

PATHOPHYSIOLOGY AND TREATMENT OF AGGRESSION

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Human aggression constitutes a multidetermined act that often results in physical (or verbal) injury to others or self (or objects). It appears in several forms and may be defensive, premeditated (e.g., “predatory”), or impulsive (e.g., “non-premeditated”). *Defensive aggression* is generally seen within the normal range of human behavior. However, *premeditated and impulsive aggressive behaviors* are commonly viewed as pathologic.

Aggression may be measured as both a dimensional and a categorical variable. However, whereas aggressive behavior (or the tendency to behave aggressively) is truly dimensional, it is difficult to estimate the societal relevance of aggressive behavior using dimensional assessments. As a categorical variable, aggressive subjects (“cases”) may be counted in populations of interest. For example, the current age-adjusted rate for homicide in the United States is 0.01% (1). With respect to physical assault, approximately one-fourth of all men and approximately half as many women report a history of physical fighting after 18 years of age (2). From these figures, it may be estimated that approximately 35 million adults in the United States have engaged in at least one *serious* act of aggression. The rate of individuals demonstrating “recurrent, problematic, aggression” is lower, of course. Using DSM-IV intermittent explosive disorder (IED) as a proxy for “recurrent, problematic, aggression,” Zimmerman et al. reported that nearly 7% of psychiatric outpatients meet criteria for IED at any point in their lives (3). Including borderline and antisocial personality-disordered patients, who are also quite aggressive, increases this number to about 13% of psychiatric outpatients. Regardless, these data suggest that the lifetime prevalence of recurrent, problematic, aggressive behavior may be 1% or higher (at least 2.5 million) in the general community (4).

Research into the etiologic determinants of both preme-

ditated and impulsive human aggression has focused on various genetic, biological, and psychosocial factors and reveals a rich and complex picture of human aggression involving both constitutional and nonconstitutional elements. Twin, adoption, and family studies all suggest a genetic influence underlying aggression (5), with heritability estimates for dimensional measures of aggression ranging from 44% to 72% in adults. A metaanalysis of more than 20 twin studies confirmed a substantial role for a genetic influence underlying aggression (6). Although behavioral genetic studies to date have not attempted to distinguish among aggression subtypes, impulsive aggression appears to be quite distinct from premeditated aggression. Overall, the recurring theme emerging from more than 20 years of empiric research is that “impulsive aggression” demonstrates the most consistent and noteworthy findings with respect to both biological correlates (7,8) and psychopharmacologic treatment (9,10). Biological factors include a variety of neurotransmitter and neuromodulator systems. Most data involve the central serotonin (5-hydroxytryptamine or 5-HT) system, although limited data is now emerging for a role for other central systems involving catecholamines, steroids, neuropeptides, and cholesterol and fatty acids. This chapter reviews the neuropsychopharmacologic data relevant to these systems and concludes with a discussion of the psychopharmacology of aggression.

NEUROPSYCHOPHARMACOLOGY OF AGGRESSION

Serotonin

The hypothesis that 5-HT modulates impulsive aggressive behavior in humans was first advanced in the same year by both Sheard et al. (9) and Asberg et al. (11). The former group demonstrated that treatment with lithium carbonate (an agent with putative 5-HT-enhancing properties), but not placebo, reduced impulsive aggressive behavior in prison inmates; the latter group demonstrated that violent (and

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eventually lethal) suicidal behavior was a characteristic of patients with low lumbar cerebrospinal fluid (CSF) concentrations of 5-hydroxyindolacetic acid (5-HIAA). This work led to a large number of subsequent studies, using a variety of 5-HT measures, designed to test the 5-HT hypothesis of aggression further.

5-HT and Aggression: CSF 5-HIAA Studies

Brown et al. first reported a strong inverse correlation between CSF 5-HIAA and a life history of aggression ($r = -.78$) in male personality-disordered adults (12). This finding was replicated in a follow-up study using another variable reflective of aggression (i.e., “psychopathic deviance,” defined as defiance of authority and impulsivity) (13). In both samples, a trivariate relationship between reduced CSF 5-HIAA and aggression and suicidal behavior was demonstrated. Later reports demonstrated that reduced CSF 5-HIAA was specific to impulsive rather than premeditated (i.e., nonimpulsive) aggression (7,14). Linnoila et al. first demonstrated that CSF 5-HIAA among violent offenders whose index crime was classified as “impulsive” (i.e., no apparent plan) were significantly lower than those among violent offenders whose index crime was classified as “non-impulsive” (i.e., knew the victim and planned the crime) (7). The hypothesis that “impulsiveness” is the key behavioral correlate of reduced 5-HT activity was later advanced in a series of studies from Virkkunen et al. (8,15,16). In these studies, CSF 5-HIAA concentrations of “impulsive” arsonists were reduced to the same degree as in “impulsive violent offenders” and were significantly lower than those observed in healthy volunteers. Because both impulsive arsonists and impulsive violent offenders had (theoretically) “impulsivity” in common, these investigators proposed that the key correlate to reduced CSF 5-HIAA was impulsivity as opposed to aggression. Closer inspection of the data reveals, however, that impulsive “arsonists” and impulsive “violent offenders” also shared a general history of impulsive aggression (e.g., similar rates of IED and suicide attempts), and, accordingly, it may be premature to conclude that the key behavioral correlate of reduced central 5-HT function is impulsivity rather than a combined construct of impulsive aggression. An inverse relationship between CSF 5-HIAA and aggression or impulsivity has also been reported in male patients with alcoholism (17), in behaviorally disruptive male children and adolescents (18), and in rhesus (19) and pigtailed macaques (20).

