Taste Aversions Conditioned with Partial Body Radiation Exposures

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SMITH, J. C., G. R. HOLLANDER AND A. C. SPECTOR. Taste aversions conditioned with partial body radiation exposures. PHYSIOL. BEHAV. 27(5) 903–913, 1981.—Radiation-induced taste aversion was compared in rats which received partial body exposure to the head or abdomen with rats receiving whole body irradiation. Exposure levels ranged from 25 to 300 roentgens (R). In additional groups, saccharin aversion to partial body gamma ray exposures of the abdomen were conditioned in animals which had prior experience with the saccharin solution. Aversion was measured with a single-bottle short-term test, a 24-hour preference test and by the number of days taken to recover from the aversion. Whole body exposure was most effective in conditioning the aversion, and exposure of the abdominal area was more effective than exposure of the head. Also, the higher the exposure, the stronger the aversion. Rats receiving prior experience with the saccharin did not condition as well as control rats with no prior saccharin experience. The possible role of radiation-induced taste aversion in human radiotherapy patients was discussed.

Radiation Saccharin Partial body exposure Taste aversion

IT is well established that profound taste aversions can be conditioned in rats by a single pairing of a taste substance with an exposure of ionizing radiation [12,19]. These aversions are quick to form [21,23] and are quite long lasting [12]. Similar aversions can be conditioned by pairing the taste solution with one of a variety of drugs [9,17]. It has been shown that learned food aversions are quite common among normal human subjects [10]. The implications of learned taste aversions for human cancer radiotherapy patients have been suggested by Smith and Blumsack [20] and have been tested on chemotherapy patients by Bernstein [3]. Bernstein has found that an aversion to various flavors of ice cream can be conditioned in both children [2] and adult patients [4] undergoing chemotherapy with several drugs. Although it is well known that cancer patients experience serious difficulties in eating [5, 6, 18, 26, 27], any role played by learned taste aversions in these overall dietary problems has not been investigated.

The ease with which radiation and chemotherapy drug-induced taste aversions are conditioned in laboratory animals suggests a possibility that these learned aversions may play some role in the eating habits of cancer therapy patients. The present authors are currently engaged in a program to test this hypothesis with radiotherapy patients. One facet of this program involves an intensive study of the dietary habits of radiotherapy patients at the local hospital. The other facet involves constructing a rat model simulating the conditions under which humans receive radiation treatment. The animal model is necessary since controlled research of the important parameters underlying radiation-induced taste aversion can not easily be conducted with human subjects. If taste aversion proves to be an important factor influencing the dietary habits of radiotherapy patients, then a rat model will be needed to investigate various forms of preventive and remedial procedures. Most of the presently available data on radiation-induced taste aversion in the rat has been collected from experiments employing procedures which differ from the conditions encompassing radiotherapy. Some of these differences are listed below:

(1) The most important difference involves the radiation parameters. Human patients most often receive partial body exposures in contrast to laboratory rats which in most studies receive whole body exposures. In the taste aversion literature there are only two papers describing partial body exposures [11,19] and these are not in agreement. These two experiments will be discussed subsequently in this paper.

(2) There is generally little or no control over what or when the human radiotherapy patient eats in proximity to the radiation exposure. Foods consumed may be novel or quite familiar to the patient. In the typical taste aversion experiment with the rat, the close temporal contiguity of the taste and the radiation is not critical (i.e., the pairing of the taste substance can precede or follow the irradiation by several hours and still result in an aversion [1,22]. It has been demonstrated, however, [7,16] that it was much more difficult to condition a taste aversion in the rat with a familiar rather than with a novel taste (even a taste that had been sampled only once [15]).

(3) The length of time that conditioned taste aversions last in laboratory animals has received relatively little attention.

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There is some evidence that radiation-induced taste aversions are not easily overcome [12,24] but little is known about the factors which influence the recovery rate. If radiation-induced taste aversion is easily overcome, then it is not likely that it would play any important role in the long term eating and drinking behavior of radiotherapy patients.

