Pharmacology Biochemistry & Behavior, Vol 24 pp 743–749, 1986 © Ankho International Inc Printed in the U S A 0091-3057/86 $3 00 + 00

A Genetic Analysis of Nicotine Effects on Open Field Activity

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Received 8 April 1985

MARKS, M J , L L MINER, S COLE-HARDING, J B BURCH AND A C COLLINS *A genetic analysis of nicotine effects on open field activity* PHARMACOL BIOCHEM BEHAV 24(3) 743–749, 1986 —The genetics of the effects of nicotine on the open field activity of mice were studied using a 5 by 5 diallel cross The five inbred strains used were A, BALB, C57BL, DBA, and C3H These strains differ both in basal open field activity as well as activity after injection of nicotine Analysis of the results of baseline activity indicated that both additive and dominance variance affected the activity of the animals The dominance was non-directional Likewise, the responses observed after injection of 0 75 mg/kg nicotine displayed both additive and dominance components However, after correcting the results for differences in basal activity, the dominance item was primarily directional This directional dominance was towards a more intense response to the effects of the drug, that is, a decrease in open field activity

Nicotine Genetics Pharmacogenetics Diallel cross Open field activity

NICOTINE, one of the drugs most widely used by humans, affects cholinergic neurotransmitter systems both in the central nervous system and in the periphery In addition, the effects of nicotine are biphasic in that low doses of the drug stimulate nicotinic cholinergic receptors, while high doses initially stimulate and then inhibit them [23] The biphasic action of nicotine has been explained by a model involving the desensitization of the receptors [20] The multisite and biphasic effects of nicotine on responses in whole animals make the pharmacology of this drug complex Nevertheless, reliable and reproducible responses to nicotine have been measured using several behavioral and physiological tests [1, 4, 6, 14, 22, 24, 30, 31, 32]

The effects of nicotine on the locomotor activity of rodents are influenced by genetic factors Selected lines of rats are differently affected by nicotine The locomotor activity of those rat lines with high baseline activity is affected more markedly than the activity of those lines with lower baseline activity [5, 10, 11, 12, 33] Various stocks of rats are also differentially affected by nicotine While nicotine decreases the activity of those stocks with high baseline activity, it increases the activity of a stock with low baseline activity [30] The effect of nicotine on the locomotor activity of mice is also influenced by genotype Differences among inbred mouse strains have been observed both in the Y-maze [14] and in the open field arena [24] after the injection of nicotine and in the open field after exposure to tobacco smoke [4] The differences in behavioral response in mice do not arise from differences in brain levels of nicotine or in the metabolism of the drug [4,14] Therefore, differences in tissue sensitivity are of major importance in determining the different responses of rats and mice to nicotine

The results of the strain comparisons discussed above strongly suggest that genetic factors influence the response of rodents to nicotine However, little has been done to characterize the nature of this genetic influence One method which is available to further analyze genetic influences on drug response is the diallel cross. In a diallel cross, members of inbred strains, which differ in the character of interest, are crossed with members of every other strain to produce all possible combinations A diallel analysis of variance can subsequently be applied to the results obtained This analysis has the structure of a two-way analysis of variance, where rows and columns detect additive genetic effects, and rows × columns detect the non-additive effects of dominance and genic interaction In addition, maternal effects can be determined by the difference between the reciprocal crosses

Diallel crosses have been used to assess the genetic contribution to differences in locomotor activity in mice [7, 13, 17] and the underlying differences have been employed in the selection of lines of mice that differ markedly in activity measures [8] Diallel crosses have also been used to evaluate the effects of drugs on locomotor activity [2, 3, 21] The results of these drug studies were not subjected to a complete diallel analysis of variance and are, therefore, primarily descriptive in nature Nevertheless, some indication of dominance in the inheritance of response to the drugs tested was seen in that the locomotor activity of the F1 hybrids resembled that of the less active parent after the administration of either amphetamine or scopolamine [2] This pattern

