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Kinetics of repair in the spinal cord of the rat

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Abstract

Purpose: Split dose experiments were carried out with two 2 Gy fractions per day at intervals ranging from 0.5 to 24 h, in order to investigate both the time to complete repair and the detailed kinetics of repair of sublethal damage in the cervical spine of rats.

Materials and methods: Male rats of the WAG/Rij strain were irradiated at 2 Gy/min with 18 MV photons to a length of 18 mm of cervical spinal cord. Four hundred twenty-three rats were irradiated without top-up doses to investigate whether repair was complete by 24 h or whether any slow repair or proliferation occurred up to 50 days after irradiation. Three hundred seventy-nine rats were also irradiated in split dose (2 Gy + Δt + 2 Gy each day) experiments, with intervals of 0.5, 1, 2, 4, 8 and 24 h. The split dose irradiations were followed by a single top-up dose of 15 Gy (producing about half the total damage).

Results: Repair was complete by 24 h as the ED50 values were the same at 1, 11 and 50 day intervals for two large fractions, and for 10 fractions in 10 or 50 days. A mono-exponential component of repair of T1/2 = 0.25 (95% CI 0.16–0.48) h was determined by direct analysis using all the data and T1/2 = 0.37 (0.28–0.53) h for the split 2 Gy doses with top-up only. A bi-exponential analysis did not fit better. The presence of a second component was demonstrated graphically, with T1/2 of about 6.5 h but with a wide confidence interval from near 0 to 13 h. However, the 24 h ED50 was significantly different from all ED50s except the 8 h value. Considering all data together, an upper limit of about 7 h could be placed on any long component, or else repair could not be complete by 24 h.

Discussion and conclusions: Two components of repair (0.7 and 3.8 h) have been reported by Ang et al. (Ang, K.K., Jiang, G.L., Guttenberger, R., Thames, H.D., Stephens, L.C., Smith, C.D. and Feng, Y. Impact of spinal cord repair kinetics on the practice of altered fractionation schedules. Radiother. Oncol. 25: 287–294, 1992) in the spinal cord of Sprague–Dawley rats. Two components have also been reported by others more recently. The present result could, with its graphical interpretation, agree in principle, but with a shorter fast component and a longer slow component. A slow component of 5.5 h was reported by Ruifrok et al. (Ruifrok, A.C.C., Kleiboer, B.J. and van der Kogel, A.J. Fractionation sensitivity of rat cervical spinal cord during radiation retreatment. Radiother. Oncol. 25: 295–300, 1992) in a related strain of WAG/Rij rats. The possible presence of a slower component than Ang et al.'s 3.8 h might help to explain the four myelopathies observed in the pilot studies for the CHART clinical trial. The presence of the definite fast component (<0.5 h) could have important consequences when pulsed brachytherapy is used to replace continuous low dose rate irradiation.

Keywords: Spinal cord; Radiation damage repair; Kinetics; Half-time

1. Introduction

A number of papers have been published about the kinetics of repair in the spinal cord of rodents [1,4,14,17,18,24,35,36,39,40]. The first study to identify two components of repair in rat spinal cord was that of Ang et al. [1], with half-times of 0.7 and 3.8 h and magnitudes of 38 and 62%, respectively. They irradiated 707 adult female rats of the F344 Sprague–Dawley strain. The slow component was not quite long enough to explain readily the four cases of human myelitis observed in the pilot studies of the CHART radiotherapy schedule [8,26], as has been well

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discussed [1,13,29], unless the half-times of repair in human patients are longer than in rats [33].

The present paper describes a series of experiments involving 802 male rats of the WAG/Rij strain, with either full fractionation courses in different overall times, or with daily pairs of 2 Gy fractions at intervals ranging up to 24 h followed by a top-up dose of 15 Gy. These irradiations were carried out at about the same time (1989–1990) as those of Ang et al. [1], but have not been published. They agree in suggesting two components of repair, of which the fast component is clearly significant as described below, but the slow component is poorly characterised and may have a longer T1/2 value than in the experiments of Ang et al. [1], employing a similar design of two small fractions each day. Other currently published results also suggest two components of repair in rat spinal cord [17,23].

