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33. Sexual Differentiation

SEXUAL DIFFERENTIATION OF GONADOTROPHIN SECRETION, SEXUAL ORIENTATION AND GENDER ROLE BEHAVIOR

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Summary—The positive estrogen feedback was found to be a relatively sex-specific reaction of the hypothalamo-hypophyseal system in rats as well as in human beings. It is dependent—most of all—on the estrogen convertible androgen level during sexual brain differentiation, but also on an estrogen priming effect in adulthood. The lower the estrogen convertible androgen or primary estrogen level during brain differentiation, the higher is the evocability of a positive estrogen action on LH secretion in later life.

In clinical studies, we were able to induce a positive estrogen feedback on LH secretion in most intact homosexual men in clear-cut contrast to intact hetero- or bisexual men. These findings were strongly confirmed by Gladue and associates. In addition, the evocability of a positive estrogen feedback was also demonstrable in most homosexual male-to-female transsexuals in significant contrast to hetero- or bisexual male-to-female transsexuals. These findings suggest that homosexual males possess, at least in part, a predominantly female-differentiated brain, which may be caused by a low estrogen convertible androgen level during brain organization.

Recently, the following relations were found between sex hormone levels during brain differentiation and sex-specific responses in adulthood: (1) estrogens—which are mostly converted, however, from androgens—are responsible for the sex-specific organization of gonadotrophin secretion and hence the evocability of a positive estrogen feedback in later life; (2) estrogens and androgens, occurring during brain differentiation, predetermine synergistically sexual orientation and (3) androgens—without conversion to estrogens—are responsible for the sex-specific organization of gender role behaviour in later life. Furthermore, the organization periods for sex-specific gonadotrophin secretion, sexual orientation and gender role behaviour are not identical but overlapping. Thus, combinations as well as dissociations between deviations of the neuroendocrine organization of sex-specific gonadotrophin secretion, sexual orientation and gender role behaviour are conceivable.

Most recently, female-type sexual orientation could be converted to male-type sexual orientation in adult rats by administration of the dopamine agonist and serotonin antagonist lisuride.

Crucial experiments on sex-specific brain differentiation were done by Pfeiffer [1] and Dantchakoff [2]. Pfeiffer was the first to discover that, independent of the genetic sex, the presence of testes during a critical perinatal period in rats resulted in acyclic gonadotrophin secretion in adulthood, whereas the absence of testes during this critical period resulted in cyclic gonadotrophin secretion in adult life. Barraclough and Gorski [3] then demonstrated that testosterone is the mediator of the testes for sex-specific differentiation of the brain. High androgen levels during brain differentiation gave rise to a more tonic gonadotrophin secretion in postpubertal life, whereas low androgen levels during this period gave rise to a cyclic gonadotrophin secretion in adulthood.

Regarding sexual behaviour, Dantchakoff [2] reported that prenatally androgenized female guinea-pigs showed significantly increased male sexual behaviour in adulthood. This finding was then confirmed and supplemented by Phoenix *et al.* [4], who distinguished between a sex hormone-dependent prenatal (or perinatal) organization period and a postpubertal activation period of the brain.

During the past two decades among many experimental findings the following data were obtained in our laboratories [5, 6]:

1. A sexual dimorphism of the brain, which is dependent on the testosterone level in perinatal life, was first found in rats [7]. The nuclear volumes of the nerve cells in discrete brain regions, e.g. in the hypothalamic ventromedial nucleus, were significantly enlarged in female rats as compared to male rats. Such sex-specific brain structures could be inverted by perinatal androgen administrations in females or neonatal castration in males. A sexual dimorphism of the brain was meanwhile confirmed for several species, including human beings [8].

2. Sexual orientation, i.e. the preference of sexual responsiveness towards partners of the opposite or of the same sex, was tested in neonatally castrated males and in perinatally androgenized females. In these tests, male rats castrated on the first day of life and treated with estrogen or even androgen in adulthood exhibited more female-like sexual orientation, i.e. "male bi- or homosexuality", while females who were androgenized in perinatal and postpubertal life displayed a complete male-like sexual orientation, i.e. "female homosexuality". A

complete inversion of sexual behaviour was even achieved. Perinatally and postpubertally androgenized females mounted neonatally castrated males who displayed receptive, female-like lordotic behaviour.

