ANIMAL MODELS OF AGGRESSION

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Over the past several decades, various animal models have been used extensively to characterize the activity of various drugs and drug classes, and from these results, to anticipate their activity in humans. However, the value of animal models that purport to predict the potential therapeutic value of new drugs is often accepted with considerable reservation and, when the therapeutic objective involves psychiatric disease, is perhaps viewed with outright suspicion.

In general, the animal models most readily accepted as a basis for predicting responses in humans are those that are homologous, that is, those in which both the condition being observed and its origin are similar to those in humans. Examples may include suppression of bacterial infections by antibiotics or hypertension in monkeys. Few, if any, models of psychiatric dysfunction, however, can be considered homologous, if only because the origin of the psychiatric condition is unknown.

In the absence of homologous models, isomorphic models (in which the observed condition is apparently similar even if the cause is not) may be fairly rapidly accepted. An example may be amphetamine-induced psychosis as a putative model for schizophrenia. Finally, there are many models in which neither the condition nor the origin can be clearly linked with the disease being modeled, but in which there is empiric evidence of some predictive validity either for the disease or some aspect of its therapy. In psychopharmacology, the evidence is usually the discovery that agents with known therapeutic activity in humans consistently correlate with some response in an animal model. It can be argued that before animal models are developed for any disorder, the essential features of the disorder should be known. Here researchers run into trouble because the essential features of many disorders in humans are unclear. Pathologic aggression is not a DSM-IV disorder for which criteria are set for determining what is normal or abnormal

(1). Moreover, there is little understanding of the biological factors underlying pathologic aggression in humans, so it is difficult to formulate a rational research program. A discussion of the characteristics of pathologic aggression is needed for the development of animal models of this disorder.

Despite the drawbacks adherent to aggression research, there is an increasing knowledge of the effects of psychoactive drugs on aggressive behavior, both in animals and in patients. Thus, two roads are emerging: one studying the fundamental causes of aggression and dysfunctions, the other studying the modification of behavior by pharmacologic interventions.

CLASSIFICATION OF AGGRESSION

Despite many attempts, a generally acceptable definition of *aggression,* particularly as it applies to individual human behavior, has not yet emerged. This failure arises in part from the following: (a) the varying theoretic or philosophic persuasions of those offering definitions; (b) the inherent difficulty in capturing the essence of a multifaceted behavior; and (c) the attempt to include within the definitions elements of motivation that cannot readily be observed or elicited. However, a generally acceptable working definition from the perspective of animal research is somewhat easier to obtain and could read "any overt behavior that produces aversive or noxious stimuli or harm to another organism." In this definition, the "motivation" of the behavior is not an essential element, but it may be deduced directly from the stimuli that elicit the behavior and from the overt behavior itself. Different types of animal aggression can be distinguished based on the environmental situations eliciting those behaviors. Moyer was the first to describe such a classification (2), later followed by alternative classifications (3).

All these classifications have their own inherent problems, such as to link the aggression to connotations of offensive and defensive aggression, using the ethology-derived term *agonistic behavior* as an important distinction to classify aggression models.

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The distinction of aggression into offensive and defensive models is universal (4), is functional, and seems to be paralleled in brain mechanisms involved in the behavior. *Offensive behavior* is characterized by the initiative of the aggressor and intended damage to the opponent (5,6). In contrast, *defensive behavior* lacks active approach (initiative), and the defensive animal (6) inflicts no intentional damage. *Predatory aggression* represents separate classification of aggression that seems to be primarily driven by appetite mechanisms and apparently has a distinct brain system involved.

Neither in humans nor in animals is agonistic behavior pathologic. In the framework of evolutionary theory, these behaviors are understood to encourage survival of the fittest, to disperse populations, to aid adaptation to threatening environments, and generally to improve the probability of individual and species survival. In humans, agonistic behavior is considered acceptable or not based on certain predetermined rules. Although "aggressive" behavior is associated with certain somatic and psychiatric disease states, and such behavior may be considered in establishing a diagnosis, there is no diagnostic category of "aggressive disease" or "offensive syndrome" *per se.* In the clinical literature, such behaviors may be referred to as "violent," "hostile," "agitated," "impulsive," or "pathologic aggressive." Although animal models of aggression try to simulate the human conditions as much as possible, this is difficult because we know so little about the underlying mechanisms of aggression in disease states. By studying several paradigms in animals with the expectation that they have at least some predictive validity for human disorders with pathologic aggression, we hope (a) to develop new drugs for treatment of patients and (b) to gain insights into the underlying mechanisms resulting in the disorder. With the emergence of molecular genetic technologies, we increasingly understand the roles of certain genes in aggression, which may ultimately lead to development of novel treatment strategies for pathologic aggression.

Instead of being exhaustive, the present chapter focuses on some selected animal models of aggression with some bearing for human pathologic conditions. Specific examples of drug effects and underlying mechanisms are also discussed.

MODELS OF OFFENSIVE BEHAVIORS

Several paradigms are used to study offensive aggression, such as isolation-induced offensive behavior (mouse), resident-intruder offensive behavior (rat/mouse/hamster), offensive behavior after electrical stimulation of the brain (rat), maternal offensive behavior (mouse/rat), offensive play-fighting among juvenile rats, and offensive behavior among piglets.

Some of these models are described, and some relevant pharmacology is outlined (benzodiazepines, neuroleptics, psychostimulants, antidepressants, serenics). The putative face, construct, and predictive validity are discussed. In addition, several models providing insights into novel neural mechanisms of aggression as well as interactions between genes and early environment are presented. Moreover, new data are introduced regarding mutant mice showing phenotypic changes in aggression, such as the serotonin ($5\text{-}HT_{1B}$) and nitric oxide synthase (NOS) knockouts. The information coming from these new genetic models can be of help in understanding possible causes of human pathologic aggression.

Isolation-Induced Offensive Behavior

A manipulation often used to induce aggression is isolation of male animals, typically mice, for several weeks. Many such isolated animals, on encountering another male, will reliably exhibit attack behavior (7). The effect of isolation on aggressive behavior is strain dependent (8). This isolation-induced aggression paradigm in mice is one of the most frequently used aggression models in behavioral pharmacology (9), and it has engendered an extensive pharmacology mainly described in median effective dose (ED_{50}) values. Because there are many ways to affect aggression in a nonspecific way (sedation, motor disturbances, psychostimulation) an ED_{50} value is not at all helpful in delineating how and why drugs reduce aggression.

