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Toward an Animal Model for Antisocial Behavior: Parallels Between Mice and Humans

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The goal of this article is to examine whether mouse lines genetically selected for short and long attack latencies are good animal models for antisocial behavior in humans. To this end, we compared male Short and Long Attack Latency mice (SAL and LAL, respectively) with the extremes of the Dunedin Multidisciplinary Health and Development Study (men who persistently displayed antisocial behavior [Persisters] and men who never manifested antisocial behavior [Abstainers]). Groups were compared on the basis of five distinct domains: aggression/violence, reproduction, cognition, behavioral disorders, and endophenotypes. Our observations point to considerable parallels between, on one side, SAL and Persisters, and, on the other side, between LAL and Abstainers (but to a lesser extent). We believe that SAL and LAL are good mouse models to study the development of antisocial behavior and will yield valuable and testable hypotheses with regard to the neurobiological and genetical architecture of antisocial behavior.

KEY WORDS: Mouse model; aggression; violence; antisocial behavior.

INTRODUCTION

It is now widely accepted that genetic variation plays an important role in the development of behavioral and psychiatric disorders (e.g., Plomin *et al.,* 1994). Antisocial behavior is no exception. A recent meta-analysis of 51 twin and adoption studies points to approximately 40% of the variation in adolescent and adult antisocial behavior being accounted for by genetic factors (Rhee and Waldman, 2002). This suggests that research on the etiology of antisocial behavior should look beyond socioeconomic contexts and parenting processes and that it should incorporate genetic explanations and develop new theories of nature–nurture interplay (Hill *et al.,* 2002).

Behavioral genetic studies have already provided some evidence of the interplay between genetic and environmental influences on antisocial behavior (e.g., Cadoret *et al.,* 1995; Jaffee *et al.,* 2003), but the actual identification of the genes involved in this type of behavior is a much slower process. The main difficulty is the assumption that there are a large number of genes involved, each of these with only a small effect, which makes them difficult to detect. In this context, there are essentially two different strategies to tackle the problem of gene identification: the candidate gene approach and the whole genome scan. The first approach applies only to genes with known location and function and to pathways that we already partially understand. Although recent findings on polymorphisms in monoamine oxidase A are very promising (Caspi *et al.,* 2002), overall results on the identification of the genes associated with risk for antisocial behavior are rather meager. The second strategy, a systematic genome scan, identifies "new," yet unidentified, QTLs. This approach has been successful to map QTLs for complex traits such as reading disability (Gayan *et al.,* 1999), but to our knowledge, this strategy has not yet been applied to find QTLs affecting variation in antisocial behavior. An alternative way forward is to use animal models. Although there is no animal model that can ever fully mirror the human situation that it is modeling (Green, 1983), there

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are clear advantages to the implications of animal models. Two obvious advantages are the ability to control the environment (raising, housing, testing), and the possibility to actively manipulate the animal model, which can be carried out at multiple levels (e.g., genetically, pharmacologically, endocrinologically). These strategies are virtually impossible in humans because of ethical and experimental limitations. A crucial question, though, is the choice of model organism. Which species and which type of manipulation can produce the most satisfying answers?

One of the most popular model organisms nowadays is the house mouse. Mice are generally easy to keep and breed well, with short generation times. Inbreeding is well tolerated; thus hundreds of inbred strains are now available (see http://jaxmice.jax.org/info/ for other types of strains and lines), which not only allows a range of comparisons to be carried out but also creates the conditions to successfully identify genes that underlie the variation in complex traits, such as aggression. Another key advantage is the possibility to isolate and maintain embryonic stem cells, which permits the creation of genetically engineered animals. Perhaps most important is the availability of the sequence of the mouse genome (Mouse Genome Sequencing Consortium, 2002) which is a key information tool for understanding the contents of the human genome and a key experimental tool for biomedical research. For more (recent) information about the house mouse, its use for comparative and functional genomics, and its history, as well as a draft version of its genome, the reader is referred to the various contributions in *Nature* issue 420 (2002).

Animal models, including mouse models, are generally evaluated on the basis of their reliability and validity. Reliability refers to the stability and reproductability of the phenotype. Validity implies four different features. Face validity refers to the similarity between the animal model and the specific human behavior of interest. In short, the animal model should mimic the human behavior as much as possible. Predictive validity usually refers to how useful animal models are for predicting the efficacy and safety of drugs for the disorders in question. Construct validity exists when the model either relies on or elucidates the same basic underlying mechanism responsible for the conditions in humans. Genetic validity exists when the risk for a disease is known to have similar genetic components in both humans and the animal model.

In the present article, we examine whether mouse lines genetically selected for short and long attack latencies are good animal models for antisocial behavior in humans. To this end, we compare the behavioral, neuronal, and neurobiological characteristics of Short and Long Attack Latency mice (SAL and LAL, respectively) (Benus *et al.,* 1991; Sluyter *et al.,* 1996b; van Oortmerssen and Bakker, 1981), with those from humans who either persistently or never manifested antisocial behavior (Persisters and Abstainers, respectively) (Moffitt, 1993). The next section describes the mouse and human groups of antisocial behavior.

