Long-term effects of accelerated or delayed sexual maturation on reproductive output in wild female house mice (Mus musculus)

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Summary. The effects of acceleration and delay of puberty in female house mice on survival and reproduction were tested using 6 experimental groups: (1) control females mated at the time of first oestrus, (2) females mated at weaning, (3) females treated with male urine starting at weaning and mated at first oestrus, (4) females housed in groups and mated at first oestrus, (5) females housed alone, treated with urine from grouped females and mated at first oestrus, and (6) females housed alone and mated at 68 days of age. Females caged with males at weaning or treated with male urine and mated at puberty had lower rates of survival to 180 days of age, but did not differ in rates of fertility from mice in the other four treatments. Those females that were housed with males from weaning or treated with male urine also had smaller total numbers of litters, fewer total young, and smaller average litter sizes than did females for which the age of mating was delayed, by grouping or treatment with urine from grouped females, or by being held until age 68 days before mating. Control females mated at first oestrus generally were intermediate or did not differ from the male treatments on these dependent variables. There were no differences in the average number of female young/litter across the 6 treatments. However, females that were delayed in age of first mating had significantly more male young/litter than did females that were accelerated in their sexual development or control females. Acceleration of puberty may therefore have certain costs for the lifetime reproduction of female mice. In contrast, females that are older at first mating apparently have larger litters, due primarily to the fact that they have more male young/litter.

Keywords: mouse; chemosignals; fertility; fecundity; puberty; lifetime reproduction

Introduction

The age of first vaginal oestrus in female mice is influenced by a number of factors, including genetics (Drickamer, 1981), environmental conditions, such as temperature, photoperiod (Laurie, 1946; Barnett & Coleman, 1959; Drickamer, 1975a, b), diet (Bronson, 1979) and social conditions, including the presence of urinary chemosignals (Vandenerbergh, 1969; Vandenerbergh et al., 1972; Drickamer, 1974; see reviews by Vandenerbergh, 1983; Drickamer, 1986). There are at least 4 urinary chemosignals that can influence the timing of sexual development in conspecific females; urine from males, urine from females in oestrus, and urine from females that are pregnant or lactating all accelerate the onset of first oestrus, whereas urine from females housed in groups delays first oestrus. Because many rodents, including house mice, mate and conceive at the time of puberty and because first oestrus coincides with puberty (Drickamer, 1977) for house mice, changes in the age at puberty will be reflected in changes in the generation time and hence can influence population growth or decline.
Throughout the years of research on chemosignals affecting the timing of puberty in female mice, the general assumption has been made that for females in which puberty is accelerated there would be some advantage with respect to lifetime production of progeny and for passing genes on to subsequent generations, relative to females in which puberty occurred at later ages (Vandenbergh, 1983; Drickamer, 1986). Progeny from females with accelerated puberty will have the potential to reproduce sooner than progeny from females that do not exhibit accelerated sexual development. One question that arises concerning reproduction in female mice that exhibit accelerated or delayed sexual development is whether they have different litter sizes. Vandenbergh et al. (1972), using laboratory house mice, determined that there was no difference in the litter size or litter viability to the age of weaning between mice born to females that did or did not have accelerated puberty because of treatment with urinary chemosignals. This question has not been thoroughly tested for wild house mice. Another question that arises concerns the survival and lifetime reproduction for females that are accelerated or delayed in attaining sexual maturation. Does alteration of the age of puberty, away from the 'normal' age measured for untreated controls, result in any measurable effects on fertility or fecundity?

The present experiment was designed to test whether accelerating or delaying the onset of puberty and time of first mating can influence the survival and reproductive output within the females of a stock of wild-caught mice.

Materials and Methods

All of the mice used in these experiments were second or third generation laboratory mice derived from wild mice (Mus musculus) caught at West Simsbury, Connecticut (U.S.A.). All mice were maintained in shoe-box cages of polypropylene measuring 15 × 28 × 15 cm deep with opaque sides and fitted wire lids. A bedding of ground wood shavings was changed once each week. Pregnant females and young female mice were provided with cotton for making nests. Wayne Lab Blox and water were supplied ad libitum to all mice throughout the experiment. All cages were maintained throughout the experiment in the same room at 21–25°C and 30–60% relative humidity on a 12 h light:12 h dark daily regimen with overhead fluorescent lights on from 06:00 to 08:00 h.