Because isolated male mice show a full repertoire of agonistic behaviors (10), ethologic techniques have been used to detect very specific drug effects (11). Although most tests are performed in the home cage of the isolated male mouse, performing the test in a neutral arena is attractive because the situation delivers a mix of offensive-defensive and flight behaviors, which are not seen or are infrequently seen in the home cage confrontation (11).

The latter model is very interesting because it shows properties of drugs that are revealed only partially, or not at all, by common pharmacologic test models (10,12,13). An extensive literature exists about the effects of γ-aminobutyric acid ($GABA_A$)–benzodiazepine agonists in this paradigm. Interestingly, classic non–subunit-selective benzodiazepine-receptor agonists show inverse U-shaped dose–response curves in this model. At lower doses, increases in aggression are seen, whereas at higher doses, no effects or decreases are observed (14), probably because of nonspecific effects such as muscle relaxation or sedation (11, 15). A similar pattern of activity can be found after alcohol administration or consumption. Miczek et al. extensively investigated the effects of various doses of alcohol on aggressive behavior of male mice, rats, and monkeys and consistently found that individual animals respond differentially to alcohol (14,16–18). Approximately 25% of mice show heightened aggression after receiving low doses of alcohol (AHA mice), whereas the remainder show no increase in aggression (ANA mice). Interestingly, this alcohol-heightened aggression is attenuated by pretreatment of $5\text{-}HT_{1A}$

and 5-HT$_{1B}$ receptor agonists (19,20), a finding indicating an essential role the serotonergic system in the modulation of offensive aggressive behavior. Enhanced aggression after benzodiazepines and alcohol treatment in some, but not all, animals is highly similar to the pattern found in humans (21–23) and supports the predictive validity of this kind of animal models for some types of human aggression.

Psychostimulants also disturb the normal agonistic behavior, although the resulting behavior is clearly differentially affected (10,11,19). D-Amphetamine–treated animals show aberrant "stimulated" behavior, which severely interferes with normal agonistic behavior (11,15,24). Neuroleptics (chlorpromazine, haloperidol) exert antiaggressive effects, but nonspecific effects, such as motor disturbances (catalepsy) (11,15), cause this. Serenics (serotonergic 5-HT$_{1B/1A}$-receptor agonists) have a highly selective antiaggressive profile in this test, reducing aggression specifically without dramatically affecting other behaviors dramatically and certainly not causing any unwanted side effects (25, 26).

In the 1990s, molecular biological techniques provided us with potentially very exciting ways of studying aggression. Several gene knockout mice were generated, and some have been tested on their aggressive behavior. Several knockouts seem to be more aggressive than their wild types, including, among others, the 5-HT$_{1B}$ receptor (27), the neural form of nitric oxide synthase (nNOS) (28), monoamine oxidase A (MAO A) (29) and calcium-calmodulin kinase II (CAMKII) (30). Interestingly, mice with a deletion in the endothelial form of the nitric oxide synthase (eNOS) (31) exhibit a virtual elimination of aggressive behavior. One has to be careful to consider the hyperaggression obtained after the mutation directly caused by the absence of the gene. Genetic background effects may cloud a clear interpretation, whereas adaptational processes over time may also influence the outcome. Most studies reported do not use extensive description of the behavioral phenotype, and conclusions whether the observed "aggressive" phenotype of the mutant is directly caused by the absence of the gene or results from maladaptation of the mutant to external stimuli have to be investigated before a mutant can be considered as a putative model for a certain kind of aggression. Nonetheless, studies screening knockout mice for alterations in aggressive behavior should prove useful in identifying novel mechanisms involved in aggression and provide useful models for development of novel drug intervention targets.

The 5-HT$_{1B}$-receptor knockout mouse (27) has been evaluated most extensively on different aspects of its hyperaggressiveness and has been proposed as an animal model of impulsivity (32,33). The latter study investigated territorial aggression in 5-HT$_{1B}$ knockout males and corresponding wild types (in a 129SV background) while equipped with telemetric senders to record heart rate and body temperature during the experiment. Ethologic analysis of the behavior showed that the knockouts where more aggressive than the wild types. The significant findings from these studies were that, although these animals displayed higher levels of offensive aggression with a faster onset, other behaviors, including social investigation, defense, and exploration were completely normal (Table 118.1).

Telemetric data on heart rate and body temperature showed no obvious abnormalities during the fight, although 5-HT$_{1B}$ knockouts responded faster to all types of sensory stimuli such as opening the cage, handling, and injection (33). This pattern of reactivity was in line with the presumed impulsivity of this mutant and lends support to the use of this animal model in research into the mechanisms underlying impulse and aggression disorders, and it will be of help in screening new potential antiaggressive or antiimpulsive drugs. Much more fundamental work, including pharmacology, has to be done on this mutant, but the appearance of new animal models of human diseases seems a realistic option (34,35).

Isolation-induced aggression in mice is an animal model of offensive aggression with excellent predictive validity toward human aggression. Although some face validity is clearly present (offensive impulsive aggression in human aggression), the construct validity is as yet largely unknown.

Resident-Intruder Offensive Behavior

This model, very frequently used in psychopharmacology, uses the resident animal's response to a conspecific intruder (24,36,37). In the *resident-intruder paradigm,* a male rat is housed with a female, a situation resembling the natural situation in which animals establish and defend territories (38). When resident or territorial males meet an unfamiliar male intruder in their territory, heavy fighting may ensue, considered natural fighting (39,40). The attacking male performs a complete agonistic repertoire including both appetitive and consummatory behaviors Aggressive behavior in this situation may consist of searching (patrolling), approach, investigation, threats fighting, chasing, and dominant posturing The nature of such interactions between an attacking resident and an opponent varies with the quality of the intruder, especially age and hormonal status, and the resident's experience. The types of behaviors displayed by the resident toward the intruder are not random but follow certain rules (15), a strong indicator of the neural substrates involved (4).

