Sex Differences in the Effect of Uric Acid on the Survival of Analbuminemic Rats Exposed to Cold: Effects of Gonadal Hormones and Uric Acid

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Summary When female analbuminemic rats were injected with 0.8 mg uric acid every 3 h, their survival time at 5°C increased from 14 h to 28 h, but uric acid had no effect on analbuminemic male rats. When female rats were oophorectomized 1 week before cold exposure, the injection of uric acid had no effect on their survival. Furthermore, uric acid did not increase the survival of the female rats that were administered a pellet containing 5 mg testosterone 1 week before the cold exposure. When the male rats were castrated 1 week before cold exposure, their survival time decreased from 20 h to 14 h, and administrations of 5 mg estradiol pellet at the time of castration and 0.8 mg uric acid every 3 h during cold exposure increased their survival time to 23 h.

Key words: uric acid, castration, estradiol.

We previously reported that the survival time of female analbuminemic rats exposed to 5°C was prolonged from 14 h to 28 h by injecting the animals with uric acid (KAWAGUCHI et al., 1986). However, it is not known whether uric acid injection has the same effect on male rats. If there are sex differences in the effect of uric acid, gonadal hormones such as estradiol or testosterone may also have some effects on the survival of these special rats.

The present study compared the effects of uric acid on the survival of male and female analbuminemic rats exposed to cold. The effects of estradiol, testosterone, castration, and oophorectomy were also examined.

Analbuminemic rats (NAR), substrain of Sprague Dawley lacking plasma albumin (NAGASE et al., 1979) were fed laboratory chow Oriental MF (Tokyo) at

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room temperatures of 23–24°C. The animals were divided into 8 groups (Fig. 1); half of each group (7–13 animals) were injected with uric acid and the remaining ones with saline. Ten to 12 animals born at one time were divided into 3 groups (3–4 animals) for each experiment: the untreated controls (Group 1) and the previously operated group injected with uric acid or saline. The same experiment was performed 2–3 times. At the age of 7 weeks, 50–60-mg pellet of testosterone was subcutaneously implanted to the female rats with or without oophorectomy through bilateral flank incisions under pentobarbital anesthesia. In the male rats, castration...
was performed at the age of 7 weeks and a 50–60-mg estradiol pellet was implanted.

Seven days after surgery (male 145 ± 6 g, female 137 ± 6 g, the operated animals were 2–3 g lighter than unoperated animals), the rats were injected ip with 0.8 mg of uric acid suspended in 1 ml of 0.9% NaCl. Then they were individually placed in a screen-bottomed stainless steel cage and quickly transferred to a cold room (5°C) at 09 : 30. The same amount of uric acid was injected at 3-h intervals until each animal was dead. In group 12 (Fig. 1), 4 of the male rats were injected with a mixture of 0.8 mg uric acid and 0.1–0.6 mg estradiol (instead of oophorectomy) on 7 days before uric acid administration. And other 4 animals of the same group were sc injected with a 10 mg of estradiol cypionate (long-acting type of estradiol, Nakarai Chemicals, Kyoto) dissolved in soybean oil.

The estradiol or testosterone pellets were made as follows: 100 mg powder of 17β-estradiol or testosterone (Nakarai Chemicals, Kyoto) and 1 g powder of cholesterol (Nakarai Chemicals, Kyoto) were mixed in a glass tube. The mixture was melted by heating the bottom of the tube. The melted mixture was quickly aspirated into 2-mm vinyl tubing. The congealed mixture was removed from the tube and cut into 7–10-mm lengths. Seven to 8 days after implantation, the size of the pellets became slightly smaller, indicating the continuous release of the hormones.

The conditions of the animals in cold were checked at 30-min intervals. The animals were alive as long as their rectal temperatures were higher than 20°C. When the rectal temperature was lowered to less than 20°C, it dropped suddenly to the room temperature. Accordingly, when the animals laid on their side with limbs spread and had a rectal temperature lower than 7°C they were regarded as the dead. Rectal temperature was measured using an electric thermister (Nihon Kohden, MGA-III, Tokyo).

