

# Acute Cocaine-Induced Seizures: Differential Sensitivity of Six Inbred Mouse Strains

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*Mature male and female mice from six inbred strains were tested for susceptibility to behavioral seizures induced by a single injection of cocaine. Cocaine was injected ip over a range of doses (50–100 mg/kg) and behavior was monitored for 20 minutes. Seizure end points included latency to forelimb or hindlimb clonus, latency to clonic running seizure and latency to jumping bouncing seizure. A range of strain specific sensitivities was documented with A/J and SJL mice being most sensitive and C57BL/6J most resistant. DBA/2J, BALB/cByJ and NZW/LacJ strains exhibited*

*intermediate sensitivity. EEG recordings were made in SJL, A/J and C57BL/6J mice revealing a close correspondence between electrical activity and behavior. Additionally, levels of cocaine determined in hippocampus and cortex were not different between sensitive and resistant strains. Additional studies of these murine strains may be useful for investigating genetic influences on cocaine-induced seizures. [Neuropsychopharmacology 24:291–299, 2001]*

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Animal models provide fundamental information regarding seizure mechanisms (Jobe et al. 1973; Taylor 1976; Seyfried and Glaser 1985; Golden et al. 1991, 1995) and studies of inbred murine strains in particular (Engstrom and Woodbury 1988; Kosobud and Crabbe 1990; Kosobud et al. 1992; Ferraro et al. 1993, 1997; Frankel et al. 1995b) have yielded considerable information regarding genetic influences on seizure susceptibility. Paralleling this are studies documenting substantial genetic influences in human epilepsy (Anderson et al.

1991; Leppert et al. 1991; Weissbecker et al. 1991; Greenberg et al. 1992).

Cocaine abuse is associated with multiple forms of toxicity and seizures represent a major source of cocaine-induced fatalities (Jonsson et al. 1983; Myers and Earnest 1984; Alldredge, Lowenstein et al. 1989; Choy-Kwong and Lipton 1989; Ernst and Sanders 1989; Ogunyemi et al. 1989; Schwartz 1989; Derlet and Albertson 1989a, 1989b; Dhuna and Pascual-Leone 1990; Dhuna et al. 1991; Holland et al. 1992; Tseng et al. 1992) with eleven percent of substance abusers reporting seizures related to cocaine use (Washton and Tatarsky 1983). As the number of users of cocaine in the U.S.A. exceeds 1.5 million (Park 1997) it can be estimated that approximately 100,000 individuals have experienced cocaine-induced seizures.

The present study represents a systematic strain investigation of acute cocaine-induced seizure sensitivity, a complex trait having genetic and environmental influences. By testing a number of mouse inbred strains for susceptibility to acute cocaine-induced seizures, this study lays the foundation for genetic mapping of specific genes involved in the expression of this complex trait. Because seizure phenomena show striking parallels between mice and humans, and because extensive

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genetic homology exists between these two species, localization of genes involved in sensitivity to cocaine induced seizures will provide an inroad for studying genetic influence in human drug abuse. The results of this study identify A/J and SJL strains of mice as sensitive to the acute seizure-inducing effect of cocaine whereas C57 mice are significantly more resistant suggesting that these strains may be particularly useful for genetic dissection of this complex trait.

## MATERIALS AND METHODS

### Animals

Mature male and female mice from six inbred strains (The Jackson Laboratory, Bar Harbor, ME) were housed by gender (5–6/cage). All mice were housed separately in the Coatesville, VA, animal facility for a least one week prior to use. Mice were tested for susceptibility to seizures induced by an acute injection of cocaine. A total of 519 mice (C57BL/6J  $n = 124$ , DBA/2J  $n = 48$ , BALB/ $n = 48$ , SJ/L  $n = 141$ , NZW/ $n = 37$ , A/J  $n = 121$ ) were tested for acute cocaine-induced seizures using ip injection of 50, 60, 70, 75, 80, 90 and 100 mg/kg of cocaine HCl. Some strains did not receive all cocaine doses. All mice were between 7 and 11 weeks of age at the time of testing and were maintained on *ad libitum* food and water and a 12-hr light-dark cycle. Prior to testing, animals were placed in an isolated, air-conditioned testing room illuminated by overhead fluorescent lighting for at least 30 minutes. All testing was conducted during the light phase of the animal's light-dark cycle (9 A.M.–4 P.M.). All experiments were approved by the Coatesville VAMC Institutional Animal Care and Use Committee.