The resident-intruder model differs both from isolation-induced aggression in mice and intermale aggression in rats, because there is no isolation, which may lead to behavioral abnormalities (8). Moreover, resident-intruder paradigms have a very wide species generality (41), including humans (42). Isolation-induced aggression, in contrast, is far more restricted to certain species (10). This model discriminates effectively the quality and behavioral mechanisms of action

TABLE 118.1. ANIMAL BEHAVIOR ANALYSIS

	Frequency		Duration	
Behavior	Wild-Type	Knockout	Wild-Type	Knockout
Nonsocial activity				
Attention	28 (19–33)	22.5 (17–26)	74.2 (53–137)	61.1 (50–90)
Rear	0.5 (0–2)	4.5 (0–9)	0.5 (0–4)	7.1 (0–28)
Sniff	22 (22–26)	17 (14–21)	60.3 (55–83)	42.4* (33–49)
Walk	23.5 (17–25)	22 (14–27)	39.0 (36–51)	28.7 (21–47)
Body care	1 (1–2)	4* (3–6)	2.7 (0.8–8.5)	18.0* (14–24)
In nest	9 (8–12)	0.5* (0–2)	86.3 (78–235)	0.5* (0–6.9)
Social activity				
Approach	8.5 (3–12)	18* (17–24)	6.6 (2.3–9.9)	19.0* (13–24)
Follow	1.5 (1–3)	1.0 (0–3)	2.0 (0.6–6.9)	1.1 (0–2.9)
Walk away	1.5 (0–4)	10* (8–13)	1.2 (0–3.4)	15.6* (11–17)
Social sniff	22.5 (16–30)	42.5* (35–48)	86.7 (55–114)	162* (145–186)
Genital sniff	10 (5–12)	10 (7–14)	29.8 (19–69)	35.7 (31–68)
Mount	0 (0–2)	1 (0–4)	0.0 (0–5.2)	2.8 (0–10)
Aggression				
Tail rattle	0 (0–2)	2* (1–7)	0.0 (0–1.5)	2.8* (0.9–11)
Lateral threat	0 (0–1)	2* (0–8)	0.0 (0–0.9)	2.3 (0–12)
Bite	2 (1–8)	9 (4–14)	1.9 (0.9–7.0)	9.6 (3.2–14)
Clinch/fight	0.5 (0–4)	7* (1–10)	0.4 (0–25)	22.1 (3.3–37)
In tube				
In tube	14.5 (13–17)	16.5 (8–25)	64.8 (47–108)	82.9 (46–108)

[a]Male wild-type and 5-HT$_{1B}$ receptor knockout mice were singly housed (residents) for several months. These mice ($n = 12$ per genotype) were equipped with telemetric devices to record heart rate and body temperature. Mice were subjected to a 10-min encounter with a group-housed male intruder, and the behavior of the resident was scored, using an ethologic method. Data are given as median (using twenty-fifth to seventy-fifth percentiles) frequencies and duration (seconds) per 10 min. Mann-Whitney U test: the asterisk means significantly different from wild-type mice ($p < .05$).

of several drugs with proaggressive and antiaggressive actions (13,15,43).

Benzodiazepines at low doses enhance aggression (14, 44), whereas at higher doses they clearly cause ataxia, which interferes with the behavioral performance. Alcohol, as in mice, enhances aggression in some rats, but not in others (14,18). Interestingly, this increased aggression in a subpopulation of the resident males was observed both after experimenter-administered ethanol and after self-administered ethanol (18). Understanding the underlying neurochemical mechanisms responsible for the individual differences in behavioral response to ethanol in these two subpopulations of rats or mice should prove valuable for understanding the factors resulting in pathologic aggression in humans.

Neuroleptics, like psychostimulants, alter the display of agonistic behavior (15), although in different ways (25). Serenics display a highly specific antiaggressive profile. This effect is caused by the activation of postsynaptic 5-HT$_{1B}$ receptors because ligands affecting other 5-HT receptors have quite different antiaggressive profiles.

The resident-intruder paradigm has also been used in hamsters to elucidate a novel neurochemical pathway involved in aggression. Hamsters, which are territorial, quickly attack intruders. The neuropeptide vasopressin has

been shown to act in the preoptic area and anterior hypothalamus to stimulate both displays of dominance and aggression (45). Vasopressin receptor antagonists injected into this area are potent inhibitors of aggression. Fluoxetine, a selective serotonin uptake inhibitor, decreases offensive aggression in male hamsters and prevents vasopressin-induced aggression. This finding has led to the hypothesis that there is an interaction between vasopressinergic and serotonergic systems in the regulation of offensive aggression. Hamsters subjected to social subjugation as juveniles displayed elevated levels of aggression toward smaller hamsters as adults (46). As adults, these subjugated hamsters had altered levels of both vasopressin and serotonin in the anterior hypothalamus, a finding providing a potential mechanism by which environmental influences may permanently alter the neural circuits regulating aggression. Interestingly, elevated levels of vasopressin in the cerebrospinal fluid has been correlated with indices of aggression in personality-disordered patients (47). This model provides an example in which discovering the neural mechanisms underlying aggression could potentially lead to new targets of intervention for therapy in pathologic aggression.

The resident-intruder paradigm has a very good predictive validity toward human aggression. Both proaggressive (alcohol and benzodiazepines) and antiaggressive effects of

psychoactive drugs are highly similar in rodents and humans. Because of the species generality of this type of aggression, the model also has considerable face validity. Construct validity is as yet less clear, but the brain mechanisms involved, the hormonal sequelae, and the behavior-evoking stimuli support reasonable construct validity. As such, this paradigm seems an excellent choice in screening for potential antiaggressive compounds (serenics), but it also indicates other drug effects such as sedation and sensory and motor impairment (15).