Several other tissues have also given results interpreted as bi-exponential repair, including human telangiectasia [3], human oropharyngeal mucosa [7], mouse lung [12,20,38], pig skin [22,34], rat kidney cells [21] and mouse lip mucosa [29]. The experiments are technically demanding and difficult to analyse because too many variables become necessary [28]. Further, Denham et al. [7] have suggested that even two components are only a rough approximation to a range of multiple T1/2 values in reality.

The subject has new importance because brachytherapy with pulsed dose rates (PDR) is expected not to differ greatly in biological effectiveness from low dose rates (LDR), unless a substantial component of repair with short T1/2 (less than about 0.5 h) is present in the tissue at risk [5,11,19]. This could be a serious practical problem for PDR in tissues which have a significant component of fast repair, if the duration of pulses approaches those values of T1/2.

2. Materials and methods

Male inbred WAG/Rij rats were used for the present experiments at the age of 12–14 weeks. They were bred and kept until the start of the irradiations in a conventional animal house. The broad spectrum antibiotic tylosine was added to the drinking water to prevent respiratory infections.

Irradiations were carried out with a linear accelerator generating 18 MV photons. A neck segment of 18 mm length, from C2 to T1 of the spinal cord, was irradiated at a focus skin distance of 100 cm. The remainder of the rat was accurately shielded by MCP blocks. A tissue equivalent bolus 2.5 cm thick was placed over the neck region to ensure full electron build-up. A dose rate of 2 Gy/min was used. To allow reproducible positioning throughout the treatments, the rats were lightly anaesthetised with a mixture of enflurane and oxygen, using a semi-closed inhalation system [2].

A total of 802 rats was irradiated in this project. Four hundred twenty-three were treated without top-up doses to investigate whether repair was complete by 24 h, or whether any slow repair or proliferation occurred up to 50 days after irradiation. In this part of the project, intervals of 1, 11, or 50 days were used between two large fractions and 10 equal fractions were given in either 11 or 50 days, i.e. with intervals of 1–3 or 5–6 days, respectively. After thus demonstrating that no further repair occurred after 24 h, 379 further rats were irradiated in the split-dose (2 Gy + Δt + 2 Gy each day) part of the project to investigate T1/2, divided evenly between the six intervals of Δt = 0.5, 1, 2, 4, 8 and 24 h. The split-dose irradiations were followed by a single top-up dose of 15 Gy, as discussed extensively and used for rat spinal cords by Ang et al. in 1983 [3] and discussed by Joiner [15]. In these experiments the top-up dose provided half of the total effect. Wong et al. [40] and Kim et al. [17] have shown that neither the sequence nor the size of top-up doses alters the results on kinetics of repair in the spinal cord of rats.

The experiments were carried out with four to eight animals per X-ray dose point. A number of dose points were repeated some months later as part of the planned project when results of the first groups were available. Forty of the 802 rats died before the expected onset of paralysis at 5 months; 36 of them were from groups given 2 Gy + 2 Gy at intervals of 4 h or less. Seventeen other rats died without paralysis before the end of the observation period. The deaths were due to oesophagitis and all 53 were excluded from the analysis of spinal cord injury.

After the irradiations, the rats were examined twice a month during the first 5 months and at least weekly for the next 4 months to evaluate movements and reflexes of the forelegs. The animals were sacrificed painlessly when definite signs of fore-limb paralysis appeared or at the end of the observation period (normally 9 months). Graphs of incidence of myelopathy versus radiation dose were plotted. The ED50 (interpolated radiation dose inducing paralysis in 50% of animals) values and curves were calculated by a logistic regression program [30] which gave identical values to a probit program. The graphs in Figs. 1 and 2 are therefore symmetrical about the 50% response level.

