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Pharmacogenetic Differences in Audiogenic Seizure Priming of C57BL/6Bg and DBA/1Bg-*asr* Mice[1]

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MAXSON, S. C., J. S. COWEN AND P. Y. SZE. *Pharmacogenetic differences in audiogenic seizure priming of C57BL/6Bg and DBA/1Bg-asr mice.* PHARMAC. BIOCHEM. BEHAV. 7(3) 221–226, 1977. – Susceptibility to audiogenic seizures can be induced in some strains of resistant mice by exposure to an initial auditory stimulus (acoustic priming). Aminooxyacetic acid, hydrazine, glutamic acid, gamma-aminobutyric acid (GABA), cycloheximide, and metyrapone antagonize the acoustic priming of audiogenic seizure susceptibility in C57BL/6Bg mice, whereas only metyrapone attenuates that of DBA/1Bg-*asr* mice. The strain difference in the effect of AOAA and cycloheximide is correlated with a small, transient fall in level of brain GABA in C57BL/6Bg but not DBA/1Bg-*asr* mice. These findings support our hypothesis that there are at least two neural mechanisms of acoustic priming, each with its own genetic basis and that corticosteroids are required by both mechanisms for the development of primed seizures.

Gamma-aminobutyric acid Pharmacogenetics Acoustic priming Audiogenic seizures Inbred mice

AUDIOGENIC seizure susceptibility has been produced in several strains of "seizure resistant mice" by exposing them to an initial auditory stimulus (IAS) during a sensitive period in postnatal development [2, 6, 9, 12, 23]. Several studies have indicated that this acoustic priming effect can be influenced by genetic variation. Starting with a heterogeneous stock of mice, Chen and Fuller [3] selectively bred for seizure prone, priming prone, moderately priming prone, and seizure resistant lines. The rapid response to selection suggested to them that only a few genes might be involved in the genetic variation of each phenotype. From another heterogeneous stock of mice, Deckard *et al.* [4] also selectively bred for high and low lines of acoustic priming. The realized heritability at the eighth generation of selective breeding was 0.22 ± 0.029 in the high line and 0.29 ± 0.037 in the low line. Genetic variation in acoustic priming also exists between closely related inbred strains of mice. The C57BL/6 Rubbo appears to be nonprimable under conditions of auditory stimulation which are effective for acoustic priming in C57BL/J and C57BL/K Bradley [2], as well as in C57BL/6J [9], and C57BL/10Bg (Maxson, unpublished data). Despite the genetic variation, it has been suggested that acoustic priming may involve a common developmental and neural mechanism. One hypothesis is that the genetic variation may be due to a difference in susceptibility of the acoustic receptors to damage by intense auditory stimulation [2,3]. Under this hypothesis, mice with a cochlea susceptible to damage by stimuli would suffer hearing loss with consequent hyperreactivity to later auditory input, whereas mice with a cochlea resistant to damage would be nonprimable. However, other findings indicate that genetic variation may result in qualitatively different mechanisms of acoustic priming.

In one of the first genetic analyses of acoustic priming, Henry and Bowman [11] exposed DBA/2J, C57BL/6J, and their F_1 hybrids to the IAS at one of 15 ages from Day 0 to 28 and tested them at 28 days of age. The F_1 hydrids, unlike the two parental strains, showed a bimodal sensitivity period, suggesting that there are different mechanisms of acoustic priming in the two parental strains. Also, a qualitative difference was found between the priming prone and moderately priming prone lines developed by selective breeding [3]. Exposure to the IAS, as well as tympanic membrane perforation, induced audiogenic seizure susceptibility in the priming prone mice; whereas exposure to the IAS, but not tympanic membrane perforation, induced susceptibility in moderately priming prone mice.