(4) Human radiotherapy patients most often receive multiple radiation exposures in contrast to the typical single exposures given to the rat.

(5) Compared with human radiotherapy patients, laboratory rats are normally subjected to some regimen of water deprivation during the conditioning paradigms and are generally limited to only the test conditions during the recovery period.

Given the contrasting conditions involved, it must first be shown that rats do develop taste aversions under conditions similar to those encountered by the human radiotherapy patient. Furthermore, it must be demonstrated that the aversion conditioned in the rat under these more “human-like conditions” is profound and long lasting.

The purpose of these initial experiments was to investigate the first three points mentioned above, i.e., partial body exposure, a familiar vs novel taste, and to plot the course of recovery from the aversion under these conditions.

EXPERIMENT 1

Using the saccharin consumption on a 6-hour single-bottle test, Garcia and Kimeldorf [11] found that abdominal radiation exposure (18 R/min) produced a more profound conditioned saccharin aversion than exposures to the pelvis, thorax or head. When higher exposures were delivered to the pelvis, thorax and head, a reduction of postconditioning saccharin consumption to approximately one-half the intake of controls was seen. The best conditioning was achieved with whole body irradiation. The authors concluded that while the abdomen is the most radiosensitive area with respect to the efficacy of partial body exposures in producing learned taste aversions, higher exposures of other areas of the body are sufficient in conditioning a taste aversion. Garcia and Kimeldorf cautioned that with their small collimated radiation beam it was only possible to expose part of the abdomen, thus the greater efficacy of the whole body exposure compared with the abdominal exposure may have been due to the fact that in the partial body exposure group the entire abdomen was not exposed.

Similar to Garcia et al., Smith [19] conditioned taste aversions using head and abdominal exposures (30 R/min). However, he found no difference between the head and abdominal groups. The measure of aversion used in the Smith study was a 24-hour two-bottle preference test (saccharin vs water). The discrepancy between the Smith and the Garcia and Kimeldorf studies could be the result of the different postconditioning aversion tests employed. Spector, Smith and Hollander [24] have shown that these dependent variables can be differentially sensitive in a radiation-induced taste aversion paradigm. Additional factors contributing to the different findings in these two studies might involve differences in the exposure rates and the total tissue area exposed.

In order to determine if the abdominal area is more sensitive than the head, the present experiment was designed to compare taste aversion in groups of animals receiving 100 R exposure to the head, 100 R exposure to the abdomen, 100 R whole body exposure or 0 R (Sham) exposure using both a single-bottle saccharin consumption test and a two-bottle preference test (saccharin vs water) as dependent measures. It is not known whether partial body exposure results in the profound and long lasting aversion seen with whole body exposure, since neither of the aforementioned studies [11, 19] measured the course of recovery from the aversion. In the present experiment the strength of the conditioned taste aversion was measured by examining the increase in preference scores during the postconditioning period as the rat recovered from the learned aversion.

METHOD

Subjects

Thirty-six Sprague-Dawley male, naïve albino rats bred at the Southern Animal Farm in Pratville, Alabama served as subjects. Upon arrival in the laboratory, the animals were individually housed in Hoeltge cages where Wayne rat chow and water were available ad lib prior to the start of the experiment. The animals were accustomed to the laboratory environment for a minimum of two weeks where lab temperature and humidity were automatically controlled and lighting was on a 12/12 hour light/dark cycle with light onset at 0700 hours. The subjects were randomly assigned to four treatment groups of nine rats in each group (with the restriction that the mean body weights for the four groups would be approximately equal). At the start of the experiment, the animals weighed 234-281 grams.

