Role of serotonin and dopamine system interactions in the neurobiology of impulsive aggression and its comorbidity with other clinical disorders☆

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Abstract
Impulsive aggression is characterized by an inability to regulate affect as well as aggressive impulses, and is highly comorbid with other mental disorders including depression, suicidal behavior, and substance abuse. In an effort to elucidate the neurobiological underpinnings of impulsive aggression and to help account for its connections with these other disorders, this paper reviews relevant biochemical, brain-imaging, and genetic studies. The review suggests that dysfunctional interactions between serotonin and dopamine systems in the prefrontal cortex may be an important mechanism underlying the link between impulsive aggression and its comorbid disorders. Specifically, serotonin hypofunction may represent a biochemical trait that predisposes individuals to impulsive aggression, with dopamine hyperfunction contributing in an additive fashion to the serotonergic deficit. The current paper proposes a modified diathesis–stress model of impulsive aggression in which the underlying biological diathesis may be a deficient serotonergic function in the ventral prefrontal cortex. This underlying disposition can be manifested behaviorally as impulsive aggression towards oneself and others, and as depression under precipitating life stressors. Substance abuse associated with impulsive aggression is understood in the context of dopamine dysregulation resulting from serotonergic deficiency. Also discussed are future research directions in the neurobiology of impulsive aggression and its comorbid disorders.

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Impulsive aggression plays a critical role in the manifestation of violent and criminal behavior and is considered an important psychopathological symptom of several mental disorders including borderline and antisocial personality disorders (Coccaro & Siever, 2000; Linnoila & Virkkunen, 1992). Previous research has reported associations among impulsive aggression, mood disorders, substance abuse, and suicidality, which suggest that these comorbid disorders have a common biological substrate (Hicks, Krueger, Iacono, McGue, & Patrick, 2004; Koller, Preuβ, Bottlender, Wenzel, & Soyka, 2002; Placidi et al., 2001). Previous studies utilizing biochemical, anatomical, and brain-imaging techniques have provided insight into the neurobiology of impulsive aggression; yet, the relationship between impulsive aggression and other comorbid conditions remains unclear. One of the problems in the neurobiology of impulsive aggression is the identification of common biological correlates for these comorbid disorders as well as differentiation among these varying comorbid conditions.

Impulsive aggression is a complex behavioral phenotype and multiple brain systems may contribute to its etiology and its high comorbidity with other disorders. The association between impulsive aggression and its comorbid disorders may result from biological predisposing factors, such as an imbalance among the functions of different neurochemical systems, or dysfunction in activities of executive brain regions. Specifically, low levels of the neurotransmitter serotonin (5-HT) have been associated with impulsive aggression in both human and animal studies (Asberg, Scalling, Trakeman-Bendz, & Wagner, 1987; Linnoila & Virkkunen, 1992). A number of studies indicate that serotonin and dopamine (DA) systems interact closely at a basic neurophysiological level (Daw, Kakade, & Dayan, 2002; Kapur & Remington, 1996; Wong, Feng, & Teo, 1995), and that impairment of the serotonin system function can lead to dysregulation of the dopamine system (De Simoni, Dal Toso, FodrIto, Sokola, & Algeri, 1987). Additionally, activation of the prefrontal cortex (PFC), specifically the orbital and ventromedial PFC, has been implicated in the behavioral control of aggression, and impairments in these areas are related to an increase in impulsive aggression (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999; Davidson, Putnam, & Larson, 2000). These lines of evidence suggest that aggression and its comorbid disorders may come from an underlying neurobiology, specifically serotonin and dopamine interaction in the prefrontal cortex. Other biological factors, such as norepinephrine (Barrett, Edinger, & Siegel, 1990) and testosterone (Giammanco, Tabacchi, Giammanco, Di Majo, & La Guardina, 2005) may also contribute to aggression. However, the focus will be on the interaction between serotonin and dopamine, because of their well-established relations with impulsive aggression and their significance in explaining comorbid disorders.

This review is divided into three sections. First, the paper reviews the neurochemical bases of impulsive aggression, with a particular focus on interactions between the serotonin and dopamine systems. Second, the paper reviews the neuroanatomical bases of impulsive aggression with an emphasis on structural and functional abnormalities in the prefrontal cortex. Finally, the paper considers the role of the serotonin and dopamine systems in brain regions associated with emotion regulation. In addition, these neurobiological characteristics will be discussed as the primary predisposing factor in impulsive aggression and its comorbid disorders. Understanding the neurochemical mechanisms of impulsive aggression in the context of dysfunctional brain regions can help to elucidate the etiology of this complex behavioral phenotype and guide the development of effective treatments for aggression and the various disorders with which it is associated.

1. Neurochemical mechanisms of impulsive aggression

1.1. Serotonin and aggression

Research indicates that, in general, the neurotransmitter serotonin has an inhibitory action in the brain (Daw et al., 2002; Yan, 2002) and that it is deeply involved in the regulation of emotion and behavior, including the inhibition of aggression (Davidson et al., 2000; Volavka, 1999). Serotonergic dysfunction has been reliably associated with aggressive behaviors in animals and humans (Coccaro, 1989; Miczek, DeBold, & Van Erp, 1994; Raleigh, McGuire, Brammer, Pollack, & Yuwiler, 1991).

