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Motility of Mice After Amphetamine: Effects of Strain, Aggregation and Illumination[1]

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DAVIS, W. M., M. BABBINI, S. F. PONG, W. T. KING AND C. L. WHITE. *Motility of mice after amphetamine: effects of strain, aggregation and illumination.* PHARMAC. BIOCHEM. BEHAV. 2(6) 803–809, 1974. – A locomotor activity study in 6 strains of male mice indicated that the BALB/c strain ranked lowest and the C57Bl/6 strain ranked highest in locomotor excitation after treatment with d-amphetamine. A further study comparing only the BALB/c and C57Bl/10 strains again showed a significant interaction of drug and strain effects. Additional significant determinants of motility were lighting and social condition during test (1 or 4 mice). Lighting (dark, dim and full light) also interacted significantly with drug, strain and grouping effects. Whereas the C56Bl/10 mice showed higher levels of motility, the BALB/c showed the greater absolute increases in motility following amphetamine. The BALB/c strain also showed greater lethality under aggregated conditions (group of 10 mice) in the dose range used for activity studies.

Amphetamine Locomotor activity Inbred mice Illumination Aggregation effects Pharmacogenetics

GENETIC variation in drug response between inbred strains of mice has been demonstrated in several studies concerning the effects of d-amphetamine. One report described a strain difference in susceptibility to amphetamine aggregation lethality [23], and several dealt with body temperature responses to amphetamine under aggregation [1, 4, 5]. Another study provided information on locomotor activity responses of several different strains, but only under non-aggregated conditions [13]. The latter study had the limitation that it utilized a single high dosage which probably did not allow maximal manifestation of the hyperkinetic action. Two recent reports also have shown contrasting activity responses to several lower doses of amphetamine between two inbred mouse strains [14,15]. To investigate the influence of aggregation, and its possible interaction with strain, on the motility response of grouped mice to amphetamine, we conducted an initial study which included 6 strains of mice. Subsequently, we examined in 2 inbred strains both the lethal toxicity and the non-lethal parameter of motility for the effects of d-amphetamine on single mice or groups of 4. Different conditions of ambient lighting constituted an additional variable in the activity experiment. The 2 strains utilized for the latter studies, C57Bl/10 and BALB/c, were chosen partly because of the results of our initial study, and also because of research by others concerning the comparative brain monoamine levels of these strains [9, 10, 19].

METHOD

Animals and Drugs

For the initial activity study (Experiment 1) 5 inbred strains were obtained from Cumberland View Farms (Clinton, Tennessee): C57Bl/6Cum, DBA/2Cum, C3H/AnCum, CBA/Cum and BALB/cCum. A non-inbred Swiss-Webster strain (NLW) also included in these comparisons was from the National Laboratory Animal Co. (Creve Coeur, Missouri). For subsequent studies of aggregation lethality (Experiment 2) and of locomotor activity (Experiment 3) the C57Bl/10J and BALB/cJ strains were obtained from Jackson Laboratory (Bar Harbor, Maine). All mice were males which were received at 30–40 days of age, and were 45–65 days old at the time of experiments. Feeding was ad lib prior to all treatments. All experimental runs were conducted between 0900 and 1600 hours with a light cycle of 0800 to 2000 hours in the housing area for the mice. Dosages of d-amphetamine refer to the sulfate salt. All injections were made intraperitoneally in a volume

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of 10 ml/kg body weight. Control groups received the same volume of 0.9% NaCl solution.

