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RESEARCH ARTICLE

THE BEWILDERING NEUROBEHAVIOURAL DISORDER: AGGRESSION VIS-À-VIS STRESS AND ALCOHOL

***Faiz Mohammed**

School of Medicine, College of Medicine and Health Sciences, Dire Dawa University, Dire Dawa, Ethiopia

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ABSTRACT

Aggression has been recognized as a near-universal behavior with substantial influence on and implications for human and animal social systems. It can be a significant problem since escalated aggression may result in serious damage to others and can reveal itself as a symptom of psycho-pathologies. It is often considered to be the product of environmental stressors, health problems, pain, psychiatric morbidity or behavioral stressors. There are different forms of human aggressive behavior which can depend on the triggering factors, social context or individual genetic predisposition. Nevertheless, the multiple etiologies, pathogenesis, and psychopharmacology of aggression in humans have not been identified and well recognized y*et al*though certain factors are understood to increase risk for persistent aggressive behavior. The drug–aggression relationship exists in a complex manner often manifested as either direct or indirect. Importantly, alcohol is frequently cited for aggressive behavior in addition to its adverse medical or social consequences. It is also believed that there is a strong correlation between aggression and stress. There is a general agreement that stress in early life can lead to behavior disturbance although both genetic and epigenetic factors may influence exposure to stressful life events. Generally, aggression has been identified as a key area for research and pharmacological intervention since scientifically expressing its context is one of the greatest and most challenging problems in society. So, study on aggression has to be a 'hot topic' in scientific investigations for many specialists from different disciplines.

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INTRODUCTION

Aggression has been recognized as a near-universal behavior with substantial influence on and implications for human and animal social systems (Filby *et al*., 2010). The potential for aggressive behavior exists whenever the interests of two or more individuals conflict (Koolhaasand Boer, 2009; Nelson and Trainor, 2007). There have been diverse definitions of aggression. It has been traditionally, for example, defined as overt behavior that has the intention of inflicting physical damage on another individual (Anderson and Bushman, 2002; Lobo *et al*., 2009; Nelson and Trainor, 2007). Currently, in its very broad definition that includes both competitive and non-competitive situations, aggression is usually considered the intentional harming of one person by another (Cashdan, 2003). Subsequently, its definition constitutes a multidetermined act and encompasses both verbal and physical aggression against self, objects and other people (Fleminger *et al*., 2008; Powers, 2005). It may also include severe irritability, violent, hostile, or assaultative behaviour and "episodic dyscontrol" (Anderson and Bushman, 2002; Fleminger *et al*., 2008; Laurentz, 2003).

****Corresponding author: Faiz Mohammed,***
School of Medicine, College of Medicine and Health Sciences, Dire Dawa University, Dire Dawa, Ethiopia.

In human and veterinary clinics, aggression can be a significant problem since escalated aggression may result in serious damage to others and can reveal itself as a symptom of psycho-pathologies (Centenaro *et al*., 2008; Koolhaasand Boer, 2009). In non-human animals, aggression typically occurs in the context of competition for limited resources including food, mates and nesting sites (Centenaro *et al*., 2008; Filby *et al*., 2010; Koolhaasand Boer, 2009). From a biological point of view, it is important in the establishment of territories maintaining of dominance, and social hierarchies (Centenaro *et al*., 2008; Filby *et al*., 2010; Koolhaasand Boer, 2009). In this respect, aggression is viewed as an adaptation that can have key effects on the lifelong success of individuals and that conveys evolutionary fitness (Centenaro *et al*., 2008; Filby *et al*., 2010; Lobo *et al*., 2009).