The 120 female young were taken from 60 different litters, using a maximum of 3 young from any particular litter, were weaned at 26 days of age, and were assigned to 1 of 6 treatments with the restriction that no more than 1 female from a particular litter was assigned to the same treatment: (1) control females were caged alone, tested for age of first oestrus, and with a male added at the day of first oestrus; (2) females caged with a male added on the day of weaning; (3) females caged alone, treated daily on the external nares with urine from male mice, tested for age of first oestrus, and with a male added on the day of first oestrus; (4) females housed 8/cage beginning at weaning, tested for age of first oestrus, and placed in a separate cage with a male added on the day of first oestrus; (5) females caged alone, painted daily on the external nares with urine from grouped females, tested for age of first oestrus, and with a male added on the day of first oestrus; and (6) females caged alone, tested for age of first oestrus, but with a male not added until the female attained 68 days of age. An analysis of variance revealed no significant differences (F = 1.16; d.f. = 5, 114; P > 0.20) for the mean body weights of the mice across all 6 treatments.

All males used for urine collection or for caging with females were adults, aged 80–130 days at the start of the experiment. All males had had previous mating experience. Males were assigned to particular female cages at random with the restriction that no test female was mated with her brother or father. In all cases, the male that was placed with the female remained caged with her for the duration of the experiment. No males died during the course of the experiment. Grouped females used for urine collection in Group 5 were adults, aged 80–130 days at the time of their use for urine collection and they had been housed 8/cage for at least 25 days before the start of the experiment.

Each test female was monitored daily from the start of the experiment to determine the age of vaginal introitus. From the day of introitus onward a daily vaginal lavage was made until first oestrus was attained. The wet-mount vaginal smears were examined immediately to determine the stage of the oestrous cycle using the criteria of Vandenbergh (1969). In Group 2, in which a male mouse was present with each young female from the day of weaning onward, the appearance of a seminal plug in the female's vagina was used as an alternative criterion to determine the age at first oestrus.

The experiment was carried out until each female had attained 180 days of age. During the period from pairing until cessation of the experiment, the following measurements were taken: (a) survival of the female; (b) successful production of one or more litters and the dam's age at the time of parturition for each litter; and (c) for each litter, the number of young at birth, sex of each young at birth, aggregate weight of the young at birth, number of young at weaning (26 days of age), sex of each young at weaning, and aggregate weight of young at weaning were determined.
Results

Mice in Group 2 attained first oestrus significantly sooner than did those in other groups (Table 1; F = 21.76; d.f. = 5, 114; P < 0.001). Puberty occurred significantly earlier for mice in Group 3 than for those in Groups, 1, 4, 5 and 6. The mean ages for puberty of mice in Groups 1 and 6 (control treatments) did not differ significantly.

Mice in Groups 4, 5 and 6 produced their first litters at similar ages which were significantly later than those for mice in Groups 1, 2 and 3 (Table 1; F = 12.13; d.f. = 5, 114; P < 0.001). Mice in Group 2 produced their first litters at a significantly earlier mean age than did those in any other treatment.

Females in which puberty was accelerated (Groups 2 and 3) had significantly lower survival to 180 days of age than did females in the other 4 groups (Table 1; χ² = 22.06; d.f. = 5; P < 0.001). Of the deaths, 3 in Group 2, 2 in Group 3 and 1 in Group 1 resulted from initial attempts by the males to mate with the females; the females were, in each instance, wounded and did not recover. All other deaths occurred when the females were over 90 days of age and, in most instances, after the female had produced at least 1 litter. There was no difference in the fertility of the females in the 6 groups (Table 1; χ² = 3.49; d.f. = 5; P > 0.20).

There were no significant differences between the 6 groups in the average number of litters produced when the results were based upon the number of fertile females in each treatment (Table 1; F = 1.54; d.f. = 5, 101; P > 0.20) but, when means were calculated for the same data using, as the denominator, the total number of females per group, then there was an overlapping pattern of significant differences (Table 1; F = 3.36; d.f. = 5, 114; P < 0.01). Females in Group 2 had smaller litter sizes than did those in all other groups except Group 3. Females in Group 3 did not differ significantly in litter production from those in Groups 1, 4 and 5. Females in Groups 1, 4, 5 and 6 had mean litter productions that were significantly larger than those of females in Groups 2 and 3.

