attempters</td>
<td>No difference in CSF–5HIAA between violent and non-violent suicide attempters (94.5 ( \pm ) 25.3 vs. 111.4 ( \pm ) 27.9 pmol/l)</td>
</tr>
<tr>
<td>Cremniter et al. (1999)</td>
<td>23 Violent suicide attempters, 14 classified as impulsive and 9 as non-impulsive, 23 healthy controls</td>
<td>Impulsive violent suicide attempters but not non-impulsive violent suicide attempters had lower CSF–5HIAA levels compared to healthy controls (51 ( \pm ) 41.9/92.4 ( \pm ) 47.3/107.3 ( \pm ) 57.5 nmol/l)</td>
</tr>
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</table>

3.3. Suicide attempt characteristics and psychiatric diagnosis

Many individuals attempting suicide by so-called violent means were diagnosed as being depressed. Van Praag (1997) has shown that violent suicide attempts are associated only with certain types of depression; calls into question the general attribution of reduced CSF–5HIAA concentrations to ‘depression’ or ‘violent suicide attempt’ (see also Maes and Meltzer, 1995). On the other hand, it has been reported that suicide attempters experience a cathartic effect after a suicide attempt that can mask a preexisting depression (Van Praag et al., 1997). Consequently, it is extremely difficult to decide whether a suicide attempter was suffering from depressive symptoms before a suicide attempt or not. Furthermore, there are suggestions that the nosological construct of ‘depression’ might not be very useful in biological psychiatry (Van Praag, 1997, 1998, 2000).

In 1981, Träskman et al. had reported reduced CSF–5HIAA levels in 30 suicide attempters (22 non-violent and 8 violent attempters, 8 of whom were depressed and 22 nondepressed) in comparison with 45 controls. The authors found significantly reduced CSF–5HIAA levels in suicide attempters as compared to controls. This difference was due to the low CSF–5HIAA levels of the violent suicide attempters and the depressed suicide attempters. Nondepressed and non violent suicide attempters did not differ statistically from the controls. This would suggest that low CSF–5HIAA levels are not associated with suicidal behavior per se but rather with violent suicide attempt and depression. However, the subdivision of suicidal patients into depressed and nondepressed patients is based on a doubtful definition of depression. Patients were classified as ‘depressed’ on a depression inventory and a depression scale based on a comprehensive psychopathological rating scale. Nevertheless, depressive symptoms were common among the patients classified as being nondepressed. The other patients received a diagnosis of personality disorder \((n = 12)\), anxiety state \((n = 7)\), manic-depressive illness \((n = 1)\) and minor depressive illness \((n = 2)\). Thus, from this study no reliable conclusion can be drawn whether CSF–5HIAA concentrations are associated with violent suicide attempts or rather with contaminating factors.

Lidberg et al. (1985) examined CSF–5HIAA concentrations in 22 suicide attempters, 15 murderers and 39 healthy control subjects. The mean CSF–5HIAA concentration in the group of suicidal patients was significantly lower than in the control group. However, 50% of all suicidal patients had a diagnosis of depression, and it was not controlled whether the reduced CSF–5HIAA level in this group was due to the depressed patients.

Similar results were observed by Banki et al. (1984), who studied CSF monoamine metabolites in 135 female psychiatric patients. They found significantly reduced CSF–5HIAA concentrations in violent suicide attempters compared to nonsuicidal individuals of the same diagnostic category. Non-violent attempters did not differ in their CSF–5HIAA concentrations from nonsuicidal patients. Violent suicide attempters, however, were usually
Table 2
CSF–5HIAA studies in aggressive individuals and possible confounding variables