When the term aggression is particularly applied to human, it becomes a complex social behavior by which a relative few of these have been applied to animal research paradigms (Blanchard *et al*., 2003; Laurentz, 2003; Nelson and Trainor, 2007). In human literature, it is defined as the action by human beings that result in physical or psychic impairment to another human being, or intent of such injury (Laurentz, 2003; Nelson and Trainor , 2007). Importantly, the perpetrator must intent

that the behavior will damage the target, and that the target is motivated to avoid the behavior (Anderson and Bushman, 2002). In humans, according to Filby *et al*. (2010), aggression has been identified as a key area for research and pharmacological intervention since scientifically expressing its context is one of the greatest and most challenging problems in society. Study on aggression has shown progress and has been a 'hot topic' in scientific investigations for more than half of a century as it has been a target for many specialists from different disciplines (Ferrari *et al*., 2005). The study of aggressiveness, however, is complicated by the fact that aggressive behavior is not a unitary trait (Blanchard *et al*., 2003; Farmer *et al*., 2011) and its analyses are correspondingly more complex and difficult to interpret than is true for many other behaviors (Blanchard *et al*., 2003).

Aggression And Violence

Violence and aggression have afflicted the globe since time immemorial (Dewall *et al*., 2006). Violence is an aggression that has extreme harm as its goal (e.g., death) (Anderson and Bushman, 2002). It has been reported that the number of victims of interpersonal violence is almost twice as high as the number of people killed in armed conflicts (Popova, 2006). In the Oxford English Dictionary, violence is defined as "the exercise of physical force so as to inflict injury on, or cause damage to, persons or property; action or conduct characterized by this; treatment or usage tending to cause bodily injury or forcibly interfering with personal freedom" (Koolhaasand Boer, 2009). Additionally, violence in healthcare has been defined as any aggressive behaviour "aimed at inflicting harm or discomfort on its victims" (Zampieron *et al*., 2010).

The terms ''aggression'' and ''violence'' do differ pragmatically as the former is predominantly an empirical term while the latter is predominantly a forensic term even though can sometimes essentially be used interchangeably (Hoakena and Stewart, 2003). Explicitly stating, all violence is aggression, but the reverse is not always true. For instance, one child pushing another off a tricycle is cannot be identified as an act of violence but as an act of aggression (Anderson and Bushman, 2002).

Types of Aggression

One of the earliest and most influential typologies of aggression related to preclinical aggression (animal aggression) was proposed by Moyer (1968) (Popova, 2006). He argued the importance of defending various types of its underlying physiological mechanisms (FieldMan *et al*., 1997). Based on the eliciting stimuli, he distinguished eight categories of aggression: predatory (attacks on prey), intermale, fear-induced, irritable, territorial, maternal, instrumental, and sex related aggression (FieldMan *et al*., 1997; Koolhaas and Boer, 2009 Popova, 2006; Pucieowski, 1987). Feldman *et al*. (1997) claim that Moyer's classification suffered from various problems, although it had great heuristic value. Recently, as the etiological approach became more popular, a new classification has been proposed by Brain (1981) (FieldMan *et al*., 1997; Pucieowski, 1987). He defined 5 classes of aggression basing on the utility of the behavior to the animal: self-defensive, parental, predatory, social, and reproduction termination (FieldMan *et al*., 1997; Pucieowski, 1987). There are different forms of human aggressive behavior which can depend on the triggering factors, social context or individual genetic predisposition (Pucieowski, 1987). Feldman *et al*. (1997) focuses on the usefulness of distinguishing among different types of aggressive interactions because of the diversity of the behavior patterns normally labeled aggressive.

According to Veenema (2009), although various classifications of aggression in humans and animals can be employed depending on the problem under investigation, it can be divided into two major subtypes (i.e. offensive and defensive aggression). The distinction between offensive and defensive aggression is based on a number of aspects of behavior, including antecedent (hormonal and experiential) conditions, organismic variables, attack topography (target of attack on the opponent's body), and typical outcomes (Blanchard *et al*., 2003). According to Pucieowski (1987), this kind of classification appears particularly suitable for investigation of the neural and neurochemical mechanisms of aggression and these subtypes appear to be differently organized in the brain as well. There are more other ways to classify aggressive behavior, for example by the targets (directed to objects, persons or self), mode (physical or verbal) or intensity (Schmidt and Prado-Lima, 2009).

