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Autosomal and Y Chromosomal Effects on the Stereotyped Response to Apomorphine in Wild House Mice

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SLUYTER, F., B. BOHUS, H. J. A. BELDHUIS AND G. A. VAN OORTMERSSEN. *Autosomal and Y chromosomal effects on the response to apomorphine in wild house mice.* PHARMACOL BIOCHEM BEHAV 52(1) 17–22, 1995.—The behavioral response to apomorphine, a dopamine agonist, was shown to be different between a selection line characterized by Short Attack Latencies (SAL) and a selection line having Long Attack Latencies (LAL) (4). Aggressive SAL mice were more sensitive to apomorphine than nonaggressive LAL males. The aim of this research was to determine whether the stereotyped response to apomorphine is affected by the Y chromosome in the same way as it influences attack latency. For this purpose, F_1 reciprocal hybrids as well as congenic lines (SAL.LY and LAL.SY) were used. The major difference between the congenic and parental lines is the nonpairing part of the Y chromosome (non-PAR). Apomorphine was injected subcutaneously at a preselected dose level of 5.0 mg/kg to induce stereotyped behavior manifested in compulsive sniffing, gnawing, and licking. Both the autosomes and the non-PAR Y chromosome affected the response to apomorphine. The effect of the autosomes was in accordance with the aggression data, whereas the effect of the non-PAR Y chromosome was different, and suggests a specific relation between dopamine systems and the non-PAR Y chromosome.

Aggression Apomorphine Dopamine Stereotyped behavior Wild house mice Y chromosome Autosomes Behavioral strategies

THE IDEA that rodents may display different behavioral strategies in response to environmental challenges is well established. Henry and Stephens (22) have presented the first evidence that differential patterns of neuroendocrine activation are related to contrasting behavioral response patterns of dominant and subordinate mice to social interaction. Three distinct artificial selection experiments support this evidence. First, two selection lines of rats for superior and inferior active shock avoidance acquisition, Roman high-avoidance (RHA/Verh) and low-avoidance (RLA/Verh), not only differ in their response to their selection criterion, i.e., a foot shock in a two-way shuttle box (9), but also in other behavioral, neurochemical, and hormonal aspects (17,18). Secondly, selection of rats for their susceptibility to the dopamine agonist apomorphine to display gnawing behavior has resulted in a line being susceptible to apomorphine (APO-SUS) and another one being not susceptible to apomorphine (APO-UNSUS) (16). The difference between these lines is not limited to the amount of gnawing elicited by apomorphine, but also extends to other behavioral and neurochemical correlates. The use of external and internal information in organizing behavior underlies all interline differences between APO-SUS and APO-UNSUS rats (16).

Thirdly, our own studies (40) have shown that male wild house mice originating from a line selected for short attack latency (SAL), i.e., artificially selected aggressive animals, differ both for this particular trait with respect to animals originating from a line selected for long attack latency (LAL), i.e., artificially selected nonaggressive animals, and for other spontaneous and induced behaviors as well. SAL perform better in a two-way shock avoidance (3), are more routine like and less flexible in their behavior (6,8), whereas LAL perform better in a changing environment (7) and suppress their activity when exposed to uncontrollable and inescapable shocks (2). All together, these differences lead to the conclusion that SAL animals show an active strategy, whereas LAL males

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display a passive strategy to environmental challenges (5). Accordingly, both in rats and in mice, a bimodal distribution originally limited to one behavioral trait, extends to other behavioral, physiological and neuroendocrinological aspects of the animal (11).

Another difference between SAL and LAL mice is the behavioral response to apomorphine. Apomorphine is considered to stimulate dopamine receptors (1) and induces stereotyped behavior (19). Aggressive (SAL) animals show more apomorphine-induced stereotyped behavior than nonaggressive (LAL) mice (4). It is suggested that this neurochemical difference underlies the diversity in flexibility between these selection lines. As stated earlier, the difference in flexibility is an important aspect on which the concept of different behavioral strategies is based. Accordingly, a difference in dopaminergic function may well be, directly or indirectly, causally related to different coping strategies. The potential role for dopamine mediating alternative, behavioral strategies is emphasized by Cools (15). He finds a significant positive correlation between the amount of fleeing a rat displays in a defeat test and the amount of gnawing elicited by the dopamine agonist apomorphine.

