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Differential Sensitivity of Long-Sleep and Short-Sleep Mice to High Doses of Cocaine[1]

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DE FIEBRE, C. M., J. A. RUTH AND A. C. COLLINS. *Differential sensitivity of long-sleep and short-sleep mice to high doses of cocaine*. PHARMACOL BIOCHEM BEHAV **34**(4) 887–893, 1989.—The cocaine sensitivity of male and female long-sleep (LS) and short-sleep (SS) mice, which have been selectively bred for differential ethanol-induced "sleep-time," was examined in a battery of behavioral and physiological tests. Differences between these two mouse lines were subtle and were seen primarily at high doses. At high doses, SS mice were more sensitive than LS mice, particularly to cocaine-induced hypothermia; however, significant hypothermia was not seen except at doses which were very near to the seizure threshold. During a 60-min test of locomotor activity, LS mice showed greater stimulation of Y-maze activity by 20 mg/kg cocaine than SS mice. Consistent with the finding of subtle differences in sensitivity to low doses of cocaine, LS and SS mice did not differ in sensitivity to cocaine inhibition of synaptosomal uptake of [^{3}H]-dopamine, [^{3}H]-norepinephrine or [^{3}H]-5-hydroxytryptamine. However, consistent with the finding of differential sensitivity to high doses of cocaine, SS mice were more sensitive to the seizure-producing effects of the cocaine and lidocaine, a local anesthetic. It is hypothesized that the differential sensitivity of these mouse lines to high doses of cocaine is due to differential sensitivity to cocaine's actions on systems that regulate local anesthetic effects. Selective breeding for differential duration of alcohol-induced "sleep-time" may have resulted in differential ion channel structure or function in these mice.

Cocaine Lidocaine Local anesthetics Locomotor activity Seizures, lidocaine-induced Seizures, cocaine-induced Reuptake, monoamine

POLYDRUG abuse, the use and abuse of more than one drug, has become widespread in our society, but little is known about the biological factors which contribute to the use of several substances by a single individual. Variable responsivity to alcohol and other agents exists in humans (19,21) and it has been suggested that differential responsiveness may explain why some people use these agents while others do not (11). It is well established that the development of alcoholism is partially regulated by genetic factors (8,21) and tobacco use may be partially regulated by heritable factors (17,18). It may be that polydrug abuse is also regulated by hereditary factors since alcoholism and smoking are highly correlated (12, 26, 50). People may drink and smoke together because common genes regulate responsiveness to these two drugs and, therefore, contribute to these two drug-taking behaviors. Similarly, the simultaneous use of cocaine and alcohol is common. Consistent with a common genetic etiology towards abuse of these two drugs, it has been reported that a positive family history of alcoholism increases the probability of cocaine addiction (43). Cocaine has been shown to antagonize the anxiolytic effects of ethanol while simultaneously augmenting ethanol's ataxic effects (2). Furthermore, chronic alcohol treatment has been shown to alter brain to plasma cocaine concentrations without affecting cocaine metabolism (48).

Genetically defined stocks of laboratory animals, specifically inbred strains or selectively-bred lines of rodents, have been utilized to establish the potential of genetic factors in influencing drug response and drug-taking behaviors in humans. If genetic factors regulate drug response or drug-taking behaviors in rodents, the potential exists that genetic factors may contribute to the use and abuse of drugs by humans. Numerous studies have demonstrated that genetically defined stocks of animals differ in acute sensitivity to alcohol (9) and several studies have demonstrated strain differences in sensitivity to cocaine (39, 42, 47) as well as a variety of other stimulant and depressant compounds (5, 27, 29, 35, 40, 41). Other studies have shown that genetic factors can regulate drug avidity (self-administration) (25,36), tolerance development (31,32) and withdrawal severity (10,20) in rodents. Thus, genetic factors regulate, in animals, several drug-related behaviors that may be related to drug dependence.

