Pharmacology Biochemistry & Behavior, Vol. 17, pp. 305–311, 1982. Printed in the U.S.A.

Dexamethasone: A Potent Blocker for Radiation-Induced Taste Aversion in Rats[1,4]

A. B. CAIRNIE[2] AND K. E. LEACH[3]

Defence Research Establishment Ottawa, Ottawa, Ontario K1A 0Z4, Canada

Received 25 March 1981

CAIRNIE, A. B. AND K. E. LEACH. *Dexamethasone: A potent blocker for radiation-induced taste aversion in rats.* PHARMAC. BIOCHEM. BEHAV. 17(2) 305–311, 1982.—Rats, trained to drink water during a single 30-min period each day, were then given 0.1% saccharin twice a week and water on other days for 30 min. If 20 rad of radiation (0.2 Gy) were given each time 30 to 40 min after the saccharin the rats developed a profound aversion to saccharin during the course of three weeks, whereas control groups failed to do so. This paradigm was then used to test the ability of drugs, given twice weekly immediately after the saccharin, to prevent the development during three weeks of an aversion when 20 rad was given, 30 to 40 min later. Insulin, domperidone, haloperidol, acetylsalicylic acid, naloxone, chlorpheniramine, cimetidine, and dimethyl sulphoxide were tested without notable success. However dexamethasone, at doses ranging from 0.013 mg/kg to 1.3 mg/kg, significantly attenuated the conditioned taste aversion by up to 60 percent. The results are discussed in terms of a search for an antinauseant and antiemetic drug effective against radiation in man.

Conditioned taste aversion Radiation and behavior Nausea Antiemetic Insulin Domperidone Haloperidol Acetylsalicylic acid Naloxone Chlorpheniramine Cimetidine Dimethyl sulphoxide Dexamethasone

THE phenomenon of conditioned taste aversion (CTA) was first described by Garcia, Kimeldorf and Koelling [26]. They demonstrated that rats given saccharin-flavoured water to drink during exposure for 6 hr to gamma rays (57 or 30 R) subsequently avoided, to a greater or lesser degree, the taste of saccharin. The explanation they offered was that the radiation produced gastrointestinal disturbances which the rats learned to associate with the novel taste of saccharin. Subsequent studies of radiation-induced CTA were reviewed by Kimeldorf and Hunt [37] and Smith [50].

From the initial reports on radiation-induced CTA has sprung an extensive literature on CTA due to a wide variety of unconditioned stimuli (US). The common link between radiation and most other agents, such as lithium chloride, which produce a CTA in rats is that they cause malaise or nausea [25]. However, some potent rodenticides are reported not to be particularly aversive [43], and some drugs, at doses which are not otherwise considered toxic, trigger a marked taste aversion [47]. Possibly it would be more categorical to relate CTA to the "strangeness" quality of the exposed animals' experience.

Coil and Garcia have suggested that CTA in the rat, which does not vomit, is an analogue of agent-induced nausea and vomiting in man [16]. In search of an effective antiemetic for irradiated humans [23], we have screened a variety of drugs for their ability to eliminate the aversive effects of radiation in rats. Most previous investigators of pharmacological blockade of CTA have first allowed rats to develop an aversion to radiation [35], lithium chloride [17], or amphetamine [11], and then tested the ability of the test drug given at the subsequent saccharin trial to prevent the expected decrease in saccharin consumption. Thus, they tested the drug's potential for dissociating the taste of saccharin from its previous association with the US, or, to put it another way, they tested for a block in the *expression* of the CTA. We, on the other hand, have tested the ability of drugs to prevent the *formation* of the association in the first place, in line with our search for an antiemetic drug. These two facets of the pharmacology of CTA are largely unrelated and we refer to that literature only to emphasize the difference.

While CTA can be induced by a single association of the aversive agent and the conditioned taste stimulus, larger effects can be obtained and smaller doses used if the pairing is repeated several times [11,27]. Further advantages of repetition are firstly that as the repeated sequence (drinking saccharin, injection and irradiation) loses its novelty neophobia should be greatly attenuated [41], secondly non-specific effects of handling or injection should disappear [24], and thirdly even small effects of drugs should be demonstrable.

In our work saccharin was offered to the rats for 30 min, instead of water, on two days per week for three weeks and this was followed each time by a low dose of radiation (20 rad) after a 30- to 40-min interval. In preliminary experiments it was found that this led to a progressively larger aversion to saccharin, whereas sham-irradiated rats consumed more saccharin. We injected anti-aversion test drugs

[1]Research carried out at the Division of Biological Sciences, National Research Council, Ottawa.
[2]Present Address: Toxic Chemicals Management Centre, Dept. of Environment, Hull, Quebec, K1A 1C8.
[3]Send reprint requests to Miss K. E. Leach, Defence Research Establishment Ottawa, Ottawa, Ontario K1A 0Z4, Canada.
[4]Issued as DREO Report No. 867.

after the drinking period; this is an important point, since those who choose to inject the drug before offering saccharin may be studying an effect of the drug on drinking behaviour. That is, they compound effects of the drug on the perception of both the conditioned stimulus (CS) and the US, as pointed out very clearly by Sessions [49]. This particular methodological difference may account for our failure to confirm here the reports of blockade of radiation-induced CTA by dimethyl sulphoxide (DMSO) [38], or chlorpheniramine [39]. The drugs used by us were insulin, domperidone, haloperidol, acetylsalicylic acid, naloxone, chlorpheniramine, cimetidine, DMSO, and dexamethasone. Only dexamethasone was found to be effective.

