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Review

Serotonin and aggressive behavior in rodents and nonhuman primates: Predispositions and plasticity ☆

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Abstract

This review analyzes psychosocial and genetic determinants of aggressive behavior in rodents and nonhuman primates and the role of the serotonin (5-HT) system on aggressive behaviors in order to trace possible evolutionary common origins between psychopathological and adaptive forms of aggression. Studies in primates suggest that deficit in serotonin activity, as indicated by the levels of the cerebrospinal fluid (CSF) serotonin major metabolite 5-hydroxyindoleacetic acid (5-HIAA) correlates with impulsive and aggressive behavior. It is possible that CSF 5-HIAA reflects the prevailing serotonergic tone and may be related to an aggressive trait. Superimposed on this tone are phasic serotonin changes that may be related to the inhibition of aggressive acts. Genetic factors determine aggressive behaviors as demonstrated by classic selection and strain comparison studies. Manipulations of genes targeting 5-HT receptors, transporters and enzymes can influence aggression. Some of these genes related to the serotonin transporter (5-HTT) and the monoamine oxidase A (MAO-A) show a polymorphism that may predispose, under specific environmental conditions, certain individuals to display pathological forms of aggression.

Keywords: Aggression; Genetics; Serotonin transporter; Monoamine oxidase A; 5-hydroxyindoleacetic acid; Microdialysis; (Monkey); (Mice); (Rat)

Contents

Research on aggression has been a 'hot topic' in scientific investigations for more than five decades as it has been a target for many specialists from different disciplines, ranging from anthropology, behavioral biology to psychology, genetics, social sciences, neurosciences and zoology. The attraction of this topic is mainly due to the fact that aggression is commonly

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part of the biology of every species and that in humans escalated forms of aggression have become costly public health and criminal justice problems, especially when expressed in its pathological forms.

Indeed, aggression is a heterogeneous phenomenon in terms of motivation, behavioral phenotype and presumed function (Moyer, 1968; Brain, 1981; Wittenberger, 1981; Eichelman, 1992; Brain and Haug, 1992). The non-unitary nature of the phenomena we incorporate under the term aggression is also demonstrated by studies in neurosciences indicating that major differences exist in the neural pathways controlling and modulating different types of aggression (Flynn, 1967; Adams, 1980; Gregg and Siegel, 2001; Miczek et al., 2002).

Behavioral studies on aggression have greatly benefited from the contribution of two disciplines: ethology and psychology. The differences between these two disciplines reside probably in the focus on the individual relative to the species and on the context in which the behavior is investigated.

Ethologists emphasize four aspects of aggressive behaviors: one related to the adaptive functions, another related to the neural mechanisms, and a focus on their ontogeny and phylogeny of these behaviors. In fact, ethological analysis relies upon the study of animal behavior from an evolutionary perspective that is, taking into account the adaptive significance of aggressive behavior and the selective pressures that act on a specific type of aggression. This analysis begins with the precise description of different patterns of aggressive behaviors, postures, signals and their sequential and temporal organization (Leyhausen, 1960; Brain et al., 1984; Marler, 1976). An important assumption of ethologists is that the description of an ethogram implies that species-specific behaviors, in order to be shared by all members of the species, must have, at least in part, inherited characteristics. This assumption is supported by the following observations: (1) the patterns of intraspecific attack are highly stereotyped (fixed action patterns) with little inter-individual variability and fully expressed the first time the animal is exposed to the proper releaser (i.e. a same sex conspecific); (2) the fixed action patterns of aggressive behavior are very similar in closely related species and (3) the neurobiological substrates of aggression are highly conservative and homologous in the subphylum of vertebrates, thus supporting the common phylogenetic origin.

Early psychologists emphasized the role of environmental variables and experience in the development of aggressive behaviors in a particular individual. These psychological theories were based on evidence that aggression is learned and can be strongly influenced by the experience with models (e.g. parents, friends; Berkowitz, 1993). Furthermore, positive rewards or punishment, as a consequence of an aggressive outburst may strongly affect future aggressive responses (Scott and Fredericson, 1951). In this view, aggression *per se* could be considered self-reinforcing as an individual can experience the 'pleasure' of fighting (Potegal, 1979).

This clear distinction between inherited and environmental determinants of aggression deals with the nature vs. nurture debate where the term "nature" means entirely "biologically" determined which often is equated with "genetic," and "nurture" means developed through experience and learning and thus entirely environmentally determined. Although these two different approaches have often been depicted as alternatives to model the origins of human and animal aggression, in recent years there is a general recognition of the interaction of these two perspectives in understanding how biological and psychological processes interact in the development of aggressive behavior and how genetic–social–ontogenetic determinants could contribute in developing pathological forms of aggression.

Pre-clinical studies of aggression are relevant because they trace the evolutionary origins of human psychopathologies linked to violence and escalated aggression. However, most animal research does not focus on the pathological forms of escalated aggression. Rather, most models of aggression emphasize the adaptive forms of aggressive behaviors such as establishing and maintaining dominance or defending a territory. From a clinical perspective, it would be useful to understand why some forms of aggression exceed the species-normative patterns, often leading to intense harm and injury. From a psychiatric point of view, these forms, of human aggression are those that require intervention both in terms of diagnosis and treatment (Eichelman, 1992; Coccaro et al., 1997). We propose that the understanding of the neural mechanisms involved in the expression of adaptive forms of aggressive behaviors may help in understanding how pathological forms can be expressed and which are the determinants that trigger excessive outbursts.

In the present review we will analyze adaptive forms of aggressive behavior comparing two phylogenetic groups: rodents and nonhuman primates (mainly Old World monkeys). The reasons of this approach are threefold. First, rodents, more specifically rats and mice, are the most studied and characterized species both in terms of their behavioral biology and in terms of their neurobiological mechanisms of aggression. Secondly, the social complexity of rodents and nonhuman primates renders these orders particularly interesting for understanding how social and genetic factors may affect their social behavior. Thirdly, more interestingly, nonhuman primates, being phylogenetically more closely related to humans, may better model human aggression as their psychological development, cognitive functions and brain structures are, in part, homologues to those of humans.

In the second part of this review we will show how individual differences in aggression maybe partly attributed to a different genetic background or distinctive social experiences, particularly during critical developmental periods.