Because of the artificial selection, at least a part of the differences in behavioral strategies may be genetically determined. One of the potential genetic factors is the Y chromosome. Selmanoff et al. (33,34) were the first to report evidence for a Y chromosomal contribution to aggression in laboratory mice. Although Y chromosomal effects on aggression have been demonstrated with certainty only in two cases (28,30), strong indications have been found in other studies [for recent reviews on Y chromosomal influences on aggression: see (13,27)]. Our experiments confirm these indications (39,41). By crossing SAL and LAL, the F_1 reciprocal hybrids bearing the SAL Y chromosome show a lower attack latency and can, therefore, be considered more aggressive than the F_1 hybrid carrying the LAL Y chromosome. Although maternal and X chromosomal factors, as well as genomic imprinting, cannot be completely ruled out, all data up till now suggest a Y chromosomal effect, possibly in interaction or coaction with maternal factors. The pseudoautosomal region (PAR), which pairs during meiosis and exchanges information with the X chromosome, is likely to contribute most to the execution of aggression (30,42).

The aim of this research is to determine whether the Y chromosome affects behavioral traits unrelated to aggression in the same direction as it acts upon aggression. For this purpose, F_1 reciprocal hybrids are used as well as congenic lines. These congenics have been developed by the backcross system of breeding and result in stocks that only differ in respect of the nonpairing part of the Y chromosome (42). Apomorphine-induced stereotyped behavior is measured on a previously used rating scale as compulsive sniffing, gnawing, and licking. This rating score is based on spontaneously occurring behaviors including nonstereotyped behavior and apomorphine-induced stereotyped behavior characterized by an aberrant way of movement/posture (Table 1).

TABLE 1

RATING SCALE OF SPONTANEOUS AND APOMORPHINE-INDUCED BEHAVIORAL CATEGORIES IN WILD HOUSE MICE

Rating	Behavior Observed
Spontaneous	
0	Grooming, feeding, drinking, climbing, sniffing, upright, digging,sitting, asleep
1	Freezing
2	Locomotion with intermittent, compulsive sniffing, and rearing
3	Stereotyped behavior in a particular pattern (not in one place)
4	Stereotyped behavior in a particular pattern (in one place)
5	Stereotyped behavior in a particular pattern in one place with intermittent gnawing and/or licking
6	Continuous gnawing and/or licking the walls and bars of the cage
Apomorphine-induced	
7	Reduced locomotor activity (slow, hesitant movements)
8	Compulsive sniffing and gnawing the sawdust; the animal is mobile but slow relative to normal
9	Compulsive sniffing and gnawing the sawdust; occasionally front paws on the cage wall
10	At least two paws on the cage wall, slow climbing
11	Slow climbing and/or maintaining the same position, stretched out vertically at a slight angle
12	Continuous compulsive gnawing or licking the walls and bars of the cage, exaggerated head nodding, arched back, extremely splayed limbs

METHOD

Mice

All strains originated from a colony of wild house mice (*Mus musculus domesticus*) maintained in our laboratory since 1971. The mice were housed in Plexiglas cages (17 × 11 × 13 cm) in a room with an artificial 12L : 12D cycle (lights out 1230 h). Food (standard laboratory chow; Hope farms AM2) and water were available at lib. At weaning age (3–4 weeks), the litters were separated from their parents. At the age of sexual maturity (6–8 weeks), the animals were paired male–female.

