Neurobiological aspect of suicide;

A review of low cerebrospinal 5- hydroxyindoleacetic acid concentration and prediction of suicidality

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Abstract

Finding an indicator that can point to a high risk group for suicide has long been a desirable aid for the prevention of completed suicides. The studies reviewed in this essay presume that a biological aspect can point out the high risk individual. The focus of the studies lies on the serotonin 5-hydroxytryptamine (5-HT) monoamine neurotransmitter and cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) which is the principal metabolite of 5-HT in depression. The studies on 5-HT metabolites have led to the belief that these may play a key role in the neurochemistry of suicidal behaviour. It is suggested that the core behavioural effect of low CSF 5-HIAA concentration might result in an increase in impulsive and violent behaviour to self and others. The predictability is based on the fact that patients with low CSF 5-HIAA are more prone to reattempt and complete suicide by violent means. A number of well-designed studies concerning suicidal individuals and control subjects have however not shown any difference in concentration of CSF 5-HIAA in suicide attempters compared to non-suicide attempters which could be explained by methodological flaws. Low CSF 5-HIAA does seem to characterize the high risk individual, but it is not yet determined what role it plays in actual suicidality.

Keywords: CSF 5-HIAA, Suicide attempts, suicide, serotonin, 5-hydroxyindoleacetic acid, depression, neurobiology of suicide.

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1 Introduction

Completed suicide attempts are responsible for one death every 40 seconds according to the mappings of death-causes around the world conducted by the World Health Organisation (WHO) (see appendix 2). It is one of the most significant public health issues in both western and eastern countries. Clinical depression affects about 7% - 18% of the population on at least one occasion in their lives before the age of 40 (Bland, 1997). Individuals suffering from clinical depression are in a high risk group of suicide, and the frequency of self-injurious behaviour among such individuals is high (Åsberg, Träskman & Thorèn, 1976). Though the numbers point to a higher frequency of suicide in patients suffering from depression, it is far from the majority amongst those that complete suicide attempts (Åsberg et al., 1976).

Finding an indicator that can point to a high suicide risk group has long been a desirable aid for the prevention of completed suicide. Such an indicator would benefit the people with high risk immensely. The more knowledge we have of the processes behind our cognitive and neurological processes that lead to suicidal behaviour, the better equipped we would be to search for the right treatment and proper medication that can match up to the disease.

Explanations for suicidal behaviour have traditionally been searched for in psychological and sociological realms. Intentional self-harm has been conceived as exclusively human behaviour, and classical sociologists have been reluctant to integrate biological variables in their models for suicidal behaviour (Åsberg & Forslund, 2000). Identifying the potentially suicidal individual using demographics, social, developmental and psychological factors has, nevertheless, offered too vague of a prediction to be substantial in clinical utility (Stoff & Mann, 1997).

The biological component has received very little attention until the rapid emergence of an association between biological variables and suicide in research literature (Åsberg & Forslund, 2000). The rise of such ideas has been mainly dependant on the discovery of links between suicide and psychiatric illnesses, such as depression (Åsberg & Forslund, 2000; Stoff & Mann, 1997). The studies conducted by empirical measures all hold the belief that a biological perspective, which is expanding more and more into a biochemical realm, is a promising approach to finding a high risk group that will complete their suicides. The aim of the researchers is that understanding the neuroscientific substrates of suicidal behaviour will lead to increased predictability in individuals with high risk for completed suicide (Stoff & Mann, 1997).

The main focus of neuroscience in the neurobiology of suicide is to create a map of the cognitive functions of the brain and discover how such cognitive processes can relate to neurochemistry and our inner mental states that cause self-injurious behaviour. The two main strategies in the study of neurobiology in suicide are neurodoctorine challenges and neurotransmitters. In this essay the main focus will be on neurotransmitters, mainly serotonin. The majority of clinical neurobiological studies of suicide are concentrated on the serotonin [1]5-hydroxytryptamine monoamine neurotransmission, abbreviated 5-HT. The 5-HT monoamine neurotransmission has a key role in behaviour displayed in humans and other species, such as impulsivity and aggression. This is due to the 5-HT systems' characteristics; they are the signal mediator for the effects of serotonin which is a powerful functional distributor of mood sensitivity.

The studies reviewed in this essay focus on the 5-HT functions and suicide. More specifically, I will concentrate on studies of the cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) which is the principal metabolite of 5-HT in depression

[1]Further explanations of words and terminologies that are marked in italics can be found in a glossary in the appendix. It is marked Appendix 3.

(Träskman-Bendz, Asberg, Bertilsson & Thoren, 1984). The studies presented here focus on the possibility of 5-HIAA being a biological suicide predictor (e.g. Åsberg & Forslund, 2000; Edman, Åsberg, Lavander & Schalling, 1986; Faustman, Ringo & Faull, 1993; Lidberg, Åsberg & Sundqvist-Stensman, 1984; Meltzer, Perline, Tricou, Lowy & Robertson 1984; Samuelsson, Nordström & Åsberg, 2006). Regardless, as suicide is often linked to depression, I will first clarify the relationship between depression and suicide.

2 Serotonin and depression

Over three decades of research and clinical observation have implicated that there is a correlation between serotonin neurotransmission disturbance and mood disorders, e.g., major depression (Stockmeier, 1997). Early evidence for the relationship was established with antidepressant treatments. First, therapeutic action of imipramine and tranylcypromine was demonstrated in depressed patients. Second, treatment with parachlorophenylalanine (PCPA), an inhibitor of tryptophan hydroxylase (TrpOH), caused a fast relapse in depressed patients responding well to imipramine and other forms of antidepressants (Stockmeier, 1997). In a study by Delgado et al. (1990), fluoxetine and flavoxamine, antidepressants specific in Selective Serotonin Reuptake Inhibition (SSRI's), were studied for correlates of serotonin and depression. Plasma levels of tryptophan, the amino acid precursor of serotonin, were experimentally decreased in depressed patients who had clinically responded to SSRI medication. Majority of the patients suffered a relapse and gained back their depressive symptoms. This relapse coincided with a decrease in serum tryptophan, and in turn a decrease in serotonin levels (Stockmeier, 1997).

Serotonergic neurotransmission has been accessed in suicide and depression by measuring receptors for serotonin in post-mortem tissue samples of the forebrain (Bachus, Hyde, Akil, Weickert, Varwter & Kleinman, 1997; Stockmeier 1997). It is hypothesized that

the diminished serotonergic activity in the forebrain is the cause of depressive symptoms and suicidal behaviour (Stockmeier, 1997).