METHOD

Rats

The specific-pathogen-free male rats used were derived from the Sprague-Dawley strain and raised at the Division of Biological Sciences, National Research Council of Canada. They were maintained at 23°C on a 12 hr/12 hr cycle. Their initial weights were between 200 and 285 g.

Drugs

The drugs used in this study were insulin ("Rapitard," Novo Industries A/S, Copenhagen, Denmark), domperidone (courtesy of Janssen Pharmaceutica, Beerse, Belgium), haloperidol ("Haldol" courtesy of McNeil Laboratories (Canada) Ltd., Stouffville, Ontario), acetylsalicylic acid (Sigma Chemical Co., St. Louis, Missouri), naloxone (courtesy of Endo Laboratories Inc., Garden City, NY), chlorpheniramine maleate (courtesy of Schering Corporation Ltd., Pointe Claire, Quebec), cimetidine (courtesy of Smith, Kline and French, Montreal, Quebec), DMSO (Fisher Scientific Co.), and dexamethasone (courtesy of Merck Frosst Laboratories, Montreal, Quebec). Domperidone was diluted in 0.1 M lactic acid to give intraperitoneal injections of 0.2 ml. Haloperidol and DMSO were administered without dilution and 0.1 M lactic acid was used as the vehicle control for haloperidol. The others were dissolved in saline to give the drug dose in 0.2 ml and the acetylsalicylic acid in 0.5 ml; they were injected intraperitoneally. In each case the dosage tested was selected as optimal on the basis of previous reports of experimentation with rats. Drugs were made up from stock on each occasion.

Irradiation

Rats to be irradiated were removed from their cages, placed in close confinement in an eight-celled holder made of acrylic sheet, and carried 20 metres to a room where the holder was positioned in an isodose plane in front of a shielded ^{60}Co AECL Gamma Irradiator. Dosimetry was carried out using a Victoreen dosimeter in the position of one rat, and a conversion factor of 0.96 from roentgens to rads [36]. After the operator left the room the source was raised to give all the rats simultaneously 20 rad (0.2 Gy) at 50 rad/min. Sham irradiations involved the same procedure except for the final step.

Blood-Glucose Measurement

Glucose determinations, to validate the effectiveness of the insulin preparation, were performed on serum using Sigma Kit no. 510 for enzymatic colorimetric determination of glucose at 425–475 nm.

Procedure

A procedure was developed for determining whether the decrease of saccharin consumption consequent on repeated irradiation was attenuated or augmented by the administration of the test drug, and whether the drug alone was capable of producing a CTA. Rats were housed singly and trained for seven consecutive days with water deprivation for 23½ hr per day. Those which lost more than 5 g during this week were discarded. The remainder were assigned randomly to make experimental groups of six, but the rats remained in their original cage, and rack position. Rats were removed only for injection or irradiation.

For the next three weeks (days 8–25) all rats were offered as their only fluid 0.1% saccharin for ½ hr on two days per week (Tuesday and Friday), and on other days water for ½ hr. Saccharin consumption was recorded. Two D groups were injected with the drug immediately after the saccharin, and two V groups with its vehicle. Thirty to forty minutes after the end of the drinking period the two R groups were irradiated with 20 rad and the two S groups were sham irradiated. The group designations are as follows:

Group	Injection	Radiation
DR	drug	20 rad
DS	drug	sham
VR	vehicle	20 rad
VS	vehicle	sham

Statistical Analysis

Two-way analysis of variance was carried out on the saccharin consumption using the BMDP 79 program P2V (Analysis of Variance and Covariance including Repeated Measures). In each case, when the variation was partitioned a highly significant treatments effect was noted but time, which was a within-subject effect, was not a significant source. Accordingly each group could be reduced to an average over the period Day 8 to Day 25, and differences between groups tested. Averages were denoted in the usual way. The effect of sham irradiating was given by $\overline{VS}-\overline{VR}$. This usually reached $p<0.001$, but there was one instance where $0.005<p<0.01$. The possibility that the drug induced a CTA was tested by $\overline{VS}-\overline{DS}$, and the possibility that the drug modified the effect of radiation by $\overline{DR}-\overline{VR}$. The probabilities that these quantities were positive for each drug condition are reported in columns 4 and 5 of Table 1.