1. Adaptive and pathological forms of aggressive behaviors

Impulsive–hostile–injurious violent outbursts differ fundamentally from the premeditated instrumental calculating attacks in their extreme forms (Vitiello and Stoff, 1997), although many forms of aggressive behavior represent a mixture of both forms, proactive and reactive. In functional terms, it is possible to distinguish between two broad categories of adaptive aggression: one concerned with competition for resources (competitive aggression) and the other concerned with protection of self or offspring from potentially dangerous conspecifics or predators (protective aggression) (Archer, 1988). Intraspecific

competitive aggression is generally characterized by "ritualized" or "offensive" patterns of attacks as animals are usually restrained in the use of the deadliest weapons at their disposal; this limits the likelihood of causing serious injuries to their rivals (Lorenz, 1966). Example to the contrary is represented by an extremely serious form of aggressive behavior adult males in a socially organized primate species, namely the "killing parties" of chimpanzees (Nishida et al., 1985; Wrangham, 1999; Wilson and Wrangham, 2003; Wilson et al., 2004; Wrangham and Wilson, 2004). While these deadly attacks by a chimpanzee troop toward their neighbors are rare, they cannot be dismissed as abnormal or accidental. The chimpanzees express their anticipatory excitement behaviorally and physiologically, and during the actual acts of killing they emit pleasurable vocalizations and postural displays that may have parallels in human psychopathology (Farrington, 1993; McElroy et al., 1998). Another example of deadly aggression observed in numerous rodents and primates species is the killing of infants by conspecific males and/or females to gain access to mates and/or resources (Hrdy, 1979; Hausfater and Hrdy, 1984; Parmigiani and Vom Saal, 1994; Parmigiani et al., 1994). This kind of infanticide originated in the context and under the selective forces of intraspecific competition and thus it has been named "sexually selected infanticide" (Hrdy, 1979).

Protective aggression against conspecifics (e.g., parental attack to protect offspring) may be characterized by much less ritualized or "defensive" form of attack. For example, in rodents (i.e. mice and rats), offensive and defensive forms of intraspecific attack can be distinguished on the basis of the behavioral phenotypes, since in defensive attack animals persistently direct their bites to vulnerable regions (i.e. head, ventrum and inguinal areas) of the opponent (Blanchard et al., 1977; Brain, 1981). It is important to note that an unambiguous distinction between offensive and defensive intraspecific aggression is impossible because some forms of aggression, depending on the context and sex of interacting animals, may result in a mixture of offensive and defensive types of attack (Archer, 1988; Parmigiani, 1986; Parmigiani et al., 1989; Sgoifo et al., 1992; Lucion and de Almeida, 1996).

The distinction between offensive and defensive forms of attack can be applied to several species, and it may be useful to catalogue the acts and postures of species-specific aggressive behavior in order to evaluate the intensity and the potential harmful features of a specific form of aggression. In clinical practice, it could be essential to detect injurious and excessive forms of aggression in order to carefully evaluate which motivational and contextual factors influence its expression.

2. Aggression in rodents

In mice the social organization may vary, ranging from exclusive male territoriality to relative territorial dominance with despotic structure, depending on different socio-ecological conditions. Under natural and seminatural conditions, house mice live in small reproductive units (demes, Berry, 1981) consisting of a dominant male who sires virtually all the litters, one or several breeding females with their offspring, and occasionally some subordinate males (Crowcroft and Rowe, 1963; Reimer and Petras, 1967; Mackintosh, 1981). Males that reach puberty are normally expelled, through aggressive behaviors, from their natal territories by the dominant male, whereas females can either remain in their natal territories or they can emigrate (Bronson, 1979; Gerlach, 1996; van Oortmerssen and Bakker, 1981). Females that are present in a territory usually show a high degree of relatedness and usually tend to form communal nests. However, females can strongly compete for reproductive opportunities showing sometimes high levels of aggression, even when outside the lactation period (Palanza et al., 2005).

Female house mice were traditionally considered to be non-aggressive and passive towards conspecifics, except when engaging in parental care, the so-called maternal or post-partum aggression (e.g., Svare and Gandelman, 1973; Mackintosh, 1981). Shortly after birth in fact, females become very aggressive towards male and female intruders. The analysis of the attack pattern towards males is characteristically non-ritualized in that the attacks target areas of the body which are particularly vulnerable: the ventrum and the head. However, it is now clear that female mice are aggressive in various situations other than the lactation period. Aggression by females can be important in the regulation of reproductive potential and population dynamics of house mice social units (Yasukawa et al., 1985; Chovnik et al., 1987; Hurst, 1987; vom Saal et al., 1995; Palanza et al., 1996). The timing and context of aggression and its targets appear to differ in females and males (Palanza et al., 1996). More specifically, females appear to become aggressive after short periods of cohabitation with a male, and they direct attacks mostly towards other females, except during lactation when males are also attacked. This pattern suggests that females compete, through aggressive behaviors, either for access to males or for reproductive resources such as space, nest sites or food (Palanza et al., 2005).

In distinction from mice, rats are colonial in nature and form more elaborate dominant–subordinate relationships (Barnett, 1975; Miczek and de Boer, 2005). The typical social organization in a rat colony involves one adult male that dominates a small group of females and their young. The dominant male defends, marks and patrols the area around the feeding and nest sites, and in this sense, this area can be considered as territory. Investigations in laboratory colonies of Long–Evans rats showed that males form and maintain a hierarchy by the display of aggressive acts and postures requiring rescue of subordinate males in order to ensure their survival (Blanchard et al., 1977, 1985, 1988). Studies in laboratory colonies of other strains of rats showed that dominant males may tolerate other subordinate or young males and complex hierarchical relationships are maintained by less injurious aggressive behaviors (Blanchard et al., 1984). Similar to feral rats (Steiniger, 1950), a dominant or alpha rat typically is characterized by prevailing in conflict situations more often than the rivals or beta males which in turn prevail over subordinate or omega males. In unstable social groups, recurrent conflict compromises the immune system, diverts energy and time from reproduction and foraging, increases the risk of injuries, disrupts circadian rhythms for endocrine and cardiovascular functions,

and eventually, shortens the life span (Fleshner et al., 1989; Stefanski, 2001).

Aggressive behavior is part of colony life in rats, particularly during the early stages of its formation, and this form of aggression can be designated as dominance or within-group aggression. The most important trigger for aggressive behavior in feral and laboratory rat colonies is the intrusion of an unfamiliar adult male. The confrontations between a resident rat and an intruder can be considered as territorial aggression in the sense that aggression is more likely in the marked surroundings than in unfamiliar areas. Moreover, resident–intruder aggression is more likely when the resident is part of a breeding unit, although the female does not have to be present during the actual confrontation (Barnett et al., 1968; Flannelly and Lore, 1977). Aggressive behavior by a female rat is more likely during the initial postpartum period, when the dam attacks both male and female intruders (Haney et al., 1989; Lucion and de Almeida, 1996).

