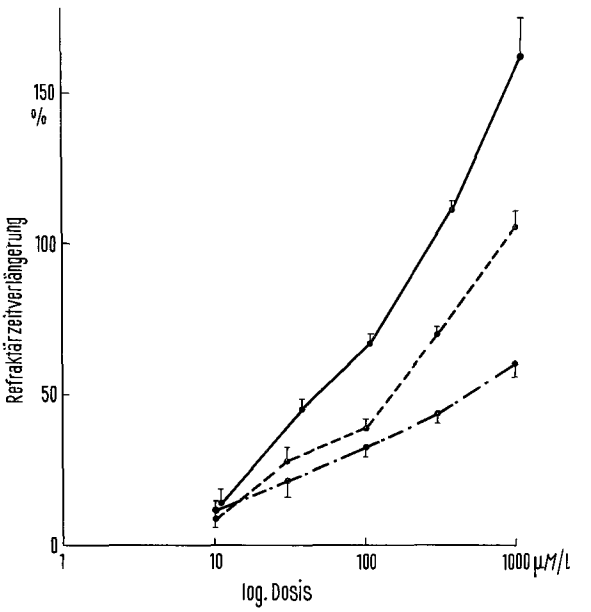
wirksame (+,−)MJ 1999 verursachte die geringste Verlängerung der Refraktärzeit, die ED_{35} lag bei 140 μM/l.

Die *Kontraktionskraft* der Vorhofpräparate wurde durch die untersuchten Substanzen verschieden beeinflusst. (+,−)MJ 1999 hatte bis zur höchsten Konzentration von 3 mM/l keinen signifikanten Einfluss auf die Kontraktilität. Die beiden optischen Isomeren des INPEA verursachten eine geringe Zunahme der Kontraktionskraft; in Konzentrationen bis zu 110 μM/l war D(−)INPEA positiv inotrop wirksam, L(+)INPEA in Konzentrationen bis zu 30 μM/l. Erhöhung der Konzentrationen jeweils um den Faktor 3,16 bewirkte einen negativ inotropen Effekt. Die ED_{35} für die Verminderung der Kontraktionsamplitude betrug für D(−)INPEA 580, für L(+)INPEA 575 μM/l (Tabelle). In β-adrenolytisch wirksamen Konzentrationen verursachte D(−)INPEA keine Hemmung der Kontraktilität, die kardiodepressive ED_{35} ist 853 mal grösser als die β-adrenolytische ED_{35}.



Verlängerung der Refraktärzeit des isolierten Meerschweinchenvorhofes durch D(−)INPEA(·——), L(+)INPEA(---) und (+,−)MJ 1999(—·—·—). Ordinate: Verlängerung der Refraktärzeit in % gegenüber Kontrollen ($\bar{x} \pm s_{\bar{x}}$, $n = 5$). Abszisse: Konzentration in μM/l.

Nach unseren Ergebnissen wird die Refraktärzeit isolierter Meerschweinchenvorhöfe durch die beiden optischen Isomeren des INPEA[8] wie auch durch MJ 1999 verlängert. Die Beobachtung, dass das β-adrenolytisch wirksame D(−)INPEA die Refraktärzeit in weit grösserem Umfang verlängert als L(+)INPEA, lässt den Schluss zu, dass mindestens zwei Mechanismen wirksam werden: 1) ein spezifischer, β-adrenolytischer gegenüber dem endogenen Noradrenalin und 2) ein unspezifischer, lokalanaesthetischer, der möglicherweise in einer Behinderung des transmembranalen Ionenaustausches besteht und somit Ursache für die Hemmung der Kontraktionskraft sein könnte. Das Ausmass der Refraktärzeitverlängerung durch die untersuchten β-Adrenolytika wird, wie die vorliegenden Versuche zeigen, durch die spezifisch β-adrenolytische sowie durch die unspezifische Wirkung in etwa gleichem Umfang bestimmt.

Summary. In isolated guinea-pig atria, the β-adrenolytic isomer D(−)INPEA provoked a stronger prolongation of the refractory period (rp) than did the inactive L(+) isomer. The β-adrenolytic drug MJ 1999 prolonged likewise the rp, although it caused no unspecific effect, i.e. an inhibition of contractile force. These observations lead to the conclusion that not only the unspecific local anaesthetic but also the specific β-adrenolytic effect is of importance for the prolongation of rp.

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The Effect of Dimethyl Sulfoxide on X-Ray Conditioned Saccharin Aversion

The ability of a wide range of biochemically active compounds to offer protection to the living organism against X-radiation death has prompted a great deal of study in this area with the past few years. Although reduction in mortality is an important criterion of the effectiveness of chemoprotection, it is equally important to determine if a chemical disrupts the behavioral effects of radiation. It is a well-established finding that a post-exposure aversion to saccharin-flavored water can be conditioned in rodents by a single pairing of the solution with a whole-body X-ray dose[1].

Recently, dimethyl sulfoxide (DMSO) has been reported to interfere with postirradiation aversion to sodium saccharin in mice[2]. However, since group effects (10 mice/cage) were measured at weekly intervals in the above study it was impossible to determine if all the animals drank saccharin or just a few.

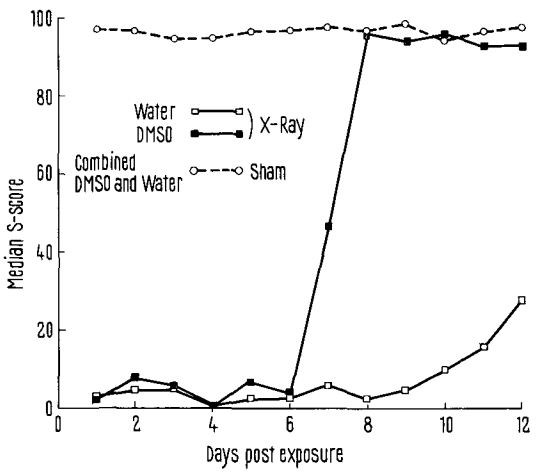
In the present study the drug effects were noted on individually housed animals at daily intervals, thereby permitting observation of within-group relationships as well as those among groups.