RESULTS AND DISCUSSION

The Basic Paradigm

In preliminary experiments (not reported here) it was shown that in the course of three weeks rats developed a profound CTA to saccharin when it was paired twice a week with 20 rad given 30–40 min after the saccharin had been offered. (Repetitions of this demonstration can be seen in the graphs in Fig. 1 by comparing the VS and VR lines.) Since no aversion to water could be produced in the same way, the effect was not on fluid intake *per se*. Furthermore, there was no effect if a sham exposure to radiation were given or if the radiation were delayed for 1–2 days after saccharin consumption (non-contingent controls). A clear effect was also

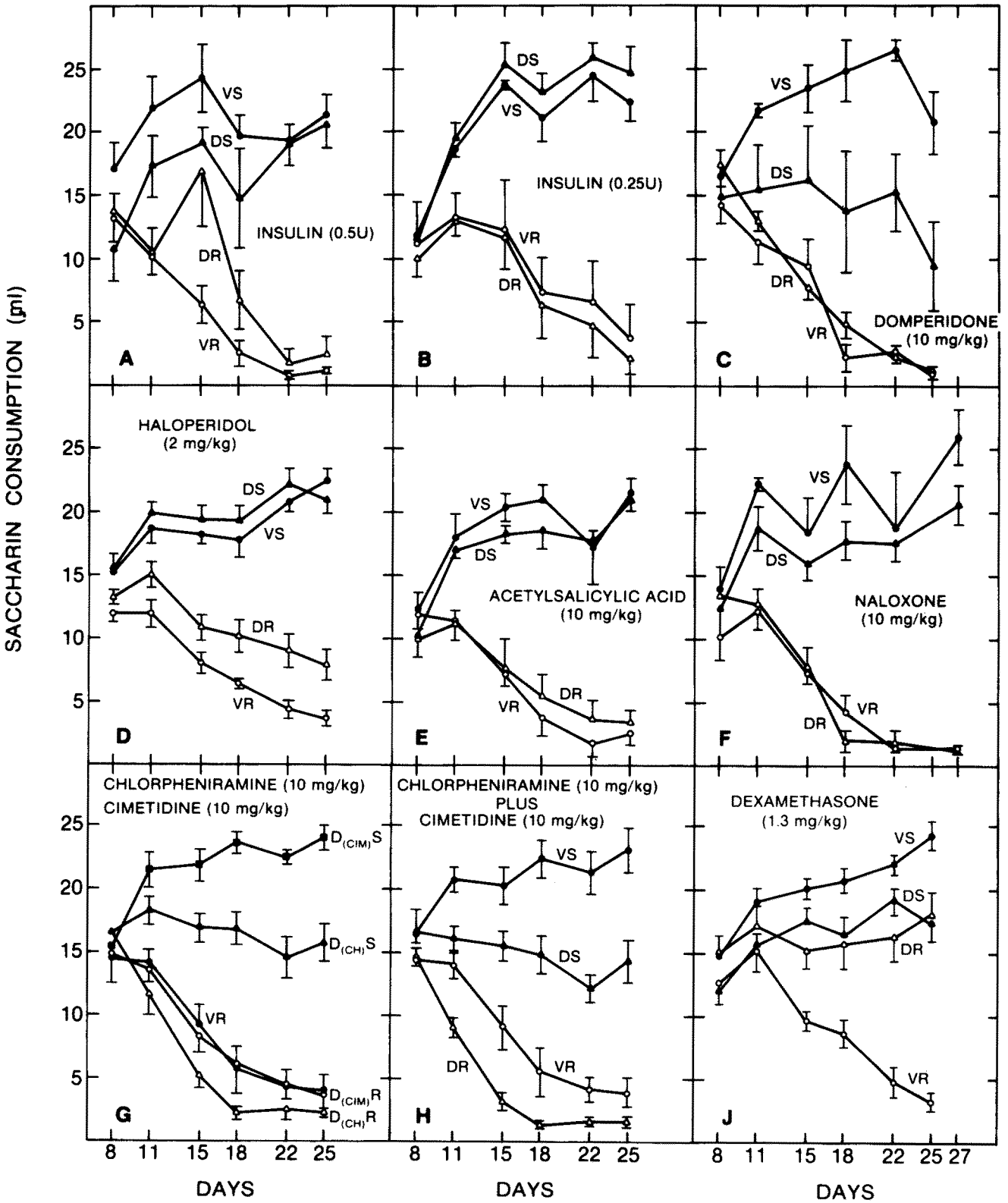

FIG. 1. Comparison of fluid consumption by groups of rats (n=6) given saccharin to drink for 30 min, then injected with a drug or its vehicle, and then irradiated (20 rad) or sham irradiated. DS–drug followed by sham radiation, VS–vehicle followed by sham radiation, DR–drug followed by radiation, and VR–vehicle followed by radiation. The drugs and their doses are indicated in the panels. Fig. 1G and 1H constitute one large experiment whereas all the others are independent of each other. In Fig. 1G the drug corresponding to each line is indicated by a subscript. The VR lines in Fig. 1G and 1H are identical and the VS line in Fig. 1H has been omitted from 1G for clarity. The means±standard error were plotted. The significance of any differences is given in Table 1.

seen after 10 rad but the 20-rad dose was preferred because it caused gradual development of an almost complete CTA.

