Antihistamines Block Radiation-Induced Taste Aversions

Abstract. When rats are treated with an antihistamine prior to being given sublethal doses of ionizing radiation, the formation of a conditioned saccharin aversion is completely inhibited. A profound aversion could be conditioned with histamine diphosphate as the aversive stimulus. The increase in histamine production after radiation exposure represents the physiological basis of radiation-induced taste aversions.

Garcia, Kimeldorf, and Koelling (1) found that a taste aversion to saccharin-flavored water could be conditioned in rats by pairing consumption of the sweetened fluid with a 37-r whole body exposure to gamma rays. Similar taste aversions have been conditioned by pairing saccharin intake with injections of lithium chloride (2), apomorphine (3), cyclophosphamide (4), and many other poisons. All of these treatments have been presumed to cause the animal to become "sick," and the pairing of sickness with intake of the novel saccharin solution resulted in the subsequent conditioned taste aversion. The injections of lithium chloride, apomorphine, or cyclophosphamide make the rats ill, and these rats can easily be discriminated from sham-injected controls. With whole body x-ray and gamma-ray exposures up to 100-r (5), the rats do not appear to be sick and cannot be distinguished from sham-exposed controls except by the subsequent aversion to the taste solution. This subtle and interesting reaction of the rat to the radiation stimulus was first demonstrated in 1955, and the physiological basis of a radiation-induced taste aversion has been the topic of considerable research.

The aversion phenomenon was formerly attributed to gastrointestinal disturbances (6), but considerable doubt has been cast on this explanation (7). Partial body exposures have shown that it is not necessary to irradiate the head of the rat in order to produce the taste aversion, thus eliminating vision, olfaction, taste, or audition as necessary for conditioning the aversion (8).

The studies by Hunt and his co-workers (9) with parabiotic pairs of male rats indicated that some humoral factor may be involved in conditioning the taste aversion. When the shielded (nonirradiated) partner of the parabiotic pair was allowed to drink saccharin 30 minutes after the nonshielded partner received a whole body exposure of 360-r, the shielded partner avoided the saccharin solution during a saccharin-water preference test administered 24 hours later.

We have shown that the maximal saccharin aversion develops 30 to 90 minutes after the onset of the radiation exposure (10), implying that the aversive consequence of the irradiation reaches a peak during this interval. The histamine concentration in the blood of rats exposed to 600 r of x-rays reaches a peak 60 to 120 minutes after the exposure (11). The purpose of the experiments reported below was to determine if the injection of an antihistamine prior to radiation exposure would inhibit the formation of a saccharin aversion, thus providing evidence for a causal relation between aversiveness of the irradiation and radiation-induced histamine production.

Chlorpheniramine maleate was chosen as the antihistamine because it is an active histamine antagonist, but it has a minimum of undesirable side effects (12). Naive male albino rats (N = 28) were placed on a 23.5-hour water deprivation schedule. For 5 days they were given access to water for 30 minutes per day. On day 6 (conditioning day), 14 rats were injected intraperitoneally with chlorpheniramine maleate (20 mg/kg). Immediately after the injection seven rats were exposed to 100 r of gamma rays at 9 r per minute (Chlor/100 r), and the other seven rats were sham-exposed (Chlor/sham). The remaining 14 rats were injected intraperitoneally with 0.15M NaCl (2 ml/kg). Again, seven rats were exposed to 100 r (NaCl/100 r) and seven were sham-exposed (NaCl/sham). Thirty minutes after the onset of the radiation or sham exposure all rats were allowed to drink approximately 10 ml of a 0.1 percent (weight to volume) sodium saccharin solution. This treatment regimen was chosen to assure maximal taste aversion conditioning (13). One day later, on day 7 (test day), all rats were allowed 20 minutes access to the saccharin solution. The mean intakes in milliliters) of saccharin for the 20-minute test were: Chlor/100 r, 15.6; Chlor/sham, 17.6; NaCl/100 r, 5.3; and NaCl/sham, 18.4. An analysis of variance across these means yielded an F of 16.6, and d.f. = 3,24, which was significant beyond the .01 level of significance. An orthogonal comparison indicated that the NaCl/100 r group was significantly different from the other three groups, which were not different from each other (F = 48.0; d.f. = 1,24; P < .01). These data show that the antihistamine injection completely inhibited the formation of a radiation-induced taste aversion.