Experimental results are expressed as the mean ± S.E. The results obtained were evaluated using 3-way analysis variance for repeated measures between control group (Group 1) and two trial groups (DUNNETT, 1964), and p value less than 0.05 was accepted to denote significant difference.

When exposed to 5°C, the female NAR died in about 14 h, while the male NAR survived for 20 h (p <0.05, Fig. 1, Groups 1 and 9). The administration of uric acid to the male and female NAR extended the survival time of the females to 28 h (p <0.05, Group 2) but not that of the male NAR (Group 10). When female NAR were administered with the testosterone pellet 7 days before the cold exposure, the survival time of the rats decreased to 12 h, and the administration of uric acid during the cold exposure did not increase their survival time (Groups 3 and 4). When the female NAR were oophorectomized 7 days before the cold exposure, their survival time was 11 h. Again, administration of uric acid had no effect on survival (Groups 5 and 6). The female NAR oophorectomized and administered with the testosterone pellets 7 days before the cold exposure died earlier, and uric acid had no effect on these animals (Groups 7 and 8). Thus, either oophorectomy or testosterone administration reduced the survival time of the
female NAR in the cold.

The survival time of male NAR administered with the estradiol pellet 7 days before the cold exposure was the same as that of unoperated male NAR (Groups 11 and 12). However, the castrated rats died 6 h earlier than the unoperated rats (Groups 13 and 14). Even without the uric acid administration, the survival time of the castrated rat was increased several hours by the administration of estradiol pellet 7 days before the cold exposure (Group 15). In this experimental group, 4 rats were administered with the estradiol for 2 days before the cold exposure, but the increase in survival time was not seen (this case is shown by short column in Group 15 of the figure).

When uric acid was administered to the male NAR previously castrated and implanted with the estradiol pellet for 7 days before the cold exposure, they survived for about 23 h, showing that the uric acid administration increased the survival time for 7 h as compared with the saline group (Group 16). However, the effect of uric acid was negated by changing the administration time of estradiol from 7 days to 2 days before uric acid injection (compare the long and short columns in Group 16.) Thus, it is suggested that animals should have a high estradiol level for a long enough time so that uric acid could extend the survival time of NAR in the cold. In addition, the effect of uric acid was found to be negated by administration of testosterone to female rats (Groups 3 and 4). Thus, it is concluded that uric acid is effective only in high estradiol and low testosterone states. Furthermore, the survival time of castrated male NAR was extended by 5 h by administration of the estradiol pellet alone (Group 15 long column), suggesting that estradiol could extend the survival. The negation of the effect of uric acid by oophorectomy of the female NAR (Groups 5 and 6) confirms this speculation.

Serum uric acid levels of NAR were not changed even after 15-mg administrations of uric acid for 5 days (our unpublished data). Furthermore, serum uric acid levels of NAR were higher than that of normal Sprague Dawley rats in contrast to the expectation (our unpublished data). Thus, it is considered that endogeneous uric acid bound to protein is physiologically inert, and only uric acid exogenously administered can induce the extension of the survival of NAR in cold.

Unoperated male NAR lived 4 h longer than female NAR in the cold. This sexual difference in survival in cold may be due to the differences of body weight (145 g in male vs. 137 g in female). However, the female Sprague Dawley rats whose body weight was almost equal to male NAR in the present study survived for 40 h in the same condition (KAWAGUCHI et al., 1986). Thus, duration of survival of male NAR is not considered to depend on body weight, but to correlate to hormone(s) other than testosterone of the blood, because castrated male NAR died sooner (Groups 13 and 14).

The mechanism by which such effect of uric acid is induced remains unknown, although uric acid may well be a factor involved in longer survival in cold for normal rat (KAWAGUCHI et al., 1986). It was previously reported that estrogen administration caused weight loss and reduced food intake in C57BL/6J-ob/ob mice and
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rats (Bray and York, 1971; Dubuk, 1976, 1985; Roy and Wade, 1977; Clark and Tarttetin, 1982), while bilateral oophorectomy led to weight gain with increased fat content (Hausberger and Hausberger, 1966; Wright and Turner, 1973; Roy and Wade, 1977; Clark and Tarttetin, 1982). Thus, it is inferred that the gonadal hormone, estrogen, activates energy production as does uric acid.

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REFERENCES