Half-times of repair were analysed from the resulting data by two methods. First, the direct analysis method was employed. This takes in every data point for every animal and by a method of maximum likelihood fits the chosen radiobiological function to the data. It has been well described in the literature [32] and is much used. The function fitted was the incomplete repair model of Thames [31]:

$$P = \exp(-\exp(\ln K - \alpha D - (1 + h\nu) \times \beta D^2/N))$$

where P is the probability of myelitis, D is the total dose, N is the number of fractions, K is the number of 'tissue rescuing units', α and β are the non-repairable and repairable parameters, respectively, of the LQ model and $h\nu$ is the incomplete repair correction calculated as in Gutten-

Table 1

Summary of experiments without top-up doses to establish completeness of repair or absence of proliferation between 24 h and 50 days

Experiment	No. of rats	No. of dose groups	ED50 (Gy) (95% CI)	Percent full width of 95% CI
Single dose	135	11	20.2 (19.3–20.5)	5.9
2 F/1 day	31	6	29.0 (28.0–30.0)	6.9
2 F/11 days	66	11	28.5 (27.7–29.3)	5.6
2 F/50 days	32	6	29.1 (27.3–31.1)	13.1
10 F/11 days	86	10	57.5 (55.7–59.3)	6.2
10 F/50 days	73	10	57.7 (55.3–60.2)	8.4
Total	423			

F, fractions.

berger et al. [13]. For the bi-exponential repair model $h\nu$ was calculated as $h\nu = \rho \times h\nu_1 + (1 - \rho) \times h\nu_2$, with $h\nu_1$ and $h\nu_2$ being the corrections for slow and fast repair and ρ being the proportion of slow repair [1]. This method gives 95% confidence intervals for $h\nu$ and hence for T1/2.

The second method of obtaining repair rates is a more traditional two-step process. First the dose causing the effect

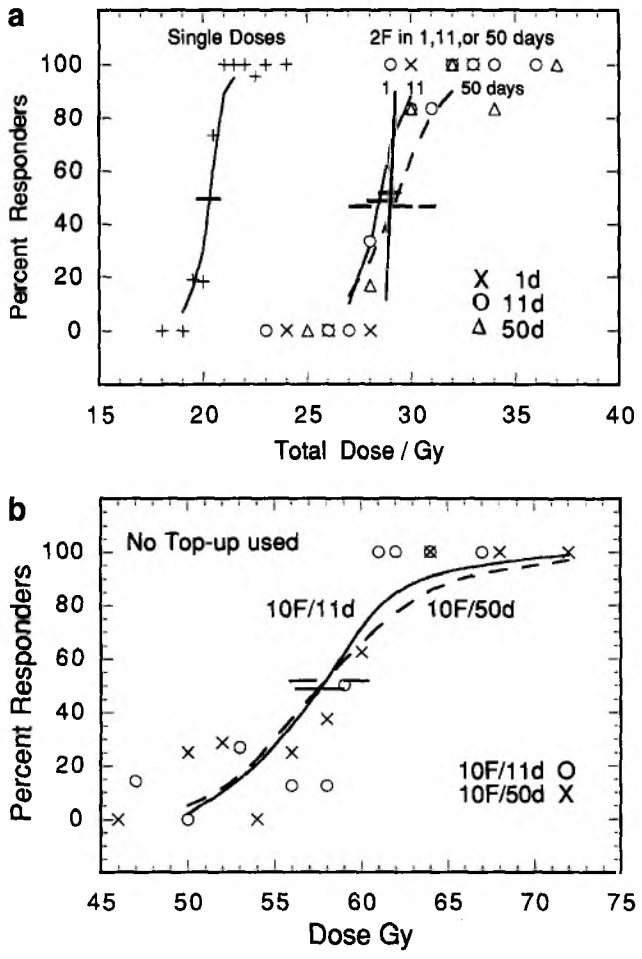

Fig. 1. Results from Table 1. No top-up doses were used. (a) Single doses and two equal fractions in 1, 11 or 50 days. (b) Ten equal fractions in 11 or 50 days. The close agreement of the ED50 values in each panel demonstrates the lack of any slow repair beyond 24 h, or any effect of proliferation up to 50 days in this biological system. Horizontal bars represent 95% confidence intervals of ED50s.