### Seizure Testing

Separate groups ( $n = 8$ –31/group) of individually housed male and female mice were injected with cocaine. Immediately following injection, mice were placed in individual plexiglass observation chambers (width: 15 cm; length: 20 cm; height: 30 cm) with a wire mesh floor and observed for 20 minutes, during which time behavioral seizure measures were recorded. Cocaine was administered as the hydrochloride salt in physiological saline (pH 6.1), injection concentration 6.0 mg/ml. Behavior was monitored for 20 minutes after the administration of cocaine. Latency to onset of behavioral seizure activity and number and type of behavioral seizures during the 20-min observation period were recorded by two observers with inter-rater reliability established in previous studies on kainate-induced seizure phenotypes in these and other strains (Golden et al. 1991, 1994, 1995; Ferraro et al. 1995a, 1995b, 1997). In contrast to other pharmacological seizure inducing agents, cocaine typically produces a much sharper tran-

sition from non-convulsive behavior to generalized convulsions with little indication of intermediate forms such as myoclonic jerks. Clonic seizure activity is the most common expression of both acute cocaine-induced seizures as well as cocaine-kindled seizures (Marley et al. 1991a). In this study, a cocaine-induced seizure was defined as the occurrence of clonic seizure activity characterized by rapid rhythmic contraction and relaxation of muscles in extremities or as episodes of violent and dramatic uninhibited running and jumping/bouncing. Although this definition of seizures includes different behaviors, these behaviors represent the natural progression of behavioral seizure severity seen in mice in response to an acute cocaine injection.

In addition to monitoring the number of mice from each strain exhibiting seizures, latency from time of cocaine injection to initiation of seizure activity was monitored and used to generate a single quantitative measure of seizure susceptibility for each animal (seizure severity score). The seizure severity score was generated by using the following weighted formula based on latencies to the three different components of seizure phenotype:

$$\text{Score} = [(\text{latency to forelimb or hindlimb clonus})^{-1} \times 1000 \times 0.2] + [(\text{latency to clonic running seizure})^{-1} \times 1000 \times 0.3] + [(\text{latency to clonic jumping/bouncing seizure})^{-1} \times 1000 \times 0.5]$$

where 0.2, 0.3, and 0.5 are the weights of the components.

The seizure phenotype components occur in a consistent progression from clonus to jumping/bouncing seizures in the most seizure-sensitive animals. The total seizure severity score was calculated from the sum of each component (reciprocal of latency  $\times$  1000) times its assigned weight (higher weights given to more severe seizure components). Thus the weighted seizure severity score included measures of both seizure latency and seizure severity. A similar weighted seizure severity score was used in a recent study of kainic acid seizure susceptibility (Ferraro et al. 1997).

### EEG Studies

Cocaine-induced behavioral seizure activity was confirmed by electroencephalographic (EEG) recordings. Eighteen mice (males, 8–10 weeks of age, 6/strain) from the C57, SJL and A/J strains underwent surgery for implantation of chronic EEG electrodes. Burr holes were made in the skull overlying the left and right parieto-occipital cortex and frontal sinus. Lead wires from a tripolar electrode (MS333/3 Plastics One, Roanoke, VA) were inserted under the skull. One lead was placed in contact with the cortical surface, one lead was inserted into the hippocampus and the third lead was connected to an inactive reference site in the frontal sinus. The tripolar electrode was attached to the skull with stainless steel screws and dental acrylic. Forty-eight hours following surgery, mice were injected with cocaine (70

mg/kg, ip) and the EEG recorded and behavior observed for 45 minutes.

### Pharmacokinetic Studies

To investigate the possibility that strain differences in cocaine-induced seizure susceptibility might reflect differences in brain absorption and distribution of cocaine, C57 mice ( $n = 10$ ) and A/J mice ( $n = 10$ ) were injected with cocaine HCl (70 mg/kg, ip) and killed at 2 minutes ( $n = 5$ /strain) or 5 minutes ( $n = 5$ /strain) post injection. Quantitative brain concentrations of cocaine and the cocaine metabolite benzoylecgonine were determined in cortex and hippocampus by National Medical Services (Willow Grove, PA) using the gas chromatography-mass spectrometry method (Javaid et al. 1978; Patrick et al. 1993).

