Metabolic alterations in patients with self-inflicted aggressive behaviour

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till min underbara, älskade familj

“What a job is this,
to measure lightning with a footrule,
the heart’s turbulence with a pair of
callipers”

Norman MacCaig

Contents

Original papers

This thesis is based on the following publications:

I. **Low CSF leptin in female suicide attempters with major depression.** Westling S., Ahrén B., Träskman-Bendz L., Westrin Å. J Affect Disord. 2004;81(1):41-8

II. **High CSF-insulin in violent suicide attempters.** Westling S., Ahrén B., Träskman-Bendz L., Westrin Å. Psychiatry Research 2004;129:249-255.

III. **Altered glucose tolerance in women with deliberate self-harm.** Sofie Westling, Bo Ahrén, Charlotta Sunnqvist, Lil Träskman-Bendz. Psychoneuroendocrinology 2009; 34:878-883

IV. **Increased levels of Interleukin-1β in patients with self-directed aggressive behaviour.** Sofie Westling, Shorena Janelidze, Bo Ahrén, Sophie Erhardt, Lennart Minthon, Martin Samuelsson, Lil Träskman-Bendz, Lena Brundin. Submitted.

Summary

Self-inflicted aggressive behaviour is a cross diagnostic phenomenon of major clinical relevance in psychiatric setting. Accumulating evidence speaks for a role of metabolic and immunological factors in aggressive behaviour. The aim of this thesis is to enlighten the role of leptin, insulin, glucagon, glucose and IL-1beta in the context of self-inflicted aggressive behaviour. We used cerebrospinal fluid (CSF-) samples from patients with a recent suicide attempt and plasma samples from a five-hour oral glucose tolerance test (OGTT) in women with deliberate self-harm and healthy controls. The main results from the different papers were:

I. Women with a recent suicide attempt and major depression have decreased CSF- leptin compared to those with other diagnoses.
II. Patients using a violent method for attempting suicide have higher CSF-insulin than those using a non-violent method.
III. Women with deliberate self-harm without an eating disorder have low plasma glucose nadir during the OGTT. In those with an eating disorder the low plasma glucose is counteracted by an increased glucagon secretion.
IV. Patients with a recent suicide attempt have increased CSF-IL-1beta compared to healthy controls, and the most pronounced elevations are found in patients with Cluster B personality disorder. Women with deliberate self-harm

have increased secretion of IL-1beta during the OGTT compared to healthy controls.

Our findings support the hypothesis of deviant metabolic and immunological components in self-inflicted aggressive behaviour. Future studies are required to further understand the mechanisms of these components, which may open up the development of new treatments for self-inflicted aggression.

Populärvetenskaplig sammanfattning på svenska

Introduktion

Ur ett evolutionsbiologiskt perspektiv är det inte svårt att tänka sig ett samband mellan aggressivt beteende och ämnesomsättning. För att skaffa sig föda har både jakt och utvidgning av det egna territoriet varit nödvändiga för många arter. Detta är aktiviteter som fordrar aggressivt beteende. Befolkningsstudier har visat samband mellan aggressivt beteende riktat mot andra och mot den egna personen. Inom psykiatrin är aggressivt beteende riktat mot den egna personen (som självmordsförsök eller självskadebeteende) ett vanligt men svårt fenomen.

I detta arbete har flera olika komponenter av ämnesomsättningen studerats i relation till aggressivt beteende. Leptin är ett hormon som utsöndras av fettceller och som har betydelse för såväl aptit, vikt, sömn och aktivitetsnivå vilket gör det av intresse att undersöka vid psykisk sjukdom.

Hos män har man sett en koppling mellan aggressivitet och en tendens att få lågt blodsocker under sockerbelastning. Ingen sådan forskning är gjord på kvinnor. Eftersom insulin sänker blodsockret är det intressant att undersöka hos personer med aggressivt beteende i det här fallet riktat mot den egna personen.

Det har dessutom kommit allt mer bevis för att immunförsvaret är av betydelse vid utvecklandet av psykisk sjukdom. Interleukin-1beta är ett immunämne av särskild betydelse för såväl aggressivt beteende som reglering av blodsockret. Denna avhandling har därför också studerat om det finns förändringar i immunförsvaret vid aggressivt beteende.

Material och metoder

Vi har undersökt leptin, insulin och interleukin-1beta i spinalvätska (den vätska som hjärnan vilar i) hos patienter som nyligen gjort ett självmordsförsök och som har olika psykiatriska diagnoser och jämfört dem med varandra och med friska kontroller. Dessutom har vi tagit blodprover från kvinnor med självskadebeteende och emotionellt instabil personlighetsstörning under en sockerbelastning och jämfört dem med friska kontroller matchade för ålder och BMI.

Resultat

Bland patienter som nyligen gjort ett självmordsförsök hade kvinnor med depression lägre leptin i spinalvätska jämfört med kvinnor med andra diagnoser. Hos patienter som gjort ett självmordsförsök fann vi också högre interleukin-1beta i spinalvätska jämfört med friska kontroller. Detta var särskilt uttalat hos de med Kluster B personlighetsstörning. Patienter som använt en våldsam metod för sitt självmordsförsök hade högre insulin i spinalvätska jämfört med dem som använt en icke-våldsam och av dessa hade kvinnorna dessutom lägre BMI.

Patienter med självskadebeteende och emotionellt instabil personlighetsstörning hade jämfört med friska kontroller en högre utsöndring av glukagon (ett ämne som höjer blodsockret) och interleukin-1beta under sockerbelastning. När vi analyserade

undergrupper visade det sig att samtliga hade en ökad interleukin-1beta utsöndring men den ökade glukagon-utsöndringen fanns enbart hos dem som hade en samtidig ätstörning. De andra hade istället en tendens att få lägre blodsocker under testet.

Diskussion

Våra fynd talar för att det finns ett samband mellan ämnesomsättningen, immunförsvaret och aggressivt beteende riktat mot den egna personen. Det finns liknande forskning som tyder på samma sak. Vårt fynd att kvinnor med depression hade lägre leptin i spinalvätska stödjer en del forskning som gjorts tidigare på området men talar emot annan. De rubbningar vi fann i sockeromsättningen hos kvinnor med självskadebeteende liknar dem man tidigare funnit hos aggressiva män. Möjligen kan dessa förändringar förklaras av den ökade utsöndringen av interleukin-1beta som vi också hittade. Utifrån den forskning som hittills är gjord går det inte att säga om det kan finnas ett eventuellt orsakssamband. Om våra resultat står sig i fler studier finns det dock möjlighet att utveckla helt nya behandlingsstrategier för patienter med självskadebeteende eller som gjort självmordsförsök.

Some abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ANOVA	analysis of variance
AQ-RSV	Aggression-Questionnaire Revised Swedish Version
AUC	Area under the curve
BMI	Body Mass Index (weight in kg/(length in meters)^2)
BPD	Borderline personality disorder
CSF	cerebrospinal fluid
CPRS	Comprehensive Psychopathological Rating Scale
CRH	corticotropin releasing hormone
DBT	Dialectical Behavior Therapy
DSH	deliberate self-harm
ELISA	Enzyme-Linked Immunosorbent Assay
5-HIAA	5-hydroxyindole acetic acid, metabolite of serotonin
HPA	hypothalamus-pituitary-adrenal
5-HT	5-hydroxytryptophan
HVA	homovanillic acid, metabolite of dopamin
IL	interleukin
KSP	Karolinska Scales of Personality
MADRS	Montgomery Asberg Depression Rating Scale
MDD	major depressive disorder
MEIU	Medical Emergency and Intensivecare Unit
mRNA	messenger ribonucleic acid
OGTT	oral glucose tolerance test
SPSS	Statistical Package for the Social Sciences
SSRI	Selective Serotonin Reuptake Inhibitor
SUAS	Suicide Assessment Scale
TNF-alpha	Tumour Necrosis Factor alpha

1. Introduction

1.1. Background

Self-inflicted aggressive behaviour is a common, serious and sometimes lethal phenomenon in psychiatric settings. Current treatment is in many cases insufficient. Although psychotherapy specifically addresses the matter, this is expensive, and there is a lack of therapists willing to work with patients with severe self-inflicted aggression. Available pharmacotherapy mainly targets co-occurring psychiatric disorders. The biological background of aggressive behaviour is not sufficiently understood although there is evidence for involvement of serotonin (5-hydroxytryptophan (5-HT)) and testosterone. Previous research also indicates an association with metabolic alterations. Therefore, in order to provide knowledge for future development of new treatment strategies, this thesis will try to elucidate the role of metabolic alterations in patients with self-inflicted aggressive behaviour.

1.2 Historical perspectives

Self-inflicted aggressive behaviour is certainly not a modern phenomenon. An early description of a completed suicide is the one of Hannibal, the Carthagian, who committed suicide by poison, probably in 183 BC when he was about to be surrendered by his sworn enemies, the Romans (Rosen 1971). There are also numerous tales of Greek and Roman generals who in order to avoid defeat and a shameful death committed

suicide (Rosen 1971). In the Holy Bible, the description of the suicide of Judas Iscariot (Matthew 27:5) is one of the more famous ones in western society.

One of the first descriptions of deliberate self-harm is by Herodotos (5th century BC), who describes Cleomenes, a Spartan leader, who after several conflicts turned "completely mad"… "As soon as the knife was in his hands, Cleomenes began to mutilate himself, beginning on his shins. He sliced his flesh into strips, working upwards to his thighs, hips and sides until he reached his belly, which he chopped into mincemeat" (Herodotos 1920). Another description of deliberate self-harm is from the Holy Bible when Jesus meets a man, possessed by an evil spirit. "This man lived in the tombs …. No-one was strong enough to subdue him. Night and day among the tombs and in the hills he would cry out and cut himself with stones." (Mark 5:3-5). A Swedish case of deliberate self-harm is Sara Stina, born in 1763 in Sweden, and who fell ill as a teenager with abdominal pains. She is described as strongly aggressive and self-destructive, ingesting needles and potsherds, biting her arms, hitting and trying to strangle herself (Johannisson 1997). In more recent years, a biography of Princess Diana gives self-inflicted aggression a modern face, exposing her self-cutting and several suicide attempts (Morton 1997).

In medical literature, case reports of deliberate self-harm have been found since mid 19th century (Favazza 1998). The first attempt to categorize self-inflicted aggression was made by Karl Menninger in his book "Man against himself" (Menninger 1938). After this, there is a large temporal gap when self-inflicted aggression receives almost no scientific attention until

Armando Favazza, against strong resistance from several publishers manages to have his work “Bodies under siege” published in 1987 (Favazza 1987). Since then, the public interest as well as medical literature on the subject, has exploded.

1.3 Definitions

In the present thesis we define self-inflicted aggression as attempted suicide and/or deliberate self-harm. Attempted suicide is in turn defined as “those situations in which a person performs a life-threatening behaviour with the intent of jeopardizing his life or to give the appearance of such an intent” (Beck 1973). Defining deliberate self-harm is, however, a more difficult matter. There are two major alignments depending on whether or not a lack of suicidal intent should be included in the definition. Those speaking in favour of including the lack of intent (Favazza 1998; Gratz 2001) mean that attempted suicide is completely different from deliberate self-harm, since the former is by the patient regarded as an escape from an unbearable life, but the latter is a way to solve problems, release tension and to endure. Those speaking in favour of excluding the intent from the definition (Menninger 1938; Hawton et al. 2002; De Leo and Heller 2004) stress that there is a sliding scale between attempted suicide and deliberate self-harm, and that the intention not always is clear. Furthermore, some forms of deliberate self-harm are lethal while attempted suicides could be far from lethal. The overlap between suicidal behaviour and deliberate self-harm is large and co-occurrence is frequent. When studying metabolic factors behind attempted suicide and deliberate self-harm, a behavioural approach seems more pragmatic. In this thesis we therefore chose to define deliberate self-harm without mentioning the lack of suicidal intent. We will neither address

other underlying reasons for deliberate self-harm but merely focus on the behaviour.

As deliberate self-harm was considered all acts “with non-fatal out-come in which an individual deliberately did one or more of the following:

- Initiated behaviour (for example self cutting, jumping from a height), which they intended to cause self-harm;
- Ingested a substance in excess of the prescribed or generally recognised therapeutic dose;
- Ingested a recreational or illicit drug that was an act that the person regarded as self-harm;
- Ingested a non-ingestible substance or object.” (Hawton, Rodham et al. 2002)

1.4 Epidemiology

The prevalence of self-inflicted aggression is difficult to estimate. As for completed suicides, it is in several cases uncertain whether death was self-inflicted or accidental. According to the WHO, suicide rates have been increasing by 60% over the last 45 years, in developing as well as the developed countries (WHO 2002). In the year 2000, one million people were estimated to have died from suicide and 10 to 40 times more people had attempted suicide. Suicide rates vary according to sex, age, ethnicity, region, time, and probably, practices of death registration (Hawton 2009). Over the past 20 years suicide rates have, however, been declining in several countries. The cause of this decline is unknown but there is a temporary association with the increased prescription of selective serotonin reuptake inhibitors (SSRI) (Olfson et al. 2003; Isacsson 2006; Castelpietra et al. 2008; Erlangsen et al.

2008). It is, however, still a subject of discussion whether there is a causal relationship between the increased SSRI prescription and the decrease in suicide rates. (Olfson and Shaffer 2007).

When it comes to deliberate self-harm, incidents may pass unnoticed, since the person involved might not seek medical care. The rates mentioned below should therefore be regarded with precaution and it should be emphasized that prospective studies are lacking. A report from 2004 concluded that data present at that time indicated a slight, but not significant, increase in the prevalence of deliberate self-harm in Sweden (Socialstyrelsen 2004). More recently, in Skåne, the prevalence of having engaged in deliberate self-harm was investigated in adolescents, aged 14-15 years (Lundh et al. 2007). A self-rating scale examining different forms of deliberate self-harm was administered to 123 adolescents in four school classes. 65.9% of the adolescents reported a history of some kind of deliberate self-harm at least once and 13.8% had done so many times. This is well above estimations made 2004 when 1-7% of the adolescent girls were approximated to self-harm (Socialstyrelsen 2004). Lower rates were also found in large surveys in the United Kingdom (13.2%) (Hawton, Rodham et al. 2002), Australia (12.4%) (De Leo and Heller 2004), and North America (13-15%) (Ross 2002; Laye-Gindhu 2005). A probable explanation for the huge difference is that the Swedish study used a questionnaire investigating 16 different forms of deliberate self-harm, and some of these might not be recognized as deliberate self-harm when not specifically asked for (i.e. “prevented wounds from healing” or “severely scratched yourself, to the extent that scarring or bleeding occurred”). Numbers, similar to those in the Swedish study, were also obtained by a study using the same questionnaire (35% having

engaged in deliberate self-harm at least once and 15% reporting more than 10 incidents) (Gratz 2001).