Offensive Behavior after Electrical Brain Stimulation

Behavior largely similar to that of offensive territorial males can be elicited by electrical stimulation in the medial-lateral hypothalamus of male and female rats (48–50). Hypothalamic aggression in male rats is sensitive to manipulations of androgen levels (51), and it can be induced in an area (52) roughly coinciding with the areas where levels of circulating sex hormones are regulated. Moreover, stimulation of this area is accompanied by elevated levels of stress hormones (adrenocorticotropic hormone, corticosterone, and prolactin) resulting from activation of the area itself and not caused by the stress of fighting (53). In female rats, aggression can be elicited in this same area (54,55). This behavior is readily reproduced under controlled circumstances, thereby meeting an important requirement for a model to study aggression. The aggressive behavior induced by the stimulation can be explosive. Depending on the stimulus intensity, extreme forms of offensive attack and severe damage to the opponent can be observed (50). The attack behavior is not purely driven by internal stimulation of the hypothalamic substrate. The animal's response is still dependent on external cues such as the age and sex of the opponent. In addition to aggressive behavior, stimulation in this area of the hypothalamus also stimulates other behaviors, including locomotion and teeth chattering (54,56), thereby allowing for the determination of the specificity of the drug. In this paradigm, the effects of drugs are measured by the changes in the current thresholds required to evoke the respective behavior (56). Increases in the current thresholds for aggression indicate antiaggressive effects, considered specific if simultaneously the drug does not affect thresholds for locomotion. Several drugs have been analyzed in this model, including benzodiazepines, neuroleptics, psychostimulants, alcohol, 5-HT$_{1A}$-receptor agonists, serenics (5-HT$_{1A/1B}$-receptor agonists) and selective serotonin reuptake inhibitors (56–59).

Chlordiazepoxide, in contrast to its effects in the isolation-induced and resident-intruder paradigms, had no effect on aggression and teeth-chattering thresholds at lower doses and enhanced the thresholds for both aggression and locomotion only at high doses, presumably reflecting the muscle relaxant properties at these doses. Alcohol, up to a dose of 2 g/kg, had no effects on any parameter, a finding suggesting that the proaggressive actions of alcohol and also the benzodiazepines seen in the territorial and isolated male paradigms are probably related to variables (anxiety?) other than aggression *per se.*

Haloperidol enhanced aggression thresholds simultaneously with locomotion, again indicative of nonspecific effects on aggression. Because thresholds for teeth chatter, which accompanies normal aggression, were not affected, it was concluded that aggression was not at all influenced by haloperidol, in line with earlier findings that antiaggressive actions of neuroleptics result from their side effects (catalepsy). D-Amphetamine had no effect on aggression and teeth chattering, but it decreased the locomotor threshold, a finding illustrating its stimulatory action without having specific effects on aggression. Scopolamine, a (muscarinic) anticholinergic drug, had effects similar to those of D-amphetamine, again illustrating that activation of substrates for locomotor activity is independent from activation or inhibition of aggression substrates in the brain. Naloxone, an opiate antagonist, did not influence any aspect of the brain stimulation–induced behaviors, in line with its absence on spontaneous aggression (11,15). Manipulation of various serotonergic mechanisms showed that activation of the 5-HT$_{1B}$ receptor, by eltoprazine, flurazine, meta-chlorophenylpiperazine, DL-propranolol and other phenylpiperazines (25,26), induces a highly specific effect on aggression. Aggression and teeth-chattering thresholds were enhanced, although aggression still could be evoked, but locomotor activity was not affected or was even somewhat decreased. The profiles of drugs that modulate other serotonergic receptors, including 5-HT$_{1A}$, 5-HT$_3$, and the serotonin transporter, demonstrate the specificity of the 5-HT$_{1B}$ receptor in aggression, a finding suggesting that the nonspecific effects of serotonergic drugs are mediated through other 5-HT-receptor mechanisms.

This hypothalamic-induced aggression model is highly relevant for modeling certain kinds of human aggression. By directly stimulating neural substrates in the brain involved in offensive aggression, this model has great potential to predict violent, pathologic aggression in humans. In contrast to the more natural models (isolation-induced, resident-intruder, maternal aggression), this model is not sensitive to certain intervening variables present in the other paradigms (anxiety, fear, sedation, and motor and sensory disturbances) and directly reflects antiaggressive properties of drugs. In addition, this model is not completely artificial or pathologic in the sense that attacking animals do not respond to nonsalient stimuli in preparation of or during the attack. For example, such animals do not attack rats that previously have defeated them or females in estrus. The predictive validity of this model seems to be somewhat less than the other models; nonetheless, the model is useful in determining how drugs bring about the antiaggressive effect.

Maternal Aggression

Although aggression is often considered a male-related phenomenon, females can be quite aggressive under certain conditions, such as in hypothalamically induced aggression in rats (54,55), aggression in nonestrus hamsters (58), and maternal aggression in several rodent species (59,60). The use of a female aggression paradigm to model human (female?) aggression has been quite uncommon, particularly for psychopharmacologic purposes. The maternal aggression model seems to constitute such a model because it shows very wide species generality, including humans (61), and it has clear neural and hormonal determinants. Maternal aggression is highly purposeful, providing protection to the offspring. The maternal aggression paradigm is based on the finding that a lactating female rat or mouse with pups will exhibit offensive behaviors toward a wide variety of intruders. This behavior is most pronounced during the first part of the lactating period (62,63). Because the critical stimulus is clearly the proximity of some threatening object to the female's young, some authors (2) consider this behavior mainly defensive. However, the behavior of the lactating female toward an intruder is clearly self-initiated, proactive, and not necessarily reactive to any threat initiated by the intruder. Although the paradigm is labor intensive and needs extensive planning, several psychoactive drugs have been tested in it and have led to a model with a comparable predictive validity as the male offensive paradigms in rats (resident-intruder) and mice (isolation-induced). The psychopharmacology of maternal aggression has been mainly studied in rats, although some work in mice has been performed (64).

Although the topography of the aggressive behavior of the attacking female is clearly different from male aggression (63), the effects of several classes of drugs were remarkably similar to those found in the male paradigms. Benzodiazepines and alcohol showed, at low doses, proaggressive effects, which faded at higher doses because of nonspecific effects (sedation, ataxia, and muscle relaxation). D-Amphetamine reduced aggression at higher doses, but this was clearly attributable to interfering effects of motor stimulation, whereas haloperidol inhibited aggression by its highly nonspecific side effects. Serenics (eltoprazine and related phenylpiperazines) have a highly selective effect in this paradigm, reducing aggression without affecting other behaviors, including pup care. The critical role of the 5-HT$_{1B}$ receptor in this effect was again demonstrated by additional pharmacology showing that modulating other serotonergic receptors did not have such effects.