Whereas the above results implicate histamine in the formation of radiation-induced taste aversions, it was necessary to demonstrate that histamine itself could indeed produce a conditioned taste aversion. Using a water deprivation regimen similar to that outlined...
above, we injected 16 rats subcutaneously on the back with either histamine diphosphate (75 mg/kg) or 0.15M NaCl (1.5 ml/kg) immediately after giving the animals 20 minutes access to saccharin (mean consumption = 10 ml). Twenty-four hours later the rats were given the usual 20-minute saccharin drinking test. Rats injected with histamine diphosphate drank significantly less saccharin (mean = 5.0 ml) than the NaCl injected controls (mean = 17.8 ml) (t = 6.31; d.f. = 14; P < .01).

These results show that it is possible to condition a pronounced taste aversion with histamine as the aversive stimulus.

Since antihistamines, in addition to their antihistaminic and antiemetic properties, produce certain central nervous system depressant effects (12), we thought it necessary to demonstrate that rats treated according to the procedure described above for chlorpheniramine do not lose their ability to learn taste aversions. Using a similar procedure, on day 6 we injected 8 rats intraperitoneally with chlorpheniramine maleate (20 mg/kg), and 16 rats intraperitoneally with 0.15M NaCl (2 ml/kg). Thirty minutes after these injections, all rats were allowed to drink approximately 10 ml of 0.1 percent saccharin solution. Immediately after saccharin drinking, 16 rats were injected intraperitoneally with a volume of 0.3M LiCl equal in weight to 1 percent of their body weight, (groups Chlor/LiCl and NaCl/LiCl). The remaining eight rats were injected intraperitoneally with a corresponding amount of 0.3M NaCl (group NaCl/NaCl). Mean intakes of saccharin (in milliliters) for the 20-minute test on day 7 were: Chlor/LiCl, 6.7; NaCl/LiCl, 5.2; NaCl/NaCl, 17.5. An analysis of variance across these means was significant (F = 62.9; d.f. = 2, 21; P < .01). An orthogonal comparison indicated that the intakes of the two groups injected with LiCl did not differ and were significantly less than that of the NaCl injected group (F = 124.1; d.f. = 1, 21; P < .01). These data indicate that rats treated with chlorpheniramine maleate are still able to learn avoidance of a taste solution if LiCl is the aversive stimulus.

Since histamine produces many different physiological effects, most of which can be blocked by appropriate doses of antihistamines, it would be premature at this time to speculate about the specific mechanisms involved in the suppression of taste aversion after irradiation. However, we do have evidence that suggests that the antimimetic properties of antihistamines are not instrumental in blocking the taste aversion formation. Prior treatment of rats with Tigan (100 mg/kg; Roche Laboratories), an effective antiemetic drug, does not inhibit the formation of radiation-induced taste aversions. The importance of the findings presented is that no other treatment has been found which could conclusively block the formation of a radiation-induced taste aversion. Marked taste aversions were observed even when the irradiation was performed while the animals were under the influence of deep ether or sodium pentobarbital anesthesia (14).

Antihistamines thus appear to be unique in their ability to suppress a radiation-induced taste aversion, a fact which strongly suggests that there is a causal relation between histamine production and "aversiveness of irradiation." This conclusion is strengthened by reports which indicate that antihistamines are effective in reducing a number of different physiological reactions associated with radiation exposure (15). For example, antihistamines have proved effective in preventing radiation-induced contraction of the gut (16) as well as reducing the early, transient incapacitation of monkeys exposed to high doses of radiation (17). Similar studies with humans have demonstrated that radiation therapy patients treated with antihistamines immediately after radiation exposure showed a marked decline in the incidence of nausea, vomiting, irritability, anorexia, and similar symptoms of radiation sickness (18). It therefore appears that increased histamine production after exposure to ionizing radiation may be the prime cause for many of the adverse physiological reactions observed in irradiated mammals.

References and Notes

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