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Neurotransmitter Function in Impulsive Aggression and Intermittent Explosive Disorder

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Introduction

Aggression involves behavior in which one individual attacks another in the context of defense or in the context of securing access to resources needed for survival. In fact, the validity of a neurobiological perspective of aggression is indicated by the evolutionary preservation of aggressive behavior over time and species. While human aggression was as advantageous to humans as it was to other species, in early times, aggression has become less and less advantageous for humans as civilization has developed and, except for self-defense, aggressive behavior is acceptable in very few circumstances.

Human aggression is typically distinguished in two forms. These are instrumental or proactive and impulsive or reactive (Dodge, 1991). The primary goal of instrumental aggression is to obtain a sought-after resource, benefit, or reward. This type of aggression is premeditated in nature and is closely associated with antisocial personality disorder (ASPD). The primary goal of impulsive aggression, in contrast, is to defend against a threat or to discharge frustration. When sufficiently frequent and severe, individuals with impulsive aggression may meet the *Diagnostic and Statistical Manual of Mental Disorders-5th Edition* (DSM-5) diagnosis of Intermittent Explosive Disorder (IED), a disorder with a lifetime prevalence of 3.6% in general population samples (Coccaro, Fanning, and Lee, 2017). While impulsive aggression is also observed in other diagnostic conditions, when aggression is not directly due to another psychiatric disorder a diagnosis of IED may be made. In addition, aggression may also be observed in the context of a medical condition or a pharmacologic agent that affects the central nervous system. Finally, it can be observed in individuals tasked with engaging in combat and/or in law enforcement. In these cases, aggression is considered socially sanctioned unless the individual commits aggressive acts that go beyond what is needed for carrying out a military mission or to subdue a criminal suspect.

Aggressive behavior is manifested by verbal and/or physical attacks on another person or object or animal. Verbal aggression includes snapping, name-calling, verbal arguments, and threatening someone. Physical aggression ranges from throwing/breaking things to pushing/hitting or physically injuring someone. Such behavior is under substantial genetic

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influence. Coccaro, Kavoussi, Cooper, and Hauger (1997) found genetic influences of 28% for verbal aggression, 40% for indirect physical aggression (e.g., damage to objects), and 47% for direct physical aggression. The fact that aggression is under genetic influence indicates that it has biological underpinnings, which may include variability in how brain chemicals (neurotransmitters) send messages across synapses in the brain. The influence of neurotransmitters and neuromodulators on aggression is the focus of this chapter.

Neurotransmitter Function

Neurotransmitters are endogenous molecules that transmit signals across synapses to enable one neuron to communicate with another. Neurotransmitters, and other molecules that impact neurotransmission, range from simple monoamines and peptides to more sizable proteins and steroid hormones. To date, the tryptamine serotonin (5-hydroxytryptamine; 5-HT) has been the most extensively studied neurotransmitter with respect to aggression.

Serotonin (5-HT)

Early behavioral studies on 5-HT focused on its role in suicidal behavior (Asberg, 1997; Asberg, Schalling, Traskman-Bendz, & Wagner, 1987; Bourne et al., 1968; Pare, Yeung, Price, & Stacey, 1969). Following this, many more studies have explored the role of 5-HT in aggression and violence. The earliest study in this area reported an inverse correlation ($r = -0.78$) between cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) and life history of actual aggressive events in navy recruits being evaluated for fitness of duty because of "aggressive" or "passive-aggressive" behavior (Brown, Goodwin, Ballenger, Goyer, & Major, 1979). Study participants with a history of suicide attempt had higher aggression scores and lower 5-HIAA concentrations compared to those with no such history (Brown, et al., 1979). The inverse relationship between CSF 5-HIAA and life history of aggression was replicated in a subsequent sample of men with borderline personality disorder (BPD) (Brown et al., 1982). Several subsequent studies reported lower levels of CSF 5-HIAA in impulsive violent offenders compared to healthy controls (Lidberg, Tuck, Asberg, Scalia-Tomba, & Bertilsson, 1985; Virkkunen, Nuutila, Goodwin, & Linnoila, 1987), while others reported inverse correlations between this 5-HT metabolite and life history of aggressive behavior (Limson et al., 1991). Despite this, not all study results have been positive (e.g., Coccaro, Kavoussi, Cooper, & Hauger, 1997; Hibbeln, Umhau, George, Shoaf, Linnoila, & Salem, 2000). Coccaro, Kavoussi, Hauger, Cooper, & Ferris (1998) found no relation between CSF 5-HIAA and life history of aggression in a sample of various personality disorders. Likewise, Simeon, Stanley, Frances, Mann, Winchel, and Stanley (1992) found no relation between several indices of 5-HT functioning and life history of aggression or impulsivity in a sample of personality disordered individuals with a history of self-harm. A more recent study found that when both 5-HIAA and the dopamine metabolite homovanillic acid (HVA) are placed in the same statistical model, CSF 5-HIAA demonstrates a significant positive correlation with aggression (Coccaro & Lee, 2010). This is consistent with a study in healthy individuals that reported a positive correlation between

