Disruption of early pregnancy by direct and indirect exposure to novel males in mice: comparison of influences of preputialectomized and intact males

D. deCatanzaro, R. Zacharias and C. Muir

Department of Psychology, McMaster University, Hamilton, Ontario, L8S 4K1, Canada

Inseminated female CF-1 mice (*Mus musculus*) were exposed on days 1 to 5 of pregnancy to unfamiliar outbred males. In the first experiment, inseminated females were each housed directly with the sire, a preputialectomized male, or an intact male. Both types of novel male attempted to mate with the female during this period, unlike the sire. Reinsemination occurred in a significant proportion of the females that were exposed to novel males; this effect was equivalent for preputialectomized and intact males. In two subsequent experiments, we refined a paradigm of indirect exposure to novel males through a wire-mesh grid, which prevents mating and reinsemination. Two or three males housed directly above each female through a grid disrupt pregnancy in most cases, but housing the males below the females is much less likely to do so. In a final experiment, each inseminated female was housed below two males that were either preputialectomized or sham-preputialectomized. Whereas 29 of 33 undisturbed controls were parturient, only eight of 32 females exposed to sham-preputialectomized males and six of 32 exposed to preputialectomized males were parturient. These results suggest that nonvolatile pheromones are involved in novel-male-induced pregnancy disruptions, but that preputial gland emissions are not necessary for such disruptions.

Introduction

Environmental changes can have adverse effects upon early pregnancy in mammals (deCatanzaro and MacNiven, 1992). Gestation can be disrupted before or during the period of intrauterine implantation of fertilized ova by diverse stressors, such as chronic restraint (Wiebold *et al.*, 1986; deCatanzaro *et al.*, 1994), daily handling (Runner, 1959), loud noise (Zondek and Tamari, 1967), high ambient temperatures (Hsu, 1948), environmental and social changes (Bronson *et al.*, 1964), and exposure to predators (deCatanzaro, 1988). Exposure to novel males can also disrupt early pregnancy in various rodent species (Bruce, 1959, 1960a, b, 1963; deCatanzaro and Storey, 1989; deCatanzaro *et al.*, 1995a, b), a phenomenon known as the 'Bruce effect'.

Several reports suggest a pheromonal mediation of the Bruce effect. Parkes and Bruce (1962) reported that exposing inseminated females to cages soiled by males was sufficient for pregnancy disruption, but only when cages were extremely soiled and air exchange was limited. The Bruce effect was prevented when the olfactory bulbs (Bruce and Parrott, 1960) or the vomeronasal organs (Bellringer *et al.*, 1980; Lloyd-Thomas and Keverne, 1982) of the females were lesioned or the lateral olfactory tract was transected (Rajendren and Dominic, 1986), although one study found that the original sire could disrupt pregnancy when the vomeronasal system of

the female was damaged (Keverne and de la Riva, 1982). There are also reports (Dominic, 1965, 1966a, b) of strong pregnancy disruptions when male urine was applied on the nasal area of normal females, and that urinary proteins salted out of male urine similarly disrupt pregnancy (Marchlewska-Koj, 1977, 1981). However, concerns have been raised (deCatanzaro and MacNiven, 1992) about human handling and genital stimulation in these latter studies, and indirect inferences about pregnancy outcome based on vaginal smears rather than litter production. Efforts to disrupt pregnancy by male urine alone, either placed in the female's bedding or topically painted on its nasal region, have not been successful in this laboratory (deCatanzaro *et al.*, 1995b). We have found that the Bruce effect depends upon androgen concentrations of novel males; it is eliminated by castration and reinstated by testosterone administration, and no effect occurs unless inseminated females are in close proximity to novel males (deCatanzaro and Storey, 1989; deCatanzaro *et al.*, 1995a, b).

