Intrauterine Position Phenomenon

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GLOSSARY

anogenital distance (AGD) The length of the perineal tissue, which becomes the scrotum in males, separating the anus and the genital tubercle (penis in males and clitoris in females). AGD is longer in males than in females.

estradiol The steroid hormone produced at high levels by cells in the ovary during the first half of the menstrual cycle (after puberty). During pregnancy in humans the placenta also produces estradiol. Estradiol is one of a family of hormones called estrogens.

intrauterine position The position of a fetus, when there is more than one fetus, within the uterus relative to adjacent male and females fetuses, with 2M animals being positioned between two male fetuses, 1MF animals being positioned between a male and a female fetus, and 2F animals being positioned between two female fetuses.

testosterone The steroid hormone produced at high levels by the testes both during fetal life (when it causes masculinization of the fetal brain and reproductive system) and after puberty (when it causes additional changes associated with puberty in boys). Much lower amounts of testosterone are also produced by the ovaries in females. Testosterone is one of a family of hormones called androgens.

I. HORMONAL TRANSPORT BETWEEN FETUSES

The intrauterine position (IUP) phenomenon is a result of hormonal transport between adjacent fetuses before birth and has been described in a range of litter-bearing mammals (including mice, rats, gerbils, and pigs) as well as in humans carrying twins (Fig. 1). To identify the IUP of animals for postnatal study, the timing of conception is determined and fetuses are removed from the uterus just before normal parturition, are marked for individual identification, and then reared by foster mothers. IUP effects have been extensively studied in house mice, a species in which male fetuses have higher serum levels of testosterone than do females and female fetuses have higher serum levels of estradiol than do males. These steroid hormones diffuse between adjacent fetuses causing both male and female fetuses occupying an IUP between two males (2M fetuses) to have higher blood concentrations of testosterone (by approximately 30%) than do their same-sex siblings occupying an IUP between two females (2F fetuses). 2F fetuses, on the other hand, have higher blood concentrations of estradiol than do 2M fetuses (also approximately a 30% difference). Those fetuses situated between a male and a female fetus (1MF fetuses) have intermediate serum concentrations of both testosterone and estradiol, and in adulthood are intermediate between 2M and 2F animals of the same sex in many morphological, physiological, and behavioral characteristics.

An important consequence of IUP research has been to increase awareness of the exquisite sensitivity of fetuses during critical periods in the development