CSF 5-HIAA concentration and aggression (Møller et al., 1996). Nevertheless, an association between low CSF 5-HIAA and impulsive behaviors has been found in a number of patient groups including those with depression (Asberg et al., 1976; Banki, Arató, Papp, & Kurcz, 1984; Lopez-Ibor, Saiz-Ruiz, & de los Cobos, 1985; Träskman, Asberg, Bertilsson, & Sjöstrand, 1981), substance use (Banki, et al., 1984; Limson, et al., 1991), and schizophrenia (Banki, et al., 1984; Ninan, van Kammen, Scheinin, Linnoila, Bunney, & Goodwin, 1984; van Praag, 1983).

While CSF metabolite studies give us a glimpse into the concentration of neurotransmitters in the central nervous system, such studies are limited in that they offer only a static view of neurotransmitter function. To assess the functionality of 5-HT synapses and receptors, the next stage of investigation utilized the pharmaco-challenge method. In this approach, a challenge agent (such as a 5-HT agonist) is administered acutely, and the downstream effects on hormonal and/or behavioral responses are assessed. Coccaro et al. (1989) observed a relationship between prolactin response to the drug d,l-fenfluramine (PRL[d,l-FEN]) and life history of aggression ($r = -0.57$) and self-reported aggressive tendencies ($r = -0.52$) in patients with personality disorder. Overall, the largest inverse correlation was seen with a combined score of "irritability and direct assault" ($r = -0.77$), which accounted for differences in PRL[d,l-FEN] that were related to history of suicide attempt, history of alcoholism, and history of BPD. In other words, apparent categorical differences in 5-HT function were better accounted for by the dimension of impulsive aggression. Similar, though smaller, associations were observed by New et al. (2004) in a large sample of male personality disordered patients between PRL[d,l-FEN] and the Buss Durkee Hostility Inventory (BDHI) irritability/assault scale ($r = -0.21$) that was not accounted for by current depression. Other studies have also found a relationship between blunted hormonal response to 5-HT challenge in BPD patients (Paris, Zweig-Frank, Ng Ying Kin, Schwartz, Steiger, & Nair, 2004), antisocial individuals (Moss, Yau, & Panzak, 1990; O'Keane, Moloney, O'Neill, O'Connor, Smith, & Dinan, 1992), and substance abusers (Moller et al., 1994). Soloff, Kelly, Strotmeyer, Malone, and Mann (2003) observed a blunted PRL[d,l-FEN] response in male (but not female) BPD subjects compared to healthy control subjects, which appeared to be accounted for by trait impulsivity, aggression, and antisociality. One of the most recent studies in this area reports an inverse correlation between PRL responses to d-fenfluramine in study participants with personality disorder (Coccaro, Lee & Kavoussi, 2010). This study reported a medium-sized correlation ($r = -0.35$) with a composite measure of aggression (including history of actual aggressive behavior and disposition to respond aggressively in selected situations).