Male pheromones are implicated in stimulation of ovulation (Whitten, 1956) and acceleration of puberty (Vandenbergh, 1967) in female mice. These chemosignals are present in male urine and their production is under androgen control (Bronson and Whitten, 1968; Vandenbergh, 1969). Inseminated female mice avoid the odour of novel males (Drickamer, 1989). However, very little is known about the chemical structure and the site of synthesis of male pheromones. The preputials, sebaceous glands situated between the skin and body wall anterior to the external genitalia, seem to be likely candidates

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as sources of pheromones. They are prominent in male mice but normally vestigial in females (Mugford and Nowell, 1971; Raso *et al.*, 1992). The absolute mass of the preputial glands relates inversely to population density in male mice (Christian, 1955). The degree of male preputial gland activity is apparently related to social experience, especially aggression (Hucklebridge *et al.*, 1972). Evidence suggests that these glands affect fighting behaviour through the release of an aggression-promoting pheromone (McKinney and Christian, 1970; Mugford and Nowell, 1970; Jones and Nowell, 1973). Testosterone administration induces a hypertrophy of the female's preputial glands while making their urine more aggression-promoting or less aggression-inhibiting (Mugford and Nowell, 1971). Preputial gland secretions are attractive to animals of the opposite sex in rats (Noble and Collip, 1941; Orsulak and Gawienowski, 1972; Gawienowski *et al.*, 1975; Thody and Dijkstra, 1978) and mice (Bronson and Caroom, 1971). They may also regulate anogenital licking (Brouette-Lahlou *et al.*, 1991) and aid in maternal discrimination of the sex of pups (Moore and Samonte, 1986). One report (Marchlewska-Koj *et al.*, 1990) indicates that male preputial glands as well as salivary glands are sources of pheromones that stimulate oestrus in female mice.

The present study was designed to examine whether male preputial glands are responsible for the Bruce effect. Inseminated female mice were exposed to novel males, either preputialectomized or not, during the first 5 days after insemination. It was assumed that, insofar as preputial pheromones mediate the Bruce effect, preputialectomized males would fail to disrupt pregnancy. This was examined through a direct exposure paradigm, in which females can be reinseminated by novel males, and an indirect exposure paradigm, in which males cannot mate with females because of separation by wire-mesh. Inseminated females were allowed to bear litters to provide a direct measure of pregnancy outcome, and human handling was minimized during the procedures.

Materials and Methods

Animals and insemination procedures

The experimental subjects and inseminating males were CF-1 strain mice bred in this laboratory from stock obtained from Charles River Breeding Farms (La Prairie, Quebec). The novel males were HS (heterogeneous strain), bred in this laboratory from stock originally obtained from the Department of Zoology (University of Toronto). The animal colony room was maintained at 21°C under a reversed 14 h light:10 h dark cycle. Housing, rearing and maintenance were as described by deCatanzaro *et al.* (1995b). At 65–100 days of age, nulliparous females were placed individually in a cage containing a male at the onset of the dark phase of the light cycle. Females were inspected for sperm plugs as described by deCatanzaro *et al.* (1995b); those with plugs were designated as subjects and the day of detection of the plug was designated as day 0 of pregnancy. On day 1, 1–3 h after the start of the dark phase of the light cycle, females were assigned randomly to one of the experimental conditions, with date of insemination counter-balanced across conditions.

Preputialectomy

The preputial glands of male mice consist of a pair of leaf-shaped ectodermal exocrine glands opening to the exterior on either side of the urethral meatus (Fekete, 1941; Bronson and Caroom, 1971). They are located bilaterally between the skin and the body wall anterior to the external genitalia. They are yellowish-brown, dorsoventrally flattened, measuring approximately 7 mm × 5 mm, although they are quite variable in size among individuals. For removal of the glands, the animals were anaesthetized with sodium pentobarbitol. Two incisions, each measuring approximately 5 mm, were made on either side of the external genitalia, or, if possible, both glands were removed via a single incision. The glands were found immediately under the skin layer. Once located, they were snipped off at the stem. In some individuals, a thin membranous tissue was present either over or between the two glands; this was snipped as necessary. Once the glands were removed, the skin incision was closed by a wound clip and animals were kept warm on a heating pad until normal activity returned. The wound clip was removed without anaesthesia 1 week after surgery. For sham-preputialectomized animals, the procedures of anaesthesia, skin incisions, and recovery were the same as in those receiving the full surgery, but the preputial glands were left undisturbed. All surgically treated males were allowed at least 2 weeks for recovery before they were used as stimulus animals in the experiments. Subsequent to the experiments, a subset of preputialectomized males was killed for histology at the site of surgery to confirm that the glands had not regenerated.