Apparatus

The radiation source was Cobalt 60 (Gamma beam 150, Atomic Energy of Canada, Ltd.). The port through which the gamma rays passed from the Gamma beam 150 when the Cobalt 60 was in the expose position was 16 cm by 19 cm. Two vertical lead plates were placed on either side of the radiation port leaving a 2.5 cm wide slit in the middle of the port. In order to expose either the abdomen or head of the rat, the animal was partly immobilized by being inserted into a Plexiglas tube 5.1 cm in diameter and 17.3 cm in length. The front end of the Plexiglas tube was conical with a 1.3 cm aperture for ventilation. At the other end of the cylinder a teflon plug (with a hole to accommodate the rat’s tail) was inserted and could be adjusted to inhibit movement by the rat. Three of these tubes could simultaneously be positioned laterally in front of the 2.5 cm vertical opening exposing the head, abdomen, or some other body part to the gamma rays. The two vertical lead plates were removed for the whole body exposures. The radiation exposure rate was 27.7 R/min as measured in air by a Victoreen thimble chamber.

Procedure

The experimental procedure consisted of three distinct phases: preconditioning, conditioning, and postconditioning. Preconditioning. The preconditioning regimen was implemented to accustom the animals to manipulative procedures to ensure that on conditioning days rats would drink the saccharin solution upon presentation. On Day 1 all water bottles were removed from the individual cages and fluid deprivation began. On Day 2 at 0800 hours water bottles were attached to the home cage for 60 minutes. On Days 3 and 4 at 0800 hours animals were allowed 30-minute and 10-minute water access, respectively.

Conditioning. On Day 5 the animals were given a 10-
minute presentation of 0.1% (w/v) saccharin as the conditioned stimulus (CS). This concentration of saccharin was used throughout the experiments reported here. Immediately upon cessation of this CS presentation the rats were placed in the Plexiglas cylinders and transported to the Cobalt 60 room where the unconditioned stimulus (US) was an exposure to Cobalt 60. One treatment group received an abdominal exposure of 100 R, a second treatment group received a head exposure of 100 R, and a third group received a 100 R whole body exposure. One sham-exposed group was placed in the irradiation cylinders, transported to the radiation source, confined for the 3.6-minute period, but not exposed. Following the irradiation or sham exposure, the animals were returned to their home cages where they remained without fluid until the next day.

Postconditioning. The postconditioning phase began on Day 6, approximately 23 hours after the CS presentation. All groups received a 10-minute single-bottle, saccharin consumption test. Immediately after the 10-minute test, a 23-hour two-bottle preference test (saccharin vs water) was initiated. After the 23-hour preference test, on Day 7, the bottles were removed, weighed, and the data were converted into saccharin preference scores which represented the percentage of the total fluid intake which was saccharin solution. On each subsequent day at 0800 hours the bottles were removed, weighed, and refilled with fresh solutions. The position of the bottles were reversed each day to note any position habits. Two-bottle preference testing was continued for each experimental group for the next 19 days.

All statistical analyses were nonparametric [13]. The presence of statistical differences among the groups was determined using a Kruskal-Wallis H-test. Paired comparisons were performed using one-tailed Mann-Whitney U-tests. The standard 0.05 level of statistical significance was employed.

RESULTS

In the preconditioning period (Days 2, 3 and 4) it was noted that the rats drank the water during the access periods. In spite of this procedure, two rats were from the whole body and one from the sham treatment group, failed to drink saccharin on conditioning day and were eliminated from the experiment. The median saccharin consumptions during the conditioning trial from each of the four groups were not significantly different (Kruskal-Wallis H=6.64, p>0.05).

The median saccharin consumptions for all groups during the postconditioning 10-minute single-bottle saccharin test are presented in the first line of Table 1. An orderly increment in saccharin intake from whole body, abdomen, head and sham-exposed animals can be seen. The Kruskal-Wallis test demonstrated significant differences among the four groups (H=20.6, p<0.001). Mann-Whitney paired comparisons indicated that all four groups were different from each other (all p’s <0.05).

The median saccharin preference scores from the first 23-hour postconditioning two-bottle test are presented in the second line of Table 1. A Kruskal-Wallis analysis detected significant differences among the groups (H=18.6, p<0.001). Except for the comparison between the head and abdomen groups (U=27.5, p>0.10), Mann-Whitney tests between each of these pairs of medians were all significant (all p’s<0.05).