Structural neuroimaging, such as Magnetic Resonance Imaging (MRI) and computerized tomography (CT) scans, of live patients suffering from depression have reported grave morphological abnormalities. In a study performed on 16 post-mortem brains by Rajkowska (1997) there were differences between the cortical structures of suicide patients compared to controls. Neurochemical studies demonstrated altered numbers of monoamine receptors in the prefrontal cortex (PFC), more specifically there was a reduction of PFC gray and white matter volume. This leads to the dysfunction of the PFC in neuropathology of suicide victims. This indicated that serotonin uptake deficiencies can affect the structure of the PFC and it would explain the mood regulatory disorders associated with depression.

2.1 CSF 5-HIAA and 5-HT

Most 5-HT studies of suicide attempters have demonstrated abnormalities in 5-HT neurotransmission (Stoff & Mann, 1997). High risk of suicidality has been strongly correlated with the low concentration of 5-hydroxyindoleacetic acid in the cerebrospinal fluid (e.g. Åsberg & Forslund, 2000; Edman et. al, 1986; Faustmam et al., 1993; Lidberg et al., 1984; Meltzer et al., 1984; Samuelsson et al. ,2006). The studies on 5-HT monoamine neurotransmitters have led to the belief that these monoamine neurotransmitters play a key role in the neurochemistry of suicidal behaviour.

According to extensive studies (e.g. Edman et. al, 1986; Faustman et al., 1993; Lidberg et al., 1984; Meltzer et al., 1984; Samuelsson et al., 2006 ; Roy, Lamparski, De Jong, Adinoff, Ravitz, George & et al., 1990), CSF 5-HIAA could be the central component in determining a biological aspect of suicide predictability. Majority of the studies have found a positive correlation between low concentration of 5-HIAA in the CSF and suicidal behaviour.

There are hypotheses about the causal relationship between low CSF 5-HIAA and the occurrence of suicidality. Live and post-mortem studies on suicide victims have provided a model for the anatomy of suicidal behaviour in the brain. “Affected” and “unaffected” regions of the brain that differ between suicide committers and controls have been identified (Arango, Underwood & Mann, 1997). The level of CSF 5-HIAA concentration should be over 92.5 nmol/l [2] or 15 ng/ml (depending on the measurement chosen) in an entire sample of the CSF for the patient, and if the levels are below the median, the patient is considered to be in the “low concentration” group, meaning that they are in the “high” risk group (Nordström, Samuelsson, Åsberg, Träskman-Bendz, Åsberg-Wistedt, Nordin & et al., 1994).

Low concentration of 5-HIAA in the CSF may be caused by deficits in the uptake of serotonin (Nordström et al., 1994). Alterations in neurotransmitter and neuromodulator receptor density could play an important role in the neurobiological basis of suicide (Bachus et al., 1997). One of the plausible causes of low concentration of CSF 5-HIAA can be explained by a deficit in platelet markers (Åsberg & Forslund, 2000). However, the link between CSF 5-HIAA level, depression and suicidality is not clear: no significant correlation between CSF 5-HIAA concentration and depression has been found. CSF 5-HIAA levels in healthy controls and clinically depressed patients do not differ, that is, there is no correlation between severity of depression and CSF 5-HIAA values (Edman et al., 1986; Åsberg, 1997).

2.2 Low CSF 5-HIAA as and indicator of suicide risk after attempted suicide

Despite scientific and medical advancement in our society that can provide a biological aspect of suicidal behaviour, clinical assessment is still complicated by one particular fact; the

[2] The expressions of the units vary in the essay due to the expressions chosen by the different authors in the original articles. In some articles the measurements are expressed in pmol/l and ng/ml as well. All of them are compatible to each other.

suicidal urge within an individual is clearly state dependant to some extent (Nordström et al., 1994). Predicting mortality is challenging, as there are many factors that have to be taken to consideration. The psychological measurements scales can only manifest a few and narrow hits and predictions that can be of use, therefore these are mixed with the biological predictors, one of them being the serotonin metabolite CSF 5-HIAA (Samuelsson et al., 2006). Nevertheless, according to extensive studies (e.g. Edman et al., 1986; Lidberg et al., 1984; Meltzer et al. , 1984; Nilsen, Goldman, Virrkunen, Tokola, Rwalings & Linnolia, 1994; Samuelsson et al., 2006) the most probable candidate for suicide prediction seems to be CSF 5-HIAA. Next, I will review the studies conducted on this issue.

In an early study by Åsberg et al. (1976), an attempt to investigate further into the serotonin and 5-HIAA hypothesis gave great results. Åsberg et al. (1976) studied 68 depressed psychiatric patients and their levels of CSF 5-HIAA. Patients were all free from brain injuries, schizophrenia and drug/alcohol abuse. Patients were divided into two samples. The first 43 patients were put in sample 1, classified as endogenous depressive (n = 27) or reactive depressive (n = 16) this according to clinical criteria. The Diagnostic Inventory was used to classify the remaining 25 patients in to endogenous (n = 17) or reactive (n = 8). The severity of depression was assessed in both samples along with suicide risk.

Lumbar puncture was performed according to standard clinical procedure (see details of lumbar puncture in Appendix 1) (Åsberg et al., 1976).The distribution of CSF 5-HIAA was bimodal. Twenty patients (29%) had level below 15 ng/ml. This classified them in to a lower mode. 15 patients tried to commit suicide during the index illness period. The suicidal act in relation to CSF 5-HIAA was significant. Eight patients within the low group (40%) and seven within the high (15%) had made one or more suicide attempt during the indexed illness period.

The study in large showed that although severity of depression may not play a key role in suicidal behaviour, there is a significant difference in-between the two groups of high versus low concentration CSF 5-HIAA, and that it could serve as a predictor that can identify high risk individuals and in that prevent suicides. The patients studied who had been more vulnerable to suicide during the experiment also were among those who had employed very violent and impulsive methods in attempting suicide.

The results started a discussion: could violence or impulsion actually be the main result of low CSF 5-HIAA concentration, and therefore be the indirect cause for that specific group of individuals to be more prone to have suffer from suicidal behaviour (Åsberg et al., 1976). The issue of violence and suicidality will be discussed further in section 3.

In a study by Roy, De Jong & Linnolia (1993), 22 patients suffering from depressive illness were studied under a follow up period of five years. Out of the 22 followed, 17 had tried to commit suicide within the five year follow-up period. All of these had a lower concentration of CSF 5-HIAA than those that had never attempted to commit suicide. Six patients had tried to commit suicide more than once, and in turn, those six were the ones with the lowest CSF 5-HIAA concentration within whole group.