In animals, deficient serotonergic function has been associated with mice killing in rodents (Gibbons, Barr, Bridger, & Leibowitz, 1979). In non-human primates, low levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) have been linked to heightened incidence of impulsive and aggressive behaviors (Fairbanks, Melega, Jorgensen, Kaplan, & McGuire, 2001; Higley & Bennett, 1999). Low CSF 5-HIAA concentrations have also been associated with poor impulse control and aggressive behaviors in adolescent monkeys (Mehlman et al., 1994). In addition, associations between impulsivity, dangerous acts, and low CSF 5-HIAA concentrations were found in female primates (Westergaard et al., 2003).

In humans, a low concentration of 5-HIAA has been associated with lifetime aggression (Brown, Goodwin, Ballenger, & Gover, 1979), aggression in patients with mental disorders (Coccaro, 1989; Virkkunen et al., 1994), violent suicide attempts (Traskman-Bendz, Asberg, & Schalling, 1986), impulsive murder (Lidberg, Tuck, Asberg, Scalia-Tomba, & Bertilsson, 1985), and recidivism of murderers (Virkkunen, De Jong, Bartko, Goodwin, & Linnoila, 1989). A meta-analytic study (Moore, Scarpa, & Raine, 2002) that examined findings from 20 separate studies found that low levels of serotonin significantly contribute to aggressive behaviors, regardless of type of crime and mental health problems.
There is a consistent link between serotonin hypofunction and aggression, with serotonin hypofunction specifically associated with impulsive forms of aggression (Coccaro, 1989; Virkkunen & Linnoila, 1993). For example, an association has been demonstrated between impulsive aggression and a blunted prolactin response to fenfluramine, a pharmacological agent that increases the level of serotonin (Coccaro, Kavoussi, Cooper, & Hauger, 1997). Other research has reported lower CSF 5-HIAA levels in impulsive arsonists compared with habitually violent offenders, as well as healthy controls (Virkkunen, Nuutila, Goodwin, & Linnoila, 1987). In another study, impulsive violent offenders were found to have lower CSF 5-HIAA concentrations than non-impulsive violent offenders (Linnoila et al., 1983). Additionally, impulsive alcoholic offenders show lower CSF 5-HIAA than non-impulsive alcoholic offenders and healthy controls (Virkkunen et al., 1994). These various lines of evidence support the hypothesis that it is the impulsive type of aggression in particular that is associated with serotonin hypofunction.

Impulsive aggression has shown to be influenced by genetic predispositions (Coccaro, Bergeman, McClear, 1993; Deater-Deckard & Plomin, 1999). For example, behavioral genetic research has demonstrated that the impulsive-aggressive symptoms of borderline personality disorder have a stronger genetic basis than the full diagnostic criteria (Siever, Torgersen, Gunderson, Livesley, & Kendler, 2002). Genetic influences of serotonin on impulsive aggression have been observed in a number of studies. Research has found associations between serotonergic dysfunction, specifically low levels of the serotonin genotype 5-HT2A-1438 GG, and criminal behavior (Berggard et al., 2003). Additionally, in individuals with anger-related traits, an association between a tryptophan hydroxylase gene polymorphism and 5-HIAA levels in CSF has been found (Rujescu et al., 2002). A polymorphism in the serotonin transporter gene (5-HTTLPR) has been associated with violent suicidal behavior (Courtet et al., 2001). Further, individual differences in CSF 5-HIAA concentrations, specifically the association between CSF 5-HIAA and impulsive aggression, tend to remain consistent throughout different environments across time (Higley, King, Hasert, Champoux, Suomi, & Linnoila, 1996; Higley & Linnoila, 1997).

These results suggest that genetic influences on serotonergic systems contribute to individual differences in impulsive and aggressive behaviors. Given that the association between serotonin and impulsive aggression has been strongly demonstrated in the literature and is considered to have a heritable foundation, serotonin hypofunction could represent a neurochemical trait that predisposes individuals to impulsivity and aggressive behaviors.

1.2. Dopamine and aggression

The dopaminergic system is involved in behavioral activation, motivated behavior, and reward processing (Everitt & Robbins, 2000; Ikemoto & Panksepp, 1999). It also plays an active role in the modulation of aggressive behaviors. In animal studies, hyperactivity in the dopamine system is associated with increases in impulsive aggression (Harrison, Everitt, & Robbins, 1997; for a review, see Netter & Rammsayer, 1991). Studies on aggressive behaviors in rodents showed that elevated dopamine levels have been continuously observed before, during, and following aggressive fights (Hadfield, 1983; Miczek et al., 1994; Tidey & Miczek, 1996). In humans, the dopaminergic system has been linked to the recognition and experience of aggression. After administering a dopamine D2 receptor antagonist, sulpiride, subjects showed an impaired ability to recognize angry facial expressions (Lawrence, 1996). Other research has reported lower CSF 5-HIAA levels in impulsive arsonists compared with habitually violent offenders, as well as healthy controls (Virkkunen, Nuutila, Goodwin, & Linnoila, 1987). In another study, impulsive violent offenders were found to have lower CSF 5-HIAA concentrations than non-impulsive violent offenders (Linnoila et al., 1983). Additionally, impulsive alcoholic offenders show lower CSF 5-HIAA than non-impulsive alcoholic offenders and healthy controls (Virkkunen et al., 1994). These various lines of evidence support the hypothesis that it is the impulsive type of aggression in particular that is associated with serotonin hypofunction.

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1.3. Serotonin and dopamine interaction

The serotonergic system has strong anatomical and functional interactions with the dopaminergic system (Kapur & Remington, 1996). More specifically, a reciprocal interaction between these two systems has been proposed (Daw et al., 2002; Wong et al., 1995). Approach and withdrawal related behaviors are thought to be determined by the balance between dopamine and serotonin activity (Deakin & Graeff, 1991), with dopamine thought to encourage appetitive behaviors (Ikemoto & Panksepp, 1999) and serotonin thought to discourage appetitive behaviors and provoke withdrawal behaviors triggered by aversive stimuli (Daw et al., 2002).