Groups

SAL and LAL

The foundation of these lines was a feral population caught in the vicinity of Groningen, The Netherlands, in 1971. Bidirectional selection for high and low intermale offensive aggressive behavior started almost immediately, and the lines have been maintained up until now at the Department of Animal Physiology (University of Groningen, The Netherlands). Aggressive behavior was—and still is—tested in a cage that takes the natural settings of the test animals into account (see van Oortmerssen and Bakker, 1981, and Figure 1).

The test measures the proneness of an experimental male mouse to attack a standard opponent (offensive intermale aggression) and takes 4 days in total nowadays. On the first day the experimental animal is habituated to the home cage (area A; slide I open, slide II

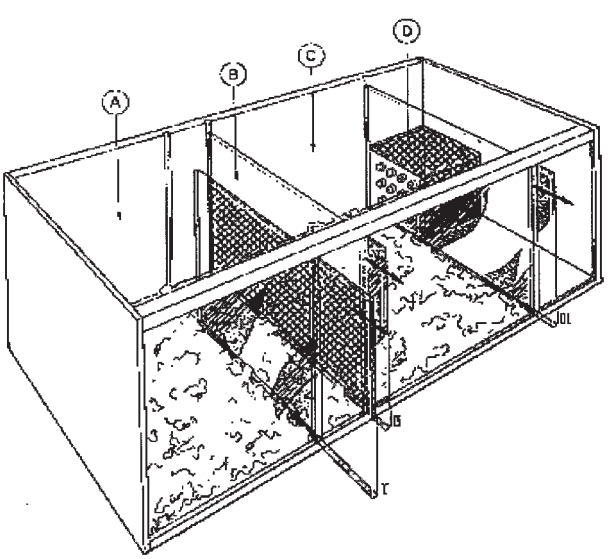

Fig. 1. The AL (Attack Latency) test cage (dimensions 80 × 30 × 30 cm) subdivided by Plexiglas slides (I, II, and III). A and B constitute the home cage of the test animal, while C is the border area and D is the chamber for introducing the opponent. For details about the procedure, see text.

closed) and, at the beginning of the dark period, is allowed to explore the border arena (area C) for a brief period (slides I and II open). On the second day the animal is trapped between slide I and II (area B) while its opponent is carefully put in the "opponent chamber" (area D). An opponent is called a standard opponent if the same type is used throughout the whole experiment ("same" in this context refers to "genetically similar," not identical as in some designs an outbred strain is used). Subsequently, slide II is opened and the experimental animal is forced to explore the border arena of its territory (area C), where under natural conditions most fights occur. When it smells the opponent and approaches the perforated part of the opponent chamber, slide III is opened and the time for the experimental animal to attack the standard opponent is measured (so-called attack latency). This procedure is repeated on days 3 and 4 and, in this way, reduces not only the effects of chance but also creates an opportunity to investigate the development of aggression over time. All tests are carried out at the beginning of the dark period when animals are most active. The behavioral measure for selection is the mean attack latency score (ALS) over 3 days. The reason we chose attack latency is not only because it is a reliable indicator of aggression (Catlett, 1961; van Zegeren, 1980) but also because other variables (e.g., number of attacks or accumulated attacking time) frequently lead to severe injuries, or even death, of the standard opponent. Selection has resulted in a high-aggression line, characterized by Short Attack Latencies (SAL), and a low-aggression to nonaggressive line, characterized by Long Attack Latencies (LAL) (see van Oortmerssen and Baker, 1981). It is important to emphasize that selection has only been performed on males. In general, females do not attack in this paradigm (but see Compaan *et al.,* 1993 after testosterone treatment following ovariectomy).

Differences between SAL and LAL are not limited to offensive intermale aggression. These selection lines are thought to represent the extremes of behavioral response patterns that coexist in a mammalian population (Henry and Stephens, 1977). One of those behavioral response patterns is through territorial control (high aggression, short attack latencies), another pattern is through immobility (low aggression, long attack latencies) (Koolhaas *et al.,* 1999). Both behaviors have been shown to be adaptive during distinct conditions (van Oortmerssen and Busser, 1989). In general, SAL mice cope actively with environmental challenges, whereas LAL mice cope passively. Typical examples are the way SAL and LAL behave in paradigms designed to tap in to those differences, such as the shock-probe/defensive burying paradigm. In this test, animals are shocked by an electrified probe, after which they can use either an active behavioral strategy, namely the pushing of bedding material toward or over the probe (defensive burying), or a passive strategy, namely increased immobility/freezing, to cope with the stressor. As expected, SAL males demonstrate more defensive burying when challenged, whereas LAL males show more immobility (Sluyter *et al.,* 1996a). This behavioral dichotomy is also reflected in the forced swim test in which LAL mice show much more immobility than SAL mice (Veenema *et al.,* 2003a, b). For a more detailed description of distinct behavioral strategies, the reader is referred to the following articles: Benus *et al.,* 1991; Bohus *et al.,* 1987; de Boer *et al.,* 2003 (this issue); Koolhaas *et al.,* 1999.

