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Emesis in Ferrets Following Exposure to Different Types of Radiation: A Dose-Response Study

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Ferrets were exposed to gamma rays (^{60}Co), fission neutrons, high-energy electrons (18.5 MeV), or iron particles (^{56}Fe, 600 MeV/amu) in order to establish the dose-response relationships for emesis following exposure to different types of radiation. The results showed that the mean effective doses (ED_{50}s) for iron particles (35 cGy) and neutrons (40 cGy) were similar. High-energy electrons were the least effective radiation, with an ED_{50} of 138 cGy. Gamma rays, with an ED_{50} of 95 cGy, showed an intermediate effectiveness. The results suggest that the relative effectiveness of different types of radiation generally increases with an increase in linear energy transfer (LET), although LET is not completely predictive of relative behavioral effectiveness.

AS THE EXPLORATION of space moves from missions in low-Earth orbit to long-duration missions outside the magnetic field of the Earth, astronauts will be exposed to different types of radiation, primarily from galactic cosmic rays. Galactic cosmic rays are composed of alpha particles, protons, and particles of high energy and charge (HZE particles). Exposure to sublethal doses of ionizing radiation produces a number of behavioral responses. One of the more common responses is emesis. Because nausea and emesis can affect the performance capabilities of astronauts, it may be of some importance to determine the relative effectiveness of different types of radiation in producing vomiting.

There is suggestive evidence to indicate that the frequency of emesis may vary as a function of the type of radiation, as well as radiation dose. Working with a suprathreshold dose of fission neutrons (1500–2000 cGy), Young (13) reported that increasing the proportion of neutrons in a mixed neutron/gamma field increased the number of bouts of vomiting in an individual monkey, but did not produce an increase in the total number of monkeys that vomited. Using the conditioned taste aversion (CTA) paradigm in rats as a model system to study the behavioral toxicity of different types of radiation, Rabin et al. (10) reported significant differences in the behavioral toxicity of high-energy iron particles (^{56}Fe, 600 MeV/amu), fission spectrum neutrons, gamma rays (^{60}Co) and high-energy electrons. Because the functional effects of a CTA and emesis are similar (i.e., to limit the intake and/or absorption of toxic foods (9,11)), these results might suggest that the sensitivity for emesis would also vary as a function of the type of radiation as well.

The present experiment was designed to establish the dose-response relationships between exposure to different types of radiation and emesis in the ferret. The ferret (*Mustela putorius furo*) has been introduced recently as a useful model to study emesis because its response to radiation exposure and to treatment with emetic compounds is similar to the human response to such stimuli (3,5,7).

METHODS

Subjects: The subjects were 131 adult male ferrets weighing between 0.9–1.4 kg obtained from Marshall Farms (North Rose, NY). The animals were castrated and descented by the supplier. They were maintained in AAALAC-accredited facilities in stainless steel cages and fed a commercial dry cat chow ad lib. The animal holding rooms were maintained at 21 ± 1°C with 50 ± 10% relative humidity and with a 12-h light:dark light cycle.

Procedure: The ferrets were brought to the exposure facilities in individual plastic cages. For irradiation, th ferrets were placed in a ventilated clear plastic tube with

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a diameter of approximately 9 cm. Following exposure, the animals were returned to their individual cages and observed until their first response (emesis or retch) or until a minimum of 1 h had passed with no response. Vomiting and retching were considered to be equivalent responses because they involve similar motor patterns and differ mainly in terms of the expulsion of stomach contents that occurs with vomiting. Because the ferrets were maintained on an ad lib diet, and because food intake may not have occurred immediately before irradiation, the presence of food in the stomach for expulsion could not be guaranteed. In addition, the various behaviors exhibited by the ferrets during the latent period were noted.

Radiation and dosimetry: For all types of radiation, whole-body exposures were utilized, and the ferrets were positioned in the center of the field with their right side facing the beam. Exposures to gamma rays (^{60}Co), high-energy electrons and fission neutrons were done using the sources at the Armed Forces Radiobiology Research Institute (AFRRI). Dosimetry at AFRRI was performed using an acrylic phantom with the dosimeter positioned in the center of the phantom. As such, all doses represent the midline tissue dose.

Irradiation with fission neutrons was performed using the TRIGA reactor, which delivered a nominal free-in-air neutron:gamma ratio of 20:1. Measured at the midline of an acrylic phantom, the neutron:gamma dose ratio was approximately 6.5:1. Reactor dosimetry was performed using the paired chamber technique (4). The doses tested and the number of ferrets exposed to each dose are presented in Table I. The dose rate ranged between 10–50 cGy/min.