The median saccharin preference scores over 19 postconditioning days for all groups are plotted in Fig. 1. In order to quantify recovery, an area score was calculated for each group by integrating the area under each animal’s saccharin preference curve for the 19 days of testing [24]. The area scores for all groups on Day 19 are shown in the third line of Table 1. The Kruskal-Wallis test found significant differences among the groups (H=11.7, p<0.05). Paired comparisons demonstrated no difference between the area scores in the abdomen, head, and whole body groups, with the exception that the sham group was significantly different from all of the irradiated groups (U=13, p<0.05).

DISCUSSION

In this experiment it has been shown that conditioned taste aversions can be formed by pairing saccharin flavored water with either a 100 R whole body, head or abdominal exposure to gamma rays. The aversion as measured by daily 23-hour two-bottle preference tests lasts from about 4 to 19 days depending on the region of the body irradiated.

The fact that the abdominal and head-exposed groups differed on the short-term single-bottle saccharin test, but not on the 23-hour two-bottle test replicates the conclusion of both Garcia and Kimeldorf [11] and Smith [19]. The difference between head and abdomen groups is apparently short-lived. From the Garcia and Kimeldorf study [11] it is clear that the difference in head and abdomen exposures lasts for at least six hours.

The findings of the present study are limited to 100 R exposures and it must be emphasized that in the rat, 100 R partial body exposure may not be comparable to the typical exposure employed in the human radiotherapy situation.

EXPERIMENT 2

In Experiment 1 it was shown that taste aversion was more severe when saccharin ingestion was paired with abdominal radiation exposure than when paired with head exposure as measured by the 10-minute test. However, this difference was short-lived and the rate of recovery from the aversion in the two groups was very similar. With human patients, it has been suggested by Smith and Blumsack [20] that

<table>
<thead>
<tr>
<th>Area of Body Exposed</th>
<th>Whole Body</th>
<th>Abdomen</th>
<th>Head</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-minute Saccharin*</td>
<td>1.1</td>
<td>4.2</td>
<td>8.3</td>
<td>12.8</td>
</tr>
<tr>
<td>1st 23-hour Preference†</td>
<td>0.03</td>
<td>0.26</td>
<td>0.38</td>
<td>0.91</td>
</tr>
<tr>
<td>Area score Day 19‡</td>
<td>8.92</td>
<td>14.30</td>
<td>13.43</td>
<td>17.22</td>
</tr>
</tbody>
</table>

*Median saccharin consumptions during the postconditioning 10-minute single-bottle test for all groups in Experiment 1.
†Median saccharin preference scores on the first 23-hour postconditioning test for all groups in Experiment 1.
‡Median Day 19 area scores for all groups in Experiment 1.
individuals receiving long term radiation therapy to the abdominal area report more severe problems with nausea and overall eating behavior. Since it is quite possible that the radiation exposures that rats received in Experiment 1 are not comparable to those which humans receive in the clinical situation, it is necessary to study the formation and the longevity of radiation-induced taste aversions with a wider range of radiation exposures. The purpose of Experiment 2 was to examine the efficacy of abdominal exposures of 25 R, 50 R, 100 R, 200 R and 300 R in conditioning taste aversions. As in Experiment 1, the dependent measures used to test for conditioned taste aversion were a 10-minute single-bottle saccharin consumption test and a series of daily two-bottle preference tests (saccharin vs water). The latter measure allows for observation of the recovery from the aversion over time.

METHOD

Subjects

Thirty-six Sprague-Dawley male, naive albino rats obtained from the Southern Animal Farm served as subjects. Upon arrival in the laboratory, the animals were adapted to the environment in the same manner as described in Experiment 1. At the culmination of the adaptation period, the subjects were assigned to one of four treatment groups (25 R, 50 R, 200 R, and 300 R) with nine animals in each group. At the start of the experiment the animals weighed 223–293 grams.