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TABLE 1
CONTROL OPEN FIELD ACTIVITY OF DIALLEL MICE

Paternal Strain	Maternal Strain A	BALB	C57BL	DBA	C3H	Row Totals
A	64 7 (11 8)	91 5 (18 9)	220 9 (18 3)	224 6 (20 5)	31 6 (7 7)	722 1
BALB	109 5 (17 8)	180 8 (31 3)	241 2 (17 6)	166 6 (24 7)	83 9 (18 8)	936 7
C57BL	212 2 (20 3)	244 5 (20 7)	252 0 (14 1)	282 7 (15 5)	203 3 (25 8)	1444 9
DBA	168 9 (31 1)	128 3 (22 2)	272 5 (13 4)	233 1 (31 0)	166 6 (37 5)	1206 0
C3H	40 5 (12 1)	137 5 (23 5)	237 1 (20 7)	206 2 (27 0)	102 4 (25 3)	837 5
Inbred Replicates	88 8 (16 9)	154 7 (28 9)	250 2 (18 6)	230 0 (34 4)	113 9 (27 2)	
Column Totals	684 6	937 4	1473 9	1343 2	676 7	

Mean open field activities (S E M) after injection of saline were determined using 7 males and 7 females per group Both row and column totals include values for the appropriate inbred replicates

was observed either before or after the administration of a foot shock [3]

In the study reported here, the influences of genetic factors on changes in locomotor activity induced by nicotine were estimated from a complete five by five diallel cross using the following inbred strains A, BALB, C57BL, DBA, and C3H The effects of an injection of saline or 0 75 mg/kg of nicotine on the open field activity of the five inbreds and 20 F1 crosses were determined The data obtained were subsequently analyzed by a diallel analysis of variance [16], as modified for analysis of a half-diallel [19]

METHOD

Animals

Five inbred strains of mice were used as the parental lines in this study A/Ibg, C3H/2Ibg, C57BL/6Ibg, DBA/2Ibg, and BALB/cByJ Four of these strains have been bred at the Institute for Behavioral Genetics, University of Colorado for more than 20 generations, while mice of the BALB strain were obtained from Jackson Laboratories, Bar Harbor, ME

Mating pairs for each of the 5 inbred strains, as well as for all possible combinations of these inbred strains, were established to produce 25 different F1 hybrids Five mating pairs were employed for each cross Mice were maintained on a 12 hr light/12 hr dark cycle (lights on 7 a m to 7 p m) and were permitted free access to food (Wayne Lab Blox) and water Mating pairs were kept in 17 5×50×20 cm (L×W×H) metal cages and transferred to 21×62×20 cm (L×W×H) metal cages when litters were born Offspring were weaned at 25 days of age and housed with 1–5 like-sexed littermates

Testing

Both male and female mice, 60 to 90 days old, were tested for the effect of nicotine on locomotor activity Littermates were divided between treatment groups After the mice were weighed, they were transferred to the testing room for at least 15 min but less than 2 hr prior to treatment This room was illuminated with red light

Testing was conducted using an automated open field arena illuminated with red light to minimize problems associated with photophobia [8] The open field arena is a square (91 4×91 4 cm) constructed of white acrylic plastic The floor area is divided into 36 equally spaced squares Movement between squares interrupts a photocell beam and thereby activates an electronic counter The 5-min period was begun 3 min after injection of the test solution During the 3-min period prior to testing, the mouse was placed in a plastic cylinder in a corner of the arena Animals were injected with nicotine (0 75 mg/kg) or saline (0 0 mg/kg nicotine) Drug was administered by IP injection Injection volume was 0 01 ml/g The effects of nicotine on locomotor activities are short-lived [14] The results obtained reflect the maximum drug effect since onset of action is similar in all of the crosses

Seven mice of each sex from each cross were tested at each dose In addition, seven additional inbred mice of each sex were tested at each nicotine dose