<table>
<thead>
<tr>
<th>Author</th>
<th>Examined individuals</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown et al. (1979)</td>
<td>26 Military men with personality disorders</td>
<td>Negative correlation of CSF–5HIAA with aggressive behavior. Impulsive individuals scored higher in aggression scales</td>
</tr>
<tr>
<td>Brown et al. (1982)</td>
<td>12 Patients with bipolar disorder</td>
<td>Negative correlation of CSF–5HIAA with aggressive behavior and suicidality</td>
</tr>
<tr>
<td>Lidberg et al. (1985)</td>
<td>15 Murderers, 22 suicidal patients and 39 healthy volunteers</td>
<td>Only murderers who had killed a sexual partner ($n = 5$) had lower CSF–5HIAA levels than controls and suicidal individuals</td>
</tr>
<tr>
<td>Limson et al. (1991)</td>
<td>57 Male alcoholics and 15 male controls</td>
<td>Negative correlation of CSF–5HIAA with aggressive behavior in alcoholics but not in controls</td>
</tr>
<tr>
<td>Gardner et al. (1990)</td>
<td>17 Patients with BPD and 17 healthy controls</td>
<td>No association of CSF–5HIAA with aggressivity or depression</td>
</tr>
<tr>
<td>Coccaro et al. (1997)</td>
<td>24 Individuals with personality disorder</td>
<td>No association of CSF–5HIAA with aggressivity</td>
</tr>
<tr>
<td>Coccaro et al. (1998)</td>
<td>26 Individuals with personality disorder</td>
<td>No association of CSF–5HIAA with aggressivity</td>
</tr>
<tr>
<td>Lidberg et al. (2000)</td>
<td>35 Homicide offenders and 35 healthy controls</td>
<td>No difference in CSF–5HIAA concentrations between offenders and controls</td>
</tr>
<tr>
<td>Stanley et al. (2000)</td>
<td>35 Aggressive and 29 nonaggressive psychiatric inpatients</td>
<td>Aggressive individuals had significantly lower CSF–5HIAA concentrations and scored significantly higher in impulsivity ratings</td>
</tr>
</tbody>
</table>

more depressed than the other patients. It must be noted that the number of violent suicide attempters in all diagnostic categories was in the range of three to six patients. Banki et al. (1984) underlined the considerable overlap of the values in all subgroups.

In summary, no convincing evidence has been found that low CSF–5HIAA is associated with suicidality per se. Studies on violent suicide attempters disregarded the fact that violent suicide attempters often had more depressive symptoms than non-violent suicide attempters. It remains an unsettled issue whether changes in serotonin neurotransmission might be related more closely to certain depressive symptoms or to suicidal behavior. Further research in this area is needed before any valid conclusion can be drawn.

### 3.4. CSF–5HIAA in aggressive individuals

The association of aggressive behavior and CSF–5HIAA concentrations has been studied in only a few studies. An association between aggression and CSF–5HIAA concentration has been reported inconsistently in various studies, leaving the potential relationship between aggressive behavior and CSF–5HIAA levels unclear (Table 2).

Biological suicide research is linked to biological aggression research since suicidal behavior has often been equated with so-called autoaggressive behavior. Thus, from biological suicide studies it has been concluded backwards that individuals with low CSF–5HIAA concentrations are prone to auto- and hetero-aggressive behavior (Ninan et al.,
1984; Stanley et al., 2000; Åsberg et al., 1987; Coccaro, 1989; Plutchik et al., 1989; Apter et al., 1990, 1993; Kotler et al., 1993; Markowitz and Coccaro, 1995; Corruble et al., 1999). Indeed, it would appear rather conclusive if the same changes in CSF–5HIAA concentrations observed in suicidal individuals could be found in aggressive individuals as well.

This interesting concept, however, is not well validated by the existing studies due to various conceptual vaguenesses. In our view, the term ‘aggressivity’ is often not well defined and not unambiguously discriminated from ‘impulsivity’. In the studies reviewed in this article, aggressive behavior is often associated with further psychological dysfunction (e.g. personality disorders, depressive symptoms, alcohol abuse). Thus, several studies reporting reduced CSF–5HIAA concentrations in aggressive individuals observed disturbances in impulse control, alcohol abuse or depressive symptoms in these subjects as well. As a result, no clearcut conclusion can be drawn from existing studies as to which of these psychological dysfunctions an observed dysregulation in CSF–5HIAA concentration of aggressive subjects can be attributed. This makes any postulated relationship of reduced CSF–5HIAA levels and aggressivity speculative.

The terms ‘aggression’ and ‘autoaggression’ are simply the result of an effort to embrace and label some sorts of behavior that appear to have aspects of similarity. However, the question arises whether behavioral analogies on the basis of arbitrary classifications (by labelling them ‘aggressive’ or ‘autoaggressive’ behavior) can be reflected by biological correlates.

Brown et al. (1979) reported a negative correlation between history of aggression and CSF–5HIAA concentrations in 26 military men. Those individuals with a diagnosis of personality disorder, which is generally associated with behavioral impulsivity, were significantly more aggressive and had significantly lower CSF–5HIAA concentrations than the subjects with a type of personality generally associated with less behavioral impulsivity.

In 1982, Brown et al. examined 12 patients with bipolar disorders. Again, they found a negative correlation between history of aggression and CSF–5HIAA concentrations. A similar negative correlation between a lifetime history of aggression scale and CSF–5HIAA was observed by Limson et al. (1991), who compared 57 male alcoholics and 15 healthy volunteers. However, the total group of alcoholics scored significantly higher in the aggression scales than the control subjects whereas their mean CSF–5HIAA concentration was even higher than in healthy controls (not significant).