As shown in Table 1, there were significant differences in the mean total numbers of young produced, calculated either on the basis of all females (F = 3.26; d.f. = 5, 114; P < 0.001), or using fertile females only for the denominator (F = 2.97; d.f. = 5, 101; P < 0.025); the details of significant differences among mean treatment values were slightly different for the two methods of measuring production of young, but the overall patterns were similar. Females in Groups 2 and 3 did not differ from those in Group 1, but they did produce fewer total young than did mice in Groups 4, 5 and 6. There were no significant differences (F = 0.89; d.f. = 5, 101; P > 0.20) in the mean weight per young at birth across the 6 groups (data not shown).

For mice in Groups 4, 5 and 6, litter sizes (F = 4.33; d.f. = 5, 101; P < 0.001) and the mean number of male young/litter (F = 11.08; d.f. = 5, 101; P < 0.001) were significantly greater than for females in Groups 1, 2 and 3 (Table 1). There were no differences in the mean numbers of female young produced per litter in the 6 groups (Table 1; F = 0.39; d.f. = 5, 101; P > 0.20).

Females in Groups 2 and 3 produced fewer weaned young over the 180 days than did females in the other 4 groups (Table 1; F = 2.94; d.f. = 5, 101; P < 0.025). Females from Group 1 were intermediate between the other treatments. More male young survived to weaning from those born to females in Groups 4, 5 and 6 than in Groups 1, 2 and 3 (F = 15.58; d.f. = 5, 101; P < 0.001), but there were no significant differences in the mean numbers of female young (F = 0.16; d.f. = 5, 101; P > 0.20) surviving to weaning age for all 6 groups (Table 1). Also, there were no significant differences (F = 0.47; d.f. = 5, 101; P > 0.20) in the mean weight per weaning mouse in the 6 groups (data not shown).

Discussion

There are two complementary conclusions that can be drawn based upon the foregoing data and the analyses of reproduction of the mice in the 6 treatment groups used in the experiment. The
Table 1. Mean ages for first vaginal oestrus, age at first reproduction, survival, fertility, fecundity, and additional dependent variables for female mice in which puberty was accelerated or delayed by housing conditions or treatment with urinary chemosignals*