Data Analysis

Results were analyzed using the diallel analysis of variance described by Hayman [16] and as applied to the half-diallel by Jones [19] Initial analyses were made on the un-

transformed data for both groups The analyses were repeated on data transformed as follows B=log(A+1), where B was the transformed score and A was the original open field activity. Since some original scores were zero, it was necessary to add 1 to each score to assure that the minimum log was zero This transformation was performed to meet homogeneity of variance requirements An additional analysis of the results of the open field activity after nicotine administration was made on data transformed as follows C=(activity, nicotine=0 75 mg/kg)/(activity, nicotine=0 mg/kg), where activity, nicotine=0 75 mg/kg was the mean activity score when the mice were injected with 0 75 mg/kg nicotine and activity, nicotine=0 mg/kg was the mean activity scores for saline-injected mice of the same cross Variances were calculated by application of Taylor's expansion This transformation has been employed previously to compare the effects of nicotine injection on the open field activity of four inbred mouse strains [24]

RESULTS

The mean open field activity scores for the control group are presented in Table 1 No significant differences between males and females were found, so the results obtained from both sexes were pooled for analysis The five cells along the leading diagonal contain the mean scores of the five inbred strains, whereas those off the main diagonal summarize the data of the various crosses and their reciprocals Replication of the inbred values is also provided The rank order for the activity of the five inbred strains was C57BL > DBA > BALB > C3H > A The mean activity of mice of the C57BL strain was more than three times that of mice of the A strain Row and column totals reflect these differences in activity as well A comparison of reciprocal row and column totals gives no indication of maternal effects Finally, examination of the off-diagonal cells indicates that the F1 hybrid scores were roughly intermediate between parental scores

The results presented in Table 1 were further analyzed using a diallel analysis of variance, the results of which are summarized in Table 2 This analysis assumes a simple additive-dominance model If this model holds, the mean squares of the items in the analysis of variance can be interpreted in simple terms For the diallel analysis on the untransformed data, significant additive and dominance effects were found and two components of the dominance item (b_2 and b_1) were also significant No maternal or other reciprocal effects were found These results were nearly identical in an analysis of the data subjected to a log transformation (significant a, b, b_2, and b_1 items were obtained, results not shown) The absence of any directional dominance is further supported when the average activity of the inbreds (165 2 crossings) was compared to that of the F1s (162 7 crossings) and by the fact that eight of the F1 hybrids showed higher activity, eight showed lower activity, and two showed activity nearly identical to that of the appropriate midparent value

The adequacy of the simple additive-dominance model can be tested with variance-covariance (W-V) analysis [7, 18, 29] The W-V analysis involves the regression of the covariance of the parental scores and an array (row or column) on the variance of the array The relationship of the points obtained provides an indication of the relative number of the dominant alleles carried by the inbred parental strains If the additive-dominance model holds, these points should also define a straight line with unit slope If the model fails (the slope differs from 1), a more complex model involving epistatic interactions must be considered The W-V analysis of the baseline open field activity is shown in Fig 1 The slope of the line (0 76±0 09, $t(3)=2\ 67$, $p>0\ 05$) does not differ from unity and the simple additive-dominance model cannot be rejected The ordering of the points on the plot indicates that the C57BL strain, which is most active, carries the most dominant alleles and the A strain, which is the least active, carries the fewest

The genetic parameters u, v, and k were estimated from the variance-covariance statistics [7, 16, 28] and are summarized in Table 2 The relative frequency of recessive alleles (v) is higher than that of dominant alleles (u) as indicated by the ratio u/v=0 28 This ratio suggests that 3 to 4 times as many recessive alleles than dominant alleles are present in the inbred strains The unequal frequency is also

TABLE 2

DIALLEL ANALYSIS OF BASELINE OPEN FIELD ACTIVITY

Item	*df*	MS	F
a Additive variance	4	30328 2	59 45‡
b Dominance variance	10	2285 5	4 48‡
b_1 Directional	1	309 4	0 61
b_2 Unequal gene	4	2883 4	5 65‡
b_3 Residual	5	2198 4	4 31†
c Maternal effects	4	944 5	1 85
d Reciprocal effects	6	225 8	0 44
Error	395	510 14	—
Heritability			
Narrow sense		0 59	
Broad sense		0 72	
uv		0 10	
u/v		0 28	
k		0 0	