Furthermore, Buss and Perry, according to Laurentz (2003), have concluded that human aggression consists of four sub traits: Physical and verbal aggressions-both comprise physical or emotional damage to others-represent the motor components of behavior; anger, the emotional component of behavior, involves the arousal and preparation for aggression; and hostility, which consists of the feeling of enmity, represents the cognitive component of behavior. Generally, it is possible to summarize the classifications of human aggression from different literatures in to physical, verbal, indirect, sexual, reactive or proactive aggression though these subtypes are neither absolute nor mutually exclusive. Physically aggressive behaviors are hostile acts directed toward others, the patient's self, or objects that may be physical or sexual in nature (Access Medical Group, 2002). It is deliberate use of force against a person resulting in physical harm or personal distress (Zampieron *et al*., 2010). It can all be resistiveness, striking out, property destruction, elopement, punching , slapping, kicking, biting, grabbing, pulling, shoving, beating, limb twisting, pushing, hitting, biting, and other such kinds of behaviors (Powers, 2005; Tremblay *et al*., 2008; Zampieron *et al*., 2010).

Verbally aggressive behaviors include making strange noises, temper outbursts, threats, screaming, cursing, accusations, and name calling (Access Medical Group, 2002). It includes threatening behavior or verbal hostility that may provoke confrontations, and frequently followed by physical aggression (Powers, 2005; Tremblay *et al*., 2008). It, according to Bushman and Cooper (1990) is considered to be either direct when the victim is actually present or indirect when the victim is absent. Indirect form of aggression is a more complex form of aggression that involves attempting to harm by spreading rumours, excluding the victim from a group etc. (Tremblay

et al., 2008). Human aggression can be narrowly but inclusively classified in to two subtypes: Proactive aggression subtype and reactive aggression subtype (Nelson and Trainor, 2007). Proactive aggression is a goal-directed, deliberate and cold-blooded action, useful to achieve goals, offensive and provocative, and may be characterized by pleasure or satisfaction (Camodeca and Goossens, 2005; Fontaine, 2007). It is unprovoked aggressive acts, or requires no stimulus (Camodeca and Goossens, 2005; Tremblay *et al*., 2008). It is also called instrumental aggression (Fontaine, 2007; Koolhaasand Boer, 2009; Schatz, 2006). On the other hand, reactive aggression is a defensive response to provocation or trouble, a way to defend oneself and to retaliate against abuse, and is accompanied by anger (Camodeca and Goossens, 2005; Tremblay *et al*., 2008). It is characterized by hot blood, impulsivity, and uncontrollable rage (Fontaine, 2007). It may be considered as either normal/desirable reaction to environmental threats or pathological when its intensity is disproportionate (or when it is misdirected, generating negative consequences) (Schmidt and Prado-Lima, 2009). It is also named as hostile aggression (Anderson and Bushman, 2002; Koolhaasand Boer, 2009; Schatz, 2006) and impulsive aggression (Schmidt and Prado-Lima, 2009).

Neuropathology of Aggression

The multiple etiologies, pathogenesis, and psychopharmacology of aggression in humans have not been identified and well recognized yet. Methodological limitations, according to Veenema (2009), might be one of the main reasons for this. Pathological aggressiveness might be a result of some disease states or different external factors such as environmental influences (Pucieowski, 1987). Tremblay *et al*. (2008) explain that certain factors are understood to increase risk for persistent aggressive behaviour. Exposure to early social deprivation or trauma, for instance, can have detrimental effects on the normal development of various neuroendocrine and neurobiological systems and can cause structural and functional brain alterations (Veenema, 2009; Zampieron *et al*., 2010). Furthermore, Tateno *et al*. (2003) stated that aggression is identified to be a disruptive consequence of traumatic brain injury (TBI). In addition to that, investigated results showed that children born to parents with aggressive or uncontrolled behaviour are more likely to continue with their physically aggressive behaviours (Tremblay *et al*., 2008).