At this point it is worth mentioning that wild house mice have certain advantages in comparison to the classic inbred strains, which are derived from a small pool of ancestors. In fact, Guénet and Bonhomme (2003) regard today's laboratory strains as recombinant strains from three parental components (*Mus musculus domesticus, Mus musculus musculus* and *Mus musculus castaneus*). In any case, the implication of wild house mice would add an extra genetic dimension (i.e., more genetic polymorphisms) to the use of mouse models in biomedical research. Regarding aggression research, there is another reason why wild house mice, and particularly the SAL line, should be included: laboratory strains are generally not that aggressive, especially in comparison to SAL males, which are extremely aggressive. SAL males attack a male conspecific within seconds and, if not stopped, will continue to fight, often until the death of the opponent. Such mice would have been excluded during the initial development of the current inbred and outbred mouse strains and, in this way, most of the "aggressive" alleles of the SAL lines are likely to have been eliminated from many mouse lines or inbred strains (and, accordingly, are not identifiable using classic inbred strains in genetic analyses).

Persisters and Abstainers

Two groups of human males will be heuristically compared in this article to the SAL and LAL mice. These two groups of men have been extensively studied in the context of a longstanding program of taxonomic research into human antisocial behavior across the life course (reviewed in Moffitt, 2003).

Contrasted versus the SAL mice are men showing "life-course persistent antisocial behavior," the so-called Persisters (Moffitt, 1993). This behavioral profile

characterizes approximately 5%–10% of the male population, whose antisocial behavior has its origins in neurodevelopmental deficits, begins in childhood and continues worsening thereafter, and is strongly persistent and pathological. According to our taxonomic theory (Moffitt, 1993) the difficult behavior of a high-risk young child is exacerbated by a high-risk social environment. The child's risk emerges from inherited or acquired neuropsychological variation, initially manifested as subtle cognitive deficits, difficult temperament, or hyperactivity. The environment's risk comprises factors such as inadequate parenting, disrupted family bonds, and poverty. Over the first two decades of development, transactions between individual and environment gradually construct a disordered personality with hallmark features of physically violent aggression and antisocial behavior persisting into midlife.

Our studies of life-course persistent offending have been carried out in the Dunedin Multidisciplinary Health and Development Study, a 30-year longitudinal study of a representative 1972–1973 birth cohort of 1000 New Zealanders assessed repeatedly from birth to adulthood (Moffitt *et al.,* 2001). These studies showed that life-course persistent antisocial behavior is predicted by individual neurodevelopmental risk characteristics from early childhood, that is, cognitive deficits, neuromotor problems, and hyperactivity (Jeglum-Bartusch *et al.,* 1997; Moffitt, 1990; Moffitt and Caspi, 2001; Moffitt *et al.,* 1994). Psychopathic personality traits of alienation, stress-reactivity, aggression, callousness, and impulsivity characterized the life-course persistent young people (Moffitt *et al.,* 1996, 2002). Followed up in adulthood, life-course persistent men were the most extreme on mental-health problems, substance dependence, numbers of children sired, financial problems, work problems, drug-related crimes, and violent crimes (Moffitt *et al.,* 2002). Life-course persistent men accounted for five times their share of the birth cohort's violent court convictions (e.g., using an attack dog on a person, presenting an offensive weapon, threatening a police officer, rape, manual assault, assault on a police officer, assault with a deadly weapon, aggravated robbery, and homicide), perpetrated physical abuse toward women, and were also most likely to report that they had hit a child out of anger (Moffitt *et al.,* 2002). The life-course persistent form of antisocial behavior is essentially a male sex-typed pattern (10 males:1 female) (Moffitt *et al.,* 2001). Finally, evidence is emerging that life-course persistent antisocial behavior is more heritable than is other garden-variety antisocial behavior (Arseneault *et al.,* 2003; Eley *et al.,* 2003; Lyons *et al.,* 1995; Taylor *et al.,* 2000).

Contrasted versus the LAL mice is a group of men who managed to avoid virtually all antisocial behavior from early childhood through adolescence and into adulthood, called the "Abstainers." The original taxonomic theory speculated that if most ordinary teens take up some delinquent behavior, then males who eschew delinquency must be extraordinary. Males committing no antisocial behavior over the life course should be rare, and we speculated that personal characteristics unappealing to other teens might cause them to be excluded from teenaged group activities such as delinquency and substance use (Moffitt, 1993). Consistent with the rarity prediction, the Dunedin birth cohort contained only a small group of males who avoided virtually any antisocial behavior during childhood and adolescence (Moffitt *et al.,* 1996). These Dunedin abstainers as teenagers described themselves on personality measures as extremely over-controlled, fearful, interpersonally timid, and socially inept, and they were latecomers to sex (i.e., virgins at age 18). Dunedin's adult follow-up data confirm that as adults these men retained their self-constrained personality, were virtually free of crime or mental disorder, were likely to have settled into marriage, were delaying children (a desirable strategy for a generation needing prolonged education to succeed), were likely to be college educated, held high-status jobs, and expressed optimism about their own futures (Moffitt *et al.,* 2002).