Also in a prediction study by Nordström et al. (1994), a correlation between low CSF 5-HIAA concentration and completed suicides was shown. In this study, 92 psychiatric mood disorder inpatients, admitted shortly after attempting a suicide, clear results were shown of a high risk group. Fourteen patients committed suicide, meaning that over all mortality was 15% during an average of six years. The overall mortality of patients within the first year of lumbar puncture was 15% (fourteen out of 92). Majority, 11 out of 14 (79%) of the patients who committed suicide did so within the first year after lumbar puncture, seven out of 14 completed their attempts early, their suicides were completed within first three months of indexed suicide attempt. The lowest CSF 5-HIAA was found in suicide completers.

(Nordström et al., 1994). Below-the-median CSF 5-HIAA identified 73% (8/11) suicides within the first year of indexed suicide attempt (Nordström et al., 1994).

Samuelsson et al. (2006) conducted a prediction study of early suicide on 15 male psychiatric patients who had tried to commit suicide, all were free from antidepressants. A lumbar puncture was performed on all patients after informed consent. The patients were then in a follow up study over a five year period. five out of 15 (33%) committed suicide within two years after indexed suicide attempt, and total mortality under the follow up period of five years was 8/15 (Samuelsson et al., 2006). The major differences in CSF 5-HIAA in nmol/l were found between suicides and survivor, with suicides levels below the median of 92.5 nmol/l. Low CSF 5-HIAA identified all of the five patients that had committed early suicide, within two years after indexed suicide attempt which is the majority (62.5 %) of the over all mortality. Low CSF 5-HIAA predicted suicide with a sensitivity of a 100 % and a specificity of 70 % (Samuelsson et al., 2006).

Another prediction study on early suicide was done by Faustman et al. (1993). The study by Faustman et al. (1993) was conducted on a larger scale consisting of 73 patients with mixed diagnosis of schizophrenia and depression and monitored death rate and CSF 5-HIAA levels over a 15 year period (1976 to 1990). The aim of the study was to track a group of early suicides amongst the group, correlated with low CSF 5-HIAA. 15 out of 73 patients who participated and gave their CSF 5-HIAA samples for the research had died during this period. One was a victim of a homicide and two were classified as seemingly accidental leaving 12 suicide diagnoses (Faustman et al., 1993). 7/12 had died below the age of 40. The levels for the seven who died below the age of 40 was 11.79 ± 3.64 ng/ml, 5 /12 that died at age above 50 was 24 ± 10.78 ng/ml. Both groups had their own matched control group, there was less difference in CSF 5-HIAA values between controls and the patients that had died at age over 50 which indicates a stronger correlate to CSF 5-HIAA values and early suicidality (Faustman

et al., 1993). The result offers the support for CSF 5-HIAA and its ability to provide a prediction for early death by suicide (Faustman et al., 1993). CSF 5-HIAA seems to be directly linked to early suicides within the first year of indexed suicide attempt, and is specific in identifying those individuals at high risk of completing their suicides shortly after hospital release and/or psychiatric monitoring (e.g. Åsberg et al. 1976; Åsberg & Forslund, 2000; Edman et. al, 1986; Faustman et al., 1993; Lidberg et al., 1984; Meltzer et al., 1984; Samuelsson et al., 2006)

Åsberg (1997) conducted a meta-analysis on the 27 largest studies examining the relationship between CSF 5-HIAA and suicidality. In majority of the studies reviewed (17/27), the results showed a positive correlation between low CSF 5-HIAA and suicidal behaviour. In majority of the studies that were positive, the patients were not only grouped by low CSF 5-HIAA but also by the fact that they more frequently reattempted suicide. In other words CSF 5-HIAA may help to define a group of people who not only will attempt to commit suicide once, but will repeat the attempt, and are the most probable candidates for completing suicide.

3 Violence, impulsiveness and CSF 5-HIAA

An association between low CSF 5-HIAA and suicidal behaviour has also been found outside of the context of psychiatric illness and clinical depression (Åsberg & Forslund, 2000). The psychiatric link between serotonin and suicide is therefore unlikely to be related to depressive illness per se, but might be related to temperamental traits that make an individual more vulnerable to depression as well as to drastic acts that lead to self harm when exposed to aggression (Åsberg & Forslund, 2000). Patients suffering from depressive illness together with low CSF 5-HIAA concentration seem to be more prone to employ violent and impulsive method of choice when attempting or committing suicide than those who have the same

severity of depression without a low level CSF 5-HIAA concentration (Åsberg et al., 1976; Åsberg & Forslund, 2000; Cremniter et al., 1999; Edman et al., 1986; Linnoila, Virrkunen, Scheinin, Nuutila, Rimon & Goodwin 1983; Nilsen et al., 1994; Mann & Malone, 1997)

It is suggested that the core behavioural effect of reduction of the 5-HT neurotransmission function might result in an increase in impulsive and violent behaviour (Kraemer, Schmidt & Ebert, 1997). CSF 5-HIAA seems to act as an inhibitor when at normal level. Decrease in the concentration seems to result in a deficit in the regulation of violence and impulses in a patient already suffering from disturbances in the monoamine systems (Åsberg & Forslund, 2000; Åsberg, 1997 Cremniter et al., 1999; Edman et al., 1986; Linnoila et al., 1983; Nilsen et al., 1994).

Linnoila et al. (1983) hypothesized that the core function of CSF 5-HIAA was more related to impulse control and aggression inhibition than depressive illness. They wanted to look in to the relationship between CSF 5-HIAA concentration and violent behaviour. If it was the case that low CSF 5-HIAA concentration was affecting the level of aggression and impulsivity within an individual, one could use CSF 5-HIAA not only to predict suicidality and self-harm but discover a key component to violent behaviour.

In the study conducted by Linnoila et al. (1983), they used the total of 36 violent offenders who voluntarily entered the experiment. All the participants were male, 21 had killed their victims and 15 had tried to kill. All had enforced unusually cruel methods in the attempt to harm, all were diagnosed with intermittent explosive personality disorder, seven were diagnosed with antisocial personality disorder and nine were diagnosed with paranoid or passive aggressive personality disorder. All subjects fulfilled the criteria for alcohol abuse. Lumbar puncture was performed. The results showed no contradictions to the earlier study performed by Åsberg et al. (1976). The investigation revealed that all acid metabolites of monoamines in the CSF are lower in the impulsive than in the paranoid or passive aggressive

murderers. The difference in concentration of CSF 5-HIAA was the most differentiated in paranoid and aggressive individuals, aggressive individuals had significantly lower CSF 5-HIAA values. Impulsivity and aggressive violence were, in other words, to be taken into consideration as causal effects for high rates of suicidality within patients suffering from low level CSF 5-HIAA (Linnoila, 1983).