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Thus, acoustic priming of mice of the moderately priming prone line cannot be due to hearing loss produced by auditory stimulus with consequent hyperreactivity of central structures to later auditory input. Strain differences have also been reported for effects of aminooxyacetic acid (AOAA) on acoustic priming. Siporin and Fuller [22] showed that AOAA attenuated acoustic priming in C57BL/6J, but not in SJL/J mice. We have also reported in a preliminary communication [17] that AOAA attenuated the acoustic priming in C57BL/6Bg, but not in DBA/1Bg-*asr*. The latter appears to be a single gene mutation from DBA/1Bg which blocks genetic but not primed susceptibility to audiogenic seizures [14,17]. It is therefore possible to study acoustic priming in the DBA/1 genotype without the confounding presence of genetic susceptibility.

In the experiments described in this study, we have further compared in C57BL/6Bg and DBA/1Bg-*asr* the effects of the following pharmacological agents on acoustic priming: drugs acting on the GABA system, inhibitors of protein synthesis, and inhibitors of adrenocortical steroidogenesis. Previous studies [17, 19, 24] have shown that each of these treatments can attenuate acoustic priming in C57BL/6Bg and suggested that there may be at least two neural mechanisms involved in acoustic priming of these mice. The present study investigates further qualitative variation for the neural mechanisms of acoustic priming in genetically different mice.

EXPERIMENT 1

Method

An approximately equal number of male and female C57BL/6Bg and DBA/1Bg-*asr* mice were used since no sex differences were observed in acoustic priming. The mice were obtained from our specific-pathogen-free mouse colony. Conditions of rearing and maintenance have been previously described [24].

Four treatment groups were used for each strain: a nonprimed control group injected with 0.1 ml/10 g of saline (C57BL/6Bg, N = 74; DBA/1Bg-*asr*, N = 79); a primed control group injected with saline prior to the IAS (C57BL/6Bg, N = 120; DBA/1Bg-*asr*, N = 35); an AOAA treatment group injected with drug (20 mg/kg, SC) 5 hr prior to the IAS (C57BL/6Bg, N = 44; DBA/1Bg-*asr*, N = 41); and a hydrazine hydrate treatment group injected with drug (50 mg/kg, SC) at 3 hr prior to the IAS (C57BL/6Bg, N = 115; DBA/1Bg-*asr*, N = 108).

For acoustic priming at 19 days of age, the IAS was applied in a chamber 38 × 43 × 38 cm. An Edwards Lungen 7.6 electric bell was used to provide a sound stimulus of 95–105 dB (re: 2×10^{-4} dyne/cm^2). The mouse was placed on the chamber floor and 60 sec later the bell was activated for 90 sec. All mice were tested for susceptibility to audiogenic seizures on Day 28 of age using the same auditory stimulus. Both incidence of wild circling activity (WCA) and that of clonic-tonic seizures (C–T) were recorded. All priming and testing occurred between 1 p.m. and 5 p.m. The test of significance between proportions was used to analyze the data here and in later experiments [1].

Results and Discussion

Table 1 shows that administration of AOAA or hydrazine reduced acoustic priming, as measured by either the incidence of WCA or C–T, in C57BL/6Bg ($p<0.02$), but not in DBA/1Bg-*asr*. These results indicate that there is a strain difference for the effects of these two drugs on acoustic priming. Siporin and Fuller [22] have also demonstrated a pharmacogenetic difference in the effect of AOAA. In their experiments, AOAA attenuates the priming of C57BL/6J, but not of SJL/J mice. Thus, the mechanism of acoustic priming, at least for exposure to the IAS on Day 19 and test on Day 28, may not be the same in C57BL/6 mice as in DBA/1Bg-*asr* or in SJL/J mice.

TABLE 1

PYRADOXAL ANTAGONISTS AND ACOUSTIC PRIMING

Strain	Treatment	% WCA	% C-T	Number Tested
C57BL/6Bg	Non-primed control	16*	9*	74
	Primed control	87	85	120
	AOAA	30*	25*	44
	Hydrazine	70†	68†	115
DBA/1Bg-*asr*	Non-primed control	18*	16*	79
	Primed control	88	80	35
	AOAA	76	71	41
	Hydrazine	80	74	108

All mice except non-primed control were exposed to the IAS at 19 days of age and all were tested at 28 days of age for a 9-day priming-test interval. The controls were injected (SC) with saline. AOAA (20 mg/kg, SC) was injected 5 hr prior to priming. Hydrazine hydrate (50 mg/kg, SC) was injected 3 hr prior to priming.

