termination of drug treatment is unclear. Since methadone has been shown to cause a variety of morphological and biochemical alterations of the brain[14-17], it might be conjectured that CNS and/or PNS structures associated with nociceptive mechanisms are damaged during the developmental period. Alternatively, since methadone has been reported to accumulate in the brains of preweaning animals[8], and a single s.c. injection of methadone has been found to persist in the adult brain for at least 3 weeks[7], perhaps methadone remaining in the brain from chronic perinatal drug treatment is effecting the continued state of analgesia.

Although it is difficult to generalize between our laboratory data and clinical situations, it seems appropriate to raise the question of whether perinatal exposure to methadone (either transplacentally or during breastfeeding) could interfere with pain perception during childhood and later stages of life. In fact, other sensory modalities may also be impaired in these drug-exposed individuals. In view of the social and emotional implications of such findings, as well as the importance of these results to such areas as the clinical management of pain, the relationship between maternal methadone consumption and the physiological integrity of their progeny needs to be evaluated.

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Potentiation of acoustic-trauma-induced audiogenic seizure susceptibility by salicylates in mice[1]

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Summary. Combined exposure to noise and salicylates was found to produce greater acoustic trauma induced audiogenic seizure risk than exposure to the noise alone. The result suggests that salicylates could make the mouse cochlea more vulnerable to the traumatic action of noise.

There are 2 major types of ototraumatic agents in our environment: various types of noise and ototoxic drugs. The ototoxic drugs may be classified into 2 categories. Irreversible ototoxic drugs such as kanamycin, neomycin or streptomycin, can cause irreversible damage to the inner ear structures resulting in a permanent loss of hearing, whereas reversible drugs such as quinine, salicylates or etacrynic acid usually produce a transient hearing loss, and recovery generally occurs after cessation of treatments.

An important practical, as well as theoretical, issue is whether simultaneous exposure to these 2 ototraumatic agents, i.e. intense noise and drugs, can result in the mutual potentiation of their ototraumatic effects. Available evidence appears to suggest that it can, when irreversible ototoxic drugs are used[2]. However, it is not clear if this interactive effect can be obtained when reversible ototoxic drugs are used. It has been concluded in a recent review paper that noise and salicylates do not interact and therefore salicylates should not pose additional hazards to organisms exposed to intense noise[2]. This report presents data suggesting that salicylates could in fact potentiate ototraumatic effects of noise in mice.

A high incidence of audiogenic seizures may be induced in genetically seizure resistant (BALB/c) mice by exposure to an intense noise a few days prior to testing for seizures[3]. This phenomenon has been termed priming for audiogenic seizure susceptibility. Available evidence suggests that the principle effect of the priming exposure is to cause stimulation damage to the cochlea and that this damage is the primary underlying condition for the development of susceptibility to seizures[4].

The major evidence supporting this contention includes the following: 1. acoustically primed mice tend to show a reduction of cochlea microphonic responses[4]; 2. extensive damage to outer hair cells can be produced by effective priming exposure[5]; 3. seizure susceptibility can be induced by ototoxic drugs such as kanamycin[5] and 6-aminonicotinamide[6]; 4. the effectiveness of a priming stimulus is an increasing function of its intensity[7], exposure duration[8], and acoustic energy[9], all of which are well known parameters of stimulation damage to the cochlea[10].

In view of these findings, it is reasonable to assume that priming for audiogenic seizures is a valid indirect method for evaluations of the ototraumatic effects of noise. The present study was designed to investigate whether exposure to an intense noise while under salicylate intoxication would result in a greater priming effect than exposure to the noise alone.

The underlying mechanism for the development of seizure susceptibility after the priming exposure is not known. It has been speculated that processes similar to disuse or deafferentation supersensitivity may be involved[4]. However, since this issue is not critical for the purpose of the present study, it will not be discussed further.