The relationship between 5-HT and aggression may be specific to impulsive, as opposed to premeditated, aggression. Specifically, Linnoila, Virkkunen, Scheinen, Nuutila, Rimon, and Goodwin (1983) found lower levels of 5-HIAA among murderers and attempted murderers who had committed impulsive crimes compared to those who committed premeditated crimes. Later, Linnoila and Virkkunen (1992) postulated that a "low serotonin syndrome" characterizes individuals who engage in violent, impulsive, and antisocial behavior. This hypothesis was largely based on studies of 5-HIAA. According to this hypothesis, 5-HT serves to constrain behavior such that a deficit in 5-HT is associated with increased impulsivity (Linnoila & Virrkunen, 1992). Another model (the Irritable Aggression Model; Coccaro, Kavoussi, & Lesser, 1992), however, suggests that a net

hypo-serotonergic state is associated with greater irritability, which can be conceptualized as a lower threshold for responding to aversive stimuli. This is consistent with findings of an inverse correlation between self-reported irritability and PRL[d,l-FEN] (Coccaro, et al., 1989) and Brown et al's (1982) observation that the relationship between history of suicide attempt and PRL[d,l-FEN] became nonsignificant when controlling for self-reported impulsivity. Indeed, research in both animals and humans suggests that noxious, threatening, or provocative stimuli may be necessary to elicit aggressive behavior in a net hypo-serotonergic state (Berman, McCloskey, Fanning, Schumacher, & Coccaro, 2009; Marks, Miller, Schulz, Newcorn, & Halperin, 2007).

Although early studies seemed to suggest that 5-HT was the predominant neurotransmitter involved in impulsive aggression, a recent meta-analysis suggests the relationship may be more modest than previously thought. Duke, Bègue, Bell, and Eisenlohr-Moul (2013) analyzed 171 studies on the serotonin–aggression relationship that employed the following: (a) 5-HIAA assay; (b) acute tryptophan depletion (ATD); (c) pharmaco-challenge; and (d) endocrine challenge methods. The authors found a small ($r = -0.12$) significant inverse relation between measures of 5-HT functioning and aggression overall. Pharmaco-challenge studies yielded the largest effect size ($r = -0.21$), while 5-HIAA yielded the smallest ($r = -0.06$, nonsignificant). Small significant average effects were found for ATD ($r = -0.10$) and endocrine challenge ($r = -0.14$), while cortisol response was not significantly related to aggression ($r = -0.02$). Notably, characteristics of the samples (e.g., gender, age, psychopathology, and history of aggression) did not moderate the relationships between indices of 5-HT functioning and aggression. Furthermore, type of drug did not moderate the relationship between pharmacological or endocrine challenge and aggression. These results, as well as null results and conflicting findings in the literature, suggest that the relationship between 5-HT and behavior is more complex than previously appreciated. This should not be surprising given the complexity of the central 5-HT system, which comprises at least 14 types of receptors distributed both pre- and post-synaptically. Furthermore, there is much pre-clinical data indicating that 5-HT receptor subtypes exert unique, and perhaps opposing, effects on aggression.

Neuroimaging methodologies have enabled further advances in studying neurotransmitter functioning. For example, Siever et al. (1999) reported reduced glucose metabolism on positron emission tomography (PET) in the left orbitofrontal (OFC) and anterior cingulate cortex (ACC), in six subjects with IED compared with five healthy control subjects, after receiving a 60 mg dose of d,l-fenfluramine. Soon after, New et al. (2002) reported a similar finding in 13 impulsively aggressive patients and 13 healthy subjects using the 5-HT receptor agonist, meta-chlorophenylpiperazine (mCPP) and placebo. Compared to healthy subjects, the impulsively aggressive subjects showed reduced glucose metabolism in OFC and ACC following mCPP relative to placebo. In addition, a 12 week course of treatment with the selective serotonin reuptake inhibitor (SSRI) fluoxetine was shown to normalize OFC function in impulsively aggressive BPD patients, supporting the notion that deficits in OFC function are at least partially supported by abnormalities in serotonin function (New et al., 2004). Other neuroimaging studies suggest that impulsively aggressive individuals have abnormal 5-HT synthesis and reuptake. For example, males with BPD showed lower trapping of a 5-HT precursor analog (i.e., reduced 5-HT synthesis capacity) in the medial frontal gyrus, anterior cingulate gyrus, superior temporal gyrus, and corpus striatum