The studies reported here used the long-sleep (LS) and short-sleep (SS) mouse lines which have been selectively bred for differential "sleep-time" following an anesthetic dose of ethanol

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(23,24). While selective breeding of these mouse lines was based on acute sensitivity to ethanol, these mice also differ in responsiveness to a variety of other agents including other central nervous system depressants (28), amphetamine (16), nicotine (13) and morphine (7). These findings suggest that the genes which regulate sensitivity to ethanol also influence sensitivity to other drugs of abuse. In the current study we have measured the cocaine response of the LS and SS selectively bred mouse lines. Responsiveness to cocaine was assessed using a battery of behavioral and physiological measures. Additionally, cocaine inhibition of synaptosomal uptake of the monoamine neurotransmitters, [^{3}H]-dopamine ([^{3}H]-DA), [^{3}H]-norepinephrine ([^{3}H]-NE) and [^{3}H]-5-hydroxytryptamine ([^{3}H]-5-HT) was measured. The seizure susceptibility of these mice to cocaine and lidocaine was also measured.

METHOD

Animals

Male and female LS and SS mice were used in this study. Mice were raised at the Institute for Behavioral Genetics, kept on a 12-hr light cycle and given free access to food (Wayne Lab Blox) and water. Mice were weaned at 25 days of age, were housed with 1–5 like-sex littermates and were 60–90 days old when tested. All testing was conducted between 9:00 a.m. and 5:00 p.m.

Materials

The radiolabeled compounds, [^{3}H]-dopamine (3,4-dihydroxy-[7-^{3}H(N)]) and [^{3}H]-5-hydroxytryptamine creatinine sulfate (5-[1,2-^{3}H(N)]) were purchased from New England Nuclear Corp. (Newton, MA). DL-[^{3}H]-norepinephrine tartrate ([8,8-^{3}H]) and scintillation fluid (Safety Solve) were purchased from Research Products International (Mount Prospect, IL). Lidocaine HCl (1% solution) was obtained from Astra Pharmaceutical Products (Westborough, MA). Cocaine HCl, (−)norepinephrine bitartrate, 3-hydroxydopamine HCl and 5-hydroxytryptamine creatinine sulfate were purchased from Sigma Chemical Co. (St. Louis, MO). Inorganic compounds were reagent grade.

Drug Administration

Both cocaine and lidocaine were dissolved in physiological saline and were administered by intraperitoneal injection. Injection volume was 0.01 ml/g body weight.

Cocaine Test Battery

A multidimensional battery of behavioral and physiological tests was used to assess the cocaine response of the LS and SS selectively bred mouse lines. Six LS and 6 SS mice of each sex received a dose of 0, 5, 10, 15, 20 or 40 mg/kg cocaine before being tested for respiration rate, startle response, Y-maze activity, heart rate, and body temperature. Six LS mice of each sex were also tested following a dose of 60 mg/kg. Using nicotine (30) and ethanol (Smolen *et al.*, unpublished data), we have demonstrated that animals tested in all five tests do not differ in response from animals tested in only a single test (i.e., there are no interest interactions). In the current study, animals were tested on all measures following a single injection of cocaine. A detailed description of the procedures and equipment used has been reported previously (30). The timing of the tests was based on previous findings that Y-maze activity is maximally stimulated 15 min following cocaine administration (39).

Respiration. Respiratory rate was measured using a Columbus Instruments Respiration Rate Monitor. Animals were injected with cocaine and placed in the monitor. After 9 min, the monitor was sealed and measurement began 10 min after injection of cocaine. Respiratory rate was monitored for 1 min during which time five equally spaced recordings were made.

Startle response. The response of mice to an acoustic startle was measured using a Columbus Instruments Responder Startle Reflex Monitor. The startle reflex was measured 13 min after injection of cocaine and 1 min after completion of respiration testing.

Y-maze activity. Locomotor and rearing activity were measured for 3 min in a symmetrical Y-maze 15 min after cocaine administration and 30 sec following startle response testing.

Heart rate. Heart rate was estimated using needle electrodes connected through a preamplifier to a Narco Biosystems E & M Physiograph. Heart rate was measured 19 min after injection and 2 min after Y-maze testing. Rate was estimated by counting the number of QRS complexes measured over 6 sec.

Body temperature. Body temperature was measured by inserting a Bailey Instruments rectal probe 2.5 cm into the rectal cavity 25 min after cocaine injection and 6 min following estimation of heart rate.

