

INDIVIDUAL DIFFERENCES IN RADIOSENSITIVITY OF MICE CORRELATED WITH THEIR METABOLIC RATE

by

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The relationship between metabolic rate and recovery half-time described by MICHAELSON & ODLAND (1962) suggests that the metabolic rate is one of the factors involved in the species difference in radiosensitivity among mammals and is related mainly to the process of recovery from radiation injury. If the relationship can be extended from the species difference in radiosensitivity to individual differences among mammals of the same species, individual differences in radiosensitivity may be explained on the basis of differences in metabolic rates. The present work was planned to investigate this possibility.

Experimental procedures. Ninety-day old male and female DBA/2 mice were housed for 30 days before the start of the experiments in the animal room in order to become adapted to the conditions. The mice were given water and Funabashi Farm's chow ad libitum. Aureomycin powder (4 g/l) was added to the water after irradiation; it had been proved in a preliminary experiment that this amount of aureomycin powder has no effect on the production of endogenous spleen colonies. The animal room was kept at $20 \pm 2^\circ$ C.

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Table 1*Relationship between ESC count and metabolic rate of mice (n: number of mice used)*

Group	ESC count			
	A	B	C	D
Metabolic rate	~-1.0	-1.0~0.0	0.0~+1.0	+1.0~
Mean±SE	8.7±1.7	9.3±1.3	12.6±1.7	7.9±1.9
n	7	51	27	16

Table 2*Relationship between mean survival time and metabolic rate of mice (n: number of mice used)*

Group	Mean survival time (days)			
	A	B	C	D
Metabolic rate	~-1.0	-1.0~0.0	0.0~+1.0	+1.0~
700 R (mean±SE)	21±2.6	24±1.7	22±1.5	14±2.6
n	15	32	38	13
850 R (mean±SE)	11±1.2	12±0.6	12±1.7	9±0.8
n	11	12	12	9

The mice were irradiated with a Toshiba deep roentgen therapy unit, operating at 24 mA, 190 kVp, with added filtration of 0.5 mm Cu and 0.1 mm Al. The target to body axis distance was 50 cm; 500 R, 700 R and 850 R (measured in air) were given. The doses and dose rate (ca 63 R/min) were checked during exposure by means of a Victoreen Radocon dosimeter. The exposure time was kept constant to avoid the diurnal rhythm of radiosensitivity (UENO 1968).

The mice were observed for 30 days after exposure for measurement of mean survival time and mortality. The surviving mice were sacrificed by cervical dislocation and the spleens removed ten days after exposure for measurement of endogenous spleen colony (ESC) counts. The spleens were fixed in Bouin's solution and ESC with diameters of more than 1 mm were counted seven days after fixation.

The metabolic rate during the 24 hours just before exposure was calculated by the Kleiber formula $g/(kg)^{3/4}$ in each mouse, where g was the consumption of diet or water in gram for 24 hours and kg the body weight in kilogram. The metabolic rates were corrected using the standard deviation (UENO 1969).

Table 3

Relationship between survival and metabolic rate of mice (D: metabolic rate induced from diet consumption, W: metabolic rate induced from water consumption)

Group	Percentage survival 30 days after irradiation to 700 R			
	A	B	C	D
Metabolic rate	~-1.0	-1.0~0.0	0.0~+1.0	+1.0~
D	53.3	68.7	55.2	23.0
W	57.1	61.7	50.0	50.0

Results

The mice were divided into four groups on the basis of the corrected metabolic rates for each mouse: less than -1.0, -1.0 to 0.0, 0.0 to +1.0 and more than +1.0. The ESC count, the mean survival time and the mortality in each group was summarized to calculate a mean value. Extremely large values were rejected by Smirnov's test of rejection before this calculation.

Table 1 indicates that when the metabolic rate induced from diet consumption was used, the ESC count in groups A and D was less than in groups B and C.

The mean survival time of each group is given in Table 2. With the metabolic rate induced from diet consumption, the mean survival time in groups A and D was less than in groups B and C, after both 700 R and 850 R of irradiation.

The survival of each group irradiated with 700 R 30 days after exposure appears in Table 3. The survival in groups A and D was less than in the other groups when the metabolic rate was calculated from diet consumption. A similar tendency was observed when the metabolic rate was obtained from the water consumption.

Discussion

The Kleiber index of metabolic rate is not a complete expression of metabolic activity, especially when determined by water consumption, but it is a convenient way of expressing it and a useful check on metabolic activity in experiments on individual differences in mice.