The observations of Brown et al. (1979), Brown et al. (1982) and Limson et al. (1991) were not confirmed by Gardner et al. (1990) or Coccaro et al. (1997, 1998).

Lidberg et al. (1985) reported that murderers and suicidal patients had significantly lower CSF–5HIAA levels than healthy controls. But only those murderers who had killed a sexual partner had low CSF–5HIAA levels, while the others did not. Furthermore, 10 of the offenders were severe alcoholics and it was not controlled if this could have influenced the results. These findings are hard to interpret and do not present convincing evidence of an association of CSF–5HIAA with aggressive or impulsive behavior, especially since Lidberg et al. (2000) were unable to reconfirm their observations.

Stanley et al. (2000) observed significantly lower CSF–5HIAA levels in 35 (23 m/15 f) nonsuicidal, aggressive psychiatric patients than in 29 (12 m/17 f) nonsuicidal, nonaggressive patients. However, since the aggressive individuals were usually more impulsive than the nonaggressive individuals, no valid conclusion can be drawn about whether low CSF–5HIAA levels are associated with aggression, impulsivity or possibly both. Interestingly, CSF–5HIAA concentrations did not correlate with patients’ scores on any impulsivity or aggression scale. Recently, Placid et al. (2001) reported a lack of correlation between lethality of suicide attempt and lifetime aggression scores of suicide attempters but a negative correlation between both variables in female attempters. Because women were less aggressive than men and the aggression scores were found to be negatively related to 5HIAA concentration in the total group, it can be assumed that female high-lethality
attempters were more frequently in the higher range of the distribution for 5HIAA and had, on average, lower aggression scores. Against this background, the conclusion of Placidi et al. (2001) that lower CSF–5HIAA concentration is independently associated with the severity of lifetime aggressivity and a history of a higher lethality suicide attempts is not conclusive. The findings might be influenced by gender ratio, presence of borderline personality disorder, and ethnicity (Franke et al., 2002).

Thus, the hypothesis that suicidality can be interpreted generally as a disturbance in aggression control must be considered as lacking strong support.

The interpretation of suicidal behavior as autoaggression appears to be an oversimplification, which cannot be attributed to suicidal individuals in general and is so far unproven. In this context the notion of ‘suicidality’, which is attributed to suicide completers, suicide attempters and even to individuals with suicidal thoughts, requires critical reflection. There are several indices that suicide completers were often not very aggressive in contrast to suicide attempters. Mann (1987) reported that suicide attempters with a high intention to die were not very aggressive, while suicide attempters with a low intention to die were more aggressive. Simply dichotomizing suicide attempts into violent and non-violent attempts according to the method used does not allow a valid statement about the existence of autoaggressive impulses or the intention to die (Van Praag et al., 1997). This issue has been discussed in more detail elsewhere (Müller-Oerlinghausen and Roggenbach, 2002). Many suicide gestures including those with an appearance of much violence (especially when rescue is assured) only marginally qualify as autoaggressive impulses. The enormous difficulties to assess the individual suicide risk reliably are well known, indicating that all suicide studies are contaminated by an unknown number of individuals without any suicidal intention at all.

In our view, it is not surprising that in various studies impulsivity and aggressivity were not associated with suicidal behavior per se (Jones et al., 1990) or with its severity (e.g. dangerous vs. non-dangerous suicide attempts. Mann et al., 1996; Mann and Malone, 1997). At present, neither the hypothesis that suicidality can be interpreted as autoaggressive behavior nor that individuals suffering from a poor aggression control have reduced CSF–5HIAA concentrations, is sufficiently supported by the existing studies. Other authors, e.g. Mitsis et al. (2000) and Balaban et al. (1996), formed similar conclusions based on a thorough review of the literature.

The constructs of ‘suicidality’ and ‘aggressivity’ are too vaguely defined for biological psychiatric research. It seems that new concepts are needed for any true progress in biological suicide and aggression research.

3.5. CSF–5HIAA in impulsive individuals

Studies on patients with poor impulse control seem to be the most promising scientific approach. However, as already mentioned, substantial problems exist in defining impulsivity and to discriminate impulsive behavior from aggressive behavior. Known confounding factors (e.g. alcoholism, depressive symptoms, aggressivity) possibly affected the outcome of such studies, further research in this area is warranted.