compared to healthy controls, while BPD women had lower trapping in the right middle cingulate gyrus and superior temporal gyrus (Leyton et al., 2001). Another study using PET radiotracer for the serotonin transporter (5-HTT) also showed reduced 5-HTT availability in ACC in impulsively aggressive subjects (Frankle et al., 2005). A follow-up study with a greater number of subjects did not find differences in 5-HTT binding between IED and control subjects (van de Giessen et al., 2014). Instead, these investigators reported a significant, positive correlation with ACC 5-HTT availability and trait callousness. Among IED subjects, a trend-level, negative partial correlation (with callousness and age as covariates) was observed between trait aggression and ACC 5-HTT availability. Finally, a study by Koch et al. (2007) using single-photon emission computed tomography (SPECT) examined binding of [I^{123}]ADAM (2-([dimethylamino] methyl) phenylthio) to the serotonin transporter and found increased binding in BPD subjects in both the hypothalamus and brainstem (Koch et al., 2007); ADAM binding correlated significantly with impulsivity but not with depression.

Dopamine

Dopamine (DA) is a catecholamine neurotransmitter that is involved in a range of functions including learning, memory, and movement. Compared to 5-HT, less is known about the relationship between DA functioning and aggression. Preclinical studies point to hyperactivity of the DA system in the mesocorticolimbic pathway during and after a provocative aggressive encounter, possibly reflecting motivational aspects of aggressive behavior (Miczek, Fish, De Bold, & De Almeida, 2002). In humans, CSF HVA, a major metabolite of dopamine, has been studied as an index of DA function, and its involvement in aggression, though the findings with CSF HVA have been mixed. Some studies find no relationship between CSF HVA concentration and aggression or suicide (Brown, et al., 1979; Brown, et al., 1982; Lidberg, et al., 1985; Virkkunen, Nuutila, Goodwin, & Linnoila, 1987), while others find an inverse relationship. Linnoila, Virkkunen, Scheinin, Nuutila, Rimon, and Goodwin (1983) observed reduced CSF HVA in antisocial impulsive violent offenders, and Virkkunen, De Jong, Bartko, Goodwin, and Linnoila (1989) reported that recidivist violent offenders had lower CSF HVA concentrations than non-recidivist violent offender controls. One study observed an inverse correlation between CSF HVA and aggression in alcohol-dependent and healthy individuals (Limson, et al., 1991). A similar relationship was reported in a sample of healthy volunteers and personality disorder study participants when CSF 5-HIAA and CSF HVA were placed in the same statistical model (Coccaro & Lee, 2010).

There is also some evidence of dopaminergic involvement in psychopathy, a personality disorder characterized by callousness and unemotionality (Factor 1 psychopathy) and social deviance (Factor 2 psychopathy). Factor 2 is particularly relevant to aggression (Coccaro, Lee, & McCloskey, 2014) because this factor includes aggressive and impulsive behavior. Soderstrom et al. (2001) observed a significant and positive correlation between CSF HVA concentration and Factor 2 psychopathy scores ($r = 0.65$) in 22 violent offenders (Soderstrom, Blennow, Manheim, & Forsman, 2001). Because an interaction between 5-HT and DA may underlie this result, these authors noted a positive correlation between the ratio of DA to 5-HT (HVA:5-HIAA) and Factor 2 ($r = 0.52$) psychopathy, suggesting that

this result may hold true even when simultaneously considering 5-HT function. This relationship was replicated for Factor 2 psychopathy in a follow-up study of violent offenders (Soderstrom, Blennow, Sjodin, & Forsman, 2003). These findings also point to a potential role of imbalance between DA and 5-HT function in Factor 2 psychopathy; however, further studies in this area are needed.

Norepinephrine (NE)

The central norepinephrine (NE) system originates in the locus coeruleus and surrounding brain structures. It comprises both tonic and phasic activity, and its activity appears to vary with degrees of wakefulness and arousal. Overall, central NE is implicated in orienting to novel stimuli, focusing attention, and enacting behavioral responses (Berridge & Waterhouse, 2003) and it is involved in the stress response as part of hypothalamic-pituitary-adrenal (HPA) axis (Dunn & Swiergiel, 2009). While a critical role for NE in behaviors related to affective instability and aggression has been suggested (Siever & Davis, 1991), empirical support for these ideas has been limited and mixed (Oquendo & Mann, 2000).