MODELS OF DEFENSIVE BEHAVIORS

Those forms of agonistic behavior in which elements of initiative and approach prevail belong to the offensive repertoire, characterized by initiative, attack, and similar proactive behavior. This sharply contrasts with the defensive repertoire, which is characterized by submission, flight, and similar reactive behaviors. Fighting, when it occurs in a defensive animal, is merely a reaction to attack. Other defensive behaviors, such as flight or submission, are apparently intended to escape from or prevent further agonistic interactions (65). Some of the drugs known to suppress offensive behaviors have highly undesirable effects on defensive behavior; for example, neuroleptics inhibit all activities including defensive and flight reactions.

Pain- or Shock-Induced Defensive Behavior

Delivering electric shock to the hind paws of a pair of rats or mice evokes so-called *foot shock*– or pain-induced aggression (66). Similar behavioral responses can be found when certain drugs (apomorphine, mescaline) are given to pairs of animals. Whereas either or both animals may attack, the behavior is conceived as defensive (5), in part because the animals mutually exhibit typical upright defensive postures and squealing and the behavior is clearly reactive; without switching on the current, no agonistic interactions will occur. Although this paradigm was extensively used in the past to assess antiaggressive activity of drugs, a confounding factor in the model is that the behavior-releasing factor (pain) can be masked by analgesic properties of drugs. This fact, together with the limited behavioral repertoire exhibited in this paradigm, limits its utility considerably.

A useful application of foot shock–induced defense behavior is to determine the ED$_{50}$ to lower the amount of fighting episodes by 50% and concurrently to determine an ED$_{50}$ for paralysis, the ability of mice, hanging by their forelimbs from a thin bar, to bring their hind limbs on to the bar within a certain time. Specificity of the antidefense effects is calculated as the ratio between these two ED$_{50}$ values. A high ratio indicates good antidefense specificity; low values suggest strong interfering effects.

Neuroleptics show very low ratios (less than 1), tricyclic antidepressants have ratios of approximately 1, whereas benzodiazepines also have ratios less than 1 because of their muscle-relaxing effects (26,67). Serenics (eltoprazine, fluprazine, and others) appear highly selective; ratios of more than 20 (fluprazine) or, in the case of eltoprazine, not determinable have been found. Eltoprazine did, up to a very high dose, not inhibit this foot shock–induced behavior, thereby illustrating its highly selective antioffense character.

Defensive Behavior in Rats (Intruder Model)

A more natural model of defensive behavior is the behavior shown by an intruder in the resident-intruder or maternal aggression situation. Defending animals in these paradigms

use special tactics to protect the more vulnerable parts of their bodies. In unconstrained conditions, animals on the defense usually flee from the territory of the residential male or lactating female, but when this is impossible, as in laboratory conditions, they defend themselves by flight, crouching, upright defensive postures, emission of ultrasounds, and submissive postures. Generally, these behaviors aim at protecting the back, the area where most wounds are inflicted by attacking rats (68).

Although this model involves at least two animals, the offender and the defender, it provides an opportunity for various drug manipulations and to study direct and indirect drug effects (69). Drugging the offender and changing its offensive behavior have clear effects on the behavior of the intruder (26,70). The quality of the intruder (i.e., age and size) also determines the behavioral outcome, and interactions between drug effects and the intruder quality have been observed for D-amphetamine and chlordiazepoxide (44,70). This finding illustrates the construct and face validity of this model because it has high resemblances to the human (psychiatric) situation.

This model has been of limited use in psychopharmacology mainly because of the complexity in interpreting the interaction between drug effect and intruder quality. However, using standardized circumstances in which the intruder is basically not threatening the role of the resident, that is, by using young or inexperienced inexperienced intruders, the direct effects of drugs on the behavior of the intruder can be studied. It appears that influencing the sensory or motor capabilities of the intruder (by neuroleptics, alcohol, benzodiazepines, or psychostimulants) leads to changes in the defense or flight responses of the animals indicating enhanced flight (D-amphetamine) or impaired defense or flight (haloperidol). This may lead to enhanced attacks on the intruder in the case of D-amphetamine or diminished interest in the intruder by the resident in the case of neuroleptics (26). Serenics do not affect the defense or flight capabilities of the intruders (26), an effect in line with their specific antioffense qualities.

The resident-intruder model is a unique animal model for different aspects of social interactions and provides an opportunity to determine not only what drugs are doing directly to an organism, but also the indirect effects on the partner. Human pathologic aggression is often associated with complex interpersonal interactions, and the resident-intruder interaction model may be particularly relevant to predict what drugs may do in humans in particular circumstances.

MISCELLANEOUS MODELS

Predatory aggression, such as mouse killing (muricide) in rats or locust killing (insecticide) in mice, occurs spontaneously in a proportion of individuals, depending on the strain used (71). There has been a great deal of dispute about the nature of muricide in rats, resulting in various descriptions of the behavior including, interspecies aggression (72), predatory aggression (73), or simply predatory behavior (74). This model is clearly different from those described earlier, and its human equivalent is questionable, although predatory aggression has been described in relation to pathologic aggression in humans. Predatory attack clearly differs from intraspecies attack with regard to neuroanatomic, physiologic, and hormonal mechanisms (75), but the pharmacology is less developed. The model is rarely used anymore because of several ethical constraints, and therefore most data are from before the 1990s (26). Benzodiazepines and alcohol, unless given at extremely high doses, do not inhibit muricide. Neuroleptics and psychostimulants do inhibit muricide but clearly not in a very specific way (cataleptic, motor stimulation). Antidepressants (tricyclics and selective serotonin reuptake inhibitors) inhibit muricide in a quite specific way, and in the 1950s up until the 1970s, the muricide test was in use in the pharmaceutical drug discovery process as an antidepressant screen. 5-HT_{1A}-receptor agonists do not inhibit muricide, whereas 5-HT_{1B}-receptor agonists (serenics) inhibit it, but only at much higher doses than the antioffense effects. Therefore, this model is not believed to have potential qualities to predict certain human pathologic aggression situations.

