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The psychobiology of aggressive behaviour

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Introduction.

Aggressive behaviour is one of many mammal instincts for survival. Among humans, advanced psychological functions contribute to several expressions of aggression. One example is suicidal aggression. There are reports on murderers who later committed suicide, or on patients with severe psychiatric illness, who committed extended suicide. About 25% of violent psychiatric patients have harmed themselves, while about 10% of suicide attempters have a history of assault (Plutchik & Van Praag, 1989). These researchers also reported a high correlation between ratings of suicide risk and ratings of violence. Furthermore, Engström et al (1999) found temperamental similarities between suicide attempters and violent offenders.

Swedish studies show a high premature mortality in criminal populations. Lidberg (1993) reported that violent deaths were common among delinquents, and about 50% of these deaths were suicides.

According to Gray (1987) and Barrat (1991), hostility and anxiety are signs of brain arousal, and individuals with high arousal are sensitive to external stressful events. Their psychic tension disappears only after a destructive break through. Another aspect of aggression is an inherent inability to control impulses. Schalling (1993) suggested impulsivity to be the link between psychopathology and biological vulnerability, as similar, or even the same, biological deviations could be seen in impulsive, self-destructive and antisocial persons. Impulsive and aggressive traits might contribute significantly to the risk of attempting suicide among alcoholics (Koller et al, 2002).

Male alcoholic individuals could be classified into type I alcoholics (late onset) or type II (early onset with antisocial traits) according to criteria described by Cloninger (1987). Finnish alcoholic, impulsive offenders have personality profiles like type II alcoholics (Virkkunen & Linnoila, 1993). According to Cloninger (1987), type II alcoholics have high family loading, less ability to abstain from alcohol, little guilt or fear associated with drinking, and more frequent alcohol-related antisocial behaviour.

Mulder (2001) performed a cross-sectional review on alcoholism and personality and concluded that there is a clear association between antisocial behaviour and alcoholism, and antisocial behaviour seems to start before alcoholism. Childhood conduct disorder and hyperactivity have also been mentioned as factors predisposing alcoholism and antisocial behaviour (Söderström, 2002). Interestingly, this typology of childhood risk-factors is not specific for alcoholism, as it is generally accepted in psychiatry that early onset of disorders means that they are most probably genetically determined, and that their life course becomes increasingly severe and complicated (Mulder et al, 1994)

Neurobiological aspects of aggressive behaviour.

Brain regions of importance for aggression are e.g. the sensory cortical areas, amygdala, hippocampi, hypothalamus, brain stem, prefrontal cortex and corpus callosum. The site of action determines the impact of various functions *(Table)*. The regulatory monoaminergic systems play an important role in this organization.

Monoamines (Fig.1).
There is a well known association between aggressive behaviour and low function of the monoamine serotonin (Valzelli, 1981). Depue and Spoont (1986) concluded that there are two behavioural systems, one inhibiting and one facilitating. The former is sensitive to environmental stimuli and is linked with serotonergic pathways in the septum-hippocampus area. The latter is activated during goal-oriented behaviour and is linked with the mesolimbic dopamine paths. This two system model, in which dopamine and serotonin modulate each other, might explain personality features such as impulsivity and mood fluctuations.
Levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA), analysed in lumbar cerebrospinal fluid (CSF), are often low in patients who make violent suicide attempts, as well as in impulsive violent offenders, impulsive arsonists, and people with a history of aggressive acts. (Åsberg et al, 1976; Träskman et al, 1981; Virkkunen et al, 1987; Lidberg et al, 1985; Brown et al, 1979). Ågren and coworkers (1986) suggested low CSF levels of both serotonin- and dopamine - metabolites among impulsive violent or suicidal individuals. Söderström et al (2003) reported a strong association of the CSF HVA~5-HIAA ratio with psychopathic traits.
In alcoholic criminal offenders, low CSF 5-HIAA was associated with irritability and impaired impulse control (Virkkunen et al, 1994).

Platelets could be regarded as neuron- models. Activity of the degradating enzyme monoamine oxidase (MAO) in platelets might be used for subtyping alcoholics (Demir et al, 2002). There are many studies which show low platelet MAO-activity in impulsive and/or sensation seeking persons, individuals with type 2 (early onset) alcoholism, and in recurrent criminality (Lidberg et al, 1985; Buchsbaum et al, 1976; Oreland et al 2002). Suicidal impulsive patients with alcoholism had low platelet MAO activity according to our studies (Engström et al, 1996). Psychotic violent offenders had lower platelet MAO-activity than other criminal persons according to another study (Belfrage et al, 1992).