### Kainic Acid Seizure Studies

A dose/response study of susceptibility to kainic acid seizures was conducted to determine if a general predisposition for seizure activity produced by pharmacologic agents is present in the mouse strains susceptible to cocaine-induced seizures. Mature C57BL/6J, DBA/2J, A/J and SJL/J mice (3–10/strain) were injected subcutaneously with kainic acid (distilled H<sub>2</sub>O, pH 7.2, 2 mg/ml) at doses of 10, 20, 25, or 30 mg/kg and observed for seizure activity for four hours using observation conditions identical to those described for cocaine seizure testing.

### Data Analysis

Dose response data were analyzed using both parametric and nonparametric methods. Three factor [strain (6) X dose (4) X sex (2)] ANOVAs (continuous data) and Kruskal-Wallis/Friedman tests (ranked data) were performed for each continuous seizure measure and  $\chi^2$  analyses for discrete seizure measures. *Post hoc* testing was conducted using the Bonferroni/Dunn multiple comparison procedure.

## RESULTS

### Cocaine-induced Behavioral Seizures

Seizure latencies following administration of cocaine were on the order of several minutes (range 0.58–13.98 min) with the rank order of latencies (longest to shortest) being C57 > NZW = DBA > BALB > SJL = A/J. A  $\chi^2$  analysis for strain differences in seizure frequency using all six strains (collapsed across sex) was highly significant at cocaine doses of 60 mg/kg ( $\chi^2 = 27.1$ ,  $p < .0001$ , Cont Coff = .40, Cramer's  $V = .44$ ), 70 mg/kg cocaine doses ( $\chi^2 = 43.2$ ,  $p < .0001$ , Cont Coff = .45, Cramer's  $V = .50$ )

and 80 mg/kg ( $\chi^2 = 11.2$ ,  $p < .0003$ , Cont Coff = .41, Cramer's  $V = .44$ ). Sex differences in seizure sensitivity to acute cocaine injection were also detected. Within the seizure resistant C57 strain, females tended to be more susceptible to cocaine-induced seizures than males (Figure 1). Statistically significant sex differences in the C57 strain were seen at the higher cocaine doses and were revealed by both the number of animals demonstrating seizures and the weighted seizure severity score (Table 1). For the more seizure susceptible strain (SJL and A/J), no sex differences in seizure susceptibility were noted, i.e., there were no statistically significant differences in weighted seizure severity score or number of mice exhibiting seizures between C57, SJL and A/J strains when females were analyzed separate from males. The 60 mg/kg cocaine dose in A/J mice was the only exception (Table 1) where 66.7% of male and 22.2% of female A/J's exhibited seizures. This difference approached but did not reach statistical significance ( $p = .058$ ).