Another study on the functionality of CSF 5-HIAA concentration and human aggression was performed by Nilsen et al. (1994). The aim of the study was to investigate if Tryptophan Hydroxylase Polymorphism (THP) is a factor influencing serotonin turnover and the behaviours that are controlled by serotonin such as violence and impulsivity (Nilsen et al., 1994). They collected DNA samples from 56 impulsive and 14 non-impulsive alcoholic violent offenders, all offspring to Caucasian Finnish parents. A group of 20 healthy volunteers were employed to serve as controls. Both Nilsen et al. (1994) and Linnoila et al. (1983) used Finnish prisoners due to two facts: the Finnish population has one of the worlds highest suicide rates as well as reported alcoholic offenders, and the population is much more homogenous than for example the one in The United Stated of America. The CSF 5-HIAA levels of violent offenders were measured. Nilsen et al.´s. (1994) results showed differences in the 5-HIAA levels between non -impulsive and impulsive violence styles in these offenders. Violent impulsive criminal offenders had significantly lower CSF 5-HIAA than non-impulsive offenders and controls.

According to Linnoila et al. (1983) and Nilsen et al. (1994), there is a relation between impulsive violence and low level CSF 5-HIAA, and as shown in Nilsen et al. (1994), an effect of the serotonin turnover and an indirect effect of serotonin controlled behaviours. The findings help to better the understanding of the mechanism of serotonin and suicide, and in accurately determining the criteria for a biochemical predictor of suicide (Åsberg et al., 1976).

3.1 Violent suicide attempts and CSF 5-HIAA levels

In an attempt to follow the line of the discoveries of Edman et al. (1986) and Linnoila et al. (1983) conducted a study to compare violence in suicide attempts in response to CSF 5-HIAA levels. The study was performed on 36 drug-free suicidal patients suffering from depressive illness. The patients were divided into three groups plus a control group. 11 were classified into suicide ideation, 16 were placed in the non-violent suicide attempt group and eight were placed in the violent attempt group. 32 were employed as the control group. The results from the standardized lumbar puncture were analyzed and showed a significant difference among the patients who had used violent methods compared to those that had used non-violent methods in attempting suicide. The patients in the violent attempt group had lower CSF 5-HIAA level than the non-violent attempters and controls.

Mann & Malone (1997) conducted a similar investigation to analyze the association between violent attempt and low CSF 5-HIAA. The study was performed on 22 inpatients with major depressive episode and had tried to commit suicide by violent means: overdose (n = 16), cutting (n = 2), hanging (n = 2), jumping (n = 1) and shooting (n = 1) (Mann & Malone, 1997). A Medical Damage Rating Scale (MDRS) was used with the ratings from 0 to 8 to assess the outcome of the attempt (0 = none, 8 = dead; 0-7 were applicable in the study) (Mann & Malone, 1997).

Patients with a high medical damage lifetime suicide attempt on the MDRS (≥ 3) had significantly lower CSF 5-HIAA compared to low medical damage attempters (≤ 3) (Mann & Malone, 1997). The severity of medical damage to oneself was in other words more prominent in patients with low CSF 5-HIAA concentration. Mann & Malone (1997) concluded that a higher level of CSF 5-HIAA is associated with a history of suicide attempts that result in a lesser medical damage. The results are consistent with earlier studies (Åsberg

et al., 1976; Cremniter et al., 1999; Edman et al., 1986; Linnoila et al., 1983) that have shown that higher levels indicate more inhibition towards impulsive and violent harm as well as self harm. If the hypothesis is true and serotonergic activity is associated with less medically damaging suicide attempts, then in turn one can hypothesize that treatments that increase serotonergic activity may not only reduce the probability for future suicide or suicide attempt but may reduce the degree of medical damage as well. Reduction of medical damage, i.e. the level of violence towards oneself increases the chances of survival in suicide attempt (Mann & Malone, 1997).

In Cremniter et al. (1999) the focus was put on impulsive versus non-impulsive suicide attempts, i.e., if impulsive behaviour could be the key to predicting suicidal behaviour. According to Cremniter et al. (1999), low CSF 5-HIAA concentration seems to be more linked to defective impulse control than to depression or suicidality, as demonstrated by Linnoila et al. (1983) and Nilsen et al. (1994). Cremniter et al. (1999) studied 23 patients admitted to the surgical intensive care unit due to violent suicide attempt. Cremniter et al. (1999) divided the patients into two groups; impulsive violent and non-impulsive violent suicide attempt. There was a control group of 23 healthy individuals. There was a significant difference in mean level of CSF-5HIAA varying between the two main groups of non-impulsive and impulsive. Both groups had a significantly lower mean value than the control group. Cremniter et al. (1999) concluded on the basis of the findings that there seems to be a strong correlation between CSF 5-HIAA values and impulsivity, and that it might be the indirect cause of increased suicide attempts and completed suicides in patients suffering from low CSF 5-HIAA concentration. The act of suicide is in the line of the discovery not due to depressive illness but rather the lack of impulse control within patients that suffer from depressive illness and CSF 5-HIAA deficiency at the same time, making CSF 5-HIAA a good measuring tool for identifying a subgroup of patients with depressive illness that do not suffer

from suicidal ideation but are more drawn towards impulsive and violent attempts which without an indicator are harder to prevent (Cremniter et al. 1999; Nordström et al., 1994; Roy et al., 1993).

3.2 CSF 5-HIAA, violence, and homicide/suicide

Lidberg et al. (1984) conducted an investigation in small sample of suicidal parents who also had committed homicidal acts on their children. The sample consisted of three case studies. These specific cases all showed strong relation between violence, suicidality and low CSF 5-HIAA concentration. Case one consisted of a 29-year-old married mother of three. She had drowned her 4-month-old son, and just days before tried to strangle him while throwing herself down the stairs. After successful treatment for the psychotic episodes and depression, she had a relapse 20 years later during which a lumbar puncture was performed. Her CSF 5-HIAA level was measured to be 54 nmol/l (Lidberg et al., 1984).