Strains

Males of four different strains were used: a) SAL, b) LAL, c) SAL.LY, and d) LAL.SY. The first two are selection lines for short (SAL) and long attack latency (LAL). They originated from the 45th and 23rd generation of selection, respectively. The latter two lines are congenic for the Y chromosome (42). The congenic line of SAL mice with the LAL Y chromosome was developed by the backcross system of breeding (20). Initially, a SAL female was crossed to a LAL male. The F_1 male progeny and those of all subsequent generations have the SAL X chromosome and the LAL Y chromosome. In this way, almost all of the LAL autosomal ones have been replaced by SAL autosomal alleles at the 10th generation of repeated backcrossing to SAL females (27). Because crossing over is a obligatory event at male meiosis, the pseudoautosomal region (PAR) of the original LAL Y chromosome has also been replaced by the SAL pseudoautosomal region. Therefore, the major genetic difference between the SAL selection line and its congenic (designated SAL.LY) is the non-PAR Y chromosome, being the conservative part of the Y chromosome. By the same procedure but in an inverse way, a congenic stock of LAL mice with the SAL non-PAR Y chromosome (designated as LAL.SY) was obtained. For this experiment we used

SAL.LY congenics from the 25th and LAL.SY congenics from the 16th generation of backcrossing.

We realize that SAL and LAL are not inbred. There exists a certain degree of heterogeneity of the genetic background. The comparisons in our congenic lines, thus, refer to average effects of the Y chromosomes involved on a similar gene pool background, either that of the SAL line or that of the LAL line. Therefore, theoretically, the gene pool background may involve differential intragenomic interaction that may influence the expression of the Y chromosome.

The F_1 reciprocal hybrid bearing the SAL Y chromosome is denoted as F_1LAL.SAL, whereas the F_1 reciprocal hybrid bearing the LAL Y chromosome is denoted as F_1SAL.LAL.

Testing Procedure

At an age of 14–17 weeks, the animals were tested for their behavioral response to apomorphine. The apomorphine (Sigma No. A-4393, 5 mg/kg) was injected subcutaneously. This dose of the drug was selected on the basis of former dose-response experiments with the selected lines (4). Individuals were their own controls. To assess possible sequential effects of drug administration, a crossover design was used. Half of the animals were injected with saline on experimental day 1 and with apomorphine on the next day; the other half of the animals were treated vice versa. The observer was not blind to the treatment and genotype of the mice. The experiment was carried out just after onset of the dark period in the home cage of the animal. The females were removed from the cages at the start of the experiment. The males were injected and after 5 min the observations were started. The behavior was observed for 30 s at intervals of 3 min for a total of 20 observations. At the end of each observation period the male's behavior was assigned a numerical score based on the rating scale described in Table I. This rating score is based on spontaneously occurring behaviors including nonstereotyped behavior (= rating 0–1), and stereotypies that are not induced either by suddenly disturbing the animals or by drugs (= rating 2–6), and apomorphine-induced stereotyped behavior characterized by an aberrant way of movement/posture (= rating 7–12). The difference between the spontaneous and apomorphine-induced stereotyped behavioural categories is clearly distinguishable, the major distinction being the slow, hesitant movements induced by apomorphine. The choice of the rating scale was not arbitrary, but is based on previously used rating scales (29,35) and was applied before to the selection lines (4). A mean stereotypy score was calculated for each individual.

Statistics

Values are expressed as median and their interquartile ranges (IQR). The Mann-Whitney *U*-test (MWU) was used to compare independent samples. If the samples were related the Wilcoxon's matched pairs test (WMP) was used. Differences between SAL and LAL in frequencies in the discrete categories of the stereotypy rating scale were tested by the χ^2-test.

RESULTS

No effect of the sequence of saline and apomorphine administration was found; hence, the data of all animals were combined in accordance with the treatment.