*Significant difference from primed control, $p<0.01$

†Significant difference from primed control, $p<0.02$

Npq test, Arkin and Colton [1].

However, Sze (unpublished) has found that a single injection of AOAA at Day 19 of age attenuates the genetic susceptibility of DBA/1Bg mice when tested at 25 days of age, but not at 28 days of age. Thus, it seems that at an early age there is an effect of AOAA on genetic susceptibility which is not apparent at a later age. It is possible that AOAA may have a similar effect on acoustic priming of DBA/1Bg-*asr*. The second experiment was a test of this possibility.

EXPERIMENT 2

Method

Only DBA/1Bg-*asr* mice were used. There were 3 treatment groups: an unprimed control group injected with saline (N = 20), a primed control group injected with saline 5 hr prior to IAS (N = 32), and a treated group injected with AOAA (20 mg/kg, SC) 5 hr prior to the IAS (N = 29). Acoustic priming was at 19 days of age and testing for audiogenic seizures was at 25 days of age. The sound stimulus was the same as that described in Experiment 1.

Results and Discussion

As shown in Table 2, there were no differences in incidence of WCA or C–T at 25 days of age for primed controls and AOAA-treated DBA/1Bg-*asr* mice. Thus, for both the 6 and 9 day interval between IAS and testing for audiogenic seizures, AOAA had no effects on acoustic priming. Since AOAA has no effect on DBA/1Bg-*asr* mice

TABLE 2

AMINOOXYACETIC ACID AND 6 DAY PRIMING-TEST INTERVAL

Strain	Treatment	% WCA	%	Number Tested
DBA/1Bg-*asr*	Non-primed control	0	0	20
	Primed control	72	63	32
	AOAA	76	66	29

All mice except non-primed control were exposed to the IAS at 19 days of age and all were tested at 25 days of age. Saline or AOAA (20 mg/kg) was injected subcutaneously at 5 hr prior to priming.

primed at 19 days of age and tested at either Day 25 or 28 of age, this effect of AOAA is not apparent at the earlier age as in DBA/1Bg mice. Thus, the effect of AOAA on the development of genetic seizures in DBA/1Bg and primed seizures in DBA/1Bg-*asr* is different and the underlying mechanism of genetic and primed seizures in DBA/1 mice may not be the same.

We have suggested elsewhere [19] that the effects of AOAA and hydrazine on acoustic priming of C57BL/6Bg mice might be due to their elevation of brain levels of GABA. It is possible that the lack of response to AOAA in DBA/1Bg-*asr* may be related to events in brain GABA system. The following two experiments were carried out to test this possibility.

EXPERIMENT 3

Method

Both C57BL/6Bg and DBA/1Bg-*asr* mice were used in this experiment and there were 4 treatment groups. Two of these (nonprimed control and primed control) are the same as in Experiment 1. The other two groups were treated with either glutamate or GABA prior to exposure to the IAS. For the C57BL/6Bg (N = 17), monosodium glutamate (1 mg/mouse) was injected intraventricularly in 5 μl of 4% sucrose 45 min prior to the IAS; surgical and other procedural details were as previously described [19]. For the DBA/1Bg-*asr* (N = 17), monosodium glutamate (2,000 mg/kg, SC) was injected 45 min prior to the IAS. The saline injected groups were used as controls since they do not differ from similar control groups receiving intraventricular injection of the 4% sucrose vehicle [19]. GABA (2,000 mg/kg, IP) was injected at 15 min prior to the IAS for both C57BL/6Bg (N = 60) and DBA/1Bg-*asr* mice (N = 17). Acoustic priming was at 19 days of age and testing for audiogenic seizures was at 28 days of age. The sound stimulus was the same as described in Experiment 1.

