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Neurobiological Basis of Reactive Aggression: A Review

Review Article

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Abstract

Reactive aggression is a response to salient threats that may have evolved as a strategy for survival. The likelihood of its outburst is mediated by several factors including the activity of serotonin and other neurotransmitters that regulate reactive aggression through the corticolimbic circuit. Specifically, this circuit is modulated by monoamine oxidase A (MAOA) such that low levels of activity incline an animal to impulsive behavior. Evidence also indicates that aggressive behavior is determined through interactions between genes and the environment. Further studies are expected for appropriate treatment.

Keywords: Reactive Aggression; Serotonin; Monoamine Oxidase A (MAOA); Gene-Environment Interaction.

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Introduction

Aggression is defined as any form of behavior that is intended to injure someone physically or psychologically [1]. While aggression was seen as a homogeneous category of behavior until the 1960s, evidence has since suggested that it can be divided into two subtypes: proactive and reactive [2, 3].

Proactive (instrumental, predatory, cold-blooded, or premeditated) aggression is a controlled attack designed to achieve a goal, such as acquiring money or social dominance over others. Individuals engaged in proactive aggression are consciously aware of the benefits gained from using violence [4]. In contrast, reactive (impulsive, affective, hostile, or hot-blooded) aggression is a physical act committed with little consideration of its consequences or harm to others, and is often accompanied by feelings of remorse or thought confusion [5]. Assessment is performed through measurements that have been developed to quantify the magnitude of each form of aggression [6, 7].

Support for categorizing aggression this way is not universal. Some believe that such a dichotomy overlooks multifaceted motivations that drive human violence, and others point out that most children who frequently use one form of aggression also frequently use the other [8]. However, distinguishing between reactive and proactive aggression has several advantages. In child inpatients, future antisocial behavior is more strongly related to proactive aggression than to reactive aggression [9]. Additionally, increases in proactive, but not reactive, aggressive behavior in young teenagers partially predicts later delinquency within a few years [10]. Furthermore, when proactive aggression is observed in adolescent boys, it also predicts psychopathic characteristics in adulthood. In contrast, reactive aggression in adolescent boys is specifically associated with negative emotions such as anxiety [11]. A meta-analysis has shown that internalizing problems [12], suicidal ideation, and suicidal behavior [13] are more strongly related to reactive aggression than to proactive aggression. These findings support the idea that aggressive behaviors exist in two fundamentally different forms, and as a corollary, that effective interventions for reactive aggression should be different from those for proactive aggression.

Reactive Aggression As A Dysfunction

The neural circuitry governing outbursts of reactive aggression has been investigated using mammalian species [14]. Based on the results, reactive aggression is now understood to be a part of a system that responds to acute threats. Low levels of threat trigger freezing, whereas high levels lead to escape-related behavior. However, a high-level threat without any possibility of flight will elicit reactive aggression [15, 16]. Thus, reactive aggression can be an alternative adaptive response to a threatening stimulus [17].

While reactive aggression can be natural and beneficial in some situations, it can be a dysfunction when frequently exhibited in inappropriate situations. Several studies have tried to explain this phenomenon as an inability to inhibit violent impulses when frustrated. This hypothesis is consistent with findings that subjects

displaying reactive aggression also show executive dysfunctions such as exaggerated perception of hostility from others [18], impaired somatic marker systems [19], and social response reversal [20]. Furthermore, patients who displayed antisocial behavior showed impaired performance on measures of executive functioning [21, 22]. Similar dysfunctions are also observed in psychopathic patients who also are at high risk for both reactive and proactive aggression [23]. In short, reactive aggression likely results from both excessive responses to stimuli and deficits in correctly interpreting stimuli and making decisions based on them.

Neuronal Circuit For Reactive Aggression

Animal studies have indicated that responses to imminent threats are mediated by a system that runs from the amygdala (AMG) downward, largely via the stria terminalis to the medial hypothalamus (MH), and from there to the dorsal half of the periaqueductal gray (PAG) [14, 23 ,24]. This AMG-MH-PAG hierarchical pathway is also found in humans. One theory is that the AMG acts as a mediator that can increase or decrease the responsiveness of the sub-cortical systems that respond to threats. Thus, lesions to the AMG can modulate the risk of reactive aggression [25]. However, studying this pathway directly is still challenging, partially because of technical difficulties in visualizing neural activity in sub-cortical regions of the human brain [25].