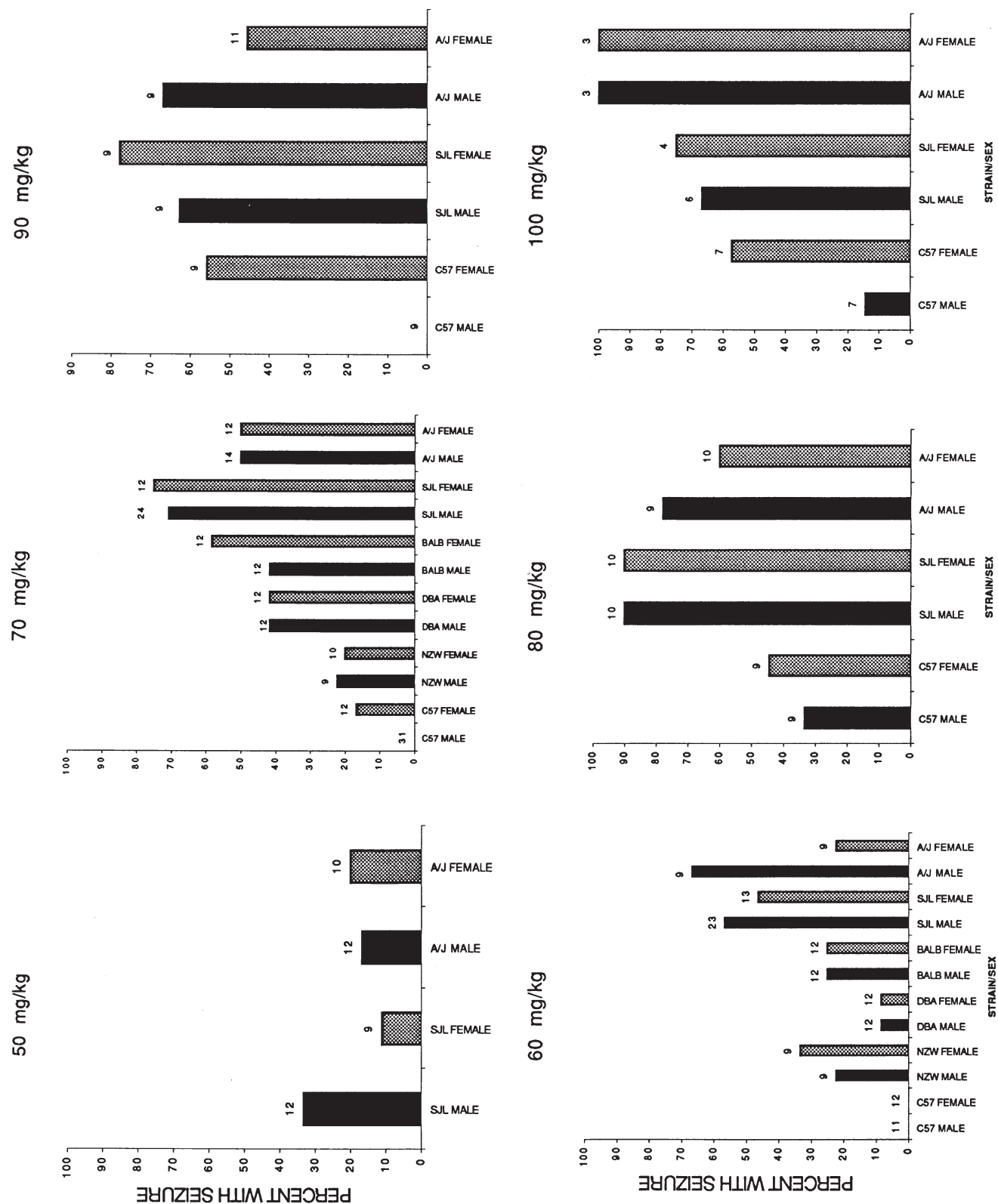
Figure 2 shows the mean ( $\pm$  s.e.) weighted seizure severity scores for each strain as a function of acute cocaine dose. A 2-factor ANOVA using STRAIN (3) X DOSE (7) was highly significant ( $p < .0001$ ) for the main effects of COCAINE DOSE and STRAIN (C57, SJL, A/J). Based on dose response seizure severity data the cocaine dose that best discriminates resistant from susceptible strains is 70–80 mg/kg. The C57 strain appears to be the most resistant to cocaine-induced seizures and the A/J and SJL strains appear to be most sensitive to acute cocaine-induced seizures.

### EEG Studies

EEG recordings made from cerebral cortex and hippocampus of C57 ( $n = 6$ ), A/J ( $n = 5$ ) and SJL ( $n = 5$ ) mice following acute injection of cocaine (70 mg/kg) detected electrographic seizure discharges associated with behavioral seizures in SJL mice; no electrographic seizure discharges were noted in any C57 mice. C57 mice did show ataxia and increased motor activity often associated with a synchronization of EEG activity first in hippocampus, then later in cortex (Figure 3). Electrographic seizure activity was also confirmed in A/J mice at the 70 mg/kg dose of cocaine (not shown).

### Kainic Acid-induced Seizures

A dose response study of the effects of kainic acid (KA) on seizure susceptibility in C57BL/6J, DBA/2J, A/J and SJL/J males mice revealed a rank order of sensitivity difference than that observed for cocaine. At KA doses of 25 and 30 mg/kg the rank order for KA seizure resistance, in order of least to greatest sensitivity, was C57 > A/J > SJL  $\geq$  DBA (Table 2).



**Figure 1.** Mouse strain dose response histograms showing the percentage of male (black bar) and female (gray bar) mice demonstrating seizures to an acute cocaine i.p. injection. The number of mice tested at each dose is shown above histogram bars.

