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CHRONOBIOASSAY OF RADIATION INJURY IN MICE WITH AND WITHOUT TIME SHIFT

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ABSTRACT

The relation between circadian temperature amplitude and radioresistance was studied in three groups of male C3H mice two of which were subjected to an 8-h time shift shortly before irradiation. In animals with unshifted schedule, the impact of the size of circadian temperature amplitude on radiation susceptibility showed a circadian rhythm depending on time of irradiation. Radiation injury could be shown to cause circadian dyschronism of body temperature and inhibition of resynchronization in time-shifted groups, the extent of dissynchronization also depending on time of irradiation.

KEYWORDS

Radiation injury; circadian temperature parameters; mice; time shift; dyschronism.

INTRODUCTION

Numerous investigations have shown that mammalian radiation response depends upon the phase of circadian systems at exposure time (Lach and Srebro,1971, Lappenbusch, 1972) It now seems generally accepted that animals such as rats (Pizzarello et al., 1963) and mice (Pizzarello et al., 1964, Haus et al., 1971) show lower radiation susceptibility during the daily light as compared to the daily dark span (compare Gerbes and Arbogast, 1983).Sudden time shift of synchronizer phase is known to impose considerable internal desynchronization to biological systems (Klein und Wegmann, 1975), before the organism accepts the new schedule. It seemed worth while to investigate

1) in which manner radiation response depends not only upon the phase but also on the amplitude of circadian rhythms and
2) inhowfar radiation injury causes dyschronisms and inhibits the process of synchronization to a new schedule after time shift.

MATERIAL AND METHODS

Three groups of male C3H mice were subjected to L:D 15:9 schedules (light 0600 - 2100, dark 2100 - 0600) for 3 weeks, the schedules of groups II and III being shifted by 8 hours as compared to the schedule of group I. Circadian profiles of body temperature were determined proving good synchroniza-

tion. Thereafter, groups II and III were suddenly shifted to the schedule of group I, resulting in a maximal reduction of the daily light and dark span, respectively. At seven about equidistant times during the following day, subgroups (10 animals each) of groups I - III were exposed to whole-body X-irradiation (X-ray unit MG 300, C.H.F. Müller, Hamburg, FRG. 250 kV, 12 mA, half-value layer 1.9 mm Cu, dose rate 88 cGy/min). At a focus-mouse distance of 40 cm, the total dose was 640 cGy. Ten animals per group remained without irradiation (controls). Mortality and temperature of each animal were measured for 30 days following irradiation as indicators of radiation susceptibility. On the 10th day following irradiation, again circadian temperature profiles were determined for all animals still alive.
Statistical analysis was performed on a Cyber 175 computer using our own Fortran programs for linear rhythmometry.

RESULTS

The maximal reduction of body temperature during the observation span- as compared to a reference temperature before irradiation - was taken as a measure of radiosusceptibility (variable $TEMP_{diff}$). Regressions of $TEMP_{diff}$ on the amplitude of circadian temperature rhythm before irradiation - computed for all subgroups separately - revealed that in group I, the subgroups irradiated at the end of the dark or begin of the light span (few hours after the time of computed greatest radiosusceptibility, see Gerbes and Arbogast, 1983) took advantages from low circadian amplitudes, while for animals irradiated at the end of the light or begin of the dark span, high circadian amplitudes were advantageous. There were no such effects in the time shifted groups II and III, possibly due to the onset of internal desynchronization after time shift. The slopes of the regressions of $TEMP_{diff}$ on circadian temperature amplitudes computed within the irradiation subgroups are displayed in figure 1.

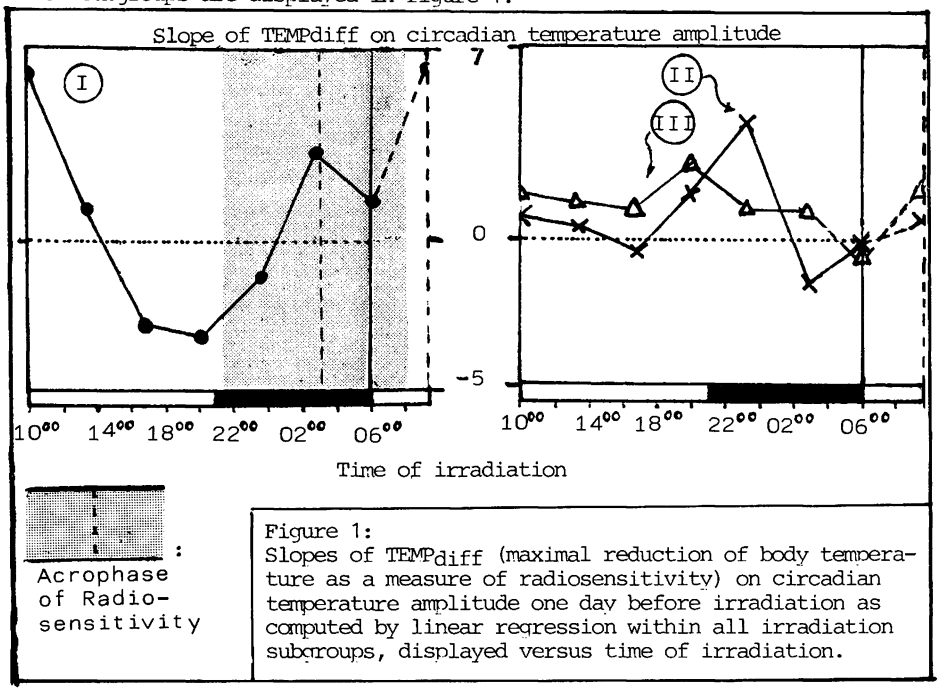


Figure 1:
Slopes of $TEMP_{diff}$ (maximal reduction of body temperature as a measure of radiosensitivity) on circadian temperature amplitude one day before irradiation as computed by linear regression within all irradiation subgroups, displayed versus time of irradiation.