Summaries of the analysis of variance of open field activity after injection of saline are provided for the results obtained from the five by five diallel cross Each cell of the cross was composed of 7 males and 7 females Replicate cells for the inbred mice were included The degrees of freedom (*df*) for each item in the analysis are indicated Both the mean square (MS) and the F-value are listed for each item The major items in the analysis are (a) additive genetic variance, sum of the average effects of the genes in a genotype, (b) dominance variance, differences between the additive genotypic value and the actual genotypic value, (c) maternal effects, effects dependent on the strain of the mother, and (d) reciprocal effects not ascribable to (c) In addition, the dominance variance (b) has been subdivided into three components (b_1) directional dominance, deviation from additive value toward the response of one of the parents, (b_2) unequal gene frequencies, an indication that some of the parents are carrying more dominant genes than are other parents, and (b_3) nondirectional dominance (residual effects), dominance variance unique to each F1 Narrow sense heritability is the fraction of the phenotypic variance resulting only from additive genetic factors, broad sense heritability is the fraction of phenotypic variance arising from all sources of genetic variance The product uv represents the cumulative products for the frequency of dominant genes (u) and recessive genes (v) The quotient u/v represents the cumulative quotients for the frequency of dominant genes (u) and recessive genes (v) The values of u and v vary between 0 and 1 The value k represents an estimate of the number of genetic loci with some dominance component influencing the trait

*$p<0\ 05$, †$p<0\ 01$, ‡$p<0\ 001$

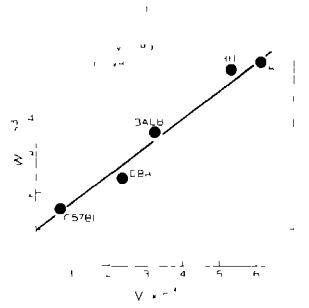

FIG 1 Variance-covariance plot for control open field activity The variances of the inbred-hybrid responses (W) were graphed as a function of the variances of the inbred responses (V) for control open field activity The points are labeled to indicate the relative position of the inbreds

suggested by the product uv=0 10 This uv product suggests that 12% of the alleles are dominant The estimate of the minimum number of loci (k) involved in control open field activity is zero

The mean open field activity scores for mice treated with 0 75 mg/kg nicotine are presented in Table 3 These values confirm what has been reported previously this dose of nicotine activated C3H mice (activity 140% of control), had little effect on BALB mice (110% of control), and depressed C57BL and DBA mice (39% and 59% of control, respectively) In addition, the activity of the A strain was also depressed (34% of control). Thus, the inbreds chosen for this study showed a wide range of nicotine effects Comparison of row and column total showed no striking indication of maternal or other reciprocal effects The row and column totals only approximately reflect relative activity after a nicotine dose because they are confounded by an interaction between the differences in control activity and drug effects In an attempt to compensate for baseline activity differences, the ratio between the activity after nicotine injection and control activity was calculated for individual subjects This data transformation has been used previously to compare the effects of nicotine on open field activity in a strain comparison [24]

Table 4 presents the results from the diallel analysis of variance of both the untransformed and the transformed (ratio) data for nicotine-treated animals Significant additive and dominance effects were found (items a and b) In addition, all three dominance components were significant A somewhat different pattern emerged from the ratio data As with the untransformed data, significant additive and dominance effects were found However, the b_1 item was no longer significant and the b_2 item was reduced Neither analysis indicated the presence of either maternal or reciprocal effects

The adequacy of the additive-dominance model to describe open field activity after nicotine injection was tested with W-V plots [7, 18, 29] of both the untransformed and transformed data These plots are shown in Fig 2 The plot of the untransformed data had more scatter (r=0 89) than that of the ratio data (r=0 98) perhaps reflecting a basal activity difference by drug effect interaction Since the slope of the W-V plot for the ratio-transformed data did not differ from unity (0 74±0 17, $t(3)=1\ 53$, $p>0\ 05$), the additive-dominance model could not be rejected for the analysis This plot indicated that the A strain carried the most dominant alleles and the BALB strain the fewest

