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BRIEF COMMUNICATION

Effect of Cortical Spreading Depression on Audiogenic Seizure Priming of C57BL/6 Mice[1]

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MAXSON, S. C. AND J. S. COWEN. *Effect of cortical spreading depression on audiogenic seizure priming of C57BL/6 mice.* PHARMAC. BIOCHEM. BEHAV. 6(3) 349–350, 1977. – At 19 days of age, C57BL/6Bg mice received KCl-induced cortical spreading depression during which they were acoustically primed by exposure to an initial auditory stimulus. At 28 days of age, the mice were tested for susceptibility to audiogenic seizures. Cortical spreading depression had no effect on acoustic priming of C57BL/6Bg mice and it had been previously reported to have no effect on acoustic priming of SJL/J mice. These findings are discussed in the context of pharmacogenetic differences for the effects of aminooxyacetic acid on acoustic priming of C57BL/6 and SJL/J mice.

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SUSCEPTIBILITY to audiogenic seizures may be induced in otherwise genetically resistant mice by exposing them to an initial auditory stimulus during a sensitive period in development [4, 5, 8, 12]. This phenomenon is known as acoustic priming. Several investigators have suggested that the initial auditory stimulus causes a loss of hearing and a subsequent disuse supersensitivity of the brain stem auditory system with increased responsiveness to later sound stimuli [10]. Consistent with this hypothesis are studies on the neural locus of acoustic priming. Since cortical spreading depression does not block acoustic priming in SJL/J mice [14] and since lesions of the inferior colliculus do attenuate acoustic priming in SJL/J mice [13], the neural site of acoustic priming appears to be located in the brain stem. However, the mechanism of acoustic priming may differ among inbred strains of mice and the neural site of acoustic priming may also differ across genotypes. Henry and Bowman [6], as well as Chen [3], have demonstrated genetic heterogeneity for this phenotype. Also, Maxson *et al.* [9] have shown that aminooxyacetic acid and cycloheximide antagonize acoustic priming in C57BL/6 but not in DBA/l-*asr* mice. Similarly, Siporin and Fuller [11] have reported that aminooxyacetic acid blocked acoustic priming in C57BL/6J but not in SJL/J mice. Thus, it is conceivable that the cortex may be involved in the acoustic priming of one strain and not in another and that the finding of no effect of cortical spreading depression on acoustic priming of SJL/J mice may not generalize to other inbred strains. We report here our results on the effects of spreading depression on acoustic priming in another strain, the C57BL/6Bg. We also relate these findings to the pharmacogenetic differences for the effects of aminooxyacetic acid on acoustic priming.

Under ether anesthesia, C57BL/6Bg mice had bilateral holes, approximately 5 mm in diameter, placed in the occipital region of the skull. Care was taken not to damage the dura. The skin wound was then closed with a single, loose suture. Six hours after this surgery – when the mouse had recovered – the suture was cut and the skull openings were washed with physiological saline. A 3 × 3 mm piece of filter paper, which had been soaked in 25% KCl, was placed on each skull opening and thus on the exposed dura. The ability of the mouse to keep its feet placed on parallel bars 3 mm in diameter and spaced 15 mm apart was used to confirm the presence or absence of cortical spreading depression [2,14]. For all mice, cortical spreading depression was evident between 5 and 15 min after the application of the KCl soaked filter paper. Both unprimed and primed controls received the same surgical procedures, but were not exposed to the KCl soaked filter paper. The primed groups (control and spreading depression) were exposed to the initial auditory stimulus from a doorbell

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(95–105 dB; re: 2×10^{-4} dyne/cm^2) for 90 sec. After the mouse was placed in the testing chamber, there was a 60 sec wait period prior to the initial auditory stimulus. Following this presentation of the initial auditory stimulus, the mice were anesthetized with ether and the skin wound was closed with sutures. At 28 days of age, all mice were tested for audiogenic seizures by exposing them to the same sound stimulus for 90 sec or until a clonic-tonic seizure. Again, exposure to the sound stimulus was preceded by a 60 sec wait period in the testing chamber. Percent wild circling activity and percent clonic-tonic seizures were calculated. The levels of significance of the difference between proportions was used to analyze the data [1].

As shown in Table 1, there is no significant difference in either wild circling activity or clonic-tonic seizures for the groups primed with and without cortical spreading depression. Thus, in both the C57BL/6 and SJL/J strain, normal cortical activity does not appear to be required for acoustic priming and in both strains the cortex is unlikely to be the site of the neural change(s) involved in acoustic priming.

Elsewhere we have suggested that there may be two mechanisms for acoustic priming [10]. One of these may involve hearing loss and may take place in the brain stem. We now suggest that this exists in both SJL/J and C57BL/6 mice. The other may be mediated by changes in brain levels of gamma aminobutyric acid and require brain protein synthesis. Since there is a strain difference in the effect of aminooxyacetic acid in acoustic priming and since aminooxyacetic acid acts on acoustic priming in C57BL/6 by elevating brain levels of gamma aminobutyric acid, we believe that this second mechanism is found in C57BL/6 mice but not in SJL/J mice [9, 10, 11]. This hypothesis is based on the strain difference in effect of aminooxyacetic acid on acoustic priming. Since cortical spreading depression does not affect acoustic priming of the C57BL/6, the neural site of this mechanism must also be subcortical. Perhaps this neurochemical mechanism takes place in the brain stem. In support of this suggestion, Henry *et al.* [7] have shown that if C57BL/6 mice are bilaterally primed and unilaterally lesioned in the inferior colliculus, ear block contralateral to the lesion but not ipsilateral to it antagonizes seizures at the time of testing. Thus, although there appears to be at least two routes to acoustic priming in the C57BL/6, both mechanisms may occur at the same neural site in the brain stem and may act at that neural site either separately or synergistically.

TABLE 1

EFFECT OF CORTICAL SPREADING DEPRESSION ON ACOUSTIC PRIMING OF C57BL/6Bg MICE

Treatment	Percent Wild Circling Activity	Percent Clonic-Tonic Seizures	N
Unprimed Control	0	0	10
Primed Control	100	100	6
Primed and Cortical Spreading Depression	100	100	8

Primed mice were exposed to the initial auditory stimulus on Day 19 and all mice were tested for audiogenic seizures on Day 28. The difference between each primed group and the unprimed group is significant $p<0.01$ (Npq test; Arkin and Colton, Ref. 1). There is no significant difference between the primed control and primed cortical spreading depression groups.

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