The individual differences in a genetically homogeneous population are generally remarkably few. A discussion of the general relationship therefore seems feasible.

The results presented in the three tables indicate that the mice with intermediate metabolic activity have relatively low radiosensitivity both at the cellular

level *in vivo* and the whole body level, as compared with the mice with high or low metabolic activity.

The relationship between radiosensitivity and metabolic activity presented in previous reports (BLOUNT & SMITH 1949, SMITH *et coll.* 1949, KIMELDORF *et coll.* 1950, SMITH & SMITH 1951, TSUCHIYA *et coll.* 1963) is that an increase in metabolic activity is always accompanied with an increase in radiosensitivity in mammals. However, it has also been found that an increase in metabolic rate is accompanied by an acceleration of the recovery process (MICHAELSON & ODLAND 1962, CASARRET 1969, WILSON 1969). The former relationship corresponds to that observed in groups C and D and the latter to that in groups A and B. Thus, the relationship between metabolic rate and radiosensitivity presented here can be analyzed into two components: one the effect of the metabolic rate on accelerating the injury process due to irradiation, and the other the acceleration of the recovery process. The relationship observed between metabolic rate and radiosensitivity is an index of a balance between the two components. In mice with a comparatively low metabolic rate, the effect of the metabolic rate on accelerating the recovery process must play the main role; and its effect on accelerating the injury process must constitute the means in mice with comparatively high radiosensitivity. An optimal metabolic rate in a population of mammals for the suppression of radiosensitivity therefore appears evident. Such consideration of balance has been reported (POSPISIL & NOVAK 1959, UENO 1968) and has been expressed mathematically as an imbalance of metabolic-energy processes (NOVAK *et coll.* 1964).

The problem of how the metabolic rate accelerates the recovery process in mice with a comparatively low metabolic rate and how it accelerates the injury process in mice with a comparatively high metabolic rate remains to be solved.

Both sexes were used in the present experiment. If the male:female ratio in each group were not similar, the present data might suggest that radiosensitivity depends on sex. The ratios were similar in the four groups. The data seem to indicate that differences in radiosensitivity depend on the metabolic rate.

Mice with comparatively low radiosensitivity appear to have a relatively large number of ESC which seem to be composed mainly of erythropoietic cells. The main factor in the so-called bone marrow death after irradiation with the doses used in the present experiment is said by PATT (1969) to be granulocytopenia. Though histologic examinations of ESC were not carried out in the present research, there may be differences in the ratio of myelocytic ESC to erythrocytic ESC depending on the metabolic rates of the host mice, in addition to the differences in numbers of ESC in the myelocytic or erythrocytic

system. At any rate, the number of ESC-forming stem cells closely related to bone marrow death is large in the mice with an optimal metabolic rate. This suggests that the optimal metabolic rate of the host mammal stimulates the production of many hemopoietic stem cells or reduces the radiosensitivity of each stem cell. If the latter mechanism is obtained, the optimal metabolic rate may stimulate stem cells to develop from less to more differentiated stages. The present data indicate the possibility that one of the mechanisms by which the metabolic rate modifies the radiosensitivity of an individual mouse at the whole body level is via the dynamics of the hemopoietic system. This possibility is also recognized in investigations on species or strain differences in radiosensitivity in mammals (TSUCHIYA et coll. 1969, FLIEDNER 1969).

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SUMMARY

The survival times, survival rates and endogenous spleen colony counts were correlated with the metabolic rates of DBA/2 male and female mice. The radiosensitivity of individual mice with low or high metabolic rates was greater than that of mice with intermediate metabolic rates in the same population; this was apparent at both whole body and cellular levels.

ZUSAMMENFASSUNG

Die Überlebenszeiten, die Überlebensraten und die Zahlen der endogenen Milzkolonien wurden zur Grösse des Metabolismus von männlichen und weiblichen DBA/2 Mäusen korreliert. Die Strahlenempfindlichkeit individueller Mäuse mit niedrigen oder hohem Metabolismus war grösser als von Tieren derselben Population mit mittleren Metabolismus; das galt sowohl für den Gesamtorganismus als auch für das zelluläre Niveau.

RÉSUMÉ

L'auteur a établi une corrélation entre les taux métaboliques de souris mâles et femelles DBA/2 et le temps de survie, le taux de survie et la numération des colonies spléniques endogènes. Dans une même population, la radiosensibilité de certaines souris ayant des taux métaboliques bas ou élevés est plus grande que celle des souris qui ont des taux métaboliques moyens; ceci apparaît aussi bien au niveau du corps entier que des cellules.

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