Automated Y-Maze Activity

We have developed an automated version of our Y-maze where we can test animals for long periods of time. Six male and 6 female LS and SS mice were tested in this maze for 60 min following injection with 0, 10, 20 or 40 mg/kg cocaine. The maze is constructed of red translucent acrylic plastic and consists of three arms which are 26 cm long, 6.1 cm wide, and 10.2 cm high. In order to count activity through the maze (crosses), photocells are situated at floor level 12 and 22.5 cm from the end of each arm of the maze. Movement interrupts the photocell beam and thereby activates a computerized counter. To count rearing activity, photocells are also located at the two ends of each arm 6 cm above the floor. Scores obtained from automated counting correlate highly with scores obtained manually (crosses: $r = .953$; rears: $r = .971$; unpublished data). Testing was begun by placing the mouse in the center of the maze immediately following injection with cocaine. Cumulative crosses and rears were measured at 60 min following injection.

Synaptosomal Uptake of [^{3}H]-Monoamines

Cocaine is known to inhibit the neuronal reuptake of the monoamine neurotransmitters [^{3}H]-norepinephrine, [^{3}H]-dopamine and [^{3}H]-5-hydroxytryptamine (38,46) and it is thought that this is a primary mechanism by which cocaine acts (37). Therefore, the potency of the cocaine-induced inhibition of uptake of the [^{3}H]-monoamines in whole brain synaptosomes was measured in female LS and SS mice. The procedure employed was that which was described previously for examination of the synaptosomal accumulation of conformationally-defined amphetamine analogs (3). Specific methods for cocaine have recently been reported (6).

Local Anesthetic-Induced Seizure Sensitivity

In addition to being a potent inhibitor of monoamine reuptake, cocaine is also a potent local anesthetic (4) which interacts at sodium and other cation channels (34,44). The relative importance of local anesthetic effects in the actions of cocaine has not been assessed, but it has been reported that human subjects are unable to discriminate between lidocaine, a local anesthetic, and cocaine

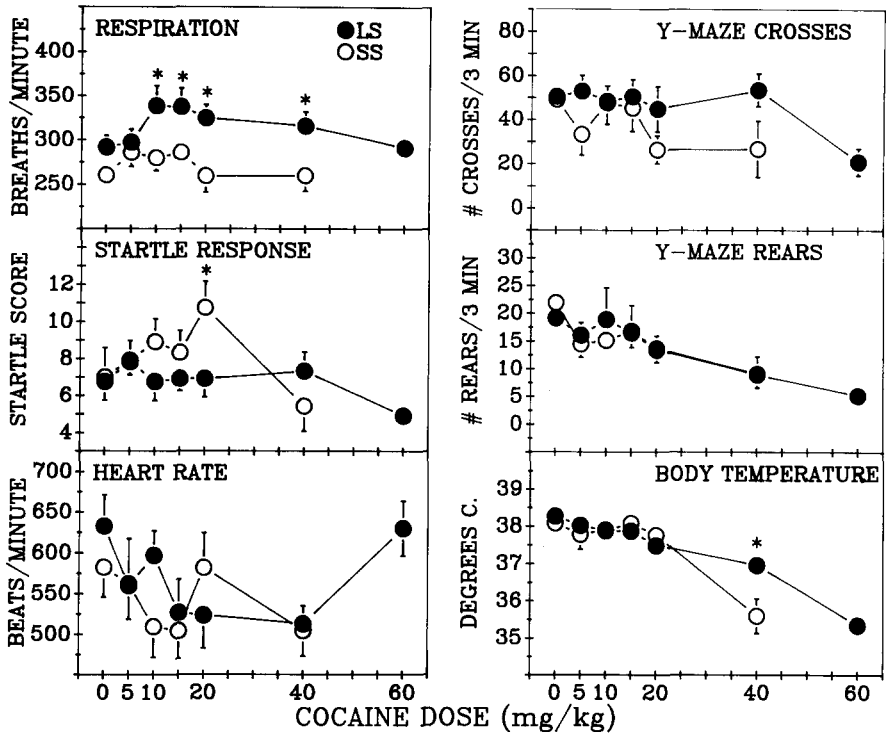

FIG. 1. Cocaine test battery response for LS and SS mice. Each point represents the mean ± SEM for 12 animals. Asterisks indicate LS-SS differences at the designated cocaine dose. (*$p<0.05$.)