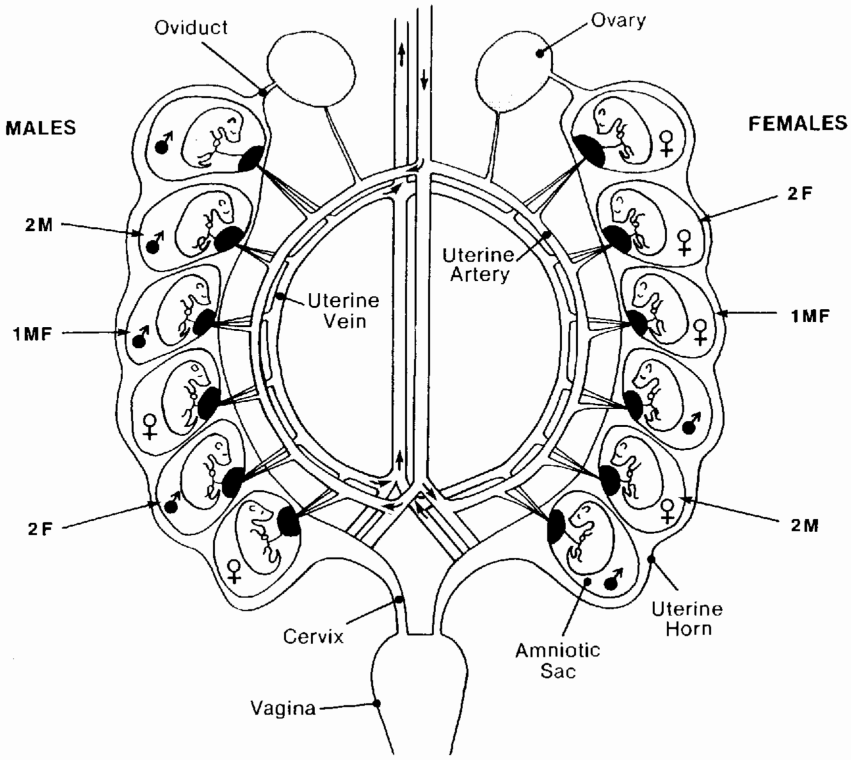

FIGURE 1 Schematic diagram of the two independent uterine horns of a mouse near the end of pregnancy. The labels 2M, 1MF, and 2F refer to the sex of adjacent fetuses, with 2M positioned between two male fetuses, 1MF between a male and a female fetus, and 2F between female fetuses.

of the brain and reproductive organs to very small differences in hormone concentrations. For example, a difference in serum estradiol between 2M and 2F male mouse fetuses of 23 pg (23 trillionths of a gram) per milliliter of serum is sufficient to induce a cascade of developmental events which, as indicated below, have profound consequences on subsequent reproductive life history.

The mechanism of transport of testosterone between fetuses has been examined directly in rats. Testosterone in a male fetus diffuses into the amniotic fluid, which both circulates through a fetus and surrounds it, thus picking up hormones from fetal blood. The testosterone in amniotic fluid diffuses across fetal membranes (amnion and chorion) surrounding each fetus and into the amniotic fluid and blood of adjacent fetuses. Consequently, at least in those litter-bearing mammals studied to date, being positioned *in utero* between siblings of the same or opposite sex leads to predictable differences in serum concentrations of testosterone and/or estradiol at a time in fetal life when these hormones influence the differentiation of virtually all morphological, physiological, and behavioral traits relating to reproduction. Furthermore, because IUP is a stochastic aspect of development, and frequency of occurrence of stochastic events is predictable in large populations, phenotypic variability induced by IUP is guaranteed in litter-bearing species.

Even before birth, the length of the tissue which becomes the scrotum in males and is located between the embryonic external genital and anus (anogenital distance; AGD) is longer in male than in female rodents, and AGD also varies within sex; 2M females have a longer AGD than do 2F females. This finding, together with the observation that in cages containing 6 female mice, one female is typically more aggressive than the others, led to experiments examining the postnatal consequences for reproductive performance and behavior of prior IUP. In litters containing 12 mice, as is typical in the stock of mice used in the experiments described in this article, 1 in 6 females is a 2M female. It thus seemed reasonable to determine whether IUP might be the source of observed variability in aggression and possibly other traits relating to reproduction and, if so, what the adaptive significance of this variability might be. It is sometimes assumed, erroneously, that only variability due to genetic differences can play a role in evolutionary processes. However, an interest in evolution and the adaptive significance of IUP effects has led to research in natural environments testing evolutionary hypotheses based on laboratory findings concerning effects of IUP on reproduction and behavior.

We first briefly review the consequences, in both gerbils and mice, of developing as a 2M or 2F fetus. We then describe recent studies in which hypotheses concerning the potential impact of IUP on individual reproductive success and population dynamics have been tested in wild mice both in seminatural environments and by using mathematical models.

II. LABORATORY STUDIES ON THE PHENOTYPE OF MONGOLIAN GERBILS AND HOUSE MICE FROM DIFFERENT IUPS

One of the more interesting findings to emerge from the study of IUP effects on members of two different species of Old World rodent is that effects of IUP on adult phenotype vary from one species to the next. Such variability in IUP effects on development should, perhaps, have been expected because, although testosterone and estradiol influence development in all vertebrates, their specific effects on development are not likely to be exactly the same in any two species. Thus, it is not surprising that as measurements of IUP effects are extended across species, what might appear as inconsistencies emerge. We hypothesize that such inconsistencies in IUP effects reflect differences in the way that testosterone and estradiol regulate development in different animals, and that as our understanding of comparative endocrinology grows, apparent inconsistencies across species in IUP effects on adult phenotypes will be explained.