The studies above do not measure temporal changes, although all of them show a high prevalence of deliberate self-harm. The only surveys investigating deliberate self-harm over time used a different approach, studying consecutive subjects referred to an emergency room after an episode of deliberate self-harm between 1985 and 1995 (Hawton et al. 1997). After a decline in rates in the late seventies and early eighties, the overall incidence rose between 1985 and 1995 with 50.9%. The rise was more pronounced in men (62.1%) than in women (42.2%). However, when investigating rates in the same geographical area between 1990 and 2000, the incidence was declining during the last three years, and at end-point there was no significant difference compared to overall rates in 1990 (Hawton et al. 2003). A weakness in this study is that cases of deliberate self-harm, not seeking medical care, passed unnoticed. Furthermore in a clinical setting, during times of heavy work load, all cases might not be reported.

Most studies considering gender variations in deliberate self-harm report higher rates in women compared to men (Schmidtke et al. 1996; Claassen et al. 2006). In contrast two studies investigating deliberate self-harm with a detailed questionnaire found no gender difference in incidence (Gratz 2001; Lundh, Karim et al. 2007). Females however reported significantly higher rates of cutting (Lundh, Karim et al. 2007). Hawton et al studied gender variations in the incidence of deliberate self-harm related to age. Overall, women were overrepresented with a ratio of 1.5:1(Hawton and Harriss 2008) . In the youngest persons, this ratio was 8:1, and slowly declining over the lifecycle to an

overweight of men in the oldest persons with a female:male ratio of 0.8:1.

1.5 A relation between self-inflicted aggressive behaviour and violence directed towards others

Epidemiological studies among adolescents in the United States suggest a strong linkage between interpersonal violence and self-inflicted aggression (Cairns 1988; Orpinas et al. 1995; Coker et al. 2000; Borowsky et al. 2001; Evans 2001; Centers for Disease Control and Prevention 2004; Swahn et al. 2008). Adolescents who have attacked others with a weapon (Evans 2001; Flannery et al. 2001), engaged in dating violence (particularly for boys)(Silverman et al. 2001) or perpetrated sexual violence (Borowsky et al. 1997; Swahn, Simon et al. 2008) have been shown to have increased risk for suicidal behaviour. Furthermore, male violent offenders and male suicide attempters have been found to share temperament traits (Engstrom et al. 1999). These strong linkages between aggressive behaviour inflicted upon the self and upon others suggest that there might be common underlying biological mechanisms. Several (but not all) studies have shown that violent suicide attempters as well as habitually violent men have low levels of 5-hydroxy indoleacetic acid (5-HIAA) (Traskman et al. 1981; Virkkunen et al. 1995) and homovanillic acid (HVA) in the CSF (Agren 1983; Traskman-Bendz et al. 1993; Virkkunen et al. 1996; Engstrom et al. 1999). In addition, patients with borderline personality disorder (BPD) (a condition associated with self-inflicted aggression) as well as violent criminal offenders show decreased metabolism in prefrontal cortex (Soloff et al. 2003). This may be associated with the reduced impulse control found in these

conditions. Some further neurobiological associations will be addressed below.

1.6 Leptin

1.6.1 Leptin and self-inflicted aggressive behaviour

Leptin is the product of the ob gene, discovered in 1994 (Zhang et al. 1994). It is mainly synthesized in adipose tissue, and its synthesis correlates to body weight. The circulating concentration of leptin is increased in obesity, and leptin has an anorexigenic effect via several neuroendocrine systems, including the hypothalamus-pituarity-adrenal axis (HPA-axis) (Ahima et al. 2000). It is transported via a satiable system to the brain, where it exerts its central effects (Banks et al. 1996). Leptin is involved in memory and learning (Harvey et al. 2006), reproduction (Ahima et al. 1996; Chehab et al. 1996), locomotion (Pelleymounter et al. 1995), sleep (Birketvedt et al. 1999; Sinton et al. 1999), and brain development (Ahima et al. 1999). Furthermore, the leptin receptor is highly expressed in areas involved in the regulation of mood and emotion, such as amygdala, hippocampus and cortex (Lu 2007). Leptin has thus become a focus of attention in psychiatric research.

It has previously been shown that circulating leptin and cholesterol are lower in suicide attempters than in healthy controls (Gallerani et al. 1995; Garland et al. 2000; Atmaca et al. 2002). Furthermore, patients having used a violent method for the suicide attempt have even lower levels of plasma total cholesterol and leptin compared to those having used a non-violent method (Atmaca et al. 2008). In contrast to this, two other studies found low serum cholesterol exclusively in patients with a violent suicide attempt, and not in those with a non-violent attempt (Alvarez et al. 2000; Vevera et al. 2003). Alvarez

et al compared the suicide attempters with healthy controls, while Vevera et al used non-suicidal psychiatric patients. Also speaking for reduced leptin activity in patients with self-inflicted aggression is a study by Eikelis et al. They found leptin messenger ribonucleic acid (mRNA) in brain tissue from persons dying from "natural causes" (mainly sudden cardiac death), but not in persons dying from suicide, indicating a reduced cerebral production of leptin in these patients (Eikelis et al. 2006). Leptin and cholesterol have also been found to be lower in patients with BPD compared to healthy controls, and the low levels were also associated with measures of impulsivity and suicidality (Atmaca et al. 2002). At the time of designing paper I, no studies investigating leptin in CSF in suicide attempters, was available.

1.6.2 Leptin and Major Depressive Disorder (MDD)

We also examined CSF-leptin in relation to MDD. This is of importance because there is conflicting evidence regarding leptin levels in patients with MDD (table 1). There are studies providing evidence for decreased levels of circulating leptin in patients with MDD (Kraus et al. 2001; Atmaca et al. 2005; Jow et al. 2006). Others indicate increased levels of leptin (Antonijevic et al. 1998) although this might be restricted to only women (Rubin et al. 2002; Esel et al. 2005) or patients with atypical depression (Gecici et al. 2005). There are also negative findings with unaltered leptin levels in patients with MDD (Deuschle et al. 1996) and seasonal affective disorder (Cizza et al. 2005). One study measuring the leptin gradient i.e. the difference in arteria brachialis compared to vena jugularis interna, found a diminished gradient in patient with MDD, compared to healthy controls, who had a positive gradient indicating local synthesis in the brain (Eikelis, Esler et al. 2006). A partially prospective epidemiological study showed elevated serum leptin levels in women with a life-time history of

depression (Pasco et al. 2007). In this study, high serum leptin levels also predicted an increased risk for depression in non-smoking women over a five year follow-up. However it is not possible from this study to see how major depressive disorder *per se* affects serum leptin, since samples were not taken during the actual depressive episode, but at a planned follow-up in an epidemiological setting.

Fewer but more consistent results have been found among rodents. Exposing rats to chronic, unpredictable stress, and chronic social defeat is a model used to induce behavioural changes resembling some symptoms of human depression (Blanchard et al. 1995; Rygula et al. 2005; Willner 2005). Rats exposed to this model show low plasma leptin along with anhedonic behaviour and behaviour despair in the forced swim test compared to unstressed controls (Lu et al. 2006). Systemic as well as intrahippocampal infusion of leptin reverses the behavioural symptoms. In contrast, the symptoms were not reversed by hypothalamic infusion. Depressive symptoms have also been observed in streptozotocin-induced diabetic mice. These have low levels of circulating leptin and the depressive symptoms are reversed by leptin injections (Hirano et al. 2007). Probably MDD in humans is a more complex matter than in rats.

AUTHOR, YEAR	MAIN RESULT
(Deuschle, Blum et al. 1996; Kauffman et al. 2005)	Unaltered levels of circulating leptin in MDD
(Cizza, Romagni et al. 2005)	Unaltered levels of circulating leptin in seasonal affective disorder
(Kraus, Haack et al. 2001; Atmaca, Tezcan et al. 2005; Jow, Yang et al. 2006)	Low levels of circulating leptin in MDD
(Eikelis, Esler et al. 2006)	No cerebral leptin production in MDD
(Antonijevic, Murck et al. 1998)	Elevated nocturnal profiles of circulating leptin in MDD
(Gecici, Kuloglu et al. 2005)	High levels of circulating leptin in atypical but unaltered in non-atypical depression
(Rubin, Rhodes et al. 2002; Esel, Ozsoy et al. 2005)	Increased levels of circulating leptin in women with MDD
(Pasco et al. 2008)	Increased levels of circulating leptin is a risk factor for MDD in women

Table 1. Research made, investigating the relation between depression and leptin in humans.

Some antidepressants have been found to raise serum leptin in depressed patients (Kraus et al. 2002; Esel, Ozsoy et al. 2005), while other studies have found leptin levels to remain unchanged during treatment (Hinze-Selch et al. 2000; Kraus, Haack et al. 2002; Kauffman, Castracane et al. 2005) (table 2). The discrepant findings in these studies could be explained by several different factors. Different antidepressants were e.g. examined. Two of the studies used small sample sizes and confirmed the null hypothesis, which might predispose for type 2 errors (Hinze-Selch, Schuld et al. 2000; Kauffman, Castracane et al. 2005). Furthermore, one of these two investigations did not make calculations for men and women separately, which also might have hampered the results. In the third study calculations were made for the entire group of 36 patients who used 4 different antidepressants, which also might be misleading, since from a biological viewpoint, different medications obviously can affect patients differently (Esel, Ozsoy et al. 2005).

AUTHOR, YEAR	MAIN RESULT
(Kraus, Haack et al. 2002)	Slightly increased levels of circulating leptin during mirtazapine treatment, no alteration during venlafaxine treatment
(Esel, Ozsoy et al. 2005)	Increased levels of circulating leptin during treatment (calculations made for amitriptyline, venlafaxine, paroxetine and fluoxetine together)
(Hinze-Selch, Schuld et al. 2000)	Unaltered levels of circulating leptin after treatment with amitriptyline, nortriptyline, paroxetine compared to no treatment. Separate analyses for different treatments.
(Kauffman, Castracane et al. 2005)	Unaltered levels of circulating leptin in women with MDD treated with citalopram compared to healthy women, treated or untreated

Table 3. Research made, investigating the relation between leptin and anti-depressant treatment.

1.7 Glucose metabolism and aggressive behaviour.

An association between violent behaviour and glucose metabolism has been suspected for many years. In 1947, Wilder reviewed a number of case reports associating hypoglycaemia with aggressive behaviour and proposed that blood sugar should be investigated as a possible etiologic factor for violent criminal behaviour (Wilder 1947). In the seventies, Bolton examined male Quolla Indians in Peru, a tribe known for their aggressive and violent behaviour. He found that those who reacted with mild to moderate hypoglycaemia during oral glucose tolerance test (OGTT) were ranked as the most aggressive individuals in the group (Bolton 1973). They also showed the most hostile fantasies (Bolton 1976). However these studies have been criticized, since glycaemia was measured with a strip test (Dextrostix^{R}), which by then was a technique reliable only within broad measures (Bolton 1976). In a later study, healthy men from United Kingdom were examined with OGTT and a questionnaire, investigating hostility and aggression, was used. A relationship between hypoglycaemia during OGTT and aggression was found (Benton et al. 1982).

Virkkunen and co-workers have made several studies on male forensic patients (Virkkunen 1982; Virkkunen and Huttunen 1982; Virkkunen 1983; Virkkunen 1984; Virkkunen 1986; Virkkunen and Narvanen 1987; Virkkunen et al. 1994). During OGTT, habitually violent patients were found to have a reactive hypoglycaemic tendency after the initial rise in blood glucose, probably due to enhanced insulin secretion. (Insulin is a hormone secreted by the pancreatic islets, decreasing blood glucose.) Many of these patients also less usual hypoglycaemic

symptoms such as motor restlessness, fatigue, difficulties to concentrate, and irritability(Virkkunen and Narvanen 1987). An epidemiological and prospective study, also in Finland, has shown that the risk for attempted and completed suicide is associated with insulin sensitivity (Golomb et al. 2002). Insulin sensitivity was here estimated indirectly with three items; extreme quartiles of high High Density Lipoprotein (HDL)-cholesterol, low body mass index (BMI) and low systolic blood pressure. The relative risk for both attempted and completed suicide was higher for patients having one to three of these items.

Glucagon is another hormone secreted by the pancreatic islets. It is the antagonist of insulin and the most potent of the factors augmenting plasma glucose (Lefébvre 2004). Glucagon secretion increases in response to hypoglycaemia and subsequently raises blood glucose levels. A recent study examining men with antisocial personality disorder and habitually violent behaviour found that they had significantly lower basal glucagon levels (Virkkunen et al. 2007). This is another aspect strengthening the association between aggressive behaviour and disturbed glucose metabolism.

The findings of an association between hypoglycaemia and aggressive behaviour in humans have however not been successfully replicated in mice (Andrade et al. 1988). Furthermore, after a mixed meal, reactive hypoglycaemia rarely occurs in healthy humans (Benton 1988). This questions the clinical relevance of a hypoglycaemic tendency in response to a glucose challenge and its relation to hostility. Benton suggests, in a review article, that rather than viewing blood glucose levels as directly influencing the brain, they should be regarded as symptoms of other neuronal activity (Benton 1988). Cerebral mechanisms must thus be studied.

1.8 Immunology and aggressive behaviour

There is abundant evidence for a role of the immune system in psychiatric morbidity (Nassberger and Traskman-Bendz 1993; Muller and Ackenheil 1998; Schiepers et al. 2005; Dantzer et al. 2008; Lindqvist et al. 2009). Current research also gives indications of a connection between the immune system and aggressive behaviour: Patients with hepatitis C, receiving interferon alpha therapy have increased irritability (McHutchison et al. 1998) and ratings on anger and hostility (Kraus et al. 2003) indicating that cytokines might facilitate expression of aggression. Cytokines are also present in brain regions associated with aggression such as hypothalamus or midbrain periaqueductal grey (Siegel et al. 1999). In our group interleukin-6 (IL-6) in the cerebrospinal fluid has been found to be increased in suicide attempters compared to healthy controls with the highest levels in patients using a violent method for the attempt (Lindqvist, Janelidze et al. 2009).

Interleukin-1beta (IL-1β) is a pro-inflammatory cytokine, mainly synthesized by macrophages but also other cells throughout the brain (Aschner 1998; Tuttolomondo et al. 2008), and has been associated with aggressive behaviour. Increased expression of plasma IL-1β in response to lipopolysaccharide stimulation was correlated to increased levels of hostility in healthy women (Suarez et al. 2004). Furthermore, injection of IL-1β into the hypothalamus or midbrain periaqueductal grey leads to defensive rage behaviour in cats (Zalcman and Siegel 2006).