Despite these data, some studies have not replicated the finding of an inverse relationship between CSF 5-HIAA and aggression (21–25). The reason probably is the presence of subjects who are less severe in their aggressive behavior. Because the relationship between CSF 5-HIAA and aggression appears to be direct (rather than inverse) in several of these studies, it is possible that the direction, as well as the magnitude (17), of this relationship is a function of the

severity of aggression. A direct relationship between lumbar CSF 5-HIAA concentration and aggression in these subjects suggests that aggressiveness may be associated with increased (rather than decreased) intrasynaptic concentrations of 5-HT. These data could be consistent with a deficiency hypothesis of 5-HT for aggression if postsynaptic 5-HT function is reduced by compensation. If postsynaptic 5-HT function is unchanged (or increased), however, these data would suggest increased “net” 5-HT function in these subjects. Evidence examining these hypotheses is discussed in the following sections.

5-HT and Aggression: Pharmacochallenge Studies

Coccaro et al. first reported a blunted prolactin D,L -fenfluramine (PRL $_{D,L-FEN}$) response in drug-free mood-disordered and personality-disordered patients compared with healthy volunteers (24,26,27). In addition, patient subjects with a history of a suicide attempt displayed blunted PRL $_{D,L-FEN}$ responses compared with those without this history. Personality-disordered, but not mood-disordered, patients also displayed an inverse relationship between various measures of impulsive aggression (but not depression) and PRL $_{D,L-FEN}$ responses. Because experimental reduction in norepinephrine (NE) activity has been shown to eliminate the expected aggressive behavior of animals with reduced 5-HT (28), a reduction in NE system function in the mood-disordered (29), but not the personality-disordered (30), subjects could have mitigated the influence reduced 5-HT function could be expected to have on the expression of aggressive behavior. For the depressed patient, reduced NE system function may be associated with a reduction in efficiency to attend to novel (e.g., aversive) stimuli. If so, only the most potent stimuli (e.g., suicidal ideation) would be likely to trigger a behavioral action that could be poorly inhibited by a dysfunctional central 5-HT system. Further study noted that PRL $_{D,L-FEN}$ responses were inversely related to CSF 5-HIAA and were directly related to PRL[meta-chlorophenylpiperazine or m-CPP] responses, an index of postsynaptic receptor activation (25). When these 5-HT measures were examined in the same personality-disordered subjects, a relationship between 5-HT and aggression was noted for both PRL $_{D,L-FEN}$ and PRL[m-CPP] responses (which were also directly correlated) but not for CSF 5-HIAA, a finding suggesting that the 5-HT–aggression relationship, as detected by PRL $_{D,L-FEN}$ response, may be caused by a reduction in the sensitivity of the postsynaptic 5-HT receptor. Available data suggest that PRL responses to FEN reflect the activation of central 5-HT $_{2C}$, but not 5-HT $_{1A}$ or 5-HT $_{3}$, receptors (27, 31,32); other 5-HT receptors have not been studied in this regard. 5-HT $_{1A}$ receptors may still play a role in human aggression as evidenced by inverse relationships noted be-

tween aggression and physiologic responses to buspirone (33,34) and ipsapirone (35,36) challenge.

Support for these pharmacochallenge findings has been reported in patients with personality disorders (37), patients with alcoholism (38,39), suicidal patients (40), violent offenders (41), healthy volunteers from the community (42), and macaques (43). Nonreplication studies involve subjects with history of primarily nonalcoholic substance abuse (44, 45) and children with disruptive behavior disorders (46, 47), in whom positive correlations between D,L-FEN challenge and aggression variables have been reported in several, although not all, studies (48–50). In substance abusers, it is possible that nonalcoholic drugs of abuse modify the neurobiological substrate of subjects so correlations between 5-HT and measures of impulsive aggression are direct rather than inverse, as are seen in patients with alcoholism (38, 39). In children, two studies reported a positive correlation between aggression and PRL[D,L-FEN] response (46,47), and one reported a negative correlation between aggression and thermal [D,L-FEN] responses (50). In adolescents or older children, two studies reported no correlation between PRL[D,L-FEN] and aggression (48,49). It is possible that changes in the 5-HT system occurring over development affect the nature of the 5-HT–aggression relationship in that this relationship is positive in some 5-HT–mediated pathways, such as the PRL[D,L-FEN] response, in prepubertal children, is absent in postpubertal children, and is inverse in adults. The neurobiological mechanisms underlying this hypothesis are unknown, although, in animal models, the overexpression of 5-HT early in development has been shown to lead to the down-regulation of the 5-HT system later in life (52).