Apparatus and Procedure for Activity Studies

Three photoactometer cages (Woodard Research Corp.) were used in all cases for motility recording. These consist of a circular track having inside and outside diameters of 13.5 and 31 cm, respectively. Six photocells are spaced equally around the outer metal wall opposite openings (fitted with red filters) in the inner wall which serve to direct beams from the light source. Counts from all photocells are registered on a single digital counter for each cage. For the initial study (Experiment 1), utilizing one saline control group and 2 dosages of d-amphetamine (1.0 and 5.0 mg/kg), the actometers were located in a room where they received ambient day-time lighting from north-facing windows. Four mice were placed together in the actometers just after the injection, and the motility was recorded after 30 min. In this study, as also in subsequent tests, there was restriction of all extraneous noise sources from the vicinity. Experiment 3 utilizing a saline control group and 5 drug groups in a geometric dosage sequence (2.0, 3.8, 7.2, 13.7, and 26.0 mg/kg), was conducted either with actometers exposed only to artificial lighting of an intensity approximating the daylight level of previous tests, or with the actometers enclosed by ventilated enclosures into which no ambient light could enter. Thus, 3 lighting conditions prevailed: (1) darkness (2) dim light consisting of illumination from a 7.5 W bulb placed 43 cm above the floor of the actometer and providing illumination intensity of 3 f-c; (3) full light, consisting of ambient laboratory illumination from incandescent lamps providing illumination of 15 f-c. Mice were placed in the actometers singly or in groups of four just after being injected, and motility then was recorded after 10, 20, and 30 min. The mice were housed prior to treatment in groups of 15–20 per plastic cage having a floor area of approximately 1015 cm^2. As the floor area of the actometers was 614 cm^2, the test condition of four mice together did not impose crowding, but merely provided the opportunity for operation of a social factor.

Experimental Design and Statistical Analysis of Activity Studies

Experiment 1 followed a 3 × 6 factorial design. Data were handled by analysis of variance according to a fixed model. Further analyses of significant differences were by means of Duncan's New Multiple Range Test [6]. In each strain-dose combination 6 groups of 4 mice were employed for a total of 72 mice of each strain.

Experiment 3 followed a 2 × 6 × 2 × 3 factorial design having repeated measures on the same subjects. The factors for the between subjects part of the design were strain (C57B1/10 and BALB/c), amphetamine (0.0, 2.0, 3.8, 7.2, 13.7, 26.0 mg/kg), grouping (1 or 4 mice) and illumination (dark, dim light, full light). Six replications were used for each factor combination. Thus, a total of 540 mice of each strain constituted the experimental population. Time (1st, 2nd and 3rd 10 min periods) was the only factor for the within subjects part of the design. Analysis of variance (ANOVA) of the first part was according to a complete model; for the second part a reduced model was used, i.e., only the first and second order interactions were considered while all others were pooled. Further analysis of the significant effects were performed by means of Student's t test or Duncan's test, according to whether comparisons were orthogonal or not. All actometer units were exposed to each level of all experimental variables, but as the variability among actometers proved to be very small, their effect was not considered in analyses. The data were log-transformed before analysis.

Procedure for Toxicity Study

A lethality study (Experiment 2) was performed following the initial motility experiment on 9-week-old mice of 2 inbred strains C57B1/10J and BALB/cJ. Doses used were in the same range as for the second motility study, ranging from 3.8 to 26.0 mg/kg for aggregated mice and from 7.2 to 26.0 for mice maintained singly after injection (isolated). Aggregation conditions consisted of ten mice placed after intraperitoneal injection of d-amphetamine into a cage having wire mesh bottom and front, but solid metal sides and top, and having floor dimensions of 18 × 10 cm and height of 12.5 cm. The mice were checked for deaths at 1, 2, 4, 6, 12 and 24 hr after treatment. Dead mice were replaced at those times with marked, untreated individuals to maintain group size. Calculation of LD50's was performed on the cumulative 24-hour mortality data by the method of Litchfield and Wilcoxon [8].

RESULTS

Experiment 1

Data are reported in Table 1 and the results of ANOVA appear in Table 2. The significance of the strains × amphetamine interaction indicated that the response of mice to d-amphetamine varied with the strain. Further analysis of this interaction shows that the difference control vs. d-amphetamine was not the same for all strains, whereas the difference dose 1 vs. dose 2 did not change significantly from one strain to another. From the result of Duncan's test it appears that the significance of the interaction strain × (control vs. amphetamine) was caused by the BALB/c strain responding to the drug significantly less than the DBA/2 and C57B1/6.