Results and Discussion

In this experiment, a pharmacogenetic difference between C57BL/6 and DBA/1Bg-*asr* was again demonstrated in the response of clonic-tonic seizures to glutamate and GABA (Table 3). Interestingly, there was no effect of either substance on WCA in C57BL/6Bg or DBA/1Bg-*asr*. Since glutamate injected systemically is known to attenuate genetic susceptibility to audiogenic seizures in DBA/1Bg [7] and in C57BL/6-Gad-1^a [13], it is unlikely that the strain difference in the effect of glutamate was due to the

TABLE 3

GLUTAMATE, GABA, AND ACOUSTIC PRIMING

Strain	Treatment	% WCA	% C-T	Number Tested
C57BL/6Bg	Non-primed control	66‡	9‡	74
	Primed control	87	85	120
	Glutamic acid*	94	41‡	17
	GABA	90	48‡	60
DBA/1Bg-*asr*	Non-primed control	17‡	16‡	79
	Primed control	88	80	35
	Glutamic acid†	94	82	17
	GABA	94	88	17

All mice except non-primed control were exposed to the IAS at 19 days of age and tested at 28 days of age. All controls were injected with saline. GABA (2,000 mg/kg, IP) was injected 15 min prior to the IAS.

*Monosodium glutamate (1 mg/mouse) was injected intraventricularly in 5 μl of 4% sucrose at 45 min prior to the IAS. In comparison with a similarly treated control, the significant difference was also at $p<0.01$.

†Monosodium glutamate (2,000 mg/kg) was injected subcutaneously in the DBA/1-*asr* mice at 45 min prior to the IAS.

‡Significant difference from primed control, $p<0.01$.

difference in the route of administration. These findings, particularly that on GABA, are consistent with the hypothesis that elevation in brain levels of GABA at the time of the IAS presentation and/or shortly thereafter can attenuate the acoustic priming in C57BL/6Bg but not in DBA/1Bg-*asr* mice. Since cortical spreading depression does not affect acoustic priming of C57BL/6Bg mice [15], the neural site of this GABA effect on priming is most likely subcortical.

Previous studies have shown a transient reduction of brain levels of GABA immediately following acoustic priming. They have also suggested that the prevention of priming effect of AOAA and other drugs may be due to their action in elevating brain GABA levels [19,23]. If this reduction of brain GABA levels is indeed causally related with acoustic priming in C57BL/6Bg, those mice such as DBA/1Bg-*asr* which do not respond to AOAA may not have this GABA-associated mechanism as a component in acoustic priming. In the next experiment, the effect of IAS on brain levels of GABA was compared in the C57BL and DBA strains.

EXPERIMENT 4

Method

For this study on the effect of the IAS on brain gamma aminobutyric acid (GABA), 19-day-old C57BL/6Bg (N = 18) and DBA/1Bg-*asr* (N = 28) mice were sacrificed at indicated intervals after the IAS (Table 4) by immersion in liquid nitrogen. The dissected frozen whole brain was homogenized in 15 ml of 75% ethanol in a cold room (0°C). The ethanolic homogenate was centrifuged and the residue washed twice in ethanol. The combined supernatant and washings were made up to 25 ml. A 2 ml portion of the ethanolic extract was evaporated to dryness at 60°C. The residue was taken up in distilled water to a volume of 1 ml

TABLE 4

BRAIN LEVELS OF GABA AT DIFFERENT INTERVALS AFTER THE INITIAL AUDITORY STIMULUS

Strain	Interval (Min)	GABA (μmoles/g)
C57BL/6Bg	0	1.80 ± 0.06 (4)
	5	1.79 ± 0.07 (4)
	10	1.52 ± 0.06 (6)*
	20	1.64 ± 0.08 (4)†
DBA/1Bg-*asr*	0	1.80 ± 0.09 (8)
	5	1.77 ± 0.14 (6)
	10	1.85 ± 0.12 (8)
	20	1.91 ± 0.12 (6)

All mice were exposed to the IAS on Day 19 of age and sacrificed at the indicated intervals. GABA levels are shown as μmoles/g at tissue ± S.D. Numbers in parentheses indicate number of animals.
*Significant difference from control, $p<0.01$
†Significant difference from control, $p<0.05$
t-test

per 10 mg of tissue. GABA was measured by the enzymatic method of Graham and Aprison [8]. Effects of the IAS on brain GABA levels were evaluated by a Student *t*-test [1].