Case two consisted of a 36-year-old father who had stabbed his 10-year-old son to death and wounded his wife as well as himself. He had received psychiatric care prior to the incident due to acute psychiatric episodes. Four weeks after the indexed suicide/homicide attempt, his CSF 5-HIAA level was measured to be only 45 nmol/l (Lidberg et al., 1984).

The last case was of a 38-year-old father who had tried to poison himself and his 4-year-old daughter. The father was admitted to psychiatric care. Six months after the incident his CSF 5-HIAA level was measured to be 26 nmol/l.

All three cases are good examples of violent and impulsive suicides and suicide attempts and in this specific case homicides aimed at own children.

4 Negative findings on CSF 5-HIAA and suicidal acts

There is scepticism aimed at the hypothesis of CSF 5-HIAA being a probable candidate for a biological suicide predictor (Roggenbach, Müller-Oerlinghausen & Franke, 2002).

Consequential number of well-designed studies concerning suicidal individuals and control subjects have not shown any difference in concentration of CSF 5-HIAA in suicide attempters compared to non-suicide attempters (Roggenbach et al., 2002). In this section, studies that have failed to show correlation between suicidal behaviour and CSF 5-HIAA will be presented.

Roy-Byrne, Post, Rubinow, Linnoila, Savard & Davis (1983) studied 45 patients with affective disorder, 14 suicidal and seven patients that had attempted suicide with violent means. The study was negative; there was no difference between non-suicidal patients compared to suicidal patients when it came to CSF 5-HIAA concentration. Also in a study by Roy, Ninan, Mazonson, Pickar, (1985), conducted on 27 suicidal schizophrenic patients, a comparison of violent versus non-violent suicide attempts was made in correlation to CSF 5-HIAA values. There was no significant difference between violent, non-violent suicide attempters and controls in CSF 5-HIAA levels. Roy et al. (1990) also performed a study on 15 non-violent and five violent suicide attempters and 108 non-suicidal controls (all were alcoholics) and 30 healthy controls.

Roy et al. (1990) measured and compared CSF 5-HIAA levels between violent and non-violent attempts. They found no significant difference between concentration levels in violent attempters and non-violent attempters. They could not, in other words, replicate the results as shown by e.g. Cremniter et al. (1999), Mann et al. (1997) & Åsberg et al. (1976).

Mann et al. (1996) employed 30 non-violent and 16 violent suicide attempters in their study; they also employed 21 psychiatric patients without a history of suicide attempts to act as controls. The study was negative; no correlation between CSF 5-HIAA levels between attempters and non-attempters was found. It appears that a mixture of inconsistencies among results and partially positive studies such as Cremniter et al. (1999) leave us with the

conclusion that it is highly unlikely that one can draw a reliable conclusion about the association between CSF 5-HIAA and suicide attempts (Roggenbach et al., 2002).

There are three main objections to the conclusion that CSF 5-HIAA should be taken for granted as being a biological suicide predictor. The first is the relatively small samples used in investigations. The second one is methodological problems: the variety of psychological diagnoses among the employed participants and the influence of the diagnoses on the results. The third one is the fact that many authors can not reproduce their own results consistently. In the case of Lidberg, Belfrage, Evenden & Åsberg (2000) the group could not reproduce their previous findings when it came to sub-grouping correlation with low CSF 5-HIAA concentration and sexual bond related aggression as well as alcohol abuse (Roggenbach et al., 2002).

4.1 Negative findings on CSF 5-HIAA in aggressive individuals

The association between aggressive behaviour and CSF 5-HIAA concentration has been studied by e.g. Linnoila et al. (1983) and Nilsen et al. (1994). A very few studies have been conducted on this subject. Aggression is often associated with personality disorders, depressive illness or alcohol abuse. It is postulated that aggression and impulse control deficiency due to the role of CSF 5-HIAA might be the indirect causality of violent suicidal acts (e.g. Åsberg et al., 1976; Cremniter et al., 1999; Edman et al., 1986; Linnoila et al., 1983). As can be viewed in table 1, majority of the studies performed on the same basis to investigate such a hypotheses have failed to find a correlation between aggressive behaviour, impulse control and low CSF 5-HIAA concentration.

Table 1 CSF 5-HIAA studies in aggressive individuals and possible confound variables

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

Note: Adapted directly from Roggenbach et al., 2006: p 199

According to Roggenbach et al.(2002) interpretation made by authors such as e.g. Åsberg et al. (976), Cremniter et al. (1999), Edman et al. (1986) and Linnoila et al. (1983) that suicidal behaviour is autoaggressive, or a result of impulsiveness, seems to be an oversimplification. As far as aggression goes, it seems to be only applied to suicide attempters. There are several indications that suicide completers were often not aggressive in contrast to suicide attempters (Roggenbach et al., 2002). Aggression and violence seem to be mainly present in the patients who have low intention of completing their suicide attempt (Roggenbach et al., 2002). Patients who are determined and often are the ones who successfully commit suicide exhibit no aggressive traits.

Many completed suicides are carefully planned long before the attempt, thus they do not seem to have an impulsive nature either (Roggenbach et al., 2002). It would entail that those suicide completers, engage in the most extreme form of suicidal behaviour, do not suffer from impulse control difficulties at all. Many suicide attempts can be seen as a lack of communication with limited intention to die, if non at all (Roggenbach et al., 2002).

5 Discussion

Why certain individuals are more prone to subject themselves to self-inflected harm than others, is still uncertain, but is a biological suicide predictor the best way to identify the high risk individual? Throughout this essay, evidence that supports the correlation between low CSF 5-HIAA concentration and increased risk for completed suicides has been demonstrated, in various studies. (e.g. Åsberg et al., 1976; Lidberg et al., 2000; Mann et al 1997; Mann & Malone, 1997; Nordström et al., 1994; Roy et al., 1993; Samuelsson et al., 2006; Träskman-Bendz et al., 1984). That is why I, and clinicians in the need for a more accurate suicide predictor, hope for and believe that a more biological approach to suicide can bring more accurate predictions.

However, as in any true science, there are some aspects that should be taken into consideration and investigated, such as variables that could conflict with the results. A few of the potential variables are; psychiatric diagnosis prior to lumbar puncture, alcohol abuse, sex, height, ethnicity and violence. I will discuss these in the order they are mentioned and bring forth some methodological flaws. I will also suggest how future studies should be conducted.

