Neuro-endocrinology

BRIEFINGS

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Nurture: Effects of Intrauterine Position on Behaviour

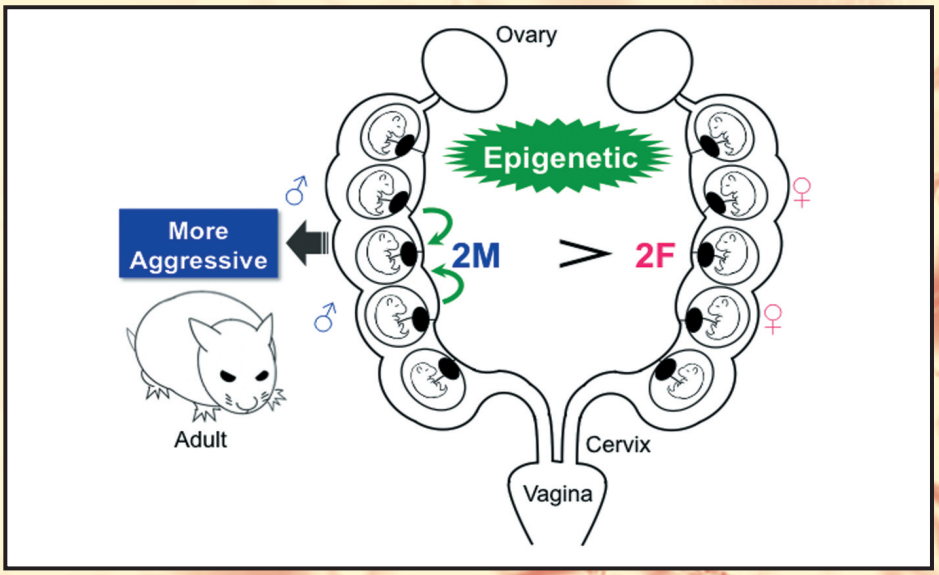
SUMMARY

Fetuses positioned next to littermates of the opposite sex may develop different sexually related traits and aggressive behaviour in later life. These effects of intrauterine position are due to hormonal transfer between fetuses. Testosterone from a male fetus that crosses the fetal membrane of an adjacent female fetus can affect molecular events in the female including modification of the steroid hormone receptors in hypothalamic neurons. The intrauterine environment may also account for the variability of laboratory animals and newborn human twins.

The study of sexual differences has a long history. The classical model states that sexual differentiation of the mammalian nervous system is determined by genetic and environmental factors, which include sex chromosome Y and gonadal steroid hormones (androgens and estrogens). In males, testosterone from embryonic Leydig cells of the testes organizes the developing brain into masculinized structures through hormone-sensitive periods, whereas in females, the absence of testosterone allows for feminization of the brain.
In rodents, the action of testosterone is exerted not only through a direct effect via binding to the androgen receptor, but through conversion to estradiol by the aromatase enzyme. Estradiol then induces brain masculinization by binding to estrogen receptors.
In humans, testosterone regulates brain masculinization without being aromatized to estradiol.
The surge of testosterone and estradiol in the critical period causes receptor activation and these activated receptors serve as transcriptional factors that lead to subsequent cascade signaling to regulate sexual differentiation of male behaviors from those of females.

Individual variation

In the laboratory, variability between animals is often encountered. Some males are more aggressive than other males, even in the same litter. Similarly, some females are more aggressive and some have higher sexual receptivity compared to other females. This raises the question of whether variability in the same sex arises from a DNA sequence variation (a single nucleotide polymorphism) or from other factors. Here, the effects of intrauterine position proposed about 30 years ago are revisited to explain variability in male-female behaviour.



A depiction of the effects of intrauterine position in animals producing multiple offspring in two independent uterine horns. Fetuses with 2 adjacent male littermates (2M) and 2 adjacent female littermates (2F) have different sexually related characteristics during later life: 2M males and 2M females are more aggressive and 2M females are more sexually receptive and tend to mount other females when they become adults.

Intrauterine testosterone

In animals giving birth to many offspring in a single birth, intrauterine position has specific effects on the development of the fetus, including genital morphology, time of puberty, length of the estrous cycle, sexual attractiveness, and sexual behavior,

"the intrauterine position has specific effects on the development of the fetus"

by providing different environmental conditions for each fetus. The phenomenon of individual variation in sexual characteristics of adults may be accounted for by steroid hormone transfer among fetuses as a critical factor in postnatal development. Testosterone can easily cross the fetal membrane and therefore the position of a fetus relative to others has an effect on development. In utero, a fetus with 2 adjacent male littermates (2M) is exposed to a higher level of testosterone than those with one or two adjacent females (2F). Sexual characteristics may then differ in later life, with 2M males and females being more aggressive and 2M females showing stereotypical male sexual behaviors (e.g. mounting other adult females).

Sexual dimorphism

The intrauterine position and sex of each fetus is difficult to determine. Pups are randomly positioned in the two uterine horns in laboratory animals such as mouse, rat and gerbil, which makes it impossible to determine the intrauterine position from birth order. Unilateral ovariectomy or Caesarean section provides a solution to obtain the exact intrauterine position. Just before birth, by Caesarean section, the sex of each fetus is determined on the basis of its anogenital distance, while the position of each fetus in the uterus can be recorded. There are currently two pieces of direct evidence for the effects of intrauterine position on brain structures related to sexual behavior. The nucleus of the preoptic area, an important sexually dimorphic brain area involved in the regulation of male sexual behavior, is well-known to have a larger volume in males than in females. The volume of the preoptic area in 2M males is larger than that in 2F males. On the other hand, the ventrolateral region of the hypothalamic ventromedial nucleus is related to female aggression and sexual behavior. In that region, protein expression and mRNA levels for the estrogen receptor alpha (ER-α) are higher in 2M females than in 2F females, but the number of neurons expressing the receptor is similar.

Epigenetic regulation

What is the mechanism underlying the difference in expression of ER-α in the ventromedial nucleus of the hypothalamus between 2M and 2F females? Analysis of DNA modification has revealed that transcriptional regulation of ER-α in rat brain differs between 2M and 2F females; with a higher rate of methylation in 2F females than in 2M females. The differences in DNA methylation status of ER-α may not explain all aspects of the behavioral differences between 2M and 2F females, but epigenetic regulation caused by factors including intrauterine position during brain development may result in individual differences.

Freemartin and human twins

The freemartin is a well-known phenomenon in the livestock field: a sterile female animal that is a twin to a male and has atrophic gonads. In this situation blood-borne factors, including hormones play a key role in sexual differentiation during intrauterine development. There have only been a small number of studies in humans. Different sexes of fetuses have developed from dizygotic twins or multiple births. An extensive survey of the characteristics of Australian dizygotic twins showed that females born with a male twin differed from females born with a female twin in the frequency of spontaneous acoustic emissions: females that develop with a male twin showed male-like levels of acoustic emissions. It remains to be determined whether other characteristics differ in dizygotic twins.

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