**Table 1.** Weighted Seizure Severity Score (mean + sd) for C57, SJL and A/J Mice: Dose Response by Gender

Strain	Sex	Cocaine Dose				
		60 mg	70 mg	80 mg	90 mg	100 mg
C57	Male	0 (0)	0*+ (0)	.7 (1.49)	0*+ (0)	.4 (1.17)
	Female	0 (0)	.19 (.46)	1.1 (1.40)	1.3 (1.33)	1.3 (1.40)
SJL	Male	1.5 (1.38)	2.0 (1.37)	4.2 (2.87)	2.7 (2.14)	2.6 (2.03)
	Female	.95 (1.09)	1.8 (1.28)	2.5 (1.38)	2.2 (1.71)	2.6 (2.05)
A/J	Male	1.6 (1.36)	1.3 (1.48)	2.9 (2.55)	2.2 (2.14)	3.8 (1.10)
	Female	.63 (1.27)	1.5 (1.59)	2.3 (2.05)	1.7 (2.18)	3.5 (1.29)

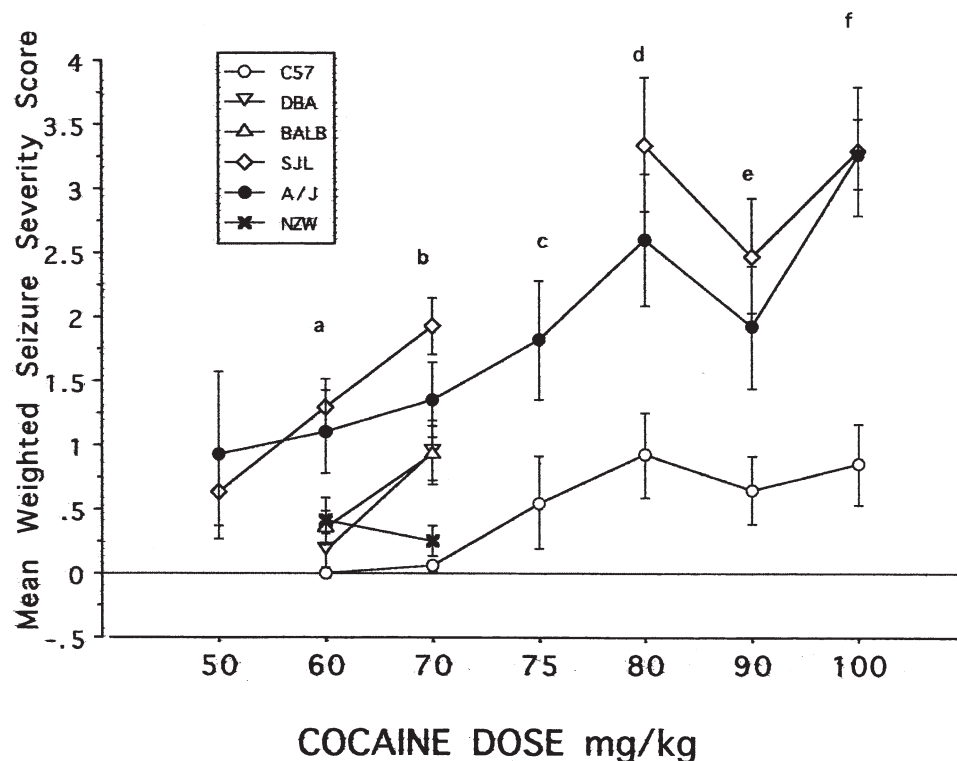
\*C57 males vs. females—70mg ( $p=.023$ ), 90mg ( $p=.009$ ) weighted seizure severity score

+C57 males vs. females—70mg (Chi Square=5.42,  $p=.019$ , Cont Coff=.34, Phi=.36  $p=.023$ ), 90 mg (Chi Square=6.92,  $p=.0085$ , Cont Coff=.53, Phi=.62) number of mice exhibiting seizures

### Pharmacokinetic Studies

No significant differences in cocaine concentrations were evident between the two strains in hippocampus and cerebral cortex at either the 5 or 10-min time point

(Table 3). The cocaine metabolite benzoylecgonine was not detected in any of the samples analyzed. All five A/J mice and none of the C57 mice exhibited seizures during the 5-min time period.



