Primate Models to Understand Human Aggression

Ned H. Kalin, M.D.

Although primate studies have yielded models of aggressive behaviors that clinicians encounter in their clinical practice, further studies need to be performed to establish insights into the biological mechanisms that underlie these behaviors. Nonetheless, studies of aggression in rhesus monkeys point to 2 chief categories of aggression—defensive and offensive—and suggest differing underlying neural mechanisms for these types of behaviors. Defensive aggression is fear motivated and related to extreme asymmetric right frontal activity in the brain and high plasma cortisol concentrations. On the other hand, offensive and/or impulsive aggression is associated with low serotonergic activity in the central nervous system, high levels of testosterone, and lower levels of cortisol. Moreover, all forms of aggression in rhesus monkeys appear to be modulated by environmental factors, and marked disruptions to the mother-infant relationship likely confer increased risk.

(J Clin Psychiatry 1999;60[suppl 15]:29–32)

The naturalistic and laboratory observation of primates allows researchers to obtain models of phenomena that are encountered clinically. Rhesus monkeys (*Macaca mulatta*) in particular show behavioral and emotional responses that resemble those in humans.[1] In addition to our laboratory studies, my colleagues and I have studied free-ranging rhesus monkeys for several years on a small island off the coast of Puerto Rico to gain insight into fearful, affiliative, and aggressive behaviors.

A greater or lesser tendency toward engaging in aggressive behaviors can be understood in the context of an individual's temperament. Research suggests that temperament, once considered simply a stable emotional or behavioral style, is actually a conglomerate of stable behavioral, emotional, and physiological characteristics.[1] Studies with rhesus monkeys have afforded researchers insight into how these characteristics interact and what mechanisms underlie individual differences in temperament.

A goal of the primate studies is to determine how biological mechanisms and the physical environment shape aggressive behavior. In addition, it will be useful to understand how aggressive behavior is related to other emotional states and affective disorders. The studies suggest that aggression can fall into 3 categories—defensive (fear-motivated), offensive (frequently impulsive and seemingly unprovoked), and self-injurious—and that these different types of aggression have different neural mechanisms. These studies also suggest that environmental factors, especially those involving early rearing, are strong determinants of the tendency to be aggressive. Self-injurious aggression also occurs in primates but has been little studied; therefore, this discussion focuses on defensive and offensive aggression.

DEFENSIVE AGGRESSION

Defensive aggression is one of several fear-related behavioral responses. Although protective responses are an important component of human behavior, extreme defensiveness may be linked to psychopathology.[2] Thus, it is important to understand both the mechanisms that underlie the expression of defensive behaviors and the factors that mediate the development of individual differences in defensive responding.

Defensive behaviors occur in all species, not just humans. Thus, studies of defensiveness in general and defensive aggression in particular in rhesus monkeys have been undertaken to provide insight into these behaviors and the environmental and biological factors that influence them.

Environmental Factors

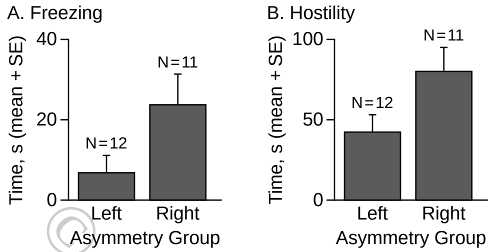
When an individual experiences a threat, defensive aggression is one of several adaptive responses. In the laboratory, my colleagues and I developed a paradigm to elicit different defensive responses including defensive aggression. The defensive behavior of rhesus monkeys, for example, differs depending on how the behavior is provoked. For instance, an infant rhesus monkey isolated from its mother will emit coo vocalizations to signal its location to its mother for retrieval. The same infant will likely freeze (keep perfectly still) when it detects the pres-

From the Department of Psychiatry, University of Wisconsin, Madison.

Presented at the closed symposium "Phenomenology and Treatment of Aggression Across Psychiatric Illnesses," held August 31, 1998, Chicago, Illinois, and sponsored by an unrestricted educational grant from Abbott Laboratories.