A. IUP Effects in Males

1. *Reproductive Organs*

Adult 2M male gerbils are more responsive to testosterone than are 2F males of their species, suggesting that IUP influences the sensitivity of target tissues to gonadal hormones. In mice, an increased sensitivity to testosterone in adult 2M males, relative to 2F males, has also been demonstrated in terms of responsivity of some accessory reproductive organs, such as the seminal vesicles. However, results of some comparisons of organs of males from different IUPs initially appeared counter to predictions concerning the role of specific steroids in sexual differentiation. For example, as adults, 2F male mice have larger prostates and smaller seminal vesicles than do 2M male mice. The enlarged adult prostates of 2F males are associated with an increase in androgen receptors, whereas the smaller seminal vesicles of 2F males are associated with a decrease in 5α-reductase activity. These two organs develop from different embryonic tissues (prostate from embryonic urogenital sinus and seminal vesicles from embryonic Wolffian ducts), and these findings suggest that testosterone and estradiol have different effects in these two embryonic tissues. Thus, in addition to species differences due to IUP effects, within a species not all embryonic tissues respond the same to an increase or a decrease in a specific hormone.

2. *Behavior*

Effects of IUP on a number of behaviors that influence reproductive success have been examined. Elevation in estradiol in 2F male mouse fetuses correlates with an increase in some indices of adult sexual performance (frequency of mounting and intromitting) relative to 2M males, whereas in gerbils, 2M males, with elevated testosterone during fetal life, are more likely to impregnate females with which they are paired than are 2F males. While less sexually proficient than 2M male gerbils, 2F male gerbils make a greater parental effort and are more effective in reducing the burden that reproduction imposes on their mates than are 2M male gerbils. In this regard, 2M male gerbils are markedly different from 2M male mice, which are more parental toward young than are 2F males of their species. In fact, 2F male mice are more likely to be infanticidal than are 2M male mice. On the other hand, 2M male mice are more aggressive toward other adult males than are 2F males. In mice, therefore, elevated levels of testosterone during fetal life lead to an increase in intermale aggression (competition for territories and mates), whereas fetal exposure to elevated estradiol and decreased levels of testosterone are related to an increase in aggression toward newborn pups sired by other males.

Study of the effects of IUP in gerbils is complicated by the fact that 2M males, in addition to having elevated testosterone levels during fetal life, have higher plasma testosterone levels in adulthood than do 2F males. Clearly, functioning of the brain–pituitary–gonadal axis, or of enzyme systems and components of plasma involved in regulating clearance of steroids (such as plasma-binding proteins), can be permanently affected by an animal's IUP. Perhaps as a result of their higher circulating levels of testosterone in adulthood, 2M adult male gerbils are more attractive to females in estrus than are 2F males. In addition, possibly because of differences in their copulatory patterns and genital musculature, 2M males are also more successful than are 2F males in impregnating females they encounter for the first time. Further experiments will be required to separate effects on reproductive behavior of gerbils due to differences in gonadal steroid levels during fetal and adult life.

B. IUP Effects in Females

IUP influences numerous reproductive traits in both female mice and female gerbils. In relation to 2F female mice, 2M females enter puberty later. In mice, 2M females show longer estrous cycles and cease producing pups at a younger age than do 2F females. Thus, 2M female mice have a shorter period in life during which they are fertile relative to 2F females. Males choose to be near and prefer to mate with 2F female mice, and when mounted by males, 2M females are less likely to lordose (exhibit sexual receptivity) than are 2F females.