5.1 Psychiatric disorders

It is well known that suicidal behaviour is more prone in individuals with psychiatric disorders, especially depressive illness (Roggenbach et al., 2002). Therefore, they are often employed as subjects in suicide studies. In the study performed by Roy et al. (1985), the employed subjects were all (N = 27) schizophrenic. It has been established that schizophrenic patients suffer from abnormalities in the dopaminergic systems, and it is also well recognized that dopamine plays a central role in motor and cognitive-emotional processes in the central nervous system (CNS), mainly in forebrain structures which in turn are responsible for impulse and mood control (Negyessy & Goldman-Rakic, 2005).

Studying individuals with a predisposition to mood sensitivity, which will not be detected by mere serotonergic changes, is not suitable when using serotonin metabolites such as CSF 5-HIAA as detectors for increased suicide risk. We would then possibly observe a mood change but no significant decrease in serotonin or CSF 5-HIAA, as demonstrated by Roy et al. (1985). In other words, correlations between low CSF 5-HIAA and suicidality could very well be disturbed by the natural dopaminergic distribution in schizophrenic patients.

5.2 Alcohol

Another variable that can create an invisible subgroup in many suicide studies is alcohol abuse. For example, Roy et al. (1990) used mainly alcohol abusers in their studies. The majority of the subjects in the studies performed by Faustman et al. (1993), Linnoila et al. (1983,) and Nilsen et al. (1994) fulfilled the criteria for alcohol abuse. Alcohol abusers are more aggressive in general and exhibit more frequently violent behaviours than non-alcoholic individuals (Hibbeln, Umhau, Linnoila, George, Ragan, Shoaf, Vaughan et al., 1998). It is also well known that impulsive violence, suicidal and aggressive behaviour, as well as early onset of alcohol abuse, have been linked to low CSF 5-HIAA concentration (Hibbeln et al., 1998).

Low CSF 5-HIAA concentrations among suicide attempters with alcoholism is one of the most replicated findings in biological psychiatry (Hibbeln et al., 1998). The fact that a high number of patients that commit suicide by violent means are alcoholics might primarily be due to the fact that they suffer from low CSF 5-HIAA concentrations. Employing alcoholics in suicide studies is not appropriate as the mere presence of alcohol abuse suggests that the brain has been affected and is, as mentioned before, already had a cause for low CSF 5-HIAA concentration. Thus, low CSF 5-HIAA concentration is present whether the alcohol abuser patient will try to commit suicide or not.

In a study performed by Hibbeln et al. (1998), CSF 5-HIAA was measured in violent alcohol abusers and non-violent abusers for a comparison study. 58 individuals were recruited to the study, 31 in the non-violent group and 27 in the violent. Both groups had lower than median or average CSF 5-HIAA levels but the violent group had significantly lower CSF 5-HIAA levels than the non-violent one. If low CSF 5-HIAA is correlated with violence and violence with suicidality, then alcoholic subjects might create a subgroup of patients that exhibit violent traits but do not show suicidality, or, in contrast, show a higher frequency of suicidality. In any case, alcoholic abusers should be grouped separately and existing alcohol related serotonergic damage should be taken in to consideration.

5.3 Sex and Height

It is also unclear how natural variables, such as sex and height, affect the results. In reports by e.g. Edman et al. (1986) and Nilsen et al. (1994) there was no significant sex difference when it came to the results. When it came to height, which might seem as a trivial fact and not a variable, it is shown that it can be an important variable in such studies as the one performed by Blennow, Wallin, Gottfries & Karlsson (1993). They demonstrated that male subjects, often being taller than female subjects, had a lower concentration of CSF 5-HIAA. Also, in studies on aggressive behaviour performed on prisoners, the subjects were all male (Linnoila et al., 1983; Nilsen et al., 1994). Thus, higher testosterone levels in males might be related to CSF 5-HIAA levels. It is not yet established whether men are more aggressive than women by nature, but one can assume that it is a biological variable that should be taken into consideration.

Similarly, other gender-dependent variables, such as hormones, need to be considered. Serotonergic activity is highly likely affected by progesterone and oestrogen (Pinto-Meza. Usall, Serrano-Blanco, Suárez & Haro, 2006). Studies have shown that women during menopause respond significantly worse to SSRIs than women who are not in

menopause. A possible explanation for this is that endocrine changes in menopause could be modifying the pharmacodynamic effects of the SSRIs. Studies have shown that oestrogens enhance serotonergic activity (Pinto-Meza et al., 2006). Gender is, in other words, an important variable in studying a biological suicide predictor because already, even in a healthy state, differences of distribution of serotonin can be observed between men and women.

5.4 Ethnicity

Pfeffer, McBride, Anderson & Kakuma (1998) pointed out that with increased knowledge one should acknowledge the ethnic differences in gene polymorphism. Differences have been observed between ethnic groups, e.g., that African Americans have higher platelet 5-HT and whole blood tryptophan concentration than Caucasians (Pfeffer et al., 1998).Consequently, one should take into consideration that more ethnically homogenous samples are needed, and that ethnicity of the subjects should be taken as a variable. A biological difference can create unreliable results in a mixed ethnical group.

5.5 Violence

The temperamental effect has been discussed widely in the studies presented in this essay, by e.g. Cremniter et al. (1999), Edman et al. (1986), Linnoila et al. (1983), Mann & Malone (1997), and Nilsen et al. (1994). Serotonin is a powerful mood determinant, thus the correlation between low CSF 5-HIAA and violence seems to appear naturally. It is, however, unclear to what extent violent tendencies play a role on suicidal behaviour and suicide attempts.

It has been postulated that low CSF 5-HIAA predicts more often aggression than suicidality (Åsberg & Forslund, 2000), but no one has yet been able to demonstrate to what extent aggression and suicidal acts are connected.

Furthermore, there seems to be a connection between impulsivity and violent acts correlated with low CSF 5-HIAA (Åsberg et al., 1976; Cremniter et al., 1999; Edman et al.,1986; Linnoila et al., 1983). It is postulated that individuals who are aggressive are more prone to commit suicide than non-aggressive individuals (e.g. Linnoila et al., 1983). This is due to the fact that aggressive individuals are more often impulsive by nature. One of the postulated side-effects of low CSF 5-HIAA is impulse control deficiency and harm inhibition, both to self and others (Åsberg & Forslund, 2000). Roggenbach et al. (2002) pointed out, however, that most suicide completers have planned their suicides well, and shown no violent traits when choosing the suicide method.

Moreover, as shown in table 1, aggressive behaviour can be found in individuals who do not suffer from low CSF 5-HIAA concentration. There is, in other words, no guarantee that low CSF 5-HIAA is actually coupled with aggression, and consequently, with impulsive suicides.