Interactions between serotonergic and dopaminergic systems have been reported in anatomical and pharmacological studies. Dopamine neuronal cell bodies and terminal sites are modulated by serotonin and receive rich projections from serotonin neurons (e.g., Kapur & Remington, 1996). These strong neuronal connections promote the functional modulation of 5-HT over DA activities in the neural network (Kelland & Chiody, 1996). For example, research has demonstrated that the 5-HT2 receptors inhibit DA activity, whereas the 5-HT2 receptor antagonists counteract the inhibition of the DA activity (Shi, Nathaniel, & Bunney, 1995; Sorensen et al., 1993). Further, administration of the 5-HT2c antagonist SB242,084 results in increased dopamine levels in the
frontal cortex of rats, indicating an inhibitory effect of the serotonergic system on frontal dopamine activity (Millan, Dekeyne, & Gobert, 1998).

Interactions of this kind between the serotonin and dopamine systems provide a framework for understanding mechanisms underlying impulsive aggression. Considering the functional regulation of serotonin over the dopamine system, deficient serotonergic function may result in hyperactivity of the dopamine system, promoting impulsive behavior. This relationship may account for co-occurring serotonin and dopamine dysfunctions in individuals with impulsive aggression. In support of this, prefrontal serotonin levels in rats decreased to 80% of baseline level during and after fights, whereas prefrontal dopamine levels increased to 120% after fights (Van Erp & Miczek, 2000). This inverse association between serotonin and dopamine levels during aggression was replicated in a subsequent study (Ferrari, van Erp, Tornatzky, & Miczek, 2003). These results suggest that decreased serotonergic activity in the context of aggressive behavior is closely associated with increased dopamine activity. Consistent with this, dopamine triggered impulsivity in rats was increased by serotonin depletion or removal of the serotonin-1B receptor gene (Harrison et al., 1997; Swann, 2003). In humans, low levels of 5-HIAA and high levels of the dopamine metabolite homovanillic acid (HVA) in CSF have been associated with high scores in the interpersonal and behavioral items of the Psychopathy Checklist—Revised (PCL-R) (Soderstrom, Blennow, Manhem, & Forsman, 2001). This result was independently replicated in a sample of violent and sexual offenders exhibiting psychopathic traits (Soderstrom, Blennow, Sjödin, & Forsman, 2003).

Although the relationship between serotonin hypofunction and impulsive aggression is a consistent finding in clinical neuroscience, only a few studies have examined the interaction between serotonergic and dopaminergic systems in individuals with impulsive aggression. Based on this strong association between serotonergic hypofunction and impulsive aggression that has a genetic basis, deficient serotonin function may be a neurochemical trait marker of impulsive aggression. In relation to this, dopaminergic hyperactivity may exert an additive effect on proneness to aggressive behavior, that is, secondary to serotonergic dysfunction. Given that the serotonergic system modulates dopaminergic activity, hyperactivity in the dopamine system in aggressive individuals may be attributed to disinhibition of the dopamine activity from deficient serotonergic function. To further understand the neurobiological bases of impulsive aggression, future research should investigate the nature of interactions between serotonin and dopamine system in individuals exhibiting impulsive aggression.

2. The neuroanatomical mechanism of impulsive aggression

Impulsive aggression has been linked to uncontrollable negative emotion, and an inability to regulate aggressive impulses, which can often lead to violent behaviors (Davidson et al., 2000; Heinrichs, 1989). Neuropsychological literature suggests that individuals with impulsive aggression may have abnormalities in brain regions involved in the control of emotion such as the prefrontal cortex, anterior cingulate cortex, amygdala, and nucleus accumbens (see reviews by Davidson et al., 2000; Friedel, 2004). In order to better understand the etiology of impulsive aggression, this section will review the roles of structural and functional abnormalities, as well as serotonin and dopamine in brain regions involved in emotion regulation.

2.1. Brain abnormalities

Previous research has consistently demonstrated that the prefrontal cortex is crucially involved in the regulation of social and aggressive behavior (Davidson et al., 2000; Dolan, 1999; Grafman & Litvan, 1999). Individuals with antisocial personality showed an 11% reduction of PFC gray matter volume in comparison with controls (Raine, Lencz, Bihrl, LaCasse, & Colletti, 2000). The orbitomedial region of the PFC has been shown to exert control over anger and impulsive aggression (Davidson et al., 2000; Lapierre, Braun, & Hodgins, 1995). Further, deficits in the ventromedial PFC have been associated with the dysregulation of negative emotion (Quirk, Russo, Barron, & Lebrón, 2000) and the abnormal processing of somatic or emotional signals (Bechara, Tranel, Damasio, & Damasio, 1996). Researchers have hypothesized that impairment in the orbitomedial PFC may result in an inability to show emotion appropriate to the consequences of behaviors, which may lead to inadequate decision-making and affiliated behavior problems (Bechara, Tranel, & Damasio, 2000). Overall, the findings from structural imaging studies suggest that the inability of the PFC to regulate emotion and impulses may contribute to impulsive aggression and socially inappropriate behavior, causing damage to oneself and others.