5-HT and Aggression: Peripheral Marker Studies

Studies examining 5-HT–aggression relationships using peripheral indices of 5-HT are relatively limited. The platelet 5-HT transporter (or 5-HT uptake activity) has been assessed in regard to aggression in children, adolescents, and adults and is the one peripheral 5-HT measure to demonstrate some consistency across studies. Positive findings in children and adolescents include the studies of Stoff et al. (53) and Birmaher et al. (54), in which platelet ³H-imipramine (B_{max}) binding was lower in aggressive subjects. In adult subjects, three of four studies reported inverse relationships between platelet 5-HT transporter binding and aggression or impulsivity in personality-disordered subjects (55,56) and aggressive institutionalized adults (57); the fourth study reported an increase in platelet 5-HT transporter binding in criminal offenders when compared with normal control subjects (58). Two studies examined the function of the platelet 5-HT transporter, with one demonstrating a reduction of platelet 5-HT uptake in aggressive adult subjects and an inverse relationship with impulsivity (59), and a second study demonstrating no differences in

platelet 5-HT uptake in boys with and without disruptive behavior disorders in a study in which no difference was found in the number of platelet ³H-imipramine binding sites between these two groups of subjects (60). Studies examining the platelet 5-HT_{2A} receptor in aggression are few, and results are mixed, with one study reporting no relationship (61), another reporting a negative relationship (62), and yet another reporting a positive relationship (63) between this 5-HT receptor and aggression.

Published studies of blood and platelet 5-HT and plasma tryptophan in humans are relatively few and inconsistent in their results. Whole-blood 5-HT concentrations have been reported as elevated in juvenile offenders compared with normal control subjects (64) and as a function of age of onset (65). A positive correlation between platelet 5-HT concentration and measures of aggression in adult depressed patients (66) has also been reported. Negative studies, however, include those performed in mentally retarded adults (67) and in children with attention-deficit/hyperactivity disorder (68). The ratio of plasma tryptophan to other competing neutral amino acids was lowest among patients with alcoholism with a history of depression or aggression and was lowest among those patients with alcoholism with a history of both depression and aggression in two studies (69,70). Other studies reported elevated levels of plasma tryptophan (or the tryptophan ratio to neutral amino acids) in violent offenders (71,72) or positive correlations with aggression in healthy volunteers (73).

5-HT and Aggression: Behavioral Studies

Behavioral measures of aggression have been available for many years and include paradigms in which subjects are instructed to deliver a noxious stimulus (e.g., electric shock or loud noise; Taylor Aggression Paradigm) (74) to, or to take monetary points away from (Point Subtraction Aggression Paradigm or PSAP) (75), “confederate” subjects under specific social conditions. In these paradigms, the amount of the noxious stimuli delivered to (or points subtracted from) the confederate represents the subject’s tendency to behave aggressively. In a study of 14 male personality-disordered subjects (56), both the PSAP and a life history measure of aggression correlated inversely with PRL[d-FEN] responses. Another study reported a similar finding with respect to 5-HT_{1A} receptor function (36). In this study, high PSAP (“high aggressive”) responders had blunted thermal responses to ipsapirone challenge compared with low PSAP (“low aggressive”) responders.

Experimental studies in which 5-HT activity is manipulated and aggressive responding is monitored have been conducted in research volunteers without documented psychopathology. Four studies in which brain 5-HT was putatively manipulated by tryptophan depletion, supplementation, or both (76–79) reported data consistent with an inverse relationship between 5-HT activity and aggressive responding

in the laboratory, although one suggested that this effect is restricted to a subgroup of aggressive subjects (79). The one negative study in this area did not use a laboratory paradigm in which provoked aggression could be assessed (80). Studies in which 5-HT activity was acutely increased by using either single doses of D,L-FEN or of the 5-HT_{1A/1B} agonist eltoprazine (34,81) reported a reduction in aggressive responding on behavioral paradigms. For D,L-FEN, but not eltoprazine, this result was specific to aggressive responding (as opposed to both aggressive and nonaggressive responding in the case of eltoprazine). These data are consistent with clinical trial data using 5-HT enhancing agents, discussed later (82).

Catecholamines

Based on animal studies, increased noradrenergic (NE) and dopaminergic (DA) activity could be hypothesized to facilitate aggressive responding in humans (83,84). Brown et al. reported a positive correlation between CSF methoxyhydroxyphenylglycol (MHPG), but not CSF homovanillic acid (HVA), concentrations and life history of aggression (12). Further analysis revealed, however, that CSF 5-HIAA accounted for 80% of the variance in aggression scores. Plasma NE was modestly, but positively, correlated with self-reported impulsivity in male personality-disordered subjects in another study (85). However, significant reductions in CSF MHPG in impulsive violent offenders was reported in one study (15), although not in a later study by the same investigators with a much larger sample (8). NE pharmacologic challenge studies in this area have been limited and include a positive correlation between the growth hormone response to the α_2 -NE agonist clonidine and self-reported "irritability" (a correlate of aggression) in a small sample of male personality-disordered and healthy volunteer subjects (30). A role of α_2 -NE receptors in aggression has been suggested by animal data in which the intrahypothalamic injection of α_2 -NE agents enhances aggressive responding in the cat (86). The authors suggested that one putative mechanism underlying this finding could involve stimulation of α_2 -heteroreceptors on presynaptic 5-HT neurons thereby inhibiting 5-HT outflow.