5.6 Future studies

To conclude, I will now give some suggestions for improvements that could be beneficial for future studies on CSF 5-HIAA and its correlation to suicidal behaviour. First, a relatively simple adjustment that could increase reliability is to exclude patients with certain psychiatric diagnosis who have a natural deficiency in mood regulation and neurotransmission, e.g, Schizophrenics. Patients suffering from schizophrenia or mood disorders are already in a high risk group, thus the treatment of these patients is drastically different than treatment of a suicidal individual without underlying psychiatric condition.

Another adjustment can be done by excluding, or grouping separately, alcohol abusers because alcohol itself affects neuromodulation in the brain. Though I am very reluctant to separate sexes because majority of the studies have not found any differences (as can be viewed in more detail in Åsberg & Forslund, 2000), natural differences in men and

women in respect to hormones are undeniable and can result in faulty results in mixed sex groups. To measure gender differences would give a clearer picture. Also, in aspect of height and body weight mentioned by Blennow et al. (1993), it is better to pair women with women since they are naturally more similar in height and weight to each other than to men.

When it comes to ethnicity it is clear that it is better to design groups that are homogenous, as mentioned before, as some ethnic groups might have a higher platelet 5-HT and whole blood tryptophan concentration and that would result in higher levels of serotonin (Pfeffer et al., 1998), and bias results.

The last adjustment might be the most complicated. Because there is such a clear correlation between temperament and low CSF 5-HIAA it is complicated to adjust the studies and incorporate more non-violent individuals. Maybe non- violent suicides are performed by individuals suffering from suicidal ideation and the completed suicides among that group are due to accidental causes, such as inadequate knowledge of safe drug dosage. It is, however, important to discover to what extent impulses and aggression play role in increased suicidality, and to do so one must find low CSF 5-HIAA even in the non-impulsive and non-violent suicide attempters or at least find the mechanism behind serotonin in suicide that will in the end not discriminate non-violent attempters and completers.

6 Conclusion

Predicting suicide through measurements has long been desirable because classical suicidology has offered too vague of a prediction. There have been a number of well-designed and extensive studies on the correlation between low CSF 5-HIAA and increased risk for reattempted and completed suicides. Majority of those studies have been demonstrated an increased suicide risk in patients with low CSF 5-HIAA concentration. It has also been observed that patients who have attempted violent and impulsive suicides have had low CSF

5-HIAA level, and so do inmates who have tried to commit homicide. Suicide combined with homicide has also been correlated to low CSF 5-HIAA concentration in suicidal parents who have tried to kill their offspring. In contrast, there are also studies that have not been able to find any connection between increased suicidality and low CSF 5-HIAA, or aggression and low CSF 5-HIAA.

It is postulated that both the negative and the positive studies contain a number of methodological errors, the main problem being the selection of the subjects. The subjects should be more carefully chosen and natural variables, such as e.g. sex and ethnicity, should be carefully looked at when creating experimental groups. There is much evidence that CSF 5-HIAA may be the perfect candidate for predicting suicidal behaviour. If this is the case, it would be a useful tool for clinicians targeting to find the high risk individuals that will reattempt suicide and complete suicide shortly after release from care. Before that stage is reached, one must keep in mind all the important variables and methodological issues that may affect the results, and the reliability of results, of future studies.

7 References

Arango, V., Underwood, M. D., & Mann, J. J., (1997). Postmortem findings in suicide victims. In Stoff, D.M., & Mann, J.J., (Eds) The Neurobiology of suicide from the bench to the clinic (pp 269-287). New York Academy of Sciences, Volume 836.

Åsberg, M., Träskman, L., & Thoren, P. (1976). 5-HIAA in the cerebrospinal fluid. A biochemical suicide predictor? Archives of General Psychiatry, 33, 1193-1197.

Åsberg, M. (1997). Neurotransmitters and suicidal behaviour, the evidence from cerebrospinal fluid studies. In Stoff, D.M., & Mann, J.J., (Eds) The Neurobiology of

suicide from the bench to the clinic (pp 158 - 181). New York Academy of Sciences, Volume 836.

Åsberg, M., & Forsberg, K., (2000). Neurobiological aspect of suicidal behaviour. International review of Psychiatry 12, 62-74.

Bachus, S., Hyde, T. M., Akil, M., Weickert, C. S., Varwter, M. P., & Kleinman, J. E. (1997) Neuropathology of Suicide; A review and an approach. In Stoff, D. M., & Mann, J. J. (Eds) The Neurobiology of suicide from the bench to the clinic (pp269-287). New York Academy of Sciences, Volume 836.

Bland, R. C. (1997) Epidemiology of Affective Disorders, A Review. Canadian Journal of Psychiatry 42, 367-377.

Blennow, K., Wallin. A., Gottfries, C. G., Karlsson, I. (1993). Cerebrospinal fluid monoamine metabolites in 114 healthy individuals 18–88 years of age. European Neuropsychopharmacology 3, 55–61.

Cremniter, D., Jamain, S., Kollenbach, K., Alvarez, J. C., Lecrubier, Y., Gilton, A., Jullien, P., Lesieur, P., Bonnet, F., & Spreux-Varoquaux, O. (1999). CSF 5-HIAA levels are lower in impulsive as compared to non impulsive violent suicide attempters and control subjects. Biological Psychiatry, 45, 1572-1579.

Delgado, P. L., Charney, D. S., Price, L. H., Aghajanian, G. K., Landis, H., & Henninger, G. (1990). Serotonin function and mechanism of antidepressant action. Archives of General Psychiatry 47, 411-418.

Edman, G., Asberg, M., Levander, S., & Schalling, D. (1986) Skin conductance habituation and cerebrospinal fluid 5-hydroxyindoleacetic acid in suicidal patients. Archives of General Psychiatry 43,586-592.

Faustman, W. O., Ringo, D. L., & Faull, K. F. (1993) An association between low levels of 5-HIAA and HVA in cerebrospinal fluid and early mortality in a diagnostically mixed psychiatric sample. British Journal of Psychiatry. 163, 519-521.

Gardner, D. L., Lucas, P. B., Cowdry, R. W. (1990). CSF metabolites in borderline personality disorder compared with normal controls. Biological Psychiatry 28, 247–254.

Hibbeln, J. R., Umhau, J. C., Linnoila, M., George, D. T., Ragan, P. W., Shoaf, S. E., Vaughan, M. R., Rawlings, M. R., & Salem, N., Jr. (1996) A Replication Study of Violent and Nonviolent Subjects, Cerebrospinal Fluid Metabolites of Serotonin and Dopamine Are Predicted by Plasma Essential Fatty Acids. Biological Psychiatry, 44, 243–249.