DISCUSSION

The present contribution has suggested a limited number of animal models for different forms of aggression, namely, offensive aggression, defensive aggression, and predatory aggression. This is absolutely not an exhaustive coverage of the field and shows a logical way to frame the existing animal tests and paradigms into meaningful categories especially for predicting the effects of psychoactive drugs for human pathologic conditions. This approach led to the development in the 1970s and 1980s of a group of serotonergic agonists, serenics, as potential antiaggressive agents to treat certain types of human pathologic aggression (26,76).

Moreover, the animal models outlined appeared to have predictable validity and enable us to predict putative outcomes when applied in humans. Good examples are the benzodiazepines, with which, at low doses, aggression-enhancing effects were often found that corresponded to the so-called "paradoxic" aggression seen after human use (22, 23). The antiaggressive effects of neuroleptics, often clinically used as first treatment in emergencies, are not specific at all but result from interference with vital functions (cognition, motor, sensory). Antiaggressive effects can be the result of many (side) effects of drugs, and the proposed animal models are capable of detecting and describing these effects. Consequently, they have a high predictable validity

toward their effects in humans, although it is very difficult to predict for which human disorder or symptom (77).

One of the biggest obstacles in the study of the psychopharmacology of aggression and the predictability for the human situation is the lack of consensus on definitions. The only primary aggression disorder in DSM-IV is intermittent explosive disorder, but all other aggression and impulsivity occurring in various disorders are considered as symptoms of different underlying disorders; this situation makes it extremely difficult to compare human with animal aggression directly. From the animal research, the evidence is very strong that there are specific neural substrates in the brain subserving these different functions in agonistic behavior, and it is more than likely that similar mechanisms are available in the human brain (78,79). The fundamental research in animals suggests that serotonin, actually only a subset of the system, such as the postsynaptic 5-HT$_{1B}$ receptor (80), is an important neurotransmitter in at least part of this brain circuitry. Genetic modification of this system (5-HT$_{1B}$-receptor knockout mouse) has added considerable evidence for the importance of this system, although it is clear that the latter is only a small part of a much bigger and very complex circuitry in the brain involved in agonistic behavior.

Preclinical aggression research is under considerable pressure because of ethical and societal constraints on doing "biologically" oriented research in understanding the neurobiology of aggression and possible disturbances of the systems involved in the case of pathologic aggression (81). However, further research, using animal models of aggression, is needed to discover new treatments for pathologic aggression and violence. Analysis of the behavioral profiles of genetically altered mice with targeted gene deletions holds great promise over the next decade for discovering novel neurochemical pathways in the brain involved in the control of aggression. New developments in the molecular biology area, generating inducible, and brain region–specific mutants will engender exciting tools to study the role of genes, environment, and their interaction in the causation of aggression, and important new clues for the study and treatment of pathologic aggression in humans will emerge.

REFERENCES

1. Eichelman B, Hartwig A. The clinical psychopharmacology of violence: towards a nosology of human aggressive behavior. *Psychopharmacol Bull* 1993;29:57–63.
2. Moyer KE. Kinds of aggression and their physiological basis. *Commun Behav Biol* 1968;2:65–87.
3. Huntingford F, Turner A. *Animal conflict.* London: Chapman & Hall, 1987.
4. Adams DB. Brain mechanisms for offense, defense and submission. *Behav Brain Sci* 1979;2:201–241.
5. Blanchard RJ, Blanchard DC, Takahashi T, et al. Attack and defensive behavior in the albino rat. *Anim Behav* 1977;25:622–634.
6. Olivier B, Van Dalen D, Hartog J. A new class of psychoactive drugs: serenics. *Drugs Future* 1990;11:473–499.
7. Valzelli L. Aggressive behaviour induced by isolation. In: Garattini S, Siggs SB, eds. *Aggressive behaviour.* Amsterdam: Excerpta Medica, 1969:70–76.
8. Valzelli L. The "isolation syndrome" in mice. *Psychopharmacologia* 1973;31:305–320.
9. Malick JB. The pharmacology of isolation-induced aggressive behaviour in mice. *Curr Dev Psychopharmacol* 1979;5:1–27.
10. Miczek KA, Krsiak M. Drug effects on agonistic behavior. In: Thompson T, Dews PB, eds. *Advances in behavioral pharmacology,* vol. 2. New York: Academic Press 1979:87–162.
11. Olivier B, Van Dalen D. Social behaviour in rats and mice: an ethologically based model for differentiating psychoactive drugs. *Aggress Behav* 1982;8:163–168.
12. Miczek KA, Barry HIII. Pharmacology of sex and aggression. In: Glick SD, Goldfarb J, eds. *Behavioral pharmacology.* St. Louis: CV Mosby, 1976:176–257.
13. Olivier B. Selective anti-aggresive properties of DU27725: ethological analyses of intermale and territorial aggression in the male rat. *Pharmacol Biochem Behav* 1981;14[Suppl 1]:61–77.
14. Miczek KA, DeBold JF, Van Erp AM, et al. Alcohol, GABA$_A$-benzodiazepine receptor complex, and aggression. *Recent Dev Alcohol* 1997;13:139–171.
15. Olivier B, Van Aken H, Jaarsma I, et al. Behavioural effects of psychoactive drugs on agonistic behaviour of male territorial rats (resident-intruder paradigm). In: Miczek KA, Kruk MR, Olivier B, eds. *Ethopharmacological aggression research.* New York: Alan R. Liss, 1984:137–156.
16. Miczek KA, Barros HM, Sakoda L, et al. Alcohol and heightened aggression in individual mice. *Alcohol Clin Exp Res* 1998;22:698–705.
17. Weerts EM, Tornatzky W, Miczek KA. "Anxiolytic" and "anxiogenic" benzodiazepines and beta-carbolines: effects on aggressive and social behavior in rats and squirrel monkeys. *Psychopharmacology (Berl)* 1993;110:451–459.
18. Van Erp AM, Miczek KA. Increased aggression after ethanol self-administration in male resident rats. *Psychopharmacology (Berl)* 1997;131:287–295.
19. Miczek KA, Hussain S, Faccidomo S. Alcohol-heightened aggression in mice: attenuation by 5–HT$_{1A}$ receptor agonists. *Psychopharmacology (Berl)* 1998;139:160–168.
20. Fish EW, Faccidomo S, Miczek KA. Aggression heightened by alcohol or social instigation in mice: reduction by the 5-HT(1B) receptor agonist CP-94,253. *Psychopharmacology (Berl)* 1999;146:391–399.
21. Ratey J, Gordon A. The psychopharmacology of aggression: toward a new day. *Psychopharmacol Bull* 1993;29:165–173.
22. Bond A, Lader M. Differential effects of oxazepam and lorazepam on aggressive responding. *Psychopharmacology (Berl)* 1988;95:369–373.
23. Weisman AM, Berman ME, Taylor SP. Effects of clorazepate, diazepam, and oxazepam on a laboratory measurement of aggression in men. *Int Clin Psychopharmacol* 1998;13:183–188.
24. Miczek KA. Intraspecies aggression in rats: effects of D-amphetamine and chlordiazepoxide. *Psychopharmacology (Berl)* 1974;39:275–301.
25. Olivier B, Mos J, Hartog J, et al. Serenics: a new class of drugs for putative treatnment selective treatment of pathological destructive behavior. *Drugs News Perspect* 1990;3:261–271.
26. Olivier B, Mos J, Raghoebar M. et al. Serenics. *Prog Drug Res* 1994;42:167–308.
27. Saudou F, Amara DA, Dierich A, et al. Enhanced aggressive behavior in mice lacking 5–HT$_{1B}$ receptor. *Science* 1994;265:1875–1878.
28. Nelson RJ, Demas GE, Huang PL, et al. Behavioral abnormalities