**Figure 2.** Weighted seizure severity scores mean ( $\pm$  s.e.) for each mouse strain as a function of acute cocaine dose. A 2-factor ANOVA using STRAIN (3)  $\times$  DOSE (7) was highly significant ( $p < .0001$ ) for the main effects of COCAINE DOSE and STRAIN (C57, SJL, A/J). *Post hoc* testing was conducted using the Bonferroini/Dunn multiple comparison procedure:

a =  $p < .0001$  SJL vs. C57,  $p = .002$ ; A/J vs. C57

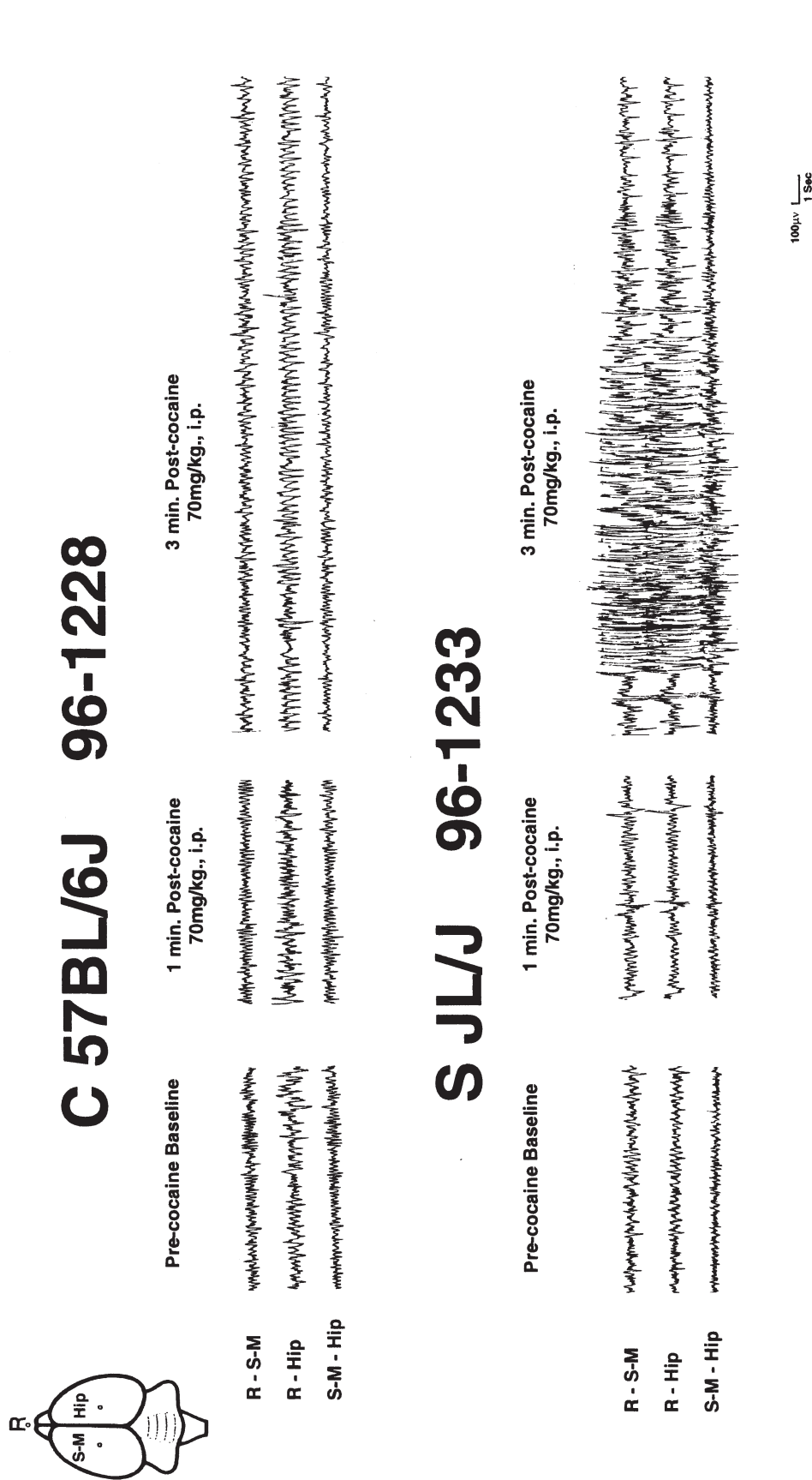
b =  $p < .0001$  A/J and SJL vs. C57

c =  $p = .05$  A/J vs. C57

d =  $p = .0007$  SJL vs. C57;  $p = .01$  A/J vs. C57

e =  $p = .003$  SJL vs. C57

f =  $p = .002$  A/J vs. C57.