Experiment 2

A comparison of 24-hr mortality (Table 3) showed that the aggregated BALB/cJ mice were considerably susceptible to the lethal effects of d-amphetamine than were the aggregated C57B1/10J mice. The respective LD50 values (and 95% confidence limits) were 4.1 (3.8–4.4) and 9.7 (8.5–11.0) mg/kg. These LD50's differed significantly, giving a potency ratio (C57B1/10J : BALB/cJ) of 2.4 with confidence limits of 2.0 to 2.8. There were few deaths among isolated mice of either strain in the range of doses tested.

Experiment 3

Data are shown in Fig. 1 and the results of ANOVA in Table 4. All main effects were highly significant ($p<0.01$): strain, amphetamine, grouping and light. In addition, the first order interactions – amphetamine × strain, amphetamine × light, strain × light, and grouping × light – were highly significant. No second order interaction was significant. Further analysis of the significant interactions dis-

TABLE 1

COMPARATIVE MOTILITY RESPONSE TO d-AMPHETAMINE IN SIX STRAINS OF MICE MEASURED IN GROUPS OF FOUR

	Mean Counts per 30-Min Period*					
Treatment	NLW	C57B1/6	DBA/2	BALB/c	C3H	CBA
Control	3473	2820	1929	1606	1539	1006
d-Amphetamine 1.0 mg/kg	4047	4467	3341	1526	3008	2387
d-Amphetamine 5.0 mg/kg	5509	7222	5474	1863	3973	2880

*Standard error of the means (calculated from pooled variance): ± 526

TABLE 2

STATISTICAL ANALYSIS OF MOTILITY DATA OF EXPERIMENT 1

A. Analysis of Variance

Source	*df*	F	*p*
Treatments	(17)	9.98	<0.01
Strains (S)	5	17.02	<0.01
Amphetamine (A)	(2)	31.97	<0.01
Control vs A	1	44.04	<0.01
Dose 1 vs Dose 2	1	19.91	<0.01
S × A	(10)	2.05	<0.05
S × Control vs A	5	2.49	<0.05
S × Dose 1 vs Dose 2	5	1.61	N.S.
error	90		
total	107		

B. Duncan's Test on the Differences Control vs. Drug for Each Strain*

C57B1/6	DBA/2	C3H	CBA	NLW	BALB/c
3024	2478	1951	1627	1305	88

*Values not sharing underline differ significantly ($p<0.05$); pooled estimate of SEM: ± 644

closed the following: (1) The motility response following amphetamine treatment was different in the two strains of mice. The difference in activity between strains seen under control conditions (significant by *t* test) disappeared after lower doses; however, the motility of C57B1/10 mice again was significantly higher than that of BALB/c mice for the 7.2, 13.7 and 26.0 dosages (Fig. 2). (2) The response to amphetamine varied according to the conditions of lighting used during the experiment. As Fig. 3 shows, motility under control conditions was higher when animals were tested in the dark than when tested in dim or full light; Duncan's test showed a significant difference only between dark and the other two conditions. This pattern of response remained when the mice were treated with 2.0 mg/kg of amphetamine, but when they received higher doses, the difference according to lighting conditions was no longer significant. However, the response was still dose-dependent, being significantly higher after the 3.8, 7.2, 13.7 dosages than with 26.0 mg/kg. (3) The influence of ambient lighting upon activity was different for the 2 strains of mice. In fact, the difference in activity between C57B1/10 and BALB/c strains (the former having higher motility) increased along with the level of illumination, being significantly higher under full light than under dark or dim light conditions (Table 5). (4) The effect of a social group also is influenced by lighting conditions. The difference in activity between single and grouped mice was significantly higher under dark than under the other two conditions. The basis for this is seen to be the greater response of the grouped mice to the condition of total darkness. The per mouse activity of groups is considerably increased over that of isolated mice under the dark condition, while it is diminished under full light. Thus, the activity totals for groups cannot be viewed as simply representing a summation of individual activities for that number of mice, the grouping effect being supra-additive with darkness, but sub-additive with full light.