In each of the graphs in Fig. 1 the classical single-bottle test for saccharin avoidance, or conditioned taste aversion, is represented by the score shown for Day 11. In many cases the conclusion we reached at the end of the experiment is not different from that apparent on Day 11. The advantage of proceeding beyond the single-pairing test is that the repeated association of the radiation exposure with the CS produces a profound effect. Yet the slowness with which the effect develops permits demonstration of even a small drug-induced modification in either direction, which might have been swamped if a large dose of radiation had been used to produce such a large aversion with a single exposure. At the end of the experiment the animals were well habituated to the procedure and there was no evidence of the effect disappearing. This procedure seems much preferable to the practice of some investigators who habituate their animals by sham irradiation before giving radiation and saccharin on a single occasion ([50], page 60). It also deals very effectively with the criticism by Mitchell of single-pairing experiments that the enhancement of neophobia and conditioned aversion are being studied simultaneously [41], for during the six repeated pairings in three weeks neophobia will disappear, or at least be greatly diminished, as seen with the sham-irradiated animals.

Pharmacological Intervention

Since the intervening steps between absorption of the radiation and development of the aversion are not known, it is difficult to define the most appropriate pharmacological attack. There is recent evidence of disruption in rats of the CTA effects of copper sulphate by vagotomy [18], which is parallel to the effects of vagotomy on emesis in dogs caused by the same agent [53]. The area postrema plays a major role in the induction of emesis by many agents [9], and ablation of this region prevents the development in rats of CTA to methylscopolamine [5]. There is evidence in favour of humoral mediation [33], but no basis for elimination of a neural component in radiation-induced CTA. Thus, our present knowledge of the physiological mechanism involved is an inadequate guide for identification of putative blockers.

The aim in these experiments was to achieve, at the time when the radiation produced its aversive effects, a pharmacologically effective level of the drug under test, and thus to test the hypothesis that the drug is able to prevent the development of CTA. It is a moot point what this time is. It is less than 3 hr since the CTA is quite weak if the saccharin is not presented before 3 hr post exposure [3]. It is at least 30 min before the aversive effects peak, for Carroll and Smith [13], in re-examining the data of Morris and Smith [42], found a significantly greater CTA when the saccharin was given 60 min rather than 30 min after exposure. We chose to give the drugs immediately after the saccharin in the expectation that they would be active when the radiation was administered about 30 min later, and during the post-radiation aversive period, but the drugs would not directly affect the saccharin intake.

The results with all the drugs tested are given in Table 1 with details of the doses and routes of administration used.

Insulin

Insulin was tested because Hulse and Patrick [32] found that 0.5 U/rat of insulin would counteract completely the delay in gastric emptying in the rat induced by exposure to 200 R of radiation. They very plausibly regarded delay in gastric emptying in the rat as an analogue of nausea and vomiting in man, and on that basis suggested insulin should be tested in man. It is our hypothesis that in the rat radiation-induced delay in gastric emptying and CTA are both manifestations of the activity of the same neural centre. If insulin were to abolish the effects of radiation on each phenomenon, the hypothesis would be supported and the argument for testing insulin in man would be strengthened. Hulse and Patrick did not give the weights of their rats; the average weight of our rats at the beginning and end of the experiment were 257 and 294 g respectively. The results are shown in Fig. 1A. Both radiation and insulin were effective in producing a taste aversion ($p<0.01$), but the radiation effect was much bigger. The rats were sacrificed for determination of serum glucose on Day 25 2 hr after they received insulin. In the VR and VS groups the level was 182 ± 10 and 176 ± 19 mg/100 ml. In the DR and DS groups it was 65 ± 13 and 118 ± 9 mg/100 ml.

In view of the CTA induced by 0.5 U of insulin, and the large effects on blood glucose, the experiment was repeated with 0.25 U/rat (Fig. 1B). There was no suggestion this time of any drug effect on the CTA. The serum glucose levels in the VR and VS groups were 184 ± 5 and 176 ± 4 mg/100 ml. In the DR and DS groups they were 99 ± 19 and 128 ± 8 mg/100 ml.

Since the serum glucose was greatly reduced 2 hr after insulin on the last day of each experiment it is apparent that the insulin had been present and effective long enough by this time to produce any other hypothetical effect of insulin.

Domperidone

Domperidone was tested because of recent interest in this drug as a non-neuroleptic ligand for dopamine receptors [4]. Dopamine may be involved at the chemoreceptor trigger zone (CTZ) of the area postrema [8], and/or in the regulation of gastric motility [45]. It has also been shown that domperidone blocks the action of several known emetic agents [44]. The doses we used, 0.1 and 10 mg/kg (only the latter shown), were greater than that necessary to elicit an elevation of plasma prolactin at 30 min which was sustained for 2 hours [15]. With the sham-irradiated rats it was found that 10 mg/kg domperidone was aversive (Fig. 1C) ($p<0.01$), but 0.1 mg/kg was not. When domperidone was given to irradiated rats the response was no different from the response to radiation alone. Since one would expect the response to two almost simultaneous aversive agents to be additive, this could be interpreted as evidence of a moderation of the radiation effect by the drug at 10 mg/kg, counteracted however by the effect of the drug itself, giving a net effect no different from that of the radiation alone.

Haloperidol

Haloperidol is also a dopamine antagonist, but it is particularly noted for its neuroleptic and antipsychotic properties. It has been found to have some value as an antiemetic in patients treated by either chemotherapy or radiotherapy, and in irradiated dogs [40]. A dose of 1 mg/kg is reported to cause in rats an elevation of plasma prolactin sustained for 2 hours [15]. At doses of 0.02 or 0.25 mg/kg it did not modify the responses of either irradiated or sham-irradiated rats (Table 1 only). At a dose of 2 mg/kg there was a small but significant diminution ($p<0.05$) of the aversion to saccharin (Fig. 1D).