Figure 2 shows single cosinor analysis of the data in figure 1. Besides the aforementioned fact that in group I (not time shifted), the impact of the size of circadian temperature amplitude exhibits a significant (p=0.05) circadian rhythm which is not the case for the time shifted groups II and III, a global deterioration of radioresistance in case of high circadian temperature amplitudes is indicated by the fact that all mesors are greater than zero. This effect is, however only significant for group III, since the confidence interval of its mesor does not include zero.

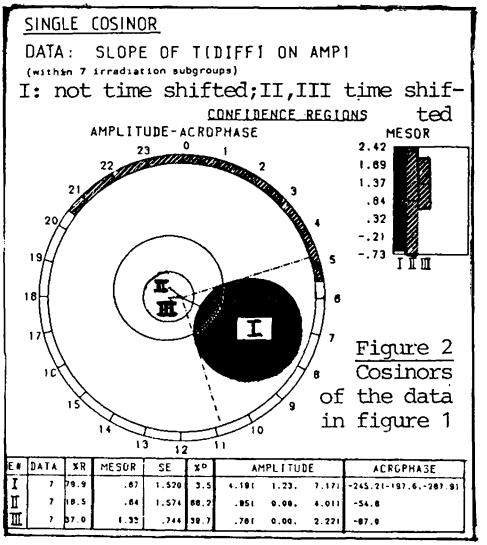


Figure 2 Cosinors of the data in figure 1

Circadian temperature profiles determined 10 days after irradiation (11 days after time shift for groups II and III)were finally used to study eventual dyschronisms caused by radiation injury. From the pooled control groups of groups I - III (a total of 30 unirradiated animals), a population mean cosinor was computed which proved good synchronization of all control animals to the new L:D schedule. The amplitude-acrophase-pairs of all irradiated animals which were still alive were then compared with a 10% - Parameterdesm computed from the control animals. (see figure 3) Just 54.3 % of the irradiated animals of group I had amplitude-acrophase pairs within the control paradesm: Radiation injury seems to cause circadian dyschronism. For groups II and III,

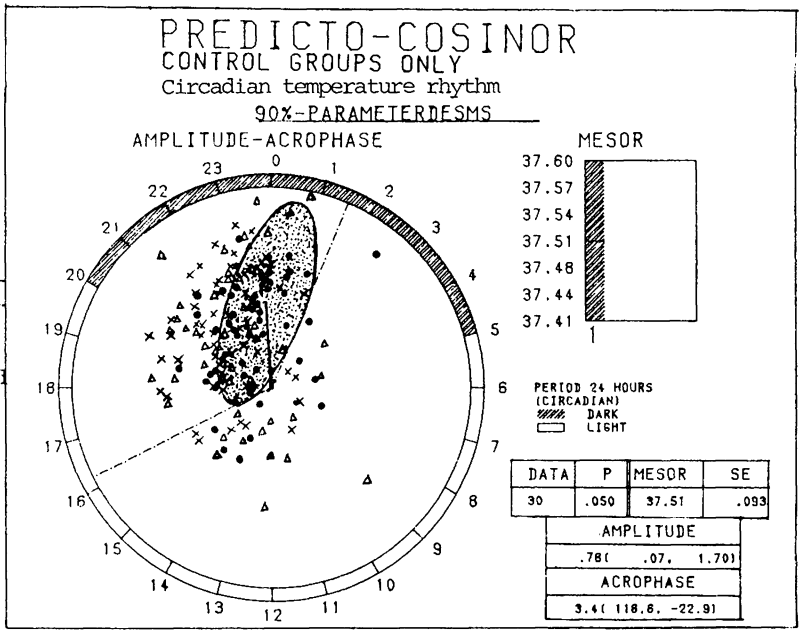


Figure 3: Predicto-cosinor computed from control animals of groups I - III and amplitude-acrophase pairs of irradiated animals:

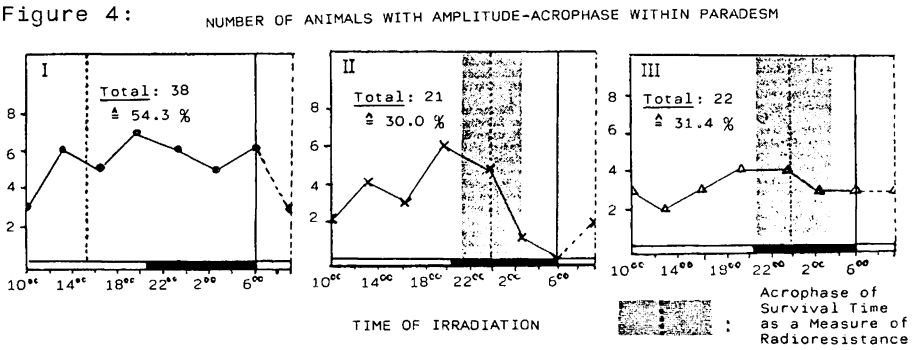
● : group I

✕ : group II

Δ : group III

the percentages of irradiated animals with amplitude-acrophase pairs of the circadian temperature rhythm within the control paradesm was even lower (30 resp. 31.4 %)indicating inhibited synchronization to the L:D schedule after time shift.

Figure 4:



The number of animals with amplitude-acrophase pairs within the control paradesm, for each irradiation group separately, is displayed in figure 4. It can be seen that most cases of dyschronism occur in subgroups irradiated around the time of greatest radiosusceptibility, especially in groups II and III.

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