In this article, we will compare the general pattern of findings for SAL and LAL mice against findings from the Dunedin Study for life-course persistent antisocial men ($n = 47$, 10% of the cohort) and abstainers ($n = 25$, 5% of the cohort). These men appear to represent the extremes of longitudinal stability for either aggressive or nonaggressive styles in the general male population, over 26 years of life. Because 96% of the cohort took part at the most recent follow up, at age 26, our data describing these two groups of men has not been affected by attrition bias (Moffitt *et al.,* 2002). Original data labeled for the groups of men can be found in the above-cited publications. Dunedin findings about the men's antisocial behavior have been replicated by findings reported from more than 20 other samples in eight countries (reviewed in Moffitt, 2003). A description of the Dunedin birth cohort, and evidence that prevalence rates of antisocial behavior in New Zealand are comparable to those from the US and UK, can be found in Moffitt *et al.* (2001).

Parallels

In this paragraph, comparisons between SAL and LAL mice, and between Persister and Abstainers, are

Table I. Parallels Between Male Mice and the Extremes of the Dunedin Multidisciplinary Health and Development Study

	MICE	HUMANS			
Measures	LAL	SAL	ABS	PERS	Measures
Aggression					**Aggression/Violence**
Attack latency	++	−	−	+	Frequency of violence
			−	++	Violent convictions
Aggression	−	++	−	++	Aggressive personality
			−	++	Violent behavior (informant's report)
Attacks against female	−	+	−	+	Domestic violence
Reproduction					**Reproduction**
Litter size	−	+	−	+	Number of children
Cognition					**Cognition**
Spatial Learning	+(?)	−(?)	+	−	IQ age 3–13
Hippocampus (IIPMF size)	+	−	+	−	Verbal memory age 13
Behavioral disorders					**Behavioral disorders**
Alcohol preference	−	+	−	++	Alcohol dependence
Anxiety	=	±	−	+	Anxiety symptoms
Depression	+	−	=	=	Depression symptoms
Endophenotypes					**Endophenotypes**
Serotonin	+	−	=	=	Serotonin
Adult testosterone	−	+	=	=	Testosterone
Corticosterone (basal levels)	±	=	=	=	Cortisol (basal levels)

Note: SAL = Short attack latency; LAL = Long attack latency; PERS = men who persistently manifested antisocial behavior; ABS = men who never manifested antisocial behavior.

Groups were compared on the basis of five distinct domains: aggression/violence, reproduction, cognition, behavioral disorders, and endophenotypes. SAL-LAL comparisons come from various studies (see text for more details), while PERS-ABS comparisons were analyzed using *t*-tests.

put in parallel to evaluate the validity of the animal model. Groups were compared on the basis of five distinct domains: aggression/violence, reproduction, cognition, behavioral disorders, and endophenotypes (see Table I). The latter, also called intermediate traits, are becoming increasingly more important in these days of (functional) genomics because it has been suggested to be easier to identify the effect of a gene on a more elementary (neuro) biological trait than to identify its effect on a complex behavior, such as antisocial behavior. Such endophenotypes should be continuously quantifiable, should predict disorder probabilistically, and should be closer to the site of the primary causative agent than to diagnostic categories (Almasy and Blangero, 2001, but see de Geus and Boomsma, 2001, for more stringent criteria). Animal models could point to valuable candidates for these endophenotypes in humans.

All comparisons should be interpreted at the level of conceptual domains rather than at the level of specific measures as, for obvious reasons, the latter differ between animal and human studies.

In general, comparisons revealed similarities among the groups of mice and humans that we studied. Firstly, SAL mice and Persisters show more aggression than LAL and Abstainers, respectively. Among humans, this finding was consistent across different measures of violence such as the self-reported frequency of violent behavior, its severity as indicated by court convictions, aggressive personality dimension, and an informant's report of violent behavior (the informant being a friend, a partner or a family member). Interestingly, the comparisons were consistent across the two species for violent acts directed toward both male and female targets. Both SAL mice and Persisters exhibited more aggression toward females. It is important to note that, although in certain conditions aggressive behavior in mice can be justified from an ecological point of view (i.e., territorial defense), attacking a female companion is, to a certain extent, maladaptive (but see Canastar and Maxson, 2003 [this issue] for alternative explanations). SAL males also persevere in their aggression and do not seem to be able to control their aggressive behavior, which, if not intervened by the experimenter, often leads to badly injured, or even killed, opponents. In addition to the fact that they are prone to attack outside their home territory (i.e., an assault on neutral or foreign territory, see Sluyter *et al.,* 2002), these animals

appear to closely mimic the pathological nature of the Persisters' violence.