TABLE 1

EFFECTS OF DRUGS IN MODIFYING THE CONDITIONED TASTE AVERSION

Drug	Route*	Dose	Drug† Effect	Anti-Radiation‡ Effect	Passes§ BBB (±)
insulin	IP	0.5 U/rat	$p<0.01$	—	+
	IP	0.25 U/rat	—	—	
domperidone	IP	0.1 mg/kg	—	—	−
	IP	10 mg/kg	$p<0.01$	—	−
haloperidol	IM	0.02 mg/kg	—	—	+
	IM	0.25 mg/kg	—	—	
	IP	2 mg/kg	—	$p<0.05$	
acetylsalicylic acid	IP	10 mg/kg	—	—	+
naloxone	IP	10 mg/kg	$p<0.05$	—	+
chlorpheniramine	IP	10 mg/kg	$p<0.01$	—	+
	IP	20 mg/kg	$p<0.01$	—	
cimetidine	IP	10 mg/kg	—	—	(+)
chlorpheniramine + cimetidine	IP	10+10 mg/kg	$p<0.01$	—	
dimethyl sulphoxide	IP	1 g/kg	—	—	+
dexamethasone	IP	0.0013 mg/kg	—	—	
	IP	0.013	—	$p<0.05$	+
	IP	0.13	—	$p<0.01$	
	IP	1.3	—	$p<0.01$	
	IP	1.3 (repeat)	$p<0.01$	$p<0.01$	
	IP	13	—	—	

Significance levels were determined by two-way analysis of variance. Standard errors are based on the within-cell variance (same drug, same radiation group, all days) in each of the cases because the interaction between the radiation and the drug effects was statistically significant.

*IP=intraperitoneal, IM=intramuscular.

†Drug-induced CTA in sham-irradiated rats; probability is given that $\overline{VS} - \overline{DS}$ is not positive.

‡Drug effect on radiation-induced CTA; probability is given that $\overline{DR} - \overline{VR}$ is not positive.

§Passes blood-brain barrier; + yes, (+) slight, −no.

This effect is probably non-specific, since the rats showed marked signs of sedation, and is in line with experience of its usefulness in clinical management [23].

Acetylsalicylic Acid

Acetylsalicylic acid was chosen because of its anti-inflammatory effects, in particular its inhibition of prostaglandin synthetase. The dose of 10 mg/kg, which is less than that sometimes used to ensure prostaglandin synthetase inhibition *in vivo*, was selected to avoid damage to the gastric mucosa and other side effects associated with repeated use of this drug [46]. The drug was without effect (Fig. 1E).

Naloxone

It has been suggested that the significance of the opiate receptors and enkephalin in the brainstem, which are found in high concentration in the vagal nuclei and area postrema, may be their role in viscero-somatic reflexes such as vomiting [51]. If β-endorphin, or some other endogenous opioid peptide, activates the area postrema, its effects should by inference be blocked by naloxone, a specific opiate antagonist. Intravenous naloxone does not block the emetic effect in cats of intracerebroventricular (ICV) morphine, but does block its anti-emetic effect [20]. While ICV naloxone has been shown to block the vomiting in cats induced by ICV met-enkephalin [14], and morphine [20,52], there is disagreement on its interaction with ICV apomorphine [20,52]. When systemic naloxone was tested in irradiated dogs the increase in ED_{50} for vomiting was not significant, though this may have been due to the very low drug dose used [19].

In testing naloxone against radiation-induced CTA we used 10 mg/kg, a dose effective in other respects in rats [31]. We found a small aversion to the drug ($p<0.05$), but were unable to demonstrate any moderation whatever by the drug (Fig. 1F). While it is possible that naloxone was without effect because it was not contemporaneous with the aversive radiation effect, this is unlikely in view of the confirmed demonstration that naloxone is effective almost immediately in the rat and for 2 hr or more after intraperitoneal administration [6,31].

Chlorpheniramine and/or Cimetidine

Histamine release has been suggested as the basis of radiation-induced CTA because of the reported abolition of the aversion by chlorpheniramine [39]. This has been disputed by Sessions [49]. Our results fully support Sessions in that, using the same drug dose (20 mg/kg), we found the drug itself to be quite aversive ($p<0.01$) and the combination with radiation to be more aversive than either alone (see Table 1 only). When we halved the drug dose the aversive effect was