Functional neuroimaging studies have also reported associations between hypofunction in the PFC and aggressive behaviors. A positron emission tomography (PET) study showed that the activity of the orbitofrontal PFC is generally reduced during the expression of aggressive behaviors in healthy individuals (Pietrini, Guazzelli, Basso, Jaffe, & Grafman, 2000). Additionally, lower glucose utilization in the orbitofrontal PFC has been reported in aggressive patients with personality disorders (Goyer et al., 1994). Further, single photon emission computed tomography (SPECT) brain scanning showed that patients with a history of violent behavior, causing damage to oneself and others. Aggressive individuals appear to have an inability to regulate negative emotion in situations where they or others are vulnerable (Davidson et al., 2000). The inability to regulate negative emotion may result from impairment in the capacity of the PFC to inhibit emotional activation arising from subcortical structures, which are typically controlled by the prefrontal cortex (Davidson et al., 2000; Raine, Stoddard, Bihrl, & Buchsbaum, 1998). Impaired regulatory control of the PFC may lead to excessive negative
emotional reactivity and consequent violent behaviors. Relevant to this, fMRI studies of emotion regulation have revealed that activity in the PFC is reciprocally related to activation of subcortical emotion systems (i.e., the amygdala and nucleus accumbens)—with activity in the PFC increasing and activity in these subcortical regions decreasing during directed efforts to suppress emotion (Ochsner et al., 2004; Phan et al., 2005). The implication is that these subcortical structures are under direct regulatory control of the PFC. From this perspective, impairments in prefrontal brain regions may contribute a biological vulnerability to impulsive aggression by limiting the capacity to inhibit subcortical emotional centers. In support of this, aggressive individuals—specifically, murderers whose crimes were considered to be affective in nature (i.e., prompted by situation rage)—exhibited reduced activity in the PFC and increased activity in the basal ganglia and limbic system (Amen et al., 1996). Other data indicate that affective murderers display decreased prefrontal activity and increased subcortical (amygdala, midbrain, hippocampus, and thalamus) activity in comparison with premeditated murderers, who exhibited typical prefrontal activity (Raine et al., 1998).

To summarize, results from structural and functional brain-imaging studies indicate that hypofunctioning of the PFC, particularly the orbitomedial area, is related to impaired regulation of emotion and aggressive behaviors. Abnormal emotional behaviors are associated with increased subcortical activity, specifically in the amygdala, resulting from deficient prefrontal control of negative emotion. This abnormality may predispose individuals to emotional dysregulation and aggressive behaviors.

2.2. Neural transmission in emotion regulation circuitry

The PFC receives abundant monoamine neurotransmitter projections, including serotonin and dopamine projections, from other brain regions (Biver et al., 1996; William & Goldman-Rakic, 1998). As reviewed in the first section, the serotonin system interacts with the dopamine system functionally and anatomically (Kapur & Remington, 1996) and greatly influences emotion and behavior (Daw et al., 2002). In order to better understand the neurobiology of impulsive aggression, this section discusses serotonergic and dopaminergic abnormalities in the neural circuitry of emotion regulation, specifically in the prefrontal cortex.

Serotonergic neurotransmission contributes to prefrontal regulation of emotional responses by influencing inhibitory synaptic transmission (Yan, 2002). The role of serotonergic neurotransmission in the PFC has been examined using fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging following administration of d-fenfluramine. Healthy subjects displayed increases in glucose metabolism in the left PFC, ventromedial PFC, and anterior cingulate cortex following d-fenfluramine administration (Mann et al., 1996). In contrast, individuals with impulsive aggression showed decreased activation in the left anteromedial orbital cortex and anterior cingulate cortex in response to a serotonergic stimulant, meta-chlorophenylpiperazine (New et al., 2002). In another study, impulsive and aggressive individuals demonstrated a decreased metabolic response to serotonin stimulation in the anterior cingulate cortex (Frankle et al., 2005). These results indicate that decreased serotonergic neurotransmission in brain regulatory systems such as the PFC and the anterior cingulate cortex may be a major neurobiological deficit that leads to inhibitory dysfunction and aggressive behaviors. These findings were replicated in several studies. For example, patients with impulsive aggression demonstrated deficient serotonergic function in the orbitofrontal and ventromedial PFC as well as cingulate cortex (Siever et al., 1999). Additionally, patients with borderline personality disorder (BPD) showed decreased responses to serotonergic stimulation in the prefrontal cortex, in particular the medial and orbitofrontal PFC (Soloff, Meltzer, Greer, Constantine, & Kelly, 2000). These findings further support the association between deficient serotonergic neurotransmission and impulsive aggression.

Dopamine hyperactivity in brain regions linked to reward-related motivation, such as the nucleus accumbens and prefrontal cortex, also leads to increases in impulsive and aggressive behaviors (see reviews by Everitt & Robbins, 2000; Friedel, 2004). Striatal dopamine transporter (DAT) density measured by [123I] beta-CIT SPECT exhibits enhanced distributional heterogeneity in the right striatum of violent offenders compared with healthy controls, suggesting disrupted dopaminergic transmission in aggressive individuals (Kuikka et al., 1998). Further, an animal study showed that dopamine levels increased and serotonin levels decreased in the prefrontal cortex during and after aggression (Van Erp & Miczek, 2000). Considering the close interaction between the serotonin and dopamine systems, impaired regulation of serotonin over dopamine in the PFC may result in the disruption of the dopamine system and aggressive behaviors. However, there have been few studies examining dopamine deficits in these brain regions, even though serotonin hypofunctioning in the PFC has been strongly found in studies on aggression.

Future research utilizing brain-imaging techniques should examine the relations between serotonin and dopamine, particularly in the PFC, anterior cingulated cortex, amygdala, and striatum.