Preclinical studies suggest that NE plays a "permissive" role in aggression by facilitating "fight or flight" responses to threat (Miczek & Fish, 2005), though study results in humans have been inconsistent. 3-methoxy-4-hydroxyphenylglycol (MHPG), a stable NE metabolite, has been studied as a marker of NE activity. While one early study reported a positive correlation between MHPG in CSF ($r = 0.64$; Brown, Goodwin, Ballenger, Goyer, & Major, 1979), other studies report no relation between MHPG and aggression (Brown, et al., 1982; Lidberg, et al., 1985; Virkkunen, et al., 1989; Virrkunen et al., 1994). In fact, some studies report an inverse relationship between plasma MHPG and aggression (Coccaro, Lee, & McCloskey, 2003). Virkunnen et al. (1987) observed a positive correlation between criminal behavior (but not violent crime) and CSF MHPG in arsonists, but also higher concentrations of NE in healthy participants compared to violent criminals and arsonists (Virkkunen, Nuutila, Goodwin, & Linnoila, 1987). Coccaro, Lawrence, Klar, and Siever (1991) used clonidine, an α2-NE receptor agonist, to assess the sensitivity of α2-NE receptors in patients with personality disorder (PD), remitted mood disorder (MD), and healthy subjects via growth hormone response in plasma (GH[CLON]). The authors reported that the GH[CLON] response differed only between MD and the other two groups, with PD and healthy controls displaying greater GH[CLON] responses to clonidine as well as a positive correlation between GH response and irritability, but not assaultiveness (Coccaro et al., 1991). This finding was not replicated, however, in a separate study in a larger group of subjects (Coccaro & Kavoussi, 2010). Another pharmacochallenge study in patients with BPD reported no difference between BPD patients and healthy controls in GH[CLON] response but reported a significant, positive, correlation between later time to peak GH[CLON] response and assaultiveness ($r = 0.47$), suggesting some degree of dysfunction at α2 NE receptors (Paris, Zweig-Frank, Ng Ying Kin, Schwartz, Steiger, & Nair, 2004), though in the opposite direction suggested by the Coccaro and colleagues study (1991).

Glutamate (GLU)

GLU is the primary excitatory neurotransmitter in the central nervous system and is involved in neurodevelopment, learning, and memory. In general, GLU is thought to play a facilitatory role in aggressive behavior because studies in cats and rodents report that defensive aggressive behavior is induced by GLU (and inhibited by ϒ-aminobutyric acid (GABA) and 5-HT) in the hypothalamus (Haller, 2013). In addition, interfering with GLU via administration of NMDA receptor antagonists, or by inhibiting glutamate synthesis, can reduce aggression in mice. While limited data are available in humans, CSF GLU concentrations are reported to correlate positively with measures of both aggression and impulsivity in personality disordered and healthy control study participants (Coccaro, Lee, & Vezina, 2013). Higher levels of CSF GLU have also been observed in pathological gamblers, individuals with an increased tendency to aggression and impulsiveness (Nordin et al., 2007). In humans, treatment with memantine, an NMDA receptor antagonist, has been reported to reduce agitation and aggression in individuals with Alzheimer's disease (Wilcock, Ballard, Cooper, & Loft, 2011).

ϒ-Aminobutyric Acid (GABA)

While glutamate is the primary excitatory neurotransmitter in the central nervous system, GABA is the primary inhibitory neurotransmitter. GABA receptors are expressed heavily in areas of frontal and limbic cortex and are found at both inhibitory-inhibitory and inhibitory-excitatory synapses. Studies of the relationship between GABA and impulsivity and aggression have been mixed. In humans, Lee, Petty, and Coccaro, 2009 found an inverse relationship between trait impulsivity (but not aggression) and CSF GABA levels in individuals with PD and healthy control subjects. Despite the null finding for aggression, GABA levels were found to be higher in individuals with a history of suicide attempt. Drugs that enhance GABA-ergic effects (including the antipsychotic drug clozapine and anticonvulsants topiramate and valproate, and the mood stabilizer lithium) have been shown to reduce aggression (Comai et al., 2012), suicide and suicide attempts (lithium; Baldessarini, Tondo, & Hennen, 2003), and behavioral dysregulation (carbamazepine; Cowdry & Gardner, 1988). Divalproate, an agent that increases GABA, has been shown to reduce aggression in individuals with IED and a Cluster B PD (Hollander et al., 2003). While these studies suggest an inhibitory relationship between GABA and aggression, other studies suggest a more complex relationship. Certain allosteric modulators of $GABA_A$ receptors show a bidirectional relationship with GABA. Specifically, these substances, which include some benzodiazepines, barbiturates, and alcohol, enhance aggression at low doses and reduce aggression at high doses. This "paradoxical" effect is likely to be influenced by the particular subunit composition of the benzodiazepine receptor at $GABA_A$ receptor sites, which may explain why some benzodiazepines show no such aggression-heightening effect. In the case of alcohol, alcohol-heightened aggressive behavior in mice is enhanced by repeated earlier exposure to alcohol (Miczek & Fish, 2005). Individuals with BPD may be particularly prone to paradoxical reactions to benzodiazepines. Cowdry and Gardner