In contrast, 2M female mice are more aggressive toward other females before mating, and after parturition they are more aggressive toward conspecific intruders than are 2F females. This finding suggests that, as competition for resources increases, 2M female mice would have increasing advantage over 2F females. An important related observations is that, as population density increases, only the most aggressive female mice reproduce.

In gerbils, as in mice, 2M females reach puberty at a significantly later age than do 2F females, and late-maturing female gerbils have substantially fewer litters, smaller litters, and half the lifetime fecundity of their early maturing sisters. Late-maturing female gerbils are more attentive mothers and less willing to accept strange males as sexual partners than are early maturing females (perhaps related to the enhanced nest defense shown by nursing 2M female relative to 2F female mice).

Evidence for direct IUP effects on brain function has been provided by a study in which cytochrome oxidase activity in brain areas involved in reproduction in female gerbils was examined. There was increased cytochrome oxidase activity in the medial and posterior anterior hypothalamus of 2M compared with 2F females.

1. *IUP Effects on Litter Sex Ratio*

There is direct evidence in both gerbils and mice that a female's prior IUP affects the sex ratio of litters she produces: 2M females give birth to male-biased litters, whereas 2F females deliver female-biased litters. Consequently, daughters of both 2F and 2M females have a greater probability than would be expected by chance alone of maturing in IUPs concordant with those of their respective mothers. Although the mechanism mediating differences in the sex ratio of litters delivered by 2F and 2M female gerbils and mice is not known, it is unlikely to be the result of differential mortality either during or shortly following vaginal delivery in gerbils.

The right ovary of female gerbils is known to produce more male than female destined eggs, and the left ovary the reverse, even though the genotype of the sperm determines an embryo's sex. However, the relationship, if any, of this phenomenon to observed effects of IUP on the sex ratio of litters born to 2M and 2F gerbil dams is not clear. Possibly, the difference in sex ratio of litters gestated by 2M and 2F females results from a difference in their timing of copulation with respect to ovulation, though no studies have examined effects of copulatory timing on litter sex ratio of either Mongolian gerbils or mice.

Regardless of the causes of differences in the sex ratio of litters produced by female gerbils and mice from different IUPs, concordance in the IUPs of mothers and daughters results in a form of hormonally mediated transmission of acquired characteristics, producing concordance between mothers and daughters in those characteristics affected by prenatal level of testosterone and estradiol. A daughter's phenotype will tend to resemble that of her mother not only because mother and daughter share a relatively large proportion of genes but also because of a stochastic tendency toward congruence in the IUPs of mothers and daughters that produces similarities in their patterns of exposure to steroid hormones during fetal development.

III. IUP EFFECTS IN SWINE

Rhode-Parfet et al. report minimal effects of IUP on various aspects of reproductive physiology of domestic swine (*Sus scrofa domesticus*). However, even though Rhode-Parfet et al.'s data analysis failed to reveal significant effects of IUP on morphology, examination of their data describing the mean AGD of 2F and 2M female swine in their study reveals what appears to be a significant difference. Rhode-Parfet et al. placed in the same analysis data from animals from many different IUPs (ends of uterine horns, 1MF females, etc.) and this could have obscured a significant difference between 2F and 2M females.

Recently, a significant relationship was established between the proportion of males in litters of swine and the mean AGD of females in those litters. The greater the proportion of males in a litter (and consequently the greater the probability that females in that litter were from 2M IUPs), the larger the mean AGD of females in that litter, suggesting a relationship between IUP and AGD in swine. Drickamer et al. examined possible reproductive consequences of gestation in a large litter with a high proportion of males. Females from litters of nine or more piglets containing 66.7% or more males were more likely to experience conception failure than were gilts and sows from litters with a lower percentage of males. This finding regarding sex ratio of swine litters and subsequent reproductive success has potentially important implications for management practices by swine producers.