Ever since the well-known case in which Phineas Gage showed a remarkable personality change after severe frontal lobe injury, it has been hypothesized that dysfunction in the frontal lobe might contribute to aggressive behavior [26, 27]. Indeed, several lines of evidence indicate that frontal cortex is involved in the modulation of the AMG-MH-PAG pathway [14, 28, 29]. Animal studies show that the AMG and medial prefrontal cortex are connected by a negative regulatory circuit [30, 31]. Disrupting this circuit causes deficits in emotion regulation,which results in impulsive behaviors [23]. Moreover, neuroimaging studies using positron emission tomography indicate frontal lobe dysfunction in patients displaying reactive aggression. Lower glucose metabolic values were observed in medial temporal and prefrontal cortices of violent patients than of control subjects [32]. Affective murderers also showed decreased activity in bilateral prefrontal cortices, but increased activity in right subcortical areas [4]. It is noteworthy that the same findings were not observed in people who exhibited predominantly proactive aggression. Dysfunctions in the ventromedial prefrontal cortex [29] and the orbital frontal cortex (OFC) [20] were shown to be associated with a higher risk for reactive aggression but not proactive aggression [16]. In contrast, the dorsolateral prefrontal cortex does not seem to have a prominent role in reactive aggression [25], although room for argument still exists [33].

The OFC modulates reactive aggression via the AMG-MH-PAG pathway through at least two separate processes. First, it computes expected rewards that accompany actions. If a reward is absent or less than expected, some OFC neurons increase their activity and excite sub-cortical systems, which may lead to reactive aggression [34]. Second, the OFC is involved in social response reversal [20]. Patients with OFC deficits have difficulty suspending ongoing behavior even though they recognize that other people are expressing anger or unfriendly emotions [20, 35].

Furthermore, the AMG and OFC are tightly connected by several pathways that are functionally linked with each other [30, 36]. Patients with intermittent explosive disorder exhibited exaggerated AMG reactivity and diminished OFC activity, but did not show AMG-OFC coupling, suggesting that their disconnection from each other caused difficulty in modulating aggression in social settings [37].

Biochemicals In Reactive Aggression

The risk of reactive aggression is higher in clinical conditions such as posttraumatic stress disorder [38, 39], anxiety disorder [40], childhood bipolar disorder [41], and impulse-control disorder. Some have hypothesized that serotonin is involved in modulating reactive aggression because abnormal neurotransmitter levels is a common root of these disorders [42].

Serotonin is a monoamine neurotransmitter derived from tryptophan that has an important role in the central nervous system. Lowered concentrations of 5-hydroxyindoleacetic (5-HT) acid, the main metabolite of serotonin, were observed in impulsively violent offenders, but not in those who were proactively violent [43]. In healthy volunteers, the effects of tryptophan depletion included an increase in aggression, which suggests that aggression is one consequence of impeding synthesis of serotonin in the brain [44]. In contrast, administering the selective serotonin reuptake inhibitor paroxetine resulted in a reduction of hostility in a double-blind trial [45]. These results are consistent with clinical observations that agitated patients had an estimated shortage of serotonin [38, 39, 40]. However, the correlation between serotonin and violence is not quite simple. Several subtypes of serotonin receptors exist in multiple regions of the brain, often with differing functions. For example, activation of 5-HT1A and 5-HT1B receptors in mesocorticolimbic areas triggers a reduction in aggressive behaviors, whereas activating them in the medial prefrontal cortex or septal area can cause aggression [46].

Some hormones are also involved in the regulation of aggressive behavior. Testosterone level has repeatedly been shown to be associated with reactive aggression in both men and women [47-49]. Conversely, low levels of cortisol have been observed in subjects with violently aggressive, antisocial tendencies [50, 51]. These findings suggest that reactive aggression is affected by an imbalance between testosterone and cortisol at the subcortical level [17]. In addition, the so-called social neuropeptides vasopressin and oxytocin are also likely to play a role in mediating impulsiveness [52].

The Maoa Gene And Reactive Aggression

Genetic factors have also been implicated in susceptibility to aggressive behavior [53]. Brunner's landmark work described a large group of related Dutch in which many people (all males) were affected by a syndrome consisting of borderline mental retardation and impulsive aggression. The work proved that a specific genetic variant was involved in the aggressive behavior, and the syndrome is now called Brunner syndrome [54]. The common factor linking all people with the syndrome was a total lack of MAOA activity. In each of five males, a point mutation was identified in the eighth exon of the MAOA structural gene. These findings had a great impact on sequential genetic research.