Interestingly, IL-1β is also involved in the regulation of glucose metabolism. The cytokine has been found to induce

hypoglycaemia by central as well as peripheral mechanisms, independently of insulin, and despite increased levels of glucocorticoids, catecholamines and glucagon (Del Rey and Besedovsky 1987; Del Rey and Besedovsky 1992; Del Rey et al. 1998; Del Rey et al. 2006). This may reflect a separate connection between IL-1β and aggressive behaviour, since a hypoglycaemic tendency in response to a glucose challenge has been found in habitually violent men (Virkkunen 1982; Virkkunen and Huttunen 1982; Virkkunen 1986; Virkkunen and Narvanen 1987; Virkkunen, Rawlings et al. 1994).

1.9 Borderline personality disorder

Two of the papers included in this thesis refer to patients with Borderline personality disorder (BPD), a sub-group of patients with self-inflicted aggression. In these patients, the self-inflicted aggressive behaviour is a diagnostic criterion (American Psychiatric Association 2000). Of patients with BPD, 60-75% have attempted suicide (Oldham 2006), and an even higher percentage is estimated to engage in deliberate self-harm. Suicide rates are also high; 3-8.5% (McGlashan 1986; Paris et al. 1987; Stone et al. 1987). Furthermore, “inappropriate, intense anger or difficulties in controlling anger” is another diagnostic criterion. Thus, this disorder has two criteria based on aggressive behaviour and is of interest in the context of self-inflicted aggression.

1.9.1 BPD - diagnostic difficulties

Patients with BPD constitute a motley group. In the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM IV) there are nine criteria describing patient characteristics, and five of them have to be fulfilled in order to set the diagnosis (American Psychiatric Association 2000). Using this method, there are numerous combinations of criteria that can constitute an official BPD diagnosis. DSM IV thus has disadvantages as a diagnostic system, most prominent in the field of personality disorders. Vast co-occurrence of disorders, as well as failure to describe personality traits not fulfilling the criteria for a disorder, are limitations of the system. These are challenges which will be addressed by the DSM V where there will probably be a radical change in the field of describing personality disorders (Widiger 2008).

In patients with BPD, co-morbidity is prevalent for axis I as well as axis II disorders (Oldham et al. 1995; Zanarini et al. 1998; Zanarini et al. 1998; Zimmerman and Mattia 1999; Philipsen et al. 2008). Skodol et al conclude that although BPD can exist as a sole diagnose, it is fair to say that a sample of such individuals cannot be considered representative (Skodol et al. 2002). Many of the symptoms in BPD overlap those of other diagnoses such as mood disorders, anxiety disorders, psychotic disorders, Attention Deficit Hyperactivity Disorder (ADHD), substance use disorders, and eating disorders. This is the most probable explanation for the vast co-occurrence of other psychiatric disorders.

Historically, diagnostic discussions have been made concerning the BPD interface with schizophrenia and MDD. No link has been found between BPD and schizophrenia and only a weak,

non-specific association between BPD and MDD (White et al. 2003). Lately, the focus has shifted towards distinctions between BPD and bipolar disorder, as well as impulse spectrum disorders. In a review article, Paris et al conclude that BPD and bipolar disorder co-occur, but their relationship is not specific and inconsistent. Family studies, treatment response and phenomenology suggest two different entities, but current research is insufficient, and a partially common aetiology for the two disorders cannot be excluded (Paris et al. 2007). Concerning impulse spectrum disorders, family studies speak for an association to BPD (White, Gunderson et al. 2003), and childhood ADHD might be a risk factor for BPD (Philipsen, Limberger et al. 2008).

1.9.2 Prevalence and aetiology

Community studies in the western society have indicated a prevalence of approximately 1% for BPD (Samuels et al. 2002). Between two thirds and three quarters of the patients diagnosed with BPD are women (Johnson et al. 2003).The aetiology of BPD is incompletely known, but seems to be multi-factorial, including biological, psychological and cultural components (Paris 2005). Biological components include heritable and/or inborn temperament traits, presenting no later than in adulthood. Heritable factors account for about half of the variability in temperament traits (in the case of BPD; affective instability and impulsivity) (Livesley et al. 1998). A twin study indicates that the diagnose BPD is heritable to a similar extent (Torgersen et al. 2000). When studying neurotransmitters, low serotonergic functioning has been associated with impulsivity, impulsive aggression and a history of suicide attempt, which are core features of BPD (Coccaro et al. 1989; Gurvits et al. 2000; Paris et al. 2004). Furthermore, low plasma cholesterol has been

found in patients with BPD (New et al. 1999; Atmaca, Kuloglu et al. 2002).

Psychological components in the aetiology of BPD could be striking but should be regarded with precaution (Paris 1997). Many patients describe difficulties during childhood such as dysfunctional families or bullying. Among BPD patients, every fourth patient reports sexual abuse from a caretaker during childhood (Zanarini 2000), and every third describes severe abuse (Paris et al. 1994). However, although child abuse is a risk factor, it is not specific for BPD. Furthermore, resilience is extensive and 80% of people with a history of sexual abuse show no psychopathology as adults (Paris 1997). A recent meta-analysis does not support a causal relation between childhood sexual abuse and deliberate self-harm, but rather suggests that the two are correlated to the same psychiatric risk factors (Klonsky and Moyer 2008). Thus, adverse life events do not seem to be pathogenic themselves, but may produce sequelae in vulnerable populations (Monroe and Simons 1991). Since personality traits are heritable gene-environment interactions might better explain the findings of traumatic childhood experiences in patients with BPD (Paris 1997).

As for the cultural aspects of BPD, no cross-cultural studies have been made so far. However core behaviours, such as attempted suicide, seem to be less common in traditional societies, but increasing in modern societies, and societies changing rapidly (Paris 2005).

1.9.3 Treatment

Treating patients with BPD is a therapeutic challenge. A variety of psychotherapies have been subjected to clinical trials with encouraging results, Dialectical Behavior Therapy (DBT) being the most evaluated (Paris 2008). However, the number of studies is still limited, and sample sizes have been too small to produce reliable evidence (Binks et al. 2006). Primary outcome measures in several studies have been reduction in suicidal acts and deliberate self-harm, as well as degree of hospitalization. Concerning pharmacological treatment, a Cochrane report concludes that present evidence for treating BPD patients with drugs is insufficient, mainly because the studies are small, but antidepressant medication might have positive effects (Binks et al. 2006). However, pharmacological treatment can, generally speaking, produce a mild relief of symptoms; SSRIs, low-dose atypical neuroleptics and mood stabilizers reduce impulsivity and anger (Paris 2008). Benzodiazepines are not very useful and might induce substance abuse in these high-risk patients (Paris 2008). Thus present pharmacotherapy does not cause remission in patients with BPD. Failure to understand this may result in the polypharmacy seen in many patients with BPD, mainly resulting in side-effects (Zanarini et al. 2001).

Psychotherapy is at present the treatment option of choice, although complementary pharmacotherapy is given in most cases. Unfortunately, current psychotherapeutic methods are expensive, and the number of educated therapists willing to work with these patients is not sufficient. In a study interviewing patients with deliberate self-harm concerning what treatment they would like, most patients answered that they wanted to talk with the same person, and several times over a longer period. Remarkably few had however received this kind of contact (Samuelsson 2009).

1.9.4 Prognosis

Remission rates are high. Long-term (10-15 years) follow up of inpatients with BPD show that 75-88% of the patients obtain remission (Paris, Brown et al. 1987; Stone, Stone et al. 1987; Zanarini et al. 2006). Psychotherapy seems to speed up the process (Paris 2008). At the age of 50 years, 90% of the patients are estimated to have recovered. A majority of the remaining 10% will however have committed suicide (Paris, Brown et al. 1987; Stone, Stone et al. 1987).

A large study investigating overall mortality in patients engaging in deliberate-self harm has found a double overall mortality compared to the normal population. The mortality is particularly increased in men. The risk for completed suicide in women and men was increased 17 fold. Furthermore, there was a rise in mortality from accidents, poisoning and homicide. More unexpectedly,, there were also significant increases in the risk of dying from several other diseases (i.e. originating from the nervous, circulatory, respiratory, or digestive system)(Hawton et al. 2006). Thus patients with deliberate self-harm behaviour have an increased likelihood of dying prematurely from most physical illnesses.

2 Aims

The general aim of this thesis was to enlighten the importance of metabolic factors in patients with self-inflicted aggression.

Specific aims:

I. In patients with a recent suicide attempt; is suicidality and the presence of major depressive disorder associated with CSF-leptin, CSF-insulin and BMI?

II. Is deliberate self-harm and borderline personality disorder associated with altered regulation of glucose metabolism?

III. Is a recent suicide attempt associated with CSF-IL-1β with respect to suicidality and Cluster B personality disorder?

IV. Is deliberate self-harm and borderline personality disorder associated with deviant plasma IL-1β, IL-6 and TNF-alpha after fasting and during the oral glucose tolerance test?

3 Material and methods

3.1 Ethical approval

All studies were approved by the Lund University Ethics Committee, and all patients gave informed consent.

3.2 Subjects

3.2.1 Subjects examined with lumbar puncture

From 1987 to 2001, patients, admitted to the University hospital in Lund after a suicide attempt, were asked to participate in the study (Figure 1). As suicide attempt was considered "those situations in which a person performs a life-threatening behaviour with the intent of jeopardizing his life or to give the appearance of such an intent" (Beck 1973). The patients were classified according to the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM III-R) (American Psychiatric Association 1987), and in most instances by two independent psychiatrists.

Finally, 145 patients were non-consecutively recruited shortly after a suicide attempt. For paper I and II, CSF from 78 patients was available, for paper IV, CSF was available from 119 patients. Plasma samples were also taken, but unfortunately not sufficient plasma was left at the time of these studies.

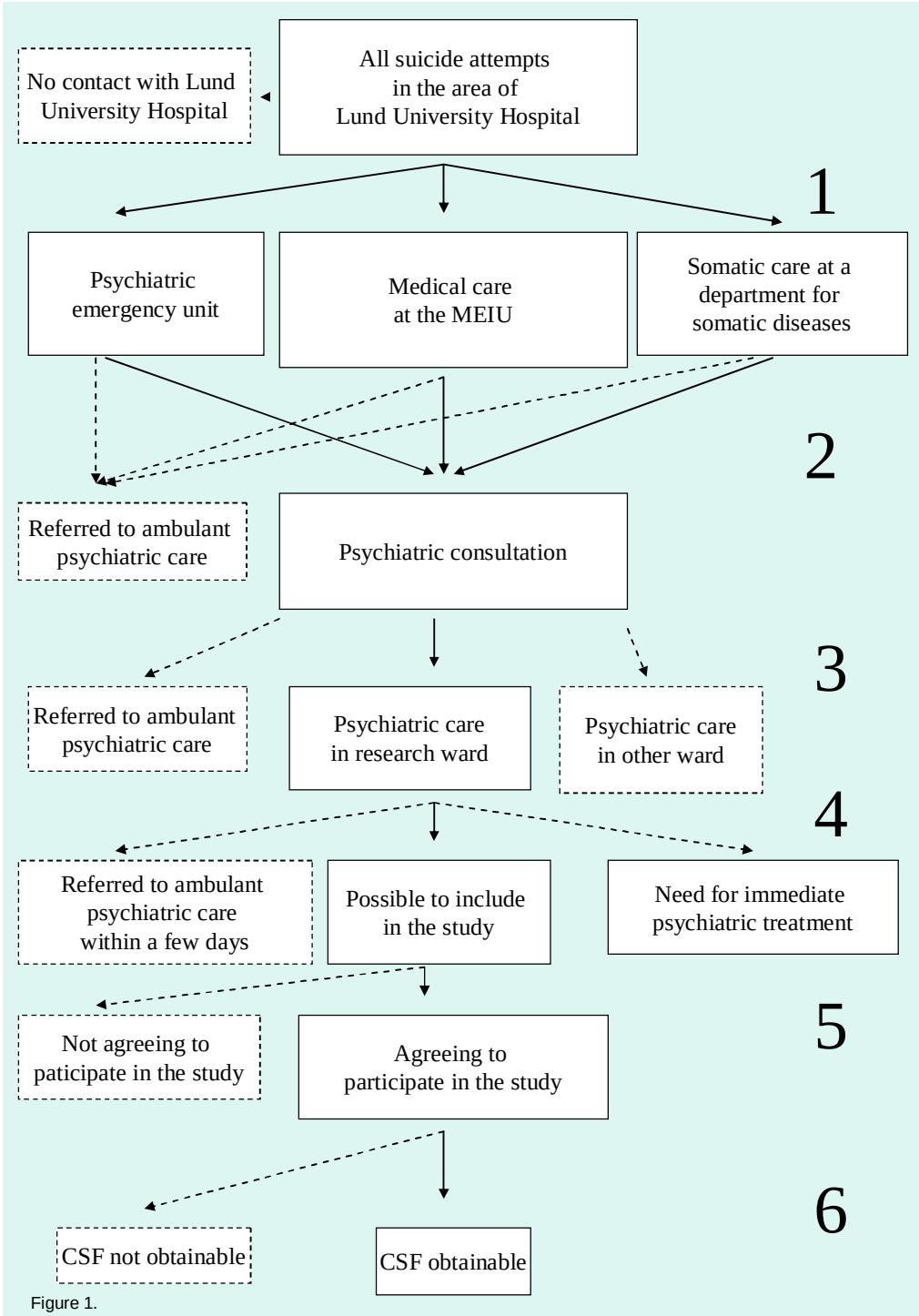
All suicide attempts
in the area of
Lund University Hospital
No contact with Lund
University Hospital
1
Psychiatric
emergency unit
Medical care
at the MEIU
Somatic care at a
department for
somatic diseases
2
Referred to ambulant
psychiatric care
Psychiatric consultation
3
Referred to ambulant
psychiatric care
Psychiatric care
in research ward
Psychiatric care
in other ward
4
Referred to ambulant
psychiatric care
within a few days
Possible to include
in the study
Need for immediate
psychiatric treatment
5
Not agreeing to
paticipate in the study
Agreeing to
participate in the study
6
CSF not obtainable
CSF obtainable

Figure 1.

Figure 1.
Recruitment of suicide attempters (paper I, II and IV).