in male mice lacking neuronal nitric oxide synthase. *Nature* 1995; 378:383–386.

29. Cases O, Seif I, Grimsby J, et al. Aggressive behavior and altered amounts of brain serotonin and norepinephrine in mice lacking MAOA. *Science* 1995;268:1763–1766.

30. Chen C, Rainnie DG, Greene RW, et al. Abnormal fear response and aggressive behavior in mutant mice deficient for calcium-calmodulin kinase II. *Science* 1994;266:291–294.

31. Demas GE, Kriegsfield LJ, Blackshaw S, et al. Elimination of aggressive behavior in male mice lacking endothelial nitric oxide synthase. *J Neurosci* 1999;19:19–30.

32. Brunner D, Hen R. Insights into the neurobiology of impulsive behavior from serotonin receptor knockout mice. *Ann NY Acad Sci* 1997;836:81–105.

33. Bouwknecht JA, Hijzen TH, Van der Gugten J. et al. Absence of 5-HT$_{1B}$ receptors is associated with impaired motor impulse control in male 5-HT$_{1B}$ knockout mice. *Biol Psychiatry* 2001;49: 557–568.

34. Murphy DL, Wichems C, Li Q, et al. Molecular manipulations as tools for enhancing our understanding of 5-HT neurotransmission. *Trends Pharmacol Sci* 1999;20:246–252.

35. Rudolph U, Möhler H. Genetically modified animals in pharmacological research: future trends. *Eur J Pharmacol* 1999;375: 327–337.

36. Adams DB. The relation of scent-marking, olfactory investigation, and specific postures in the isolation-induced fighting of rats. *Behaviour* 1976;56:286–297.

37. Olivier B. The ventromedial hypothalamus and aggressive behaviour in rats. *Aggress Behav* 1977;3:47–56.

38. Barnett SA. *The rat: a study in behaviour.* Chicago: University of Chicago Press, 1975.

39. Blanchard RJ, Blanchard DC. Alcohol and aggression in animal models. In: Olivier B, Mos J, Brain PF, eds. *Ethopharmacology of agonistic behaviour in animals and man.* Dordtrecht: Martinus Nijhoff, 1977:145–161.

40. Miczek KA. A new test for aggression in rats without aversive stimulation: differential effects of D-amphetamine and cocaine. *Psychopharmacology (Berl)* 1979;60:253–259.

41. Wilson EA. *Sociobiology.* Cambridge: Belknap Press of Harvard University Press, 1975.

42. Malmberg T. *Human territoriality: survey of behavioural territories in man with preliminary analysis of meaning.* The Hague, Mouton, 1980.

43. Mos J, Olivier B, Tulp MThM. Ethopharmacological studies differentiate the effects of various serotonergic compounds on aggression in rats. *Drug Dev Res* 1992;26:343–360.

44. Mos J, Olivier B, Van der Poel AM. Modulatory actions of benzodiazepine receptor ligands on agonistic behaviour. *Physiol Behav* 1987;41:265–278.

45. Ferris CF, Melloni RH, Koppel G, et al. Vasopressin/serotonin interactions in the anterior hypothalamus control aggressive behavior in golden hamsters. *J Neurosci* 1997;17:4331–4340.

46. Delville Y, Melloni RH, Ferris CF. Behavioral and neurobiological consequences of social subjugation during puberty in golden hamsters. *J Neurosci* 1998;18:2667–2872.

47. Coccaro EF, Kavoussi RJ, Hauger RI, et al. Cerebrospinal fluid vasopressin levels: correlates with aggression and serotonin function in personality-disordered subjects. *Arch Gen Psychiatry* 1998; 55:708–714.

48. Koolhaas JM. Hypothalamically induced intraspecific aggressive behaviour in the rat. *Exp Brain Res* 1978;32:365–375.

49. Kruk MR, Van der Poel AM. Is there evidence for a neural correlate of an aggressive behavioural system in the hypothalamus of the rat? *Prog Brain Res* 1980;53:385–390.

50. Kruk MR, Van der Poel AM, De Vos-Frerichs TP. The induction of aggressive behaviour by electrical stimulation in the hypothalamus of male rats. *Behaviour* 1979;70:292–322.

51. Bermond B, Mos J, Meelis W, et al. Aggression induced by stimulation of the hypothalamus: effects of androgens. *Pharmacol Biochem Behav* 1982:16:41–45.

52. Kruk MR, Van der Poel AM, Melis W, et al. Discriminant analysis of the localization of aggression inducing electrode placements in the hypothalamus of male rats. *Brain Res* 1983;260:61–79.