when the two drugs are given intranasally (49). Lidocaine does not, however, block the reuptake of monoamines (1). At high doses, both cocaine and lidocaine can produce seizures which can lead to death (22,45). This action presumably arises from blockade of ion channels in the CNS. Therefore, in order to assess whether the LS and SS mouse lines differ in sensitivity to local anesthetic-induced seizures we measured the lidocaine- and cocaine-induced seizure sensitivity of these animals. Depending on genotype, animals were injected with 40–100 mg/kg lidocaine or 30–90 mg/kg cocaine and placed in a $10 \times 25 \times 13$ cm metal cage, the bottom of which was covered with aspen shavings. Preliminary studies indicated that lidocaine-induced seizures could not be induced without concurrent environmental stimulation. Therefore, 2 min following injection with lidocaine and every 2 min following until a seizure occurred, animals were picked up by their tails and gently spun 360° clockwise, counterclockwise and again clockwise before being returned to their cages. For cocaine, no concurrent environmental stimulation was necessary. Whether a clonic seizure occurred, as well as the latency to that seizure, was recorded for each animal. Animals were observed for 10 min following injection.

Data Analysis

All data, with the exception of the seizure data, were analyzed using a two- or three-way Analysis of Variance (ANOVA) to determine main effects of line (i.e., mouse line), dose and sex, as well as interactions among these variables. For those analyses in which significant effects were observed, the results were subjected to Newman-Keuls' post hoc test. Additionally, *t*-tests were run as a post hoc test at each dose to determine whether the LS and SS mouse lines or the two sexes differ.

Due to the nonparametric nature of the seizure data, sex differences were assessed using χ^2 tests and testing for differences in the dose-response curves of the two mouse lines was conducted via a regression line comparison. This line comparison involves sequential testing for: 1) differences in homogeneity of variance (an F-test), 2) differences in slope (a *t*-test) and 3) superimposability of the curves (a *t*-test) (15). Nonsuperimposable dose-response curves that did not differ in homogeneity of variance or slope were taken to indicate differences in seizure sensitivity. This method of analysis takes into account all points on the dose-response curves and is therefore more powerful than using a *t*-test to test for differences in ED_{50}. Testing for differences in latency to seizures was done by a regression line comparison of the dose-response curves for seizure latency and via a *t*-test at the one dose where both LS and SS mice seized. Latency to seizure could only be measured in animals that actually seized; therefore, only data from these mice were used.

RESULTS

The effects of cocaine on the test battery response of the LS and SS mouse lines are presented in Fig. 1. A three-way ANOVA indicated significant differences between the LS and SS lines for respiratory rate, $F(1,120) = 22.201$, $p<0.0001$. The post hoc analyses of cocaine effects indicated that the LS and SS mice differ in respiration rate following the 10–40 mg/kg doses ($p<0.05$) with LS mice having a greater rate of respiration. However, if differences in baseline respiration rate are controlled, all of these effects are nonsignificant. Thus, the control LS and SS mice differ in respiration rate and cocaine increases respiration rate in both mouse lines to approximately the same degree. The three-way ANOVA indicated significant differences between the LS and SS lines for the Y-maze crosses test, $F(1,120) = 5.461$, $p = 0.0211$. Post hoc analyses of the Y-maze crosses data failed to detect