It is clear that in mice and rats, male aggression is a tool for excluding other males from a breeding unit or to maintain dominance within a more complex social structure. From an evolutionary perspective, the aggressive behavior displayed by the dominant is highly adaptive as territorial males have access to reproduction and thus have greater reproductive success than sub-ordinates and non-territorial males. In this case, there is a close link between fighting capabilities, rank and reproductive success (Palanza and Parmigiani, 1994; Parmigiani et al., 1999; Palanza et al., 2005).

3. Aggression in Old World monkeys

One interesting aspect of most nonhuman primates is their sociability and the complexity of the social organization. In particular, various Old World monkeys demonstrated that the social organization is based on a complex equilibrium of social relations in which relatedness, coalitions, alliances and hierarchies play a major role (Smuts, 1987). Such an equilibrium is often based and regulated by aggressive acts, postures and displays. Although living in groups could potentially favor the likelihood to display aggressive behaviors, it has been estimated in various monkey species that aggressive episodes account for 2–5% of an individual's daily activity (Bernstein and Ehardt, 1986). Most of these episodes are in relation to the defense or the establishment of a rank within a group (de Waal, 1982).

Aggression appears to be crucial, especially in large groups in which members live with defined kinship relationships and social dominance hierarchies. Rhesus monkeys (*Macaca mulatta*) can serve as an example to illustrate the complexity of social life in Old World monkeys. In their natural habitats rhesus monkeys typically reside in large, distinctive social groups (termed "troops") composed of several female-headed families, each spanning three or more generations of kin, plus numerous immigrant adult males (Melnick and Pearl, 1987; Cheney, 1987). The typical social organization of rhesus monkeys is based on the fact that females spend their entire life in the troop in which they were born, whereas virtually all males emigrate from their natal troop around the time of puberty and eventually join other males forming new troops (Cheney, 1987). Rhesus monkey troops are also characterized by multiple social dominance relationships, including distinctive hierarchies both between and within families, as well as a hierarchy among the immigrant adult males (Lindburgh, 1971).

Aggression among monkeys occurs frequently during the course of attaining a higher social status. Once dominance has been established and the group is characterized by a social hierarchical stability, rates of physical aggression markedly decrease. Intense aggression is replaced by threat displays and avoidances during a period of relative stability in which the dominance–subordinate relationship is recognized by group members (Bernstein, 1964; Bernstein and Ehardt, 1986; van Noordwijk and van Schaik, 1985; van Noordwijk and van Schaik, 2001).

Studies in rhesus macaques and vervet monkeys (*Cercopithecus aethiops*) showed that high-ranking animals are not necessarily the most aggressive individuals in a social group (Higley and Suomi, 1989; Fairbanks et al., 2001; Higley, 2003). However, when dominant monkeys engage in social conflict they tend to win aggressive encounters with others. One factor that plays a major role in conflicts relates not only to the fighting ability but also to the ability to form coalitions and social support from other group members (Chapais, 1986; Higley and Suomi, 1996; Fairbanks et al., 2001).

When exposed to social challenges, monkeys are likely to engage in aggressive encounters (Higley, 2003). For example, in macaques, males migrate from their natal group and may join other males, so-called bachelor groups, temporarily, in order to join eventually a new social group. Entrance in a new female family group is a difficult challenge for a male. In this case aggression can be successful to help immigration. In species in which the size between male and female strongly favors the former (e.g., baboons), males encounter less hostility from females but more from males (Cheney, 1987). While in macaque and vervet monkeys females are 70–85% of the weights of males, coalitions of females against strange males are more common (Cheney, 1987). This period of migration into a new group is known to be very critical for a young male as it involves a high rate of aggression with other males and with females of strange groups that use aggression to prevent all males to enter the new troop. The mortality in this period is very high, with 30% to 50% of emigrating males being killed or disappear (Higley et al., 1996a,b; Higley, 2003).

Aggression can escalate during encounters between groups. In species characterized by male dispersal, the core of the society is represented by the female such as in rhesus macaques and baboons (Cheney, 1987; Melnick and Pearl, 1987). In this case, female aggression in intergroup encounters can be relatively intense as it involves often the defense of a territory or of a resource (Cheney, 1987). These intergroup aggressive encounters seem to be critically affected by availability of food resources and demographic factors, such as crowding.

The studies reported from rodents and primates depict the ultimate causes or adaptive functions of intraspecific aggression and its importance in the regulation of social dynamics. However to fully understand aggression we need to know the underlying biological determinants (i.e. the proximal mechanisms) such as

for example the neurochemical substrates involved in the modulation of aggressive behavior.

4. The neurobiology of aggression: the 5-HT deficiency trait. Is brain serotonin activity linked to trait or to state aggression or both?

Brain 5-HT more than any other neurotransmitter has been implicated in the neural control of expressing aggressive behavior (Miczek et al., 1995). The wealth of literature on the relationship between aggression and serotonin continues to grow despite the fact that the first reports that proposed such a link date back about four decades (Maas, 1962; Garattini et al., 1967; Giacalone et al., 1968; Valzelli, 1981).The approaches to investigate 5-HT involvement in aggression, derive from different fields of biology and psychiatry, involving different methodologies. In principle, we can distinguish three basic approaches: (1) neurohistochemical; (2) pharmacological; (3) genetic and biomolecular.

Using the neurohistochemical approach, specific assay parameters are used to evaluate the content of 5-HT and of its primary acidic metabolite 5-HIAA either at the brain level or as sampled in the CSF, often post-mortem (Brown et al., 1979; Linnoila et al., 1983). This retrospective approach correlates assay data of 5-HT or 5-HIAA in CSF or tissue to the preceding history of aggressive behavior. More recently, it has been possible to monitor in real time in vivo serotonin release with the microdialysis technique, while the animal is initiating, executing and terminating and recovering from the aggressive bout (van Erp and Miczek, 2000; Ferrari et al., 2003).

The second approach is very common because it allows direct and ready manipulation of 5-HT functioning in the living organism with drugs that are designed to act at specific receptor subtypes or by influencing the synthesis or the transporter sites of the neurotransmitter. These pharmacological manipulations become increasingly informative with the development of more selective drugs and with the possibility to target, with intracerebral microinjections, specific brain regions (de Almeida and Lucion, 1994, 1997; de Almeida et al., 2005, in press). For example, the prefrontal cortex has been identified to be significant in the inhibitory control of behavior, including also impulsive and aggressive behavior (Blair, 2001; Seguin, 2004; Cardinal et al., 2004; Spinella, 2004; Kheramin et al., 2005; de Almeida et al., in press).

