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Infantile Auditory Exposure and Unusual Response to Antipsychotic Drugs (38510)

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Drug idiosyncrasies are unusual qualitative or quantitive responses attributed to individual biological peculiarity. Most investigators emphasize the contribution of genetically determined factors, perhaps because the role of environmental factors in pharmacologic individuality is often elusive and difficult to identify. The data presented here document a sound-induced convulsive idiosyncrasy to prochlorperazine and to reserpine in laboratory animals, and suggest that neurologic changes induced by environmental noise may be operative in uncharacteristic responses to CNS-active drugs. Idiosyncrasies to the antipsychotic drugs—which frequently evoke tremors and rigidity resembling Parkinsonism, and less commonly convulsions—are of particular interest to this report.

Noise has recently been recognized as an environmental hazard with potential for inducing chemical and physiological disturbances of the endocrine, cardiovascular and nervous systems, in addition to effects on audition (1). The immature are especially susceptible to sound induced alterations (2). Of specific interest to this report, a brief auditory stimulus during a critical period of neuronal development in young rodents induces a period of sensitivity to sound-induced convulsions (2–4). No seizures occur at the initial sound exposure. Seizure susceptibility develops several days later and lasts about 5 days. Thereafter animals have normal responses to auditory challenge, and appear normal physiologically.

Reserpine and prochlorperazine are potent tranquilizers that normally produce a marked calming-sedative effect from which animals are easily aroused. However, when reserpine was fortuitously administered to a group of adult mice, some of which had been audiosensitized as weanlings, uncharacteristic responses occurred in those that had been sensitized. These animals displayed rigidity and tremors, and if stimulated by handling (or other stimuli), developed grand mal-type convulsions.

The present study was conducted to examine infantile auditory exposure as a cause of idiosyncratic response to antipsychotic drugs.

Methods. Animals used were offspring of CAW:CF1 mice (Carworth Farms) and LVG:LAK hamsters (Lakeview Hamster Colony).

Experimental groups representing various ages from both species were subjected to 30 sec of electric doorbell sound (95 db above 0.002 dyne/cm^2) in a glass chamber. Mice were tested for response to reserpine or prochlorperazine 2 wk after this auditory exposure, and hamsters were tested 1 mo after exposure. Control litter mates were also tested for response to reserpine and prochlorperazine. A postdrug auditory challenge was used in all groups to recruit seizures and thus to quantify their incidence at specific time intervals after drug administration.

Drugs were administered in aqueous solution ip. Reserpine base and prochlorperazine edsylate were used.

Results. Data showing idiosyncratic convulsive response in tranquilized mice and hamsters that had been audiosensitized during postnatal development are shown in Table I. In nondrug treated mice, only 7.6% of the audiosensitized mice had seizures upon auditory challenge, and none of the normal animals convulsed. In reserpinized nonaudiosensitized mice, seizure incidence was low, with a maximum seizure incidence of 21% occurring at extremely high and lethal dosage (over 25 mg/kg). Compared to these controls, reserpine or prochlorperazine administration to the previously audiosensitized mice caused strikingly higher incidences of seizures.

Seizure incidence in reserpinized audiosensitized mice was dose related. These mice also showed irreversible entry into seizure

TABLE I. EFFECTS OF AUDIOSENSITIZATION AND ANTIPSYCHOTIC DRUG TREATMENT ON SOUND INDUCED SEIZURES.