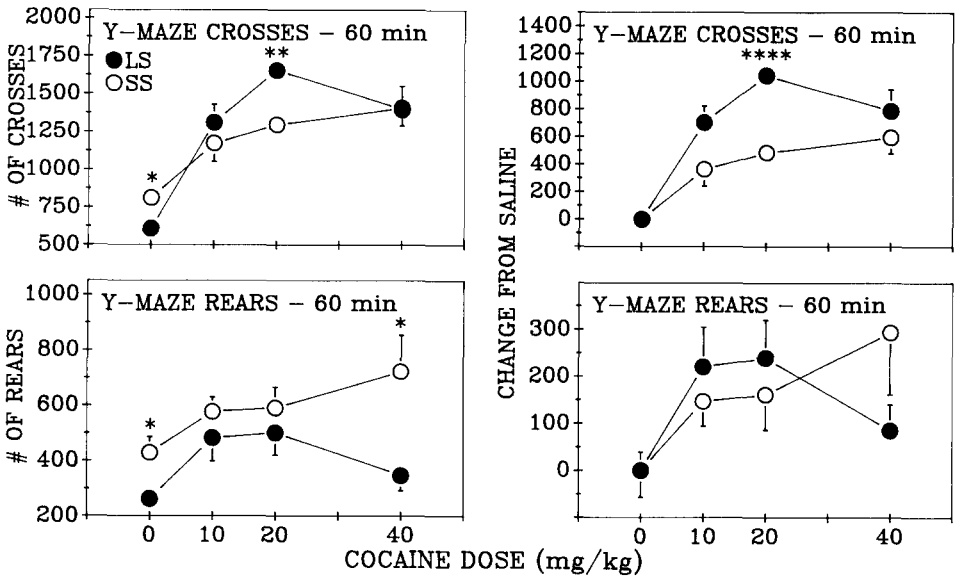

FIG. 2. Cumulative Y-maze activity at 60 min following cocaine administration in LS and SS mice. In the left-hand panels, absolute values for Y-maze activity are presented. In the right-hand panels, values are expressed as a change from saline value. Each point represents the mean ± SEM for 12 animals. Asterisks indicate LS-SS differences at the designated cocaine dose. (*$p<0.05$; **$p<0.005$; ****$p<0.0001$.)

significant LS-SS differences at any single dose. The mean activities of LS and SS animals treated with 20 or 40 mg/kg cocaine approach, but do not attain significance. *t*-Test analysis of the body temperature data indicate that SS mice display greater hypothermia following a cocaine dose of 40 mg/kg, $t(22)=2.50$, $p=0.0203$. SS mice show a significantly great startle response following 20 mg/kg cocaine, $t(22)=2.19$, $p=0.0391$; however, no overall difference was found between the two mouse lines. There was a significant effect of cocaine dose on Y-maze rearing activity, $F(5,120)=3.213$, $p=0.0092$, and body temperature, $F(5,120)=11.182$, $p<0.0001$. Males are affected by cocaine slightly more than females on the acoustic startle response, heart rate and body temperature measurements (average $p<0.05$).

A two-way ANOVA indicated no significant effect of cocaine dose on the respiration rate, startle response, Y-maze crosses and heart rate tests in LS mice. Significant effects of dose were obtained for LS mice in the Y-maze rears, $F(6,69)=2.909$, $p=0.0137$, and body temperature, $F(6,69)=12.33$, $p<0.0001$, tests. Post hoc analyses (Newman-Keuls') indicates that LS mice treated with 60 mg/kg had depressed Y-maze rearing activity ($p<0.05$) and animals treated with 40 or 60 mg/kg cocaine developed significant reductions in body temperature (40 mg/kg: $p<0.05$; 60 mg/kg: $p<0.01$). In SS mice, no significant effect of cocaine dose was found for any of the tests except for the body temperature test, $F(5,60)=9.785$, $p<0.0001$. The 40 mg/kg dose elicited a significant reduction in body temperature ($p<0.01$). Thus, with the exception of body temperature, cocaine failed to elicit profound effects on any of these measures and effects on body temperature were only observed at high doses.

The dose-response curves for cumulative Y-maze activity at 60 min following cocaine injection are presented in Fig. 2. There is a significant effect of cocaine dose on Y-maze crossing activity, $F(3,80)=22.324$, $p<0.0001$, and rearing activity, $F(3,80)=2.831$, $p=0.0432$. SS mice rear significantly more than LS mice, $F(1,80)=10.194$, $p=0.002$ following saline, $t(22)=2.41$, $p=0.0247$, and following a dose of 40 mg/kg, $t(22)=2.61$, $p<0.0159$. SS mice also make significantly more crosses than LS mice following saline, $t(22)=2.38$, $p=0.0265$; however, LS mice display greater stimulation of Y-maze crossing activity following a dose of 20 mg/kg, $t(22)=3.68$, $p=0.0013$. If baseline differences are controlled, LS mice show significantly more crossing activity than SS mice, $F(1,80)=13.83$, $p=0.0004$, and LS-SS differences in rearing activity disappear.