(1988) observed that BPD patients engaged in more severe acts of aggression and self-aggression while taking alprazolam compared to placebo in a six-week double-blind crossover trial (Cowdry & Gardner, 1988).

Neuropeptides

Neuropeptides are signaling molecules that share many characteristics of classical neurotransmitters. Neuropeptide molecules are characteristically larger than traditional neurotransmitters, are released from distinct large dense-core vesicles located in various parts of the neuron, and are not recycled back into the cell following secretion. As such, their effects are often more diffuse than those of typical neurotransmitters and can take place over longer distances and time spans.

Vasopressin (VASO)

Preclinical research suggests that vasopressin (VASO) plays a facilitatory role in aggressive behavior. Microinjections of VASO into the hypothalamus of hamsters increase offensive aggression (Ferris, Melloni, Koppel, Perry, Fuller, & Delville, 1997), while V1a receptor antagonists injected in the anterior hypothalamus in hamsters inhibit intermale aggressive behavior (Ferris et al., 2006; Ferris & Potegal, 1988). 5-HT has been shown to block VASO-facilitated aggression (Delville, Mansour, & Ferris, 1996). An early study on basal CSF VASO levels in humans found no difference between clinical groups (ASPD, IED, and alcohol dependence) and healthy individuals (Virrkunen, et al., 1994). However, CSF VASO has been found to correlate ($r = 0.41$) with life history of aggressive behavior (Coccaro, Kavoussi, Hauger, Cooper, & Ferris, 1998). VASO has also been found to inversely correlate with PRL[d-FEN] response, and emerged as an independent predictor of aggressive behavior in a hierarchical regression analysis (Coccaro, Kavoussi, Hauger, Cooper, & Ferris, 1998). In the latter study, VASO did not correlate with a measure of trait impulsivity, state depression, or state anxiety and VASO levels did not vary as a function of any subtype of PD. fMRI studies show that VASO activates neural structures involved in fear regulation and social cognition (Zink, Kempf, Hakimi, Rainey, Stein, & Meyer-Lindenberg, 2011; Zink, Stein, Kempf, Hakimi, & Meyer-Lindenberg, 2010). This is relevant because impulsive aggressive individuals have anomalies in social cognition and are particularly sensitive to social threat (Coccaro, Fanning, Keedy, & Lee, 2016). In one fMRI study (Brunnlieb, Münte, Krämer, Tempelmann, & Heldmann, 2013), male participants engaged in a laboratory aggression paradigm with a research confederate during which the pair set noise blasts of varying intensity for each other. While intranasal VASO administration had no effect on aggressive behavior, VASO was associated with activation in the amygdala when participants were deciding the level of noise to set for the other person, an effect not observed in the placebo condition. As such, it is possible that VASO facilitates aggressive behavior by sensitizing the amygdala to respond to social threat.

Oxytocin (OXY)