in 50% of the animals is determined (the ED50) by logistic regression of the proportion of responders in each group on dose. These ED50 values can be plotted linearly against the interval between the two 2 Gy doses each day to show the pattern of repair. The ED50 at 24 h was taken as corresponding to complete repair, as confirmed in the first experiments described here. The difference between the ED50 at any other time interval and the ED50 at 24 h was taken as a measure of the incomplete repair and plotted logarithmically as a percentage of the difference between the 24 h and the zero-time ED50, against the linear time interval. The (inverse) slope of the resulting regression line would give T1/2 if mono-exponential repair were appropriate. If bi-exponential repair were present, two straight lines would have to be deconvoluted by successive subtraction from the full curve in the standard way of compartment theory. Their intercepts on the zero-time axis should add up to unity and indicate relative proportions of the two components of repair. This method has been criticised [16,25] because dose is not a linear surrogate for damage (log cell kill), certainly with big single or only two large split doses. However, that objection does not apply for multi-equal-fraction dose-response curves, as in the design of these '2 Gy + Δt + 2 Gy per day' experiments where total dose is many times larger than 2 Gy.

Results are presented as graphs of all the dose points with proportions of rats responding and tables show ED50 values with the 95% confidence intervals and numbers of rats irradiated in the 12 experiments. Original data can be provided by the authors to interested correspondents.

3. Results and discussion

Fig. 1 and Table 1 show the results of the three types of experiment carried out without top-up doses, i.e. single doses, two equal fractions at intervals of 1, 11 or 50 days and 10 equal fractions at overall times of 11 or 50 days, i.e. at intervals of 1, 3 or 5 days (not at weekends). They show generally steep dose response curves with small 95% confidence intervals. It should be noted that the 95% CIs listed in the tables are percent full width, so that 6% here means ±3% CI and ±1.5% SD. These are technically very good

Table 2

Summary of experiments with a top-up dose of 15 Gy to investigate intervals (0.5–24 h) between two fractions of 2 Gy each day

Interval Δt (h)	No. of rats	No. of dose groups	ED50 (Gy) (95% CI)	Percent full width of 95% CI
0.5	59	6	46.7 (44.2–49.4)	11.1
1	58	8	54.0 (50.5–57.7)	13.3
2	62	8	52.2 (49.7–54.8)	9.8
4	70	9	52.2 (49.4–55.2)	11.1
8	71	8	56.5 (53.7–59.4)	10.1
24	59	8	61.2 (58.0–64.6)	10.8
Total	379			

experiments. The CIs are naturally somewhat larger when top-up doses are used to provide about half of the effect. The ED50 values then averaged ±2.5% SD (Table 2) which is still technically good. For the two fractions in the 1-day experiment in Fig. 1a the CI is arbitrary because all the doses up to and including 28 Gy gave zero responders (in 15 rats) and all doses of 30 Gy and above gave 100% response (16 rats), with no intermediate values. The absence of a calculated CI is a well known failure of statistical methodology.

All three of the two-fraction experiments gave closely similar ED50 values, which is good evidence against repair beyond 24 h or of slow repair or proliferation up to 50 days after a large dose of 13–16 Gy, as also determined earlier [35].

Fig. 1b and Table 1 show that the two 10-fraction experiments given in overall times of 11 or 50 days yielded the same ED50 within 0.2 Gy. The coincidence of the computed regression curves, in spite of some scatter at the lower dose points, is convincing evidence that no further repair and no proliferation occurs between these smaller doses (5–6 Gy) over the period of 11–50 days after starting the 10 fractions and thus for intervals of 1–5 days. It should be noted that the average interval for the 10 fractions in 50 days was 5 or 6 days and that the 10 fractions in 11 days schedule consisted of 24 h intervals with one weekend gap of 3 days.

These data support the evidence that repair is fully complete by 24 h in this biological system and that changes in the overall time between 1 and 50 days do not alter the ED50 value [35].