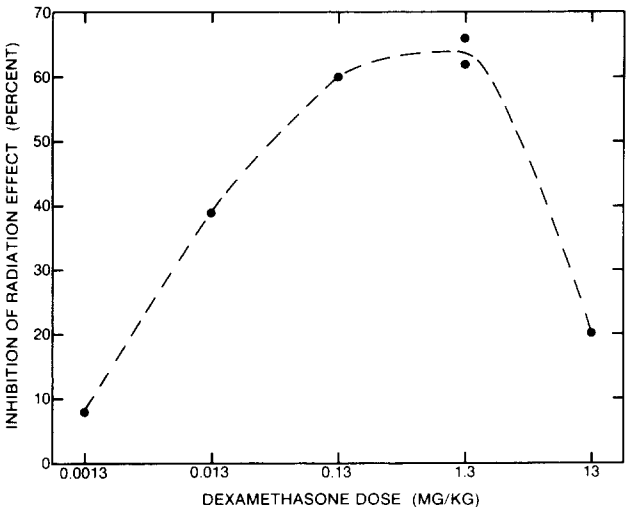

FIG. 2. Inhibition of the effect of 20 rad radiation by dexamethasone, as a function of the drug dose. The inhibition was calculated from $\overline{DR}-\overline{VR}/\overline{VS}-\overline{VR}$.

slight, but there was no evidence that chlorpheniramine alleviated the aversive effects of radiation (Fig. 1G). Because of the interest in H_2-receptor blockers we also tested (without success) cimetidine (Fig. 1G), and a combination of chlorpheniramine and cimetidine (Fig. 1H) to block both H_1 and H_2 receptors. The intraperitoneal dose of cimetidine used was 10 mg/kg, which has been shown to affect hypothalamic levels of histamine in the rat [34].

Dimethyl Sulphoxide

DMSO was claimed to have a radioprotective effect on the saccharin preference of mice [38], but this report is peculiar in a number of respects. The mice were exposed to a choice of saccharin or water for three weeks before, and five weeks after, irradiation with 450 R. Their saccharin consumption fell throughout the post-radiation period, but DMSO treatment prevented most of this. We accordingly tested DMSO in our system, but found it had no effect (Table 1 only). The dose we used was 1 g/kg, a high sublethal dose [21].

Dexamethasone

Radiation is reported to cause activation of the pituitary-adrenal axis leading to secretion of corticosterone [2,28], presumably by the mediation of ACTH. ACTH and ACTH fragments also have behavioural effects not dependent on the adrenal cortex [7]. ACTH secretion has been implicated in the mechanism of CTA [1, 10, 29, 30] since dexamethasone given before conditioning attenuated the CTA induced by lithium chloride in one study [29] (but the effect was not significant in a repetition by the same group [30]). One hypothesis of dexamethasone action is inhibition of ACTH release, thus preventing both elevation of endogenous corticosteroids and, presumably, extra-adrenal effects of ACTH.

Although dexamethasone has not been reported to be an anti-emetic drug, we decided to test its ability to block radiation-induced CTA. We used a dose of 1.3 mg/kg, which approximates that used by Hennessy *et al.* [29]. As can be seen in Fig. 1J, this blocked to a large degree the radiation-induced CTA, and only produced a small aversion by itself. Thereafter we used a wide range of doses and found that the drug had a significant blocking effect at a dose of 13 μg/kg as well as at higher doses (Table 1). The dose-response curve for dexamethasone is shown in Fig. 2. Although this effect of dexamethasone is reproducible in our hands, we would caution that we have been unable to prevent the development of CTA to larger doses of radiation with 1.3 mg/kg of the drug. It is therefore clear that dexamethasone is effective against only the most sensitive mechanism of radiation-induced CTA and that other mechanism(s) are triggered by larger doses of radiation. It is not surprising that the CTA phenomenon evoked by so many disparate stimuli would also be aroused by multiple pathways in the case of an insult such as radiation.

This marked effect of dexamethasone holds promise of eventually contributing to an understanding of both radiation-induced CTA and emesis. We have already indicated one possible mechanism, namely inhibition of ACTH secretion. However an equally viable alternative at this stage would be through indirect inhibition of prostaglandin synthesis [22,48]. Further work is necessary to test these possibilities.

ACKNOWLEDGEMENTS

We acknowledge Dr. R. K. Harding's advice about choice of drugs and their doses, and the help of other colleagues who commented on a draft of the manuscript. Mr. P. Clay, Biomathematics Group, National Research Council of Canada, and Mr. R. Ings of the Department of Psychology, Carleton University, Ottawa, performed the statistical analysis. Mrs. L. Prud'homme-Lalonde gave skilful technical assistance. We thank Mrs. S. Billo for typing the manuscript.

REFERENCES

1. Ashe, J. H. and M. Nachman. Neural mechanisms in taste-aversion learning. *Progr. Psychobiol. physiol. Psychol.* **9:** 233–262, 1980.
2. Bacq, Z. M. and P. Alexander. *Fundamentals of Radiobiology* (Second Edition) chapter 15. London and New York: Pergamon Press, 1961.
3. Barker, L. M. and J. C. Smith. A comparison of taste aversions induced by radiation and lithium chloride in CS-US and US-CS paradigms. *J. comp. physiol. Psychol.* **87:** 644–654, 1974.
4. Baudry, M., M. P. Martres and J. C. Schwartz. ^{3}H-domperidone: a selective ligand for dopamine receptors. *Naunyn-Schmiedeberg's Arch. Pharmac.* **308:** 231–237, 1979.
5. Berger, B. D., C. D. Wise and L. Stein. Area postrema damage and bait shyness. *J. comp. physiol. Psychol.* **82:** 475–479, 1973.
6. Bläsig, J., V. Höllt, V. Bäuerle and A. Herz. Involvement of endorphins in emotional hyperthermia of rats. *Life Sci.* **23:** 2525–2532, 1978.
7. Bohus, B. and D. de Wied. Pituitary-adrenal system hormones and adaptive behaviour. In: *General, Comparative and Clinical Endocrinology of the Adrenal Cortex,* volume 3, edited by I. Chester Jones and I. W. Henderson. London and New York: Academic Press, 1980, pp. 265–347.
8. Borison, H. L. Area postrema: chemoreceptor trigger zone for vomiting—is that all? *Life Sci.* **14:** 1807–1817, 1974.
9. Borison, H. L. and S. C. Wang. Physiology and pharmacology of vomiting. *Pharmac. Rev.* **5:** 193–230, 1953.