Results and Discussion

As shown in Table 4, the IAS produced a significant fall in brain level of GABA in C57BL/6Bg mice at 10 and 20 min ($p<0.05$), whereas it had no effect in DBA/1Bg-*asr* mice. Thus, there was a correlation between the effects of the IAS on brain level of GABA and the effects of AOAA and other drugs on acoustic priming. The present finding suggests that a GABA-related mechanism exists only in C57BL/6Bg but not in DBA/1Bg-*asr*. This is consistent with the hypothesis that more than a single mechanism may exist in acoustic priming.

We have also shown in previous studies [18,24] that inhibition of brain protein synthesis or adrenal glucocorticoid synthesis attenuates the acoustic priming in C57BL/6Bg. If these biochemical responses involving protein synthesis and glucocorticoids as well as brain GABA levels are all associated in a sequence of events, and if this mechanism is absent in DBA/1Bg-*asr*, then the DBA mice should also show no response to drugs acting on protein synthesis and corticoid effect. The next experiment was to test this possibility.

EXPERIMENT 5

Method

Both C57BL/6Bg and DBA/Bg-*asr* mice were used in this experiment. There were 4 treatment groups. Two of these (nonprimed control and primed control) were the same as those used in Experiment 1. The other two were treated with either cycloheximide (30 mg/kg, IP) at 0.5 hr prior to the IAS (C57BL/6Bg, N = 54; DBA/1Bg-*asr*, N = 82) or metyrapone (metapirone; metapyrone) at 5 hr prior to the IAS (C57BL/6Bg, N = 26; DBA/1Bg-*asr*, N = 36). At the dose and time, cycloheximide inhibits brain protein synthesis of C57BL/6Bg mice by approximately 100% at 1 hr after injection [18]. Metyrapone inhibits adrenal steroid 11-β-hydroxylase activity and thereby specifically blocks the formation of 11-dehydro-corticosterone and corticosterone [5]. Acoustic priming was at 19 days of age and testing for audiogenic seizures was at 28 days of age. The sound stimulus was the same as that described for Experiment 1.

Results and Discussion

Cycloheximide attenuates the acoustic priming in C57BL/6Bg, but not in DBA/1Bg-*asr* mice (Table 5). This difference is unlikely to be due to strain differences in the effects of cycloheximide on protein synthesis. Similar doses were shown to produce 85 to 95% inhibition of brain protein synthesis in DBA/2J mice [21], which is closely related to the DBA/1Bg-*asr*. Thus, there is not only a strain correlation between the effects of the IAS on brain GABA level and effects of gaba-ergic drugs on acoustic priming, but also between these and the effect of protein synthesis inhibitors on acoustic priming. Elsewhere we have also shown that puromycin, another inhibitor of brain protein synthesis, also attenuates acoustic priming of C57BL/6Bg mice [18].

TABLE 5

CYCLOHEXIMIDE, METYRAPONE AND ACOUSTIC PRIMING

Strain	Treatment	% WCA	% C-T	Number Tested
C57BL/6Bg	Non-primed control	16*	9*	74
	Primed control	87	85	120
	Cycloheximide	52†	50†	54
	Metyrapone	0*	0*	26
DBA/1Bg-*asr*	Non-primed control	17*	16*	79
	Primed control	88	80	35
	Cycloheximide	85	82	82
	Metyrapone	64†	53†	36

All mice except non-primed control were exposed to the IAS at 19 days of age and all were tested on Day 28 of age. The controls were injected with saline. Cycloheximide (30 mg/kg, IP) was injected at 0.5 hr prior to acoustic priming. Metyrapone (100 mg/kg, SC) was injected at 5 hr prior to priming.
*Significant difference from primed control, $p<0.01$
†Significant difference from primed control, $p<0.02$
Npq test, Arkin and Colton [1].