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (days) at 1st oestrus</td>
<td>54:7 (1:3)c</td>
<td>40:6 (1:4)*</td>
<td>47:7 (1:6)b</td>
<td>68:1 (1:2)d</td>
<td>66:9 (1:4)e</td>
<td>55:2 (1:5)g</td>
</tr>
<tr>
<td>Age (days) at 1st litter</td>
<td>75:9 (1:0)e</td>
<td>65:4 (1:0)*</td>
<td>70:8 (1:3)b</td>
<td>91:0 (1:5)d</td>
<td>92:4 (1:4)d</td>
<td>88:4 (1:4)d</td>
</tr>
<tr>
<td>No. surviving to 180 days of age</td>
<td>19</td>
<td>12</td>
<td>13</td>
<td>20</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>No. of mice fertile</td>
<td>18</td>
<td>16</td>
<td>17</td>
<td>18</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>No. of litters/fertile female</td>
<td>3:0 (0:2)</td>
<td>2:6 (0:3)</td>
<td>2:5 (0:3)</td>
<td>3:1 (0:2)</td>
<td>3:0 (0:2)</td>
<td>3:2 (0:2)</td>
</tr>
<tr>
<td>No. of litters/female</td>
<td>2:7 (0:3)bc</td>
<td>2:0 (0:3)*</td>
<td>2:2 (0:3)ab</td>
<td>2:8 (0:8)bc</td>
<td>2:8 (0:2)bc</td>
<td>3:0 (0:3)e</td>
</tr>
<tr>
<td>No. of young/fertile female</td>
<td>15:6 (1:3)abc</td>
<td>13:1 (1:7)*</td>
<td>12:6 (1:5)ab</td>
<td>17:3 (1:2)c</td>
<td>16:8 (1:1)bc</td>
<td>18:2 (1:1)bc</td>
</tr>
<tr>
<td>No. of young/female</td>
<td>14:0 (1:6)abc</td>
<td>10:5 (1:8)*</td>
<td>10:7 (1:6)a</td>
<td>15:6 (1:6)b</td>
<td>16:0 (1:3)b</td>
<td>17:2 (1:4)b</td>
</tr>
<tr>
<td>Mean litter size/fertile female</td>
<td>5:2 (0:2)*</td>
<td>5:0 (0:3)*</td>
<td>4:9 (0:2)*</td>
<td>5:7 (0:2)b</td>
<td>5:7 (0:2)b</td>
<td>5:8 (0:1)b</td>
</tr>
<tr>
<td>No. of male young/litter</td>
<td>2:3 (0:1)*</td>
<td>2:2 (0:2)*</td>
<td>2:3 (0:2)*</td>
<td>3:3 (0:2)b</td>
<td>3:2 (0:2)b</td>
<td>3:4 (0:1)b</td>
</tr>
<tr>
<td>No. of female young/litter</td>
<td>2:8 (0:2)</td>
<td>2:8 (0:2)</td>
<td>2:7 (0:1)</td>
<td>2:5 (0:1)</td>
<td>2:5 (0:1)</td>
<td>2:5 (0:1)</td>
</tr>
<tr>
<td>Total no. of young weaned</td>
<td>14:4 (1:3)abc</td>
<td>12:3 (1:6)*</td>
<td>11:8 (1:4)*</td>
<td>16:1 (1:0)b</td>
<td>15:6 (0:8)b</td>
<td>16:9 (1:0)b</td>
</tr>
<tr>
<td>No. of male young weaned/litter</td>
<td>2:2 (0:2)*</td>
<td>2:0 (0:2)*</td>
<td>2:0 (0:2)*</td>
<td>3:0 (0:1)b</td>
<td>3:1 (0:2)b</td>
<td>3:2 (0:1)b</td>
</tr>
<tr>
<td>No. of female young weaned/litter</td>
<td>2:5 (0:2)</td>
<td>2:5 (0:2)</td>
<td>2:6 (0:1)</td>
<td>2:3 (0:2)</td>
<td>2:3 (0:1)</td>
<td>2:3 (0:1)</td>
</tr>
</tbody>
</table>

Values are means (± 1 s.e.m.) for 20 mice/group.
Means in the same horizontal row with different superscript letters are significantly different at the 0.02 level (Duncan's New Multiple Range Test).
*Group 1 = control, caged alone, mated at 1st oestrus; Group 2 = caged with male from day of weaning; Group 3 = treated with male urine, mated at 1st oestrus; Group 4 = housed 8/cage, mated at 1st oestrus; Group 5 = treated with urine from grouped females, mated at 1st oestrus; Group 6 = control, caged alone, mated at 68 days of age.
results may be assessed with respect to the costs associated with earlier attainment of puberty, and they may be examined with respect to potential benefits that may accrue to females in which puberty is delayed, or which do not mate until they are older than the age of first oestrus (see Krebs & Davies, 1987, for a discussion of cost/benefit theory in animal behaviour).

There is a higher mortality associated with acceleration of first oestrus and earlier ages for production of the first litter. That is, females who attain puberty earlier and conceive at the time of first oestrus incur a greater risk of dying at a younger age than do females that have delayed puberty or are not mated for the first time until an age that is equivalent to that for females in which puberty is delayed. As a consequence of the higher mortality, the production of progeny to the age of 180 days is somewhat lower for females who attain puberty and mate at earlier ages than for females that are delayed in the age of initial pairing with a male, but not those that are mated at the time of first oestrus. The patterns of overlapping significant differences between mean values as noted in Table 1 suggest that the effect of age of initial mating on total production of litters and young is a graded one, rather than being all-or-none.

The higher total production of young by females in treatments with delayed matings is largely a consequence of these treatments resulting in larger mean litter sizes and the larger litter sizes are a consequence of a greater proportion of males being born to females in these three groups. The differential production effect related to age of puberty and age of initial pairing with a male and the sex ratio bias toward males both persist until the time of weaning, with more total young weaned and more male young weaned over the experimental period by female mice that were delayed in age at first mating relative to those that were accelerated in their sexual development or were mated at the time of first oestrus.