Aggression is also identified to be disruptive consequences of neuropsychiatric disorders that have been recognized for many years (Tateno *et al*., 2003). Nelson and Trainor (2007) list psychiatric illnesses, substance abuse and dementia as factors that can produce a chronic problem with aggression. Similarly, Nguyen *et al*. (2008) describe that aggressive symptoms, which are stressing to both the caregiver and patient, are often present in persons with dementia. Importantly, Powers (2005) adds to these points that those retarded individuals are more prone to aggression if they develop psychiatric problems. Mania, psychosis, depression, and severe anxiety may cause sufficient distress to produce hostile or aggressive activities (Fleminger *et al*., 2008; Powers, 2005). More importantly, some data specifically show that there was a strong relationship between depression and aggression (Tateno *et al*., 2003). As mentioned above, alcohol seems to lead to various form of violence (Hoakena and Stewart, 2003; Zampieron *et al*., 2010). Aggression is also associated with some diseases such as phenylketonuria, hepatic encephalopathy, allergy, lead poisoning, herpes simplex viral infection, organic chronic degenerative diseases, high blood levels of toxins, and endocrine disorders such as hyperthyroidism, Cushing's syndrome, hypoglycemia or disturbed parathyroid function (Pucieowski, 1987; Zampieron *et al*., 2010). Nguyen *et al*. (2008) emphasize on the limitation of treating most of the distinguished aggressive factors although some factors have been started to be identified as treatable. Generally, aggression behaviors are often the products of environmental stressors, health problems, pain, psychiatric morbidity or behavioral stressors (Powers, 2005).

As a highly complex behavior, the expression of aggression involves the activation of brain structures involved in emotion control and cognitive processes (Koolhaas and Boer, 2009; Veenema 2009). Tateno *et al*. (2003) stated that injury to the frontal lobe can result in aggression in some patients since this lobe regulates higher "executive" functions of the brain. Moreover, a number of perspectives on aggression informed by neuroscience emphasize the role of specific regions in the prefrontal cortex (PFC) that support top-down control over anger and aggressive urges (Dewall *et al*., 2006). Interestingly, reduced prefrontal gray matter has been associated with autonomic deficits in patients with antisocial personality disorders (American College of Neuropsychopharmacology, 2002). Although prefrontal orbital cortex and adjacent ventral medial cortex appears to play a central role in aggression, temporal cortex, cingulate cortex, and amygdala may also play important roles since aggression, as an emotional behavior (American College of Neuropsychopharmacology, 2002; Koolhaasand Boer, 2009).

The amygdalar complex (AMY) and the nucleus accumbens septi (NAS), particularly, are the brain structures of essential importance for the control of affective behavior (Pucieowski, 1987). Importantly, functional neuro-imaging has implicated the fronto-subcortical brain circuits including the basal ganglia, thalamic structures and frontal cortical areas in the pathophysiology of aggressive obsessions (Obsessive–Compulsive Disorder) (Perez-Rodriguez *et al*., 2008). Additionally, according to Koolhaas and Boer (2009), recent meta-analyses suggest that certain aggression-related psychopathologies are associated with low functioning of the hypothalamo-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS). So, it is expected that these brain structures might be involved in affective aggression even though much research is directing towards determining their exact role in affective aggression (Pucieowski, 1987).