The genetic and biomolecular approach has become recently very attractive with the introduction of more sophisticated genetic analysis and biomolecular manipulation that can affect the expression of specific brain proteins that are involved in the 5-HT neurotransmission process (Lesch and Merschdorf, 2000). In particular, the link between low 5-HT activity and aggression found strong support from mice missing specific genes that either directly or indirectly affect serotonin inactivation (Nelson and Chiavegatto, 2001).

A traditional proposal posits that a deficit in serotonin activity correlates with impulsive and violent personality traits (Brown et al., 1979; Linnoila et al., 1983; Mehlman et al., 1994; Mann, 1999). This view has been supported by many studies in human and nonhuman primates based on the CSF concentrations of the 5-HT major metabolite 5-HIAA obtained from subjects with antisocial personality (Brown et al., 1979; Virkkunen et al., 1989, 1994; Linnoila et al., 1983) and in monkeys which have been rated as impulsive and that have been described as violent in unprovoked and unrestrained social interactions (Higley et al., 1992; Mehlman et al., 1994; Higley et al., 1996b; Bennett et al., 2002; Westergaard et al., 2003; Higley, 2003). Preclinical studies in rodents add some supporting evidence to the hypothesized serotonin deficiency trait. In fact, the reduction of brain serotonin by 5-HT synthesis inhibition with *para*-chlorphenylalanine increases some forms of rodent aggression (Valzelli et al., 1981; Vergnes et al., 1986). Conversely, pharmacological manipulations aimed at increasing brain 5-HT activity, blocking the 5-HT reuptake at synaptic terminals with the chronic treatment of SSRIs or increasing 5-HT production with 5-hydroxtryptophan administration (a 5-HT precursor), decreases aggression (Olivier, 2004; Nelson and Chiavegatto, 2001). It should be noted that many studies have generated contradictory evidence without any negative correlation between CSF 5-HIAA and aggressive behavior in primates and rodents (for example, Yodyingyuad et al., 1985; van der Vegt et al., 2003).

Human studies indicate that brain serotonin deficiency is limited to some forms of aggressive behaviors related to impaired impulse control (Coccaro, 1989; Virkkunen and Linnoila, 1993). Soubriè (1986) suggested that low CSF 5-HIAA tends to be correlated with forms of aggression that escalate out of control and that prompt negative social consequences. Impulsivity can be considered as a personality disorder as it leads to impaired social relationships (Cloninger, 1988).

In line with the human studies, monkeys with low CSF 5-HIAA do not necessarily show high levels of overall aggression but only an increase in those forms that are escalated to excessive levels, i.e. injurious and persistent (Higley, 2003). For example, in macaques, males with low CSF 5-HIAA tend to engage in few social interactions causing them to be more socially isolated (Higley et al., 1992, 1996a). Other studies in different species of Old World monkeys showed that individuals with low CSF 5-HIAA take risks during their moves in the forest canopy by jumping long leaps at dangerous heights and repeatedly jumping into baited traps (Mehlman et al., 1994; Higley et al., 1996a; Fairbanks et al., 1999). Laboratory studies indicate that male rhesus macaques with low CSF 5-HIAA are quicker to approach a novel black box compared with males with high CSF 5-HIAA (Bennett et al., 1998) thus suggesting that they tend to approach more promptly unknown objects or situations that could be a potential risk.

A key question in the neuropsychiatric evaluation of the negative correlations of 5-HT metabolism with aggression is whether such correlations reflect causal relationships such as a trait marker of impulsivity. In addition to the problematic nature of deducing causality from correlational data, there are the phasic and dynamic serotonin changes in the course of aggressive bouts that are superimposed on the prevailing serotonergic tone.

The possibility to monitor transient changes in 5-HT activity during aggressive confrontations has been attempted in recent

investigations using in vivo microdialysis in rats (van Erp and Miczek, 2000; Ferrari et al., 2003). With this methodology it has been possible to monitor on-line extracellular 5-HT release from corticolimbic structures in distinctive phases of an aggressive confrontation: (1) under resting conditions, (2) in anticipation of an aggressive encounter; (3) during the initiation of an aggressive interaction; (4) during the execution of aggressive acts and postures, and (5) during the recovery phase when the confrontation was terminated. The main source of serotonin in the mammalian brain derives from neurons located in the dorsal and median raphe nuclei with ascending and descending projections to terminals in several forebrain structures such as the prefrontal cortex, hippocampus, striatum and the nucleus accumbens, and to the spinal cord, respectively. Microdialysis studies revealed that during a brief aggressive episode resident rats in whom this behavior was an integral part of their behavioral repertoire, showed a marked decrease in 5-HT levels in the prefrontal cortex but not in the nucleus accumbens (van Erp and Miczek, 2000; Ferrari et al., 2003). The prefrontal cortical 5-HT decrease is prolonged and may persist for at least one hour after the end of the confrontation. In resident male rats that are conditioned to attack an intruder at exactly the same time every day over a 10-day period, 5-HT levels in the nucleus accumbens decrease by 30–35% relative to the baseline levels on day 11 at the time of the anticipated confrontation, but in the absence of the actual aggressive confrontation (Ferrari et al., 2003; see Fig. 1). Concurrently, dopamine levels increased by 60–70% above baseline. These data indicate that the display of aggressive behaviors is linked to acute 5-HT changes in mesocorticolimbic structures. However, the 5-HT decrease in prefrontal cortex and in the nucleus accumbens may persist also in the absence of the motor activation associated with aggressive outbursts suggesting a possible role of 5-HT release in mesocortical structures as part of a system that prepares an individual for an aggressive confrontation that are dissociated from the execution of motor plans related to aggressive behaviors. Future studies are required to investigate how acute changes in 5-HT release may differ in individuals with tonic high or low levels of brain serotonin activity in order to understand the relationship between long-term changes assessed with CSF assays and the phasic local response during an aggressive bout.