Second, we observed similarities in the reproduction pattern of SAL mice and Persisters. The litter size (mice) and the number of children (humans) were both elevated in SAL and Persisters (as compared to LAL and Abstainers). In general, LAL animals are less fertile than SAL animals, a finding that does not seem to come from differences in sperm count and sperm motility (Sluyter *et al.,* 1994b). Third, Persisters had lower childhood IQs (measured by the Peabody Picture Vocabulary Test at age 3, the Stanford-Binet Intelligence Scales at age 5, and the Weschler Intelligence Scales for Children–Revised) and more adolescent difficulties in verbal memory than Abstainers. Verbal memory, in this sample measured by the Rey Auditory Verbal Learning Test, has been shown to be, at least partly, regulated by the hippocampus (Rolls, 2000). Because of distinct, mostly practical reasons, we have not tested SAL and LAL in hippocampus-dependent learning and memory paradigms, such as the radial maze and the Morris water maze. However, we do have indications that LAL mice might be better performers on these tasks. When animals that were trained to use only one arm in a Y maze, are suddenly forced to use the other arm, LAL males are able to acquire that information much faster than SAL males, which seem to be more rigid and more routine-like in their behavior (Benus *et al.,* 1990; Sluyter *et al.,* 1996c). Another indication with respect to LAL's possibly better performance in cognitive tasks comes from larger sizes of the intra- and infra-pyramidal mossy fiber (IIPMF) terminal fields (Sluyter *et al.,* 1994). There is substantial evidence (different laboratories, different strains) that the size of this hippocampal structure correlates positively with spatial memory (e.g., Crusio *et al.,* 1987) and negatively with intermale aggression in mice (Guillot *et al.,* 1994; Sluyter *et al.,* 1994a, 1999). Moreover, this correlation seems to be genetic, suggesting that the same (set or) gene(s) affect(s) the variation of the IIPMF sizes and spatial memory (Crusio *et al.,* 1987; Guillot *et al.,* 1994), either in a linear of collaterative pleiotropic way. As for humans, neuropsychological measures suggesting possible central nervous system dysfunctions, such as verbal and executive functions and memory deficits, have been persistently associated with antisocial behavior and might play a crucial role in the etiology of such behavior (e.g., Raine, 2002; Seguin *et al.,* 2002).

Fourth, we examined whether SAL males and Persisters showed a higher incidence of disorders associated with antisocial behavior such as alcohol, anxiety, and depression problems. Persisters had obviously more alcohol problems than Abstainers. Findings in SAL and LAL point in the same direction. When exposed to an alcohol solution in a two-bottle, free choice paradigm, SAL males drink more alcohol than LAL males (Hensbroek *et al.,* 1996). Whether this finding is as robust and reliable as the original selection criterion (i.e., attack latency) or more volatile remains to be investigated. Comparisons for anxiety and depression were not consistent for mice and humans, although SAL males tended to be slightly more anxious than LAL males in the tunnel maze (Hogg *et al.,* 2000). Findings in the elevated plus maze and the light-dark box were, however, not in line with this result (Hogg *et al.,* 2000; Veenema *et al.,* 2003b). Furthermore, LAL animals showed more immobility in the Porsolt Swim Test (Veenema *et al.,* 2003b), a paradigm that has been pharmacologically validated to reflect depressive behavior in animals (Porsolt *et al.,* 1977).

In the fifth domain endophenotypes were compared. A major question is whether there exist endophenotypes that predict the risk to develop antisocial behavior in the same way that serum cholesterol predicts the risk of cardiovascular disease (Almasy and Blangero, 2001). Historically, the search for these factors has been aimed at various neuronal and endocrinological domains. Of all the neurotransmitters possibly implicated in aggression, serotonin is still the strongest suspect (Nelson and Chiavegatto, 2001), while testosterone—and recently, cortisol—is the hormone most frequently investigated. Serotonin, testosterone, and cortisol levels do not vary between Persisters and Abstainers, whereas findings in SAL and LAL have been rather inconsistent. LAL males have been shown to display higher levels of serotonin (Olivier *et al.,* 1990), although recently only higher levels of serotonin were found in the brainstem of SAL mice and not in other brain regions (Veenema, unpublished data). LAL males have also been shown to display lower levels of testosterone (van Oortmerssen *et al.,* 1992), although this finding does not seem robust (Sluyter, unpublished data). A similar story concerns corticosterone, the animal equivalent of cortisol. While Korte *et al.* (1996) observed a reduced rise in plasma corticosterone concentration during the early dark phase in SAL males, Veenema *et al.* (2003a) found no difference in basal levels between SAL and LAL.