When injected with saline there were no differences in median stereotypy score between genotypes (Fig. 1). In response to a saline injection, all genotypes showed behaviors of the spontaneous category only (Fig. 2). However, the distribution

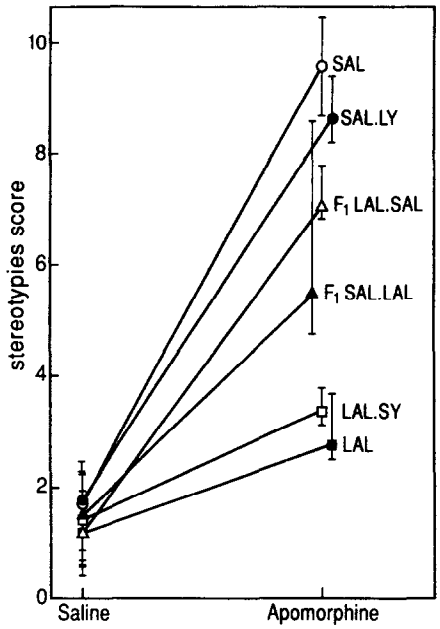

FIG. 1. Median stereotypy score (+ IQR) in all genotypes after a saline and 5.0 mg/kg apomorphine injection.

of these behaviors over the rating scale was significantly different between all genotypes (χ^2, $p < 0.01$), except for SAL and SAL.LY (χ^2, $p = 0.39$), and LAL and F_1SAL.LAL (χ^2, $p = 0.06$). A striking difference was the presence of higher rating stereotypies 5 and 6 (see Fig. 2) in SAL, SAL.LY and, to a less extent, F_1SAL.LAL.

All genotypes showed a significant increase in stereotypy score in response to an apomorphine injection (all genotypes: WMP, $p > 0.01$). SAL showed highest median scores, followed by SAL.LY. The F_1 hybrids showed intermediate values, whereas LAL.SY and LAL showed lowest scores (see Fig. 1). Table 2 summarizes the statistical differences in stereotypy scores between all genotypes. The distributions of behavioral items over the rating scale were significantly different between all genotypes (χ^2, $p > 0.01$). A remarkable difference was the near absence of apomorphine-induced stereotypies in the LAL group and intermediate scores for the F_1 hybrids. In contrast, a relatively large percentage of the highest rating stereotypies appeared in SAL and SAL.LY mice (see Fig. 2).

DISCUSSION

The main finding of these experiments is that the dopamine agonist apomorphine induces different degrees of stereotyped behavior in SAL and in LAL male mice with intermediate values in congenics and F_1 hybrids. Because of the absence of differences between the F_1 hybrids and the dissimilarity between congenic and parental lines, one may conclude that both autosomes and Y chromosome, the nonrecombining part to be specific, affect the response to apomorphine in wild house mice.

Artificially selected, aggressive, male wild house mice differ in their response to apomorphine, a dopamine agonist, in comparison to their nonaggressive counterparts. SAL individuals show more stereotyped behavior after acute apomorphine administration than LAL males, confirming the findings of Benus et al. (4). In this context it is important to recall that