The results of the monoamine uptake experiments are presented in Fig. 3. No differences between the LS and SS mouse lines were found in the inhibition by cocaine of uptake of [^{3}H]-NE, [^{3}H]-DA or [^{3}H]-5-HT; however, cocaine inhibited uptake of each of these monoamines in a concentration-dependent manner. IC_{50} values for inhibition by cocaine of monoamine uptake are presented in Table 1.

During testing for response to cocaine in the test battery, 33% of the SS mice tested at the 40 mg/kg dose seized while no LS mice seized at this dose. This differential seizure sensitivity is significant, $\chi^2(1)=4.80$, $p<0.05$. At the 60 mg/kg dose, 33% of the LS mice seized. SS mice were not tested in the test battery with this dose of cocaine.

The dose-response curves for cocaine-induced seizures in LS and SS mice are presented in Fig. 4. The ED_{50} value for LS mice (65.29 mg/kg; 0.20 mmol/kg) is more than 50% higher than the SS value (42.96 mg/kg; 0.13 mmol/kg). Analysis of the dose-response curves revealed that SS mice are more sensitive than LS mice to cocaine-induced seizures, $t(8)=6.37$, $p<0.001$. The dose-response curves for latency to cocaine-induced seizures in LS and SS mice are also presented in Fig. 4. Analysis of the dose-response curves revealed that LS mice have significantly higher seizure latencies than SS mice, $t(75)=5.37$, $p<0.001$. At the 60 mg/kg dose, a *t*-test revealed the differential seizure latency, $t(16)=3.35$, $p=0.004$.

The dose-response curves for lidocaine-induced seizures in LS and SS mice are presented in Fig. 5. The ED_{50} value for LS mice (76.26 mg/kg; 0.28 mmol/kg) is more than 50% higher than the SS value (50.54 mg/kg; 0.19 mmol/kg). Analysis of the dose-response curves revealed that SS mice are more sensitive than LS mice to lidocaine-induced seizures, $t(7)=3.83$, $p<0.01$. The

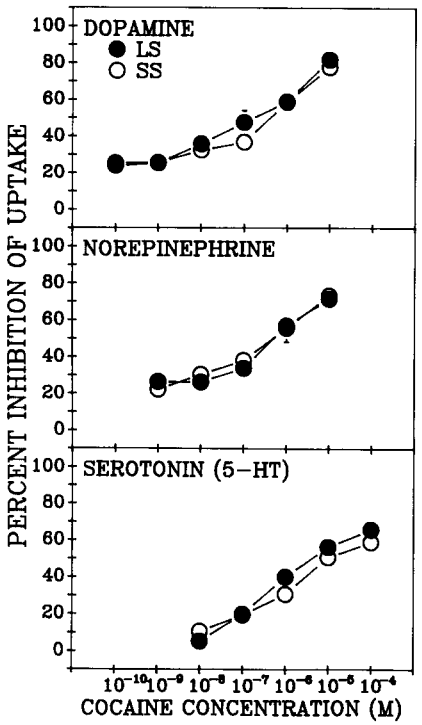

FIG. 3. Inhibition of monoamine uptake by cocaine in whole brains from LS and SS mice. Each point represents the mean ± SEM for 4 to 8 assays.

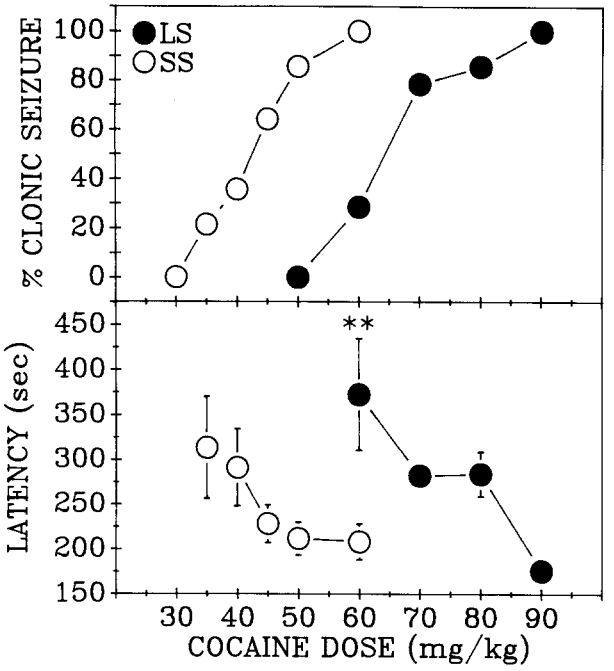

FIG. 4. Cocaine-induced seizure sensitivity in LS and SS mice. In the top panel, each point represents the percent of 14 animals which seized at that dose. In the bottom panel, latency to clonic seizure is expressed as a mean ± SEM. Asterisks indicate LS-SS differences at the designated cocaine dose. (**$p<0.005$.)