Non-significance of the strain × amphetamine × grouping interaction showed that the strain difference in response to amphetamine was displayed to no greater extent by the single mice than by grouped mice. Similarly, the nonsignificance of the strain × amphetamine × light interaction shows that the strain difference was the same under all light

TABLE 3

COMPARATIVE LETHAL RESPONSE TO d-AMPHETAMINE OF TWO MOUSE STRAINS TESTED SINGLY OR IN AGGREGATED CONDITIONS

Dosage mg/kg	Incidence of Deaths through 24 Hr			
	Aggregated		Isolated	
	BALB/cJ	C57B1/10J	BALB/cJ	C57B1/10J
3.8	4/20	0/10	–	–
4.2	15/20	–	–	–
5.0	18/20	–	–	–
7.2	9/10	3/20	0/10	0/10
10.0	–	9/20	–	–
13.7	10/10	19/20	0/10	0/10
26.0	–	10/10	1/10	1/10

conditions, according to the additive model we have followed.

Further analysis of the data concerning the nature of the dose-response relationship confirmed the occurrence of a significant quadratic component, as well as the linear component, across strain, grouping and lighting conditions. In other words, motility dropped off significantly with the higher doses of amphetamine, 7.2 mg/kg being the dose which most often gave the peak motility response. This pattern is attributable to the increasing occurrence of stereotyped, non-locomotor activities as amphetamine dosage increases.

The within subjects part of the ANOVA was performed mainly to see if time response to amphetamine was different in the two strains (Table 5). As the interaction strain × amphetamine × time was not statistically significant we conclude that both strains have the same time-response pattern to amphetamine, although they differ in response levels as described above. The significance of (amphetamine × grouping × time), (amphetamine × light × time) and (grouping × light × time) interactions shows that the time responses to amphetamine were not the same under different conditions of illumination and grouping. As such findings were not of special interest further analyses of these interactions were not made.

DISCUSSION

It has been demonstrated that spontaneous (running wheel) activity of mice varies not only with presence or absence of light, but according to the color of visible light prevailing [4]. Moreover, the results clearly indicated that daylight fluorescent lighting consistently had the most inhibitory effect on activity across both sexes of 2 strains (C57B1/6 and an RFM-derived albino stock), and for 2 ages (6 weeks and 6 months). However, the albino strain was much more sensitive to the inhibitory effect of the daylight condition on motility than was the black strain. Similar results were seen in a comparison of open field activity of one albino strain and one pigmented strain of inbred mice under dim and bright illumination [12]. Seegal and Isaac [13] also concluded that the presence of light inhibits an active process subserving locomotor activity. In rats they found that absolute levels of activity after amphetamine did not differ between light and dark conditions, but the increase over control activity was much greater in the former case. In our case also the mice showed equal absolute activity levels after amphetamine for all conditions of lighting, but much greater relative increments over control activity for the dim and full light groups than for the dark condition. Similarly, the greatest increase of motility among pentobarbital-treated mice was found to occur with aggregated mice in a lighted environment [22].

Because of the well-recognized variations in spontaneous motor activity or exploratory behavior between different inbred strains of mice [11, 12, 17, 18], we anticipated that the motility responses of such strains to amphetamine treatment also would differ. The data of Experiment 1 confirmed that there were pronounced inter-strain variations in response to the same dosage of the drug – some strains showing greatly increased activity while others showed little or no response. There was not a simple or direct relationship between drugged and undrugged activity levels, however, as the three strains ranking lowest in control activity included strains showing both high and low responsiveness toward amphetamine treatment. Despite distinct differences in test conditions and dosage, there was general agreement between the present results and those of Meier *et al.* for 4 of the same strains [13]. Namely, in both instances the C57B1/6 and DBA/2 were "high responders," whereas the C3H and BALB/c were "low responders" to d-amphetamine. Moreover, Oliverio *et al.* [15] also found a striking superiority in the response of the C57B1/6By strain to 0.5, 1.0 and 2.0 mg/kg doses of amphetamine over that of the BALB/cBy strain.

