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Aggression in Wild House Mice: Current State of Affairs

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This paper reviews our present state of knowledge of genetic variation in (offensive) aggression in wild house mice. The basic tools in this research were lines bidirectionally selected for attack latency (fast attacking SAL and slow attacking LAL males), descended from a feral population. Using congenic lines for the nonpseudoautosomal region of the Y chromosome (Y^{NPAR}), reciprocal crosses between (parental) SAL and LAL, and crosses between parentals and congenics, an autosomally dependent Y chromosomal effect on aggression has been found. Both the pseudoautosomal (Y^{PAR}) region and the Y^{NPAR} play a role. As for environmental sources of variation, prenatal and postnatal maternal effects are of minor importance for the development of aggression differences. One of the physiological factors by which genetic effects may be mediated is testosterone (T). Besides quantitative aspects, the timing of T release seems crucial. Two important time frames are discussed: the perinatal and pubertal time periods. Finally, neurochemical and neuroanatomical correlates are considered. Differences in neostriatal dopaminergic activity, and sizes of the intra- and infrapyramidal mossy fiber terminal fields, as well as Y chromosomal effects on the latter two, are discussed.

KEY WORDS: Aggression; wild house mice; Y chromosome; maternal environment; testosterone.

INTRODUCTION

The abundance of mouse strains available and the interstrain aggression differences observed create a problem in the choice of a proper model for the study of the genetics of (offensive) aggression. What strains (inbred, outbred) or lines should one choose, and how many? In our laboratory, we have selected wild house mouse lines for Short Attack Latency (SAL) and Long Attack Latency (LAL). The decision for using selection lines and attack latency as an indicator for aggression is rather clearcut. Selection lines are an important tool to analyze genotypic variation in behavior; attack latency is an easily determined and reliable index of attack behavior (Catlett, 1961; van Zegeren, 1980). The justification for choosing the wild house mouse is less evident. First, the preference for the wild house mouse is to prevent an arbitrary choice. For most strains it is virtually unknown how they relate to natural genetic variation in aggression observed in a wild population. At least, when using true representatives of a natural population, we know that the individual (genetic) variation is closely related to a functional variation in nature (van Oortmerssen and Busser, 1989). Second, this model provides a good opportunity to test ecological hypotheses and to combine these findings with behavioral and neuroendocrinological data.

WILD HOUSE MICE

The house mouse is a typical colonizing species. Individuals either live as residents in demes

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(family groups that are reproductively isolated by acting as a closed colony) or migrate and colonize until they have settled somewhere else (van Oortmerssen and Busser, 1989; van Zegeren, 1980). Successful reproduction takes place only within demes. These family groups each contain one or more males, mostly more females than males, and a number of juveniles born in that group. Migrating and colonizing portions of the population mainly contain young adult and subadult animals that have left their parental demes (van Oortmerssen and Busser, 1989; Oakshott, 1974). These two life styles (resident or colonizer) require distinct behaviors of the individuals involved, particularly concerning their aggression. Variation for attack latency, i.e., aggression, has been found to show a bimodal shape in wild house mouse populations of the subspecies *Mus musculus domesticus*. Two distinct, genetically different, behavioral groups of slow and fast attackers exist, mimicked by nonaggressive LAL and aggressive SAL (van Zegeren, 1980). Slow attackers (LAL) are better able to gain territory when migrating, whereas fast attackers (SAL) perform better in a settled population (van Oortmerssen and Busser, 1989). Accordingly, different genotypes for aggression are of functional significance for the population dynamics of wild house mice.

Testing conditions are of crucial importance for genetic analyses of aggression. For the measurement of aggression we have used a test situation which is designed to mirror the biology of the species as closely as possible (van Oortmerssen and Bakker, 1981). Since male house mice regularly patrol the borders of their territories, and most agonistic confrontations occur there, such a border situation was created. Consequently, tests have been performed only after a period of time during which the experimental animal could become familiar with the test cage.

There are three types of dyadic paradigm (Fuller and Hahn, 1976; Simon, 1979): (1) the homogeneous set test, in which all encounters are between mice of the same genotype; (2) the panel of testers, in which each experimental group is tested against opponents from a panel of genotypes; and (3) the standard opponent test, in which the experimental groups are tested against a single standard genotype. For our experiments we have used the standard opponent test. Standard opponents should elicit offensive behaviors from the animal to be tested, but not initiate offensive behaviors themselves (Denenberg *et al.*, 1973). In this study we have used males from an inbred albino strain (MAS-Gro). These mice very rarely attack the experimental animals.