Direct exposure paradigm

In an initial experiment, each inseminated female was assigned randomly on day 1 of pregnancy to housing in a clean cage with one of the following animals: (1) a novel intact HS male, (2) a novel preputialectomized HS male, or (3) the sire of the pregnancy (control condition). Each female remained housed directly with the stimulus male for 120 h. Behavioural interactions between the male and the inseminated female were monitored during the first day of such housing. Immediately after the experimental procedures began, each male–female pair was observed continuously for 2 h. During this observation period, a trained observer recorded the occurrence of sexual activity (including mounts and intromissions; see McGill, 1965; deCatanzaro and Gorzalka, 1979). Additional observation periods of 10 min of the same behaviour were taken on each pair at about 5 h and 8 h after commencement of the dark phase of the normal lighting cycle on that day.

Indirect exposure paradigm

On day 1 of pregnancy, each inseminated female was either designated as a no-male-exposure control subject, or began 120 h of indirect exposure to one or more novel males, which was accomplished in a double-decker apparatus separating the female from the males by a wire-mesh partition, as described by deCatanzaro *et al.* (1995b). Initial parametric work was undertaken to establish a strong baseline effect using various numbers of intact novel HS males. The two compartments of

the double-decker apparatus were separated by a wire-mesh grid with openings measuring 1 cm × 1 cm. In one experiment, each female was housed in the lower compartment of such an apparatus, exposed to one, two or three HS males in the upper compartment. In a subsequent experiment, each female was housed in the upper or the lower compartment so that she was above or below three novel HS males in the other compartment.

Subsequently, as it was established that a strong and reliable pregnancy disruption occurred when each inseminated female was housed below multiple males, a major experiment was begun with females assigned randomly to three conditions: (1) housed below no male (control condition), (2) housed below two novel preputialectomized HS males, and (3) housed below two novel sham-operated HS males. Incidental aggression between the paired novel males was prevented by placing a partition between them in each upper compartment of the experimental apparatus. This was achieved initially via a wire-mesh grid that divided the upper compartment in two. For subsequent replications, the apparatus was modified such that a double Plexiglas partition in the upper compartment prevented all contact between the two males, and the wire mesh between the upper and lower compartments was replaced with finer mesh (openings measuring about 0.5 cm × 0.5 cm).

Pregnancy outcome measures

At the end of the 120 h period of exposure to novel males, each female was housed individually in a clean cage with fresh bedding and was left undisturbed for the duration of gestation. On day 18 after the detection of the initial sperm plug, females were checked on three occasions each day for parturition. Such inspections continued until 30 days after detection of the plug. Pregnancy outcome was measured by counts of the number of pups born, duration of gestation, and number of pups 3 days after birth (cannibalizations and stillbirths were recorded). In the direct exposure paradigm, coat colour was measured by retaining pups until they were 10 days of age; this was taken as an indication of sire, since CF-1 (original sire) litters are homogeneously white whereas HS (novel sire) litters are multicoloured.

Results

Direct exposure paradigm

All novel males, except one intact and one preputialectomized male, showed some mounting behaviour towards the previously inseminated females during the interval samples, whereas only three of the original sires did so. The mean number of mounts ($\pm$ SEM) was 0.4 ± 0.3 for sires, 35.2 ± 4.4 for preputialectomized males, and 50.8 ± 6.2 for intact males. Generally, females resisted such mounting, but intromission by seven intact novel males, seven preputialectomized novel males, and no sires was observed. The mean number of intromissions was 1.7 ± 0.8 for preputialectomized males and 3.5 ± 1.9 for intact males. No aggressive interactions between males and females were observed. Analysis of variance among the three experimental conditions was significant for number of

Fig. 1. Percentage of females with litters attributable to the original sire after direct exposure to the sires (control), novel preputialectomized (PPX) outbred males, or novel intact outbred males on days 1–5 of pregnancy, by criteria of coat colour and duration of gestation (■) or coat colour alone (□).