Kreamer, G. W., Schmitdt, D. E., & Ebert, M. H. (1997). The behavioural neurobiology of self injurious behaviour in Rhesus monkeys: current concepts and relation to impulsive behaviour in humans. In Stoff, D. M., & Mann, J. J. (Eds) The Neurobiology of suicide from the bench to the clinic (pp 12-38). New York Academy of Sciences, Volume 836.

Lidberg, L., Asberg, M., & Sundqvist-Stensman, U. B. (1984) 5-hydroxyindoleacetic acid levels in attempted suicides who have killed their children. The Lancet, II, 928.

Lidberg, L., Belfrage, B. L., Evenden, M. M., & Åsberg, M. (2000). Suicide attempts and impulse control disorders are related to low cerebrospinal fluid 5-HIAA in mentally disordered violent offenders. Acta Psychiatrica Scandinavica 101, 395-402.

Linnoila, M., Virrkunen, M., Scheinin, M., Nuutila, A., Rimon, R., & Goodwin, F. K. (1983) Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from nonimpulsive violent behaviour. Life Sciences. 33, 2609-2614.

Mann, J. J., Malone, K. M., Sweeney, J. A., Brown, R. P., Linnoila, M., Stanley, B., Stanley, M. (1996). Attempted suicide characteristics and cerebrospinal fluid amine metabolites in depressed inpatients. Neuropsychopharmacology 15, 576–586.

Mann, J. J., & Malone, K. M. (1997) Cerebrospinal fluid and higher-lethality suicide attempts in depressed inpatients. Biological Psychiatry 41, 162-171.

Mann, J. J., Malone, K. M., Nielsen, D. A., Goldman, D., Erdos, J., & Gelernter, J. (1997). Possible association of a polymorphism of the tryptophan hydroxylase gene with suicidal behavior in depressed patients. American Journal of Psychiatry, 154, 1451-1453.

Meltzer, H. Y., Perline, R., Tricou, B. J., Lowy, M., & Robertson, A. (1984). Effect of 5-hydroxytryptophan on serum cortisol levels in major affective disorders. II. Relation to suicide, psychosis, and depressive symptoms. Archives of General Psychiatry 41, 379-387.

Negyessy, L., & Goldman-Rakic, P. S. (2005) Subcellular Localization of the Dopamine D2 Receptor and Coexistence with the Calcium-Binding Protein Neuronal Calcium Sensor-1 in the Primate Prefrontal Cortex. The journal of comparative neurology 488, 464–475.

Nilsen, D. A., Goldman, D., Virrkunen, M., Tokola, R., Rawlings, R., Linnoila, M. (1994) Suicidality and 5-Hydroxyindoleacetic Acid Concentration Associated with Tryptophan Hydroxylase Polymorphism. Archives of General Psychiatry, 51, 34-38.

Nordström, P., Samuelsson, M., Asberg, M., Träskman-Bendz, L., Åsberg-Wistedt, A., Nordin, C., & Bertilsson, L. (1994). CSF 5-HIAA predicts suicide risk after attempted suicide. Suicide & Life-Threatening Behavior, 24, 1-9.

Pfeffer C. R., McBride P.A., Anderson G. M., Kakuma, T. (1998) Peripheral serotonin measures in prepubertal psychiatric patients and normal children: Associations with suicidal behaviour and its risk factors. Biological Psychiatry 44, 568–577.

Pinto-Meza, A., Usall, J., Serrano-Blanco, A., Suárez, D., & Haro, J. M. (2006) Gender differences in response to antidepressant treatment prescribed in primary care. Does menopause make a difference? Journal of Affective Disorders 96, 53–60.

Rajkowska, R. (1997) Morphometric methods for studying the prefrontal cortex in suicide victims and psychiatric patients. In Stoff, D. M., & Mann, J .J., (Eds) The Neurobiology of suicide from the bench to the clinic (pp 269-287). New York Academy of Sciences, Volume 836.

Roggenbach, J., Müller-Oerlinghausen, B., Franke, L. (2002). Suicidality, impulsivity and aggression – is there a link to 5-HIAA concentration in the cerebrospinal fluid? Psychiatric Research 113, 193-206.

Roy-Byrne, P., Post, R. M., Rubinow, D.R., Linnoila, M., Savard, R., Davis, D. (1983). CSF 5-HIAA and personal and family history of suicide in affectively ill patients: a negative study. Psychiatry Research 10, 263–274.

Roy, A., Ninan, P., Mazonson, A., Pickar, D., van Kammen, D., Linnoila, M., Paul, S. M., (1985). CSF monoamine metabolites in chronic schizophrenic patients who attempt suicide. Psychological Medicine 15, 335–340.

Roy, A., Lamparski, D., De Jong, J., Adinoff, B., Ravitz, B.,George, D. T., Nutt, D., Linnoila, M. (1990). Cerebrospinal fluid monoamine metabolites in alcoholic patients who attempt suicide. Acta Psychiatrica Scandinavica 81, 58–61.

Roy, A., De Jong, J., & Linnoila, M. (1993). Cerebrospinal fluid monoamine metabolites and suicidal behavior in depressed patients. Archives of General Psychiatry 46, 7, 609-612.

Samuelsson, M., Nordstrom, P., & Asberg, M. (2006). Suicide intent and hopelessness in the prediction of early suicide in male high risk suicide attempters, Acta Psychiatrica Scandinavica, 113, 44-47.

Stockmier, C. A. (1997). Neurobiology of serotonin in depression and suicide. In Stoff, D. M., & Mann, J. J., (Eds) The Neurobiology of suicide from the bench to the clinic (pp269-287). New York Academy of Sciences, Volume 836.

Stoff, D. M., & Mann, J. J. (1997) Suicide Research, an overview and introduction. In Stoff, D. M., & Mann, J. J., (Eds) The Neurobiology of suicide from the bench to the clinic (pp1-11). New York Academy of Sciences, Volume 836.

Träskman-Bendz, L., Asberg, M., Bertilsson, L., & Thoren, P. (1984). CSF monoamine metabolites of depressed patients during illness and after recovery. Acta Psychiatrica Scandinavica 69, 333-342.

Appendix

The Online medical dictionary Medline Plus Retrieved: May 30 2007

http://www.nlm.nih.gov/medlineplus/mplusdictionary.html

World Health Organisation. Retrieved: May 17, 2007

http://www.who.int/mental_health/prevention/suicide/suicideprevent/en/