Exposure to high-energy electrons was performed using a linear accelerator with 1 ms pulses (0.47 pulses/s) of 18.5 MeV electrons delivered at a nominal dose rate of 65 cGy/min. The maximum variation in dose from the center to the edges of the beam was 3% of the target dose, based on measurements made with acrylic phantoms using lithium fluoride thermoluminescent dosimeters. Irradiation with gamma rays was provided by a ^{60}Co source using a dose rate of 50–100 cGy/min. Primary dosimetry measurements for both radiation types were performed using a standard protocol (12). The doses that were delivered and the number of ferrets tested at each dose are presented in Table II.

Irradiation with iron particles was done using the BEVALAC at the Lawrence Berkeley Laboratory. Ferrets were exposed to doses of ^{56}Fe particles (Table I) at a dose rate of 10–50 cGy/min. The nominal extraction energy of the particles was 600 MeV/amu, so that all exposures were in the plateau of the Bragg curve. Entrance dose measurements were performed by the staff of the BEVALAC using parallel plate ionization chambers with Mylar windows and nitrogen gas flow positioned in the beam line. Because the exposures were in the plateau region of the Bragg curve, which is characterized by a relatively constant depth/dose distribution, the midline tissue dose received by the ferrets was the same as the entrance dose. However, because of the thickness of the animal and the holder, it is possible that the exit dose could have been as much as 25% greater than the entrance dose because of an increase in the linear energy transfer (LET) of the ^{56}Fe beam at this depth. Beam dose uniformity measurements, determined by film measurements, indicated that it was not possible to detune the beam sufficiently to produce a uniform exposure field large enough to encompass the entire restraining tube. Because the beam was aimed at the center of the restraining tube and because the animals were able to move around slightly within the restraining tube during the exposure, some reduction (up to 8%) in the dose delivered to either the head or tail of the ferret is possible.

Data analysis: The primary data consisted of the incidence and latency of emesis or retching at each dose tested. Probit analysis was used to calculate the mean effective dose (ED_{50}) and the 95% confidence limits. Confidence limits could not be calculated for the neutron data because, although five doses were tested, there was only a single dose in which there was a response other than 0% or 100%.

RESULTS

Tables I and II show the incidence of retching or emesis following exposure to the different types of radiation. Fig. 1 summarizes these results. The dose-response relationships varied as a function of the type of radiation. Iron particles and fission spectrum neutrons were the most effective in producing emesis, with nearly identical calculated ED_{50}s of 35 cGy (95% confidence limits: 25 cGy/46 cGy) and 40 cGy, respectively. High-energy electrons were the least effective, with an ED_{50} of 138 cGy (95% confidence limits: 109 cGy/169 cGy), while gamma rays were intermediate in effectiveness, with an ED_{50} of 95 cGy (95% confidence limits: 83 cGy/109 cGy).

The probit analysis indicated that the dose-response function for emesis for the ferrets exposed to gamma rays was significantly different than that for the ferrets exposed to high-energy electrons ($t = 1.45$, $p < 0.001$). The comparison between the emetic dose-response functions for gamma rays and ^{56}Fe particles was also significant ($t = 2.71$, $p < 0.001$). Although the probit analysis could not be used with the neutron data to determine the confidence intervals, the overlapping probit lines shown in Fig. 1 would suggest that the differences in frequency of emesis between ferrets exposed to fission spectrum neutrons and those exposed to ^{56}Fe particles were not significant.

Fig. 2 presents the latency (in min) to the first response following exposure to the four types of radiation. Only those doses of radiation which caused a re-

TABLE I. INCIDENCE OF EMESIS OR RETCHING FOLLOWING EXPOSURE TO IRON PARTICLES (^{56}FE) OR FISSION NEUTRONS.

Radiation	Dose (cGy) 20	30	40	50	60	90
^{56}Fe	0/5[a]	2/5	—[b]	4/5	5/5	—
Neutron[c]	—	0/4	2/5	5/5	5/5	5/5

[a] Number of ferrets responding/number tested.
[b] Dose not tested.
[c] Midline neutron/gamma ratio of 6.5/1.

TABLE II. INCIDENCE OF EMESIS OR RETCHING FOLLOWING EXPOSURE TO GAMMA RAYS (^{60}Co) OR HIGH-ENERGY ELECTRONS.