The outcomes of genetic analyses of aggression may depend upon the type of behavioral variables used as indices of aggression. For example, Popova and Kulikov (1986) showed that the proportion of mice attacking may have a different mode of inheritance than that of number of attacks or accumulated attack time. Most analyses use a single composite score or a few discrete scores of offense: proportion of fighting animals, rating scales (based on, among others, allogrooming, tail rattling, wrestling, and fighting) or attack characteristics (attack latency, number of attacks, accumulated attack time) (Maxson, 1992). In our studies, we have used attack latency, which has been shown to be a robust indicator of aggression. The mean time of the scores on three consecutive test days is calculated and represents the attack latency score (ALS). ALS is a reliable index of aggression because it is strongly and negatively related to the frequency of other aggressive behavioral elements, including attacking, fighting, and chasing (van Oortmerssen and Bakker, 1981; van Oortmerssen *et al.*, 1985; van Zegeren, 1980).

Y CHROMOSOMAL EFFECTS

We have focused on Y chromosomal effects on aggression for two reasons. First, the Y chromosome has received full attention in aggression research since Selmanoff *et al.* (1975, 1976) found the first indications of a Y chromosomal involvement in the development of aggression. Although Y chromosomal effects on aggression have been demonstrated with certainty only upon three occasions (Maxson *et al.*, 1979; Carlier *et al.*, 1991; Roubertoux *et al.*, 1994), strong indications have been found in other studies [for recent reviews on Y chromosomal influences on aggression, see Carlier *et al.* (1990) and Maxson (1992)]. Second, in comparison to other chromosomes, effects of the Y chromosome are relatively easy to analyze. By means of reciprocal crosses and backcrosses influences of specific parts of the Y chromosome can be determined.

The standard first step for testing possible Y chromosomal effects is to demonstrate differences

between two reciprocal F_1 males. When differences are observed, a Y chromosomal effect may be present since the two F_1 males differ for the Y chromosome and bear the same autosomes. Differences in ALS in reciprocal F_1's between the aggressive SAL and the nonaggressive LAL selection line demonstrate that the F_1's bearing the aggressive SAL Y chromosome show shorter ALS, i.e., are more aggressive, than those bearing a nonaggressive LAL Y chromosome (van Oortmerssen, 1984; van Oortmerssen *et al.*, 1992; Sluyter, 1994; Sluyter *et al.*, 1994b). However, differences between reciprocal F_1's may be due not only to the the Y chromosome, but also to the X chromosome, maternal cytoplasm including mtDNA, genomic imprinting, and/or prenatal and postnatal maternal environments. Therefore, a Y chromosomal hypothesis based on F_1 data alone should be confirmed with other methods.

Another limitation of the use of reciprocal F_1's in the analysis of Y chromosomal effects is that it cannot discriminate between the two distinct parts: the nonpseudoautosomal region, which does not recombine during meiosis and is transmitted only from father to son (abbreviated Y^{NPAR}), and the pseudoautosomal region, which exchanges information with a part of the X chromosome and therefore behaves in an autosomal manner (abbreviated Y^{PAR}).

In inbred strains, Y^{NPAR} effects can be tested by means of comparing parental strains and strains congenic for this part of the Y chromosome. The congenic strains are developed according to the repeated backcrossing system of breeding (see, e.g., Maxson *et al.*, 1979; Roubertoux *et al.*, 1994). After a large number of backcrosses it may be assumed that each congenic differs from its parental strain only in the origin of its Y^{NPAR}, whereas all other genetic (Y^{PAR}, autosomes, X chromosome, and mtDNA) and environmental (cytoplasm, pre- and postnatal maternal environment) factors are identical. Things are more complicated with selection lines because of the genetic variance still present within each line. However, by developing more than one congenic (replicated lines), no systematic differences are likely to exist between the autosomes of the parental line and its congenic. Y^{NPAR} effects on aggression have been found in DBA/1 and C57BL/10 (Maxson *et al.*, 1979). Using two other inbred strains (CBA/H, abbreviated H; and NZB/B1N, abbreviated N), the group of Roubertoux and Carlier demonstrated that the Y^{NPAR} effect is dependent upon the test situation (Roubertoux *et al.*, 1994; Guillot *et al.*, 1995a). However, if we compare parental and congenic lines in wild house mice (SAL vs. SALLY and LAL vs. LAL.SY), we do not find an effect on aggression (van Oortmerssen and Sluyter, 1994). So, combining the aggression scores of the reciprocal F_1's and the congenics, the Y^{PAR} is a more probable candidate for the Y chromosomal effect.