Procedure

The procedures for the preconditioning, conditioning and postconditioning phases were identical to those described in Experiment 1. Following the saccharin presentation (CS) on conditioning day, the animals were transported to the Cobalt room where abdominal exposures of either 25 R, 50 R, 200 R, or 300 R were delivered. Twenty-three hours following the conditioning trial, a postconditioning 10-minute single-bottle saccharin consumption test was administered, followed by a 23-hour two-bottle preference test (saccharin vs water). Two-bottle preference testing was continued for 19 postconditioning days. Because the procedures were identical to Experiment 1, the data for two groups (Sham and Abdomen 100 R) were added from Experiment 1 for the analysis.

The statistical procedures employed were the same as those in Experiment 1.

RESULTS

During the conditioning trial, three animals, one from the sham, one from the 200 R, and one from the 300 R treatment groups, failed to drink saccharin during the 10-minute CS presentation and their data were discarded.

The median saccharin consumptions on the postconditioning 10-minute single-bottle test for all groups can be seen in Fig. 2. Saccharin consumption decreased as a function of increasing radiation exposure. A Kruskal-Wallis analysis demonstrated the presence of significant differences in the saccharin consumptions of the six groups (H=36.7, p<0.001). With the exception of the Sham vs 25 R groups (U=31, p>0.10), and the 200 R vs 300 R groups (U=29.5, p>0.10), paired comparisons demonstrated that all groups were different from each other (all p's >0.05).

The median saccharin preference scores on the first 23-hour postconditioning two-bottle test for each group can also be seen in Fig. 2. Saccharin preference scores decreased as a function of increasing radiation exposure. A Kruskal-Wallis analysis of these scores indicated the presence of significant differences among the groups (H=36.4, p<0.001). With the exception of the Sham vs 25 R (U=18.5, p>0.05), 100 R vs 200 R groups (U=22, p=0.10), and the 200 R vs 300 R groups (U=24, p>0.10), Mann-Whitney U-tests between each of the pairs of medians were significant (all p's <0.05). Since the 25 R group did not differ from the Sham group on the postconditioning 10-minute test and on the first 23-hour postconditioning two-bottle test, they were discontinued and were not included in further data analysis.

In Fig. 3, median saccharin preference scores are plotted.
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for the 19 postconditioning days. As can be seen, the sham-exposed rats showed a strong preference for saccharin throughout the experiment. An area score was computed for each group encompassing the 19 days of testing. The Kruskal-Wallis analysis of the area score on Day 19 postconditioning indicated the presence of significant differences among the five groups (H=22.5, p<0.001). Paired comparisons of the area scores demonstrated that the Sham group differed significantly from each of the irradiated groups (all p's<0.05). It was also noted that the 50 R group differed from the 200 R and 300 R groups; and the 100 R group differed from the 300 R group. All other comparisons were not significant.

DISCUSSION

In general, the higher the radiation exposure, the more pronounced was the subsequent aversion. In addition, the radiation exposures used tended to result in three kinds of effects. The group receiving the lowest abdominal exposure (25 R) showed essentially no aversion. The groups receiving intermediate abdominal exposures (50 R and 100 R) differed from each other on initial tests but showed comparable recovery over the 19 day test period. The groups receiving the higher abdominal exposures (200 R and 300 R) showed profound initial aversion and little sign of recovery during the extended testing period.

FIG 2. Median saccharin consumptions on the postconditioning 10-minute single-bottle test for all groups in Experiment 2 (open triangles). Median saccharin preference scores on the 1st 23-hour postconditioning two-bottle test for all groups in Experiment 2 (open circles).

FIG 3. Daily median saccharin preference scores over 19 postconditioning days for all groups in Experiment 2.
EXPERIMENT 3

In Experiment 2, the magnitude of the aversion was shown to be directly related to the level of abdominal radiation exposure. The purpose of Experiment 3 was to see if increasing the radiation exposure of the head would result in a more severe taste aversion.

METHOD

Subjects

Eighteen naive, male albino rats weighing 235–289 grams were housed and fed as in Experiments 1 and 2. Animals were assigned to one of two treatment groups (Head 200 R or Head 300 R) with nine rats in each group.

Procedure

The procedure was identical to that of Experiments 1 and 2. Following the 10-minute CS (saccharin) drinking period, one group received a 200 R exposure to the head and the second group received a 300 R head exposure. Twenty-three hours after the conditioning trial, the rats received a postconditioning 10-minute single-bottle saccharin consumption test followed by a 23-hour two-bottle preference test (saccharin vs water).