However, metyrapone attenuates the acoustic priming of both C57BL/6Bg and DBA/1Bg-*asr* (Table 5). At a dose of 100 mg/kg, metyrapone completely blocks acoustic priming of C57BL/6Bg mice whereas it only attenuates that of DBA/1Bg-*asr* mice for WCA by 24% and for C–T by 27% ($p<0.02$). Thus, there is a quantitative pharmacogenetic effect which may be dose-dependent. This finding implies that glucocorticoids are required for both mechanisms of acoustic priming.

It is of interest to note that although acoustically primed susceptibility is attenuated by metyrapone, this inhibition of glucocorticoid synthesis has no effect on the development of genetic susceptibility of DBA/1Bg mice [16]. The

differential effect of metyrapone as well as those of AOAA suggest that the mechanisms for the development of genetic and primed susceptibility in DBA/1 mice are not the same.

GENERAL DISCUSSION

We have previously proposed that there may be at least two different mechanisms involved in acoustic priming [18, 19, 24]. In one of the mechanisms, the IAS damages the acoustic receptors and thereby causes partial deafness [10,26], and the partial hearing loss results in a disuse supersensitivity of the brain stem auditory system which now responds to subsequent sound stimulation with an altered pattern of neural activity in the auditory brain stem and with consequent neural and behavioral seizure [20,27]. This mechanism of hearing loss appears to be available in almost all mice, since either tympanic rupture and/or mechanical ear block can induce susceptibility to audiogenic seizures in C57BL/6, DBA/1Bg-*asr*, BALB/c, SJL/J inbred strains and both the priming prone and seizure resistant selected lines of Chen and Fuller [3]. In this mechanism, genetic variation may, primarily, affect the sensitivity of the cochlear receptor to damage by sound stimulation [2,3]. The other proposed mechanism of acoustic priming is mediated by a sequence of biochemical events involving GABA and protein synthesis during a brief time following the IAS. This mechanism appears to exist in C57BL/6 mice of either J or Bg substrains, but not in the DBA/1Bg-*asr* and SJL/J strains. Elevation of brain levels of GABA and inhibition of protein synthesis were shown to attenuate acoustic priming only in C57BL/6 but not in DBA/1Bg-*asr*. Similarly, acoustic priming of SJL/J was not affected by AOAA. There is also a strain correlation between a post-IAS fall in brain level of GABA and effects of gaba-ergic drugs and cycloheximide on acoustic priming. Therefore, there may be a gene or genes which in one allelic form, present in C57BL/6 mice, results in the IAS causing a transient fall in brain level of GABA with the production of seizure susceptibility and which in another allelic form, present in DBA/1Bg-*asr* and SJL/J mice, results in the IAS having no effect on the brain level of GABA and thus in its not being a causal event in the acoustic priming of these strains. Since the DBA/1J and DBA/2J strains are closely related to the DBA/1Bg-*asr*, it is most likely that these strains have the same alleles as the DBA/1Bg-*asr* for the effect of the IAS on brain levels of GABA. On the other hand, since the acoustic priming of C57BL/10Bg and Rb/3Bg mice can be attenuated by AOAA (unpublished data), it is most likely that they have the same alleles as the C57BL/6 for the effect of the IAS on brain levels of GABA.

Interestingly, these two different mechanisms of acoustic priming of audiogenic seizure susceptibility with different genetic foundations share some aspects of their development. Both appear to be located subcortically, since cortical spreading depression does not effect the acoustic priming of C57BL/6Bg [15] or SJL/J [25] mice. Also, both C57BL/6Bg and DBA/Bg-*asr* mice appear to require glucocorticoids for full development of acoustically primed audiogenic seizure susceptibility. Thus, although the two mechanisms of acoustic priming are initially divergent, there may be a convergence on some common aspect of neural development which is altered in acoustic priming of susceptibility to audiogenic seizures.

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