Radiation	Dose (cGy) 60	70	80	90	110	120	130	160	200	250
Gamma	0/10[a]	1/8	2/5	3/5	2/4	5/6	4/5	5/5	5/5	—
Electron	—[b]	—	—	1/5	1/5	—	3/8	5/7	5/6	3/3

[a] Number of Ferrets Responding/Number Tested.
[b] Dose not Tested.

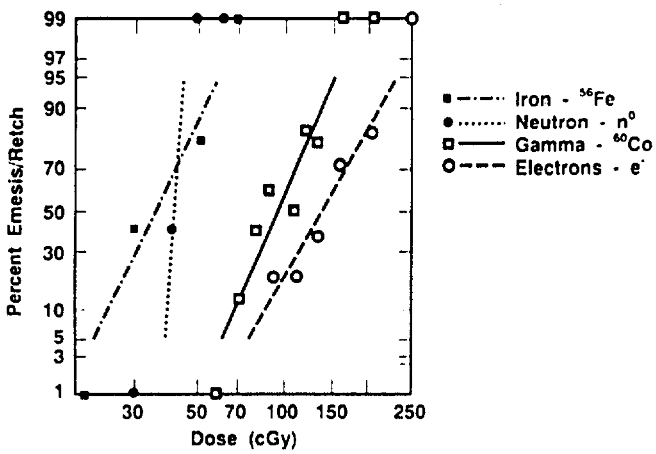

Fig. 1. Probit lines for emesis/retching in ferrets for different types of radiation: n^0, fission neutrons; ^{56}Fe, 600 MeV/amu iron particles; ^{60}Co, gamma rays; e$^-$, 18.5 MeV electrons.

sponse in two or more ferrets have been included in the graph. The latencies to the first bout of retching or vomiting, which ranged between 25–60 min, were similar for all types of radiation. No initial response was observed with a latency greater than 60 min. Also, there was no clear relationship between the radiation dose and the latency to the first response.

The pattern of behavioral responses was identical across all four types of radiation. Immediately following the exposure, the ferrets tended to lie quietly in their cage. After approximately 10 min, they would start moving around the cage and pawing at its bottom. When the radiation dose was above threshold, these movements were accompanied by mouth movements, primarily yawning and lip-licking. These behaviors, resting and pawing at the cage bottom, alternated during the entire latent period of 25–60 min. For those animals that ultimately retched or vomited, the frequency of mouth movements increased leading up to the actual response.

While yawning and lip-licking were always precursors to retching or emesis, not all ferrets who showed these mouth movements actually vomited. After one or more bouts of emesis or retching, usually within a 10–15 min period, the animals would lie quietly in their cage for the remainder of the observation period. In general, the higher radiation doses tended to produce an increase both in the number of animals who vomited or retched and in the number of bouts of emesis or retching observed in individual animals. Those ferrets that did not respond to radiation with retching or vomiting showed a similar pattern of motor activity, including occasional yawning and licking movements, before becoming quiescent within 40–60 min following the exposure.

DISCUSSION

These results clearly indicate that the effectiveness of ionizing radiation in producing emesis in ferrets depends on the type of radiation to which they are exposed. These differences in effectiveness were reflected as differences in the threshold dose, in the dose required for 100% incidence of emesis or retching and in the ED_{50}. The most effective types of radiation were high-energy iron particles and neutrons, while gamma rays were significantly less effective in producing emesis and retching, and high-energy electrons provided the least effective stimulus.

Within the range of doses tested in the present experiment the latency for vomiting or retching (25–60 min) was similar for all types of radiation and did not decrease as the dose was increased. The independence of latency and dose observed in the present experiment may reflect the relatively restricted range of doses tested. In contrast, King (7), reported significant decreases in the latency of emesis following exposure of ferrets to higher doses of ^{60}Co photons (200–600 cGy).

The present results on the incidence of emesis and retching following exposure to ionizing radiation are generally consistent with previously published research. The dose-response curve to ^{60}Co exposure observed in the present experiments is similar to that reported by King (7), although the calculated ED_{50} for emesis/retching in the present experiment is somewhat higher (95 cGy as opposed to 77 cGy). Similarly, the present observation of a lower threshold for emesis following exposure to fission spectrum neutrons than to ^{60}Co photons is concordant with the finding that monkeys exposed in a mixed neutron/gamma field and irradiated with a suprathreshold dose show an increased frequency of vomiting as the ratio of neutrons to gamma rays is increased (13).