MAO catalyzes the oxidative deamination of biogenic amines.

The two isoforms (MAOA and MAOB) are localized to the outer mitochondrial membrane in the presynaptic terminal of monoamine projection neurons and in astrocytes, where they are positioned to regulate the amount of intracellular substrate available for release and the degree of monoamine inactivation [53]. While MAOB primarily metabolized dopamine, MAOA also metabolizes serotonin and norepinephrine. Therefore, genetic variation in the MAOA gene may cause disruption at serotonergic synapses. Although Brunner syndrome is rare, many common polymorphic variants have been identified in the MAOA gene region. Among them, a variable number of tandem repeat (VNTR) polymorphisms located in the promoter region of the gene have been the most widely studied. The MAOA upstream VNTR comprises a 30-bp sequence that is repeated 2, 3, 3.5, 4, or 5 times [55]. Higher expression linked to 3.5 or 4 repeats is referred to as MAOA-H, and is related to normal enzymatic activity, while 3 repeats or less are referred to as MAOA-L and is associated with reduced MAOA activity [56].

A wealth of evidence in animal research suggests that MAOA is an important biological regulator of aggressive behavior. MAOA knockout mice exhibited frequent reactive aggression [57]. Serotonin concentration was increased up to nine times in the brains of isolated transgenic mice in which transgene integration caused a deletion of the gene encoding MAOA [58]. Additionally, MAOA knockout mice lack the characteristic barrel-like clustering of layer IV neurons in the primary somatosensory cortex [59]. It is likely that some change in serotonin function occurs in the MAOA gene-deficient mice [46]. Intriguingly, with early administration of a serotonin-synthesis inhibitor, the mice restored the formation [59]. This result suggests that the impact of genetic risk might be mitigated during critical periods in youth and early adolescence [53]. This lends credence to the importance of gene-environment interactions in modulating aggressive behavior, and shows the potential benefits of early intervention for at-risk subjects.

The MAOA-L gene has been linked to aggressive behavior in humans [60]. A meta-analysis showed that MAOA-L was significantly associated with antisocial behaviors [61]. The importance of MAOA genetic variation in determining aggressive behavior is consistent with the fact that most violent criminals are male. Because the MAOA gene is linked to the X chromosome, men only need one copy of the MAOA-L gene to be affected, while women are affected only if both alleles contain the abnormal MAOA gene [60]. The relationship between MAOA gene variations and aggression in women is still controversial [62].

Few studies investigating the MAOA gene definitively distinguish reactive aggression from proactive aggression [63]. Evidence suggests MAOA-L is associated with aggressive reactions in highly provocative situations [63, 64]. In contrast, no evidence decisively indicates that proactive aggression is dominant in subjects with MAOA-L. MAOA gene variation may therefore be associated with impulsivity rather than antisocial behavior itself.

Supporting evidence comes from investigating what happens in brains of male carriers of the MAOA-L gene. The subjects showed a pattern of enhanced AMG activation and lower cortical volume [65, 66]. Dorsal anterior cingulate cortex, which is associated with rejection-related distress, is activated in MAOA-L individuals [67, 68]. It is highly likely that this imbalance within the corticolimbic circuit is the cause of disrupted emotion regulation. Recently, the interaction between the MAOA gene and the environment has become a hot topic. Maltreated children with an MAOA-L genotype were more likely to develop antisocial behavior [69] than those who were not maltreated. This finding was replicated by several studies [70] and substantiated by two meta-analyses [71, 72]. Successful visualization of altered brain structure and function in maltreated children with MAOA-L should be the next step in studying this issue, as well as assessing interventions that might reduce their risk of developing aggressive tendencies [67].

Conclusion

Reactive aggression has been attracting attention of many professionals in not only forensic science and criminal justice, but behavioral biology. Among recent studies, the results regarding the MAOA gene and gene-environment relationship greatlycontributed to the deep understanding of this antisocial, but originally functional phenomenon. In the near future, it is expected to apply these findings to the treatment setting. For example, children identified as high-risk may be educationally intervened in the early stage so that subsequent aggressive behaviors would be prevented. On the other hand, the clarification of the biological basis of reactive aggression is possible to visualize the effect of behavioral therapy, leading to further development of the psychological interventional technique. Collaboration of professionals with several backgrounds can reduce the victims of violence through utilizing the scientific research.

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