The least reactive strain (BALB/c) and a strain (C57B1/10) closely related to the most reactive one (C57B1/6) of Experiment 1 were chosen for further study

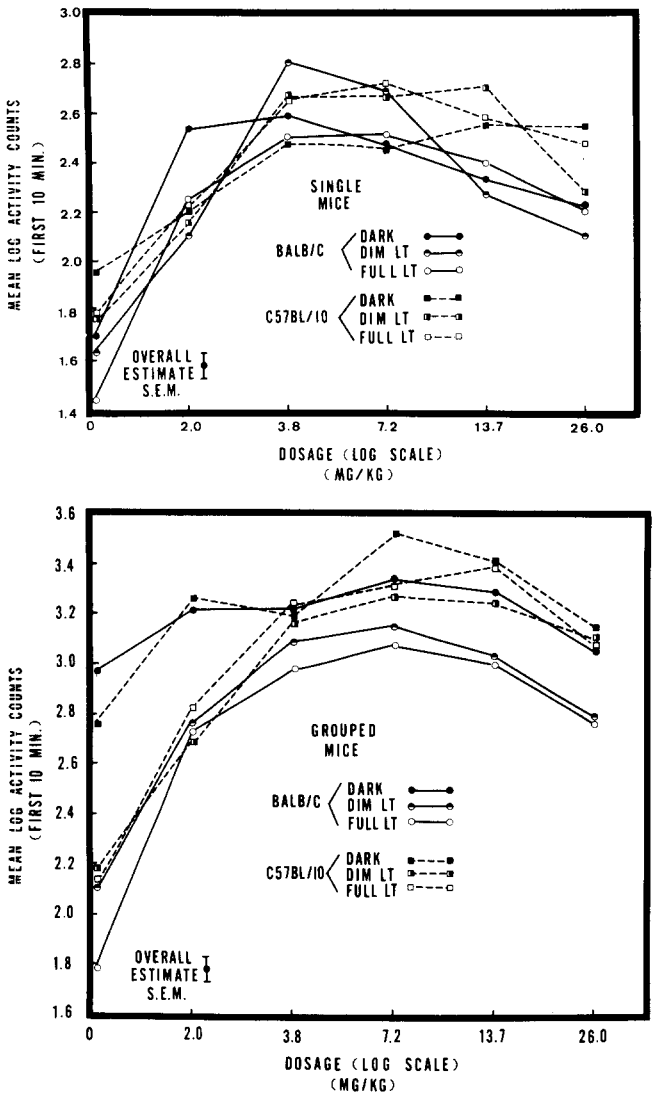

FIG. 1. Motility data of Experiment 3 comparing BALB/cJ and C57B1/10J strains under three levels of illumination for single mice (Top) or groups of four (Bottom) at several dose levels of d-amphetamine.

in Experiments 2 and 3. In the aggregation lethality test of Experiment 2 the BALB/cJ strain proved to be significantly more susceptible than the C57B1/10J mice to the toxic mechanism(s) of d-amphetamine action causing death under these conditions. The degree of crowding for groups of mice in our actometric tests was insignificant compared to that for this toxicity test. However, it may be possible that an action responsible for lethality under greater crowding was sufficiently operative so as to contribute to the subsequent finding of a more pronounced decrement in motor activity of the BALB/cJ mice at the 2 highest amphetamine dosages (Experiment 3).