The 100 R head exposed group from Experiment 1 was included in the analysis of the results from this experiment.

RESULTS

The median saccharin consumptions on the postconditioning 10-minute single-bottle test for each of the three head exposure groups (100 R from Experiment 1) can be seen in the upper panel of Fig. 4. A Kruskal-Wallis test did not detect any significant differences among the groups (H=3.79, p>0.10). The median saccharin preference scores on the first 23-hour postconditioning two-bottle tests are plotted in the lower panel of Fig. 4. A Kruskal-Wallis analysis of these preference scores found no differences among these groups (H=1.09, p>0.10). The recovery from the conditioned aversion over the 19 day postconditioning period is illustrated in Fig. 5. A Kruskal-Wallis analysis of the area scores for the three head-exposed groups for Day 19 was not significant (H=1.45, p>0.10).

Completion of the data collection in Experiment 3 made it possible to compare taste aversion resulting from head and abdomen exposures at all exposure levels (100 R, 200 R, 300 R) used in Experiments 1 and 2. As can be seen in the upper panel of Fig. 4, at each exposure level animals from the abdominal groups drank less saccharin than the head groups in the postconditioning 10-minute single-bottle saccharin test. These differences were all significant: 100 R (U=14.5, p <0.01), 200 R (U=8, p <0.005), 300 R (U=2, p<0.001). The same general result was obtained with the first 23-hour postconditioning two-bottle preference test as can be seen in the bottom panel of Fig. 4. However, the difference between abdominal and head exposure at the 100 R level did not reach statistical significance (U=27.5, p>0.10). The recovery curves for the abdominal and head exposures for each of the three radiation exposure levels can be seen in Fig. 6. No differences were found in the Day 19 postconditioning area scores between the abdominal and head groups at both the 100 R (U=34, p>0.10) and 200 R (U=22, p=0.10) levels. The difference between the abdominal and head groups at the 300 R exposure level was significant (U=10, p<0.01).

DISCUSSION

In contrast to the results observed with abdominal exposure presented in Experiment 2, increasing radiation exposure to the head had no effect on the magnitude of the subsequent taste aversion as measured by the short-term single-bottle test, the 23-hour preference test or by the time taken to recover from the conditioned aversion.

As the radiation exposure was increased from 100 R to 300 R, the difference between abdominal and head exposure became apparent. This finding is consistent with earlier results reported by Garcia and Kimeldorf [11]. Since histamine has been shown to play an important role in radiation-induced taste aversion [14], it is possible that the difference between head and abdominal irradiation seen in these experiments reflects a difference in the amount of histamine resulting from the radiation exposure of these respective body regions. One could speculate that a 100 R exposure produces...
the maximum histamine possible in the head region and that
increasing the exposure to 200 R or 300 R has little additional
effect. In contrast, abdominal exposures of 300 R could
result in more histamine than the 100 R or 200 R exposures and
therefore result in the graded effect of taste aversion learning
demonstrated in Experiment 2.

EXPERIMENT 4
The first three experiments have demonstrated that taste
aversions can be conditioned in the rat with partial body
exposures to the abdomen or head. Moreover, it has been
shown that when the radiation exposure is high, the abdo-
men is more sensitive than the head in conditioning an aves-
sion. As was stated earlier in this paper, in order to establish
an appropriate animal model for learned taste aversion in the
human radiotherapy patient, an attempt must be made to
condition rats employing both partial body exposures and
familiar taste substances.