TABLE 3

OPEN FIELD ACTIVITY OF DIALLEL MICE AFTER ADMINISTRATION OF 0 75 mg/kg OF NICOTINE

Paternal Strain	Maternal Strain A	BALB	C57BL	DBA	C3H	Row Totals
A	31 0 (7 7)	47 4 (15 0)	20 7 (5 9)	24 3 (8 7)	14 8 (3 4)	154 6
BALB	16 8 (6 8)	213 5 (44 9)	35 0 (20 6)	18 5 (7 2)	11 0 (4 9)	480 5
C57BL	41 3 (18 1)	41 6 (23 0)	82 6 (23 0)	53 6 (25 5)	164 1 (43 4)	493 8
DBA	5 3 (2 2)	22 6 (12 6)	19 1 (9 1)	130 0 (44 7)	72 3 (24 5)	383 4
C3H	10 3 (5 3)	118 4 (49 7)	156 9 (43 4)	86 4 (27 2)	158 6 (39 7)	665 4
Inbred Replicates	16 4 (6 8)	185 7 (46 0)	110 6 (27 2)	134 1 (46 2)	134 8 (31 6)	
Column Totals	121 1	629 2	424 9	446 9	555 6	

Mean open field activity (S E M) was determined after an injection of 0 75 mg/kg of nicotine Each value represents data obtained from 7 males and 7 females per group

The genetic parameters u, v, and k were calculated for the open field activity after a dose of 0 75 mg/kg of nicotine and are shown in Table 4 In contrast to the ratio (u/v) obtained for the control activity, the ratios of gene frequencies for the activity after nicotine treatment were greater than one for both the untransformed (1 524) and the ratio-transformed (1 956) data, suggesting that dominant alleles are more frequent than recessive alleles The products (uv) indicate that approximately 75% of the alleles are dominant for the untransformed data and that approximately 86% of the alleles are dominant for the transformed data The minimum number of loci influencing open field activity after nicotine administration was estimated to be 2 84 and 6 74 for the untransformed and ratio-transformed data, respectively In contrast to the basal activity, where no directional dominance was found, significant directionality was observed after nicotine injection The mean number of crossings of the F1 hybrids (50 1 crossings, 31% of control) was markedly less than that of the inbreds (117 9 crossings, 77% of control) This result suggested that the directional dominance was toward depression of activity Figure 3 was constructed to further examine this result For the untransformed data 9 of 10 F1 crosses were more affected than would have been predicted from the midparent value The ratio data, which may better represent the drug effect by removing basal activity differences, are very similar For these data, however, all of the F1 hybrids were more affected than would have been predicted if the effects were purely additive

DISCUSSION

The diallel analysis presented here confirms and extends

TABLE 4

DIALLEL ANALYSIS OF OPEN FIELD ACTIVITY AFTER A DOSE OF 0 75 mg/kg OF NICOTINE

		Results Analyzed			
		Untransformed		Ratio	
Item	*df*	MS	F	MS	F
a Additive variance	4	9615 8	12 98‡	0 461	10 82‡
b Dominance variance	10	6453 9	8 71‡	0 206	4 85‡
b_1 Directional	1	30731 9	41 51‡	1 487	34 99‡
b_2 Unequal	4	4651 1	6 27‡	0 126	2 98*
b_3 Residual	5	3036 5	4 10*	0 013	0 31
c Maternal effects	4	1089 1	1 47	0 051	1 19
d Reciprocal effects	6	504 2	0 68	0 031	0 72
Error	395	740 8	—	0 043	—
Heritability					
Narrow sense		0 18		0 19	
Broad sense		0 58		0 45	
uv		0 19		0 12	
u/v		1 52		1 96	
k		2 84		6 74	

Results of open field activity of the diallel mice after injection of 0 75 mg/kg nicotine were analyzed either without transformation or after transformation by normalizing the data by defining the control activity of the corresponding cross as 1 00 to eliminate differences in basal activity among the mice Each cell contained 7 males and 7 females Replicate cells of the five inbred strains were also included Explanation of the items of analysis is provided in the legend to Table 2