For reasons that are not evident, in Experiment 3 the BALB/c strain was distinctly more responsive to amphetamine than mice of the same strain (but a different colony) had been in Experiment 1. However, the BALB/cJ mice again showed significantly lesser activity, except at the

TABLE 4

SUMMARY OF STATISTICAL ANALYSIS (ANOVA) ON LOG-TRANSFORMED MOTILITY DATA OF EXPERIMENT 2

Source	*df*	F	*p*
BETWEEN SUBJECTS	(431)		
Strain (S)	1	28.7	<0.01
Amphetamine (A)	5	143.9	<0.01
Grouping (G)	1	757.7	<0.01
Lighting (L)	2	24.8	<0.01
S × A	5	3.8	<0.01
S × L	2	5.0	<0.01
A × L	10	6.2	<0.01
G × L	2	19.6	<0.01
S × G	1	<1	N.S.
A × G	5	1.6	N.S.
S × A × G	5	1.13	N.S.
S × A × L	10	<1	N.S.
A × G × L	10	1.60	N.S.
S × G × L	2	<1	N.S.
S × A × G × L	10	1.05	N.S.
Animals within treatments	360	–	–
WITHIN SUBJECTS	(864)		
Time (T)	2	14.6	<0.01
S × T	2	7.5	<0.01
A × T	10	31.6	<0.01
G × T	2	41.2	<0.01
L × T	4	8.8	<0.01
A × G × T	10	2.5	<0.01
A × L × T	20	2.2	<0.01
G × L × T	4	7.2	<0.01
S × A × T	10	1.6	N.S.
S × G × T	2	<1	N.S.
S × L × T	4	<1	N.S.
Pooled higher order interactions	794	–	–

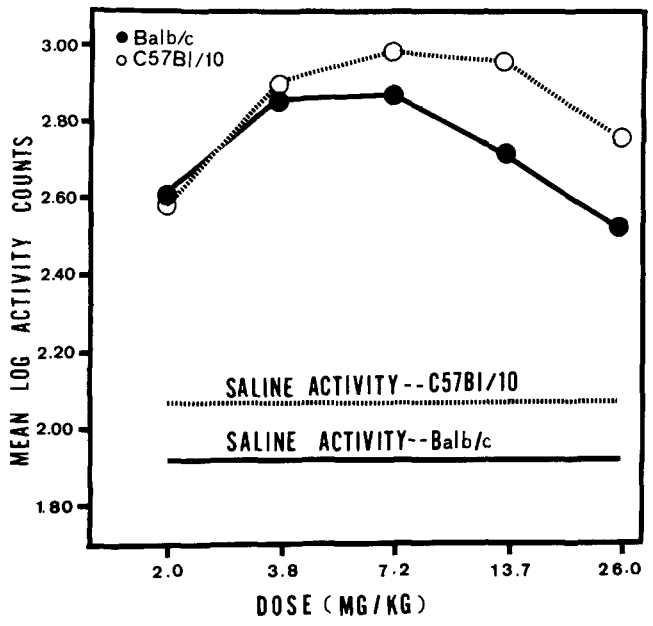

FIG. 2. Dose-effect relationship for the motility response to d-amphetamine in the BALB/cJ and C57Bl/10J strains combining data for mice tested singly or in groups of 4. Dosage scale is logarithmic.

TABLE 5

ANALYSIS OF STRAIN X LIGHT AND GROUPING X LIGHT INTERACTIONS*

	Dark	Dim Light	Full Light
Strain			
C57Bl/10	2.790	2.656	2.695
BALB/c	2.745	2.547	2.469
Difference	0.045	0.109	0.226
Grouping			
4 Mice	3.197	2.881	2.849
1 Mouse	2.338	2.322	2.315
Difference	0.859	0.548	0.534

*Data represent log-transformed 30-min activity counts. Values of differences not sharing underline differ significantly ($p<0.05$).