Most of the work on individual differences in CSF serotonin metabolites in relation to aggression has been conducted in nonhuman primates. These data have been replicated several times in macaques and also in vervet monkeys. In addition, they agree with many similar correlational analyses conducted in humans who are characterized by certain types of aggressive behavior, impulsivity, risk-taking and alcoholism (Linnoila et al., 1983; Kruesi et al., 1990; Virkkunen and Linnoila, 1993; Mehlman et al., 1994; Manuck et al., 1998). Post-mortem tissue measurements of 5-HT and 5-HIAA in mice, hamsters, rats and tree shrews had generated a complex pattern of increases and decreases when correlated with earlier patterns of aggressive behavior (Welch and Welch, 1968; Karczmar et al., 1973; Lasley and Thurmond, 1985; Payne et al., 1985; Raab, 1971). A recent investigation conducted in male rats which correlated CSF 5-HT levels with aggression illustrates such complexity (van der Vegt et al., 2003). These results are difficult to reconcile with those reported in primates and humans as the data showed a positive correlation between duration of male aggressive behaviors, as measured in a 10-min resident–intruder test, and CSF concentrations of 5-HT and 5-HIAA. However, when CSF levels of 5-HT were measured a few minutes after an aggressive confrontation, serotonin levels are decreased compared to baseline. Thus, the rat CSF data may represent an index of an aggressive trait, and these data contrast with many findings in human and nonhuman primates. However, when serotonergic activity is measured to evaluate a rapid change in state, then the results seem to reconcile with other findings obtained in primates. van der Vegt et al. (2003) interpret these results in terms of the adaptive significance of aggressive behavior by a resident toward an intruder in rodents relative to intra-group conflict in primates. The types of aggressive behavior that are usually measured in rodents fulfill biological functions such as acquiring resources, establishing and maintaining dominance and dispersing rivals. Thus, aggression is viewed as a behavioral strategy for survival and for increasing the individual's reproductive success. Studies in primates focus on excessive forms of aggression which are indicative of the individual deficits in impulse control (Higley, 2003). In most of the nonhuman and human primate studies there is a tendency to use the term aggression as synonymous with impulsivity.

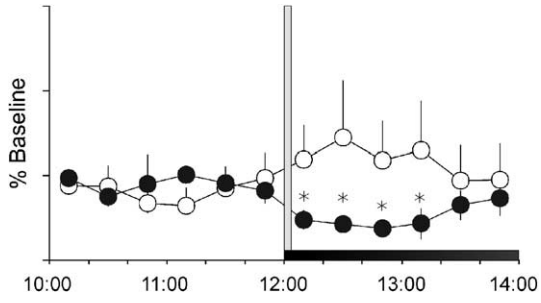

Fig. 1. Proportion of animals attacking conspecifics intruders in different genetic lines (Modified from: Parmigiani et al., 1999).

It is possible to hypothesize that in primates CSF levels of 5-HT may reflect primarily traits of impulsivity that may include some types of aggressive acts. The display of aggressive behaviors constitutes only a secondary result of dysfunctional social relationships. These impulsive aggressive acts result in impaired social interactions, and they emerge from inadequate responses to social communication. Higley (2003) refers to evidence that correlates rates of impulsivity with rates of aggressive acts.

The predictions that can be derived from this hypothesis are that individuals with a low CSF 5-HIAA trait tend to be socially isolated from the other group members and thus fail to reach higher dominance status within the group. From an evolutionary perspective these individuals have very few possibilities to reproduce successfully as their social behavior is maladaptive. Data from rhesus macaques and vervet monkeys support this hypothesis as they show that low levels of CSF 5-HT

characterize individuals who are removed from the social network (Westergaard et al., 1999). The high rates of wounds received (Mehlman et al., 1994) and the high rate of violent deaths (Higley, 2003) provide evidence for their frequent involvement in injurious and less ritualized agonistic behavior.

It is possible to construct a hypothetical framework that relates the data on CSF concentrations of 5-HT and its primary acidic metabolite 5-HIAA in primates and the corresponding data in rodents, to aggressive confrontations. Accordingly, we postulate that, in primates, CSF 5-HIAA could be considered as a marker for maladaptive behavior while those in rats are to be considered as a marker for aggressive behavior with a defined biological function. In rodents the fighting ability and aggression levels of an individual are correlated with and predictive of dominance. High social status impacts on an individual's survival and reproductive success. For example, in a small group of mice the levels of aggression of each individual is predictive of the social status of an individual (Ferrari et al., 1998; Parmigiani et al., 1999). In contrast, in nonhuman primates an excessively aggressive individual in a troop is not necessarily the highest-ranking animal (Chapais, 1983; Kaufmann, 1967). In macaques and other Old World monkeys, males may form coalitions in order to rely on social support when engaging in conflicts with other males and this support may facilitate access of males to a new troop (van Noordwijk and van Schaik, 1985). Thus, the ability to engage in and strengthen specific social relations in the absence of impulsive behaviors may help males in acquiring a high social status. Overall, high-ranking individuals clearly show good fighting abilities as dominant macaques win more aggressive encounters than others (Kaufmann, 1967; Chapais, 1983; Higley, 2003).

In most nonhuman primates living in complex social societies, the display of excessive forms of aggression is not conducive to survival as well as reproduction because this strategy can be highly risky in stable social groups as it increases negative social interactions with other group members without necessarily gaining some long-term advantages. The control of impulsivity may facilitate affiliative behaviors and coalition formations. This requires competent social skills in order to use aggression contextually and to understand the type of social relations engaged by the members of a group. Thus, in some nonhuman primate species failure in impulse control and the display of excessive aggression could be considered as an index of psychosocial impairment and, in some cases, of social psychopathologies.

5. 5-HT, genes and aggression. Interaction between genes and environment

A significant portion of individual differences in aggressive behavior has been traced to genetic inheritance. For several decades animal research has addressed this topic by using mice and rats as animal models for aggression. Initial reports on genetic differences of male aggressive behaviors in mice were based on strain comparisons (Scott, 1942). Since then, a large number of studies have investigated aggressive behaviors in inbred and outbred strains of mice, recombinant lines or selected lines in order to map or identify genes for aggressive behavior, and to determine the mechanisms through which genes influence aggression (see Brain et al., 1989; Maxson, 1981; Parmigiani et al., 1999; de Boer et al., 2003; Miczek et al., 2001). The use of genetic lines specifically selected for aggressive behaviors was first initiated in Finland by Lagerspetz (1964). Since then, several genetic lines of mice were generated based on the levels of male (van Oortmerssen and Bakker, 1981; Cairns et al., 1983) and female (Ebert and Hyde, 1976) aggressive behavior. These classic behavior genetics studies succeeded in selecting, within a few generations, animals with different levels of aggressive behavior suggesting that the propensity to engage in intraspecific attack is an inherited trait.