Support for a DA hypothesis of human aggression is also limited. Although some studies reported no relationship between CSF HVA and aggression (12,15), other studies suggested the presence of an inverse relationship between these variables. A reduction in CSF HVA in antisocial, though not "explosive," impulsive violent offenders was reported in one study (7). A reduction in CSF HVA has also been reported among recidivist violent offenders in comparison with nonrecidivist violent offender controls (16), a finding suggesting that reduced dopaminergic function plays a role in predicting future aggressive behavior. These findings must be taken with caution, however, because an inverse relationship between CSF 5-HIAA and aggression

was also present in each of these studies. Because CSF 5-HIAA may "drive" CSF HVA (87), it is possible that these findings are related to a more primary relationship between CSF 5-HIAA and aggression. Conversely, an imaging study of striatal dopamine transporters in human subjects reported greater heterogeneity in these receptors in impulsive violent offenders compared with control subjects (88), a finding suggesting that a reduction in CSF HVA may not be secondary to alterations in 5-HT function.

Neurosteroids

Testosterone

Testosterone and related androgens generally play a facilitative role in aggressive behaviors (see refs. 89 and 90 for review). Positive correlations between plasma testosterone concentrations and measures of aggression have been reported, although not entirely consistently in nonpsychiatric subjects (see refs. 89 and 91 for review). Correlations have also been reported in volunteers between reports of relatives and spouses of their global aggressive behavior and both testosterone and NE (92), and basal testosterone levels have been reported to be higher in subjects with high-normal than those with low-normal aggressiveness (93).

Plasma testosterone levels have also been reported to be higher in psychiatric and criminal populations characterized by high aggression. For example, male criminals with personality disorders had significantly higher levels of circulating testosterone than criminal patients with schizophrenia (94), and high free testosterone concentrations were associated with increased aggression in Finnish violent offenders with alcoholism (8). Plasma concentrations of testosterone appear to be higher in persons with alcoholism with a history of repeated episodes of domestic violence than in comparison groups (95). In criminal offenders, higher CSF testosterone concentrations were found in antisocial impulsive violent offenders, but they were not found in nonantisocial impulsive or nonimpulsive violent offenders, in comparison with a healthy volunteer control group.

There are some reports from in prospective, blinded studies suggesting that administration of exogenous testosterone may result in aggressive behaviors (96), but the percentage experiencing severe mental disturbances is likely to be small (97–99). Anabolic steroid administration may not be uncommon among prisoners (100), and it may induce abnormal personality traits in body builders (101). Naturalistic studies of testosterone concentrations are limited in their interpretation because of the pulsatile nature of testosterone release, so particularly plasma concentrations may be quite variable, whereas CSF may be more reflective of average values. Studies of exogenous steroid administration are complicated by, in most cases, the uncontrolled nature of this steroid use.

Cortisol

In general, cortisol concentrations are reported to be relatively low in aggressive individuals. This finding is consistent with the negative correlation between cortisol and testosterone concentrations (102) in volunteer subjects under controlled conditions. Correlations have been found among plasma PRL, testosterone, and aggression, but not with cortisol, although cortisol and PRL concentrations were correlated with each other in their day-to-day changes in one study (103). In children, increases in cortisol during the day were correlated with increased aggression (104). A low concentration of salivary cortisol was associated with persistent aggression in boys referred because of disruptive behavior (105). In criminal offender or antisocial populations, reduced urinary-free cortisol and CSF adrenocorticotrophic hormone (ACTH) concentrations are found compared with healthy volunteers (8). Plasma cortisol has also been reported to be reduced in persons with alcoholism and a history of repeated domestic violence (95) but increased after cessation of drinking in incarcerated persons with alcoholism (106). However, the data in both animals and man are inconsistent because a positive correlation has been observed between plasma ACTH and aggression in nonhuman primates (19), and cortisol rises during competition for dominance in vervet monkey males (107). The relationship between cortisol and aggression is thus likely to be complex and dependent on social context and stress.

Neuropeptides

Among peptides neurotransmitters and modulators, limited data suggest a positive relationship between aggression and central vasopressin and central opioid activity.

Vasopressin

Whereas Virkkunen et al. reported no difference in CSF vasopressin concentrations among impulsive and nonimpulsive violent offenders (8), Coccaro et al. reported a positive correlation between CSF vasopressin concentration and life history of aggression in 26 personality-disordered persons, particularly men (108). Despite a significant inverse correlation between CSF vasopressin and PRL_[d-FEN] response, the positive relationship between aggression and CSF vasopressin remained even after the influence of PRL_[d-FEN] response on the aggression score was taken into account. These data are consistent with those from animal studies in which vasopressin antagonists reduced aggression in golden hamsters, whereas 5-HT uptake inhibitors increased central 5-HT activity and reduced central vasopressin concentration and levels of aggressive behavior in the same species (109). Differences between the two human studies may be accounted for by significant differences in the sample population (e.g., criminally versus non-

criminally violent subjects). It is possible that agents that dampen central vasopressinergic activity could have anti-aggressive efficacy.

Opiates

Although opiate withdrawal may precipitate aggressive behavior, there has been little study of the relationship of aggression with endogenous opiates. In one study, a CSF opioid-binding protein was positively correlated with "assaultiveness" in healthy male volunteers (110). Circulating levels of met-enkephalins have been associated with self-injurious behaviors in a limited number of studies (111). Post-mortem brain studies of violent suicide victims have also found greater numbers of μ -opioid receptors as well (112). Male undergraduates receiving 45 mg of oral morphine tablets or placebo displayed more aggression in the morphine-induced than the placebo conditions (113), whereas naltrexone, an opiate blocker, attenuated self-injurious behavior (114). These studies suggested that increased opioid activity may increase the likelihood of aggressive behavior.