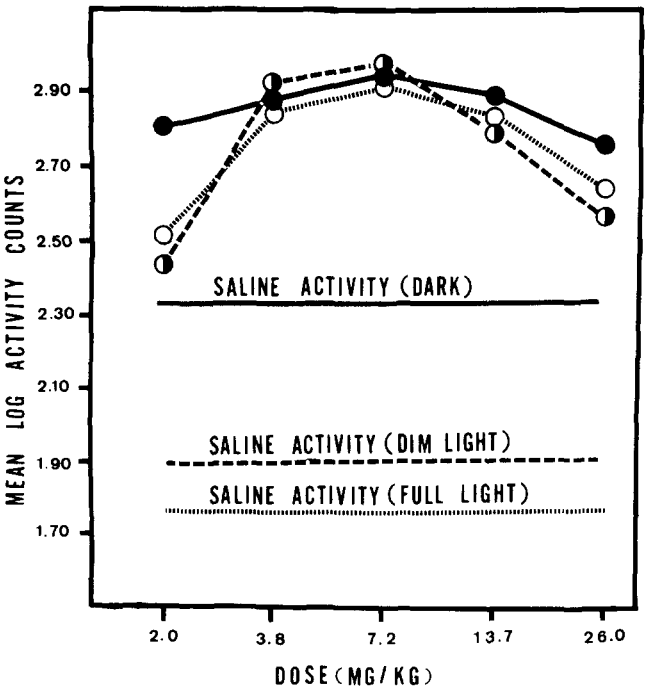

FIG. 3. Dose-effect relationship for the motility response of mice to d-amphetamine under different conditions of illumination (● total darkness; ◑ dim light; ○ full light) during activity testing. Dosage scale is logarithmic.

lowest two doses of amphetamine, than did the C57Bl/10J strain. This was true also for the same two strains with a 5.0 mg/kg dose of d-amphetamine in open field motility testing [14]. It was especially evident when the testing was under the "full light" conditions, which were closest to those prevailing in Experiment 1. The lesser activity of the BALB/c strain after amphetamine appears initially to be in accord with the finding of Irwin *et al.* [7] in rats that a low control activity correlated strongly with a low locomotor reactivity to CNS stimulant drugs (pipradol, d-amphetamine). On the other hand, if one concentrates on the degree of increase over control, our results also may be taken to agree with data indicating that mice which had a lower control activity level were more responsive to the locomotor excitatory effect of methamphetamine [3]. However, in making such comparisons one must bear in mind that both of these studies [3,7] compared within a single genetic stock rather than between genetically-differentiated strains as in our experiments.

While our own studies included no biochemical measures, it is appropriate to consider the results in relation to the literature concerning brain chemistry. Brains of male mice of the BALB/cJ strain were found to show twice as much tyrosine hydroxylase, the rate-limiting enzyme for brain catecholamine synthesis, as those of the C57Bl/10J strain [2]. This suggests an inverse relationship between brain tyrosine hydroxylase activity and spontaneous locomotor activity. Such an inverse, and seemingly paradoxical, relationship also has been demonstrated among six inbred rat strains [17]. Moreover, from these and other findings, the latter authors conclude that a "relatively high adrenergic receptor activity is associated with low levels of transmitter biosynthesis [i.e., low brain tyrosine hydroxylase] and vice versa." Furthermore, they infer "the existence of a

direct relationship between spontaneous behavioral activity and central adrenergic receptor activity" [17].

This concept of central adrenergic receptor activity as a major determinant of spontaneous behavioral activity is most useful for the interpretation of our data, in conjunction with Wilder's [24] principle known as the "law of initial value" (LIV). Wilder's law states that the higher the initial level of a physiological function (e.g., higher central adrenergic activity), the smaller will be the response to function-activating stimuli (e.g., the drug amphetamine), and vice versa. Such relationships may at times be explainable, at least in part, to the operation of a ceiling effect, but that does not seem likely in the present instance. From previous studies cited above, it would be expected that the C57Bl/10J strain and the environmental factors of aggregation and darkness should manifest higher central adrenergic activity (or arousal) when compared to the BALB/c strain and the conditions of isolation and dim or moderate illumination. Therefore, according to the LIV, the absolute increase in activity after d-amphetamine should be less for the black mice, for all aggregated mice and for all mice tested in illumination, even though the resulting absolute levels of activity might still be equal to or greater than those seen with the opposite factors. Close examination of our data of Experiment 3, considering differences in initial values, shows that these expectations are indeed fulfilled.

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