CORRESPONDENCE

Radiation-Induced Taste Aversion: Effects of Radiation Exposure Level and the Exposure–Taste Interval

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Radiation-induced taste aversion has been suggested to possibly play a role in the dietary difficulties observed in some radiotherapy patients. In rats, these aversions can still be formed even when the radiation exposure precedes the taste experience by several hours. This study was conducted to examine whether increasing the radiation exposure level could extend the range of the exposure–taste interval that would still support the formation of a taste aversion. Separate groups of rats received either a 100 or 300 R γ-ray exposure followed 1, 3, 6, or 24 h later by a 10-min saccharin (0.1% w/v) presentation. A control group received a sham exposure followed 1 h later by a 10-min saccharin presentation. Twenty-four hours following the saccharin presentation all rats received a series of twelve 23-h two-bottle preference tests between saccharin and water. The results indicated that the duration of the exposure–taste interval plays an increasingly more important role in determining the initial extent of the aversion as the dose decreases. The course of recovery from taste aversion seems more affected by dose than by the temporal parameters of the conditioning trial. © 1986 Academic Press, Inc.

INTRODUCTION

Rats that consume distinctly flavored novel foods or fluids immediately followed by the administration of a poison will avoid ingesting those same foods or fluids on future presentations. This is referred to as a learned taste aversion and has been shown to occur in a wide variety of animals including humans (1–4) and with a wide variety of toxins including ionizing radiation (5–7).

Cancer patients can experience significant loss of appetite during the course of the illness [e.g., (8)]. Alterations in metabolism [e.g., (10)], changes in absorption [e.g., (9)], and anorexia [e.g., (10)] associated with neoplastic disease and/or with the direct effects of treatment are known to occur and to affect eating behavior. Recently, it has been suggested that the cachexia observed in cancer patients receiving chemotherapy or radiation treatment might be due, in part, to learned taste aversions (1, 4, 11).

Work done in this laboratory has shown that radiotherapy patients dramatically reduce their intake of initially preferred fruit juice over the course of the radiation treatment period after only a few pairings of that particular juice with abdominal radiation exposure (4). Furthermore, in a very abbreviated clinical survey, 50% of the cancer patients interviewed receiving abdominal radiation treatment showed evidence of a food aversion (4).
Concomitant with the above clinical studies, this laboratory has been developing an animal model in an attempt to simulate the conditions encompassed in radiation treatment (4, 7, 12, 13). The impetus behind this effort has been the prospect of delineating more clearly the circumstances under which radiation-induced taste aversions occur and how these learned aversions can be prevented or eliminated. Much of this research has focused on radiation dose, body region exposed, frequency of taste–radiation pairings, and the level of familiarity of the tastant. The present report is concerned with the temporal parameters involved in the taste–radiation pairings.

It has been known for some time that taste aversion conditioning can still occur in rats even if the taste experience and the exposure to ionizing radiation are separated by 12 h (forward conditioning) (14, 15). Interestingly, when rats are exposed to ionizing radiation first and then receive the tastant several hours later, these animals still form an association between the effects of the radiation and the tastant (backward conditioning). Ionizing radiation is unique in this respect since most other toxins must be presented either simultaneously with or following the presentation of a tastant for a learned aversion to form [e.g., (14)]. The temporal aspects of an effective taste aversion conditioning trial seem to be dependent on a particular toxin’s time course of action and duration of effect.

Carroll and Smith (16) demonstrated that water-deprived rats given a 100 R whole-body 60Co exposure and then immediately presented with a normally preferred saccharin solution drank steadily for 90 min and then abruptly terminated intake in contrast to control animals. These investigators suggested that the onset of the “aversive” physiological consequences of the radiation occurred approximately 90 min following exposure. Therefore, if a tastant were given anytime up to 90 min following a 100 R whole-body radiation exposure, it should result in a forward pairing since the taste is preceding the pertinent physiological effect of the radiation. Similarly, if the duration of the radiation-induced physiological effect is long enough, then presenting the tastant beyond 90 min postirradiation should at least result in a somewhat contiguous pairing of the tastant with the effects of the radiation. The point here is that what may seemingly be backward conditioning in a radiation-induced taste aversion paradigm may actually be forward conditioning if one considers the physiological effects of the radiation rather than the time of its administration. This is important since in most classical conditioning procedures backward conditioning paradigms are considered to be relatively ineffective.