3. A sex-specific evocability of the positive estrogen feedback on LH secretion was found in rats. The evocability was significantly higher in female than in male rats [9, 10]. It could be significantly increased by neonatal castration in males and decreased by perinatal androgen administration in females [5, 11]. In addition, a positive estrogen feedback could be evoked in homosexual men in contrast to heterosexual men. This finding suggested that homosexual men may possess, at least in part, a more female-differentiated brain based on an androgen deficiency during brain differentiation [12]. In view of this finding, which was clearly confirmed most recently by Gladue *et al.* [13], a world-wide dispute was started about the question whether prenatal sex hormone levels or postnatal psychosocial learning processes may be more important for sexual differentiation of the brain, sexual orientation, gender role behaviour and gender identity. In my opinion, effects of sex hormones and of the psychosocial environment on sexual differentiation and function of the brain represent rather than supplement alternatives, since both appear to be mediated by neurotransmitters in the brain.

However, the findings obtained in human males with Imperato—McGinley's syndrome suggest that prenatal testosterone levels may be even more important for sexual differentiation of the brain than postnatal psychosocial influences. Thus, Imperato-McGinley *et al.* [14] described male pseudohermaphrodites born with ambiguity of the external genitalia. Biochemical evaluation revealed normal testosterone levels, but a marked decrease in plasma dihydrotestosterone levels due to 5α-reductase deficiency. The decrease of dihydrotestosterone *in utero* resulted in incomplete masculinization of the external genitalia. Thus, the affected males were born with more female-like external genitalia and were therefore considered and raised as girls. Psychosexual orientation, however was unequivocally male. They considered themselves as males and had a libido directed towards females. Despite being reared as females, almost all of them changed gender identity at the time of puberty. Hence, testosterone exposure *in utero* appears to be most important for the development of a male sex drive, male sexual oreintation and even male gender identity.

Most recently, Ehrhardt *et al.* [15] performed an analysis of sexual orientation in women who had been prenatally exposed to the synthetic estrogen diethylstilbestrol. In comparison to hormone-unexposed women and even to their unexposed sisters, a variety of indicators showed statistically significant shifts towards bi- or homosexuality in the prenatally estrogen-exposed women. In this context, it should be noted that natural and synthetic estrogens can exert paradoxical, i.e. androgen-like effects on male-type brain differentiation [16]. Several findings suggest that endogenous and exogenous androgens are even aromatized in the brain to estrogens—at least in part—for male-type brain differentiation [17].

However, prenatal psychosocial influences should also be regarded as possible aetiogenetic factors in the development of sexual deviations. Thus, Ward [18] reported that prenatal stress in male rats demasculinized and feminized sexual behaviour potentials in adult life. Since similar findings were obtained in male rats castrated on the day of birth, we have measured the plasma testosterone levels in such prenatally stressed males, i.e. in male foetuses and newborns following maternal stress between day 14 and 21 of gestation. The testosterone level was found to be significantly decreased, in fact, in these prenatally stressed males during the early postnatal life as compared to non-stressed control males [19].

More recently, we have observed bi- or even homosexual behaviour in prenatally stressed male rats after castration plus estrogen treatment in adulthood, whereas prenatally non-stressed but later equally treated males displayed heterosexual behaviour [20]. Hence, prenatal stress can predispose to the development of bi- or even homosexual behaviour in males.

In view of these data, a retrospective study was carried out to answer the question whether stressful maternal life events occurring during pregnancy may have irreversibly affected sexual differentiation of the brain in men who were born in Germany during the stressful period of World War II. Out of about 800 homosexual males highly significantly more homosexuals were born during the stressful war and early post-war period than in the years before or after World War II [21]. This finding suggested that stressful maternal life events, if occurring during pregnancy, may represent, in fact, an aetiogenetic risk factor for the development of sexual variations in the male offspring.