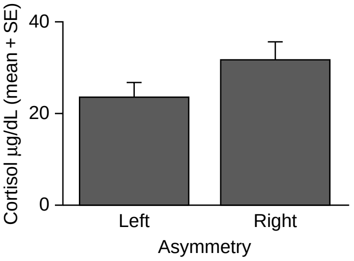
Reprint requests to: Ned H. Kalin, M.D., Department of Psychiatry, University of Wisconsin, 6001 Research Park Boulevard, Madison, WI 53719-1179.

Figure 1. Freezing Behavior and Hostility in Rhesus Monkeys With Extreme Left Frontal Brain Activity Versus Those With Extreme Right Frontal Brain Activity[a]



[a]From reference 1, with permission.

Figure 2. Basal Cortisol Levels In Rhesus Monkeys With Extreme Left Frontal Brain Activity Versus Those With Extreme Right Frontal Brain Activity[a]



[a]From reference 1, with permission.

ence of a potential environmental threat. In our paradigm, a human enters the room and never makes eye contact with the infant, which responds by freezing. Cooing and freezing may be modulated by different underlying mechanisms; research has shown a lack of relationship between an infant rhesus monkey's tendency to coo when isolated from its mother and to freeze when a human enters its presence without making eye contact.[2] In addition, opiate systems appear to regulate cooing, whereas benzodiazepine systems have a more prominent role in regulating threat-related behaviors.

Aggressive defensive responses are seen in infant rhesus monkeys when a human who previously had made no eye contact with a monkey begins to stare at it. Such staring often leads a rhesus monkey to bark (vocalize aggressively) and make threatening gestures, such as dropping its lower jaw or exposing its canine teeth. While defensive responses are apparent very early in life, it is not until about 3 months of age when infant monkeys are able to adaptively regulate these responses.[3]

Biological Factors

Even though human aggressive behavior can be modeled in primates, these models have thus far provided only limited insight into the biological mechanisms that underlie these behaviors. Research in rhesus monkeys has shown, however, that fear-related responses, including aggression, are associated with increased electrical activity in the right frontal region of the brain and that rhesus monkeys with extreme right frontal activity have higher plasma cortisol concentrations.

Right frontal activity and fear-related behaviors. Studies have demonstrated that stable differences in the degree of relative right and left frontal brain electrical activity, as shown by analysis of electroencephalograms (EEGs), exist in humans and that these differences may be associated with different temperaments. Specifically, extreme right frontal activity may be a marker for fear-related behavior.[1] For instance, Davidson et al.[4] found that infants who cried upon separation from their mothers had greater amounts of right frontal brain activity during a baseline condition than did infants who did not cry upon maternal separation.

Rhesus monkeys also show individual differences in relative amounts of left and right frontal activity that correspond to differences in behavior. My colleagues and I[1] found that rhesus monkeys with extreme asymmetrical right frontal brain electrical activity showed more freezing and aggressive barking than did monkeys with extreme asymmetrical left frontal brain activity (Figure 1). However, although greater right frontal brain activity in rhesus monkeys is associated with increases in defensive aggressive behavior, little is known about the mechanisms that underlie asymmetries in frontal brain activity. Other studies from our laboratory show that the antianxiety agent diazepam shifts activity from right to left frontal regions.[5]

Right frontal activity and cortisol concentrations. Basal levels of cortisol have been found to be higher in rhesus monkeys who display increased fear-related behaviors like freezing. My colleagues and I[1] found that monkeys with greater right frontal brain activity also tended to have higher cortisol concentrations (Figure 2). The nature of the link between extreme right frontal asymmetry and cortisol levels has not been determined.

OFFENSIVE AGGRESSION

Not all aggressive behavior is in direct response to external stimuli. In a colony of free-ranging rhesus monkeys, one can observe a threatening monkey attacking another unsuspecting monkey. Such an attack is a form of offensive aggression. Sometimes, this aggressive behavior is impulsive and seemingly unprovoked. On the other hand, offensive aggression can be mild and take the form of displacement (one monkey causing another monkey to leave a specific location just by moving toward it) or threats (open-mouth expressions, staring); it can also involve more intense expression, including chasing and even slapping, hitting, and biting.[6]

Primate studies have, so far, yielded only limited insight into the biological mechanisms that underlie offensive aggressive behaviors. In addition, problems may exist in

Figure 3. Relationship of Plasma Testosterone Levels to Offensive Aggression in Adolescent Male Rhesus Monkeys