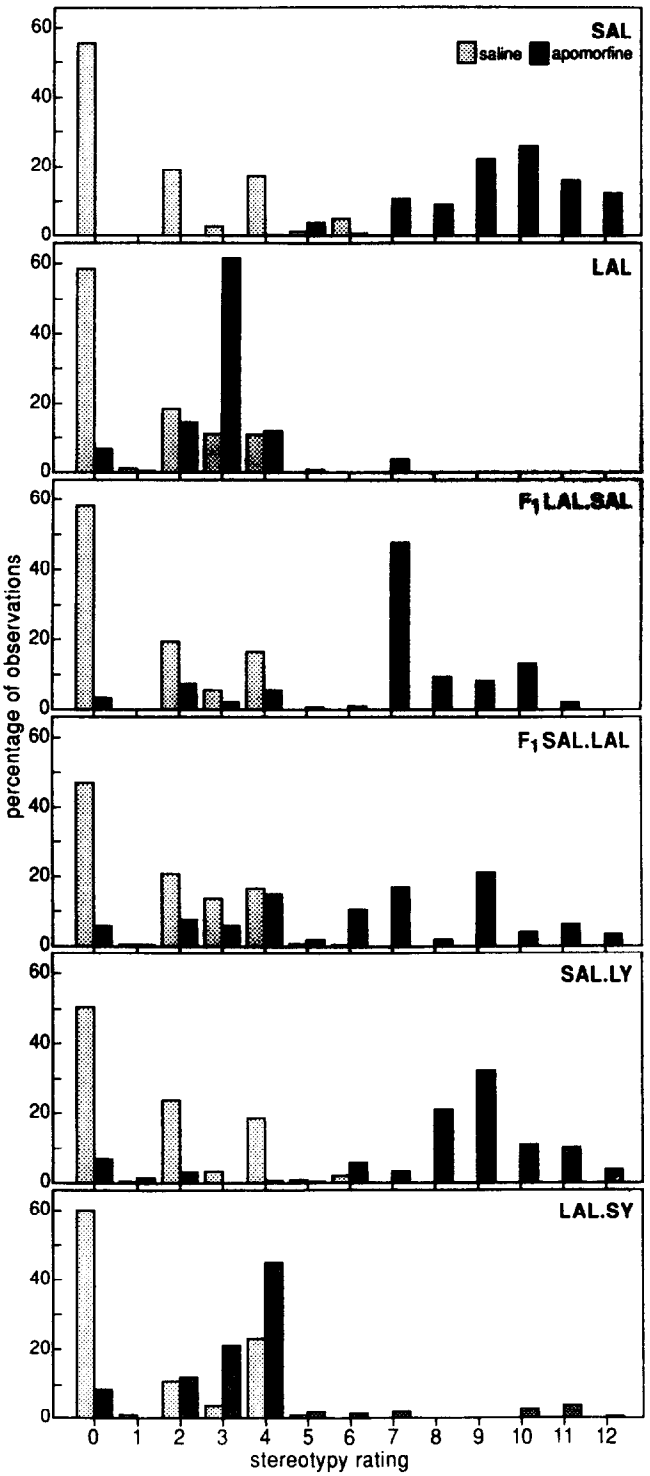

FIG. 2. Mean frequencies expressed as a percentage of total observations, per rating category in all genotypes after a saline and 5.0 mg/kg apomorphine injection.

agonist drugs are poorly effective at high values of fractional occupancy of the receptors by the endogeneous agonist, but strongly effective at low values of fractional occupancy of the receptors by the endogeneous agonist (16). This principle implies that mice showing a weak response to the dopaminergic agonist apomorphine, i.e., LAL males, have a functionally high activity of dopamine, while the reverese applies to mice showing a strong response to apomorphine, i.e., SAL males. Because stereotyped behavior can be initiated by intrastriatal injections of dopaminergic drugs like apomorphine, the intensity of behavioral responses can be considered as an index of striatal dopaminergic functions (35). Therefore, these findings suggest that SAL mice are characterized by a low neostriatal dopaminergic activity and LAL mice by a high activity.

Previous results by Benus et al. (4) have indicated that SAL and LAL differ in sensitivity to apomorphine and not in the character of the induced response. They demonstrated that at a higher dose LAL mice showed qualitatively the same apomorphine-induced behaviors as SAL males. Accordingly, it can be concluded that SAL and LAL mice differ in sensitivity to apomorphine rather than in the character of the induced response.

The F_1 hybrids, the product of a reciprocal cross between SAL and LAL, show intermediate values pointing to no dominance of the measured character, i.e., apomorphine sensitivity. Therefore, these results suggest an autosomal and intermediate inheritance of neostriatal dopaminergic activity. The finding that both F_1 hybrids (F_1SAL.LAL and F_1LAL.SAL) show identical values implies either the absence or opposing actions of cytoplasmatic, maternal, heterosomal effects, and genomic imprinting. Opposing actions seem plausible because both congenics differ from their parental lines for apomorphine sensitivity. Because SAL show higher values than SAL.LY and LAL.SY than LAL, and also because the congenics only differ in respect of the conservative, nonpairing part of the Y chromosome (non-PAR), an additional effect of this part of the Y chromosome seems obvious. In the F_1 hybrids this Y chromosomal effect is likely to be overruled by one or more of the abovementioned factors.