In addition, 100 bi- or homosexual men as well as 100 heterosexual men of similar age were asked about maternal stressful events that might have occurred during their prenatal life. Indeed, a highly significantly increased incidence of prenatal stress was found in bisexual and, in particular, in homosexual men as compared to heterosexual men [22]. About a third of the homosexual men reported to have been exposed to severe maternal stress—such as bereavement, repudiation by the partner, rape or severe anxiety—and about an additional third to moderate maternal stress during their prenatal life. On the other hand, none of the heterosexual men was found to have been exposed to severe and less than 10% to moderate maternal stress during their prenatal life. These data also indicate that prenatal stress may represent a risk

factor for the aetiogenesis of sexual variations in later life.

In male rats, prenatal stress led to a significant decrease of plasma testosterone levels and hypothalamic norepinephrine levels of fetuses and newborns followed by hypo-, bi- or even homosexual behaviour in adulthood. Such perinatal biochemical changes and postnatal long-term behavioural changes produced by prenatal stress in male rats could be prevented by perinatal administration of testosterone and—at least in part—by prenatal administration of the norepinephrine precursor tyrosine [23, 24].

In rats, acute prenatal stress, i.e. enforced immobilization for 2 h on day 20 of gestation resulted in a significant decrease of β-endorphin content in the fetal pituitary associated with a significant increase of plasma corticosterone and androstenedione levels as well (Fig. 1). Similar findings were obtained by Wilke *et al.*[25]. Furthermore, daily exposure to prenatal stress between days 15 and 21 of pregnancy increased significantly male-type gender role behaviour, i.e. play-fighting in prepubertal life (Fig. 2) as well as heterotypical male sexual behaviour in postpubertal life of female rats (Fig. 3). These changes were combined with significantly reduced ovarian weights and some irregularities of the ovarian cycles. All these short- and long-term effects of prenatal stress could be prevented, at least in part,

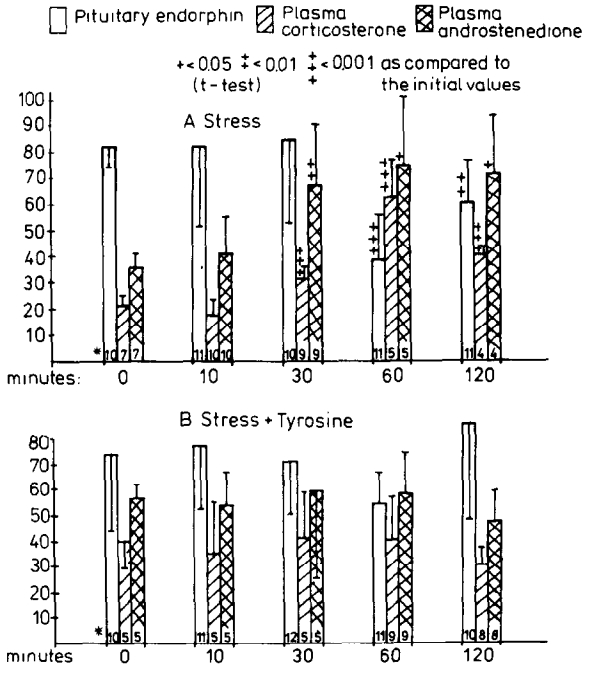

Fig. 1. Pituitary β-endorphin-like immunoreactivity ☐ (ng/pituitary) and plasma corticosterone ▨ (μg/dl) and androstenedione ▩ (ng/dl) levels (means ± SD) of rat fetuses following enforced immobilization of their mother animals for 2 h on day 20 of gestation without or with tyrosine pretreatment (tyrosine methylester i.p. 200 mg/kg 1/2 h before stress).

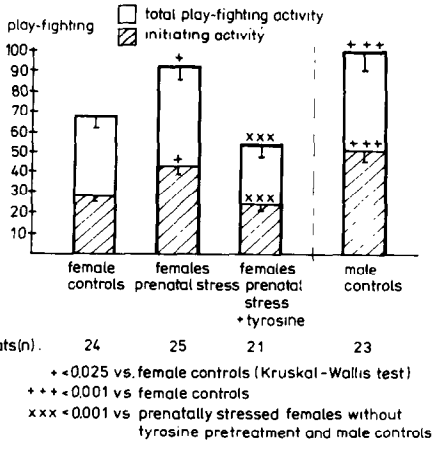

Fig. 2. Mean (±SE) number of 20-s sessions in which female and male controls as well as prenatally stressed females without or with tyrosine pretreatment (see Fig. 1) between days 15 and 21 of gestation were observed to be engaged in play-fighting (70 observation sessions per rat and day between days 26 and 40).

by simultaneous administration of the norepinephrine precursor tyrosine (Dörner *et al.*, in preparation).