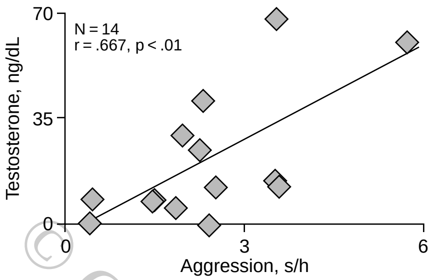
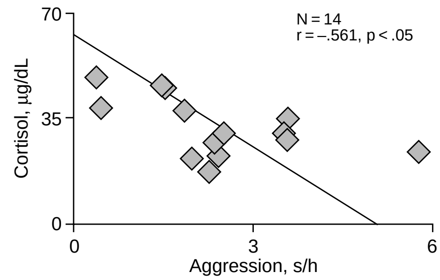


Figure 4. Relationship of Cortisol Levels to Offensive Aggression in Adolescent Male Rhesus Monkeys



trying to generalize the offensive aggression observed in primates to human behavior. Rhesus monkeys are known to be particularly aggressive. In rhesus monkeys, offensive aggression sometimes appears to be part of the normal fabric of life. Higley et al.[7] suggest that competitive aggression might serve functional, even positive purposes in rhesus monkeys, especially as it relates to social dominance.

Environmental Factors

Researchers have observed that a higher incidence of offensive aggressive behavior is found within certain physical contexts. Male-on-male aggressive attacks, for example, become more frequent during the mating season. Mehlman et al.[8] reported significant increases in both low- and high-intensity aggression, as well as in grooming behavior and heterosexual mounting, during the mating season in free-ranging rhesus monkeys.

Dramatic disruptions of early attachment in primates, especially during the first several months of an infant's life, are a risk factor in developing the tendency to be inappropriately aggressive in later life. In 1964, Seay et al.[9] reported that "motherless mothers"—female rhesus monkeys separated from their mothers at birth and isolated from other monkeys for 18 months—lacked appropriate childrearing skills. These motherless mothers displayed more aggression as well as indifference toward their infants than did normally raised monkeys. This inadequate and abusive parenting style likely contributes to developmental problems in offspring associated with difficulties in regulating affect.

Biological Factors

Presently, many of the biological mechanisms that underlie offensive aggression are not fully understood. Nonetheless, primate studies suggest several possible biological explanations for this sort of aggressive behavior: decreased serotonin and increased testosterone have been shown to be associated with offensive aggression.

Human as well as animal studies have shown that impulsive, violent aggression is often observed in individuals with low central nervous system (CNS) serotonergic activity as determined by cerebrospinal fluid (CSF) concentrations of the major metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA). Higley et al.[10] found this association between low CSF levels of 5-HIAA and offensive aggression in free-ranging adolescent rhesus monkeys on Morgan Island, off the coast of South Carolina. In a subsequent study of adolescent monkeys on Morgan Island, Mehlman et al.[6] found low CSF concentrations of 5-HIAA to be associated specifically with impulsive and violent (as opposed to low-intensity) aggressive behavior. Low 5-HIAA concentrations were also recorded in monkeys who exhibited hazardous, risky behavior, i.e., leaping long distances from tree to tree, leading Mehlman and colleagues to suggest that impaired impulse control lies behind the offensive aggression of monkeys with low CSF concentrations of 5-HIAA.

Data suggest that different types of offensive aggression are associated with different biochemical systems. Recent research on offensive aggression in rhesus monkeys has begun to distinguish between 2 types of offensive aggression: impulsive aggression, resulting from loss of impulse control and associated with low CSF 5-HIAA concentrations, and assertive, competitive (and less violent) aggression, associated with high levels of CSF free testosterone.[7] Furthermore, serotonin and testosterone may exert separate, independent influences on aggressive behavior.

My colleagues and I also found, in a small sample of adolescent male rhesus monkeys in Cayo, Santiago (N = 14), a correlation between plasma testosterone levels and offensive aggressive behavior (Figure 3). In addition, an inverse relationship between plasma cortisol levels and offensive aggressive behavior was found in these monkeys (N.H.K., unpublished data, 1998) (Figure 4).