DISCUSSION

To investigate whether mouse lines genetically selected for short and long attack latencies are good models for antisocial behavior in humans, we compared

behavioral, as well as (neuro) biological, features of these lines to those of the extremes of a human birth cohort of a 26-year longitudinal study (Dunedin Multidisciplinary Health and Development Study). Our observations indicate substantial similarities between, on one side, genetically selected aggressive male mice (SAL) and men persisting in antisocial behavior (Persisters), and, on the other side, between genetically selected male mice with low-aggressive behavior (LAL) and men who have never manifested aggressive behavior (Abstainers). The comparisons were, to a large content, consistent across different domains of characteristics associated with antisocial behavior: aggression/violence, reproduction, cognition, and behavioral disorders. Admittedly, SAL are more similar to Persisters than LAL to Abstainers, which is not surprising because LAL generally show more variation in all types of behavior.

Because we have selected our animal model on the basis of aggression (differences), similarities between mice and humans were, of course, the most convincing for measures of aggression. SAL males seem to adequately mirror the violence acts of the Persisters in both qualitative and quantitative ways, and seem to parallel human intermale aggression and domestic violence incidents. This is arguably the most important behavioral domain of the mouse model for antisocial behavior—certainly from a practical point of view—as violence represents its most feared, damaging, and costly form of expression. Another feature in which the mouse model seems to parallel the human situation is alcohol consumption. Together with violence, excessive alcohol intake is a key characteristic of the antisocial personality and these traits seem to intercorrelate strongly (Robins, 1998). Persisters are clearly more dependent on alcohol than Abstainers, whereas SAL males are inclined to show a higher alcohol preference to water than LAL males, although it should be noted that consumption of alcohol and alcohol problems are not necessarily similar. Differences in reproduction are also apparent, but whether increased litter sizes in SAL animals can be compared to higher number of children in Persisters, is another issue. Other, more species-specific characteristics, such as many different sexual partners or early-onset sexual activities, which are associated with an antisocial lifestyle (Jaffee *et al.,* 2001), are likely to play a more important role. Cognitive differences between SAL and LAL seem to parallel those between the Persisters and Abstainers. Admittedly, no analogues were observed for anxiety and depression. Persisters tend to be more anxious and depressed than Abstainers, whereas SAL and LAL do either not differ in the equivalent mouse paradigms, including the elevated plus maze and light-dark box, or vary in a direction not anticipated.

Overall, the model seems to have some notable face validity. Whether the biological mechanisms involved in the etiology of antisocial behavior are similar to those underlying the development of aggressive behavior—in other words, whether the mouse model has construct validity as well—remains to be investigated. Data so far are inconclusive and further, more detailed, research is certainly needed. At first glance, there does not seem to be a strong case for construct validity because the endophenotypes do not differ between Persisters and Abstainers, whereas they tend to differ between SAL and LAL. Thus, serotonin, testosterone, and cortisol levels do not vary in the human sample. However, to infer from these data that varying levels of such biological variables are not decisive in the development of antisocial behavior would be premature and not take into account the vast complexity and dynamics of these variables nor the restrictions of the measurements, which are partly due to ethical limitations. For instance, serotonin concentrations were determined in blood (Moffit *et al.,* 1998), a rather crude method that weakly reflects the complicated nature of serotonin in the brain. The problem of measuring cortisol and testosterone is the diurnal variation of these steroid hormones. Cortisol, in particular, is highly variable during the day, with high peaks in the morning and relatively low values in the evening. Hence, for a reliable picture of cortisol levels, multiple samples are needed (and preferably over several days, see Bartels *et al.,* 2003b for methodological considerations concerning cortisol measurements). One sample per subject, as is the case in the Dunedin sample and the Korte *et al.* study (1996), is rather meager and the results are hard to interprete. As for SAL and LAL, Veenema *et al.* (2003a) conducted a more thorough study of the dynamics of corticosterone and collected four samples, two in the light phase and two in the dark phase. They found no substantial differences in basal levels. Interestingly, they did find a difference in stress-induced levels of corticosterone. Not only did forced swimming induce high immobility behavior in LAL mice, this stressor was also associated with an enhanced and prolonged corticosterone response as compared to SAL mice (Veenema *et al.,* 2003a), an observation also confirmed in experiments where the same lines had been exposed to novelty stress (van Riel *et al.,* 2002). Although these types of experiments are, to some extent, still feasible in humans (especially multiple sampling, see Bartels *et al.,* 2003a), detailed examinations of specific brain areas are not and this is where

animal models become certainly invaluable (see Feldker *et al.,* 2003a; Korte *et al.,* 1996; van Riel *et al.,* 2002).