Cholesterol and Fatty Acids

Some studies, both from persons who attempted suicide and from healthy persons, suggested that reduced serum cholesterol may be associated with aggressive behavior (115, 116). Male monkeys randomized to a low-fat and low-cholesterol diet displayed more aggressive behavior and less prosocial behaviors than those randomized to a high-cholesterol diet (117,118). In humans, pharmacologic reduction of cholesterol may increase the risk of non-illness-related mortality such as death by suicide or trauma related to aggression (119). Naturally occurring reduced cholesterol may also be associated with non-illness-related mortality (116, 120–123), largely attributable to suicide (116,122). Low serum cholesterol has been reported in psychiatric inpatients associated with suicide attempts (124–127). Reduced serum cholesterol has also been related to the severity of borderline personality disorder traits (115), as well as to antisocial personality disorder and the violence associated with it (128, 129). It is also found in male forensic patients (130), aggressive conduct-disordered children and adolescents with attention deficit disorder (131), and suicidal adolescents (132).

MOLECULAR GENETICS

An understanding of the molecular genetics of impulsive aggression is currently emerging with the rise of association studies involving various DNA polymorphisms of candidate genes. One of the first notable studies in this area was that of Brunner et al. (133), who reported an association between a point mutation for the monoamine oxidase A (MAO A)

gene in an extended family pedigree and impulsive violence in males of low intelligence. The presence of this mutation was associated with evidence of altered catecholamine metabolism (i.e., reduced brain catecholamine breakdown and increased activity at central catecholamine receptors). Although no other families with this specific MAO A point mutation have been reported, this report highlighted the potential of the candidate gene approach to the molecular genetics of aggression. At about the same time, Nielson et al. reported that the presence of the L allele for the (intronic) biallelic tryptophan hydroxylase (TPH) polymorphism was associated with a reduction of CSF 5-HIAA concentration in impulsive violent offenders (nearly all with DSM-III IED) (134). In the same study, the presence of the L allele was also associated with history of suicide attempts in all violent offenders. Although this finding was not replicated by Abbar et al. (135), using a different TPH polymorphism, Nielson et al. did replicate this finding in a second group of violent offenders (136), specifically in impulsive violent offenders and more specifically for severe suicide attempts. Linkage for this TPH polymorphism was also noted in a sib-pair analysis in this same report. New et al. reported a linear association between the TPH genotypes and dimensional measures of impulsive aggression (137). In this brief report of only 21 personality-disordered subjects, those with the LL genotype had significantly higher aggression scores than subjects with the UU genotype. However, an association with the U allele of the TPH polymorphism in patients with a history of suicide attempts has also been reported (138), as has an association with the U allele and aggression scores in community-recruited healthy volunteers (139). It may be that the TPH polymorphism is in linkage disequilibrium with different genes in different populations. Lappalainen et al. reported an association between “antisocial alcoholism” (i.e., alcoholism with antisocial personality disorder or DSM-III IED) and the C allele biallelic polymorphism for the 5-HT_{1Dβ} receptor (140). A study of a 5-HT₆ receptor allelic variant in patients with schizophrenia and in controls was negative for an association with aggressive behavior (141). Finally, Lachman et al. (142) reported replication of a report by Strous et al. (143) of an association between the “low activity” allele of a biallelic polymorphism for catechol-O-methyltransferase (an enzyme that degrades NE) and violence in patients with schizophrenia.

NEUROPSYCHOLOGY OF AGGRESSION

The relationship between aggression and neuropsychology is in part dependent on the syndrome in which aggression is observed. For example, the cognitive impairment of dementia may be associated with aggressive behavior. In adolescents with conduct disorder, verbal processing deficits are associated with greater aggressiveness and antisocial behavior (144). Low executive cognitive function is also related

to aggressive antisocial behavior (145,146). Low executive function also contributed to failures to inhibit responses to stimuli associated with punishment on a “go/no-go” learning task, and poor “self-awareness” possibly related to right cerebral dysfunction has also been related to increased hostility. Verbal signal decoding and P300 amplitudes in an evoked potential paradigm predicted impulsiveness and anger in prison inmates (147). In terms of regional localization, neuropsychological tasks sensitive to frontal and temporal dysfunction have best characterized aggressive antisocial subjects (148,149). Thus, neuropsychological and cognitive studies do suggest that abnormalities of higher integrative functions, consistent with reduced cortical inhibitory influences on aggression, result in more disinhibition of aggressive behaviors. As described earlier, certain laboratory paradigms may discriminate aggressive individuals from comparison groups including the PSAP (150) and a “go/no go” version of the Continuous Performance Task (151). The PSAP has been externally validated in violent and nonviolent male parolees, in that violent parolees emit more aggressive responses than nonviolent parolees; furthermore, the number of aggressive responses correlated with other psychometric measures of aggression (76). However, the heritability of these laboratory measures has not been systematically assessed in studies of families or sibs of impulsive or aggressive probands, a logical prerequisite to an endophenotypic approach to borderline personality disorder.