Like vasopressin, oxytocin (OXY) plays a role in regulating social behavior, although these two neuropeptides often display opposing effects. With regard to aggression, while CSF vasopressin levels correlate positively with aggression, CSF OXY correlates inversely with aggression (Lee, Ferris, Van de Klar, & Coccaro, 2009). Intranasal oxytocin administration has been linked to improved emotional recognition, empathy, and attachment (Buchheim et al., 2009; Hurlemann et al., 2010), and has also been shown to enhance positive communication between couples during a disagreement and reduce cortisol responses during the interaction (Ditzen et al., 2013). Oxytocin has also been shown to reduce laboratory-assessed aggressive behavior among women with high state anxiety, suggesting an aggression-reducing anxiolytic effect of OXY (Campbell & Hausmann, 2013). However, OXY has also been shown to increase negative emotions such as envy and schadenfreude (Shamay-Tsoory et al., 2009) and to increase noncooperation toward members of out-groups (see De Dreu, 2012 for a review), suggesting that OXY's effect on behavior may not always be prosocial in nature. Given the importance of amygdala hyperactivation in impulsively aggressive individuals (Coccaro, McCloskey, Fitzgerald, & Phan, 2007; McCloskey, Phan, Angstadt, Fettich, Keedy, & Coccaro, 2016), it is of note that OXY has been shown to reduce the enhanced amygdala activation during exposure to angry/fearful faces in females with BPD, suggesting that OXY may reduce sensitivity to social threat in women with BPD (Bertsch et al., 2013). Clearly, further research is needed to better understand whether and how oxytocin may be involved in modulating impulsive aggression.

Substance P

The endogenous receptor for substance P is neurokinin-1 (NK1), and both substance P and the NK1 receptor are widely distributed in the CNS, specifically in the limbic system regions (Yip & Chahl, 2001). Both receptor types are also found in close association with 5-HT and NE-containing neurons (Gobbi et al., 2007), and a modulatory role for substance P in aggressive behavior is suggested by its high concentrations in brain regions relevant to mammalian aggression (e.g., the amygdala, periaqueductal gray; Smith et al., 1994). Studies in lower mammals have provided evidence that substance P promotes aggressive behavior by activating hypothalamic NK1 receptors and inducing rage and aggression (Bhatt, Gregg & Siegel, 2003; Greg & Siegel, 2001; Han et al., 1996; Shaikh et al., 1993). In addition, intrathecal injections of substance P in the rat results in agonistic behavior (Beyer, Caba, Banas, & Komisaruk, 1991), as well as in behavioral excitation (Barbeau et al., 1980; Elliott & Iversen 1986). Finally, NK1 receptor antagonists have been shown to reduce defensive aggression in cats (Shaikh, Steinberg, & Siegel, 1993). A recent neurochemical study from our group reported a positive correlation between CSF levels of substance P and measures of aggression in PD and control subjects, suggesting that substance P concentrations may facilitate aggression in humans (Coccaro, Lee, Owens, Kinkead, & Nemeroff, 2012). While an antagonist for NK1 receptors is available for human use (aprepritant), to date no study using this agent has been published to test the hypothesis that blocking NK1 receptors can reduce aggression in human subjects.

Neuropeptide Y

A similar modulatory role in aggressive behavior in mammals is suggested by the fact that high immunoreactivity of NPY can be found in brain regions relevant to mammalian aggression (Gregg & Siegel, 2001) and that animal models of aggression suggest that NPY may be associated with aggressive behavior (Rutkoski, Lerant, Nolte, Westberry, & Levenson, 2002; Kask & Harro 2000; Karl et al., 2004). Increased impulsivity is also seen in Y2 receptor knockout mice (Greco & Cari, 2006). A recent neurochemical study from our group reported a positive correlation between CSF NPY and measures of aggression (Coccaro, Lee, Liu, & Mathe, 2012), suggesting that NPY concentrations may facilitate aggression in humans as well.

Other Neuromodulatory Systems

Testosterone (TEST)

Testosterone (TEST) facilitates aggression when administered to adults (Kouri, Lukas, Pope, & Oliva, 1995, Pope, Kouri, & Hudson, 2000), perhaps by increasing anger and hostility (O'Connor et al., 2004). Several studies have found evidence for higher plasma/saliva TEST levels in males with criminal aggression (Banks & Dabbs 1996, Bergman & Brismar 1994) and in volunteers with higher levels of behavioral aggression (Gerra et al., 1996, 1997). Our own studies of TEST in the CSF revealed a relationship only with venturesomeness, a behavioral construct that is related to sensation seeking, but not aggression (Coccaro, Beresford, Minar, Kaskow, & Geracioti, 2007).