The relation of aggression with drugs, alcohol and stress

Overview of drugs and aggression

The drug–aggression relationship exists in a complex manner often manifested as either direct or indirect. Hoakena and Stewart (2003) describe this relationship as the direct one is commonly explained as aggression (or violence) following pharmacological activity of drugs while the indirect one is

violence occurring in order to attain drugs such as violent behavior in narcotic abstinent addicts. Aggressive behaviour occur following drug abuse to morphine, heroin, codeine, LSD, cocaine, cannabis, amphetamine and/or methylenedioxymethamphetamine, alcohol, benzodiazepines, anabolic–androgenic steroids, bronchodilators etc. (Hoakena and Stewart, 2003; Powers, 2005; Pucieowski, 1987). The aggression occurring is especially strong when environmental factors are superimposed on drug-induced pathology (Pucieowski, 1987). A number of clinical studies have established a positive correlation between aggressive behaviour and the long-term use of cocaine and amphetamine (Deleon *et al*., 2002). Similarly, it has been well documented that heroin addicts have abnormal hypothalamic-pituitary-gonadal axis and the HPA axis and during withdrawal they become irritable and aggressive (Katzung *et al*., 2009).

Alcohol and Aggression

Alcohol is one of the substances that are more frequently consumed throughout the globe. In addition to its adverse medical or social consequences, and genetical and environmental determinants which are manifested in alcoholism, it is frequently cited for aggressive behavior (Bègue *et al*., 2009; FieldMan *et al*., 1997; Katzung *et al*., 2009). Importantly, according to Bushman and Cooper's meta-analysis (1990), alcohol induces aggressive behavior in humans as much as any other social or non-social behavior. Additionally, Brown *et al*. (2010) claim that evidences such as geographical, temporal and observational show that there is correlation between alcohol and aggressive behavior. Hoakena and Stewart (2003) refer to our most conventional wisdom to show that individuals who are under the influence of alcohol will act aggressively.

They make their claim pragmatic by relying on empirical results on the relation of alcohol and violent crimes in which alcohol is estimated to contribute more violent crimes than nonviolent crime (Hoakena and Stewart, 2003). Interestingly, Feldman *et al*. (1997) states the estimation that when certain aggressive acts and/or violent crimes are committed, it can be expected that, either victims of violent crimes or perpetrators or both are likely to have consumed alcohol prior to the act. In USA, for example, on 1997 approximately to two third of homicides committed show that either the offender or victim or both were alcohol intoxicated (Meyerand Quenzer, 2005). Therefore, we have a clue and there appears to be a growing consensus, that alcoholics are more likely to have a history of violent behavior even though not all alcoholics are violent (Feldman *et al*., 1997). But there are arguments regarding whether alcohol directly causes aggressive behavior or it indirectly trigger or heightens aggressive behavior.

Laurentz (2003), for instance, argue that alcohol does not directly cause violence but heightens aggressive behavior in a genetically predisposed population. He bases on a study made in mice that received a moderate dose of alcohol by which only 25% of the mice doubled or tripled their aggressive behavior towards a competitor. Contrastingly, proponents of pharmacologically-based models (the disinhibition model) purport that aggression following the consumption of alcohol is due to the pharmacological properties of alcohol itself (Bègue *et al*., 2009; Giancola, 2002). It is considered to be a very general explanation of the alcohol-aggression relation which contends that alcohol has a direct effect on aggression by pharmacologically disinhibiting brain centers which are important in maintaining inhibitory control over behavior (Bushman and Cooper**,** 1990; Giancola, 2002). Bushman and Cooper (1990) briefly states that disinhibition theorists contend that alcohol facilitate aggression not by 'stepping on the gas' but rather by paralyzing the brakes.'' Opponents of pharmacologically-based models such as expectancy models theorists argue that it is not the pharmacological properties of alcohol that facilitate aggression (Giancola, 2002). They stipulated that the behavior following the ingestion of alcohol is a function of the drinker's belief regarding the effects of alcohol (Bègue *et al*., 2009; Giancola, 2002).