The availability of many strains of mice prompted their use in aggression research to evaluate genetic variability in the expression of aggressive behaviors (Maxson, 1992; Parmigiani et al., 1999; Miczek et al., 2001). Many of these studies examined to which extent the strain differences in mouse aggressive behaviors could be attributed to maternal factors, and eliminated these factors as the major source of the variation (see also Sluyter et al., 1996). Furthermore, in each genetic line of mice different forms of aggression, such as intrasexual aggression, infanticide and maternal aggression co-vary (Parmigiani et al., 1999—see Fig. 2). More specifically, a strain that shows high levels of intermale attack also engages in high levels of interfemale attack and male infanticide. This co-variance probably indicates that phenotypically different forms of aggression, such as intrasexual attack and infanticide, which share similar functions (i.e. competition for mates and resources) may also share a similar pattern of genetic inheritance.

Artificial selection aimed at producing different genetic lines of mice has provided also some information on 5-HT activity in strains with different aggression levels. For example, different strains of mice have different 5-HT levels in some limbic areas (Valzelli and Bernasconi, 1979; Serri and Ely, 1984; Maas, 1962). Strains with low 5-HT brain levels also show high levels of aggression in accord with the traditional view that serotonin is inversely correlated with aggressive behavioral traits.

Chromosome analyses of different wild house mice populations revealed that in different geographical areas it is possible to find house mice with a different number of pairs of chromosomes (Corti et al., 1989). One of the behavioral

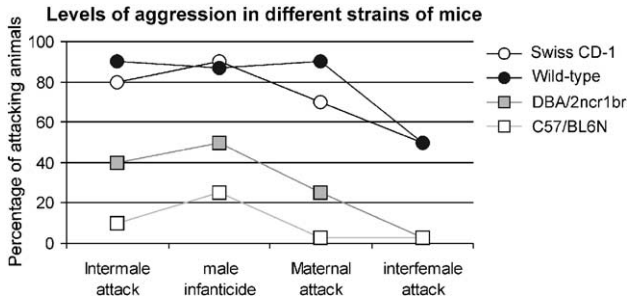

Fig. 2. A schematic illustration of a serotonergic neuron with a description of synthesis, release, re-uptake and de-amination processes involved. Location of receptors and enzymes involved in 5-HT metabolism have been described with particular emphasis on the process of production of CSF 5-HIAA.

consequences of this chromosomal difference is that males differ in their levels of aggression. Moreover, these genetic differences seem to have a significant impact on mouse population dynamics, but the link to brain serotonin activity remains to be established.

Using a different approach, it has been possible to identify specific regions of a chromosome that are significantly implicated in the genetic control of aggression. In particular, the Y chromosome has been one of the first targets for genetic analysis of aggression. It has been shown that the non-pseudoautosomal region (NPAR) of the Y chromosome influences male aggressive behavior (Maxson, 1996). By comparing reciprocal F1's, it has been shown that variants of one or more genes on the Y chromosome differ in their levels of aggression.

Recent advances in the field of molecular biology enabled the identification of some of the genes that regulate 5-HT brain neurotransmission and its metabolism (Nelson and Chiavegatto, 2001). The use of mutant mice with a specific gene mutation or deletion increased the information on the interaction between a specific genotype and the aggressive behavioral phenotype. These studies are based on the principle that the expression of some genes is involved in the synthesis of proteins that are related to 5-HT neurotransmission. The blockade of this expression can lead to the alteration of 5-HT neurotransmission because it interferes with processes at specific stages of the serotonin synthesis, release regulation, re-uptake or metabolism (Fig. 3). In the meantime, compensatory changes during the maturation of the gene-manipulated mouse as well as its genetic background have emerged as critical factors in the ultimate behavioral phenotype in addition to the targeted gene (Crawley et al., 1997; Crawley, 1999).

One of the first attempts to apply this 'knock-out' methodology to aggression research showed that mice of the 129 Sv strain lacking the 5-HT_{1B} receptor (−/−) are more aggressive than the corresponding wild-types (+/+) although the actual increases in the frequency of aggressive behavior compared to baseline are very small (Saudou et al., 1994; Ramboz et al., 1995; Brunner and Hen, 1997). The results of these studies are in accord with the view that drugs acting as 5-HT_{1B} agonist selectively decrease aggressive behaviors in mice probably via postsynaptic 5-HT_{1B} receptors (Fish et al., 1999; Miczek and de Almeida, 2001; Miczek et al., 2002; Olivier, 2004; de Almeida et al., in press). Agonists for the rodent 5-HT_{1B} receptors (named r5-$HT_{1B,}$ homologue to the h5-HT_{1B} of humans) have been known since the development of anti-aggressive drugs called 'serenics' (Olivier and Mos, 1986; Olivier et al., 1987, 1990). However, these drugs with anti-aggressive properties (Parmigiani and Palanza, 1991; Ferrari et al., 1996) were mixed agonists for the 5-$HT_{1A/1B}$ receptors, such as eltoprazine and fluprazine, thus their effects could still be mediated, at least in part, by their activity at 5-HT_{1A} receptors. Selective 5-HT_{1A} receptor agonists are efficacious and potent in suppressing aggressive behavior, although their sedative and motor suppressive effects may contribute to their anti-aggressive