Interval after drug treatment	Seizure incidence (percent)[a]	
	Normal animals	Audiosensitized[b]
		14 days after sensitization
Mice		
No drug	0 ($N = 15$)	7.6 ± 3.1[c] ($N = 104$)
One hr after Reserpine 1 mg/kg	0 (16)	37.5* (16)
2.5 mg/kg	0 (15)	86.7* (15)
5 mg/kg	4.2 (24)	95.8* (24)
25 mg/kg	21 (19)	100 * (19)
Prochlorperazine 5 mg/kg	0 (20)	50 * (20)
Twenty hr after Reserpine 5 mg/kg	10 (10)	8.3 (12)
Prochlorperazine 5 mg/kg	0 (20)	5.0 (20)
		30 days after sensitization
Hamsters		
No drug	0 (23)	7.7 (13)
One hr after Reserpine 2.5 mg/kg	0 (13)	76.9* (13)
Prochlorperazine 5 mg/kg	0 (13)	38.5* (13)
		100 days after sensitization
Reserpine 2.5 mg/kg	0 (10)	50 * (10)

[a] Clonic-tonic convulsion within 30 sec of 95 dbA stimulus.

[b] Exposed to 30 sec of 95 dbA on day 18 (mice) or day 28 (hamsters).

[c] Mean ± S.E. of seven groups of littermate controls.

* Significantly different from drug treated normal animals and from nontreated audiosensitized animals ($P < 0.01$, X^2 test with Yates correction).

in that all seizures were maximal (i.e. tonic extension). This latter is in contrast to the reactions seen in animals tested in the absence of the drug where the crisis episode may terminate with wild running (3). Both drugs markedly increased the lethality of a sound-induced seizure.

The temporal progression of audiosensitization and postsensitization events is slower in hamsters than in mice (3, 4). Reserpine administered to audiosensitized hamsters after apparent recovery restored seizure susceptibility for several months (Table I). Reserpine administration before development of audiosupersensitivity does not alter its onset.

Age at the initial auditory exposure is extremely important. Reserpine did not precipitate tremor or convulsions when sensitization was attempted in mice younger than 12 days or over 35 days of age. In both species the highest incidence of the abnormal response to reserpine occurred in animals that were exposed to noise during the "critical period" for audiosensitization (age 15–21 days for mice and age 28–33 days for hamsters). It should be noted that during the postsensitization period when these animals would have been susceptible to sound-induced convulsions, no auditory challenge was presented, and that the test for tranquilizer response was not made until this period had passed.

Audiosensitization insufficient to cause seizures upon sound challenge alone may result in seizures in the presence of both sound and drug. In an additional experiment 44 weanling mice were exposed to 30 sec of sound from a different bell known to be incapable of precipitating an audiogenic crisis. Three days later half of the animals were given reserpine (5 mg/kg) and tested with the same bell an hour later. Twenty (91%) of the reserpinized mice had tonic-clonic convulsions and eight died. Only one (4.5%) animal in the control group convulsed.

Discussion. Although infantile auditory exposure dramatically alters the response to reserpine and prochlorperazine in adult animals, attribution of a biochemical mechanism is difficult as both reserpine and prochlorperazine have myriad actions.

Reserpine pretreatment is known to facilitate convulsions produced by electroshock (5); "handling by the tail" (6) or by chemical convulsants (7). However, the effect starts at 4 hr, reaches a maximum at 12 hr, declines by the 20th hr, with measurable changes persisting for 6 days (7). The uncharacteristic effect of reserpine in audiosensitized animals observed in our experiments are maximal 1 hr after drug administration, with seizure incidence greatly diminished by 4 hr and indistinguishable from audiosensitization alone by 20 hr after dosage (Table I). Such a time course suggests a mechanism that is unrelated to reserpine's sedative (8) or excitatory properties (5–7) or its ability to deplete brain amines.

The etiology of audiosensitization seems to involve a complex balancing of hazard and defense factors. The termination of seizure susceptibility following audiosensitization is proposed to involve the development of a more prominent inhibitory system (9). If this assumption is valid, prochlorperazine and reserpine may act by disrupting inhibitory function, and allowing spread of seizure activity throughout the brain and spinal cord. Alternatively, the agents might activate latent foci in the audiosensitized animal.