1. In the year 2000 Lund University Hospital served a population of almost 215.000 inhabitants. During the years the study was conducted (1987-2001) approximately 190 suicide attempters were admitted every year to the Medical Emergency and Intensivecare Unit (MEIU) (Niméus 2000; Backman et al. 2003). The number and characteristics of persons attempting suicide without seeking care at the hospital is impossible to estimate.
2. At the MEIU every patient was seen by a consultant psychiatrist. Approximately 2/3 of these consultations are made during week-ends, evenings and vacations when the research team was not on duty (Ojehagen et al. 1991). During weekdays (Monday to Friday) approximately half of consultations were made by a psychiatrist in the research team (Niméus 2000). A study on a part of the material considered the patients evaluated by the research team comparable to the ones receiving a regular psychiatric consultation concerning age, gender, frequency of ongoing or previous treatment (Ojehagen, Regnell et al. 1991) and risk for completed suicide (Öjehagen, personal communication). Another study, also on part of this material found no indications of significant differences in gender, age or proportion of repeaters between the research sample and all patients with deliberate self-harm admitted to the ICU (Backman, Ekman et al. 2003).
3. Of the patients evaluated by a research psychiatrist, approximately 50% were referred to the hospital's psychiatric research ward, 10% to other psychiatric wards and 40% to ambulatory care.
4. Within one week after admission to the research ward, patients were asked if they wanted to participate in the research program. Patients referred to ambulatory care within a few days (approximately 3%) and patients with immediate need for psychiatric treatment (approximately 8%) were excluded (Magne-Ingvar et al. 1992). Several patients were also missed during periods of high work load at the ward.
5. Approximately 9% of the patients did not agree to participate in the study (Magne-Ingvar, Ojehagen et al. 1992).
6. CSF was not obtainable from all patients willing to participate in the study. Moreover, when the analyses for this thesis were made, all CSF samples were not available.

Of the 78 patients in paper I and II, thirteen patients used medication for somatic diseases; treatment for gastric ulcus/gastritis (n=4), treatment for hypertension (n=3), antibiotics (n=1), testosterone (n=1), beta 2 receptor stimulating medication (n=1) and acetylsalicylic acid (n=1), insulin and levothyroxine (n=1), glibenclamide (n=1). Seven patients also had detectable levels of psychotropics in plasma; clomipramine (n=2), amitriptyline (n=1), perfenazine (n=1), maprotiline (n=1), tioridazine (n=1) and citalopram (n=1). For two patients, it was not known whether there were detectable levels of psychotropics in plasma or not.

Patients were sub-grouped according to the presence of MDD as well as diagnosis of Cluster B. They were also divided with respect to previous suicide attempt(s) ("repeaters") or not. Drug overdoses by ingestion, single wrist cuts, or combinations of these were classified as non-violent attempts, while all other attempts were considered as violent (eg. hanging, drowning, gas poisoning, several deep cuts) (Traskman, Asberg et al. 1981). Seventeen patients had somatic diagnoses, of which migraine headache and/or chronic pain were the most common (n=10).

Paper I

The original sample consisted of 78 patients recruited between 1987 and 1998. Since a recent study showed that plasma leptin is lower in patients with schizophrenia as compared to healthy controls (Kraus, Haack et al. 2001), six patients with a diagnosis of a psychotic syndrome were excluded after the data collection. The 72 remaining patients were included. Three patients had diagnoses that might affect leptin levels. One had insulin dependent diabetes mellitus in combination with hypothyroidism and belonged to the MDD group. Two patients had non-insulin

dependent diabetes and belonged to the non-MDD group. For further description of the patients, please see paper I.

Paper II

The original sample consisted of 78 patients recruited between 1987 and 1998. Patients with diabetes were excluded (n=3). One patient was excluded due to the lack of CSF for the analysis. The remaining 74 patients were included. For further description of the patients, please see paper II.

Paper IV

The original sample consisted of 119 patients recruited between 1987 and 2001. Patients with diabetes (n=4), hepatic steatosis (n=1) or current antibiotic treatment (n=2) were excluded from analyses in the current study, as well as all patients who received antidepressant or neuroleptic drugs (n=6). For further description of the patients, please see paper IV.

3.2.2. Subjects submitted to OGTT (paper III and IV)

From July 2004 to December 2007 female patients with borderline personality disorder and current self injurious behaviour, attending Division of Psychiatry at the University Hospital in Lund, were asked to participate in the study (Figure 2). Inclusion criteria were a borderline personality disorder and self-injurious behaviour for at least two years. At least five incidents of deliberate self-harm should have occurred during the last 6 months, and one of them during the last month, unless the patient was hospitalised in order to avoid self-harm.

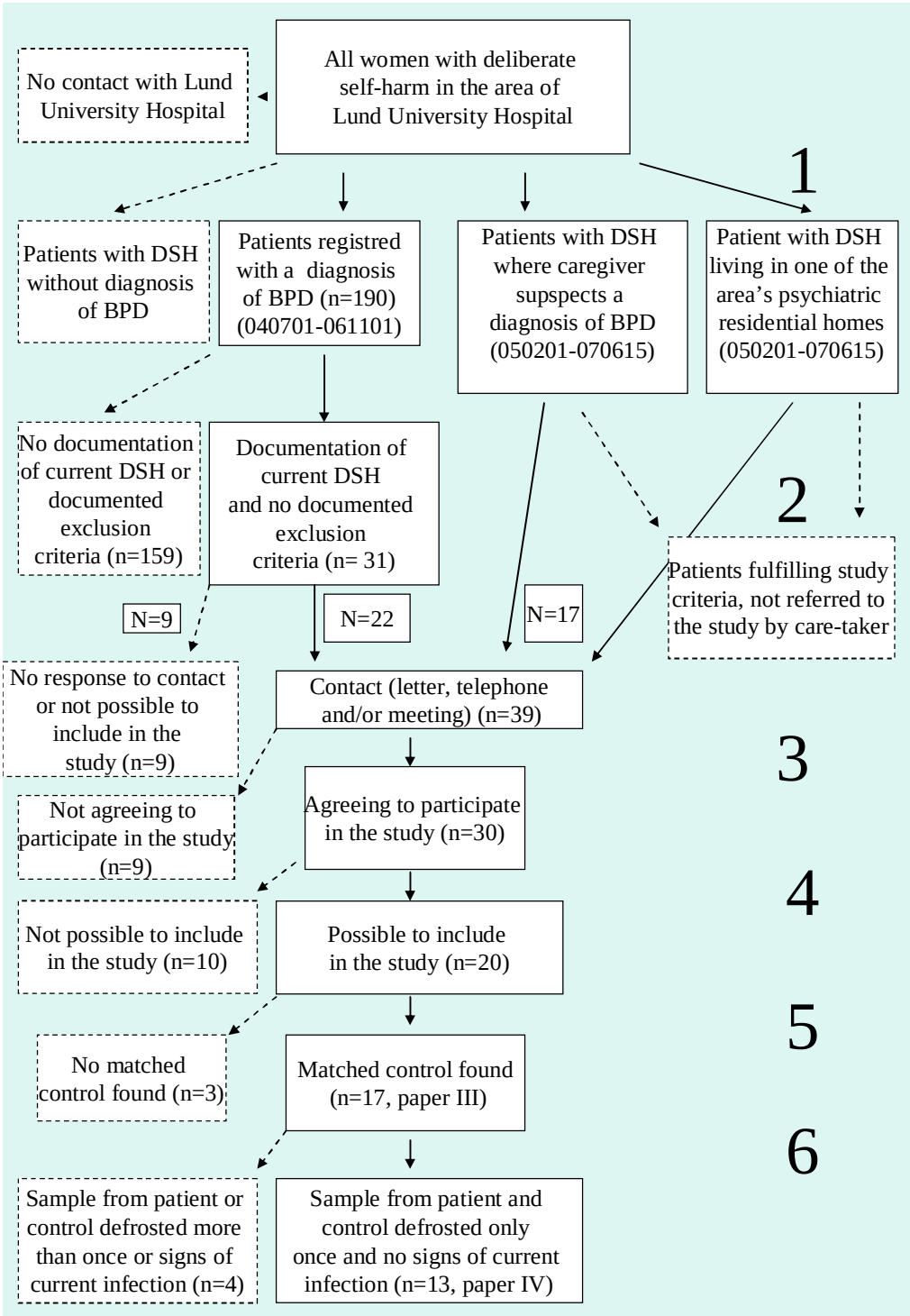
All women with deliberate self-harm in the area of Lund University Hospital
No contact with Lund University Hospital
1
Patients with DSH without diagnosis of BPD
Patients registred with a diagnosis of BPD (n=190) (040701-061101)
Patients with DSH where caregiver supspects a diagnosis of BPD (050201-070615)
Patient with DSH living in one of the area's psychiatric residential homes (050201-070615)
No documentation of current DSH or documented exclusion criteria (n=159)
Documentation of current DSH and no documented exclusion criteria (n= 31)
2
Patients fulfilling study criteria, not referred to the study by care-taker
N=9
N=22
N=17
No response to contact or not possible to include in the study (n=9)
Contact (letter, telephone and/or meeting) (n=39)
3
Not agreeing to participate in the study (n=9)
Agreeing to participate in the study (n=30)
4
Not possible to include in the study (n=10)
Possible to include in the study (n=20)
5
No matched control found (n=3)
Matched control found (n=17, paper III)
6
Sample from patient or control defrosted more than once or signs of current infection (n=4)
Sample from patient and control defrosted only once and no signs of current infection (n=13, paper IV)

Figure 2.
Recruitment of patients with deliberate self-harm, paper III and IV.

1. It is impossible to estimate how many women are involved in deliberate self-harm in the Lund area. This thesis only addresses women with severe deliberate self-harm and BPD. Patients with BPD are often help-seeking and thus likely to have contact with Lund University Hospital. Some drop-outs are however probable.
2. All charts of patients with BPD were skimmed in order to detect acts of deliberate self-harm. If there was any suspicion (n=31), a letter was sent to advertise the patient and a telephone call made approximately a week later. Nine of the patients were not possible to contact, or were after a brief telephone contact found not to be able to include in the study.
   Patients were also recruited from clinicians and psychiatric residential homes. Here might be a large number of drop-outs, possibly excluding the most severe cases, where the care-giver did not want to put further strain on an already labile patient.
3. 39 patients seemed, after a brief telephone contact, possible to include in the study. Nine of these did not agree to participate. Some of them argued that they were not feeling well enough to participate in a study; others did not give any reason.
4. Of the 30 patients agreeing to participate, ten were not possible to include for the following reasons; seven did not fulfil the criteria for BPD, and in three patients it was not possible to insert a working intravenous cannula (one of the three latter was also found to have diabetes).
5. Controls were matched for age and BMI. After the inclusion of 17 matched controls, we stopped recruiting, since 17 couples were sufficient, according to the power analysis.
6. IL-1β is very sensitive to defrosting. One patient and one control (matched for another patient) had samples defrosted more than once. Furthermore, one patient had an elevated c-reactive protein (CRP), and another had current antibiotic treatment. We thus included only 13 matched couples in paper IV.

We used the definition of Hawton et al for deliberate self-harm (please see Introduction) (Hawton, Rodham et al. 2002; De Leo and Heller 2004).

Exclusion criteria in paper III were a history of diabetes mellitus or active liver disease, defined as at least a twofold rise in plasma (p-) aspartat aminotransferase and p-alanin aminotransferase (ALAT). If the subject had fever (>37.5 degrees Celsius), she was asked to come back after one to two weeks. During the first four months of the study, exclusion criteria also included any changes in medication during the last month and /or any ingestion of medication that could affect plasma glucose. Since we were not able to include one single patient during these four months, we decided to keep only the three first listed exclusion criteria. Twenty patients were included. We found 17 healthy controls who would match the patients for sex, age (±8 years) and BMI (±2 kg/m^2). Thus, 17 patients and controls were included in paper III. Controls were recruited from a random selection of the population register of the city of Lund, and non-randomly among medical students at the University hospital in Lund, and by advertisements in sites visited by students at the University.

All patients had BPD. Six of them had co-morbid axis II diagnoses. One had an avoidant personality disorder, one had a dependent personality disorder, one had a passive aggressive personality disorder, one had a paranoid personality disorder and one fulfilled the criteria for both paranoid and schizotypal personality disorder, and one fulfilled the criteria for both paranoid and passive aggressive personality disorder. Six of the patients had a history of conduct disorder, and one fulfilled the criteria for anti-social personality disorder.

All subjects were classified by the corresponding author according to the DSM IV, (American Psychiatric Association 2000). Sixteen patients fulfilled the criteria ranging from one to four axis I diagnoses; 7 had an eating disorder (eating-disorder NOS, n=4, bulimia, n=3), 7 had substance use disorder, 6 suffered from MDD, one of them with melancholia, 5 had post traumatic stress disorder due to abuse (sexual and/or violent) during childhood, 5 had obsessive compulsive disorder, 3 had panic disorder and 2 of them with agoraphobia, 2 had bipolar II disorder, two had ADHD, 2 had social phobia, one had a dissociative disorder, one had acrophobia, one had general anxiety disorder, one had dysthymia, and one had psychotic symptoms, not otherwise specified.

Thirteen patients had somatic diagnoses, of which asthma/allergy (n=6) and hypothyroidism (n=2) were the most common ones. The other diagnoses were epilepsy, tinnitus, lactose intolerance, unspecific problems with a knee, irritable bowel syndrome, chronic gastritis, ulcerations in oesophagus, inactive hepatitis C and a history of multiple urinary infections.

All patients used medication. Fifteen used psychotropic medication. Concerning antidepressant medication: 7 used an SSRI, 4 used venlafaxine, 2 used clomipramine and 2 used duloxetine. Concerning moodstabilising/ antiepileptic medication: 2 used valproic acid and 1 used lamotrigine. Concerning antipsychotic medication: 3 used olanzapine, 2 used haloperidol, 1 used risperidone, 1 used perfenazine, 1 used ziprasidone, and 1 used chlorprotixene. Benzodiazepines/tranquilizers: 5 used diazepam, 4 used hydroxizin, 4 used alimemazin, 3 used oxazepam and 1 used lorazepam. Sleep-medication: 6 used propiomazin, 5 used zopiklon, 4 used zolpidem, 2 used nitrazepam, 2 used levomepromazin and 1 used zaleplon. Other psychotropic

medication: 2 used disulfiram. Medication for somatic diseases: 6 used inahalators/anti-allregic medication, 5 used contraceptives, 4 used omeprazol, 1 used ranitidine, 1 used levothyroxine, 1 used tramadol, 1 used tolterodin, 1 used sodiumflouride, 1 used alginate, 1 used hydrotalcite and 1 used a multivitamin pill. The patients' medication had not been changed for a median of 33 days (range 9-210 days). Four of the patients did not remember when they last changed medication.

Only 9 of the 17 patients had regular menstruation.

In paper IV, patients with signs of current infection (n=1) or antibiotic treatment (n=1) were excluded together with their matched controls. Furthermore, subjects whose plasma samples had been defrosted more than once were excluded together with their controls (n=2).We thus included 13 patients with matched controls. For further description of these patients, please see paper IV.