Since it was shown that DMSO has a radioprotective effect on rats[3], and since most of the previous data and techniques on saccharin aversion had been demonstrated with rats, this species was used in the present study.

[1] D. J. KIMELDORF and E. L. HUNT *Ionizing Radiator: Neural Function and Betravion.* (Academic Press, New York 1965).
[2] H. LEVAN and W. S. MOOS, Experientia *23*, 276 (1967).
[3] B. HIGHMAN, J. R. HANSELL and D. C. WHITE, Radiat. Res. *30*, 563 (1967).

Methods. The subjects for this study were 40 female, 90-day-old Charles River rats. The X-rays were generated by a General Electric 300 kV Maxitron, operated at 250 kV, 20 mA, at a subject-to-target distance of 47 inches. The subjects were irradiated in individual rectangular Plexiglas chambers at a dose rate of 30 R/min for a total dose of 100 R. The chambers were placed radially on a slowly rotating (3.3. rpm) turntable so that each subject received an equal radiation exposure. For the application of the treatment solution the animals were confined in individual cylindrical Plexiglas chambers (2.5 × 8 inches) in an upright position. At one end of the cylinder were many small ventilation holes; at the other end was a single large opening for the insertion of the tail. 10 cylinders were placed on a circular rack with 125 ml flasks containing the treatment solution placed under each.

The subjects were gentled and housed in individual cages. Prior to exposure all subjects received 2 sham trials in order to give the animals some habituation to the manipulative procedures. For these trials the subjects had their tails immersed in water for 10 min each day following 24 h of water deprivation. The subjects were then placed in the rectangular Plexiglas boxes and given a sham exposure. The sham exposure consisted of placing these chambers on the rotating turntable under the X-ray machine. The voltage to the X-ray tube was not turned on. After the sham exposure, the subjects were returned to their home cages where water was available for 20 min. On the third day, after the 24 h deprivation period, 20 of the subjects were placed in the dipping chamber and had their tails immersed in DMSO for 10 min. 20 control animals were also placed in the dipping chamber and had their tails dipped in water for 10 min. After the tail immersion, half of the subjects in each group were placed in Plexiglas chambers and given a 100 R exposure to the X-rays. The remainder of the subjects were placed in Plexiglas chambers and sham exposed. The subjects were then returned to their home cages where saccharin solution (0.1% by weight) was available for 20 min. After the saccharin presentation, water was presented for 24 h and followed by a 2-bottle preference test. One bottle contained the saccharin solution and the other water. At the end of 24 h the position of these bottles was reversed to note possible position habits. The total liquid consumption and the 'S-score' were determined for a 12-day period. The 'S-score' was the per cent of the total liquid consumption which was saccharin and was used as an index of saccharin aversion during the preference test.



The median saccharin preference score (S-score) for each treatment solution (DMSO or water) and X-ray exposure condition are plotted for all animals given saccharin 5 min after exposure. Also plotted are all sham exposed animals, regardless of treatment solution, treated as a single group.

Results and discussion. Mann-Whitney U-tests performed on the 2 sham exposure groups resulted in no significant differences between the DMSO and water treated sham groups on any of the days. As a result of this analysis, all sham exposed animals were treated as a single group and compared to all irradiated animals. The Figure shows the median 'S-scores' for each of 12 days following exposure for the 2 irradiated groups plus the combined sham exposed animals. A Kruskal-Wallis analysis of variance showed a significant difference ($p < 0.05$) among these 3 groups for each of the 12 days. Subsequent Mann-Whitney U-tests showed that the differences were due to a difference between irradiated and sham groups for days 1–6, DMSO vs water groups for days 8–12, and for differences in both on day 7.

There is evidence from this study that treatment with DMSO lessens the effect of saccharin aversion in rats while having no effect on sham exposed animals. The traditional dependent variable used in most saccharin aversion studies is to measure the amount of water and saccharin consumed for 48 h post exposure[4]. The effect of DMSO in the present study is not evident in the first 48 h post exposure, but in the progressive increase in saccharin consumption (e.g. extinction data). Of the previous studies conducted on saccharin aversion extinction, it has been reported that rats given saccharin and gamma exposure simultaneously over 6 h require 50 days to extinguish[5]. In the present study, rats treated with DMSO have extinguished their aversion to saccharin by day 8 while rats treated with water show saccharin aversion on all 12 days post exposure.

It is also interesting to note that these data agree with the results obtained by LeVan and Moos[2]. Since LeVan and Moos measured only after the first week of preference testing, it was not known if differences occurred during the first 48 h or what the daily changes were. However, after 1 week post exposure they reported that mice treated with DMSO prefer saccharin solution to water; this agrees with the results of the present study on day 8.

The results of this study suggest that perhaps a more sensitive measure of saccharin aversion is the extinction of the aversion rather than the traditional 48 h preference test[6].

Zusammenfassung. Ganzkörperbestrahlung von Ratten mit 100 R führt zu einer ausgeprägten Aversion gegen Na-Saccharinlösung. Die Vorbehandlung mit Dimethylsulfoxyd (DMSO) lässt diese Aversion 6–8 Tage nach der Bestrahlung wieder verschwinden.

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[5] J. Garcia, D. J. Kimeldorf and R. A. Koelling, Science *122*, 157 (1955).

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