Reserpine has been extensively studied (over 30 publications) in animals genetically susceptible to audiogenic seizures and a contradictory literature reports either increase in seizure severity, no effect or protection from seizures. Reserpine potentiation of genetic susceptibility to convulsions has been attributed to changes in norepinephrine (10, 11), serotonin (12, 13) and dopamine (14). In another study in this laboratory, no difference in brain levels of norepinephrine, dopamine, or serotonin could be detected in reserpinized control and audiosensitized mice (15). Interpretation is complicated by the fact that in weanling CF1 mice (i.e. at the critical age for audiosensitization), the levels of norepinephrine, serotonin, and monoamine oxidase change radically from day to day (16). Furthermore, conclusions based on studies limited to these variables may not be justified as inhibition of protein synthesis also potentiates audiogenic seizures (17).

In addition to reserpine and prochlorperazine, other potent neuroleptics that enhance seizure response in audiosensitized mice are thioperazine, trifluoperazine, and under certain conditions, chlorpromazine. Valette and Raynaud (18) propose a relationship between these drugs' propensity to induce extra-pyramidal manifestations in human medicine and their ability to increase audiogenic seizure susceptibility in genetically susceptible mice.

Although the mechanism of tranquilizer-induced seizures in audiosensitized laboratory animals remains enigmatic, its occurrence raises the question of whether idiosyncratic drug responses in humans can be correlated with previous auditory exposure. If a phenomenon analogous to audiosensitization occurs in humans it will be extremely difficult to show. The sensitizing sound exposure would have to occur during a brief period of neural development (which could conceivably be prenatal) and would be followed by a long refractory period.

Recent reports suggest that the immature and the diseased may be particularly vulnerable to the stressful effects of noise (19, 20). Children whose prenatal development occurred near airports have been observed to be smaller and to have altered responses to noise (21). Both hypertensive and psychotic patients have altered responses to noise (22, 23). Increased mental hospital admissions have also been correlated with airport environments (24).

Many psycho-acousticians doubt that noise had deleterious behavioral aftereffects (25) since man adapts so well to environmental noise. However, Glass and Singer (26) emphasize the importance of psychological (cognitive) factors in physiological adaptation and suggest man's adaptability has a "psychic price." Theoretically, drugs could increase the adverse consequences of noise by modifying those cognitive processes essential to adaptation.

Until the above questions have been resolved, prior and current auditory experience and the possibility of infantile audiosensitization should be included whenever potential causes of idiosyncratic excitatory responses to neuroleptic drugs are being considered. Previous studies of the adverse effects of noise have emphasized the immediate and temporary effects of sound exposure. The idiosyncratic drug response of audiosensitized animals extends the deleterious effects of sound to long-lasting changes induced by long-past auditory stimulation.

Noise is least understood of the environmental hazards (1, 20, 26). The proconvulsive effects of antipsychotic agents in audiosensitized rodents may provide a useful experimental model to study the pathologic effects of noise in the developing nervous system.

Summary. Reserpine and prochlorperazine were administered in separate experiments to adult CAW:CF1 mice and to adult LVG:LAK hamsters that had recovered from audiosensitization induced by 30 sec of doorbell sound during a critical period of infantile development. In contrast to controls that showed tranquilization in response to these drugs, the previously audiosensitized animals of both species responded with a high incidence of convulsive seizures.

The proconvulsant effect of reserpine and prochlorperazine in previously audiosensitized mice was present one hour after drug administration, but had subsided 20 hr post-administration. The proconvulsant effect of reserpine in previously audiosensitized mice was shown to be dose-dependent. The proconvulsant effect of reserpine in previously sensitized hamsters was present 100 days after audiosensitization.

Although the mechanisms of the proconvulsant effects of reserpine and prochlorperazine are poorly understood, possible mechanisms are discussed.

Environmental noise during early infantile development appears to have significant residual effects persisting into adult life. This study has shown that idiosyncratic responses to antipsychotic drugs in adult laboratory animals can result from infantile auditory exposure, and it is speculated that human idiosyncrasies to psychoactive drugs may be similarly based.

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