mounts, $F(2,79) = 35.24$, $P < 0.0001$, but not for number of intromissions, $F(2,79) = 2.12$, $P = 0.1253$. Multiple comparisons (Newman–Keuls' test, $P < 0.05$) showed differences for number of mounts among all three conditions. Although most females were parturient in each condition, the duration of gestation and the coat colours suggested that the original pregnancy was replaced in a subset of females exposed to intact or preputialectomized males. In the sire-exposed (control) condition, 24 of 27 females were parturient; all litters yielded exclusively white pups, and the maximum duration of gestation was 21 days. Of 27 females exposed to intact males, two were not parturient and the duration of gestation of nine of the litters produced was of 23 days or greater, or the litter contained coloured pups. Of 26 females exposed to preputialectomized males, four were not parturient and the duration of gestation of nine of the litters was 23 days or greater, or contained coloured pups. Given that we have never observed a gestation exceeding 22 days for CF-1 mice by the original sire in any study in this laboratory, and CF-1 mice are homogeneously albino while HS mice are multicoloured, it was inferred that the pregnancies were replaced by the novel male in such cases. An albino litter is possible but not common with HS × CF-1 crosses. Figure 1 illustrates the number of females in each group bearing litters that were attributable to the original sire, using these criteria as well as a more conservative estimate that ascribed a pregnancy disruption only to cases in which a litter was absent or coloured, excluding consideration of duration of gestation. A test of association comparing conditions was significant with both the stronger set of criteria ($\chi^2(2) = 11.22$, $P < 0.005$) and the more conservative set of criteria ($\chi^2(2) = 7.06$, $P < 0.05$).

Indirect exposure paradigm

Initial parametric work indicated that loss of pregnancy was more likely to occur in females with greater numbers of males in their vicinity, and that such disruption was more probable when males were housed above females than when they were housed below females. Intense intermale aggression was observed in a subset of grouped males housed near females. In the experiment in which the number of males above females was varied, 16 of 19, 8 of 15, 4 of 15, and 2 of 15 females were parturient, respectively, with zero, one, two, or three novel males. A test of association between conditions and the presence or absence of parturition showed significance ($\chi^2(3) = 20.12$, $P < 0.001$). The number of pups born, with zeros assigned to nonparturient females, was, respectively, 10.0 ± 1.2 , 6.9 ± 1.8 , 3.1 ± 1.4 , and 1.8 ± 1.3 ; analysis of variance was significant ($F(3,60) = 7.43$, $P < 0.0005$) and multiple comparisons identified difference between conditions with zero versus two or three males, and with one versus three males. In the experiment in which three HS males were housed above or below each female, 14 of 16 control females, 3 of 16 females housed below males, and 10 of 16 housed above males were parturient ($\chi^2(2) = 15.75$, $P < 0.001$). The number of pups born was, respectively, 10.5 ± 1.1 , 2.2 ± 1.2 , and 7.2 ± 1.5 ; analysis of variance was significant ($F(2,45) = 10.50$, $P < 0.0005$) and multiple comparisons identified a difference between the condition with males above and the two other conditions.

Figure 2 gives data for the proportion parturient in each condition of the experiment comparing the influences of two preputialectomized males and two sham-preputialectomized males. Most females (29 of 33) in the control group produced litters, but substantially fewer did so in either the preputialectomized novel male or the sham-preputialectomized novel male conditions. The effect was equally present when males were separated by a wire grid (2 of 11 females exposed to preputialectomized males and 1 of 11 sham-exposed females were parturient) as when males were separated by a Plexiglas barrier (4 of 21 females exposed to preputialectomized males and 7 of 21 sham-exposed females were parturient) so data were combined. A test of association between conditions and the presence or absence of parturition showed significance ($\chi^2(2) = 38.69$, $P < 0.001$). A test of association comparing just the control and preputialectomized groups was similarly significant ($\chi^2(1) = 31.23$, $P < 0.001$) as was one comparing the control and the sham-operated groups ($\chi^2(1) = 26.20$, $P < 0.001$) but not comparing the preputialectomized and sham-operated groups. The number of pups born to control females was 10.36 ± 0.74 ; for females exposed to preputialectomized males, 1.97 ± 0.74 ; and, for those exposed to sham males, 3.34 ± 1.05 . Analysis of variance on this measure was significant ($F(2,94) = 27.83$, $P < 0.0001$) and multiple comparisons identified a difference between the control condition and each of the other two conditions, but not between the preputialectomized and sham conditions.

Histology

Ten animals that had been preputialectomized were killed, four at 2 months after the surgery and six others at 5 months

Fig. 2. Percentage of females delivering litters after housing during days 1–5 of pregnancy below two novel outbred males that were either preputialectomized (PPX) or sham-preputialectomized (Sham).

after the surgery. In each case, the former site of the preputial glands could be identified. In all animals, full removal of the preputial glands was confirmed, and in no case was there any sign of regeneration of these glands.