Fig. 2 and Table 2 show the results of the split dose experiments with 2 × 2 Gy repeated daily to the chosen total dose, with the interval Δt stated for each group. The dose response curves are of similar steepness and CI except for the 1 and 24 h interval curves which show more variation. The point for $\Delta t = 0$ h was estimated as described below.

From the data above, direct analysis [32] yielded an estimated α/β ratio of 2.0 (1.7–2.4 CI) Gy. The value 2 Gy was not significantly different from the α/β value calculated simply by LQ algebra from the weighted (by rat numbers) mean of the ED50 values, which was 1.86 Gy (no CI available by this so-called two-step method). The α/β ratio of 2.0 was used in the following calculations of T1/2.

It is clear that a large proportion of the damage was repaired within the first hour, whether we take the direct analysis result or consider a two-step analysis described below and plotted in Figs. 3 and 4. Direct analysis of all the data yielded a fast component of T1/2 = 0.25 (CI 0.16–0.48) h when a mono-exponential LQ model was fitted to the data. Although visual inspection of the data and of Fig. 3 suggested bi-exponential repair, direct analysis did not show an improved fit using the bi-exponential model. The problem is that there are no data between 8 and 24 h to fix the parameters of the slow component, whose slope is poorly defined by the points between 0.5 and 8 h. Repair was complete at 24 h so there is of course no zero-time data point on an exponential plot at that time in Fig. 3.

In another run of direct analysis, only the data obtained with top-up doses were analysed (Table 2). The resulting T1/2 was 0.37 h with 95% CI of 0.28–0.53 h. This value was not significantly different from the 0.25 (0.16–0.48) h result obtained from all data as reported in the previous paragraph. There was no doubt that there was a major com-

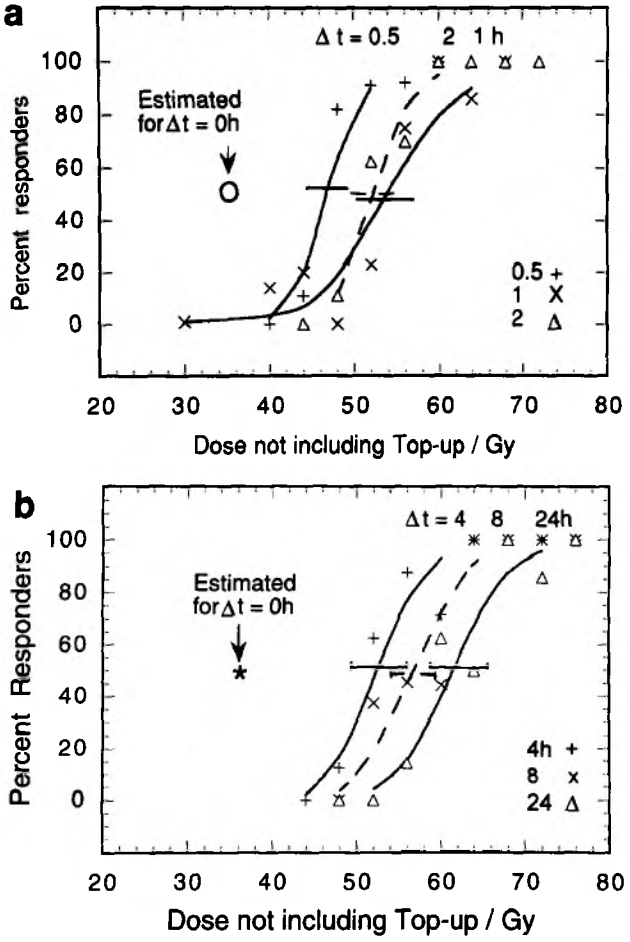

Fig. 2. Results of the split dose experiments from Table 2. Top-up doses of 15 Gy were added after the total doses shown. Percent responders versus total dose given as 2 Gy + Δt + 2 Gy on successive days. Horizontal bars represent 95% confidence intervals of ED50s.

ponent of fast repair of T1/2 less than 0.53 h from both data sets (all data and only top-up). However, direct analysis could not find a significant second repair time. Using bi-exponential repair the model became overparameterised, or the log likelihood did not change significantly.