10. Braveman, N. S. What studies on pre-exposure to pharmacological agents tell us about the nature of the aversion-inducing agent. In: *Learning Mechanisms in Food Selection*, edited by L. M. Barker, M. Best and M. Donjan. Dallas: Baylor University Press, 1977, pp. 511–530.
11. Cappell, H. and A. E. Le Blanc. Punishment of saccharin drinking by amphetamine in rats and its reversal by chlordiazepoxide. *J. comp. physiol. Psychol.* **85:** 97–104, 1973.
12. Carroll, M. E., H. I. Dinc, C. J. Levy and J. C. Smith. Demonstrations of neophobia and enhanced neophobia in the albino rat. *J. comp. physiol. Psychol.* **89:** 457–467, 1975.
13. Carroll, M. E. and J. C. Smith. Time course of radiation-induced taste aversion conditioning. *Physiol. Behav.* **13:** 809–812, 1974.
14. Clark, W. G. Emetic and hyperthermic effects of centrally injected methionine-enkephalin in cats (39713). *Proc. Soc. exp. Biol. Med.* **154:** 540–542, 1977.
15. Cocchi, D., I. Gil-Ad, M. Parenti, E. Stefanini, V. Locatelli and E. E. Muller. Prolactin-releasing effect of a novel antidopaminergic drug, domperidone, in the rat. *Neuroendocrinology* **30:** 65–69, 1980.
16. Coil, J. D. and J. Garcia. Conditioned taste aversions: the illness US. In: *Biological Approaches to Learning*, papers presented at the Northeastern Regional Meeting of the Animal Behavior Society, October 1977, at St. John's, Newfoundland.
17. Coil, J. D., W. G. Hankins, D. J. Jenden and J. Garcia. The attenuation of a specific cue-to-consequence association by antiemetic agents. *Psychopharmacology* **56:** 21–25, 1978.
18. Coil, J. D., R. C. Rogers, J. Garcia and D. Novin. Conditioned taste aversions: vagal and circulatory mediation of the toxic unconditioned stimulus. *Behav. Biol.* **24:** 509–519, 1978.
19. Cooper, J. R. and J. L. Mattsson. Control of radiation-induced emesis with promethazine, cimetidine, thiethylperazine, or naloxone. *Am. J. Vet. Res.* **40:** 1057–1061, 1979.
20. Costello, D. J. and H. L. Borison. Naloxone antagonizes narcotic self-blockade of emesis in the cat. *J. Pharmac. exp. Ther.* **203:** 222–230, 1977.
21. David, N. A. The pharmacology of dimethyl sulfoxide. *Am. Rev. Pharmac.* **12:** 353–374, 1972.
22. Flower, R. J. and G. J. Blackwell. Anti-inflammatory steroids induce biosynthesis of a phospholipase A_2 inhibitor which prevents prostaglandin generation. *Nature* **278:** 456–459, 1979.
23. Frytak, S. and C. G. Moertel. Management of nausea and vomiting in the cancer patient. *J. Am. Med. Ass.* **245:** 393–396, 1981.
24. Garcia, J., N. A. Buchwald, B. H. Feder and C. Wakefield. Habituation as a factor in radiation-conditioned behaviour. From: *Effects of Ionizing Radiation on the Nervous System*, proceedings of the Symposium on the Effects of Ionizing Radiation on the Nervous System sponsored by the International Atomic Energy Agency at Vienna on 5–9 June 1961, published by IAEA, Vienna, 1962.
25. Garcia, J., W. G. Hankins and K. W. Rusiniak. Behavioral regulation of the milieu interne in man and rat. *Science* **185:** 824–831, 1974.
26. Garcia, J., D. J. Kimeldorf and R. A. Koelling. Conditioned aversion to saccharin resulting from exposure to gamma radiation. *Science* **122:** 157–158, 1955.
27. Garcia, J. and R. A. Koelling. A comparison of aversions induced by X rays, toxins, and drugs in the rat. *Radiat. Res. Suppl.* **7:** 439–450, 1967.
28. Hameed, J. M. A. and T. J. Haley. Plasma and adrenal gland corticosterone levels after X-ray exposure in rats. *Radiat. Res.* **23:** 620–629, 1964.
29. Hennessy, J. W., W. P. Smotherman and S. Levine. Conditioned taste aversion and the pituitary-adrenal system. *Behav. Biol.* **16:** 413–424, 1976.
30. Hennessy, J. W., W. P. Smotherman and S. Levine. Investigations into the nature of the dexamethasone and ACTH effects upon learned taste aversion. *Physiol. Behav.* **24:** 645–649, 1980.
31. Holaday, J. W., E. Wei, H. Loh and C. H. Li. Endorphins may function in heat adaptation. *Proc. natn. Acad. Sci. U.S.A.* **75:** 2923–2927, 1978.