Barker and Smith (14) systematically varied the interval separating a 100 R radiation exposure and the presentation of a novel saccharin solution. They found that radiation–saccharin intervals as long as 6 h still resulted in the formation of a saccharin aversion. This suggests that the “aversive” effects of a 100 R whole-body radiation exposure may last for at least 6 h. In general, the longer the radiation-tastant interval the lesser was the magnitude of the subsequent taste aversion.

Very little is known how radiation dose would interact with the radiation–tastant interval. There is reason to believe that increasing the dose would widen the effective range of this interval, since increasing the dose generally increases the severity of a learned aversion across a wide variety of experimental conditions (17). Furthermore, it is known that various tissues in the body are differentially sensitive to the damaging effects of ionizing radiation (18). Increasing the dose might broaden the range of
adverse physiological effects; some of these effects might vary in their latency of onset and thus effectively extend the maximum radiation–tastant interval that would support the formation of a learned taste aversion. The purpose of this study was to examine the effects of radiation dose on the conditioning of a taste aversion while systematically varying the radiation–tastant interval.

**METHOD**

**Subjects.** Seventy-two Sprague–Dawley male, naïve albino rats (Southern Animal Farm; Pratville, Alabama) served as subjects. Upon arrival in the laboratory the animals were individually housed in Holtge cages where Wayne Rat Chow and water were available *ad libitum* prior to the start of the experiment. The animals were accustomed to the laboratory environment for a minimum of 2 weeks where temperature and humidity were automatically controlled and lighting was on a 12/12 h light/dark cycle with light onset at 0700 h. At the start of the experiment the rats weighed 229–384 g.

**Procedure.** The experimental procedure consisted of three distinct phases: preconditioning, conditioning, and postconditioning.

**Preconditioning:** The preconditioning phase of the experiment was implemented to accustom the animals to manipulative procedures to ensure that the animals would drink the conditioned stimulus solution (saccharin) upon presentation during the future conditioning trial. On Day 1 all water bottles were removed from the individual cages and fluid deprivation began. On Day 2, at 0800 h the animals were given access to water for 60 min. On Day 3 animals were given access to water for 30 min.

**Conditioning:** On Day 4 the animals were randomly divided into nine groups of eight. Each group differed in either the radiation dose it was to receive (0, 100, 300 R) or the duration of the temporal interval separating radiation exposure and the subsequent presentation of the conditioned stimulus (1, 3, 6, or 24 h).

At 0800 h on Day 4, all groups received a 10-min access to water. The groups received their radiation exposure at various times throughout Day 4 and the early portion of Day 5 such that all groups could receive their saccharin presentation at approximately the same time (0800) on Day 5. When it was time for a specific group to be irradiated the animals were placed in individual Plexiglas chambers and transported to the room containing the *60Co* source (Gamma Beam 150, Atomic Energy of Canada, Ltd). This was done in darkness if it occurred during the night. These animals then received a whole-body radiation exposure (except for sham animals) at a rate of 20.0 R/min as measured in air by a Victoreen thimble chamber. Following radiation exposure, the rats were returned to their home cages where they remained without fluid for the prescribed interval of time at the end of which they received a 10-min presentation of a 0.1% (w/v) sodium saccharin solution (conditioned stimulus). Some animals failed to drink saccharin during the conditioning trial, and they were discarded from the experiment resulting in the following altered group sizes: 100 R-1 h (*n* = 7), 100 R-24 h (*n* = 6), 300 R-24 h (*n* = 6). Following the presentation of the conditioned stimulus (saccharin) on Day 5, the animals were deprived of fluid for the next 24 h.

Rats in the SHAM-1 h group were treated identically to the rats in the 100 R-1 h group except that the *60Co* source was not raised from its shielded housing.

**Postconditioning:** The postconditioning phase began on Day 6. At 0800, all groups began a 23-h two-bottle preference test between 0.1% saccharin and water. After the 23-h preference test the bottles were removed, refilled with fresh solutions, and replaced on the cages in reverse position. Two-bottle preference testing was continued in this fashion for a total of 12 days.