The role of testosterone in aggression has always been controversial, and it remains unclear whether naturally occurring variation in adult testosterone levels is associated with differences in aggression in healthy subjects. Hence, although the lack of difference in testosterone levels between Persisters and Abstainers may not have been anticipated, this result is not surprising. In fact, findings in rodents mirror the ambivalent situation in humans. For instance, the previously reported difference in testosterone between SAL and LAL—SAL having higher levels (van Oortmerssen *et al.,* 1987, 1992)—does not seem to be a robust phenomenon (Sluyter, unpublished data). Although there may be alternative explanations for a lack of replication of this finding, such as diurnal variation in adult testosterone levels, a more straightforward rationalization is the insignificance of varying adult testosterone levels. Indeed, adult testosterone levels do not play a decisive role in SAL and LAL: castration followed by testosterone replacement does not abolish or diminish the orginal differences in aggression (van Oortmerssen *et al.,* 1987). Differences in sensitivity to testosterone, as well as differential processing of testosterone into its metabolites dihydroxy testosterone (DHT) and estradiol, seem to be more relevant in the execution of aggression, whereas other time frames, such as the perinatal and pubertal period, are likely to be more important than adult age. Thus SAL and LAL males have been reported to differ perinatally in circulating testosterone, testosterone secretory capacity of the testis, and brain aromatase (Compaan *et al.,* 1994; de Ruiter *et al.,* 1992). The pubertal period is another time frame in which the sensitivity to testosterone later in life might be organized (Sluyter, unpublished data).

However, rather than discarding this mouse model because of its lack of construct validity, we believe that this animal model might generate valuable information about and new hypotheses on the biological basis of aggression in humans. Detailed research on the neural and genetic determinants that underlie individual differences in aggression in mice might give us indications where and what to look for when investigating similar phenomena in humans.

Genetic and predictive validity are yet unknown territories as, to date, they have only been explored to some extent. In view of the predictive validity of this mouse model, some pharmacological experiments are worth mentioning: both the full 5HT1A receptor agonist alnespirone and the preferential somatodendritic 5HT1A autoreceptor agonist S-15535 are able to reduce aggression considerably in SAL males (in a dose-dependent manner). In fact, after treatment with the highest dose only 25%–30% of the SAL males attack (de Boer, unpublished data). These findings warrant further research on this type of agonists in SAL males as they might lead to the development of new drugs capable of reducing aggression in men.

In view of the association between genes and antisocial behavior, Caspi *et al.* (2002) reported an interaction between a functional polymorphism in the promoter region of the monoamine oxidase A (MAOA) gene, which codes for an enzyme (MAOA) that degrades serotonin and norepinephrine. Two variants of this gene interacted with childhood maltreatment in the Dunedin sample. Children who were maltreated and who had the higher-activity MAOA genotype were less likely to develop antisocial problems than children with the same maltreatment past, but with low-MAOA activity genotype. The involvement of MAOA in the development of antisocial behavior is not unexpected. In a kindred in The Netherlands, Brunner *et al.* (1993) associated a syndrome of borderline mental retardation and abnormal behavior, including disturbed regulation of impulsive aggression, with a point mutation in the eighth exon of the MAOA structural gene, which changes a glutamine to a termination codon. More subtle variations in the MAOA gene have also been associated with impulse control and antagonistic behavior. Similar to the Caspi study, Manuck *et al.* (2000) focused on variation in the regulatory region of the MAOA gene and found that differences in the transcriptional activity in MAOA promoter constructs were associated with differences in dispositional aggressiveness and impulsivity. There is evidence that MAOA also plays an important role in mouse aggression. Mice lacking a functional MAOA gene (MAOA knockouts) show higher levels of aggression than mice with an intact MAOA gene (Cases *et al.,* 1995). Whether slight variations in the MAOA gene also affect mouse aggression, in the same way that polymorphisms in the human promoter may influence aggression in humans is currently being investigated in SAL and LAL (see D'Souza *et al.,* 2003 [this issue] for more details on variation in regulatory DNA sequences).

Future research on the genetic variation underlying aggressive behavior should include other serotonergic genes, such as those coding for the receptors 5HT1a (see above) and 5HT1b. The latter is particularly interesting as polymorphisms in the 5HT1b have been associated with antisocial alcoholism (Fehr *et al.,* 2000; Lappalainen *et al.,* 1998), whereas 5HT1b knockouts show increased alcohol preference and increased

aggression (Crabbe *et al.,* 1996; Saudou *et al.,* 1994). Other candidate genes are those that code for tryptophan hydroxylase (TPH, a rate-limiting biosynthetic enzyme) and the serotonin transporter (SERT, a protein that transports serotonin from the synapse). Manuck *et al.* (1999) reported an association between a polymorphism in intron 7 of the gene coding for TPH and aggression and anger-related traits. In some studies (e.g., Hallikainen *et al.,* 1999) the short serotonin transporter allele was found to be associated with increased risk of type 2 alcoholism, in which prominent features include antisocial, impulsive, and violent behavior, whereas other studies did not observe such an association (e.g., Kranzler *et al.,* 2002). SERT knockouts appear to be less aggressive than their wild types (Holmes *et al.,* 2002).