In addition, a highly significant correlation was found between the plasma corticosterone levels of pregnant rats exposed to acute stress and the androstenedione levels of their female fetuses [$y = 54.5 + 0.284\ (x - 110.4)$; $r = 0.8$; $P < 0.001$]. In a preliminary pilot study, a weak but significant correlation was also observed between the salivary cortisol levels of pregnant women exposed to slight or moderate acute stress and the testosterone levels

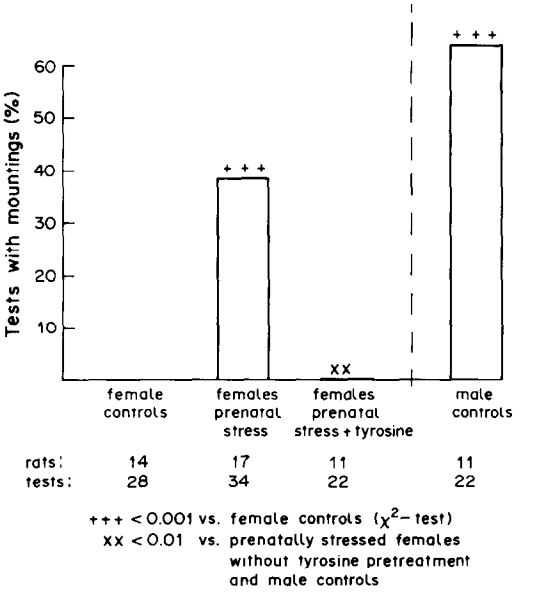

Fig. 3. Male sexual behaviour (tests with mountings) in adult female and male control rats as well as prenatally stressed females without or with tyrosine pretreatment (see Fig. 1) between days 15 and 21 of gestation.

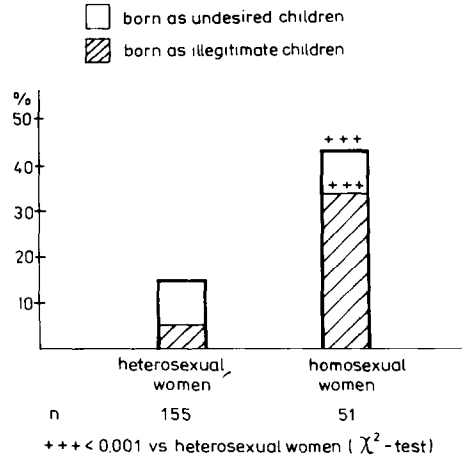

Fig. 4. Percentages of age-matched heterosexual and homosexual women who were born as illegitimate ▨ and/or □ undesired children.

in the amniotic fluids of their female fetuses [$y = 9.78 + 12.3\ (x - 0.39)$; $r = 0.61$; $P < 0.05$].

These findings indicated that prenatal stress may predispose to male-type gender role behaviour and sexual orientation in females. In mothers of homosexual men, undesired and illegitimate children were often found to be the reason for stressful events during their pregnancies [22]. Therefore, 51 homosexual women were also interviewed in comparison with 150 heterosexual women to find whether they were born as illegitimate and/or undesired children. As demonstrated in Fig. 4, highly significantly more homosexual than heterosexual women were born, indeed, as illegitimate and/or undesired children (Hess, Höck and Dörner, in preparation).

Thus, prenatal stress appears to be able to dedifferentiate sex-specific brain organization in both sexes, i.e. reproductive functions cannot only be inhibited in both sexes transiently by postpubertal stress (importence or transient amenorrhoea) but even permanently by prenatal stress.

In sexual differentiation of the human, five steps may be distinguished (Fig. 5):

(1) The genetic or gonosomal sex is determined by the presence of an X- or Y-chromosome in the fertilizing sperm cell.

(2) The gonadal sex is then differentiated under the control of sex-determining genes.

(3) The somatic or genital sex is organized under the control of the Mullerian inhibiting substance (MIS) and of androgens.

(a) During the 2nd and 3rd prenatal month the internal genitalia are organized by MIS and testosterone (T).