dose-response curves for latency to lidocaine-induced seizures in LS and SS mice are also presented in Fig. 5. Analysis of the dose-response curves revealed that LS mice have significantly higher seizure latencies than SS mice, $t(75)=2.71$, $p<0.01$. At the 70 mg/kg dose, a t-test revealed the differential seizure latency, $t(16)=3.51$, $p<0.003$. No sex differences were found.

DISCUSSION

The results reported here clearly demonstrate that LS-SS differences in sensitivity to cocaine as measured by the test battery are subtle. This is consistent with the finding that these two mouse lines do not differ in cocaine inhibition of monoamine uptake. Visual analysis of Fig. 1 reveals that differences in the test battery response of these two mouse lines do not exist at low doses if baseline differences are controlled. At higher doses, differences between these two mouse lines emerge, particularly for the body temperature test. These effects, however, may be due to the fact that some of the SS mice were seizing (note that no SS animals were tested at the 60 mg/kg dose in the test battery because of this problem). Nevertheless, this emphasizes that while LS and SS mice do not differ in response to low doses of cocaine, they differ markedly in response to higher doses.

There was considerable variability in the cocaine response of both the LS and SS mice for the test battery responses, especially at the lowest doses of cocaine. Considering that the LS and SS mouse lines were selectively outbred (24), this variability suggests that cocaine response in these mice is an outbred response. This is consistent with the notion that cocaine acts primarily on systems which do not play a role in determining duration of alcohol-induced "sleep-time," specifically the monoamine reuptake systems. Conversely, the large differential responsiveness of these mice to the seizure-producing effects of local anesthetics is consistent with the notion that local anesthetics act on systems which play a role in determining the duration of alcohol-induced "sleep-time."

The results reported here demonstrate that LS mice display greater stimulation in the automated Y-maze test than SS mice. Considering that no differences in locomotor activity were observed at low doses during the 3-min test in the test battery, the differences observed during this test were surprising. It could be argued that due to the long duration of this test, differential rates of cocaine metabolism could explain the differential stimulation in these two mouse lines. This explanation is doubtful for a number of reasons. Visual analysis of Fig. 2 reveals that differential stimulation is only seen at the 20 mg/kg dose. If differential metabolism was involved, differences should be seen at all the doses tested. Furthermore, although we only report cumulative crosses and rears at 60 min, we were able to examine the data from these animals during every 5-min interval of the 60-min test. This examination revealed that animals given 20 mg/kg cocaine were

TABLE 1

COCAINE CONCENTRATIONS RESULTING IN HALF MAXIMAL INHIBITION OF [^{3}H]MONOAMINE ACCUMULATION BY MOUSE BRAIN SYNAPTOSOMES

	IC_{50} (-log M) for Inhibition of Uptake		
Mouse Line	[^{3}H]5-HT	[^{3}H]DA	[^{3}H]NE
LS	6.44 ± 0.26	7.85 ± 0.37	7.60 ± 0.36
SS	6.21 ± 0.28	7.45 ± 0.39	7.66 ± 0.43