NEUROIMAGING OF AGGRESSION

Neuroanatomy of Aggression

Prefrontal cortex, particularly prefrontal orbital cortex and adjacent ventral medial cortex, appears to play a central role in the regulation of aggressive behavior, but temporal cortex, cingulate cortex, and amygdala may also play important roles in the generation of aggression as well. The critical role of prefrontal orbital cortex is exemplified by the case of Phineas Gage, a solid, upstanding railroad worker, who, after a penetrating injury to his orbital frontal cortex, became irritable, hostile, and displayed poor social judgment. Careful reexamination of his skull led to a reconstruction of the location of the lesion at the anterior and mesial aspects of the orbital cortex as well as anterior cingulate and anterior mesial aspects of frontal cortex superior to orbital cortex, with more marked damage in the left hemisphere (152). Other clinical cases support the central role of orbital prefrontal cortex in regulation of aggression (153–157). Irritability and angry outbursts have also been associated with damaged orbital frontal cortex in neurologic patients (158), and frontal and temporal hypoperfusion has been noted in frontotemporal dementias (159). Lesions of prefrontal cortex, particularly orbital frontal cortex, early in childhood can result in antisocial disinhibited, aggressive behavior later in life (160).

Temporal lobe lesions have also been associated with a susceptibility to violent behavior, as suggested by multiple case reports of patients with temporal lobe tumors. In one study of violent patients, many anterior inferior temporal lobe tumors were reported (161,162), and aggressive behavior has been associated with temporal lesions (163). Although temporal disease may express itself in a variety of ways, there does appear to be a clear association between temporal pathology and aggressive behavior.

The amygdala is also implicated in the regulation of aggression both in electrical stimulation studies, associated with rage attacks, and studies of patients who have undergone amygdectomy (164), although destructive behaviors have also been observed in the context of coagulation of the amygdala (165). Patients with bilateral amygdala damage judged unfamiliar persons to be more trustworthy than controls, a finding consonant with the role of the amygdala in social judgments of potential threat (166).

The association of violent behavior with aggressive behavior with localized seizure activity provides a further guide to brain regions implicated in the modulation of aggression. Aggressive behavior has been found to be associated with frontal lobe seizure activity (167,168) and temporal lobe seizures (169). However, only a few patients with temporal lobe epilepsy engage in aggressive behaviors in the interictal or periictal periods (170–172). These clinical correlations, although pointing to regions of interest for imaging studies, cannot directly address the circuitry involved in impulsive aggression in the absence of specific neurologic disease. These data do support the importance of prefrontal, temporal, and limbic cortex in the regulation of aggression.

Structural Imaging and Aggression

Reduced prefrontal gray matter has been associated with autonomic deficits in patients with antisocial personality disorders characterized by aggressive behaviors (173). Although these deficits are not visually perceptible, they reach statistical significance and are consistent with the neurologic literature (described earlier) and functional imaging data (described in the next section).

Functional Imaging and Aggression

One technique used to identify brain activity in individuals displaying aggressive behavior is the assessment of *in vivo* cerebral glucose metabolism through positron emission tomography. Studies of this type tend to implicate brain hypometabolism in a variety of regions but particularly frontal and temporal cortex. In psychiatric patients with a history of repetitive violent behavior, decreased blood flow consistently has been found in temporal cortex and, to some extent, in frontal cortex (174,175). In a study of homicide offenders, bilateral diminution of glucose metabolism was observed in both medial frontal cortex and at a trend level

in orbital frontal cortex (176). These deficits were more pronounced in persons without psychosocial deprivation (177). In a study of patients with personality disorders, an inverse relationship was found between life history of aggressive impulsive behavior and regional glucose metabolism in orbital frontal cortex and right temporal lobe. Patients meeting criteria for borderline personality disorder had decreased metabolism in frontal regions corresponding to Brodmann's areas 46 and 6 and increased metabolism in superior and inferior frontal gyrus (Brodmann's areas 9 and 45) (178). Single photon emission computed tomography studies have also suggested reduced perfusion in prefrontal cortex, as well as focal abnormalities in left temporal lobe and increased activity in anteromedial frontal cortex in limbic system in aggressive persons with reduced prefrontal perfusion in antisocial personality-disordered alcoholism (179), and hypoperfusion in the left frontoparietal region associated with attacks of bizarre, impulsive behaviors (180). Cingulate cortex has also been implicated especially in posterior regions in aggressive borderline patients (178), a finding consistent with the putative role of cingulate cortex in the control of affective evaluation of incoming stimuli (134).

Extensive connections between amygdala and prefrontal cortex have been described, suggesting an inhibitory influence of frontal cortex on the amygdala (181). Amygdectomy has been associated with reduced aggressive outbursts in patients with intractable aggression (182), but there have been no direct imaging studies to date reporting the relationship of amygdala activity and aggression.