Other genetic regions generated by mouse research, including SAL and LAL (see Sluyter *et al.,* 1996b), are the recombining part of the Y chromosome, also called the pseudoautosomal region, as well as the male (nonrecombining or nonpseudoautosomal) part of the Y chromosome. Candidate genes in these region are SRY, the male determining gene, on the nonpseudoautosomal and STS on the pseudoautosomal part. SRY is a transcription factor that shows strain polymorphisms (Coward *et al.,* 1994) and is transcribed in the mouse brain at adult age (Lahr *et al.,* 1995) (see Maxson, 1996, for an extensive argumentation on SRY). Interestingly, a recent in silico survey of genes associated with offensive aggression in male mice showed the presence of SRY binding sites in the regulatory sequences of a selection of these "aggression" genes (D'Souza *et al.,* 2003, this issue). The STS gene codes for the enzyme steroid sulfatase, which is of major importance in the metabolism of neurosteroids. The STS gene is the only functional gene that has been mapped on the pseudoautosomal region and is therefore the main candidate for explaining the effect of this region in the development of individual differences in aggression (Roubertoux *et al.,* 1994). For a more detailed description of Y chromosomal effects in mice and also humans the reader is referred to, among others, Maxson *et al.* (2001), while Miczek *et al.* (2001) take a more general approach on the development of aggressive behavior in mice, including genetic effects.

Animal models are also useful in the identification of new candidate genes. QTL approaches, for instance, can lead to the discovery of genetic variants that are responsible for individual variation in aggression (Brodkin *et al.,* 2002), although the actual identification and cloning of the gene(s) from the original QTL region is extremely hard. Other important tools are large scale gene expression profiling techniques, including Serial Analysis of Gene Expression and DNA Microarrays. These techniques enable the screening of thousands of genes simultaneously and thus the generation of new hypotheses regarding the molecular architecture underlying individual differences in behavior, that is, aggression (see Feldker *et al.,* 2003b [this issue] for a discussion of these techniques). Using both SAGE and microarrays (Affymetrix), Feldker *et al.* (2003a) found that, in the hippocampus, LAL males had higher expression levels of numerous cytoskeleton genes, such as cofilin and several tubulin isotypes, as well as several calmodulin-related genes and genes encoding components of a MAPK cascade. Whether the same genes are also differentially expressed in the hippocampi of Persisters and Abstainers, is another question—and difficult to investigate, but it would be worth examining variation in the regulatory and coding sequences of the cytoskeleton and calmodulin-related genes in Persisters and Abstainers. Similarly, the difference in the size of IIPMF terminal fields between SAL and LAL point to a possible important role of this specific hippocampal structure in the ontogeny of antisocial behavior and certainly merits further pursuing in human populations, such as the Dunedin sample. In fact, this structure might be one of the more promising candidate phenotypes because it meets all the rigorous criteria proposed by de Geus and Boomsma (2001, see also de Geus, 2002): reliability, stability, heritability, causality, and phenotypic and genetic correlation.

Last, but not least, we realize that the comparison in this paper between mice and men is necessarily superficial, because it was based on surface appearance of the behavioral constructs. We have ascertained attack latency under certain stimulus conditions in the mouse, whereas in the men, we have ascertained physically violent behavior toward victims. What we have not ascertained, or matched across species, is the meaning of the behavior. We do not know if the mouse and the man attacked for the same reason, nor if they expected their attacks to yield the same consequences. Mouse aggression may be motivated by territory defense, for example, but when a man assaults another man who has flirted with his girlfriend, is this territory defense, or not? Contexts may differ as well; none of the mice were drunk when attacking, but some of the men were. The mice attacked alone in this paradigm, but in some cases the men attacked with co-offenders as part of gang conflict. We did not ascertain intentions, expectations, contexts, or consequences, which would allow us to interpret the "meaning" of behavior. These things were

not assessed by the two research teams for obvious reasons. Mice cannot tell us their motivations. Men, despite having better language skills than mice, do not provide accurate reports of their own subjective motivations, particularly for behavior that is socially undesirable. (For example, the Dunedin Study asked all its men to rank themselves on a scale of 1–10 describing whether they were more or less antisocial as compared to other men their age; virtually all men in the sample rated themselves between 4 and 6. Despite extreme individual differences in crime careers, each man presumed he was average.) Investigations of the equivalence of interpretation of behaviors awaits further investigation, and the success of such investigation will depend on developing valid techniques for ascertaining the ethological contexts of human and animal behavior. However, without a reason, this work has not gotten underway, although it is badly needed if animal models are going to be useful tools in molecular genetics research. The comparison in this paper is intended to give a reason for such work.

CONCLUSION

We are hopeful that SAL and LAL are good mouse models to study the development of antisocial behavior. Insights that are emerging from the neurobiological and genetic architecture underlying aggression differences in this mouse model, may very well lead to the delineation of the complex causal pathways of antisocial behavior in humans.

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