32. Hulse, E. V. and G. Patrick. A model for treating post-irradiation nausea and vomiting in man: the action of insulin in abolishing radiation-induced delay in gastric emptying in the rat. *Br. J. Radiol.* **50:** 645–651, 1977.
33. Hunt, E. L., H. W. Carroll and D. J. Kimeldorf. Effects of dose and of partial-body exposure on conditioning through a radiation-induced humoral factor. *Physiol. Behav.* **3:** 809–813, 1968.
34. Huszti, Z. Regulation of histamine synthesis: altered synthesis and level of histamine in the hypothalamus of rats by repeated administration of histamine H_1 and H_2 receptor antagonists. *Agents Actions* **10:** 98–100, 1980.
35. Jolicoeur, F. B., M. J. Wayner, D. B. Rondeau, A. D. Merkel and D. A. Bassano. Effects of phenobarbital on taste aversion induced by X-irradiation. *Pharmac. Biochem. Behav.* **11:** 709–712, 1979.
36. Johns, H. E. and J. R. Cunningham. *The Physics of Radiology*. Springfield, Illinois: Charles C. Thomas, 1969, Third Edition, p. 736.
37. Kimeldorf, D. J. and E. L. Hunt. *Ionizing Radiation: Neural Function and Behavior*, Chapter 9. Academic Press, London and New York, 1965.
38. Le Van, H. and W. S. Lemoos. An effect of DMSO on post-irradiation saccharin avoidance in mice. *Experientia* **23:** 276–277, 1966.
39. Levy, C. J., M. E. Carroll, J. C. Smith and K. G. Hofer. Antihistamines block radiation-induced taste aversions. *Science* **186:** 1044–1046, 1974.
40. Luthra, Y. K., J. L. Mattsson and M. G. Yochmowitz. Inhibition of radioemesis by disruption of catecholamines in dogs. *Radiat. Res.* **85:** 583–591, 1981.
41. Mitchell, D. The psychological vs the ethological rat: two views of the poison avoidance behavior of the rat compared. *Anim. Learn. Behav.* **6:** 121–124, 1978.
42. Morris, D. D. and J. C. Smith. X-ray conditioned saccharin aversion induced during the immediate postexposure period. *Radiat. Res.* **21:** 513–519, 1964.
43. Nachman, M. and P. L. Hartley. Role of illness in producing learned taste aversions in rats: a comparison of several rodenticides. *J. comp. physiol. Psychol.* **89:** 1010–1018, 1975.
44. Niemegeers, C. J. E., K. H. L. Schellekens and P. A. J. Janssen. The antiemetic effects of domperidone, a novel potent gastrokinetic. *Archs int. Pharmacodyn.* **244:** 130–140, 1980.
45. van Nueten, J. M. and P. A. J. Janssen. Is dopamine an endogenous inhibitor of gastric emptying? In: *Gastrointestinal Motility in Health and Disease*, edited by H. L. Duthie. Proc. 6th Int. Symp. on Gastrointestinal Motility, Edinburgh, 1977, pp. 173–181.
46. Rainsford, K. D. Prostaglandins and the development of gastric mucosal damage by anti-inflammatory agents. In: *Prostaglandins and Inflammation*, edited by K. D. Rainsford and A. W. Ford-Hutchinson. Basel: Birkhauser Verlag, 1980, pp. 193–210.
47. Rondeau, D. B., F. B. Jolicoeur, A. D. Merkel and M. J. Wayner. Drugs and taste aversion. *Neurosci. Biobehav. Rev.* **5:** 279–294, 1981.
48. Russo-Marie, F., M. Paing and D. Duval. Mechanism of glucocorticoid-induced inhibition of prostaglandin synthesis. *Agents Actions* Suppl. **4:** 49–60, 1979.
49. Sessions, G. R. Histamine and radiation-induced taste aversion conditioning. *Science* **190:** 402–403, 1975.
50. Smith, J. C. Radiation: its detection and its effects on taste preferences. *Prog. physiol. Psychol.* **4:** 53–118, 1971.
51. Snyder, S. H., G. R. Uhl and M. J. Kuhar. Comparative features of enkephalin and neurotensin in the mammalian central nervous system. In: *Centrally Acting Peptides*, edited by J. Hughes. Proceedings of a Symposium 4–5 April 1977, London: Macmillan Press, 1978, pp. 85–97.
52. Stewart, J. J., T. F. Burks and N. W. Weisbrodt. Intestinal myoelectric activity after activation of central emetic mechanism. *Am. J. Physiol.* **233:** E131–E137, 1977.
53. Wang, S. C. and H. L. Borison. Copper sulphate emesis: a study of afferent pathways from the gastrointestinal tract. *Am. J. Physiol.* **164:** 520–526, 1951.