Nevertheless, in view of many previously published results which demonstrated a mono-exponential fit to repair data with T1/2 of 1–1.8 h [4,35,36,39], it seems extremely unlikely that there is not a second and longer component to complement the well defined short component identified here. A simple plot of the logarithm of unrepaired dose against interval, using differences between ED50 values expressed as a proportion of the ED50 for 24 h minus that for zero-interval (Fig. 3) visually suggests two components of repair, with the inflection probably between 0.5 and 2 h and a poorly defined tail. It may also be noted that the shape of this curve, with its dip at 1 h and subsequent rise, is similar to the classic in vitro cell survival recovery curves first described by Elkind and Sutton [9]. For the present experimental design (with only 2 Gy + 2 Gy doses given at daily intervals), the artefacts in the two-step analysis (using ED50s) that have been well described [16,25] do not apply here. In particular, the dose-response curve for repeated small fractions is essentially linear with log cell survival and not a continuously bending curve as for single doses.

Fig. 4, a linear plot, also shows the problem clearly. No matter what the poorly defined rate of a possible slow component might have been, there was this cluster of points at 0.5–8 h situated between 70 and 25% short of the complete repair ED50, which we know to be complete at 24 h from Figs. 1 and 2. These points indicate some slower component than the 0.25–0.37 h determined above. It is understandable that the direct analysis might be unable to specify an estimate of slope (T1/2) and therefore would recognise no significant second component, so it would not comment on the possible proportion or even the presence of such a component.

The present data as shown in both Figs. 3 and 4 clearly require further investigation of some possible slow component, which might perhaps throw some light on the nature of the different approaches. To make the semilog plot in Fig. 3 required an estimate of the zero-interval ED50, that is with a 4 Gy dose given daily; this dose-response curve was not obtained in the present set of experiments.

A simple LQ calculation was made from the 10-fraction data without top-up of the expected total dose if 4 Gy fractions had been given daily instead of the 5–6 Gy actually used, assuming an α/β ratio of 2 Gy [6,27]. From this the estimated ED50 for the 4 Gy doses was 33.6 Gy, based on 159 rats. A similar LQ calculation was made from the weighted average of all three two-fraction experiments (Table 1 and Fig. 1); the result was 36.6 Gy, in reasonable agreement. Their combined weighted average was 34.8 Gy, based on the 258 animals.

This estimate represented the ED50 for zero-repair, to be contrasted with the ED50 of 61.2 Gy for Δt = 24 h (without the top-up dose of 15 Gy) representing 100% repair. Further, reiterating these calculations assuming α/β values at each end of the CI range of 1.7–2.4 Gy yielded less than 1% variation in the estimated zero-repair ED50.

A somewhat larger uncertainty was involved if we considered the range of CI values of the individual ED50s, with a weighted average of ±4.2 Gy for the combined estimate of zero-time ED50. The final result yielded an approximate range for the proportion of repair occurring by the slow component of 20–75%, with an average value from several estimates of 33%. Its T1/2 cannot be determined accurately from Fig. 3 and not at all by the direct analysis program (because its slope cannot exclude zero), nor of course by a linear plot as in Fig. 4, which includes the 24 h point at 61.2 Gy.

The point about the slope 1/T1/2 of the slower component being not significantly different from zero is of crucial importance. If that T1/2 were indeed infinite, then the 24 h point could not be at 61.2 Gy, but only at the average of all the values beyond 0.5 h, of which the best fit would then be 51.9 Gy. Reference to Fig. 4 shows that there then would remain only the fast component shown by incomplete repair at 0.5 h, that is with the T1/2 of 0.25 h. However, the 24 h data point is clearly not near 51.9 Gy; it is at 61.2 Gy with a 95% confidence interval of 58.0–64.6 Gy (Table 2). This experimental fact is in favour of the graphical two-step interpretation. Indeed, the ED50 for Δt = 24 h was significantly different from all of the ED50s for 0.5, 1, 2 and 4 h because, as can be seen from Table 2, their confidence intervals do not overlap with that for 24 h.