(b) During the 3rd and 4th prenatal month the external genitalia are organized by 5α-dihydrotestosterone (DHT). Therefore, clear-cut dissociations between hormone-dependent malorganizations of the internal and external genitalia are possible and also known.

(4) The neuronal sex, i.e. female-type or male-type gonadotrophin secretion, sexual orientation and gender role behaviour are organized by sex hormones and mediated, at least in part, by neurotransmitters [6]. The critical periods for sex-specific differentiation of the corresponding sex, mating and gender role centres in the brain are not completely identical but overlapping [5, 25]. Moreover, different sex hormones appear to be responsible—at least in part—for the organization of sex-specific gonadotrophin secretion, sexual orientation and gender role behaviour [25].

In Fig. 6 the influence of intracerebral im-

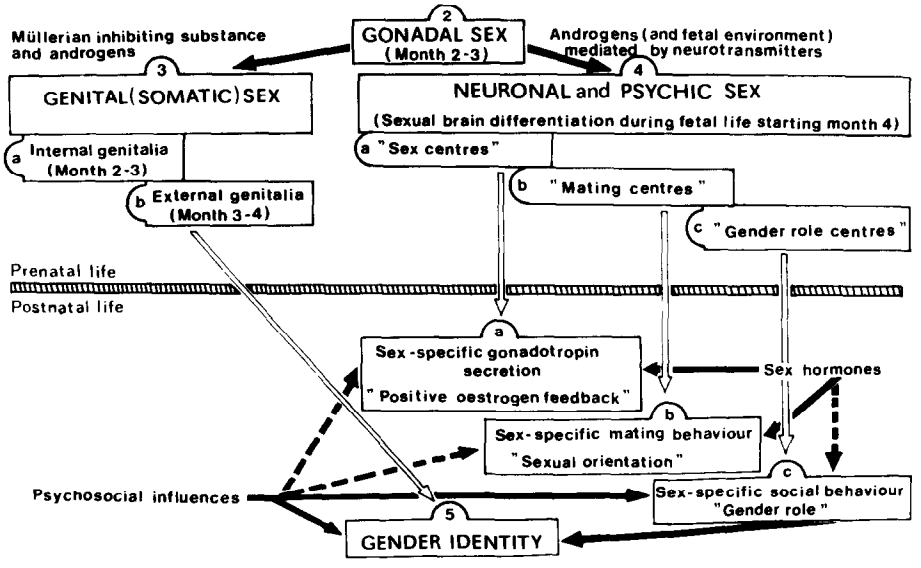

Fig. 5. Sexual differentiation in the human. MIS—Mullerian inhibiting substance; T—testosterone; DHT—5α-dihydrotestosterone; Oe—estrogen; A—androgen.

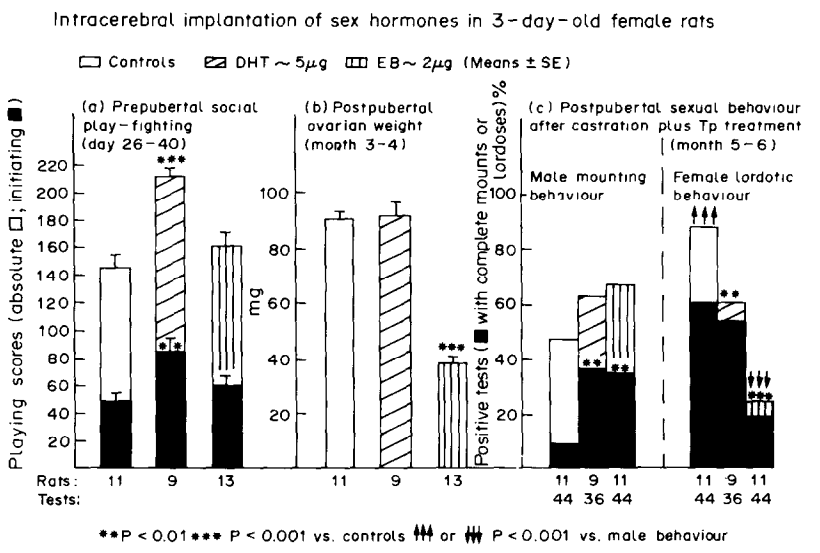

Fig. 6. Prepubertal play-fighting, postpubertal ovarian weight and sexual behaviour in female rats implanted into the mediocortical amygdala with paraffin pellets □, 5 μg DHT ▨ or 2 μg EB ▥ at 3 days of age. $^{++}P<0.01$; $^{+++}P<0.001$ vs controls implanted with paraffin; ↑↑↑ or ↓↓↓ $P<0.001$ vs male behaviour.