3. Impulsive aggression and its comorbid disorders

Impulsive aggression has been associated with various pathological conditions including depression, suicidal behavior, and substance abuse (Fava, Bless, Otto, Pava, & Rosenbaum, 1994; Koller et al., 2002). Studying impulsive aggression from the perspective of its relationship with comorbid disorders may provide insight into the etiology of impulsive aggression and the mechanism that predisposes individuals to develop this cluster of comorbid symptoms. This section discusses the biochemical and anatomical abnormalities of impulsive aggression and its interrelated disorders.

3.1. Depression and impulsive aggression

Impulsive aggression has been linked with depression as well as violent acts (Mammen, Kolko, & Pilkonis, 2002; Newman, Shapira, & Lerer, 1998). Forty-four percent of individuals diagnosed with major depressive disorder have physically or verbally
attacked another individual (Fava et al., 1994). Further, the severity of major depressive disorder has been associated with anger attacks (Tedlow et al., 1998).

Serotonergic hypofunction has been implicated as a possible source of comorbidity in individuals with depression and accompanying impulsive aggression. For example, research findings indicate that the prolactin response to fenfluramine, an indicator of serotonergic activity, is blunted in depressed patients (Mulder, Porter, & Joyce, 2003) and as well as in impulsive-aggressive individuals (Newman et al., 1998). Pharmacological research has demonstrated that symptoms of impulsive aggression and depression were reduced by administration of fluoxetine, a selective serotonin-uptake inhibitor (Zanarini, Frankenburg, & Prchini, 2004). These results indicate that deficient serotonergic functioning underlies the link between impulsive aggression and depression, and may in part account for the comorbidity of these disorders.

3.2. Suicide and impulsive aggression

Impulsive aggression has been shown to be a robust predictor of suicidal behavior (Dumais, Lesage, & Alda et al., 2005), which can be regarded as a form of self-directed aggression. Further, individuals who have exhibited suicidal behavior in the past demonstrate more impulsive and aggressive traits (Carballo et al., 2006; Turecki, 2005). Suicidal ideation has been linked with impulsivity and irritability in a sample of 625 individuals (Conner, Meldrum, Wieczorek, Duberstein, & Welte, 2004). In addition, in a study of individuals with a diagnosis of mood disorder, those with a history of suicidal behaviors had higher levels of impulsivity and hostility than those without a history of suicidal behaviors, after controlling for severity of depression and length of lifetime illness (Michaelis et al., 2004). More specifically, violent suicidal behavior has been linked to elevated levels of impulsivity and lifetime aggression (Dumais, Lesage, & Lalovic et al., 2005).

Deficient serotonergic function is known to play an important role in the high comorbidity between impulsive aggression and suicide (Kamali, Oquendo, & Mann, 2001). Low serotonin activity is associated with high-lethality suicide attempts (Mann & Malone, 1997), as well as impulsive and aggressive behaviors (Coccaro et al., 1989). Specifically, diminished serotonin activity is linked with the most violent type of suicidal behavior. For example, lower prolactin response to fenfluramine was seen in individuals with high-lethality suicide attempts (Malone, Corbitt, Li, & Mann, 1996). In addition, several studies report strong associations between deficient serotonin system function and violent suicide attempts (Asberg, Traskman, & Thoren, 1976; Mann et al., 1996; Mann & Malone, 1997).

Brain-imaging studies suggest that individuals who display suicidal behavior may have shared brain dysfunction with individuals showing impulsive aggression. Vivo and postmortem studies report an association between suicidality and deficient serotonergic function in the ventral prefrontal cortex (see review by Kamali et al., 2001). A postmortem autoradiography study found that serotonergic abnormalities were localized in the ventral and ventro-lateral prefrontal cortex of those who committed suicide (Arango, Underwood, & Mann, 1997). Additionally, high-lethality suicide attempters exhibit dysfunctional serotonergic activity in the ventromedial PFC and increased suicidal intent, when compared with low-lethality suicide attempters (Oquendo et al., 2003). Subsequently, Kamali et al. (2001) have theorized that the source of impulsive and aggressive behaviors may be the deficient inhibitory capabilities of the ventral PFC due to serotonergic hypofunction, which can result in self-directed impulsive aggression or suicide in the context of significant life stressors. The comorbidity of impulsive aggression and suicidal behavior suggests a common neurological mechanism, resulting in a predisposition to these behaviors that may be traced to deficient serotonergic function in the ventral PFC.

3.3. Substance abuse and impulsive aggression

Substance abuse is closely associated with impulsive aggression and increased levels of impulsive behavior in general (Brady, Myrick, & McElroy, 1998; Cascella et al., 1994). Research on substance abuse indicates that impulsive aggression may be related to personal characteristics that are evident before the onset of substance use (Cloninger, 1987; Higley & Bennett, 1999). This implies the possibility of a predisposition to substance abuse in individuals with impulsive aggression. To better understand the underlying basis for this comorbidity, research in the area of prefrontal dysfunction and neurochemical abnormalities will be considered.