Linnoila et al. (1983) found lower CSF–5HIAA levels in 27 impulsive violent offenders than in 9 violent offenders who premeditated their suicidal acts.

Virkunnen et al. (1987) examined 20 mostly non-violent male arsonists, 20 male violent offenders, and 10 healthy volunteers: the CSF–5HIAA concentration in the group of arsonists was significantly lower compared to violent offenders and healthy controls. The CSF–5HIAA concentration in the group of male offenders was also significantly lower than in the control group. The authors concluded that low CSF–5HIAA concentrations are associated with poor impulse control. However, most of the arsonists and all the violent offenders fulfilled the criteria for alcohol abuse, which must be taken into account as a possible explanation for the lowered CSF–5HIAA concentration. While 85% of all arsonists fulfilled the criteria for a
dysthymic disorder, this held true for only 35% of the violent offenders. Since it was reported that many of the violent offenders had other, less severe violent crimes in their criminal record, it can be speculated that those violent offenders were suffering from poor impulse control as well. Thus, the low CSF–5HIAA levels in the group of violent offenders and arsonists possibly were related to alcohol abuse and, especially in the group of arsonists, to the coexistence of depressive symptoms.

Lidberg et al. (2000) found a lower mean CSF–5HIAA concentration in homicide offenders with a diagnosis of an impulse control disorder (n = 9) compared to offenders without this diagnosis (n = 26). However, CSF–5HIAA levels did not correlate with the impulsivity rating scale (EPQ) indicating the difficulty of identifying impulsivity reliably with psychological procedures.

Cremniter et al. (1999) observed significantly reduced mean CSF–5HIAA levels in 14 impulsive suicide attempters compared to 23 healthy controls and nine non-impulsive suicide attempters. Eight impulsive suicide attempters had a diagnosis of a personality disorder and five of alcohol abuse, while in the group of non-impulsive suicide attempters, none had a diagnosis of a personality disorder and only one patient had shown alcohol abuse. Thus, confounding factors existed that might have influenced the results.

Coccaro et al. (1997, 1998), did not find any relationship between impulsivity or aggression and CSF–5HIAA levels.

Findings from these studies in many ways contrast with those from other 5HIAA studies. Where are these differences to be located? Low CSF–5HIAA concentrations often have been associated with violent and more serious (e.g., more lethal) suicide attempters. Irrespective of suggestions that violent suicide attempts are not more dangerous than non-violent suicide attempts (Van Praag et al., 1997), completed suicides tend to be carefully planned and not a matter of impulsivity (Montgomery and Montgomery, 1982; Mann, 1987; Klerman, 1987; Mann and Arango, 1992; Plutchik, 1995). This would imply that suicide completers (certainly the most extreme form of suicidal behavior) in general do not suffer from poor impulse control. This could be one of the reasons why approximately 85% of all suicide completers succeed in their first attempt (Duckworth and McBride, 1996; Felber, 1993). In contrast, impulsive suicide attempts are often not very dangerous, and impulsive suicide attempters have mostly a rather low intention to die. Verkes et al. (1998) studied multi-impulsive individuals after a suicide attempt and observed a low suicide intention and a low degree of planning. If it were verified that the serotonin system is rather associated with impulse control than with the construct of ‘suicidality’, then markers of the serotonin system would not be a useful tool to identify individuals at high risk of completing suicide. On the other hand, such markers might be helpful to identify individuals with poor impulse control and consequently at high risk of repeating suicide attempts or crimes (Lidberg et al., 1997).

However, all the reports indicating an association between reduced CSF–5HIAA concentration and impulsivity are weakened by the same methodological problems found in suicide studies. The existing preliminary findings have to be replicated by carefully designed studies before any reliable conclusions can be drawn.

### 3.6. Methodological shortcomings in assessment of CSF–5HIAA: the role of confounders

Growing evidence exists that several factors have an important impact on the assessment of CSF–5HT and its metabolite. Factors like age, sex, season, body height, premedication, length of washout period, and amount of exercise before lumbar puncture might influence study results (Banki et al., 1981; Gjerris et al., 1987; Åsberg, 1997; Hartikainen et al., 1991). While there is general agreement that medication can influence the CSF–5HIAA concentration, various studies still differ in terms of washout period (7 days to 2 weeks) and medication allowed during the washout period. The comparability of various studies is additionally limited by the amount of fluid drawn for assessment, and the subject’s position during lumbar puncture. However, there is still ongoing debate which clinical variables possibly influence CSF–5HIAA measures. For example, Coccaro et
al. (1997) found a negative association between age and CSF–5HIAA and only controlled the results for this specific variable. Linnoila et al. (1983) and Peabody et al. (1987) reported no correlation between CSF–5HIAA and age, while Roy et al. (1990) observed a positive correlation between CSF–5HIAA and age and a negative correlation with height. Role of height is potentially significant since male suicidal individuals more often attempt suicide by violent means. Thus, an uncontrolled proportion of male individuals among violent suicide attempters might explain the often observed lower CSF–5HIAA concentrations in the latter population.