They rest on the assumption that people have a priori beliefs that alcohol will lead to aggression (Giancola, 2002). Alcohol, according to their claim, facilitates aggression indirectly by causing certain cognitive, physiological, and emotional changes that increase the probability of aggression (Bushman and Cooper**,** 1990). So, the pharmacological model has limited empirical support because not all persons become aggressive when they drink alcohol, although a large body of literature till suggests that alcohol has pharmacological effects (Hoakena and Stewart, 2003; Giancola, 2002). It seems that the main problem is studying alcohol-induced aggression in humans by itself has several limitations even though the researches regarding this thematic area have been wide (Echevarria and Hammack, 2010; Feldman *et al*., 1997; Veenema, 2009). But one solution to these problems has been to use animal models (Feldman *et al*., 1997). For example, a study made in adult zebrafish by acute alcohol exposure has been shown to modulate locomotor activity and shoal cohesion behaviors (Echevarria and Hammack, 2010).

Generally, it can be suggested that intoxicated aggression is not solely due to the direct pharmacological effects of alcohol rather it is the product of individual difference and contextual variables interacting with alcohol pharmacodynamics (Bègue *et al*., 2009). Therefore, there are multiple risk factors that make alcoholics primarily to engage in alcohol misuse and act aggressively. Consequently, the alcohol–aggression relationship tends to be determined by individual difference, and pharmacological, contextual, situational factors (Bègue *et al*., 2009; Hoakena and Stewart, 2003). According to Brown *et al*. (2010), a behavioral disturbance is a well-known risk factor for adolescent alcohol misuse and aggression. Individual differences in nonhuman primates appear to be associated with early rearing experiences and remain stable throughout the individual's life (Feldman *et al*., 1997). Furthermore, childhood histories of experienced or witnessed domestic violences, for instance, are correlated with alcohol misuse (Ameican Psychiatric Press, 1996).

Additionally, a family history of alcohol dependence such as bringing up being sons or daughters of alcoholic fathers is associated with severe symptoms of alcohol dependence in addition to greater prevalence of psychopathology (Ameican Psychiatric Press, 1996; Feldman *et al*., 1997). Moreover,

adverse early life experiences such as maltreatment or neglect can lead to the development of aggressive behavior (Koolhaas and Boer, 2009). Pharmacodynamically, alcohol increases aggressive behavior by chemically modulating neurotransmitters such as GABA, dopamine and serotonin although it acts mainly through its regulatory effects on the first (Laurentz, 2003). Giancola (2002) lists the contextual variables mainly as blood alcohol concentration limb effects, alcohol type and dose, social pressure, provocation and traits that are potentially important in moderating the alcohol-aggression relation.

Stress and Aggression

It is believed that there is a strong correlation between aggression and stress. There is a general agreement that stress in early life can lead to behavior disturbance although both genetic and epigenetic factors may influence exposure to stressful life events (Craig, 2007). Aggression is sometimes displayed as part of the effort to cope with a stressor. Koolhaas and Boer (2009) mentions that adverse early life experiences such as maltreatment can lead to the development of aggressive temperamental disturbances. It has been deducted that early life stress contributes to the development of maladaptive behavior in humans although its psychopharmacology is less recognized (Veenema, 2009). At the peripheral level, any perceived stressor activates two main physiological pathways: the sympatho-adrenomedullary (SAM) system and HPA axis (Koolhaas and Boer, 2009). The SAM system appears to be involved in the mediation of the initial reactions to stress are typically those of ‘‘fight or flight’’ (Craig, 2007). The HPA axis activation consists of the release of corticotropin releasing hormone (CRH) and vasopressin from the paraventricular nucleus (PVN) of the hypothalamus into the anterior pituitary gland (Brunton *et al*., 2011; Veenema, 2009).

