Hormonal Influence on Experimental Infections by a Toxic Shock Strain of Staphylococcus aureus†

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Subcutaneous infection chambers in rabbits were infected with a strain of Staphylococcus aureus isolated from a patient with toxic shock syndrome. Estrogens (mestranol and 17β-estradiol) protected male rabbits and prolonged survival. Neither androgens (testosterone and dihydrotestosterone) nor progesterone affected the susceptibility of intact or ovarihysterectomized female rabbits.

There have been several approaches to developing an animal model for the study of toxic shock syndrome (TSS). Many of these have focused on intravenous injections of the distinctive protein associated with many of the Staphylococcus aureus strains isolated from patients with TSS. This protein, designated TSST-1, produces a rash in guinea pigs and mice infected with Staphylococcus aureus strains, and a rash has also been observed in humans infected with Staphylococcus aureus. However, the TSST-1 model has several disadvantages, including the need for intravenous injection and the use of guinea pigs and mice as animal models.

To overcome these limitations, a subcutaneous infection model was developed (Best et al., 1984). In this model, rabbits were inoculated intramuscularly with Staphylococcus aureus, and the infection was then allowed to progress for several days. The infection was then harvested and characterized using a variety of techniques, including immunoassay and radioimmunoassay.

The results of this study indicate that estrogens (mestranol and 17β-estradiol) protect male rabbits from the effects of TSST-1 infection, whereas androgens (testosterone and dihydrotestosterone) and progesterone do not. These findings suggest that estrogens may have a protective effect on male rabbits infected with TSST-1, whereas androgens and progesterone do not.

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level comparable to that of intact males not receiving mestranol and was the only rabbit in the group which did not survive. Each of the other rabbits in group C had serum testosterone levels below those consistently associated with mortality (see groups A and B, Table 2). A comparison of the testosterone levels observed in group B rabbits indicates the hormone pellets permitted consistent steroid levels to be established. The serum testosterone levels in untreated, castrated males were 81 ± 5.8 pg/ml (mean ± standard error), and 25-mg testosterone pellets restored the serum testosterone levels of the rabbits in group B to the lower range of normal.

The apparent association of serum testosterone with mortality in male rabbits prompted attempts to enhance the susceptibility of 6-month-old female rabbits by using testosterone or dihydrotestosterone implants to elevate serum androgen levels. Intact females had 123.9 ± 17.5 pg of testosterone per ml of serum, and testosterone implants elevated this level to between 1 and 3 ng/ml. However, neither androgen caused a significant increase (data not shown) in the mortality of either intact or gonadectomized female rabbits infected with S. aureus 555 (\(P > 0.1\) by Fisher’s exact test).

\(P_4\) at two levels was given to 6- and 9-month-old female rabbits to determine whether \(P_4\) itself, or perhaps metabolites of \(P_4\), could affect the mortality of female rabbits. Rabbits of both ages were used, because 9-month-old females are somewhat more susceptible to S. aureus infections than are younger animals. Assays for serum \(P_4\) were conducted on blood samples taken from each rabbit just before infection. The control animals had 442 ± 68 pg of \(P_4\) per ml at the time of infection. Pellets (25 mg) of \(P_4\) increased the level to 874 ± 78.5 pg/ml. The 100-mg pellets given to neutered females produced serum levels of 897 ± 69 pg/ml. \(P_4\) had no effect on the infections in female rabbits of either age when given in 25- or 100-mg pellets. If \(P_4\) were protective, this should have been evident when older females were used. If \(P_4\) enhanced mortality, this should have been observed when 6-month-old ovariectomized rabbits were used (data not shown).

The close association of mortality with serum testosterone levels in male rabbits (9 of 9 rabbits with testosterone >1.7 ng/ml, 3 of 6 rabbits with testosterone of 1.6 to 1.7 ng/ml, and 0 of 6 rabbits with testosterone <1.6 ng/ml) indicates that the level of circulating androgen may be an important factor in determining host susceptibility to the toxin(s) of the TSS strain of S. aureus. The protection afforded by estrogen treatment of male rabbits might be explained by the observed reductions in serum testosterone levels. However, the absence of a significant enhancement of the susceptibility of female rabbits by androgen treatment, which yielded serum testosterone levels comparable to those of intact males, suggests that estrogens are protective by some mechanism(s) other than their effects on serum testosterone levels.

It is not yet clear how our results with this rabbit model of TSS reflect on TSS in humans. It is interesting to note, however, that Garbe et al. (6) recently reported on 32 cases of nonmenstrual TSS in which 7 of 16 male patients died, compared with none of 16 female patients. Thus, the role of sex steroids in TSS deserves further investigation.

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LITERATURE CITED

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