Imaging Neurotransmitter Systems in Aggression

Serotonin

Ascending serotonergic neurons from the raphe nuclei project widely throughout the brain, including projections to dorsolateral prefrontal cortex and medial temporal lobe. Dorsal raphe-median forebrain bundle also directly innervates the amygdala, where dorsal raphe tracts outside the medial forebrain bundle project to parietotemporal cortex. Diffuse tracts extend from dorsal and medial raphe project to frontal lobe. Both 5-HT_{2A} and 5-HT_{1A} receptors are found in high concentrations in human prefrontal cortex, as are 5-HT transporter sites (183), and patients with localized frontotemporal contusions show significantly lower 5-HT metabolites in CSF than patients with diffuse cerebral contusions (184). Greater β -CIT binding to 5-HT transporters has also been reported in nonhuman primates with a higher β -CIT binding associated with greater aggressiveness (185). 5-HT_{2A} receptor number has been inversely related to aggressive behavior in posterior orbital frontal cortex and medial frontal cortex in the amygdala, whereas increased 5-HT_{2A} number in orbital frontal cortex, posterior temporal

cortex, and amygdala have been correlated with prosocial behavior in primates (186). Thus, serotonergic modulation of frontal and temporal cortical activity by 5-HT receptors, possibly of the 5-HT_{2A} type, may be particularly important in aggression.

The administration of FEN has been shown to increase cortical metabolism in frontal, temporal, and parietal cortex (187–189). In a study of depressed patients that included patients with a comorbid diagnosis of borderline personality disorder and a history of suicide attempts, activation of cortex including orbital and cingulate cortex was significantly blunted in the depressed patients, particularly in those who attempted suicide, compared with the control subjects. The depressed patients showed no significant changes in their glucose metabolic response to FEN compared with placebo, in contrast to the controls (189). In another study, intravenous administration of m-CPP in patients with alcoholism resulted in blunted glucose metabolic responses in right orbital frontal cortex, left anterolateral prefrontal cortex, posterior cingulate cortex, and thalamus compared with controls (190). In the first study directly comparing glucose metabolism after FEN and placebo in personality-disordered patients with impulsive aggression, neurologically normal subjects showed increased metabolism in orbital frontal and adjacent ventral medial frontal cortex as well as cingulate and inferior parietal cortex after FEN compared with placebo, whereas impulsive-aggressive patients appeared to show significant increases only in the inferior parietal lobe. Between-group comparisons demonstrated blunted responses of glucose metabolism in orbital frontal, ventral medial frontal, and cingulate cortex in the impulsive personality-disordered patients compared with the neurologically normal subjects. This study's results were replicated in a study of patients with borderline personality disorder (191), who displayed reduced regional uptake of fluorodeoxyglucose (relative to placebo) compared with control subjects in right medial and orbital frontal cortex, left middle and superior temporal gyri, left parietal lobe, and left caudate. In more recent pilot data from a study of patients with impulsive-aggressive personality disorders and controls that evaluated glucose metabolism after the administration of the 5-HT₂ agonist m-CPP, reduced metabolic responses were found in the aggressive patients, particularly in orbital frontal cortex, compared with controls (192), a finding inviting more direct assessment of components of serotonergic activity such as 5-HT_{2A} receptor number, transporter site number, and 5-HT_{2A} receptors.

In summary, imaging studies of the 5-HT system in impulsive-aggressive patients suggest reduced activation by ascending serotonergic projections on critical cortical inhibitory regions such as orbital frontal and related medial frontal cortex (137). Reduced serotonergic activation of these inhibitory regions mediated in part through 5-HT_{2A} receptors, but probably by other serotonergic mediators as well,

may have a disinhibiting effect on the generation of aggression by amygdala and related structures.

Dopamine

In animal studies, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced unilateral striatal dopamine deficiency in vervet monkeys was associated with increased frequency of aggressive behaviors toward other members of the group in the monkey colony (193). Greater heterogeneity was also found in striatal dopamine transporter density, as assessed by ¹²³I (β-CIT distribution) of impulsive violent offenders than controls (88), a finding possibly consistent with hypotheses that aggressive behavior is associated with increased dopaminergic transmission

PHARMACOLOGIC TREATMENT OF AGGRESSION

The rational clinical psychopharmacology of aggressive behavior began in the mid-1970s with the first placebo-controlled, double-blind, study of lithium carbonate in prison inmates (9). In this study, impulsive, but not premeditated (or other antisocial behavior), aggression was reduced to extremely low levels during a 3-month course of treatment with lithium carbonate; levels of aggression remained unchanged in inmates treated with placebo. Notably, all gains were lost within a month after a switch to placebo. An antiaggressive effect of lithium was replicated in subsequent studies including a blinded placebo-controlled trial in hospitalized aggressive children with conduct disorder (194) and a blinded, placebo-controlled trial of 42 mentally disabled patients (195). The mechanism of action for lithium in this regard is unknown, but it likely includes an enhancement of 5-HT function and a dampening of catecholaminergic function.

Other agents that may have antiaggressive efficacy include 5-HT-enhancing agents (i.e., 5-HT selective uptake inhibitors and 5-HT_{1A} agonists), anticonvulsants, typical and atypical neuroleptics, β-blockers, and antiandrogenic agents, among others.

The rationale to treat impulsive-aggressive patients with 5-HT-enhancing agents is rooted in the consistent findings of an inverse relationship between 5-HT and impulsive aggression, reviewed earlier. Since the early 1990s, numerous open and blinded, placebo-controlled, studies have documented the efficacy of these agents, specifically with respect to the 5-HT selective uptake inhibitors (SSUIs). Among the controlled trials, SSUIs have been shown to reduce verbal and nonassaultive physical aggression in personality-disordered patients selected for a history of recurrent, problematic, impulsive-aggressive behavior (82), to reduce nonassaultive physical aggression in patients with borderline personality disorder who were recruited from the commu-

nity (196), to reduce anger attacks in depressed patients undergoing a clinical trial for the treatment of aggression (197), and to reduce impulsive aggression in adults with autistic disorder (198).