23-day-old BALB/c mice (± 1 day) were primed for audiogenic seizures by exposure to a bell sound (125–127 dB ref. 0.0002 dyne/cm^2) for 10 sec. These mice were then tested for audiogenic seizures by re-exposure to the same acoustic stimulus 7 days later for a maximum of 30 sec., or until seizure occurred. At the time of testing, the incidence of 4 stages of audiogenic seizures (wild running, clonic seizure, tonic seizure and death) were recorded. Each mouse was injected s.c. with either water or 500 mg/kg of sodium salicylate either 0.5, 2.5 or 6.0 h prior to the priming exposure. These intervals were selected on the basis of a physiological study on the effect of sodium salicylate on cochlea function[11]. Since the injection-priming intervals did not produce any differential effect in the 3 water control groups their results were combined, thus resulting in the formation of 4 main experimental conditions (table). 12 sham-primed mice were injected with sodium salicylate to determine the effect of salicylate exposure on seizure susceptibility. Animals were assigned to each of the experimental conditions on a split-litter basis.

90 23-day old (± 1 day) mice were used in a second experiment which followed the design of the first experiment, except that commercially available aspirin tablets (soluble) were used. This drug was given orally at a dosage level of 500 mg/kg, 0.5 h, 2.5 h, or 6.0 h, before the priming exposure. 11 sham-primed mice were injected with the same amount of aspirin to determine the effect of exposure to aspirin alone.

None of the animals exposed to sodium salicylate or aspirin alone showed any type of seizure reactions at testing, suggesting that transient disruptions of the cochlea functions by these drugs were not effective in inducing susceptibility to audiogenic seizures. The major results of experiments 1 and 2 are summarized in the table. They indicate that the proportion of animals exhibiting audiogenic seizures were higher in every noise-salicylate combined group except for the 0.5 h-noise-sodium salicylate group, than in their respective noise-exposure alone groups. Applications of the χ^2-test indicated significant overall group differences in the incidences of wild running, (experiment 1: $p < 0.01$; experiment 2: $p < 0.05$) and clonic and tonic seizures (experiment 1 only, $p < 0.01$). Thus the overall results indicate that combined exposure to salicylate and noise is more effective in inducing a priming effect than is exposure to the same noise alone. It is worth noting that extensive damage to the cochlea is required to increase seizure risk. It has been shown that in seizure-stricken mice, 70–90% of the basal turn hair cells were damaged of missing, whereas damage of less than 40% to these hair cells was found to be ineffective[5]. Thus if one accepts the previously argued assumption that the effect of priming is to some extent a reflection of the degree of cochlea dysfunction caused by priming exposure, the present findings may be taken as indirect evidence suggesting that salicylate could potentiate the ototraumatic effect of noise exposure.

The nature of the interaction between salicylate and noise is not known. Theoretically it is of interest to speculate whether the enhanced priming effect is produced by a summation of these 2 ototraumatic agents or by an interactive potentiation of their actions. If the combined effects are to be additive in nature, the ototoxic effects of both agents would have to be relatively lasting, at least up to the time of testing. However, it should be noted that testing for seizures was not conducted until 7 days after the salicylate intake, which should give the drugs sufficient time to be metabolized and excreted. Furthermore, general findings in other animals have consistently shown that salicylates do not cause obvious structural lesions to the inner ear and their ototoxic effects usually disappear within 3 days of salicylate withdrawal[11–14]. Possible disappearance of the ototoxic effects of salicylates at the time of testing suggests that the combined actions of salicylate and the priming stimulus is less likely to be the result of a simple independent summation of their separate ototoxic effects than the result of mutual potentiation. This contention is further supported by the findings of experiment 1, which shows that the enhanced effect is to some extent dependant upon the interval between salicylate intake and noise exposure (table). Furthermore, this result also indicates that the interaction could have occurred at the time of noise exposure (e.g., salicylate intake might increase the vulnerability of the cochlea to noise damage) rather than after the noise exposure (e.g., hindering recovery from a dysfunction caused by noise damage).

Potentiation of acoustic priming for audiogenic seizures by salicylates

Experimental conditions	N	Seizure reactions (% animals)		
		Wild running	Clonic seizure	Tonic seizure
Experiment 1				
Noise alone	21	38%	24%	19%
0.5 h sodium sylicylate and noise	12	25%	8%	8%
2.5 h sodium salicylate and noise	16	69%	50%	38%
6 h sodium sylicylate and noise	18	94%	83%	67%
Experiment 2				
Noise alone	23	13%	9%	4%
0.5 h aspirin and noise	23	35%	22%	17%
2.5 h aspirin and noise	22	55%	35%	27%
6 h aspirin and noise	22	45%	32%	23%

* 8 mice in the 0.5 h condition, 4 in the 2.5 h and 2 in the 6 h groups died from acute salicylate intoxication within 24 h of injection.

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