**Figure 3.** EEG recordings made from cerebral cortex and hippocampus of C57 (n = 6) and SJL (n = 5) mice following acute injection of cocaine (70mg/kg, i.p.). S-M—somatomotor cortex, Hip—dorsal hippocampus, R—reference electrode in frontal sinus.

**Table 2.** Dose/Response Effect of Kainic Acid in Mature C57BL/6J, DBA/2J, A/J and SJL/J Mice<sup>1</sup>

Dose (mg/kg)	Number of Mice Tested				% with Generalized Seizures			
	C57	DBA	A/J	SJL	C57	DBA	A/J	SJL
10	3	3	0	5	0	0	—	0
20	4	5	5	5	0	20	20	60
25	10	10	5	5	0	80	20	60**
30	4	4	5	5	25	100	40	100*

<sup>1</sup>Mice were injected with kainic acid at the indicated dose and observed for 4 hours to determine behavioral seizure susceptibility, \* $p < .03$ , \*\* $p < .002$ ,  $\chi^2$  Analysis.

## DISCUSSION

A systematic survey of acute cocaine-induced seizure sensitivity was conducted on inbred mouse strains as a prelude to genetic dissection of this complex trait. A range of strain-specific sensitivities was documented with C57 mice being most resistant and SJL and A/J mice most sensitive. This characterization is based both on population seizure frequency experiments as well as on estimation of individual seizure severity using a broad-based seizure score. Pharmacokinetic studies indicate that differences between C57 and A/J mice are not explained by a differential rate of absorption or metabolism of cocaine. Previous studies of C57 and DBA mice also failed to show strain differences in brain cocaine levels after acute injection (Jones et al. 1993). Previous systematic studies on genetic factors that influence cocaine-related seizures have been reported but are limited (DeFiebre et al. 1989; Marley et al. 1991a, 1991b; George 1991b). Most notably, the results and conclusions from our strain analysis conflict with those of Marley (Marley et al. 1991a) who found that C57 mice are the most sensitive to acute cocaine-induced seizures whereas SJL mice are the most resistant with DBA and BALB mice being intermediate. A/J mice were not included in that study (Marley et al. 1991a). These apparently opposite sets of results raise concerns regarding evaluation of acute cocaine seizure phenotypes.

**Table 3.** Cocaine concentrations<sup>1</sup> in Hippocampus and Cerebral Cortex from Male A/J and C57BL/6J Mice<sup>2</sup>

Brain Region	A/J		C57BL/6J	
	2 Min	5 Min	2 Min	5 Min
Hippocampus	9.5 (1.3)	28.5 (6.2)	10.0 (5.3)	24.1 (5.1)
Cortex	12.2 (0.4)	25.0 (4.6)	13.5 (4.7)	24.1 (5.0)

<sup>1</sup>Values are Mean (+S.E.) and are given in ( $\mu\text{g/g}$  protein)

<sup>2</sup>Groups of mice ( $n=5$ /strain/time point) injected with cocaine (70mg/kg, ip) and killed at 2 and 5 min. post injection