Prefrontal dysfunction, particularly in the orbitomedial area, has been demonstrated as a common pathology for both impulsive aggression and substance abuse. As reviewed above, research studies in humans and primates have indicated that the prefrontal cortex plays an important role in the regulation of aggressive behavior (see review by Davidson et al., 2000). The prefrontal cortex also plays a critical role in the regulation of drug-seeking behaviors (Volkow, Fowler et al., 1993) and is susceptible to damage by continuous substance abuse (Nader et al., 2006; Robinson, Galetta, McCluskey, Forman, & Balcer, 2001). Brain-imaging research has characterized substance abusers with poor impulse control and orbitofrontal cortex dysfunction (Goldstein et al., 2005; Volkow, Wang et al., 1993). In addition, cocaine use has been found to produce morphological changes in the PFC and the nucleus accumbens (Robinson et al., 2001). Dysfunction in the orbitofrontal PFC is associated with an inability to inhibit aggressive behaviors and poor inhibitory control (Davidson, 2002; Friedel, 2004), as well as compulsive drug intake (Volkow, Wang et al., 1993). This suggests the possibility of a common biological factor between impulsive aggression and substance abuse.

Strengthening the association between impulsive aggression and substance abuse, similar neurochemical abnormalities, specifically in the dopaminergic system, have been observed in individuals at risk for aggressive behavior as well as substance abuse (Blum et al., 2000; Soderstrom et al., 2001, 2003). The dopaminergic system plays a critical role in the processing of addictive qualities of drugs (Hyman, Malenka, & Nestler, 2006; Volkow et al., 2006). Research examining the relationship between dopamine and addiction indicates that low dopamine levels contribute to drug- and alcohol-seeking behavior (see review by Volkow, Fowler,
reported (Kamali et al., 2001; Oquendo et al., 2003). Further, aggression and impulsivity has been closely linked to a history of substance abuse. The differences in behavioral manifestation associated with substance abuse may be caused by variations in dopaminergic neurotransmission. Specifically, two alcoholic subtypes with differential biological predispositions have been proposed (Cloninger 1987; Cloninger, Bohman, & Sigvardsson, 1981; Sigvardsson, Bohman, & Cloninger, 1996). Type I alcoholism is characterized by a later age of onset and the presence of anxiety symptoms. Type II alcoholism is characterized by an early age of onset, impulsivity, and antisocial behavior. In support of this, a SPECT study examining striatal DA transporter density levels found that violent alcoholics showed elevated density levels compared with control subjects, whereas non-violent alcoholics showed diminished levels suggesting differential dopamine abnormalities in non-violent versus violent alcoholics (Tiihonen et al., 1995). Similarly, using human postmortem brain autoradiography, dopamine D2 receptor density in dorsal striatal structures was observed to be lower in type I alcoholics than in controls, whereas no difference was found between type II alcoholics and controls (Tupala et al., 2003). Additionally, type I and type II alcoholics exhibit differentiated dopamine receptor densities in cortical regions. Type I alcoholics exhibited lower levels, whereas type II alcoholics showed higher cortical dopamine D2 receptor density in comparison to controls. In this study, the cortical dopamine D2 receptors observed in type II alcoholics significantly reduced with age, perhaps resulting from decreased aggressive behaviors with age (Tupala, Hall, Halonen, & Tiihonen, 2004). Recent research has also demonstrated significantly higher cortical dopamine transporter (DAT) levels in type II alcoholics (Tupala, Halonen, & Tiihonen, 2006).

Given that the serotonergic system modulates the dopamine system, the high dopaminergic activity seen in type II alcoholics may be attributed to deficient serotonergic regulation of the dopamine system. In Cloninger’s model, type II alcoholics have a serotonergic hypofunction (Cloninger, 1987). Further, serotonin deficits were found in early-onset alcoholism in animal and human studies. Rhesus monkeys that exposed to stressors during early developmental stages showed low serotonin levels, which were linked to aggression and high tolerance to alcohol (Heinz et al., 1998). These findings are consistent with low precursor serotonin availability in anxiety-prone, early-onset alcoholics (Buydens-Branchey, Branchey, Noumair, & Lieber, 1989). In addition, primates with low CSF-5-HIAA concentration show behaviors similar to type II alcohol abuse: poor impulse control, risky behavior, and huge amounts of alcohol consumption (see review by Higley & Bennett, 1999). When comparing early- versus late-onset alcoholics, early-onset alcoholics show more reduced 5-HIAA levels than late-onset alcoholics, indicating differential serotonergic function in subgroups of alcoholism (Fils-Aime et al., 1996).

The involvement of deficient serotonin function in reward-seeking behaviors has been demonstrated in animal studies with rats. Manipulations that increased serotonin activity decreased the effects of d-amphetamine and reactiveness for conditioned reward (Fletcher, 1996). Further, a 5-HT receptor antagonist, metergoline, counteracted the regulatory effects of serotonin on d-amphetamine and reward-related behavior (Fletcher, Korth, & Chambers, 1999). These results suggest that 5-HT plays an important role in substance use and may serve as a predisposing factor by increasing the vulnerability to drug-seeking behaviors. More specifically, the serotonergic deficiency appears to contribute to substance abuse and aggression by facilitating greater impulsivity. In a sample of alcoholics, lower levels of 5-HIAA have been observed in impulsive offenders than in non-impulsive offenders (Virkkunen et al., 1994). Furthermore, serotonin hypofunction has been associated with impulse control problems in type II early-onset alcoholism (Cloninger, 1987; Higley & Bennett, 1999).

In summary, the comorbidity observed between impulsive aggression and substance abuse suggests that a common biological mechanism, perhaps involving a hypofunction in orbitomedial cortex and neurochemical abnormalities in serotonin and dopamine systems, may underlie these impulsive behaviors. Specifically, studies on alcoholism suggest that impulsive aggression is associated with a certain subtype of substance abuse (i.e., type II alcoholism). A possible explanation for these relations may be deficient serotonergic regulation of dopaminergic activity, which results in poor behavioral inhibition characterized by acts of impulsive aggression and substance abuse.