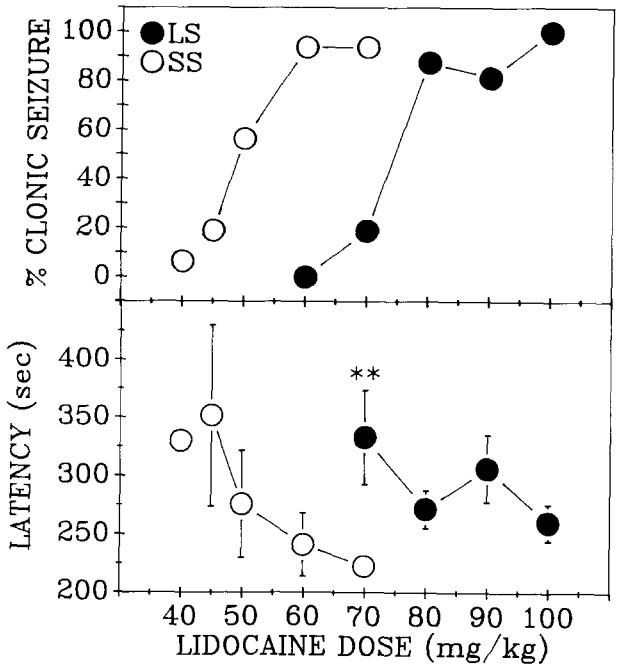

FIG. 5. Lidocaine-induced seizure sensitivity in LS and SS mice. In the top panel, each point represents the percent of 16 animals which seized at that dose. In the bottom panel, latency to clonic seizure is expressed as a mean ± SEM. Asterisks indicate LS-SS differences at the designated lidocaine dose. (**$p<0.005$.)

stimulated differentially across all 5-min time periods. If differential metabolism was involved, differences between these mouse lines should increase with increasing time. Furthermore, this examination revealed that at other doses, the LS and SS mouse lines did not differ during any 5-min period, indicating that the finding of differential stimulation following 20 mg/kg is not indicative of any overall trend of differential stimulation in these mice.

Although the LS and SS mouse lines were originally selectively outbred, fertility problems during selection resulted in a fair amount of inbreeding (24). Therefore, caution should be used when hypothesizing that alcohol "sleep-time" is correlated genetically with other traits measured in these animals. Nevertheless, the measurement of correlated traits in these animals can be used to disprove a genetic hypothesis. For example, a number of studies have implicated catecholaminergic, but not serotoninergic, systems in the differential responsiveness of LS and SS mice to ethanol [e.g., Masserano and Weiner (33)]. This suggests, but does not prove, that catecholaminergic systems may be related genetically to alcohol-induced "sleep-time." However, the results presented here strongly suggest that catecholaminergic uptake systems have nothing to do with the "sleep-time" differences found in these mice and can be used to disprove a hypothesis of a genetic correlation between "sleep-time" and monoamine uptake systems. Other components of catecholaminergic systems may be important in determining duration of alcohol-induced "sleep-time."

Dibner *et al.* (14) have found that cortices from LS mice have fewer β-adrenergic receptors than cortices from SS mice; however, no differences were found in cAMP accumulation following isoproterenol. Therefore, it appears that while receptor numbers differ in these mice, there are no differences in the innate responsiveness of the β-adrenergic systems of these mice. Dibner *et al.* have also reported that no differences exist in the striatal dopamine receptors of these mouse lines, but adenylate cyclase is stimulated to a greater degree by dopamine in LS mice. Therefore, it is possible that differential dopamine responsiveness may be important in regulating the cocaine sensitivity of these mice. This is doubtful, however, because these mouse lines do not differ in responsiveness to low doses of cocaine. Therefore, other mechanisms must explain the differential high dose sensitivity of cocaine found in these mouse lines.

The results presented here clearly demonstrate that the LS and SS mouse lines differ in responsiveness to the seizure-producing effects of the local anesthetics cocaine and lidocaine. While both lidocaine and cocaine have been shown to interact with sodium and other ion channels (34,44), lidocaine does not affect catecholamine reuptake (1). Although cocaine is slightly more potent than lidocaine, the dose-response curves for lidocaine- and cocaine-induced seizures are nearly superimposable. These data suggest that the differential responsiveness to cocaine seen at high doses in the LS and SS mice is due to differential responsiveness to cocaine's effects on those mechanisms that underlie cocaine's local anesthetic effects. Thus, it may be that selective breeding for differential ethanol sensitivity has resulted in differential ion channel structure or activity in LS and SS mice. Studies in these mice of cation channel interactions with ethanol and interactions of cation channels with cocaine in conjunction with ethanol may provide an increased understanding of the mechanism(s) of the differential ethanol and cocaine sensitivities of these mice and may lead to an understanding of why people use alcohol and cocaine together.

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