Deviances in serotonin receptor function, or abnormal binding to platelet-membrane receptors, or receptor-binding in Single Photon Emission Computerized Tomography (SPECT) studies of the brain, have also been reported in depressed suicidal, violent and/or impulsive patients with or without alcoholism (Simonsson et al, 1991; Pandey et al, 2002; Tiihonen et al, 1997; Lindström et al, 2004; Audeanuert et al, 2001; Heinz et al, 2001).

Blunted responses after serotonin-challenge reflect decreased serotonin function in the limbic system and hypothalamus. Associations between such blunted responses and impulsivity, irritability, aggression, suicidal behaviour and antisocial behaviour have been reported by several researchers (Coccaro et al, 1990; Manuck et al,. 2002). Similarly, Fishbein et al (1989) reported blunted reactions in impulsive and aggressive substance users. Low serotonin function was also seen in children with a familial type of aggression (Halperin et al, 2003). Gerra et al (2004) observed impaired serotonin function in heroin addicts, which in combination with certain temperamental traits, could increase the proneness for addiction, and probably complicated clinical pictures, e.g. comorbidity, as well.

King (1986) reviewed the role of catecholamines for aggressiveness, and reported that several studies showed that mesolimbic dopamine causes an impairment of the behavioural response-threshold, which in turn results in increased aggression.

Neuroactive steroids (Fig.2).
Higley et al (1992) studied aggressive rhesus monkeys and found low CSF 5-HIAA and high CSF noradrenaline as well as high levels of corticotrophin (ACTH) and cortisol in plasma. This indicates that these monkeys not only were aggressive (serotonin) but also had a high arousal (noradrenaline and steroids).
Deviances in steroid metabolism have been proven in relation to both suicidal and violent behaviour. High corticosteroid concentrations as well as nonsuppression of cortisol in the dexamethasone suppression test have been observed in depressed suicidal patients (Coryell & Schlesser, 2001). In contrast, suicidal individuals with impulsive personality disorders have low 24 h urinary and plasma concentrations (Westrin et al, 2003).

High serum testosterone was seen in male delinquents of different ages (Mattsson et al, 1980; Rasanen et al, 1999). In violent and alcoholic offenders, high free CSF testosterone was associated with aggressiveness, monotony avoidance, sensation seeking, suspiciousness and reduced socialization (Virkkunen et al, 1994). These findings are in contrast to results reported by Gustavsson et al (2003), where depressed males had significantly lower CSF testosterone than others. CSF 5-HIAA did not correlate significantly with CSF testosterone in this study. The reason for this is probably that 5-HIAA is related to impulsivity rather than to aggressiveness (Linnoila et al, 1983; Virkkunen & Linnoila, 1993).

At present, there are interesting discussions concerning the possible role of low cholesterol in violent behaviour. Originally, epidemiological investigations found an association between low cholesterol and violent death in the county of Värmland, Sweden (Lindberg et al, 1992). Later, studies on suicidal patients and aggressive primates have shown relationships between low serotonergic function and low cholesterol, which probably could be explained by disrupted cellular membranes due to shortage of cholesterol, and hence receptors becoming increasingly weak or sensitive (Scanlon et al, 2001). Golomb et al (2000) reported low cholesterol in violent criminals. A recent study by Repo-Tiihonen et al (2002) showed that low levels of another lipid, triglyceride, were associated with childhood onset of conduct disorder and premature death.

Carbohydrates.
Low blood-glucose has been noticed in aggressive individuals, probably due to high insulin levels. (Linnoila et al, 1989; Virkkunen et al, 1994). In our group, Westling et al (2004) have shown high CSF insulin in patients who made violent suicide attempts, and this was regardless of psychiatric diagnosis.
In one study of alcoholics, a 5-hour oral glucose tolerance test, in which glucose, prolactin and cortisol responses were measured, was performed by Fishbein et al (1992). Low nadir cortisol and blunted prolactin response to glucose were linked with antisocial personality and aggressiveness.
Virkkunen et al (1994) reported that type 2 alcoholics were vulnerable to hypoglycemic reactions after an oral load of glucose.