3.3 Methods

3.3.1 Lumbar punctures (paper I, II and IV)

Lumbar punctures were performed after a mean "wash out" period of 13 (9-18) days. During this period psychotropic medication was avoided except for occasional doses of benzodiazepines. Spinal taps were performed in the morning between 8 and 9 am after one night of fasting and rest in bed. Two samples of 12 ml (portion 1) and 6 ml (portion 2) respectively, were collected from the L4-L5 interspace, using a standardized protocol. The samples were thereafter stored in aliquots of 2 ml, frozen in -80 ° C, and defrosted once before analysis. Aliquots from portion 2 were used in paper I and II and from portion 1 in paper IV. Since some of the samples had been

stored ever since 1987, we analysed the correlation between CSF-leptin, CSF-insulin, CSF-IL-1β and sample storage time.

3.3.2 Dexamethasone suppression test (paper I, II and IV)

Serum samples for analysis of cortisol were drawn at 3PM on the first day (sample 1, pre dexamethasone). One mg of dexamethasone was then given at 10PM. Additional serum samples were drawn at 8AM in the following morning (sample 2, post dexamethasone) and at 3PM (sample 3, post dexamethasone). A subject who did not suppress serum cortisol to a value below 140 nM at either 8AM or 3PM post dexamethasone was considered as a non-suppressor of cortisol.

3.3.3 Psychiatric ratings in patients where CSF was examined

Clinical ratings were performed during the same day as the lumbar punctures. The patients were rated according to the Comprehensive Psychopathological Rating Scale (CPRS), the Suicide Assessment Scale (SUAS) and filled in the Karolinska Scales of Personality (KSP). CPRS consists of 65 items covering a wide spectrum of psychopathology (Asberg et al. 1978). From the CPRS, a 10-item subscale, the Montgomery Asberg Depression Rating Scale (MADRS), has been derived, aimed to measure symptom-severity of depression (Montgomery and Asberg 1979). SUAS is an interview based expert rating scale and consists of 20 items (Stanley et al. 1986).The scale is aimed at assessing suicidality over time. KSP is a self-reported inventory consisting of 135 items, sub-grouped into 15 scales (Schalling et al. 1987). It is specifically aimed to measure vulnerability for different forms of psychopathology.

Paper I

From the CPRS, we chose seven items covering areas known to be concerned with leptin metabolism (appetite, reproduction, locomotion and sleep). The CPRS-items most closely linked to these areas are appetite, lassitude, fatigability, increased sexual interest, reduced sexual interest, increased sleep and reduced sleep. We also used the total MADRS score. In this thesis (but not in paper I) we, in addition, analysed correlations between CSF-leptin and the individual items included in MADRS.

Paper II

We used the total MADRS and SUAS score respectively. From SUAS we also used the items for hostility and impulsivity as well as the total sum of the items assessing suicidality (16-20). From KSP we used the items for indirect aggression, verbal aggression, irritability, suspicion, inhibition of aggression, impulsivity and monotony avoidance.

Paper IV

From the CPRS we used the total score of the 65 items, rating self-reported and observed symptoms, and four items covering symptoms associated with aggression and borderline personality disorder; hostile feelings, inability to feel, hostility and labile emotional responses. We also used the total MADRS and SUAS scores.

3.3.4 Oral glucose tolerance test

The subjects arrived after one night of fasting. Blood samples were examined for possible infections, anemia, hepatic and thyroid diseases, plasma-lipids and electrolytes. Test samples included glucose, insulin, c-peptide, glucagon, IL-1β, IL-6 and TNF-α. After baseline sampling the subjects ingested 300ml solution of water mixed with 75g glucose. Additional plasma samples were drawn after 15, 30, 45, 60, 75, 90, 120, 150, 180, 240 and 300 min. 10000 IE trasylol/ml blood was added to the tube collected for glucagon analysis. All test samples were immediately put on ice and centrifuged at +4°C, 3000 r/min, within at most 3 hours. Plasma was frozen at –80°C and defrosted once before cytokine analyses.

3.3.5 Ratings in the OGTT sample

Level of aggression was estimated by use of the Aggression-Questionnaire Revised Swedish Version (AQ-RSV) (Prochazka and Agren 2001). AQ-RSV is the Swedish translation of the Aggression Questionnaire (Buss and Perry 1992), originally developed from the Buss-Durkee Hostility Index (Buss and Durkee 1957). It consists of 29 items, distributed into four scales, measuring the aggression factors Physical aggression (nine items), Verbal aggression (five items), Anger (seven items) and Hostility (eight items). The total aggression score is the sum of all 29 items. Each item is rated on a 4-point scale, from the least to the most characteristic of the subject. The raw score used for correlation analysis is the total sum of the rated items included in each sub-scale. Reliability and validity has not been tested in the Swedish version. However, the internal consistency of the four aggression subscales and the total score was evaluated by the alpha coefficients (Cronbach's alpha). The alphas of the Total Aggression score, Physical Aggression and

Hostility have been found to be comparable in the Swedish and American populations, but concerning Verbal aggression and Anger, the alphas were lower in the Swedish population (Prochazka and Agren 2001).

3.3.6 Assays

Leptin, insulin, C-peptide and glucagon concentrations were analyzed with double antibody radioimmunoassay techniques (Linco Research, St Charles, Mo); glucose was determined with the glucose oxidase method. IL-1β, IL-6 and TNF-α were quantified in plasma and CSF using multiplex sandwich ELISAs with electrochemiluminescence in the quantifying step. We employed MesoScale Discovery assays as per the manufacturer´s protocol. Plasma analyses were performed on a SECTOR 2400 instrument and CSF samples were analyzed on a SECTOR 6000 instrument (http//:www.mesoscale.com).

3.3.7 Statistics

The software SPSS for Windows was used for all statistical calculations. The BMI was calculated by dividing the patients' weight (in kilograms) by the squared height (in meters). Non-parametric statistics was used in paper I, III and IV. Comparisons between groups were then made using Kruskal-Wallis test and Mann-Whitney U test, with significance levels corrected for multiple comparisons (Bonferoni-Dunn's method) when applicable. We used Wilcoxon signed ranks test for comparisons between cytokine levels within patients. Spearman's rho was used for correlations. The alpha level of significance was set at $P \leq 0.05$.

In paper I, leptin was corrected for BMI by dividing CSF-leptin by BMI. Since several patients had undetectable CSF-leptin, linear regression was not used.

Parametric statistics was used in paper II. One-way ANOVA was used for group comparisons. Correlations were calculated with Pearson's correlation coefficient. Calculations with non-parametric statistics (Mann Whitney-U test and Spearman's rho) yielded, however, similar results.

In paper III, a power analysis was made before the study was initiated. We used p-glucose nadir as a primary effect variable which in former studies have shown a standard deviation of ±0.5mM. With a clinically relevant difference of 0.5 mM and power of 0.8, a significance level of 5% demands a sample of 17 matched couples. Results are presented as median and interquartile range. Area under curve (AUC) was calculated with the trapezoid method. As a measure of insulin sensitivity, we used insulinogenic index defined as $(insulin_{30min} - insulin_{0min}) \times (glucose_{30min} - glucose_{0min})^{-1}$ (Ahren et al. 2008). Calculations for patients with missing values are described in detail in paper III.

For the OGTT sample in paper IV, calculations were performed as in paper III.

4 Results

4.1 CSF-leptin (paper I)

Due to well known gender differences in leptin secretion (Ostlund et al. 1996; Rosenbaum et al. 1996; Schwartz et al. 1996; Dotsch et al. 1997; Saad et al. 1997), all calculations were performed for men and women separately.

4.1.1 CSF-leptin, gender, BMI, height, age and sample storage time.

Of the men, 75% showed undetectable CSF-leptin (i.e. ≤0.001ng/ml) compared to only 12.5 % of the women. Mean CSF-leptin for men was 0.0151± 0.0376 (SD) ng/ml (median: 0.001ng/ml) and for women 0.141±0.116 ng/ml (median: 0.138ng/ml). A positive correlation was found between CSF-leptin and BMI in women ($r=0.735$, $P<0.01$) and in men ($r=0.505$, $P<0.01$). No significant correlation was found between height, age or sample storage time and CSF-leptin.

4.1.2 CSF-leptin, BMI and diagnoses

Figure 3 shows that in women with MDD, CSF-leptin was significantly lower than in women with other diagnoses (P=0.007). By contrast, CSF-leptin in men with MDD did not differ from those in the non-MDD group (P=0.8). Mean BMI did not differ between the diagnostic groups of women (P=0.1) or men (P=1.0). There was still a significant difference (P=0.013) in CSF-leptin between women with and without MDD after adjusting for BMI. A significant negative correlation was found in women, but not men, between CSF-leptin and MADRS (r= -0.444, P=0.006). When analyzing the different items, significant correlations were found for the items Sadness (r=-0.341, p=0.039), Inability to feel (r=-0.518, p=0.001), Pessimistic thoughts (r=-0.403, p=0.032), Suicidal thoughts (r=-0.353, p=0.032) and Reduced appetite (r= -0.394, P=0.016). In either sex no significant correlation was found between CSF-leptin and the investigated items: inner tension, lassitude, fatigability, concentration difficulties, reduced or increased sleep, and reduced or increased sexual interest. No significant difference was found between patients with and without Cluster B diagnosis in either sex.

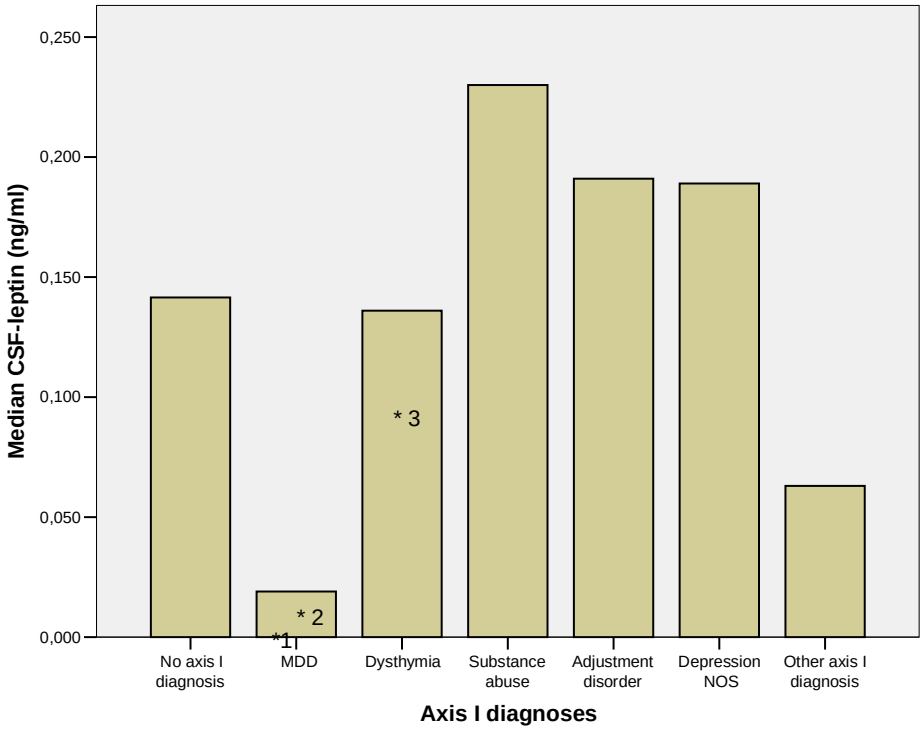

Figure 3.
Median CSF-leptin in female suicide attempters with no axis I diagnosis (n=2), MDD (n=14), dysthymia (n=5), substance abuse (n=3), adjustment disorder (n=10), depression NOS (n=3), other axis I diagnosis (n=3).
Abbreviations and explanations: No axis I diagnosis: Borderline personality disorder and Schizoid personality disorder, MDD: Major depressive disorder, NOS: not other specified, "Other": cyclothymic disorder (2) and anorexia nervosa (1).
* 1 Patient with traces of clomipramine treatment in plasma, CSF-leptin=0.001ng/ml.
* 2 Patient with traces of clomipramine treatment in plasma, CSF-leptin=0.010ng/ml.
* 3 Patient with traces of perfenazine treatment in plasma, CSF-leptin=0.090ng/ml

4.1.3 CSF-leptin, BMI and suicidal behaviour

No significant differences were found in CSF-leptin when comparing patients with repeated suicide attempt to those with a first attempt (men P=0.8, women P=0.2). Neither were there any significant differences in BMI (men P=1.0, women P=0.1) or in CSF-leptin after adjusting for BMI (men P=0.8, women P=0.3). BMI was lower in women with violent suicide attempt than in those with a non-violent attempt (P=0.015) (Figure 4) and there was a trend for women with a violent suicide attempt to have lower CSF-leptin than those with a non-violent attempt, but this did not reach significance in the present small sample (P=0.07). To further examine the patients with violent suicide attempt we compared those with a violent attempt versus those with a non-violent first excluding MDD, and then non-MDD patients. This did not, however, give any further information. Of the three patients who by February 2003 had completed suicide, one was a man with substance abuse and undetectable CSF-leptin (0.001ng/ml), one a woman with MDD and CSF-leptin 0.010 and one was a woman with adjustment disorder and CSF-leptin 0.309.

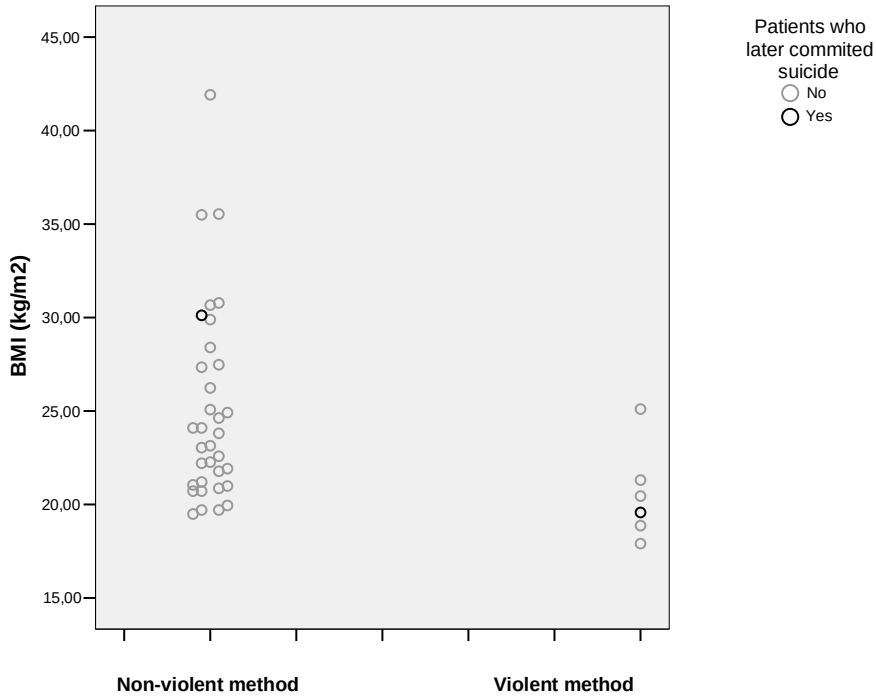

Figure 4.
Body Mass Index (BMI) in female suicide attempters using a non-violent (n=34) vs. a violent method (n=6).