*$p<0$ 05, †$p<0$ 01, ‡$p<0$ 001

the observation that genetics are important in influencing the responses of mice to nicotine We have previously reported on strain differences in the effects of nicotine on open field activity [24] By extending the analysis from a strain comparison to a diallel cross, information on the inheritance of the response has been obtained Such information can be useful in identifying the biological basis of drug-induced behavior While strain differences imply genetic influences on the biological substrates of drug-induced behavior, they provide only a starting point for the investigation of these differences Further genetic analyses, e g , a classical cross (F1, F2, backcross) or the diallel cross, are necessary to provide more useful information concerning the genetic control of a trait In particular, the classical or diallel crosses can provide an estimate of gene number as well as information about genic interaction Once this information has been obtained, further studies such as an assessment of the relationship between nicotine effects on open field activity and brain nicotinic receptors can be designed The data obtained in the diallel analysis of nicotine-induced changes in open field activity indicate that nicotine's effects on open field activity are regulated by a large number of genes (ca [7]) It should be emphasized that this number is merely an estimate because many assumptions are made in the calculation of gene number [29] However, the observation that a large number of genes influence nicotine's effects on locomotor activity indicates that a correlational analysis of open field response and any biochemical trait would not likely be very fruitful In contrast, we [28] have observed, using a classical cross, that nicotine-induced seizures may be regulated by a single gene and have obtained evidence which suggests that nicotine-induced seizures may be regulated by the number of hippocampal nicotinic receptors Thus, the diallel method, or other such genetic cross methods, has usefulness in that it may serve to aid in the identification of simpler drug-induced behaviors Once these less complex behaviors have been identified, the likelihood of successfully testing hypotheses which attempt to explain these behaviors is enhanced

While the results obtained in the diallel analysis suggest that further investigation of the genetic and/or biochemical regulation of nicotine's effects on open field activity would be difficult, the diallel analysis did provide information which is of general biological interest The diallel cross used inbred strains Mather [26,27] has argued that the genetic architecture of inbreds may be regarded as a vestigial form of that found in natural populations despite the considerable selection that occurs during inbreeding Thus, the genetic architecture for genes controlling a response seen in inbred strains has some implications for the biological importance of this trait In natural populations of mice, outbreeding is common and consequently most gene combinations should be heterozygous The F1 mice obtained with a diallel cross will be heterozygous at those loci where their inbred strain progenitors differed Thus, the analysis of F1 mice may provide data which are more relevant to the genetic regulation of a trait in a natural population than is the study of inbreds The data obtained in the present study indicate that dominance towards an enhanced response to nicotine occurs

In an earlier diallel analysis of nicotine-induced hypothermia, we also observed dominance towards an intense drug response [25] This type of directional dominance in an F1 population can be interpreted from an evolutionary point of view The striking dominance towards sensitivity to nicotine effects seen for both the hypothermic response and

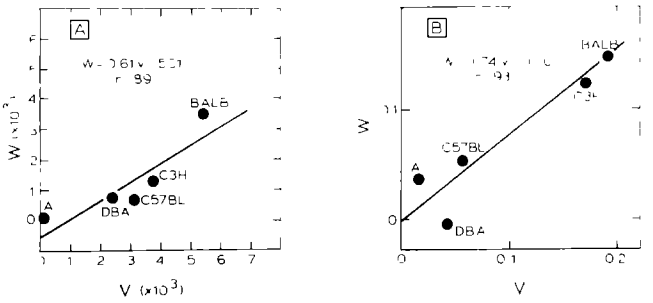

FIG 2 Variance-covariance plots for open field activity after administration of 0 75 mg/kg of nicotine The variances of the inbred-hybrid responses (W) were graphed as a function of the variances of the inbred responses (V) for both untransformed data (panel A) and ratio-transformed data (panel B) The points are labeled to indicate the relative position of the inbreds