Discussion

The experiments reported here demonstrate that a Bruce effect can be obtained with both direct and indirect exposure to novel outbred males, but that the effect is qualitatively different in the two cases because of behavioural interactions and reinsemination in the case of direct exposure. Effects are all-or-none and probabilistic, given that some control females do not produce litters and some females exposed to novel males do produce litters, while litter size of parturient females is in the normal range regardless of condition. With either direct or indirect exposure, preputialectomy does not diminish the capacity of novel males to disrupt pregnancy.

With direct exposure of each inseminated female to one novel male, pregnancy disruption is complex, involving various qualities depending upon the individual. The novel male typically attempts to mate with the female; this attempt is met initially with resistance, but some females subsequently permit intromissions. A substantial proportion of females in this strain of mice retain the original pregnancy, whereas others lose the initial pregnancy and often are reinseminated by the novel male, as evidenced by the duration of gestation and coat colours of the litters. The reinsemination rate with CF-1 females in the present study was greater than that found with C57BL females in similar conditions (deCatanzaro and Storey, 1989).

Since preputialectomized males in the present study replaced at least as many pregnancies as did intact males, we conclude that the preputial gland is not necessary for the Bruce effect under conditions of direct exposure.

The current experiments also refine the paradigm for production of the Bruce effect by indirect exposure. CF-1 females show a higher baseline (control) pregnancy rate than do C57BL females studied elsewhere (deCatanzaro *et al.*, 1995b). Greater numbers of males in their proximity provide a larger effect. These refinements produce a strong and reliable pregnancy disruption, permitting statistical sensitivity to other parametric manipulations. Although intense aggression among males can be a by-product in some groups, apparently stimulated by the proximity of the female, the elimination of this aggression by barriers between males does not diminish the pregnancy disruption. It is noteworthy that exposure to three males disrupts most pregnancies when males are above but not below females. This finding suggests that a nonvolatile chemosignal is involved, given that females housed below males receive far greater quantities of the males' excretions, while there is no obvious behavioural difference between animals in the two conditions.

Marked disruptions of pregnancy occurred when inseminated females were housed below two males that were separated from one another. This was equally the case when the males were preputialectomized as when they were sham-preputialectomized. This is perhaps the clearest demonstration of a Bruce effect, uncomplicated by reinsemination and behavioural interactions among animals, and of the irrelevance of the preputial glands. Several human observers in this laboratory have noted independently that a subjectively foul and distinct odour is present in the experimental room when inseminated females are in the double-decker apparatus with males, and that the walls of the males' compartments are smeared with an oily emission during this exposure. There is no apparent difference in the magnitude of these observations with preputialectomized versus intact males. Accordingly, we suggest that a nonvolatile emission of the males is involved in the Bruce effect induced by indirect exposure, that the frequency of pregnancy disruption is a function of the quantity of this emission, but that this emission is not of preputial origin. Other male glands could be the source of such pheromones; some evidence suggests that there are pheromonal emissions from the coagulating glands (Jones and Nowell, 1973), and other sources could include the bulbourethral glands, kidneys and even salivary glands.

The involvement of androgens and oestrogens in both the capacity of males to produce the Bruce effect (Dominic, 1965; deCatanzaro *et al.*, 1995a, b) and endogenously in females, in which intrauterine implantation is very sensitive to increased androgen and oestrogen concentrations is of interest (Harper, 1967; deCatanzaro *et al.*, 1991). Evidence suggests that stress-induced early pregnancy disruptions may be mediated by adrenal androgens and oestrogens (deCatanzaro and MacNiven, 1992; deCatanzaro *et al.*, 1994). Thus, in the context of the Bruce effect, excretions of oestrogens by novel males may merit attention. In contrast to this notion is evidence that the Bruce effect might be subserved in the female by pheromone-altered prolactin concentrations (Bellringer *et al.*, 1980; Rosser *et al.*, 1989). It is clear from an evolutionary–

ecological perspective that both chronic stress and strange males are associated with poor prospects for gestation and nurture of young; whether the adaptations to these contingencies are common or distinct remains to be determined.

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