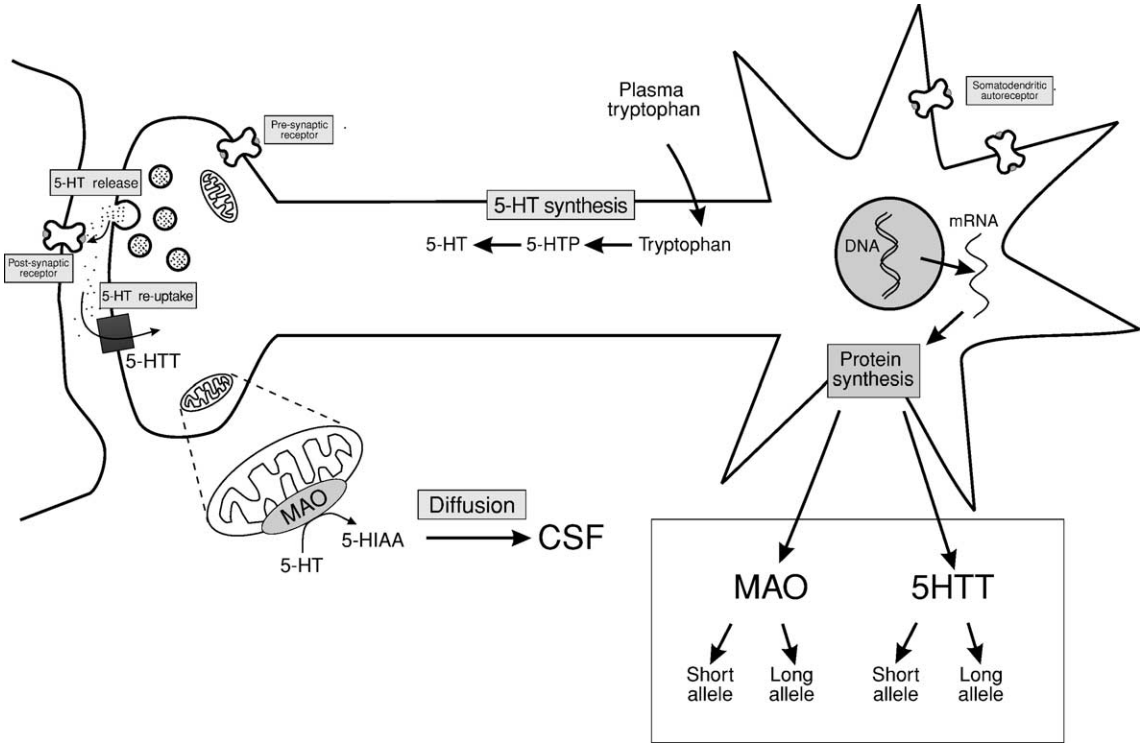

Fig. 3. Extracellular 5-HT concentrations in the nucleus accumbens on day 11 after 10 days of regularly occurring aggressive confrontations (modified from Ferrari et al., 2003). On this day no confrontation took place. The time point at which the confrontation was scheduled on previous days (1200 h) is indicated by a gray vertical bar. The dark phase of the light cycle is indicated by a horizontal black bar. Closed symbols depict data from rats that confronted an intruder during the previous 10 days ($n=7$). Open symbols depict the light-entrained control group ($n=7$). Asterisks depict values that are significantly different compared to light entrained animals ($P<0.05$). Data are expressed as percentage of baseline and are presented as group means±S.E.M.

effects (Miczek et al., 1998, de Almeida and Lucion, 1997). The development of more selective drugs for the 5-HT_{1B} receptors has been advantageous, but it still leaves the question open as to pre- vs. post-synaptic receptors as the relevant sites of action. In fact, it has been shown that 5-HT_{1B} receptor agonists CP-94,253, zolmitriptan and anpirtoline reduce aggressive behaviors without affecting motor activity (de Almeida et al., 2001; Fish et al., 1999; Miczek et al., 2002; de Almeida and Miczek, 2002; de Almeida et al., in press). This effect seems to be even more robust when aggression is escalated as for example in individuals who are stimulated to attack after alcohol consumption or social instigation (see Miczek et al., 2002).

The development of mice in which the gene is deleted that encodes for the MAO-A enzyme is another example in which molecular biology methodologies direct attention to the link between serotonin and aggression. Such gene encodes for a degradative enzyme that preferentially catalyze the deamination of serotonin and norepinephrine. MAO-A knockout mice have been shown to exhibit increased aggression despite the elevated levels of brain serotonin (Cases et al., 1995). Apparently, this outcome stands in contrast to the effects of pharmacological inhibitors of monoamine oxidase enzymes in reducing male mouse aggression (Florvall et al., 1978) and foot shock-induced defensive aggression in rats (Datla and Bhattacharya, 1990). It is possible that these contrasting results could be related to the fact that aggression-heightening effects of MAO-A deletion is not directly linked to serotonergic activity but to secondary effects in other neurochemical systems.

Up to now there is little information about the role of these genes in human aggression in relation to the serotonergic system. Among males of a Dutch family with a chain termination mutation in the eighth exon of the MAO-A gene, a correlation was found between impulsivity and mild retardation (Brunner et al., 1993). Another study identified a functional length polymorphism in the promoter region of the MAO-A gene (Sabol et al., 1998). It has been shown that this polymorphism is associated with interindividual variability in impulsivity based on indirect measurements evaluated via questionnaires (Manuck et al., 2000). Furthermore, in most subjects the serotonergic activity was evaluated by measuring the magnitude of the prolactin response to an acute fenfluramine challenge. In a group carrying one of the four variants of the polymorphism an inverse correlation between impulsivity and responsivity to the serotonergic agonist challenge was found.

One informative aspect of these findings is that MAO-A gene polymorphism seems to be influenced by early life experiences. This may represent a potential model for investigating the interaction between gene and environment in relation to the serotonergic system and aggressive behavior. From this perspective, an important series of studies in humans reported that negative early experiences such as childhood maltreatment interact with the presence of alleles associated with low MAO-A activity (Caspi et al., 2002; Foley et al., 2004). It has been proposed that such interaction could modulate the emergence of pathological forms of aggressive behaviors (Newman et al., 2005). However, the neural mechanisms for these environment–gene interactions is still unknown. Newman et al. point to the hypothalamic–pituitary–adrenal axis as an important system sensitive to early rearing experience (Higley et al., 1993). In fact, rhesus monkey that are deprived of maternal contact exhibit alterations in the neuroendocrine stress axis (Suomi, 1987).

The issue of early adverse experiences as crucial factors in influencing the development of pathological social behavior was empirically addressed by Harlow (1959). Since then a number of studies in nonhuman primates provide evidence that early maternal deprivation in rhesus monkeys leads to the development of aberrant social behaviors together with changes in neurochemical functions and neuroendocrine activity (Suomi, 1987, 1999, 2003; Maestripieri, 2003). A recent study in male rhesus monkeys investigated the interaction between early rearing experiences and the genetic background at the level of the MAO-A gene promoter region (Newman et al., 2005). In rhesus macaques, the MAO-A gene shows a polymorphism in the transcriptional control region (rhMAO-A-LPR) coding sequence that is orthologous to that of humans (MAO-A-LPR). Males who experienced normal rearing by the mother, showed higher levels of aggressive behaviors related to competition for food only when they carried the low-activity rhMAO-A-LPR allele (Newman et al., 2005). This finding is in accord with previous studies in humans and mice which showed that low MAO-A activity is correlated with increased aggression (Brunner et al., 1993; Cases et al., 1995). However, peer-reared males (i.e. individuals with impoverished infancy) with the high-activity rhMAO-A-LPR allele showed species-typical levels of competitive aggression. Clearly, these data are difficult to interpret in light of the relation between the genetic polymorphism at the rhMAO-A-LPR allele and serotonergic activity because there are no data available yet on serotonin activity. Thus, low- and high-activity MAO-A polymorphs need to be characterized in terms of their brain serotonin levels and activity. Secondly, the measures of aggression used in the study are not related to escalated forms of aggressive behaviors rather to adaptive competitive behavior. These studies should be complemented by measurements of impulsivity in order to relate them to the characterization of an impulsive trait. Clearly, these types of studies emphasize the necessity to comprehend how genes that are related to aggressive behaviors, interact with social experiences and how specific rearing experiences affect gene expressions, especially in situations in which the genetic background is indicative of susceptibility to develop pathological forms of aggressive behaviors.