IV. IUP EFFECTS IN HUMANS

In humans, females born with a male twin differ from females born with a female twin in the frequency of spontaneous acoustic emissions from their inner ears. Females that develop with a male twin show male-like levels of acoustic emissions. The interesting aspect of this particular finding is that levels of acoustic emissions are set by prenatal factors and do not change between birth and adulthood. Consequently, a measurement made in adulthood can provide accurate information concerning a prenatal event. Whether other traits differ in people who share their prenatal life with a twin of the same or opposite sex remains to be determined.

V. IUP EFFECTS IN HOUSE MICE UNDER FIELD CONDITIONS

Studies have been conducted with house mice to determine whether IUP effects would also occur under free-living conditions . Of particular interest were potential consequences of variation due to IUP with respect to life history traits. Zielinski et al. determined whether the IUP of wild female house mice influenced their home range size, survival, and reproduction. Wild mice were captured, bred in the laboratory for one generation, and then used as stock to produce animals of known IUP. As young adults, 2M and 2F females, along with 1MF males, were released into segments of a highway cloverleaf approximately 1 ha in size. The only effect of IUP on behavior found was that the home range size occupied by 2M females was approximately 45% larger than that of 2F females. The failure to detect a difference in survival rate or reproductive characteristics of females from different IUPs may have been the result of the relatively short duration of the 8-week experiment.

Under field conditions it is not possible to determine the actual IUP of female and male fetuses. However, because there is a relationship between the anogenital distance of female house mice and their prior IUP, it is possible to identify probable 2M and 2F females in wild populations. Using the AGD measure as an indicator of prior IUP, Drickamer studied the characteristics of wild house mice living in 0.1-ha outdoor enclosures. Male mice with larger AGDs were more aggressive and had larger home ranges than did males with shorter AGDs. Survival was not related to AGD for either sex. However, female mice with smaller AGDs were more likely to attain reproductive status, had a higher rate of pregnancy, and had more pregnancies, on average, than did females with larger AGDs. Thus, in the enclosures, female mice with larger AGDs were at a selective disadvantage with respect to reproductive success. These findings are consistent with results obtained in the laboratory relating IUP and aggression in male mice and IUP and fecundity in female mice.

VI. ELIMINATION OF IUP EFFECTS IN MICE BY MATERNAL STRESS

A number of studies have shown that in female mice, maternal stress can override variability in reproductive characteristics due to IUP. It is interesting that maternal stress results in the elevation of serum testosterone levels by a similar amount in 2M, 1MF, and 2F female mouse fetuses. However, only 2F female fetuses, with the lowest background serum levels of testosterone as a result of their IUP, show a marked change in traits relative to unstressed 2F females, such that stressed 2F females resemble 2M females in all traits that have been examined. In contrast, maternal stress appears to have no effect on the traits of 2M females, such that stressed and unstressed 2M females do not differ in their reproductive characteristics, even though maternal stress does significantly increase testosterone in 2M female fetuses. One possible explanation for this finding is that the high background levels of testosterone in unstressed 2M females renders them less sensitive to an increase in testosterone relative to unstressed 2F females.

Zielinski et al. examined effects of crowding of mothers on female offspring by placing pregnant mice into social groups with strangers at one of three densities: low (stud only), moderate (4 animals per cage), or high (10 mice per cage). There was a great deal of social turmoil in the high-density populations and essentially none in the low-density environments. All female pups, regardless of intrauterine position, born to mothers experiencing high social stress had anogenital distances similar to those of 2M females, whereas females born to mothers subjected to either moderate or low social stress during pregnancy showed the typical result (i.e., 2F females had short AGDs, 1MF females had intermediate AGDs, and 2M females had long AGDs). The findings of vom Saal et al. (1990) and Zielinski et al. (1991) that maternal stress renders all female offspring 2M-like in their reproductive traits are thus consistent, but the mechanisms by which this occurs remain unknown.