Testing for Y^{PAR} effects is rather complicated, however, Y^{PAR} influences can be examined by crossing congenic and parental lines in such a way that, while keeping the autosomal background identical, "mosaic" Y chromosomes are formed: one part, e.g., Y^{NPAR}, originating from one strain or selection line, e.g., SAL or LAL, and the other, e.g., Y^{PAR}, coming from the other strain or selection line, e.g., LAL or SAL. By juxtaposing the F_1's with the "mosaic" Y chromosome to the reciprocal F_1's (which have either a 100% SAL or a 100% LAL Y chromosome), and controlling for the maternal environment, Y^{PAR} effects can be discriminated from Y^{NPAR} effects. Using this design and excluding all factors that may also be responsible for aggression differences in reciprocal F_1's from the H and N strains, Roubertoux *et al.* (1994) demonstrated cosegregation of intermale aggression with the Y^{PAR}. Applying the "mosaic" Y chromosome model, although not ruling out all factors as did Roubertoux and Carlier's group, we showed that both Y^{NPAR} and Y^{PAR} need to be present to have an effect in our selection lines (Sluyter *et al.*, 1994b).

The congenic and "mosaic" F_1 results appear to be contradictory in wild house mice. On the one hand, we do not find a Y^{NPAR} effect, which leads us to conclude that the Y^{PAR} is responsible for aggression differences. On the other hand, we do find a Y^{NPAR} effect, albeit in combination with the Y^{PAR}. One explanation may be the difference in autosomes. Congenics are autosomally either 100% SAL or 100% LAL, whereas reciprocal F_1's consist of 50% SAL and LAL. Apparently, Y chromosomal effects depend on the constitution of the autosomal background. Results on inbred strains are in accordance with these findings in wild house mice. Maxson's group first hypothesized that an epistatic interaction between one or more Y chromosomal and autosomal genes influences variation in and development of offense (Maxson *et al.*, 1979). Roubertoux and Carlier's group clearly

demonstrated a contribution of homozygotic alleles to intermale aggression. These autosomal correlates may contribute in an additive or interactive manner to the pseudoautosomal correlates (Roubertoux *et al.*, 1994). In our mice, autosomes are also most likely to play a role in the development of aggression.

Besides Y chromosomal factors, environmental sources of variation may also play a role in the development of aggression. Regarding SAL and LAL, we have limited ourselves to possible maternal influences on aggression.

MATERNAL EFFECTS

Three maternal components can be defined: cytoplasmic, prenatal (uterine), and postnatal. Only the latter two are dealt with here.

The effect of the prenatal environment on behavioral traits, i.e., aggression, can be tested by comparing animals having identical genotypes, the same mitochondrial DNA, and the same postnatal environment but differing in their uterine environment. Carlier *et al.* (1992) summarized the experimental designs necessary for determining prenatal effects. Two techniques are available: the ovarian graft (OG) method and embryo transfer (ET). The latter has been used to study the maternal effects on aggression in SAL and LAL and their reciprocal F_1's.

Contrary to ovary grafting, embryo transfer (ET) does not require histocompatibility and thus allows for a transfer between different strains. Embryos may be transferred either surgically or nonsurgically. Using a new nonsurgical ET technique (van der Hoeven *et al.*, 1991) on genetically standardized females in combination with fostering methods, prenatal maternal effects can be determined. It appears that sharing an identical maternal environment does not influence aggression in SAL and LAL and their reciprocal F_1's (Sluyter *et al.*, 1996). These findings are in line with those from Roubertoux and Carlier (1988). They were able to exclude pre- and postnatal maternal effects on attack behavior in two (H and N) inbred strains. By transplanting H and N ovaries to HNF_1 females, the difference in attack behavior remained similar in H and N offspring.

The postnatal maternal environment runs from birth to weaning, i.e., from 0 to about 21 days. Effects of the postnatal maternal environment can be measured by means of the adoption (also called fostering) method. With mice, the method consists of transferring an entire litter of a given female to another female. Since lactating females readily accept alien newborns, the adoption procedure is generally very easy to carry out (for a detailed experimental design, see Carlier *et al.*, 1992).

