Effect of Priming and Testing for Audiogenic Seizures in BALB/c Mice as a Function of Stimulus Intensity

Certain strains of inbred mice are not susceptible to audiogenic seizures; however, it has recently been shown that audiogenic seizure susceptibility can be induced in these genetically seizure-resistant mice by exposing them to an intense acoustic stimulus[1–4]. On re-exposure to this acoustic stimulus after a suitable incubation period, the mice exhibit seizure behaviour. This phenomenon, termed 'priming' or 'sensitization', may provide a useful model for investigating the effects of early, intense auditory stimulation on functional development of the auditory system.

Recent evidence indicates that the effect of priming could be mediated by a process similar to disuse supersensitivity; disuse in the auditory system results from stimulation damage to the receptor organ, the cochlea[5–7]. If cochlear deafness or dysfunction is the prerequisite condition for the development of seizure susceptibility, then it could be expected that the intensity of the priming stimulus is a critical factor in determining the degree of damage and therefore the effectiveness of priming in inducing seizure susceptibility.

In all priming studies the same prime-test intensity level has been used, hence it has not been established whether intensity at priming is more important than intensity at testing. Although there is some suggestion that intensity at priming may be critical to subsequent development of seizure susceptibility[8], no one has systematically studied this important parameter. The purpose of the present experiment was to examine this problem by combining three priming and testing intensities in a 3×3 factorial design. Frequency-modulated tones were used instead of the sound of a ringing-bell in order to facilitate the manipulation of stimulus intensity and to ensure that the frequency characteristics of the priming and testing stimuli were the same.

All frequency-modulated tones had a centre frequency of 18 kHz with frequency deviation of 200 Hz and modulation rate of 32 Hz. The tones, generated by a Wavetek model 136 oscillator, were externally modulated by a ramp generator. The oscillator output was amplified by a 20-watt audio-amplifier and the sound source was a Goodmans H12 speaker. A decade attenuator between oscillator output and audio-amplifier permitted control of stimulus intensity. The intensity levels used were 85, 98 and 114 db relative to 0.0002 dyne/cm^2. Priming and testing for audiogenic seizure were carried out in a 15-cm-diameter glass jar. 126 BALB/c mice, randomly divided into 3 groups of 42 mice each, were exposed to an 85, 98 or 114 db tone for 2 min at 21 days. At 28 days of age, each group was subdivided into test samples of 14 mice and testing for audiogenic seizures was carried out at either 85, 98 or 114-db. Testing consisted of placing each mouse in the glass jar and re-exposing it to the modulated tone for two min. or until seizure occurred. The incidence of wild running and clonic and tonic seizure, as well as latencies to wild running and to clonic seizure, were recorded.

The data from the test exposure are summarized in the Table. It is clear that the intensity of the priming stimulus is far more significant than the intensity of the testing stimulus. A very low seizure rate was obtained in mice primed at the 85 and 98-db levels, regardless of the intensity of the testing stimulus used. However, a high incidence of seizure reaction was shown in mice primed at the 114-db level no matter which of the three intensity levels was used at testing. Significantly more mice primed with the 114-db tone exhibited seizure reactions when tested at the 85-db (two-tailed Fisher exact tests, wild running, $p < 0.05$; clonic seizure, $p < 0.10$) and 98-db level ($p < 0.005$) even though these two intensity levels were clearly ineffective in inducing audiogenic seizure susceptibility. Thus priming at the 114-db level appears to increase the reactivity of the auditory system to a loud sound.

Although the intensity of the priming stimulus is critical in inducing seizure susceptibility, the intensity used during testing also influences seizure rate. Chi-square tests on the incidences of wild running and clonic seizure indicate that the 114-db groups tested at different intensity levels differed significantly ($p < 0.001$).

The present finding, that a high-intensity, frequency-modulated tone is more effective than a low-intensity, frequency-modulated tone in inducing seizure susceptibility, is consistent with the sensory deprivation hypothesis of acoustic priming in mice[5–7]. More intense sounds are expected to be more effective in causing cochlear damage than low intensity sounds. As a consequence of greater cochlear damage, auditory input to higher neural structures is adequately reduced and therefore the sensitization process is effectively achieved. If no cochlear damage is induced by the priming stimulus then there would be no reduction of auditory input and the postulated supersensitive state would not develop; consequently, no seizure reaction could be obtained, even if a higher-intensity testing stimulus were used[9].

Zusammenfassung. In Abhängigkeit von der Intensität einer Vorbehandlung mit akustischen Reizen können bei Mäusen Anfälle durch Reexposition hervorgerufen werden. Eine Schädigung in der Cochlea im Sinne einer «sensory deprivation» wird als Voraussetzung für die Anfallsentstehung aufgefasst.

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Incidence of seizure reactions as a function of tone intensity

Priming intensity (db)	Testing Intensity (db)								
	114 ($n = 14$)			98 ($n = 14$)			85 ($n = 14$)		
	WR[a]	C[a]	T[a]	WR	C	T	WR	C	T
114	13	12	5	10	10	2	5	4	1
98	1	1	1	1	1	0	0	0	0
85	0	0	0	0	0	0	0	0	0

[a] Seizure reactions: WR, wild running; C, clonic seizure and T, tonic seizure.

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