In rats it has been shown that previous experience with the
taste solution reduced the magnitude of the aversion [16]. As
little as one 20-minute exposure to saccharin on the day pre-
ceding the conditioning trial can markedly reduce taste
aversion learning [25]. McLaurin et al. [15] reported that
with an exposure as low as 64 R, prior experience with the
taste solution inhibited the conditioning of a radiation-
induced saccharin aversion, while subjects receiving the
same low dose and having no previous experience with the
taste solution exhibited a profound saccharin aversion. By
increasing the radiation exposure, an aversion can be con-
tioned with a familiar taste substance [8]. The purpose of
Experiment 4 was to examine the effects of limited preexpos-
ure to the taste solution (CS) on the conditioning of a partial
body radiation-induced taste aversion using abdominal ex-
posures with varied radiation levels. Of interest was whether
CS familiarity attenuates learned taste aversion in rats
treated with various levels of abdominal radiation exposure.
Particular emphasis was placed on whether the recovery
from the aversion is more rapid when the subjects had pre-
exposure to the taste solution.

METHOD

Subjects
Fifty-four Sprague-Dawley male, naive rats weighing
210-301 g, were housed and fed as in Experiment 2. They
were assigned to six groups (Sham, 25 R, 50 R, 100 R, 200 R,
or 300 R) of nine animals in each group.

Procedure
The procedure was identical to that of Experiment 2, ex-
cept that two 10-minute saccharin habituations (2H) were
given on Days 5 and 6 of the preconditioning phase of the
experiment. Thus, the conditioning trial for all groups was

FIG. 5. Daily median saccharin preference scores over 19 postconditioning days for all
groups in Experiment 3.
FIG. 6. Upper panel: Daily median saccharin preference scores over 19 postconditioning days for abdomen and head 100 R. Middle panel: Daily median saccharin preference scores over 19 postconditioning days for abdomen and head 200 R. Lower panel: Daily median saccharin preference scores over 19 postconditioning days for abdomen and head 300 R.

FIG. 7. Median saccharin consumptions on the postconditioning 10-min single-bottle test for all groups in Experiment 2 (OH) and Experiment 4 (0H).

given on Day 7, and consisted of a 10-minute saccharin presentation followed by the appropriate abdominal radiation exposure. A control group received the two prior CS exposures to saccharin and on conditioning day received saccharin paired with sham exposure. The postconditioning phase began on Day 8. The rats all received a 10-minute saccharin test followed by the initiation of a 23-hour two-bottle preference test. Preference measures were continued for 12 postconditioning days.

RESULTS

The median saccharin consumptions for all groups during the postconditioning 10-minute saccharin test are plotted in Fig. 7. A Kruskal-Wallis analysis of variance indicated the presence of significant differences among the six exposure levels ($H = 34.8$, $p < 0.001$). To allow for comparison, the medians from comparably irradiated groups which had no prior experience with saccharin (OH, taken from Experiment 2) are also plotted in Fig. 7. It is evident that the magnitude of the aversions measured by the 10-minute test are greater for the groups that received no experience with the saccharin prior to the conditioning trial. At each exposure level, the difference between the 0H (Experiment 2) and the 2H (Experiment 4) groups was significant beyond the 0.01 level when tested with the Mann-Whitney U statistic.
The medians for the first 23-hour saccharin preference scores are plotted in Fig. 8. The Kruskal-Wallis analysis across the five irradiation conditions was significant ($H = 39.2, p < 0.001$). The first 23-hour median preference scores for the comparably irradiated groups from Experiment 2, that received no experience with saccharin prior to conditioning, are also plotted in Fig. 8. At each radiation level except 300 R, the 0H groups show more aversion than the 2H groups.

The 25 R, 50 R, and 100 R groups (2H) were discontinued after the second day of preference testing since they had no longer demonstrated a significant difference from the Sham group. Median recovery curves for the 200 R and the 300 R groups can be seen in the upper and lower panels of Fig. 9. To allow for comparison, the median recovery curves of the 200 R and 300 R groups which received no experience with saccharin prior to conditioning (0H, Experiment 2) are also plotted in Fig. 9. Mann-Whitney paired comparisons indicated that the area scores (Day 12) in the 0H groups (Experiment 2) were significantly lower than those in the 2H groups (Experiment 4) at both the 200 R and 300 R exposures (all $p$'s < 0.05).