PHARMACOLOGIC APPROACHES TO AGGRESSION

Insight into the possible neurobiological explanations for defensive aggressive behaviors has led to research on potential pharmacologic management of these behaviors. Individual differences in freezing and barking, as well as in asymmetrical frontal brain activity, appear to be related to benzodiazepine systems[11]; not surprisingly, benzodiazepines have been shown to be effective in reducing hostility in primates. My colleagues and I studied the effects of the benzodiazepines alprazolam[12] and diazepam[5] on fear-related measures in infant rhesus monkeys. In general, the benzodiazepines reduced freezing and barking behaviors in the infants. β-Carboline, an inverse benzodiazepine agonist, increases these defensive responses.[13] Venlafaxine, a serotonergic/noradrenergic antidepressant, administered chronically also produced reductions in barking and hostility in rhesus monkeys (N.H.K., unpublished data, 1998). Other pharmacologic treatments, however, have not shown the same effectiveness. Although opiates[14] have a prominent role in mediating separation-induced coo vocalizations, they do not reduce defensive hostility in monkeys.

CONCLUSION

Primate models have thus far provided insight into the biological correlates of aggression. Further study is needed not only of the nature of the biological factors that mediate aggressive behaviors but also on the relationship of these factors to rearing and other environmental stimuli that can predispose to aggression. Studies with rhesus monkeys have furthered the supposition that different biological mechanisms underlie offensive and defensive aggression. Future studies are needed to further elucidate underlying mechanisms with the hope that this neurobiological understanding will suggest novel treatment approaches to pathologic human aggression.

Drug names: alprazolam (Xanax and others), diazepam (Valium and others), venlafaxine (Effexor).

REFERENCES

1. Kalin NH, Larson C, Shelton SE. Asymmetric frontal brain activity, cortisol, and behavior associated with fearful temperament in rhesus monkeys. Behav Neurosci 1998;112:286–292
2. Kalin NH, Shelton SE. Ontogeny and stability of separation and threat-induced defensive behaviors in rhesus monkeys during the first year of life. Am J Primatol 1998;44:125–135
3. Kalin NH, Shelton SE, Takahashi LK. Defensive behaviors in infant rhesus monkeys: ontogeny and context-dependent selective expression. Child Dev 1991;62:1175–1183
4. Davidson RJ, Fox NA. Frontal brain asymmetry predicts infants' response to maternal separation. J Abnorm Psychol 1989;98:127–131
5. Davidson RJ, Kalin NH, Shelton SE. Lateralized effects of diazepam on frontal brain electrical asymmetries in rhesus monkeys. Biol Psychiatry 1992;32:438–451
6. Mehlman PT, Higley JD, Faucher I, et al. Low CSF 5-HIAA concentrations and severe aggression and impaired impulse control in nonhuman primates. Am J Psychiatry 1994;151:1485–1491
7. Higley JD, Mehlman PT, Poland RE, et al. CSF testosterone and 5-HIAA correlate with different types of aggressive behaviors. Biol Psychiatry 1996;40:1067–1082
8. Mehlman PT, Higley JD, Fernald BJ, et al. CSF 5-HIAA, testosterone, and sociosexual behaviors in free-ranging male rhesus macaques in the mating season. Psychiatry Res 1997;72:89–102
9. Seay B, Alexander BK, Harlow HF. Maternal behavior of socially deprived rhesus monkeys. J Abnorm Soc Psychol 1964;69:345–354
10. Higley JD, Mehlman PT, Taub DM, et al. Cerebrospinal fluid monoamine and adrenal correlates of aggression in free-ranging rhesus monkeys. Arch Gen Psychiatry 1992;49:436–441
11. Kalin NH, Shelton SE. Defensive behaviors in infant rhesus monkeys: environmental cues and neurochemical regulation. Science 1989;243:1718–1721
12. Kalin NH, Shelton SE, Turner JG. Effects of alprazolam on fear-related behavioral, hormonal, and catecholamine responses in infant rhesus monkeys. Life Sci 1991;49:2031–2044
13. Kalin NH, Shelton SE, Turner JG. Effects of beta-carboline on fear-related behavioral and neurohormonal responses in infant rhesus monkeys. Biol Psychiatry 1992;31:1008–1019
14. Kalin NH, Shelton SE. Effects of clonidine and propranolol on separation-induced distress in infant rhesus monkeys. Brain Res 1988;470:289–295

DISCLOSURE OF OFF-LABEL USAGE

The author of this article has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented herein that is outside Food and Drug Administration–approved labeling.