Therefore, while the repair process might be explained only by a mono-exponential component with T1/2 as short as 0.25 h, (from the direct analysis alone), the data are also consistent with two components of repair, as suggested graphically in Fig. 3, with the longer component having a T1/2

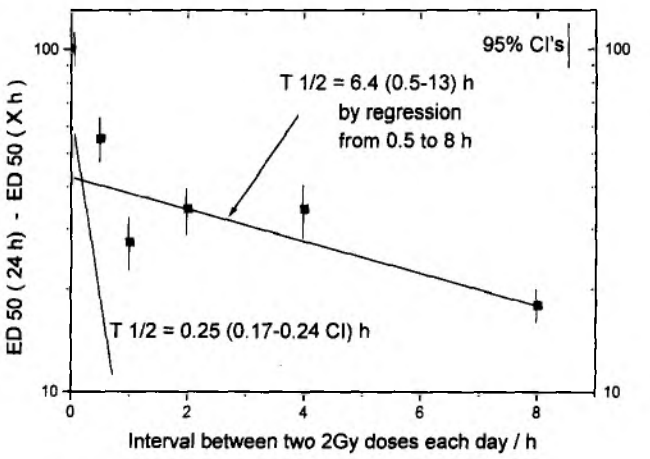

Fig. 3. Semilogarithmic plot of ED50 values from Table 2 expressed as percentages of the difference between the 24 h value of 61.2 Gy and an estimated ED50 for zero-repair (see text), as a function of the interval between two 2 Gy fractions per day. Vertical bars represent 95% confidence intervals of log ED50s.

of about 6 h, although with a very large confidence interval. The data cannot exclude either interpretation.

The obvious uncertainties are shown by the scatter of the data points in Fig. 3 between 1 and 4 h, so the direct analysis estimate above is the definitive result which gives the best values of T1/2 obtainable for the fast component. However, from Fig. 3, after iterative subtraction of the 0.25 h component, a wide but not infinite range of slow components remained graphically, as shown. One extreme was 70% of a 4.5 h half-time, the other about 25% of a 12 h T1/2, with a more probable (graphically central) value of approximately 40% of a 6.5 h T1/2. Linear regression of the points in Fig. 3 from 0.5 to 8 h inclusive yielded a slope of T1/2 = 6.4 h, with however a very wide confidence interval (0.5–13 h) which is why direct analysis classified it as a repair rate not significantly different from zero.

It is important that repair was shown in these experiments to be complete by 24 h (Figs. 1 and 2) for two reasons. First, it excludes any accumulation of effect due to slow repair which might otherwise accumulate over the 10–49 days of the split dose experiments and affect the final ED50. This possible artefact of the two-step process can therefore be excluded. The other main artefact, curvature of the single-dose response curve, is avoided by using only split 2 Gy fractions daily, so that the total-dose response curve is close to linear. Secondly, an upper boundary is placed on the T1/2 value. Repair at 24 h would be complete except for either 3 or 1% of the repairable injury with T1/2 of 6.5 or 4.5 h, respectively, from a 40% slow component. A slow component of 25% with T1/2 of 12 h can be excluded on this basis.

4. Conclusions

The conclusion from the present experiments is clear, i.e. that a fast component of repair was present in these rats (<0.53 h) whatever analysis was done. A possible slow component existed with T1/2 ≈ 4.5–6.5 h, which is of similar or somewhat smaller magnitude to the fast component (20–75%). This does not disagree in principle with the conclusion of Ang et al. [1] in Sprague–Dawley rats and with other very recent data [17,23]. It is interesting also that Ruifrok et al. [24] reported the possible existence of a slow component of 5.5 h in a related random-bred WAG/Rij strain of rats, as indeed did the preliminary results for Ang's Sprague–Dawley rats, with 0.8 and 5.8 h [10].