The finding that environmental stress appears to create hormonal signals within a pregnant female that can eliminate differences due to IUP suggests that the social stress that occurs at high population densities will reduce the degree of variability in reproductive traits in the next generation. Since natural selection operates on variability in phenotype, factors that alter phenotypic variability within a population have the potential to alter the course of evolution in the population. Also, effects on population dynamics would be expected. Because all female offspring of stressed mothers are prenatally androgenized and thus 2M-like females, they may be more likely to emigrate (or at least to have relatively large home ranges) and more likely to attain puberty at a later age than female offspring of nonstressed mothers. The suite of characteristics seen in the offspring of socially stressed dams could cause members of a population stressed by crowding to disperse.

VII. IMPLICATIONS OF THE IUP PHENOMENON FOR POPULATION DYNAMICS

As has been documented in both laboratory and field populations of rodents, a significant component of phenotypic variation can be attributed to effects of IUP. Taken together, the results of over two decades of work on IUP in rodents suggest that IUP can significantly affect the dynamics of rodent populations by affecting the reproductive behavior of population members. All traits relating to reproduction of small mammals can be affected by IUP. If, as seems to be the case, animals from different IUPs respond differentially to environmental changes, such as the stress produced by overcrowding, this will have consequences on their reproductive physiology and behavior. Therefore, changes in population size (cyclic changes, irruptions, or crashes) for rodents could be mediated, in part, via IUP effects interacting with environmental stressors. Such reasoning also leads to the notion that population cycles, such as those exhibited by some microtine rodents, could involve IUP effects. A scenario by which IUP effects could play a role in the population dynamics of rodents has been proposed, and this prediction has recently received support using mathematical modeling.

Aggression can be a key factor in population dynamics. Thus, IUP influences on levels of aggression could directly impact reproduction and thus affect population dynamics. Dennis Chitty and Charles Krebs had also proposed that shifts in the proportion of aggressive animals in a population could contribute to changes in population dynamics, but their assumption was that variation in traits, such as aggression and other sociosexual behaviors, was mediated solely by genes and that such traits would thus be heritable. In contrast, IUP effects appear to be mediated by levels of gonadal steroids during fetal life due to where fetuses happen to be positioned in the uterus, which is a random event. During fetal life hormones (and other intercellular signaling molecules) determine which genes in differentiating cells are turned on or off, and for genes that are turned on, hormones determine the rate of activity of the genes. These genetic imprinting events, once set, are irreversible, but they do not involve changing the genetic code. This would lead to the prediction that IUP effects are not directly heritable, and that aggressive animals in a population (due to developing in an IUP between male fetuses) would not produce aggressive offspring. In this regard, the intriguing finding that in both gerbils and mice, a mother's prior intrauterine position (and thus her fetal hormone levels) biases the sex ratio of her litters, leading to what amounts to heritable differences in the traits of her offspring, raises the possibility of as yet unexplored factors governing the heritability of traits.

See Also the Following Articles

Testosterone Biosynthesis; Twinning

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In Vitro Fertilization

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GLOSSARY

blastocyst A stage of embryo development at 96–120 hr post-fertilization in humans. The blastocyst consists of the inner cell mass, destined to become the fetus, and the trophectoderm, which will develop into the placenta.

blastomere A cell in the early preimplantation embryo.

cryopreservation The freezing of oocytes or embryos and their storage at low temperature.

GIFT Gamete intra-Fallopian transfer, a surgical procedure in which egg(s) and sperm are laparoscopically placed in the Fallopian tube.

gonadotropin A hormone secreted by the anterior pituitary to stimulate gonadal growth and development. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) stimulate oocyte growth and maturation through ovulation.

gonadotropin-releasing hormone (GnRH) A peptide neurohormone that regulates the synthesis and secretion of LH and FSH by the anterior pituitary gland. Synthetic GnRH analogs are administered to shut down endogenous gonadotropin secretion.

in vitro fertilization (IVF) Fertilization of oocyte(s) in the laboratory.

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