4.1.4 CSF-leptin and the dexamethasone suppression test

There were negative correlations in women between CSF-leptin and cortisol levels during the dexamethasone suppression test (sample 1 r = -0.352, p = 0.028, 2 r= - 0.385, p= 0.019 and 3r= -0.387, p= 0.018). However, a scatter diagram is not impressing (Figure 5).

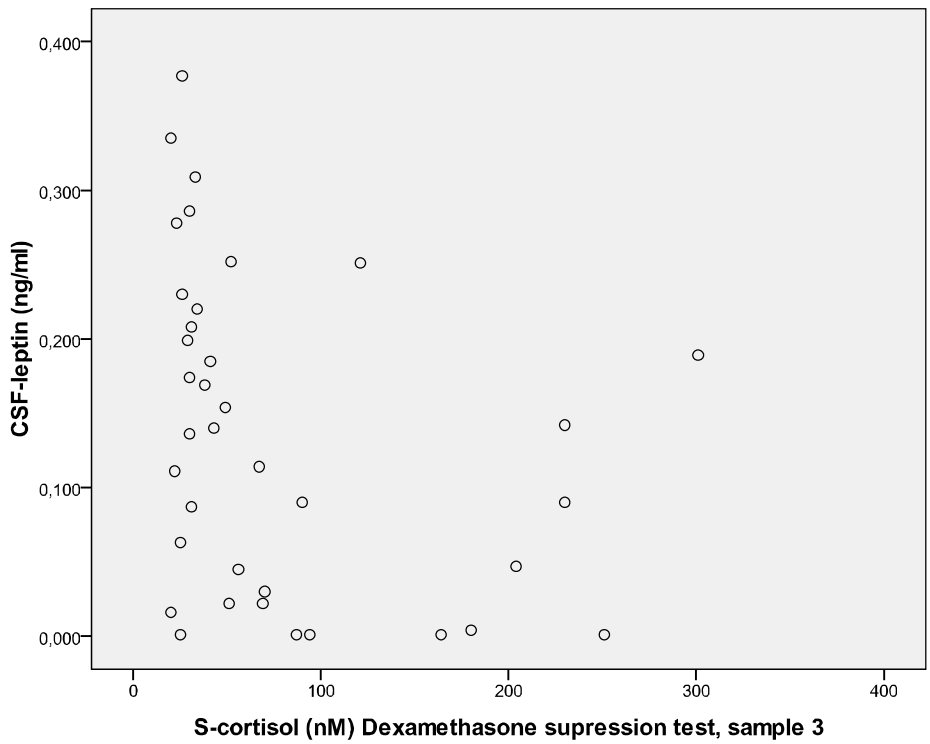

Figure 5.
Women with a recent suicide attempt (n=40). CSF-leptin and s-cortisol at 3PM, post-dexamethasone, day 2, dexamethasone suppression test.

4.2 CSF-insulin (paper II)

4.2.1 CSF-insulin, gender, height, age, BMI and sample storage time

There were no significant differences in CSF-insulin between men and women. (5.6±0.7 pmol/l vs.5.3±0.9 pmol/l). No significant correlation was found between CSF-insulin and height, age or BMI. CSF-insulin did not correlate significantly with sample storage time.

4.2.2 CSF-insulin and diagnoses

No significant differences in CSF-insulin were found between the patients with and without MDD (5.5±1.0 pmol/l vs. 5.4±0.7 pmol/l). There were no significant correlations between MADRS total score and CSF-insulin. CSF-insulin did not differ between patients with and without cluster B personality disorder (5.3±0.7 pmol/l vs. 5.5±0.8 pmol/l).

4.2.3 CSF-insulin and suicidal behaviour

Patients with a violent suicide attempt had significantly higher CSF-insulin (5.9±1.0 pmol/l) than those with a non-violent attempt (5.3±0.7 pmol/l, P=0.002) (Figure 6). Since there were more men among the violent suicide attempters a multiple linear regression including gender as a variable was also calculated in which the significant difference (P=0.004) remained. There was no significant difference in CSF-insulin between patients having made a first suicide attempt compared to those who had made a repeated one (5.5±0.9 vs. 5.4±0.6 pmol/l). CSF-insulin did not correlate significantly with either SUAS total score or the sum of the items aimed to investigate suicidality.

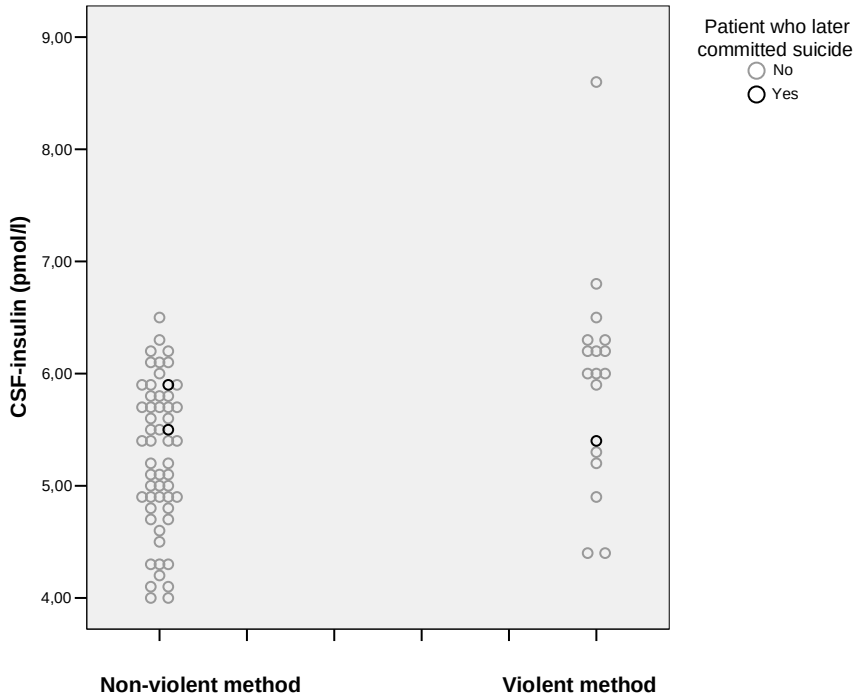

Figure 6.
CSF-insulin in suicide attempters using a non-violent (n=56) vs. a violent method (n=18).

4.2.4 CSF-insulin and monoamine metabolites

CSF-insulin correlated significantly with CSF-5-hydroxy indeolacetic acid (CSF-5-HIAA) (r=0.354, p=0.002) and CSF-homovanillic acid (CSF-HVA) (r=0.311, p=0.007). Scatter diagrams were however not impressing.

4.2.5 CSF-insulin and the dexamethasone suppression test

There were no significant correlations between CSF-insulin and levels of serum cortisol at 3PM pre-dexamethasone, 8AM and 3PM post-dexamethasone.

4.2.6 CSF-insulin and ratings

There was no significant correlation between CSF-insulin and SUAS items for hostility and impulsivity, or the total sum of the SUAS items investigating suicidality (item 16-20), the KSP items for indirect aggression, verbal aggression, irritability, suspicion, inhibition of aggression, impulsivity and monotony avoidance, or MADRS.

4.3 Glucose, insulin, c-peptide and glucagon during OGTT (paper III)

4.3.1 All patients and controls (n=17+17).

Basal characteristics
There were no significant differences between patients and controls in BMI, age, p-glutamyltransferase (GT) or p-ALAT.

AQ-RSV
Patients had significantly higher scores on Physical aggression (23[16-28]) compared to controls (11[9-12]) ($p<0.001$). When relating to a sample of women in the general Swedish population, our patients had higher scores with a ratio of 1.45:1 (1.04-1.74:1) (Helena Prochazka, personal communication).

Glucose
There was no significant difference between patients and controls in fasting plasma (fp-) glucose. Following the glucose administration, glucose levels increased to a peak after 30 (30-

45) min; and thereafter glucose levels fell. After 180 (120-180) min, a nadir was reached. Patients had significantly higher p-glucose after 30 min (8.2 [7.2-9.2] mM) compared to controls (7.0 [5.6-7.6] mM) (p=0.007). There were no significant differences in p-glucose nadir (Figure 7), p-glucose at 300 min or in glucose AUC between patients and controls. There was no significant correlation between p-glucose nadir and scores on Physical aggression

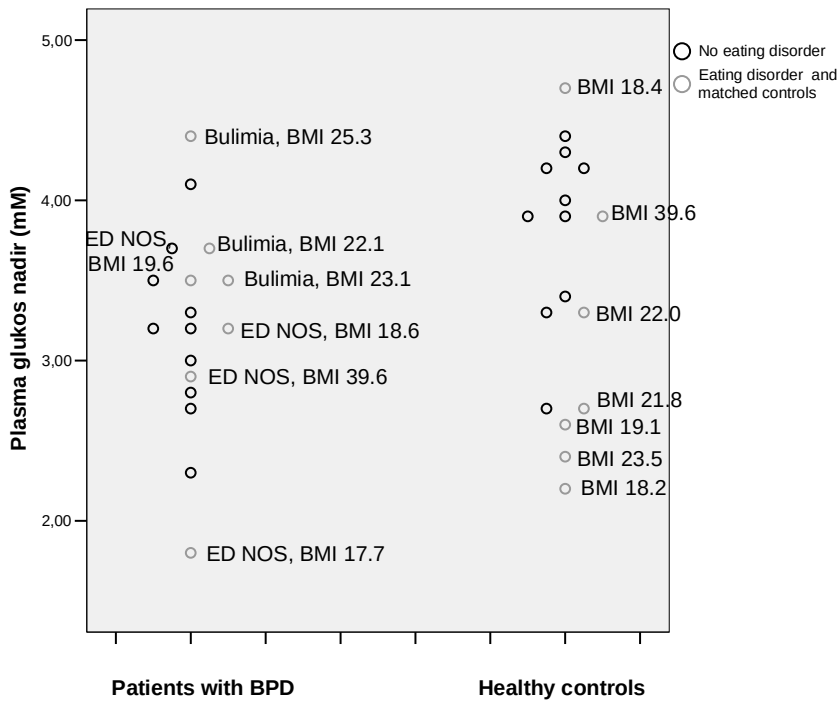

Figure 7.
Plasma glucose nadir during the oral glucose tolerance test in patients with BPD (n=17) and healthy controls (n=17). (Abbreviations: ED NOS; eating disorder not other specified, BMI; body mass index).

Insulin
There were no significant differences in fp-insulin, p-insulin after 30 min or insulin AUC between patients and controls. No significant difference was found between patients and controls in insulin sensitivity measured as insulinogenic index.

C-peptide
There were no significant differences between patients and controls in fp-c-peptide, p-c-peptide 30 min or c-peptide AUC.

Glucagon
There were no significant differences between patients and controls in fp-glucagon or p-glucagon 30 min although a trend could be seen towards increased 30 min levels in patients (60 [50-78] ng x l^{-1}) compared to controls (46 [37-65] ng x l^{-1}) (p=0.053). Patients had a significantly increased glucagon AUC (16 [15-23]µg x min/l) compared to controls (13 [10-15] µg x min/l) (p=0.011) (Figure 8).

4.3.2 Patients without an eating disorder and controls (n=10+10).

Patients without an eating disorder showed significantly increased scores on AQ-RSV Physical aggression (24 [20-29]) compared to controls (11 [9-12]) (p=0.001). These patients had significantly lower p-glucose nadir (3.2 [2.8-3.6] mM) than controls (4.0 [3.4-4.2]) mM) (p=0.015) (Figure 7). They also had lower p-glucose at the end-point (300 min) (4.0 [3.3-4.6] mM) than controls (4.7 [4.3-5.2] mM) (p=0.029). There was no significant difference between patients and controls in p-glucose 30 min or glucagon AUC. None of the other parameters measured showed any significant differences between patients and controls. There was no significant correlation between p-glucose nadir and scores on Physical aggression.

4.3.3 Patients with an eating disorder and controls (n=7+7).

Patients with an eating disorder showed significantly increased scores on AQ-RSV physical aggression (22 [14-24]) compared to controls (11 [9-12]) (p=0.012). These patients showed significantly increased glucagon AUC (17 [16-29] µg x min/l) compared to controls (13 [12-21] µg x min/l) (p=0.038) (Figure 8). They also showed a trend towards increased p-glucose 30 min (7.8 [7.2-9.4] mM) compared to controls (7.0 [5.0-7.4] mM) (p=0.053). None of the other parameters measured showed any significant differences between patients and controls.

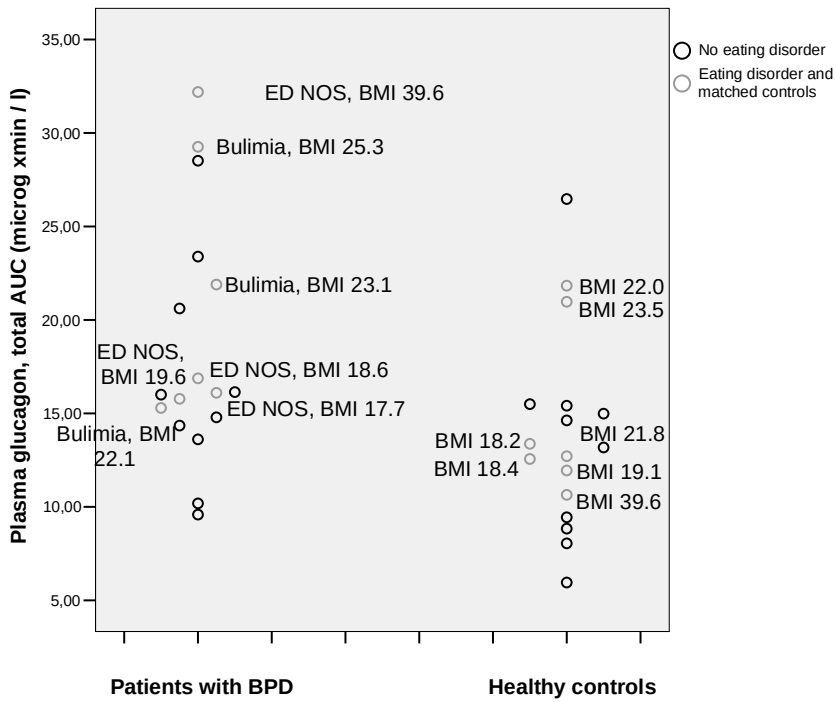

Figure 8.
Glucagon total area under the curve during the oral glucose tolerance test in patients with BPD (n=17) and healthy controls (n=17). (Abbreviations: ED NOS; eating disorder not other specified, BMI; body mass index).