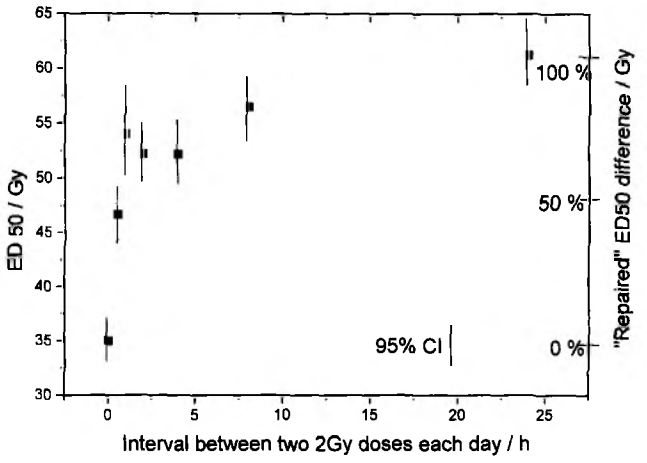

Fig. 4. Linear plot of the ED50 values from Table 2 as a function of the interval between two 2 Gy fractions per day, together with the estimated value for zero-repair at zero-time interval. Vertical bars represent 95% confidence intervals of ED50s.

Clear evidence was obtained that repair in this section of the spinal cord of these rats was complete by 24 h, whether two fractions of 13–16 Gy or 10 fractions of 5–6 Gy were used, delivered over 1–50 or 11–50 days, respectively. These data exclude both repair and significant proliferation between 24 h and 50 days, as reported earlier [35,36]. These data enabled a reliable value for α/β to be found of 2.0 (1.7–2.4 CI) Gy, obtained by direct analysis. Using this value, it was possible to calculate an LQ estimate for an ED50 with Δt = 0 h (daily fractions of 4 Gy).

The 2 Gy + Δt + 2 Gy data enabled a fast component of repair to be estimated by direct analysis of 0.25 (0.17–0.48 CI) h taking all the data, but no better fit was obtained with a bi-exponential LQ model. A semilogarithmic graph of incomplete repair versus fraction interval suggested a wide range of possible slow components, with T1/2 most likely to be about 6.5 h (95% CI 0.5–13 h), together with the fast component of approximately equal or greater magnitude (Fig. 3). An upper limit of about 7 h is placed on the possible slow component, or else repair could not be complete by 24 h as it was demonstrated to be. For the same reason it is likely that the slower component is the smaller one.

Of the two possible interpretations, the second is preferred: (i) a fast component of 0.25 h (0.17–0.48 h), with no significant proportion of the repair at a slower rate. This was the direct analysis result; (ii) two components of repair, the fast one (0.25 h) constituting 25–80% of repair and the slow one 22–75% with a T1/2 of roughly 6.5 h (by regression of the points from 0.5 to 8 h inclusive in Fig. 3). This was the two-step analysis.

That two possible components of repair are present agrees in principle with other experiments in spinal cord of rats [1,10,17,23]. The presence of a longer component than the 3.8 h of Ang et al. [1] could help in the interpretation of the four myelopathy cases seen in the pilot studies for the CHART clinical trial [8,26], as has also been discussed by others [1,13,37].

It is interesting that a number of reports of two-component repair in other tissues are appearing in the literature, including very recently [12,17,20–22,29,34,38]. Further, Denham et al. [7] have suggested that a continuum of repair rates may be present, for which two components is only a poor approximation, even though attempts to deconvolute more than two components are fruitless because of the wide confidence intervals of published data from all biological experiments.

There is a particular timely importance in finding the possible presence of a fast component of repair in any tissue. It is with the presence of a substantial component of fast repair that pulsed brachytherapy (PDR) might be more damaging than conventional low dose rate brachytherapy (LDR), given to the same total dose in the same overall time. This risk is greater if doses per pulse as large as 2 Gy are used and is minimised by using small doses per pulse of less than 1 Gy each [5,11]. The risk of more damage from PDR than from equivalent LDR irradiation is particularly great for T1/2 values of less than 0.25–0.5 h because the pulse durations approach the T1/2 values.

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