Molecular biology studies have identified another important genetic polymorphism that is involved in the serotonergic modulation of aggressive behavior, namely the 5-HT transporter gene (5-HTT; Lesch et al., 1997; Heinz et al., 1998; Holmes et al., 2002). This gene plays an important role in the expression of a protein which regulates the reuptake of 5-HT from its terminals and cell bodies thus constituting the major route of inactivation (Hoffman, 1993; Swann, 2003). It has been shown that the activity of the 5-HTT is correlated with 5-HT turnover and aggression (Holmes et al., 2002; Daws et al., 2005). In fact, drugs inhibiting the 5-HT reuptake such as the SSRIs, fluoxetine and fluvoxamine, reduce aggressive behaviors in different situations in rodents as well as in nonhuman and

human primates (Miczek et al., 2002; Swann, 2003; Pinna et al., 2003; Villalba et al., 1997). The effect of the 5-HTT gene deletion on aggressive behaviors has been recently investigated in mice (Holmes et al., 2002). 5-HTT knockout male mice (−/−) showed reduced aggressive behaviors and longer attack latencies compared to wild type controls (+/+). These effects seem to be rather specific to aggressive behavior as other social parameters were not affected (Holmes et al., 2002). In rhesus macaques the 5-HTT gene has a length variation in its promoter region (*rh*5-HTTLPR). There are two allelic promoter variants: a heterozygous short allele (LS) and the homozygous long allele (LL). The LS variant confers low transcriptional efficiency to the 5-HTT promoter relative to the LL variant. It has been proposed that the low 5-HTT expression may result in decreased serotonergic function (Lesch et al., 1997). Similar allelic promoter variants have been also found in humans (named 5-HTTLPR; Heils et al., 1996; Lesch et al., 1997), although the relationship between these variants and specific types of aggression in humans awaits further study (see Holmes et al., 2002).

By contrast, studies in monkeys provide more information on the 5-HTT gene polymorphism in relation to early experiences and aggression/5-HT interaction. More specifically it has been shown that early rearing experiences can affect the effects of these variants on CSF 5-HIAA concentration and on the probability to display aggressive behaviors. In general, the LS allele in peer-reared but not in mother-reared macaques influences alcohol consumption and sensitivity to alcohol as well as the response of the hypothalamic–pituitary–adrenal axis to social stress separation (Champoux et al., 2002; Barr et al., 2003a,b). More interestingly, juvenile male macaques carrying the LS allele showed higher rates of unprovoked aggressive behaviors than mother-reared animals (Barr et al., 2003b). These findings seem to suggest that early rearing experiences in which the relation between the mother and the infant is disrupted, can be at risk to develop psychopathologies in adulthood such as escalated aggression. This could apply to individuals who have specific predispositions such as by carrying the LS allele of the 5-HTT. Further investigations need to characterize the nature of this aggression and the precise link to abnormal serotonergic function.

6. Conclusions

We have focused on aggressive behavior in two phylogenetic groups: rodents and nonhuman primates. Despite clear differences in species-typical aggressive behaviors, in terms of behavioral patterns, motivations, triggering stimuli, behavioral biologists still consider the importance of emphasizing continuities in adaptive functions of aggressive behaviors across rodents and primates. This approach is important since it characterizes possible homologies with human aggression, and it traces the evolutionary origins of human psychopathologies.

Studies of aggression in nonhuman primates are of particular relevance as the social system of most species of Old World monkeys, such as those of macaques and of chimpanzees, is complex and, in some cases, also very variable in terms of organization. Understanding these social systems promises to provide insights into aggressive behaviors with clear biological functions, and also into pathological forms of escalated aggression.

A number of investigations generated evidence for a lack of impulse control as a potential contributor to an increased risk for harm and injury and, ultimately, leading to an individual's exclusion from a social group. Individuals showing impulsive temperament are usually excluded from reproduction (Higley, 2003). Thus, the display of violent and escalated aggressive behaviors could be used as an index of psychosocial impairment.

From a neurobiological perspective aggression has been extensively investigated. In particular the serotonergic system is implicated in its modulation. Clearly, serotonin is not the only neurotransmitter involved in aggressive behaviors, and it has reciprocal relations with other amines, amino acid neurotransmitters and neurosteroids. Traditionally, studies in humans and nonhuman primates indicate that 5-HT activity (assayed from samples of CSF 5-HIAA) is inversely related to certain kinds of aggression such as impulsive hostile aggressive behavior in explosive antisocial personality disorders. However, future research should clarify to which extent CSF 5-HIAA reflects an aggressive trait and to which extent it incorporates changes in state. From this perspective, an important question in the neurobiology of aggression research still remains unanswered: how transient changes of 5-HT activity can affect and are superimposed on a potential serotonergic trait? Resolving this issue is crucial to our understanding of how the whole serotonergic system is working in the brain and how single measurements of 5-HT activity can predict potential predispositions in expressing pathologically excessive forms of aggressive behaviors. Only recently more advanced techniques such as in vivo microdialysis enabled measures of phasic changes in 5-HT activity in the brain while aggressive behavior is in progress (van Erp and Miczek, 2000; Ferrari et al., 2003). However, we are still not able to detect more accurately serotonin activity with a moment-to-moment resolution and to predict to which extent these transient changes in specific brain areas affect the overall serotonin content in the brain when measured at the level of CSF.

Genetic research of aggressive behavior has been carried out for decades by using a "top–down" approach. Clearly, the traditional methodologies available to behavioral geneticists produced fruitful information aimed to demonstrate the inheritance of different forms of aggressive behaviors in mammals. In the last decade, bio-molecular technologies complemented the traditional approach of behavioral genetics by proposing a "bottom–up" approach in which changes in aggressive behaviors could be recorded after the identification and manipulation of a single gene. We discussed some examples in which specific genes are present in different allelic forms. The presence of such polymorphism has been found clearly for two genes involved in 5-HT inactivation: the 5-HTT and MAO-A. There are encouraging results in humans and macaques showing that individuals bearing variants of these alleles are differentially sensitive to experiential factors leading to higher rates of aggressive behaviors (Barr et al., 2003b; Newman et al., 2005).

Although studies in nonhuman primates are still at a very early stage, the understanding of the relationship between genetic factors that predispose an individual to display aggressive behaviors and the early experiences, promise to characterize the pathological types of human aggression.

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