The contribution of the postnatal environment to adult offensive behavior is still unclear. To our knowledge, 10 studies have used the crossfostering method to assess effects of the postnatal maternal environment on strain differences in male offensive behaviors. Seven showed no effect, three did (for a partial review, see Roubertoux and Carlier, 1988). As for wild house mice, studies have shown no postnatal maternal effect on SAL and LAL (van Oortmerssen *et al.*, 1985; van Zegeren, 1980). Minor effects have been found in reciprocal F_1's (Sluyter *et al.*, 1995b). Using the OG method, crossfostering, and Mendelian crosses (including reciprocal F_1's) in the N and H strains, Carlier *et al.* (1991) demonstrated that there probably exists an interaction between the Y chromosome and the postnatal maternal environment. This emphasizes again that one cannot generalize results from one genotype to another.

PHYSIOLOGICAL CORRELATES

In a variety of species, including rats and mice, aggressive behavior depends on the hormonal status of the animal (for a review see, e.g., Albert *et al.*, 1992). Testosterone (T) and its metabolites are the major candidates in organizing and eliciting aggression. The effects of T are of two kinds. Quantitatively, plasma testosterone concentrations (pTc) may influence aggression; qualitatively, the timing of T release is of great importance.

Van Oortmerssen *et al.* (1992) demonstrated an overall dominant inheritance pattern for adult pTc levels. SAL and both reciprocal F_1's show identical levels, but higher than that of LAL. Consequently, given the aggression differences between SAL and the reciprocal F_1's, adult changes in pTc levels appear not to be the sole explanation for the causation of aggression differences. These differences also cannot be explained by differential capacities to produce T at adult age because SAL and LAL males show identical pTc after hCG administration (Sluyter *et al.*, 1993). Genetic, especially Y^{NPAR}, effects on hCG sensitivity have been

found in both Maxson's D1 and B10 strains and Roubertoux and Carlier's N and H strains (Roubertoux *et al.*, in preparation). However, as in wild house mice, the direction of the effect is not related to the aggression differences. Accordingly, both studies question the generally assumed link between T action and intermale aggression in adults.

Variation in sensitivity to T is an alternative explanation. Previous studies already showed a variation in responsiveness to T between both selection lines and their reciprocal F_1's. When SAL, LAL, and their F_1's are castrated at day 50 of age and subsequently treated with identical T therapy, the aggression differences still persist (van Oortmerssen *et al.*, 1987; Sluyter, unpublished research), confirming the relative unimportance of adult pTc levels as a causation for aggression differences. These findings suggest either differential T metabolism in adults or differential T action before 50 days of age.

If we concentrate on the latter, this leaves us with two potential time periods at which the Y chromosome may mediate variation in aggression by means of influencing T levels. One is puberty, which is characterized by a rise in pTc. Based on the rise of relative seminal vesicle weights, this period is estimated to last from 30 to 50 days of age in male wild house mice (de Ruiter, unpublished data). Preliminary results show that castration and subsequent identical T therapy at 28 days of age eliminate aggression differences in reciprocal F_1's between SAL and LAL, but not in the original selection lines. Keeping in mind the persisting aggression differences after castration followed by implantation of a T pellet at day 50, one is tempted to consider pubertal pTc differences to be, at least partly, responsible for aggression differences in reciprocal F_1's at adult age. These findings suggest an autosomally dependent involvement of the "aggressive" SAL Y chromosome in the development of aggression by means of influencing the pubertal pTc rise (de Ruiter *et al.*, in preparation). Y chromosomal effects during the pubertal period have been reported before in D1 and B10 (inbred) males (Selmanoff *et al.*, 1977).

The second period is the perinatal time frame. Differences between SAL and LAL males have been reported, perinatally, in circulating T (Compaan, 1993), testosterone secretory capacity of the testis (de Ruiter *et al.*, 1992), and brain aromatase activity (Compaan, 1993). Although the specific processes are not evident yet, all these findings demonstrate differences in perinatal gonadal steroid related mechanisms to affect aggressive behavior in SAL and LAL. Therefore, besides the puberty, the perinatal period is also a potential time frame for the Y chromosome to exercise its influence.

Another mechanism through which the Y chromosome may exert its effect, is urinary chemosignaling. Animals are able to discriminate urine from a pair of Y chromosomal congenics in a maze (Monahan *et al.*, 1993; Yamazaki *et al.*, 1986). Not only the Y^{NPAR}, but also the major histocompatibility complex on chromosome 17 influences individually unique urine odors. Moreover, these odors are not androgen dependent (MacIntosh Schellinck *et al.*, 1993). Following the hypothesis of Adams (1980), which considered urine signals to be almost exclusively the external motivating stimuli of offense in male mice, Maxson's group found evidence for an additional involvement of Y chromosomal and autosomal genes in the response to urinary chemosignals for offense (chemoperception) and offensive motivation (Maxson and Monahan, in preparation). Hence the Y chromosome may affect offense not only by chemosignaling but also by chemoperception. However, we have no experimental evidence indicating that these mechanisms also hold for wild house mice.