CRH and vasopressin stimulate the secretion of adrenocorticotrophic hormone (ACTH) into blood and ACTH, in turn, stimulates the adrenal glands to produce and release glucocorticoids (Craig, 2007; Veenema, 2009). Production of cortisol assists in restoring homeostasis in response to stress although prolonged exposure can be potentially harmful since a long-lasting physiological activation in response to stress can lead to the development of aggression (Craig, 2007; Koolhaas and Boer, 2009). Overall, the HPA axis exhibits three prominent features that interact to alter regulation of ACTH and corticosteroid secretion. These are a circadian rhythm in basal activity, a feedback mechanism moderated by corticosteroids and, finally, differences in response to acute and to chronic stress (Brunton *et al*., 2011; Craig, 2007). The HPA axis plays a key role in the regulation of aggression.

Subsequently, a hyper- as well as a hypo-active HPA axis is associated with increased aggression in psychopathological conditions (Veenema, 2009). Stress overcomes negative feedback regulation of the HPA axis, leading to a marked rise in corticosteroid production (Brunton *et al*., 2011). Several studies in humans and animals demonstrated that excessive aggressive and violent behaviors are associated with low 5-HT (Serotonin) function (De Castro *et al*., 2001; Nelson and Trainer, 2007; Parikh *et al*., 2008; Veenema, 2009), and central nervous system regulation of serotonin has also been implicated in aggressive behavior (Parikh *et al*., 2008), suggesting that 5- HT inhibits aggression (De Castro *et al*., 2001; Parikh *et al*., 2008; Veenema, 2009). It should be noted that many studies have generated contradictory evidence without any negative correlation between CSF 5-HIAA (Hydroxyindoleacetic acid) and aggressive behavior in primates and rodents (Ferrari *et al*., 2005). A considerable body of research indicates that initial responses to stress result in increased serotonin synthesis and turnover (Craig, 2007).

CSF concentrations of 5-HIAA are presumed to reflect central 5-HT activity (Veenema, 2009). Since 5-HIAA formation accounts for nearly 100% of the metabolism of 5-HT in brain, the turnover rate of brain 5-HT is estimated by measuring the ratio of 5-HIAA/5-HT (Brunton *et al*., 2011). Alterations in 5-HIAA concentrations are thought to underlie changes in 5-HT turnover or metabolism (Veenema, 2009). 5-HIAA from brain and peripheral sites of 5-HT storage and metabolism is excreted in the urine along with small amounts of 5-hydroxytryptophol sulfate or glucuronide conjugates. 5-HIAA is actively transported out of the brain by a process that is sensitive to the nonspecific transport inhibitor, probenecid (Brunton *et al*., 2011). The serotonin transporter plays a pivotal role in brain serotonin homeostasis and aggression (Craig, 2007; Ferrari *et al*., 2005).

It is well established that individuals manifesting persistent impulsive, externally directed aggression, have low levels of the serotonin metabolite, HIAA, in their cerebrospinal fluid in the long term (Craig, 2007). Reactions to acute stress are usually accompanied by perturbations of serotonergic activity indicated by altered levels of serotonin in nerve synapses, or its metabolites, in cerebrospinal fluid, CSF (Craig, 2007; Ferrari *et al*., 2005). At the presynaptic level, numerous stressors increase nerve firing and release of extracellular serotonin in nerve terminals (Ferrari *et al*., 2005). Furthermore, evidence suggests that there are reduced levels of both serotonin and its metabolite, HIAA, in postmortem brains of depressed patients who have frequently experienced long-term stressful environments (Craig, 2007). Some comorbid attributes such as a history of alcohol and substance abuse and mild hypoglycaemia have been proposed by Linnoila to comprise a ‘‘low serotonin syndrome’’ (Craig, 2007).

It has been proposed that there is a reliable association between low blood glucose levels and individual differences in aggressive behavior. Acute decreases in glucose have been implicated in reduced self-control since glucose fuels brain processes (Dewall *et al*., 2006). It should also be figured that an inverse relationship was found between regional glucose metabolism in orbital frontal cortex and right temporal lobe, and life history of aggressive impulsive behavior and (American College of Neuropsychopharmacology, 2002).

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