Genes and the family
Delinquent behaviour can be seen across generations. Long-term studies have shown that conduct disorder during childhood may predispose school-problems, deviant peers, antisocial criminal adult behaviour and/or alcoholism (Olweus, 1978). Much of this effect is genetically determined (Heath et al, 1997). When healthy individuals, who had alcoholic fathers, were subject to stress tests with and without alcohol, it was found that alcohol given to these

subjects attenuated the stress-response, which was not the case concerning subjects without alcoholic fathers (Zimmerman et al, 2004)
Recent investigations reveal that a functional polymorphism in the gene coding for MAO A (high MAOA expression) could moderate the effect of maltreatment during childhood (Caspi et al, 2002).
Genetic factors are supposed to contribute to about 40% of personality variance.
Among monoaminergic genes, MAOA gene polymorphisms, e.g. the low activity 3-repeat allele, confer increased susceptibility of antisocial and aggressive behaviour (Samochowiec et al, 1999; Manuck et al, 2002). Behavioural deviances often seen in people with low platelet MAO-B activity, could be explained by the presence of two long alleles of the transcription factor AP-2 beta gene (Oreland et al, 2002).
Serotonin transporter genes have also been studied in various populations, and the 5HTTLPR polymorphism might contribute to early onset alcoholism and violent behaviour rather than to suicidal behaviour (Hallikainen et al, 1999; Zalsman et al, 2001).
According to Manuck et al (1999), an aggressive disposition is associated with an intronic polymorphism of the tryptophan hydroxylase (TPH) gene

Conclusion.
So far, psychobiological research suggests that monoaminergic genes, childhood conduct disorder as well as environmental stress predispose deviant behaviour such as antisocial aggressive behaviour or type II alcoholism later in life. Excitatory and inhibitory biochemical and psychosocial powers are constantly acting in consert. Apart from monoamines, steroids and carbohydrates are involved in aggression and violence. Current research using brain-imaging techniques will certainly offer further understanding of biological events and hopefully a chance to invent specific treatment tools for this behaviour, socio-economically deleterious for the individual, his/her immediate surroundings, and society at large.

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Table. The role of different brain regions for aggressive behaviour

Brain region	**Main function related to aggression**
Sensory cortical areas	Input becomes conscious
Amygdala	Colouring of input by memories, emotions, and urges from the limbic system
Hippocampi	Associative learning
Hypothalamus	Connects to autonomic input and output
Brain stem	Stereotyped responses to emotions and urges
Prefrontal cortex	Executive functions such as planning, impulse control, and strategies
Corpus callosum	Connections between the dominant, language-steering hemisphere and the subordinate hemisphere responsible for interpretation of emotions an non-verbal information

(From Söderström, 2002)

Figure 1. Monoamines are degradated by use of the enzyme monoamine oxidase (MAO) to 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA), and 3-methoxy- 4-hydroxy-phenyl glycol (MHPG), which are found in the brain as well as in the rest of the body.

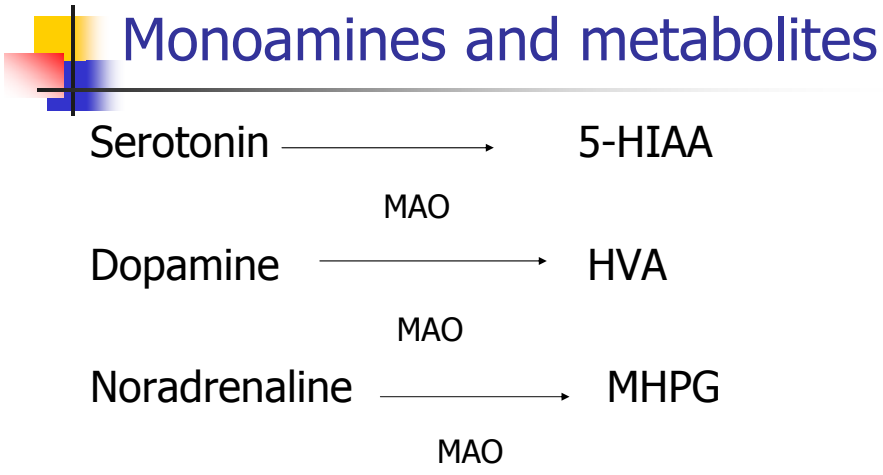

Figure 2. Parts of steroid metabolism of relevance for aggressive behaviour.