plantation of sex hormones in 3-day-old female rats on prepubertal gender role behaviour (social play-fighting), postpubertal gonadotrophin-dependent ovarian function and sexual orientation are demonstrated: the androgen DHT, which is not aromatizable to estrogens, showed a significant male-type organization effect on prepubertal gender role behaviour as well as on sexual orientation, but not on the organization of gonadotrophin secretion and hence on ovarian weight. On the other hand, the estrogen estradiol displayed a significant male-type organization effect on gonadotrophin secretion resulting in the anovulatory ovary syndrome with significantly decreased ovarian weights due to failure of corpora lutea formation as well as on male-type sexual orientation, but not at all on male-type gender role behaviour.

In view of these findings, the following conclusions can be drawn:

(a) The "sex centres" controlling female-type or male-type gonadotrophin secretion are organized only by estrogens, which are mainly converted, however, from androgens within the brain. Thus, male-type differentiation of gonadotrophin secretion is achieved by estrogens or by androgens which are convertible to estrogens, but not by non-convertible androgens.

(b) The "mating centres" controlling sexual orientation are organized by estrogens and androgens as well. Thus male-type differentiation of sexual orientation is achieved by synergistic effects of estrogens and androgens which are convertible or non-convertible to estrogens.

(c) Finally, the "gender role centres" controlling female-type or male-type gender role behaviour are organized only by androgens.

Thus, not only the absolute levels of sex hormones, but also the ratios of androgens to estrogens are responsible for a specific sexual differentiation of the brain. Therefore, several combinations and dissociations between sex hormone-dependent deviations of gonadotrophin secretion, sexual orientation and gender role behaviour are possible.

Recently, the evocability of a positive estrogen feedback action on LH and FSH secretion was investigated in 28 male-to-female transsexuals [26, 27]. As demonstrated in Figs 7 and 8, a positive estrogen feedback effect on LH and FSH secretion was only induced by a single i.v. injection of 20 mg Presomen (Premarin) in homosexual male-to-female transsexuals, in contrast to hetero- or bisexual male-to-female transsexuals. These data may also be explained by the fact that estrogens are responsible for sexual differentiation of gonadotrophin secretion, estrogens and androgens of sexual orientation and androgens of gender role behaviour [26].

(5) In a final step, sexual differentiation in the human is completed by the establishment of gender identity, i.e. by a consciously experienced self-concept of being male or female. This self-concept is dependent on the sex hormone-controlled differentiation of the somatic and psychic sex in prenatal life and on psychosocial influences in postnatal life. All these differentiation and activation processes in the brain appear to be mediated—at least in part—by neurotransmitters and neuromodulators.

As shown in Fig. 9, a conversion of female-type to male-type sexual orientation was achieved most recently in adult rats by administration of the dopamine agonist and serotonin antagonist lisuride (Dörner *et al.*, in preparation). In prepubertally

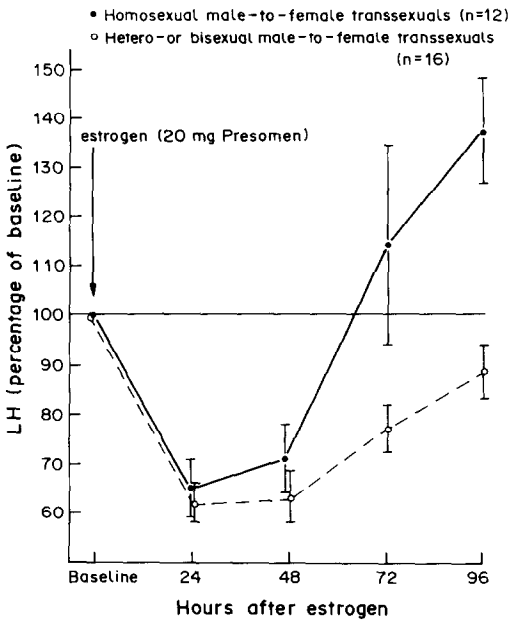

Fig. 7. Serum LH response to an i.v. estrogen injection expressed as per cent of the LH baseline levels in homosexual and hetero- or bisexual male-to-female transsexuals.