There are therefore costs associated with earlier puberty, costs that could override any benefits in terms of more rapid perpetuation of genes to subsequent generations, that might exist for females that are capable of producing early maturing progeny. In contrast, females that delay puberty or delay the initial mating and conception may be able to produce additional progeny, both on a per litter basis and over their reproductive lifespan. The natural mean lifespan for house mice has been estimated at 160–210 days depending upon geographical location, although mean life expectancies for some wild mice may range as high as 18 months (Berry & Jakobson, 1971; Bellamy, 1981).

The age of first oestrus in female house mice is apparently under a relatively high degree of genetic control (Drickamer, 1981). It is possible that, with respect to the genetic control of the age of puberty in house mice, natural selection is working in several directions. On the one hand, earlier puberty for some females is a means of successfully passing on genes more rapidly to subsequent generations and a means of ensuring at least some reproduction in a species with a short lifespan and with low probability of surviving to produce more than a few litters. On the other hand, selection could also be favouring some females that delay the onset of their reproduction, by even a few weeks, when, as a consequence of that delay, those females will produce more young. Females that mate for the first time at first oestrus, i.e. with neither accelerated nor delayed young, as the present results indicate, generally intermediate in terms of the measured effects on reproduction. The result of the differing selection pressures could be the polymorphic system that appears to exist for house mice with respect to the timing of puberty and initial reproduction and the consequences of age of first reproduction on production of progeny.

An alternative explanation of the observed variability in age of puberty may be the existence a mechanism(s) that has evolved to provide flexibility in the development of each mouse with regard to the timing of sexual maturation. In this manner, each mouse could have the capacity to respond to the various environmental factors, e.g. diet, social conditions. The extent conditions during the mouse's development would, through its physiology, affect the timing of puberty and the onset of reproduction. For example, a mouse that is developing when conditions are excellent, e.g. abundant food supplies, would be able to grow more rapidly, could attain first oestrus sooner and might, as a result of the more rapid body growth attributable to the good diet, be better able to
withstand the stresses of pregnancy and lactation. Under 'good' conditions we might expect to observe more females reproducing earlier in life, possibly without the higher mortality associated with earlier reproduction although, in the present experiment food was both abundant and of high nutritional quality and yet there were still higher mortality rates for mice in those treatment groups that were subjected to puberty-acceleration. Further investigations of the importance of any inherent variability in the programme controlling sexual development will be necessary to determine the relative importance of genetic determination of puberty and any genetically based capacity to respond physiologically to environmental conditions.

Bronson (1979) proposed that one of the reasons for the delay of first oestrus for female mice that occurs through exposure to other females, or to urine from grouped females, may be that sexual maturation is postponed until the mice have emigrated from the natal deme. The results of the present experiment would extend that finding by adding that females with a delay of first reproduction would have higher probabilities for more lifetime reproduction than their counterparts that reproduced at earlier ages.

Several authors, most notably Trivers & Willard (1973) and Clutton-Brock et al. (1981), have discussed the fact that secondary sex ratios of some mammals apparently can vary in relation to the nutritional status and general condition of the mother. The major hypothesis presented is that, since the reproduction of males varies more than that of females (e.g. in Mus musculus) in species that are polygynous and promiscuous, the development and later reproduction of sons is more probably related to the condition of the mother than for the reproduction of daughters. Therefore, if all other conditions are equal, the model predicts that, when the mother is in poor condition, she will produce more daughters than sons, and when she is in good condition, she will produce more sons than daughters. The results of the present experiment seem to conform with the general predictions of the model. Female mice that are in a control treatment, not subject to conditions leading to acceleration or delay of puberty, do not attain full adult body weight until about 90–110 days of age. With a complete balanced diet present at all times, we can therefore assume that a female that is older (~65–75 days of age) at the time of first reproduction will, on average, have completed more or her body growth and will be in better condition to withstand the stresses of pregnancy and lactation than a younger female (~40–50 days of age) that has not progressed as far in terms of body growth and may be stressed a great deal more by pregnancy and lactation. The higher mortality rates recorded for the females in the two treatments in which first oestrus was accelerated may be, in part, a function of the extra stresses placed on these mice by the early conception and pregnancy.

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