Cholesterol/Fatty Acids

Low peripheral levels of cholesterol have been linked to aggression for more than three decades (Virkkunen, 1983). There has been some evidence that cholesterol-lowering drugs may increase deaths caused by violence, suicide, and accidents (Pekkanen, Nissinen, Punsar, & Karvonen, 1989; Muldoon, Rossouw, Manuck, Gluech, Kaplan, & Kaufmann, 1993), but these findings have not always been replicated, and a definitive neural mechanism has yet to be specified. Curiously, while treatment with statins lowers cholesterol, they also lower TEST, and this may be why aggression was lower among statin-treated males in a recent study (Golomb et al., 2015). Reduced intake of omega-3 fatty acids has also been linked to suicide and MDs. While the mechanism is not well understood, such a relationship is biologically plausible given the role of fatty acids in constituting the neural lipid bilayer membrane. One double-blind, placebo-controlled study, conducted more than 10 years ago, reported that omega-3 fatty acids were superior to placebo in leading to reductions in anger and depressive symptoms in patients with BPD (Zanarini & Frankenburg, 2003). Subsequent studies have reported an anti-aggressive effect of omega-3 fatty acids on aggression and/or impulsivity in healthy adult males (Long & Benton, 2013), in adult patients with BPD when combined with divalproex (Bellino, Bozzatello, Rocca, & Bogetto, 2014), and in children and adolescents in one study (Raine, Portnoy, Mahoomed, & Hibbeln, 2015) but not in another recent study (Dean, Bor, Adam, Bowling, & Bellgrove, 2014).

Inflammatory Cytokines

Inflammatory cytokines have been shown to modulate aggressive behavior in the brains of animals (i.e., defensive-rage aggression model in the cat). IL-1β increases defensive rage in the cat when injected into the medial hypothalamus (MH; Hassanain, Bhatt, Zalcman, & Siegel, 2005) or periaqueductal gray (PAG) (Hassanain, Zalcman, Bhatt, & Siegel, 2003). The effect of IL-1β may be mediated by its stimulation of 5-HT_2 receptors in MH (Hassanain et al., 2005); the identity of the mediator of the effect of IL-1β in PAG is not currently known. IL-2 also increases defensive rage in the cat when injected into the PAG (Bhatt & Siegel 2006), but reduces this behavior when injected into the MH (Hassanain et al., 2005). The effect of IL-2 may be mediated by $GABA_A$ receptors in the MH (Hassanan et al., 2005) and by NK-1 receptors in the PAG (Bhatt & Siegel, 2006). In addition, IL-2 levels are higher in mice bred for high aggression versus low aggression (Petitto, Lysle, Gariepy, & Lewis, 1994) and knockout of tumor necrosis factor-alpha (TNF-α) receptors eliminate aggressive behavior in TNF-α-knockout versus wild-type mice (Patel et al., 1999). In human studies, self-assessed anger and tendency toward aggression increases in patients treated with cytokine immunotherapy (McHuthison, Gordon, & Schiff, 1998; Kraus, Schafer, Faller, Csef, & Scheurlen, 2003). Further, circulating levels of C-reactive protein (CRP) (Suarez, 2004, Marsland, Prather, Petersen, Cohen, & Manuck, 2008), a marker of inflammation, and IL-6 (Suarez, 2003; Marsland et al., 2008) also correlate positively with self-assessed hostility and tendency toward aggression in healthy adult subjects. Our group recently reported similar findings in personality disordered individuals (Coccaro, 2006) and in individuals with recurrent, problematic, impulsive aggressive behavior with IED (Coccaro, Lee, & Coussons-Read, 2014; Coccaro, Lee, et al., 2016). Specifically, we found that plasma CRP and plasma IL-6 (Coccaro, Lee, & Coussons-Read, 2014) are higher in individuals with IED compared with psychiatric and healthy controls and that these inflammatory markers, as well as a marker of IL-1β, correlate directly with measures of aggression (Coccaro, 2006; Coccaro, Lee, & Coussons-Read, 2014; Coccaro, Lee, et al., 2016). A study of tryptophan metabolites suggests that these findings are not likely due to an effect of inflammation on 5-HT itself, suggesting a possible direct effect of these inflammatory mediators on aggressive behavior directly (Coccaro, Lee, et al., 2016). While studies of anti-inflammatory agents have been ongoing in depression (Köhler et al., 2014), such studies have not yet been published on aggressive individuals.

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