3.4. Diathesis–stress model

Impulsive aggression is strongly associated with depression, suicidal behaviors, and substance abuse (Dumais, Lesage, & Alda et al., 2005; Koller et al., 2002; Placidi et al., 2001; Sher et al., 2005). Heightened susceptibility to psychological dysfunction and suicidal behavior has been attributed to these high comorbidities (Hawton, Houston, Haw, Townsend, & Harris, 2003). To more fully explicate mechanisms underlying impulsive aggression, it will be important to understand the common predisposing factor that links impulsive aggression with these other comorbid conditions.

In this regard, research on the relations that depression and impulsive aggression show with suicidal behavior is of interest. Major depression has been strongly linked to suicidal behaviors (Henriksson et al., 1993). However, studies report that lifetime suicide risk associated with depression is quite low, being 3.4% for depressed individuals (Blair-West, Cantor, Mellors, & Eysenck, 1999) and 2.2% for mixed inpatient/outpatient with affective disorders (Bostwick & Pankratz, 2000). This raises the question of what the specific factor underlying vulnerability to suicidal behavior might be. Impulsive aggression has been suggested as a risk factor for this vulnerability, and evidence of a shared neural substrate for impulsive aggression and suicidal behavior has been reported (Kamali et al., 2001; Oquendo et al., 2003). Further, aggression and impulsivity has been closely linked to a history of substance abuse (Wang, & Swanson, 2004; Nader et al., 2006). However, high dopamine levels have also been observed in some populations of substance users such as type II alcoholics. For example, elevated dopamine activity in limbic brain regions, specifically the nucleus accumbens, has been associated with substance use (Hurd & Ungerstedt, 1989), type II alcoholism (Tiihonen et al., 1995) and aggression (Miczek, Fish, DeBold, & de Almeida, 2002). This result suggests that the dysregulation of the dopamine system, both hypo- and hyperactivity, may contribute to the etiology of substance abuse.
suicidal behavior (Mann, Waternaux, Haas, & Malone, 1999). More specifically, impulsive aggression appears to be an underlying risk factor for lethal suicidal attempts in depressed individuals. In a study comparing two groups of males suffering major depression, one composed of those still living and the other of individuals who committed suicide, cluster B personality disorders and substance abuse/dependence were associated with a higher suicide risk. Further, suicide completers were found to be more impulsive and aggressive (Dumais, Lesage, & Lalovi et al., 2005).

In order to better explain the roles of impulsive aggression and depression in suicidal behaviors, a diathesis–stress model has been developed, in which impulsive aggression and low serotonergic activity are considered the diathesis factor, and depression is considered the precipitating stressor (Placidi et al., 2001). Supporting this model, both the severity of lifetime aggression and higher lethality of suicide attempt were linked to lower CSF 5-HIAA concentrations in individuals suffering a major depressive episode (Placidi et al., 2001). This result suggests a biological association between impulsive aggression and severity of suicidal behavior in depressed individuals. Placidi et al.’s model presents a viable explanation for comorbidities associated with impulsive aggression. It explains the biological relationship between impulsive aggression and suicide while differentiating their roots from depression. However, a weakness of the model is that depression is viewed not only as a precipitant for suicide, but also as an outcome that arises from some underlying vulnerability in combination with depressogenic life events. That is, depression may reflect a concomitant disturbance triggered by low serotonin activity in individuals with impulsive aggression, rather than a precipitating stressor. Additionally, this model does not specify the anatomic basis of the proposed neurological deficit and fails to consider the role of substance use, another condition that is frequently comorbid with impulsive aggression.

Nevertheless, in support of this model, brain-imaging studies provided evidence of differences between patients with depression and suicidal victims. Serotonergic abnormalities in widespread brain regions were found for depression, whereas localized serotonergic deficits in ventral PFC were found for suicide and impulsive aggression. For example, postmortem brain investigation revealed that an extensive lack of serotonergic transporter (5-HTT) binding in the PFC was found in individuals with major depression, while deficient 5-HTT binding in only the ventral part of the PFC were associated with suicidal behaviors (Mann et al., 2000). It is also consistent with the results of brain-imaging studies demonstrating associations between depression and widespread serotonergic abnormalities (Anderson et al., 2004). Further, deficient serotonin function in the ventromedial PFC was associated with high-lethality suicide attempts (Oquendo et al., 2003) and impulsive aggression (Siever et al., 1999). These results suggest that suicide and impulsive aggression are associated with deficient serotonin function in the localized PFC, specifically in the ventral PFC. Therefore, low serotonergic activity in the ventral PFC may be the underlying biological diathesis that predisposes individuals to both impulsive aggression and suicide. Although the serotonin hypofunction is localized, it may potentially lead to depression as well. A key precipitating stressor that activates this constitutional predisposition to impulsive aggression and other comorbid conditions may be psycho-pathogenic life events such as failure, loss of employment or relationship partner, and severe family discord, etc. As a function of such life stressors, underlying pathological processes may be exacerbated and possibly give rise to extreme manifestations of self-destructive behavior.