Accordingly, these experiments illustrate an effect of the non-PAR of the Y chromosome on neostriatal dopaminergic activity. Because the parental selection lines are not inbred, we realize that autosomal gene(s) may also be responsible for the difference between SAL and SAL.LY. However, keeping in mind the degree of inbreeding in wild populations of wild house mice and the number of successive backcrosses in the congenic lines used, we estimate the chance that (an) autosomal gene(s) is/are responsible for the difference in apomorphine-induced stereotyped behavior between the congenic and parental lines, very low.

The non-PAR of the Y chromosome is, among others, involved in individually unique urine odors (26), plasma testosterone concentrations (21,24), sensitivity to exogeneous testosterone (24), and testis and kidney weight (36). All these studies used strains congenic for the non-PAR Y chromosome. Effects of the Y chromosome on brain-related variables have been demonstrated earlier by Van Abeelen et al. (38). They randomized autosomal, X-linked, cytoplasmic, and maternal factors over Y chromosomal groups by means of a four-way cross and obtained evidence of Y linked influences on, among others, right-side hippocampus weight and hippocampal asymmetry.

Many mouse strain differences have been found in the number of dopamine neurons (31), dopamine synthesis (37), dopamine binding sites (10), reactivity of dopaminergic neurons to stress (23), and apomorphine related behavioral traits (12,25,32,42). However, to our knowledge, no specific Y chromosomal effect on dopamine-related behavior or physiology is known. Benus et al. (4) have related the difference in poten-

TABLE 2

STATISTICAL DIFFERENCES OF EXPERIMENTAL VARIABLES FROM DIFFERENT GENOTYPES

Saline	SAL	SAL.LY	F_1 LAL.SAL	F_1 SAL.LAL	LAL.SY	LAL
Apomorphine	SAL	SAL.LY	F_1 LAL.SAL	F_1 SAL.LAL	LAL.SY	LAL

Twelve to 14 male mice were used per genotype. Underlined genotypes are statistically equivalent ($p > 0.05$). The Mann-Whitney U-test was used to compare the scores of the different genotypes.

tial dopaminergic activity between SAL and LAL to their difference in behavior in a defeat test (2) and a Y maze (6). Low dopaminergic activity (indicated as high sensitivity to apomorphine) accompanies a fight-flight strategy characterized by aggressive, routine-like, stereotyped behavior, whereas high dopaminergic activity (indicated as low sensitivity to apomorphine) underlies a conservation-withdrawal strategy characterized by more flexible behavior, i.e., a higher degree of freedom in shifting arbitrarily their ongoing behavior. Cools (14) has found a correlation between dopaminergic activity, behavioral flexibility, and strategy. Following his line of reasoning, one would expect a parallel with aggression: the more sensitive an animal to apomorphine, the lower the dopaminergic activity, and the more aggressive is the animal. Our findings partly confirm this argumentation. Both for aggression and apomorphine sensitivity, SAL and SAL.LY show higher values than the F_1 hybrids, which, in their turn, are more aggressive and more sensitive to apomorphine than LAL and LAL.SY. However, the congenic lines differ in sensitivity to apomorphine from their parental, selection lines with SAL.LY being less sensitive than SAL and LAL.SY more sensitive than LAL, whereas SAL.LY animals have been proved to be equally aggressive with SAL. LAL.SY and LAL appeared equally nonaggressive, as indicated by their long attack latencies (42). Taken together, the present data suggest that the genetical information underlying the basic idiosyncrasy between behavioral strategies is located on the autosomes. Whether dopamine is a correlative or a causal factor in the differences remains to be further investigated.

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