**Dependent measures.** To quantify the initial extent of the aversion, a saccharin preference score was computed for each animal for both of the first two postconditioning days:

\[
\text{saccharin preference score} = \frac{\text{saccharin intake (ml)}}{\text{total fluid intake (ml)}}
\]

The saccharin preference scores for Days 6 and 7 were averaged and served as an animal's "S score" representing the initial magnitude of the aversion. The Arcsin-Root transformations of the scores were used in the statistical analyses (19).

To quantify the persistence of and recovery from the aversion, saccharin preference scores were computed daily and an area score was calculated for each animal by integrating the area under the curve of saccharin preference scores across the 12-day postconditioning period (7).
The presence of statistical differences among the groups was determined using two-way ANOVAs. Dunnett's procedure was employed for comparisons between the control and experimental groups (20). The standard 0.05 level of statistical significance was employed.

RESULTS

The mean S scores for all of the groups can be found in Fig. 1. The two-way ANOVA revealed significant main effects for both dose [$F(1,58) = 15.02; P < 0.01$] and interval [$F(3,58) = 6.14; P < 0.01$], with a significant interaction [$F(3,58) = 3.30; P < 0.05$]. The SHAM-1 h control group significantly differed from each of the irradiated groups [all $P$'s $< 0.01$; overall $F(1,58) = 104.14; P < 0.01$]. A close inspection of Fig. 1 reveals that the radiation–taste interval had a much greater effect on the groups receiving a 100 R, as opposed to a 300 R exposure.

Figure 2 contains the mean 12-day area scores computed for all groups. A two-way ANOVA revealed a significant main effect for dose [$F(1,51) = 8.99; P < 0.01$]. Although there was a tendency for the 12-day mean area score to be directly related to the length of the radiation–taste interval, especially for the 100 R groups, there was not a significant main effect for interval [$F(3,51) = 1.99; P > 0.10$]. Likewise, the interaction between

![Fig. 1](image-url)  
**Fig. 1.** The mean S score derived from the first two 23-h two-bottle saccharin preference tests is plotted as a function of the radiation–taste delay. The Y axis represents the mean of the proportion of fluid intake which was saccharin during the first two postconditioning test days for the various groups. The X axis represents the duration of the interval separating the radiation exposure from the taste experience.
dose and interval was not significant \( F(3,51) = 0.71; P > 0.25 \). Therefore, it would seem that the duration of the radiation–taste interval plays an increasingly more important role in determining the initial extent of the aversion as the dose decreases. However, differences in the initial magnitude of an aversion among groups which are attributable to the radiation–taste interval are relatively transient. The course of recovery seems more affected by dose than by the temporal parameters of the conditioning trial.

**DISCUSSION**

Overall, these results demonstrate that a radiation-induced taste aversion can be conditioned even when up to 24 h separate the radiation exposure and the presentation of the tastant. Moreover, the effectiveness of radiation exposure at any interval condition was augmented by increasing the dose. When separate ANOVAs of the 12-day area scores were conducted comparing each of the irradiated groups with the SHAM-1 h control group, only the groups receiving 300 R and the 100 R-1 h group were significantly different from the nonirradiated animals. Collectively, the data suggest
that radiation-induced taste aversions are transient when the conditioned stimulus follows a 100 R exposure, especially by 3 h or more. On the contrary, when the dose is increased to 300 R, radiation–taste intervals of up to 24 h can still produce aversions that have a relatively more pronounced longevity. It seems reasonable to conclude that increasing the dose does indeed extend the effective range of the radiation–taste interval that will support the formation of a conditioned taste aversion.

The nature of the physiological effects of the radiation exposure which are involved in the conditioning of a taste aversion are not clearly understood. There is some evidence that a histamine release may be involved (21). However, there is some disagreement regarding this hypothesis (22, 23). There are also indications that the area postrema, a midline circumventricular organ on the floor of the fourth ventricle in the caudal brainstem, is involved in the formation of radiation-induced taste aversions (24, 25). Regardless of the exact nature of the physiological mechanisms underlying radiation-induced taste aversion, it is important to investigate dose–response effects so that data collected from the rat will be clinically meaningful since dose equivalence between rat and man remains unclear.

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REFERENCES