4.4 IL-1 β in patients with self-inflicted aggressive behaviour (paper IV)

4.4.1 Patients where CSF was examined

General characteristics

IL-1β levels were non-normally distributed, and therefore non-parametrical statistical methods were used for all analyses. There was no significant difference in CSF-IL-1β between women (0.072 (0.064 - 0.088) pg x ml^{-1}) and men (0.069 (0.063 - 0.082) pg x ml^{-1}) (NS, Mann-Whitney U test). Age, body mass index (BMI) or smoking did not influence CSF IL-1β levels (NS, Mann-Whitney U test, Spearman's Rho). There was no significant correlation in patients between CSF-IL1β and sample storage time.

CSF-IL-1β, Cluster B personality disorder and suicidal behaviour

CSF-IL1β was higher in patients (0.075 (0.066 - 0.088) pg x ml) compared to healthy controls (0.066 (0.063-0.075) pg x ml) (p=0.012, Mann-Whitney U test) (Figure 9). When excluding patients with MDD, patients still had significantly increased levels of IL-1β compared to controls (p=0.001, Mann-Whitney U test). Furthermore, there was a significant difference in CSF-IL1β between the groups of patients with (median 0.075 (0.067 - 0.091) pg x ml^{-1}) and without a cluster B diagnosis (0.073 (0.064 - 0.088) pg x ml^{-1}) and controls (0.066 (0.063 - 0.075) pg x ml^{-1}) (p=0.034, Kruskal Wallis test) (Fig 9). Post-hoc tests revealed that cluster B patients had a significantly higher CSF IL-1β level than controls (p=0.011, alpha-level of significance 0.05/3=0.017). In contrast, there was no significant difference between patients without cluster B and controls (NS, Mann-Whitney U test). There was a trend for increased levels of CSF-IL-1β in patients with violent suicide attempt but this failed to

reach significance after corrections for multiple analyses (p=0.027 alpha level of significance 0.017). No significant difference in CSF-IL-1β was found between patients with a first suicide attempt compared to those who had made repeated attempts.

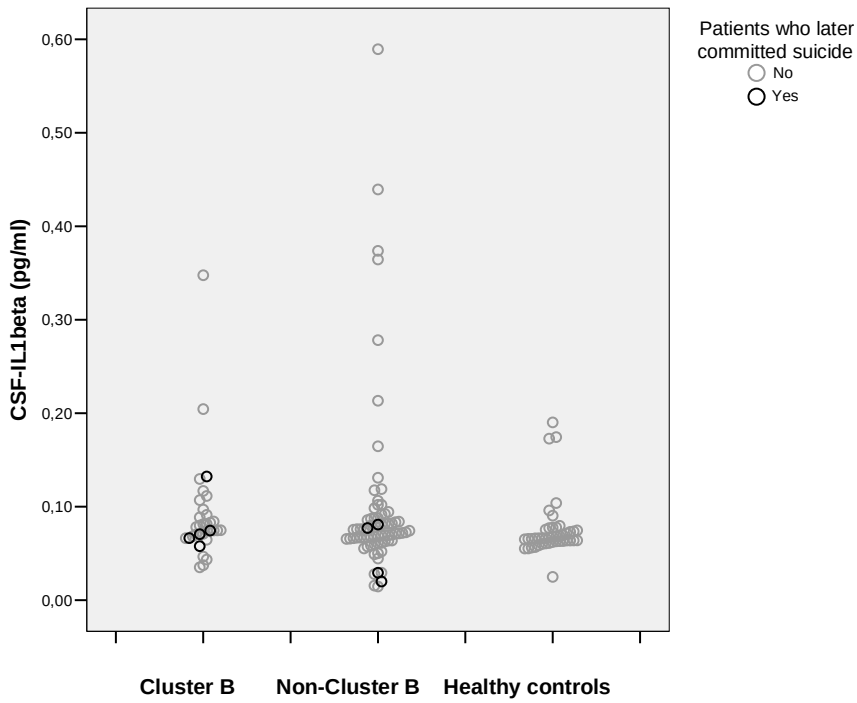

Figure 9.
CSF-IL-1β in suicide attempters with (n=32) or without Cluster B diagnosis (n=74) and healthy controls (n=44).

CSF-IL-1β and psychiatric symptoms

In patients with cluster B personality disorder, positive correlations were found between CSF-IL-1β and CPRS total score (Spearman's rho=0.396, p=0.025, n=32) as well as SUAS total score (Spearman's rho=0.400, p=0.029, n=32). Of the individually investigated CPRS items, CSF-IL-1β levels in patients with cluster B personality disorder correlated positively with the CPRS item "lack of emotion" (Spearman's rho=0.362, p=0.036, n=32). No significant correlation was found in patients with cluster B personality disorder between CSF-IL-1β and MADRS total score or the items "hostile feelings", "hostility" or "labile emotional responses" (Spearman's rho, NS). In the patients without cluster B diagnosis, no association was found between CSF-IL-1β and CPRS total score, SUAS total score, MADRS or individual CPRS items.

CSF-IL-1β, CSF-5-HIAA and the dexamethasone suppression test

There were no significant correlations between CSF-IL-1β and levels of serum cortisol at 3PM predexamethasone, 8AM and 3PM post dexamethasone. Neither was there a significant correlation between CSF-IL-1β and CSF-5-HIAA.

4.4.2 Plasma IL-1β in patients with deliberate self-harm submitted to the OGTT

General characteristics

There was no significant difference in median BMI between patients (19.6 (18.4 - 24.0) kg/m^2) and controls (20.3 (19.0 - 23.6) kg/m^2) (p=0.65, Mann-Whitney U test). Neither was there a significant difference in age between patients (20 (19 - 24) years) and controls (24 (21 - 26) years) (p=0.1, Mann-Whitney U test).

Cytokine levels in plasma during the OGTT

There was no significant difference in basal plasma levels of p-IL-1β, p-IL-6 and p-TNF-alpha between BPD patients and controls (Mann-Whitney U-tests, NS). Patients had a significantly elevated incremental area under the curve (AUC) IL-1β (76 (29 - 110) pg x min x ml^{-1}) compared to controls (22 (-10 - (+) 35) pg x min x ml^{-1}) (p=0.002, Mann-Whitney U-test), as a measure of total IL-1β secretion during the glucose challenge (Figure 10).

When analyzing all subjects (n=26) there was a significant correlation between incr. AUC IL-1β and the AQ-RSV subscale Hostility (Spearman's rho 0.586, p 0.002). When analyzing patients and controls separately a trend was found in patients (n=13, Spearmans Rho 0.455, p=0.118) but not in controls (n=13, Spearmans Rho NS). No significant correlations were found between incr. AUC IL-1β and the other sub-scales of AQ-RSV.

There were no significant differences in TNF-alpha and IL-6 incremental AUC.

Possible confounders in the OGTT study

All subjects were analyzed with respect to intake of birth-controlling hormones or not (n=8 vs 18) and the occurrence of asthma/allergies or not (n=5 vs 21). The incremental AUC IL-1β did not differ between these groups, respectively (Mann-Whitney U-tests, NS). Furthermore, the incremental AUC IL-1β did not differ significantly between BPD patients with and without benzodiazepine treatment and psychotropics. The

difference in IL-1β incremental AUC between patients and controls remained significant after excluding patients with an eating disorder (remaining n=9+9, p=0.003), with MDD (remaining n=7+7, p=0.007) or all patients with either an eating disorder or MDD (remaining n= 6+6, p=0.004).

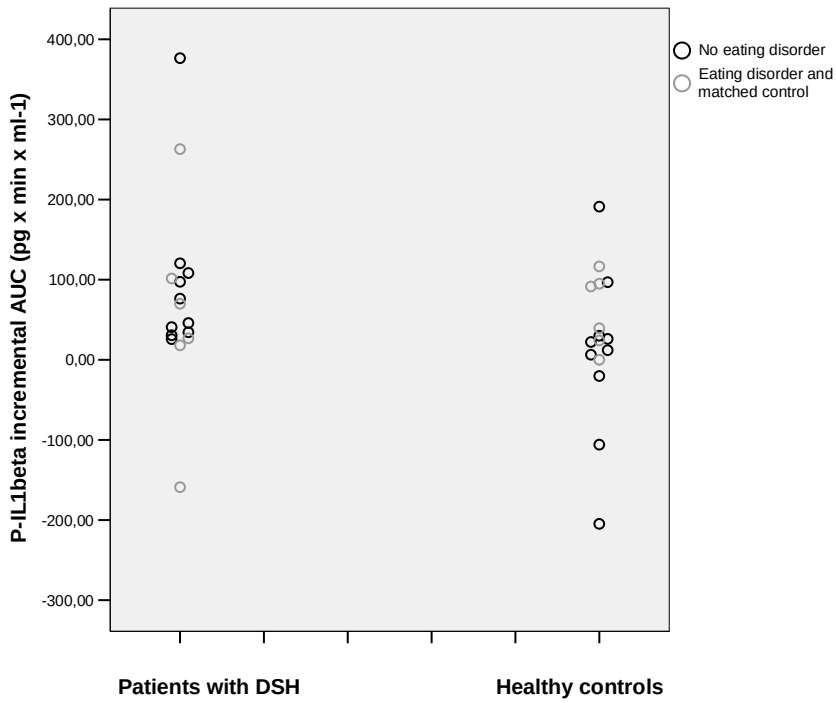

Figure 10.
Plasma IL-1β, incremental area under the curve in patients with deliberate self-harm and BPD (n=13) and healthy controls (n=13).

4.5 Results involving papers I, II and IV.

There were no significant correlations between CSF levels of leptin, insulin and IL-1β respectively. (Correlations with leptin were calculated for men and women separately).

5 Discussion

5.1 Leptin

5.1.1 Leptin, BMI and self-inflicted aggression

We found a low BMI in women with a violent suicide attempt compared to those with a non-violent attempt. This is interesting since a register study of more than one million men has found an association between low BMI and increased risk for suicide. BMI was in that study measured at the age of 18-19 years and subjects were followed up for as long as 31 years (Magnusson et al. 2006). Furthermore a Norwegian prospective cohort of 74 332 men and women confirmed this association in both men and women (Bjerkeset et al. 2008). In our study we found no association between a violent method for suicide attempt and BMI in men. The scope of our study is however somewhat different from these large scale studies examining population cohorts, as we studied suicide attempters and no healthy controls.

We found a trend towards low CSF-leptin in women using a violent method for their suicide attempt. This is in line with several studies measuring plasma leptin and cholesterol in suicide attempters (Alvarez, Cremniter et al. 2000; Vevera, Zukov et al. 2003; Atmaca, Kuloglu et al. 2008). In contrast, we found no such difference in men. This is probably explained by the fact that 75% of the men in our study had undetectable levels of CSF-leptin which does thus not exclude an association.

There is not sufficient knowledge to explain the relation between leptin and violent behaviour. One of the more consistent findings concerning aggressive behaviour, self-inflicted as well as directed towards others is its association with low central 5-HT metabolism (Traskman, Asberg et al. 1981; Virkkunen, Goldman et al. 1995). Leptin is ambiguously related to 5-HT. A high percentage of 5-HT neurons in the raphe nuclei express the leptin receptor supporting a possible interaction between leptin and 5-HT (Finn et al. 2001). Reduced expression of the 5-HT transporter was also observed in the raphe nuclei of leptin deficient mice (Collin et al. 2000). In addition, leptin injection (intracerebroventricular as well as intraperitoneal) increased 5-HT content and metabolism in the forebrain and hypothalamus of rodents (Calapai et al. 1999; Hastings et al. 2002). By contrast, chronic intracerebroventricular infusion of leptin was found to decrease the number of binding sites for paroxetine (a SSRI) in rats (Charnay et al. 2000).

Another possible explanation involves cholesterol which is linked to leptin. There is substantial evidence for an association between low cholesterol and violent behaviour (Golomb 1998). In monkeys, low dietary cholesterol has been associated with aggressive behaviour and low serotonergic activity (Kaplan et al. 1994). Animal models have shown that levels of dietary and plasma cholesterol affect the cholesterol content of cell membranes (Mason et al. 1991). The cholesterol content of the membrane alters viscosity, fluidity and receptor activity in neurons (Mason, Herbette et al. 1991; Engelberg 1992). 5-HT is particularly sensitive to this, since in vitro studies show that addition or removal of cholesterol alters 5-HT binding in synaptic membranes (Heron et al. 1980).

We found no associations between leptin, BMI and the number of attempted suicides.

5.1.2 Leptin, BMI and MDD

We found low CSF-leptin in women with a recent suicide attempt and MDD compared to those with other diagnoses. (Women with bipolar disorder did however not have particularly low levels.) This is in line with studies reporting low levels of circulating leptin in MDD patients (Kraus, Haack et al. 2001; Atmaca, Tezcan et al. 2005; Eikelis, Esler et al. 2006; Jow, Yang et al. 2006), but contrast several other reports (Deuschle, Blum et al. 1996; Antonijevic, Murck et al. 1998; Rubin, Rhodes et al. 2002; Cizza, Romagni et al. 2005; Esel, Ozsoy et al. 2005; Gecici, Kuloglu et al. 2005; Kauffman, Castracane et al. 2005). One probable explanation for the divergent findings is that MDD is a heterogeneous disorder (Andreasson et al. 2007).

In women we also found weak, but significant, negative correlations between CSF-leptin and all three measurements of serum (s-) cortisol during the dexamethasone test. This is in contrast with the findings that glucocorticoids stimulate leptin gene expression and leptin production (Larsson and Ahren 1996; Miell et al. 1996; Cleare et al. 2001; Udden et al. 2003). Leptin however, in turn, also seems to play a role in regulating the HPA-axis (Stephens et al. 1995; Bornstein et al. 1997; Gaillard et al. 2000). When looking at the scatter diagrams of CSF-leptin as a function of s-cortisol (Figure 5), it seems as if patients responding normally to the dexamethasone supression test with subsequent low s-cortisol show a wide variety of leptin levels. However, no patients with increased s-cortisol show high levels of CSF-leptin. This is probably what creates the negative correlation, and might indicate that cortisol somehow inhibits leptin uptake across the blood brain barrier. Since high cortisol levels sometimes are found in patients with MDD (Arana et al.

1985; Tichomirowa et al. 2005) this might explain the low levels of CSF-leptin that we found in these patients.

The most prominent difference between our study and the previous ones, seeking a relation between leptin and MDD is that we measured in CSF and not in plasma. However the antidepressant effects of leptin are probably central and CSF-leptin is thus more interesting than peripheral. Furthermore Eikelis and co-workers have shown attenuated leptin secretion from the brain in patients with MDD compared to healthy controls indicating a down regulation of central leptin production in these patients (Eikelis, Esler et al. 2006).