The effectiveness of the different types of radiation in producing emesis generally paralleled the LET of the radiation: the higher LET radiations were the most effective in producing emesis and retching, and the lower LET radiations were the least effective. As such, the present results are consistent with those of other studies examining a variety of biological endpoints which show a similar relationship between relative biological effectiveness (RBE) and LET (1,8). However, the present results clearly indicate that LET is not completely predictive of RBE because the relatively small difference in LET between high-energy electrons (~0.2 keV/μm) and ^{60}Co photons (~0.3 keV/μm) was associated with a significant difference in the ED_{50}, while the much larger difference in LET between fission neutrons (~70 keV/

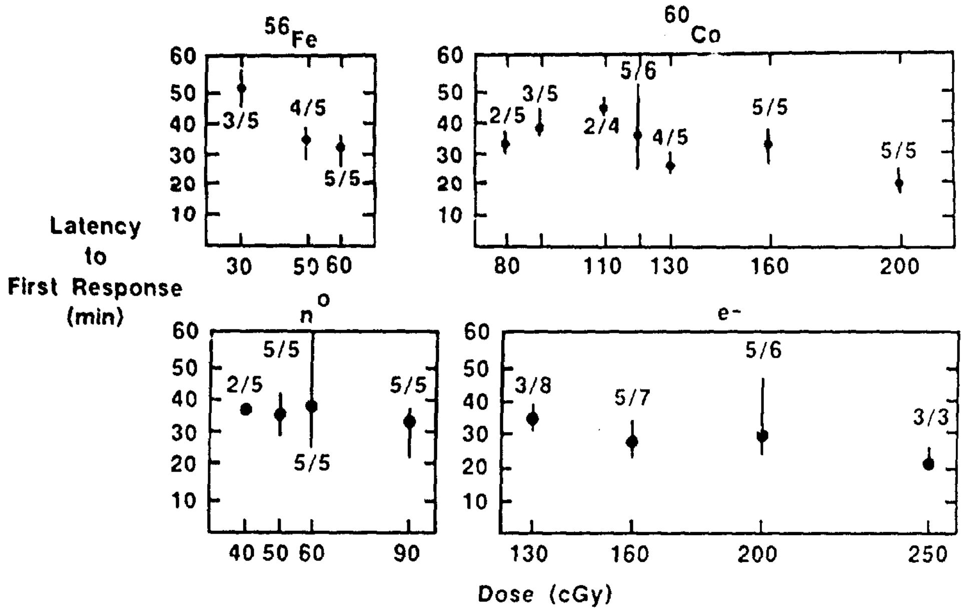

Fig. 2. Latency to the first response (emesis or retching) following exposure to the different radiations. The vertical line indicates the range of latencies (in min) and the filled circle indicates the average latency. Only those doses of radiation that produced a response in two or more animals have been included. The numbers above or below each vertical line indicate the number of ferrets responding/number of ferrets tested. Abbreviations as in Fig. 1

μm) and high-energy iron particles (~190 keV/μm) was not associated with differences in the ED_{50} for emesis. The observation of relatively high RBE for fission spectrum neutrons is consistent with a previous report that exposure to a single dose of fission spectrum neutrons is significantly more effective in producing life shortening in mice than is exposure to ^{56}Fe particles (1).

In contrast, other studies using different behavioral endpoints (e.g., active avoidance responding (6) or motor performance measured by the accelerod (2)) have found that exposure to high-energy electrons produces a significantly greater disruption of performance than does exposure to gamma rays or fission spectrum neutrons. Thus, the present results support the hypothesis that both the type of the radiation stimulus as well as the specific endpoint being evaluated are significant factors in determining the behavioral effects of exposure to ionizing radiation.

Overall, the present results indicate that exposure to low doses of ^{56}Fe particles produces vomiting at doses significantly below those needed following exposure to ^{60}Co photons or high-energy electrons. As such, there is the possibility that the nausea and vomiting which may occur as a consequence of exposure to these particles in a space environment outside the magnetic field of the Earth may affect the performance capabilities of astronauts. However, this conclusion is limited by the fact that the experimental dose rates in an accelerator are high compared to the fluence of heavy particles in space, which is typically low. Nonetheless, the present results, which show behavioral effects following exposure to low doses of ^{56}Fe, indicate the need for additional research using a variety of behavioral endpoints in order to determine the range of behaviors that may be affected by exposure to heavy particles and the mechanisms that may produce these effects.

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