In the present study, electrographic correlates of behavioral effects of cocaine were investigated in both C57, A/J and SJL mice. C57 mice were never observed to exhibit abnormal electrical discharges characteristic of seizure activity whereas behavioral seizure activity in SJL and A/J was always associated with EEG spiking. These results are consistent with a large body of literature documenting that C57 mice are unique in their relatively high degree of resistance to many types of experimental seizures (Schlesinger et al. 1968; Deckard et al. 1976; Kellogg 1976; Engstrom and Woodbury 1988; Kosobud and Crabbe 1990; Ferraro et al. 1995a, 1998). The study by Marley (Marley et al. 1991a) relied solely upon behavioral observation for evaluation of seizure activity and it is possible that motor dysfunction such as ataxia or other involuntary movements, which we observed in cocaine-treated C57 mice, were scored as seizures. In our studies the presence or absence of behavioral seizures was corroborated by using EEG recordings. Measurement of EEG is considered by most to be the gold standard for seizure detection. Marley (Marley et al. 1991a) did not record EEG activity from any of the strains used in his study (personal communication). Another potentially significant experimental difference between the present study and that of Marley (Marley et al. 1991a) relates to housing conditions for mice. In the latter study, all mice were group housed until the time of seizure testing (Marley et al. 1991a) whereas in the present study, mice were housed individually for one week before the time of testing. Since SJL males exhibit highly aggressive behavior, it is likely that in group-housing conditions these mice would be exposed to a relatively stressful home cage environment. Thus, the ability of stress to increase seizure threshold (Oliverio et al. 1983) may have contributed to the relative resistance of SJL mice noted by Marley (Marley et al. 1991a). While differences in housing (single vs group) conditions prior to testing might account for the differences observed by Marley (Marley et al. 1991a) and the present study, this can not be determined without further investigation. All other conditions in our study were similar to Marley's (Marley et al. 1991a) study. In both studies mice were obtained from the same supplier (Jackson Laboratory); mice were removed from their home cages and tested in novel test environment (conditioned for 30 minutes) at the same time of day; mice were the same age (Marley study, 55–70 days, present study, 49–77 days). In general, differences in housing conditions and seizure evaluations between the present study and that of Marley (Marley et al. 1991a) hinder direct comparison results.

Results of our study also document an influence of sex on acute cocaine-related seizure susceptibility; however, of the four strains studied, only C57 mice exhibited this trait with females significantly more sensitive than males. This is consistent with the fact that female C57 mice have a significantly lower maximal electroshock

threshold compared to males (Ferraro et al. 1998). Other strains were characterized by equivalent sensitivities for the two sexes although for A/J and SJL mice there was a trend for increased sensitivity among males. In rats, prenatal cocaine exposure results in differential sex effects on seizure sensitivity in adulthood with males more susceptible to cocaine kindling and females more susceptible to acute cocaine-induced seizures (Snyder-Keller and Keller 1995). Reproductive hormones appear to cause cocaine to have greater behavioral effects on females than on males in both acute and long-term abuse (van Haaren et al. 1990). In humans, female cocaine users have been found to experience cocaine-related seizures at a rate three times greater than male cocaine users, a difference not explained by ethnicity, cocaine dose, or route of administration (Dhuna et al. 1991). Additionally, greater numbers of women experience a seizure with their first cocaine usage compared to men (Dhuna and Pascual-Leone 1990). Apart from seizures, a number of other cocaine-related effects have been observed to occur in a sex-specific manner as well (Morse et al. 1993, 1995; Kelley and Middaugh 1996; Xu et al. 1997). The activities of cocaine metabolizing enzymes are also documented to exhibit significant sex-specific differences (Leibman et al. 1990). Overall, the potential for cocaine to have sex-specific effects reflect the complexity of the mechanisms influencing pharmacological responses and emphasizes the need for careful phenotypic evaluations.

In order to evaluate the possibility that susceptibility to cocaine may be a more general phenomenon related to overall seizure predisposition rather than to a specific action of cocaine, strain sensitivities to kainic acid (KA) induced seizures were compared with sensitivities to cocaine-induced seizures. Confirming several literature reports for sensitivity to KA seizures (Engstrom and Woodbury 1988; Ferraro et al. 1995a, 1997), results showed that DBA mice were most sensitive whereas C57 mice were most resistant. A/J mice were more like C57 whereas SJL mice were more like DBA. The lack of correlation between strain responses to KA and cocaine suggests that the molecular substrates underlying sensitivity to the seizure-inducing effects of these drugs are not identical. Thus, although quantitative trait loci mapping studies have begun to localize genes that influence response in KA seizure (Ferraro et al. 1997) and other conventional seizure paradigms, it is likely that QTL mapping for acute cocaine seizures in crosses between C57 and A/J or SJL will provide novel information relevant to the pharmacology of cocaine.

In summary, results of this study document substantial strain variation in susceptibility to seizures induced by acute high doses of cocaine. C57 mice were observed to be the most resistant with A/J and SJL mice equally the most susceptible. These differences are not associated with brain cocaine levels and cannot be explained by a general strain-specific predisposition to seizures. Estima-

tion of the relative influence of genetic and environmental factors in this model will determine the feasibility of using QTL strategies to identify specific genetic components of the response. Successful genetic dissection of this complex trait will provide a better understanding of the action of cocaine in the brain and will yield important information directly relevant to cocaine toxicity.

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