Some studies have not been controlled for any of these important confounders (Roy et al., 1986), while others have only been controlled for age and gender (Åsberg et al., 1976; Brown et al., 1979), age (Cremniter et al., 1999), gender (Oreland et al., 1981) or height (Gjerris et al., 1987).

Studies that considered all these factors, possibly contributing to abnormalities in CSF–5HIAA concentrations in psychiatric patients, are rare. Thus, it can be concluded that various changes in CSF–5HIAA levels that have been reported in psychiatric patients compared to controls are, at least partially, due to contaminating differences of patient variables between the groups.

4. Conclusions and summary

It was the aim of this short review to rediscuss common concepts of present biological suicide research. Two major problems were addressed. First of all, various factors have an important impact on CSF–5HIAA concentrations. The impact of age, height, sex, premedication, washout period and possibly season should be further assessed and clarified. Study samples are often too small for reliable conclusions. Carefully designed studies with larger sample sizes are urgently needed.

Secondly, beyond methodological problems, we pointed to difficulties in accepting the view that the common constructs of ‘suicidality’ and ‘aggression’ are suitable for biological suicide research (see also Müller-Oerlinghausen and Roggenbach, 2002). Various psychological dysfunctions can result in ‘suicidal behavior’, while the performance and outcome of a suicide attempt are obviously influenced by environmental factors. Since an unambiguous relationship between CSF–5HIAA concentrations and suicidality has not been shown, neither in general nor with subgroups of suicidal behavior, it must be assumed that a suicidal act is not necessarily associated with peripheral indicators of serotonergic neurotransmission. Certain psychological dysfunctions that eventually lead to suicidal behavior might be more closely related to disturbances in 5HT metabolism. Fawcett et al. (1997) suggested a ‘four dimensional pathway’ leading to suicidality (anxiety, agitation, hopelessness, severe anhedonia, and trait impulsiveness associated with low brain serotonin turnover). We agree with Fawcett et al. that the postulated association between low brain serotonin turnover and impulsivity appears to be a promising approach. However, this interesting concept lacks specificity to identify suicidal individuals. Nevertheless, the hypothesis of a deficient serotonin system, possibly in a subgroup of suicidal individuals (e.g. suicidal individuals with impulse-control disturbances) remains heuristic and attractive. In speculating that a low brain serotonin turnover is unrelated to a specific psychiatric diagnosis and associated with impulsivity and that some impulsive individuals are prone for a behavior has been created for which the term ‘suicidality’, we could forward a more satisfactory explanation of why indices for a dysregulation of brain serotonin turnover can be found in individuals with various psychiatric diagnoses, even when they are not suicidal. Many arguments discussed in this article would speak for leaving the classical though vague concept of ‘suicidality’ in neurobiology and turning to possibly more promising constructs. These arguments are summarized below:

(1) The association between low CSF–5HIAA concentration and suicidality, expressed as suicide attempt in the index illness period or as lifetime suicide attempts, is weak. Most studies did not find a general relationship between suicidality and CSF–5HIAA concentration. Many studies in which a relationship between some suicide attempt characteristics and reduced CSF–5HIAA levels was observed are inconsistent with other studies.
Violent suicide attempts are probably not related to low CSF–5HIAA concentrations. An association between violent suicide attempts and certain depressive symptoms or certain types of depression might be more likely.

(3) Suicidal individuals with reported low CSF–5HIAA concentrations often have comorbid psychiatric diagnoses (e.g., depression or depressive symptoms, schizophrenia, personality disorder, and alcoholism) that make any general attribution of reduced CSF–5HIAA concentrations to ‘suicidality’ hazardous.

(4) The hypothesis that suicidality could be interpreted as autoaggressive behavior is doubtful and not warranted by the studies reviewed above.

(5) The constructs of suicidality, subtypes of suicidal behavior and aggressivity possibly do not possess a specific neurobiological correlate. Other constructs are needed.

(6) Various studies do not consider sufficiently the impact of confounding patient variables on CSF–5HIAA measures. Reported abnormalities in CSF–5HIAA concentrations might be explained by methodological shortcomings.

References