**DISCUSSION**

In Experiment 2 it was demonstrated that abdominal radiation exposure, ranging from 50 R to 300 R, is a sufficient US when conditioning a saccharin aversion in rats. The present experiment shows that this is still the case even when rats have received two saccharin preexposure trials. In these 2H groups the magnitude of the conditioned aversion was directly related to the level of radiation exposure as measured by the 10-minute test and the first 23-hour saccharin preference score. This finding was similar to that obtained with the 0H groups in Experiment 2.

Although the two saccharin preexposure trials did not
block conditioning, they did have an attenuating effect. There are primarily three indications of this attenuation. First, at all radiation exposure levels the 2H groups consumed significantly more saccharin than the 0H groups (Experiment 2) during the 10-minute test. Second, the 2H groups had higher saccharin preference scores than the 0H groups at all radiation exposure levels except 300 R. The fact that no significant difference was detected between the 0H and 2H groups at 300 R possibly reflects the influence of a "floor effect." Finally, it is clearly evident that the animals in the 2H groups exhibited a facilitated recovery from the aversion compared with the 0H groups. Animals in the 2H groups receiving 25 R, 50 R and 100 R had recovered by the second postconditioning day. Furthermore, animals in the 2H groups had significantly higher area scores (Day 12) than those in the 0H groups with exposures of 200 R and 300 R. Therefore, it can be concluded that the magnitude of the aversion was much greater in the 0H groups at all the radiation exposure levels.

GENERAL DISCUSSION

The findings from these experiments demonstrate that partial body radiation exposure can serve as an adequate US in taste aversion conditioning. However, the magnitude of the aversion depends on the level of radiation to which the rat is exposed and the region of the body irradiated. The abdominal region appears to be more sensitive to increases in radiation exposure than the head region. This is based on the results of the first 3 experiments in which increasing abdominal radiation exposure generally resulted in stronger taste aversions. In contrast, head exposures of 100 R, 200 R, and 300 R all resulted in comparable levels of conditioning. At the higher radiation levels, abdominal exposure was more effective in conditioning than head irradiation as demonstrated by the initial magnitude and longevity of the taste aversions which subsequently developed. It is interesting to note that increasing the abdominal radiation exposure not only resulted in more severe taste aversion initially, but also prolonged the recovery from the aversion.

It is apparent from the results of Experiment 4 that the presentation of two saccharin preexposure trials attenuates the conditioning of a saccharin aversion when abdominal radiation exposure is employed as the US. This is consistent with previous findings in this laboratory [24] using whole body radiation exposures in rats. This CS preexposure effect was observed in both the initial magnitude of the aversion and its subsequent longevity. It should be emphasized that the two CS preexposure trials merely attenuated conditioning but did not prevent the formation of a taste aversion. If the CS preexposure training were more extensive, then perhaps the taste aversion could have been totally blocked. Indeed, evidence from other investigators using either whole body radiation exposure or various toxic drugs suggest this may be possible [7, 8, 15].

Since learned taste aversions have been shown to occur in human cancer patients undergoing chemotherapy [4], it is conceivable that radiotherapy patients can similarly develop taste aversions. Both radiation and antineoplastic drugs (e.g., cyclophosphamide) serve as effective USs in taste aversion conditioning in laboratory rats. However, the relationship between these toxins, with reference to their temporal course of action and their dose-response equivalence, remains unclear. Furthermore, it is unknown to what extent the physiological effects of various radiation exposures are comparable in rat and man. Nevertheless, the fact that taste aversion does occur in rats given partial body radiation exposures and with taste substances which are somewhat familiar, lends further support to the possibility that learned aversions might play a role in the dietary abnormalities of human cancer radiotherapy patients. These studies employed only single exposures to the gamma rays. Human patients normally receive fractionated exposures often protracted over several weeks. A more adequate "rat model" of the radiotherapy patient would be a rat receiving multiple conditioning trials over several days. Using our rat model, studies of interactions among multiple trials, partial body exposures and various levels of familiarity with the taste substance are now in progress in our laboratory. In addition, systematic observations are being made of the foods ingested by radiotherapy patients during the course of radiation therapy.

REFERENCES