NEURONAL CORRELATES

Two neuronal variables correlated to the selection for aggression have been analyzed.

First, SAL males show a higher stereotyped response to apomorphine, a dopamine agonist, than LAL males (Benus *et al.*, 1991a). Additional experiments also showed an effect of the Y^{NPAR}. SAL and LAL differ from their congenics, with the SAL Y^{NPAR} increasing the apomorphine-induced stereotyped response in comparison to the LAL Y^{NPAR}. Reciprocal F_1's do not differ, they exhibit intermediate scores with respect to SAL, LAL, and their Y^{NPAR} congenics (Sluyter *et al.*, 1995a). Apparently, the correlation between aggression against a standard opponent and neostriatal dopaminergic activity depends on the strain background (autosomes, X chromosome, Y^{PAR}, mtDNA, and/or maternal environment), whereas the effect of the Y^{NPAR} suggests a specific relation between dopamine systems and Y^{NPAR}.

The second variable examined in SAL and LAL and their congenics is the size of the intra- and infrapyramidal mossy fiber terminal fields (IIPMF). SAL males show smaller IIPMF sizes than LAL males (Sluyter *et al.*, 1994a). Congenics also differ from their parentals with an incremental effect of the LAL Y^{NPAR} on the size of the IIPMF terminal fields and a decremental effect of the SAL Y^{NPAR} (Hensbroek *et al.*, 1995). Therefore, besides background influences related to aggression, there appears to be an explicit Y^{NPAR} effect which, just like differential dopaminergic neostriatal activity, stands for itself and is not related to aggression. The general relation between IIPMF sizes and aggression is not restricted to wild house mice. Guillot *et al.* (1994) found a strong genetic correlation between sizes of IIPMF terminal fields and the capacity to initiate attack behavior using 140 male mice belonging to seven inbred mouse strains. They contribute this correlation to pleiotropic gene effects and suggest two hypotheses: (1) a direct involvement of the hippocampus in the regulation of attack behavior, possibly via its projections to the hypothalamus (O'Keefe and Nadel, 1978), and (2) a common mediator acting on both variables. A combination of the results on inbred strains and wild house mice suggests that this pleiotropic effect is probably mediated by (an) autosomal gene(s) and not the Y^{NPAR}, the more so as no Y^{NPAR} effects on the sizes of IIPMF terminal fields have been found in the previously mentioned N and H strains (Guillot *et al.*, 1996).

As for wild house mice, these neuronal correlates seem to be part of a coherent set of characteristics. In general, aggressive animals show an active response to challenging situations, whereas nonaggressive ones cope passively (Bohus *et al.*, 1987; Benus *et al.*, 1991b).

GENERAL REMARKS AND CONCLUSIONS

One important factor which may have affected the outcome and conclusion so far is our choice of mouse strain. The contributions of the Y^{NPAR} or Y^{PAR} or both parts of the Y chromosome to aggression depends not only on the test situation and recorded variables, but also on the strain origins. Maxson's and Roubertoux and Carlier's laboratories use different inbred strains, whereas our group uses selection lines from a population of feral mice. The advantages and justification of our choice have been postulated in the introduction. Nevertheless, the fact that our mice are not systematically inbred has a disadvantage, too. We can never tell for sure if one SAL or LAL is genetically identical to another SAL or LAL. Within-line autosomal differences may both conceal or falsely display small Y chromosomal effects and influence the congenic lines for the Y chromosome. However, the latter is not very likely since for each Y^{NPAR} congenic line three replicated lines have been developed, which show no differences in attack latency.

In conclusion, genetic effects play an important role in the development of aggression in wild house mice. Both the Y chromosome, with the major effect possibly exercized by the Y^{PAR}, and the autosomes contribute to this effect. Regarding the maternal environmental sources of variation, both prenatal and postnatal ones are of only minor significance. In addition, physiological (testosterone) and neuronal (sizes of the intra- and infrapyramidal mossy fiber terminal fields and neostriatal dopaminergic activity) correlates are candidates through which these genetic effects may be mediated.

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