Although enhancement of central 5-HT function by the SSUI is presumed to underlie the antiaggressive effect in these subjects, the one study that examined 5-HT function before treatment actually found a positive relationship between pretreatment 5-HT function, assessed by PRL[α -FEN] response, and improvement in aggression scores at end of trial (199). These data suggest that SSUIs may work best in patients whose postsynaptic 5-HT receptors are normal, or only moderately impaired, in function. If so, other agents that do not work primarily on presynaptic neurons may be necessary in patients with severe impairment of postsynaptic neurons. Such agents could include 5-HT receptor agonists or anticonvulsants, for example. Although evidence for the antiaggressive efficacy for 5-HT_{1A} agonists is limited, buspirone, at doses of 20 to 50 mg per day, was shown to reduce aggression in two studies of mentally retarded patients (200,201). More data, however, are available to support the antiaggressive efficacy of anticonvulsants.

Carbamazepine has been shown in blinded, placebo-controlled, trials to reduce episodes of behavioral dyscontrol markedly in borderline personality disorder (202) and to reduce agitation and aggression in nursing home patients with dementia (203), although not in children with conduct disorder (204). Phenytoin was also shown to reduce impulsive, but not premeditated, aggressive behavior in a blind, placebo-controlled, study of prison inmates (10). Divalproex sodium, another anticonvulsant, showed promise in open (205–208) and early blinded, placebo-controlled, trials (50) of personality-disordered patients and conduct-disordered adolescents. Open trials also suggested that this agent may reduce behavioral agitation and mood lability in elderly demented patients (209,210) and in patients with aggression and mood lability secondary to brain trauma (211).

The use of typical neuroleptics in the treatment of aggression has largely been aimed at sedating psychotic patients or to reduce the psychotic thinking that may trigger aggressive behavior. In addition, these agents have also been used in nonpsychotic patients to treat aggression and agitation, with mixed results. Thioridazine was reported to diminish impulsive behavior in an open-label study of patients with borderline personality disorder (212), and low-dose haloperidol was reported to reduce hostility and impulsivity compared with amitriptyline and placebo in patients with borderline or schizotypal personality disorder (213). These findings were not reproduced in two other double-blind, placebo-controlled studies of borderline and schizotypal personality-disordered patients treated with thiothixine (214) or trifluoperazine (202). Treatment with the newer, atypical neuroleptics may prove to be more effective than that with the earlier typical antipsychotic agents. Antagonism of 5-HT₂

receptors appears to decrease aggression in animal models, and this effect may explain the ability of newer antipsychotic agents (which, unlike the older medications, block 5-HT₂ receptors) to produce a reduction in aggression and agitation independent of effects on psychotic symptoms (215,216). Studies suggest that the overall frequency of assaults, use of seclusion, mechanical restraint, and chemical restraint in patients with schizophrenia who are treated with clozapine are reduced over traditional neuroleptics (217). In a double-blind study, risperidone had a greater selective effect on hostility than haloperidol or placebo in patients with schizophrenia (218). Finally, an open-label study of olanzapine in 11 patients with borderline personality disorder reported significant reductions in anger (219), a finding suggesting that the potential benefit of atypical neuroleptics in treating aggression may extend to nonpsychotic patients as well.

Given the potential facilitatory role of the central noradrenergic system, agents that dampen the function of this system could be expected to have antiaggressive efficacy. Notably, β -noradrenergic blockers have been found effective in reducing aggressive behavior in patients with organic brain syndromes or chronic psychosis. Propranolol has been shown to reduce aggressive behavior in patients with traumatic brain injuries (220,221) or in patients with dementia (222). Both propranolol and nadolol have been shown to be effective in reducing aggressive behavior in chronic psychiatric inpatients, independent of psychotic symptoms (223,224). The use of these medications is limited, however, by hypotension and bradycardia, which can be side effects at the higher doses that are often used in these cases.

The use of antiandrogens in the treatment of some types of aggression, specifically sexual aggression, has undergone limited study. Antiandrogens such as medroxyprogesterone acetate and cyproterone acetate appear to lower both deviant and nondeviant sexual drive and activity in men with paraphilias, and this behavioral improvement is associated with decreases in testosterone level (225). However, although no data support the routine use of antiandrogens in nonsexual aggressive behavior, patients with sexual aggression do appear to respond, in some cases, to antiandrogen treatment.

SUMMARY

The study of the pathophysiology and pharmacologic treatment of aggression has undergone much progress since the 1980s. Extensive evidence supports an important role for central 5-HT function in the regulation impulsive aggressive behavior. In addition, more is known about potential regulatory roles of other central neurotransmitters and modulators, as well as their possible interaction with 5-HT. This knowledge has led to the development of a more rational approach to the psychopharmacologic treatment of impulsive aggression (e.g., treatment with 5-HT uptake inhibitors). Recent work examining the relationship of DNA poly-

morphisms and aggression and work examining the relationship between brain structure and function in aggressive persons could yield critical data that will bring our understanding of the pathophysiology of aggression to a new level.

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