5.2 Insulin and self-inflicted aggression

We found a high CSF-insulin in suicide attempters using a violent method compared to those using a non-violent method. The interpretation of this finding is intriguing. Peripherally insulin mainly regulates glucose homeostasis acting on target tissues such as adipocytes, muscles and liver. The central effects of insulin seem to be more diverse. Insulin and insulin receptors are found throughout the brain with the highest density in the olfactory bulb, cerebral cortex and the limbic system (Hill et al. 1986; Unger et al. 1991; Wozniak et al. 1993). Healthy controls receiving intravenous as well as intranasal insulin have shown improvement in memory and mood (Kern et al. 2001; Benedict et al. 2004). Immediately after the first intra nasal insulin administration there was also a reduction in anger. However the effect on anger was acute and after eight weeks administration, there was no significant difference in mood between the groups receiving insulin and placebo. This is in total contrast with our finding, although the effect of a prolonged excess of brain insulin on anger is uncertain.

Another pathway for insulin to affect behaviour is through 5-HT, known to be decreased in subjects with violent behaviour. In our material, however, there was a positive correlation between CSF-insulin and CSF-5-HIAA (metabolite from 5HT). In line with this finding, but in contrast with the hypothesis of an association between high insulin and violence, studies in streptozotocin diabetic rats show that these have decreased 5-HT activity. This rather suggests a stimulatory effect of insulin on 5-HT (Crandall et al. 1981; Mans et al. 1987; Broderick and Jacoby 1989; Henley and Bellush 1992). Furthermore, low 5-HT levels have been reported in type 1 diabetic subjects (Jonnakuty and Gragnoli 2008). Since we found increased levels of CSF-insulin this is in contrast with the low central 5-HT activity usually associated with aggressive behaviour.

We also found a significant positive correlation between CSF-insulin and CSF-HVA. This was expected since many studies have shown positive correlations between CSF-5-HIAA and CSF-HVA (Agren and Terenius 1985; Engstrom, Alling et al. 1999)

There is clear evidence for transport of insulin across the blood brain barrier but also indications for central insulin production (Rosenzweig et al. 1980; Wozniak, Rydzewski et al. 1993; Woods et al. 2003). If the increased levels of insulin that we found are related to aggressive behaviour, they are more likely to originate from the brain, since there are no reports of increased aggression in patients with high level of circulating insulin (ie type 2 diabetic patients).

High CSF-insulin does not seem applicable to use as a marker for violent behaviour such as using a violent method when attempting suicide. Using a cut-off at 5.85 pmol/l gives a

specificity; 0.79 with a sensitivity of 0.67. This cut-off is in between the mean for violent suicide attempters (5.9±1.0 pmol/l) and non-violent attempt (5.3±0.7 pmol/l) but set at an upper level in order to produce a higher specificity (see figure 6).These numbers are definitely too low to justify a CSF-sample in a clinical setting. Furthermore CSF-insulin may be increased in conditions with high levels of circulating insulin such as type 2 diabetes. This condition is not associated with violent suicide attempt.

5.3 Glucose homeostasis and self-inflicted aggression

We found a low plasma glucose nadir in women with self-inflicted aggressive behaviour without an eating disorder in comparison with healthy, matched controls. This adds a new dimension to the abundant reports of a hypoglycaemic tendency in habitually violent men, since no research has been conducted in women. A causal relationship between aggressive behaviour and the hypoglycaemic tendency that we found is however unlikely. First, the levels of plasma glucose (although significantly lower than controls) were not low in a clinically significant way; median plasma glucose nadir in patients was 3.2 mM compared with a limit of approximately 3.0 mM where hypoglycaemic symptoms usually start (Cryer 1993). Second, the situation during an oral glucose tolerance test (to consume large amounts of sugar and then wait for five hours before eating) is extremely unlikely to occur in everyday life. In patients under investigation for a presumed reactive hypoglycaemia, a mixed meal test has failed to reproduce hypoglycaemic tendencies (Hogan et al. 1983). A mixed meal test should be more comparable to daily life and thus more clinically reliable (Buss et al. 1982; Benton 1988). Third, results

from an animal study investigating the relation between hypoglycaemia and aggressive behaviour was unimpressive (Andrade, Benton et al. 1988). Benton rather suggests that rather than discussing the hypoglycaemic influence on the brain, the hypoglycaemic tendency should be regarded as an indication of other neural or metabolic activity. He suggests 5-HT as a common link as it is known to participate in glucose metabolism as well as aggressive behaviour. However although some evidence suggests that 5-HT might have a hyperglycaemic effect, there are more indications of a glucose lowering effect (Lam and Heisler 2007; Jonnakuty and Gragnoli 2008). This thus contrasts our findings, since in persons with aggressive behaviour a hypoglycaemic tendency should be accompanied by low 5-HT levels.

5.4 IL-1β and self-inflicted aggressive behaviour

We found significantly increased levels of CSF-IL1β in patients with a recent suicide attempt compared to healthy controls. This was particularly accentuated in patients with cluster B personality disorder and is in line with earlier studies where Il-1β has been associated with aggressive behaviour (Suarez, Lewis et al. 2004; Zalcman and Siegel 2006). Eight patients had higher levels of CSF-IL-1β than all controls. Journal studies of these patients did not reveal any common characteristics concerning diagnosis, method or severity of the suicide attempt.

We also found increased secretion of IL-1β during the OGTT in women with deliberate self-harm compared to healthy matched controls. In a subgroup of these women, i.e. those without an eating disorder, we found a low plasma glucose nadir. In those with an eating disorder, the hypoglycaemic tendency was instead counteracted by an increased secretion of glucagon. Above we

discussed that the aggressive behaviour (here deliberate self-harm) is unlikely to be caused by the hypoglycaemic tendency. A more likely suggestion is that both the hypoglycaemic tendency and the aggressive behaviour are symptoms of some other neuronal or metabolic factor. Our finding of an increased secretion of IL-1β during the OGTT fits well with this hypothesis, since IL-1β can induce hypoglycaemia and is linked to aggressive behaviour. It is then not surprising that we found increased levels of IL-1β, regardless of a co-morbid eating disorder, since the patients with such a disorder probably share the hypoglycaemic tendency, but it is counteracted by the increased glucagon secretion.

There are several interfaces between IL-1β and 5-HT. Although some pro-inflammatory cytokines reduce levels of accessible tryptophan and subsequently 5-HT, this has not yet, to our knowledge, been proven for IL-1β. In rodents, instead, systemic or intracerebroventricular injections of IL-1β enhance levels of tryptophan and 5-HIAA and stimulate 5-HT release in the hypothalamus and extra hypothalamic sites (Anisman et al. 2002). The effect of IL-1β on aggressive behaviour is mediated by 5HT2 receptors (Zalcman and Siegel 2006). What in this context remains intriguing is that IL-1β mainly promotes 5HT activity, and usually violent behaviour is associated with decreased levels of 5HT and its metabolites. In addition, we found no significant correlation between CSF-IL-1β and CSF-5-HIAA. However CSF-levels must not necessarily reflect levels at a local brain site, but may rather be an image of the general activity in the brain. Thus a local increase in 5HT production might not be shown as increased levels of CSF-HIAA. Furthermore, in the same regions as where IL-1β facilitates aggressive behaviour through 5HT2 activity, 5HT1a receptors act suppressing. Thus, a general low 5HT activity could fail to suppress aggressive behaviour. Somewhat in line with our

results is the finding from our group of a tendency towards higher whole blood concentrations of 5HT in patients with a violent suicide attempt (Träskman-Bendz L. 1991). This is however a completely different compartment and possible associations must be interpreted carefully.

IL-1β also has effects on the hypothalamus-pituarity-adrenal (HPA)-axis (Tsagarakis et al. 1989; Shintani et al. 1995; Dantzer et al. 1999). It stimulates the release of corticotropin releasing factor (CRH) (Berkenbosch et al. 1987; Sapolsky et al. 1987; Tsagarakis, Gillies et al. 1989). This is important since CRH secretion often is altered in psychiatric patients with suicidal behaviour (Roy 1992; Traskman-Bendz et al. 1992; Brunner et al. 2001; Pfennig et al. 2005)

Evidence exists for central as well as peripheral production of IL-1β (Aschner 1998; Dantzer, Aubert et al. 1999). In addition, IL-1β receptor mRNA has been identified in several regions of the brain (Ericsson et al. 1995), and IL-1β has effects on a wide range of behaviours, including sleep, food intake and cognitions, producing what is generally termed "sickness behaviour" (Licinio and Wong 1999; Anisman et al. 2008). IL-1β induced aggressive behaviour has however been located to more specific areas (the hypothalamus and the periaqueductal grey) (Siegel, Roeling et al. 1999; Hassanain et al. 2005). This might speak in favour of a local production of IL-1β, since peripherally produced IL-1β is more likely to spread throughout the brain and to have more general effects such as sickness behaviour and fever.

Although the differences in CSF-IL-1β between patients and controls were significant, absolute levels are low compared to those seen after stroke or brain injury(Sun et al. 2009). It is not possible to know if the small elevation of IL-1β in the CSF

reflects increases of greater magnitude at specific locations in the brain.

Although IL-1β is involved in glucose metabolism, there was no significant correlation between CSF-IL-1β and CSF-insulin. It is however still a subject of discussion whether insulin in the brain has direct effects on glucose metabolism or only indirect through feeding behaviour (Kern, Peters et al. 2001). Changes in plasma insulin concentrations do not affect insulin concentrations in the brain (Rosenzweig, Havrankova et al. 1980), which means that cerebral insulin is not necessarily linked to glucose homeostasis the way peripheral insulin is. This is in line with the lack of significant correlations between IL-1β and insulin.

In the context of this thesis, it is interesting that many of the effects of leptin are exerted by IL-1β (Anisman, Merali et al. 2008). We however found no significant correlations between CSF-leptin and CSF-IL-1β.

5.5 Limitations

The most obvious limitation in paper I and II is the lack of healthy controls. Choosing a relevant control group is a delicate matter, though. The control groups used in paper I and II were, although not healthy, subjected to a similar amount of stress (a recent suicide attempt and being hospitalized). In paper IV we used healthy controls, which usually is the recommendation. The confounding effect of stressors must then be taken into account and the results therefore be interpreted with caution. In paper III and IV, a major limitation is the prevalent medication and co-morbidity of the patients submitted to OGTT. Patients with current deliberate self-harm and BPD are severely ill, with a sometimes life threatening condition. It would be unethical to

keep these patients absent from medication for a reasonable wash-out time. Concerning the prevalent co-morbidity, axis I as well as axis II, our sample was comparable to those of other studies (Philipsen, Limberger et al. 2008).

For a more detailed discussion concerning the limitations, please see the different papers. A complete list over confounding effects of present medication in paper III is however lacking and the missing parts are thus presented here: duloxetine, olanzapine and haloperidol could possibly affect glucose metabolism. Duloxetine can induce hyperglycemia, mainly in patients with diabetes. None of our patients had diabetes or showed a hyperglycemia. Studies on approximately 500 patients have shown that 1% of the patients treated with olanzapine had diabetes, compared to 0.9% in the placebo group. 2% of the patients with olanzapine had an impaired glucose tolerance and 1.6% of the subjects receiving placebo. Haloperidol could in less than 1/1000 patients induce hypoglycemia. Inhalation steroids could theoretically also affect glucose metabolism, however we considered this influence to be of little importance.

6. Conclusions

In this thesis, all patients have expressed self-inflicted aggression and have been investigated with measures associated with metabolism. Although we found significant differences between the groups that were the focus of attention, scatter diagrams show large overlapping of the measured parameters. Self-inflicted aggression can thus not be explained by one or several factors that are obviously pathological, since all of the levels measured in these patients also can be found in persons without aggressive behaviour. Rather, it seems as if self-inflicted aggression is associated with a complex metabolic and/ or immunological imbalance, not necessarily striking when looking at one single factor, but still pathological when considered as a whole. The findings in this thesis thus represent pieces in the puzzle of altered metabolism in persons with self-inflicted aggressive behaviour.

Major conclusions:

I. In women with a recent suicide attempt, low CSF-leptin is associated with major depressive disorder and low BMI associated with choosing a violent method for the attempt. High CSF-insulin is, regardless of sex, associated with choosing a violent method for the attempt.

II. Deliberate self-harm and borderline personality disorder is associated with altered glucose metabolism. In patients without eating disorder plasma glucose

nadir is low. In those with an eating disorder this is counteracted by an increased glucagon secretion.

III. CSF-IL-1β is increased in patients with a recent suicide attempt, and this is particularly accentuated in those with a Cluster B personality disorder.

IV. Deliberate-self-harm and borderline personality disorder is associated with an increased secretion of IL-1β during the oral glucose tolerance test, but not to alterations in fasting levels or to secretion of IL-6 or TNF-alpha.

Based on these conclusions and current knowledge, this thesis shows that metabolic and immunological alterations are of importance in the context of self-inflicted aggressive behaviour. Causal associations are not possible to make, but leptin, insulin and IL-1β are all related to 5-HT and the HPA-axis, which are systems known to be associated with aggression and psychiatric morbidity. Of course, self-inflicted aggressive behaviour is far too complicated a behaviour to be understood by only one approach. Other biological variables as well as psychological and cultural ones have to be considered. This thesis thus adds only a metabolic and immunological aspect to the complex matter. However, this is important, since new treatment strategies may emerge. For this, additional research is however needed.

7. Future outlook

To further elucidate the questions raised by the findings in this thesis it would be interesting to perform an extended study of patients with deliberate self-harm by means of the oral glucose tolerance test. A two hour test may then be sufficient for measuring differences in IL-1β secretion in response to the glucose challenge, since in our studies, the largest difference was shown in the beginning of the test. A preferable approach to the matter of healthy controls would be to match for allergy and smoking, since this is prevalent in the patients as well as in possible healthy controls.

Another interesting subject would be to analyze mRNA expression of IL-1β, insulin and leptin in cerebral biopsies from suicide victims. This would give a more accurate description of variations than CSF-levels. One study has already been made measuring leptin mRNA, but findings need to be reproduced (Eikelis, Esler et al. 2006). This study also proposes the following interesting approach to add further knowledge to the hypothesis of local insulin secretion in the brain. The leptin gradient between the right jugular vein and the brachial artery was measured. In this way a possible insulin gradient could be estimated.

Anakinra^{R}, an interleukin-1 receptor antagonist is already in clinical use in autoimmune diseases. It would be interesting to measure hostility and aggression, perhaps by a self-rating scale in patients before and during treatment with Anakinra^{R}. If

measures of aggression and hostility are reduced, this would strengthen the associations that we found.

The findings in this thesis cannot immediately be applied for clinical use. However they emphasize the importance of biological factors in association with self-inflicted aggression, and this may relieve some of the guilt that these patients often experience.

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Papers I-IV