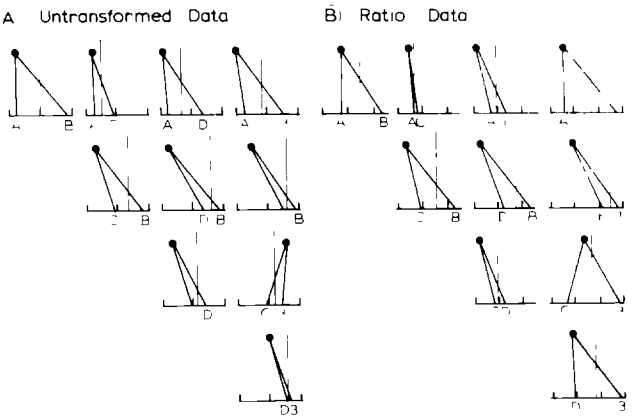

FIG 3 Comparison of activity of F1 hybrids to the parental inbred strains Panel A shows the relative activity of the F1 hybrids after administration of 0 75 mg/kg of nicotine and Panel B shows the relative activity after ratio transformation of the data The mean activity of the F1 hybrids is represented by the point (●) at the apex of each triangle The activity of the F1 hybrid is compared to the activities of the parental strains, which are the values at the base of each triangle The vertical line in each diagram is the appropriate midparent activity The strains have been identified by the following single letter codes A by A, BALB by B, C57BL by C, DBA by D, and C3H by 3 A tilt of the triangle to the left indicates that the F1 was more affected by nicotine than predicted by the midparent value

depression of open field activity may be postulated to have a selective advantage for mice Perhaps an intense response to nicotine would serve either to limit the intake of the compound and prevent the ingestion of a toxic dose or, once ingested, to depress the movement of the animal and thereby reduce its exposure to predators while it is impaired

Only a single dose of nicotine was used in this study, and the results might have differed if other doses had been used In a previous study of the effects of nicotine on open field in various inbred mouse strains [24], we determined that the nicotine dose-response curves for effects on open field activity are steep The dose of 0 75 mg/kg was chosen because it differentiated the parental inbred strains used in the present study Higher doses (1 0 mg/kg or more) result in complete inhibition of activity in most strains, while lower doses (less than 0 5 mg/kg) have little effect in many strains It seems likely, therefore, that genetic influences on open field response would be best detected using a nicotine dose which approximated the midpoint of the dose-response curve for the majority of the genetic stocks being studied It may be that the conclusions reached from the present study are restricted to those intermediate doses which maximally differentiate among the strains and would be invalid after administration of lower or higher doses of the drug Such was the case for nicotine's effects on body temperature [25]

Several studies have demonstrated that nicotine has more pronounced effects on the activity of rat stocks with high baseline activity than on stocks with low baseline activity [5, 10, 11, 12, 29, 32] This suggests that the effects of nicotine are influenced by the basal activity of the animal However, in the present study the A strain, which is most sensitive to nicotine, also has the lowest baseline activity, while the more active strains have intermediate responses to the drug This result suggests that nicotine effects on open field activities are not necessarily dependent on the basal activity of the animals tested

The genetic control of open field activity of saline-injected mice appears to be primarily additive (see Table 2), i e , the activity of the F1 hybrids tends to be intermediate between that of the two parents Those non-additive (dominance) interactions that occurred were non-directional This observation is similar to observations made in several other diallel cross analyses of locomotor activity [7, 13, 17] These results suggest that no selective advantage for either high or low baseline locomotor activity is likely

When the number of genes which regulate basal open field activity was calculated, an estimate of zero genes was obtained The calculation of gene number is based on directionality of the response and, as a consequence, an estimate of zero for the number of genes influencing basal open field activity is not unexpected in view of the observation that the dominance relationships were non-directional, i e , some of the F1 hybrids were more active and some less active than would be predicted from the midparent value The opposing directions of these effects presumably cancelled each other in the calculation of the gene number

In summary, the genetic regulation, in the mouse, of basal open field activity and nicotine-induced changes in this measure is different While the F1 crosses appeared to be intermediate between their parents for basal activity, they resembled their more sensitive parent after the administration of 0 75 mg/kg nicotine The strong directionality for a more intense response to nicotine suggests selective advantage It would be of interest to conduct studies on other naturally occurring drugs or toxins to determine if an intense response to the effects of other compounds occurs and thereby determine whether a generalization of the results presented here to other compounds to which wild populations may be exposed is possible

ACKNOWLEDGEMENTS

This work was supported in part by a grant from the National Institute on Drug Abuse (DA-03914), by Training Grant support from the National Institute for Mental Health (MH-16880) for LLM and by the Biomedical Research Support Grant (RR-07013-17) awarded to the University of Colorado by the Biomedical Research Support Program, Division of Research Resources, National Institutes of Health The authors appreciate the assistance and advice of Dr David W Fulker.

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