It is unclear whether the comorbid pathology of substance abuse might also arise from deficient serotonin function in the ventral PFC, as there has been no brain-imaging research in this area. However, substance abuse may result from a concomitant biological vulnerability such as dopamine dysregulation, resulting from serotonergic deficiency and leading to disrupted reward-seeking behavior. The close relation between these disorders in previous research points to the possibility of a similar biological vulnerability. For example, alcoholics who exhibit suicidal behavior tend to have strong impulsive and aggressive features (Koller et al., 2002). Additionally, the severity of alcoholism and impulsivity/aggression increases the risk for suicide (Sher et al., 2005; Sher, 2006). Also consistent with this possibility are findings from a recent study of depressed individuals with comorbid alcoholism. In comparison to depressed individuals without alcoholism, depressed subjects with alcoholism in this study showed higher impulsivity, aggression, and suicidal behaviors. Further, alcoholism was significantly associated with aggression in these subjects (Sher et al., 2005). The implication is that substance abuse and impulsive aggression may result from a common biological predisposing factor. Research demonstrating strong family transmission of substance use in conjunction with impulsive–aggressive tendencies (Hicks et al., 2004) also strengthens the possibility that substance use in impulsive–aggressive individuals may result from a common biological predisposition, such as dopamine disinhibition due to deficient serotonergic inhibitory function.

To summarize, a modified diathesis–stress model should include the role of a possible serotonin deficiency in the ventral PFC as a biological diathesis. The behavioral manifestation associated with this diathesis would be an inability to regulate negative emotion and aggressive impulses, which are directed both toward oneself and others. Individuals with this underlying diathesis may be easily drawn into violent fights and impulsive behaviors due to a deficient regulatory influence of the PFC over subcortical structures such as the amygdala. Additionally, such individuals—because they lack the normal regulatory control over the dopamine system that is provided by efficient serotonergic system function—may be prone to artificially regulating their negative emotions through the use of chemical substances. As a function of this, they may become even more impulsive and aggressive, creating a continuing vicious cycle of aggressive and addictive behaviors. Ultimately, this predisposition may result in self-directed aggression or suicide during severe depressive episodes or under significant life stressors.

4. Conclusions and research directions

Impulsive aggression is a behavioral disposition characterized by the inability to regulate negative affect and impulses to harm oneself or others. It is highly comorbid with depression, substance use, and suicidal behaviors (Hicks et al., 2004; Horesh, Gothelf, Ofek, Weizman, & Apter, 1999; Koller et al., 2002). The available literature suggests that deficient serotonergic activity in emotion regulation circuitry, such as the prefrontal cortex and the anterior cingulate cortex, may be an important predisposing factor to
impulsive aggression (New et al., 2002; Parsey et al., 2002; Siever et al., 1999). Additionally, serotonergic hypofunction may contribute to the hyperactivity of the dopaminergic system, which further promotes impulsive and aggressive behaviors. Considering that serotonin hypofunction in impulsive aggression has been reported frequently across the literature and has a heritable foundation, serotonin hypofunction may be a neurochemical vulnerability marker of impulsive aggression. Dopamine hyperactivity may secondarily contribute to impulsive aggression, given the modulation of the serotonin system over dopaminergic activity.

Serotonergic dysfunction in the PFC also appears to underlie the comorbidity of impulsive aggression with depression, substance abuse, and suicidal behaviors. A modified diathesis–stress model has been proposed, in which a biological diathesis is regarded as a serotonergic deficiency in the ventral PFC. This deficiency can lead to dopamine hyperactivity as a result of reduced serotonergic control over the dopamine system. These pathological processes may result in a failure to regulate emotion, leading to impulsive and aggressive behaviors towards the self and others. Additionally, dopamine hyperactivity resulting from deficient serotonergic regulation can promote substance abuse and other addictive behaviors. Further, individuals with impulsive aggression are vulnerable to depression as a function of low serotonergic activity. The presence of depression may contribute further to self-directed aggression or suicide during severe depressive episodes or under significant life stressors.

Understanding brain mechanisms underlying impulsive aggression and identification of risk factors are important to the prevention and treatment of impulsive aggression. Research has shown that pharmacological interventions such as serotonin reuptake inhibitors or antipsychotics can reduce impulsive aggression by increasing serotonergic activity or decreasing dopaminergic activity (Miczek et al., 2002; Swann, 2003). In addition, aggressive behaviors have been moderated by environmental enrichment, parental treatment, social skills training, and nutritional supplements (August et al., 2002; Caspi et al., 2004; Gesch, Hammond, Hampson, Eves, & Crowder, 2002; Raine, Mellingen, Liu, Venables, & Mednick, 2003). These results emphasize the importance of the identification of risk factors by demonstrating that a good environment or proper treatment can have a beneficial impact on individuals with impulsive aggression. Successful treatment of impulsive aggression should also consider the vulnerability to comorbid conditions. For example, early education on substance abuse prevention as well as training of emotion regulation techniques may be important to vulnerable individuals in order to prevent substance abuse.

Future studies should continue to invest effort toward identifying the biological and genetic risk factors underlying impulsive aggression. Specifically, future research efforts should be directed toward identifying the common and differential neurobiological characteristics of impulsive aggression and its comorbid disorders. In particular, brain-imaging studies are needed to investigate the exact relations between serotonin and dopamine in the PFC. Different types of neurotransmitter receptors may contribute differently to the pathological conditions of impulsive aggression and its comorbid disorders. Selective radioligands labeled for SPECT and PET may assist in identifying structural distribution and density of serotonin and dopamine receptors.

The combination of PET and fMRI imaging will also allow us to locate neurochemical abnormalities by providing high-resolution brain images. Further, the identification of genetic risk factors through the development of neurobiological endophenotype measures could facilitate proper intervention or treatment in the early stages of these disorders.

Understanding the neural mechanisms of impulsive aggression and the identification of risk factors will advance our understanding of complex brain–behavior relations and will provide insight into the etiology of impulsive aggression. This will help develop effective treatment strategies across impulsive aggression and its comorbid disorders.

References