53. Kruk MR, Westphal KGC, Van Erp AMM, et al. The hypothalamus: cross-roads of endocrine and behavioural regulation in grooming and aggression. *Neurosci Biobehav Rev* 1998;23: 163–177.

54. Kruk MR, Van der Laan CE, Mos J, et al. Comparison of aggressive behaviour induced by electrical stimulation in the hypothalamus of male and female rats. *Prog Brain Res* 1984;61:303–314.

55. Mos J, Olivier B, Lammers JHMC, et al. Pregnancy and lactation do not interact with current thresholds for brain stimulation induced aggression in female rats. *Brain Res* 1987;404:263–266.

56. Van der Poel AM, Olivier B, Mos J, et al. Anti-aggressive effect of a new phenylpiperazine compound (DU27716) on hypothalamically induced behavioural activities. *Pharmacol Biochem Behav* 1982;17:147–153.

57. Olivier B, Mos J, Rasmussen D. Behavioural pharmacology of the serenic eltoprazine. *Drug Metab Drug Interact* 1990;8:31–83.

58. Floody OR, Pfaff DW. Aggressive behavior among female hamsters: the hormonal basis for fluctuations in female aggressiveness correlated with estrus state. *J Comp Physiol Psychol* 1977;91: 443–446.

59. Siegel A, Roeling TAP, Gregg TR, et al. Neuropharmacology of brain-stimulation-evoked aggression. *Neurosci Biobehav Rev* 1999;23:359–389.

60. Floody OR. Hormones and aggression in female animals. In: Svare BB, ed. *Hormones and aggressive behavior.* New York: Plenum, 1983:39–89.

61. Svare B, Mann M. Hormonal influence on maternal aggression. In: Svare B, ed. *Hormones and aggressive behavior.* New York: Plenum, 1983:91–104.

62. Archer J. *The behavioural biology of aggression.* Cambridge: Cambridge University Press, 1988.

63. Erskine MS, Barfield RJ, Goldman BS. Intraspecific fighting during late pregnancy and lactation in rats and effects of litter removal. *Behav Biol* 1978;23:206–208.

64. Olivier B, Mos J. A female aggression paradigm for use in psychopharmacology: maternal agonistic behaviour in rats. In: Brain PF, Ramirez MJ, eds. *Cross-disciplinary studies on aggression.* Seville: University of Seville Press 1986:73–111.

65. Yoshimura H. Ethopharmacology of agonistic behaviour in male and female mice. In: Olivier B, Mos J, Brain PF, eds. *Ethopharmacology of agonistic behaviour in animals and man.* Dordtrecht: Martinus Nijhoff, 1987:94–109.

66. Dixon AK, Kaesermann HP. Ethopharmacology of flight behaviour. In: Olivier B, Mos J, Brain PF, eds. *Ethopharmacology of agonistic behaviour in animals and man.* Dordrecht: Martinus Nijhoff, 1987:46–79.

67. Ulrich RE, Azrin NH. Reflexive fighting in response to aversive stimulation. *J Exp Anal Behav* 1962;5:511–520.

68. Tedeschi RE, Tedeschi DH, Mucha A, et al. Effect of various centrally acting drugs on fighting behavior of mice. *J Pharmacol Exp Ther* 1959;125:28–34.

69. Mos J, Olivier B, Van Oorschot R, et al. Different test situations for measuring offensive aggression in male rats do not result in the same wound pattern. *Physiol Behav* 1984;32:453–456.

70. Blanchard DC, Griebel G, Rodgers RJ et al. Benzodiazepine and serotonergic modulation of antipredator and conspecific defense. *Neurosci Biobehav Rev* 1998;22:597–612.

71. Mos J, Olivier B, Van Oorschot R. Maternal aggression towards different sized male opponents: effect of chlordiazepoxide treatment of the mothers and D-amphetamine treatment of the intruders. *Pharmacol Biochem Behav* 1987;26:577–584.

72. Karli P. The Norway's rat killing response to the white mouse: an experimental analysis. *Behaviour* 1956;10:81–103.

73. Karli P, Vergnes M, Didiergeorges F. Rat-mouse interspecific aggressive behaviour and its manipulation by brain ablation and by brain stimulation. In: Garattini S, Sigg EB, eds. *Aggressive behaviour.* Amsterdam: Excerpta Medica, 1969:47–55.

74. Potegal M. The reinforcing value of several types of aggressive behavior: a review. *Aggress Behav* 1979;5:353–373.

75. Adamec RE, Himes M. The interaction of hunger, feeding, and experience in alteration of topography of the rat's predatory response to mice. *Behav Biol* 1978;22:230–243.

76. Huntingford FA, The relationship between intra- and inter-specific aggression. *Anim Behav* 1976;24:485–497.

77. Mak M, De Koning P, Mos J, et al. Preclinical and clinical studies on the role of 5-HT$_1$ receptors in aggression. In: Hollander E, Stein DJ, eds. *Impulsivity and aggression.* Chichester, UK: John Wiley, 1995:289–311.

78. Kavoussi R, Coccaro EF. Psychopharmacological treatment of impulsive aggression. In: Maes M, Coccaro EF, eds. *Neurobiology and clinical views on aggression and impulsivity.* Chichester, UK: John Wiley, 1998:197–211.

79. New AS, Novotny SL, Buchsbaum MS, et al. Neuroimaging in impulsive-aggressive personality disorder patients. In: Maes M, Coccaro EF, eds. *Neurobiology and clinical views on aggression and impulsivity*> Chichester, UK: John Wiley, 1998:81–93.

80. Stein DJ, Van Heerden B, Hugo F. Neuropsychiatry of aggression and impulsivity. In: Maes M, Coccaro EF, eds. *Neurobiology and clinical views on aggression and impulsivity.* Chichester, UK: John Wiley, 1998:95–107.

81. Olivier B, Mos J, Van Oorscht R, et al. Serotonin receptors and animal models of aggressive behaviour. *Pharmacopsychiatry* 1995; 28[Suppl]:80–90.

82. Enserink M. Searching for the mark of Cain. *Science* 2000;289: 575–579.