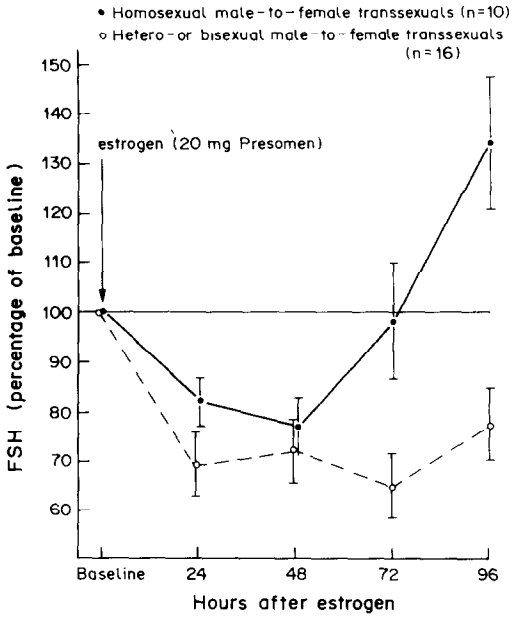

Fig. 8. Serum FSH response to an i.v. estrogen injection expressed as per cent of the FSH baseline levels in homosexual and hetero- or bisexual male-to-female transsexuals.

castrated and later androgen-treated adult females, lisuride induced a significant decrease of female-type lordotic behaviour towards males and simultaneously a significant increase of male-type mounting behaviour towards estrous females. Thus, predominantly homotypical ("heterosexual") behaviour in androgen-treated females was converted to predominantly heterotypical ("homosexual") behaviour.

Furthermore, in neonatally castrated and later androgen-treated adult males, lisuride administration resulted in a highly significant decrease of female-type lordotic behaviour towards vigorous males and simultaneously in a significant increase of male-type ejaculatory behaviour towards estrous females. Hence, ambiguous ("bisexual") or even predominantly heterotypical ("homosexual") behaviour in neonatally castrated adult males was converted to predominantly homotypical ("heterosexual") behaviour.

The effects of lisuride on changes of sexual orientation in rats were even stronger than those observed

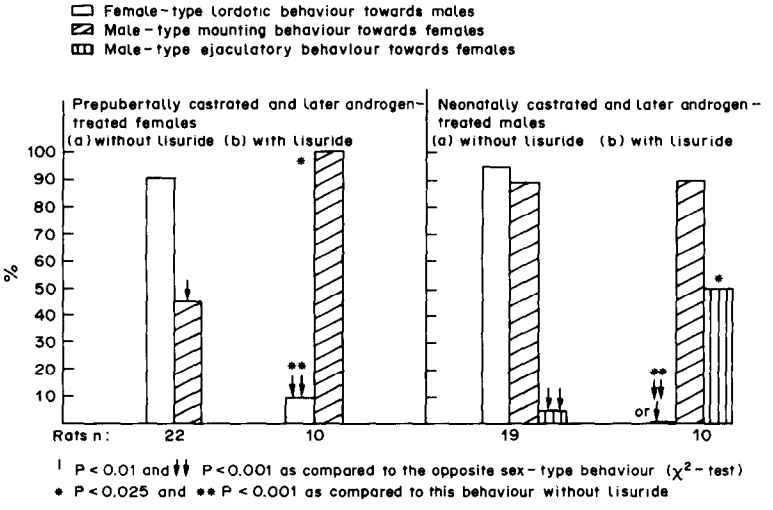

Fig. 9. Conversion of female-type and male-type sexual orientation in prepubertally castrated and later androgen-treated (0.2 mg TP daily) female or neonatally castrated and later androgen-treated male rats induced within 1 h by s.c. injection of 0.25 mg/kg lisuride.

after stereotaxic lesioning of the "female mating centre" in the hypothalamic ventromedial nuclear region in rats [28] or human beings [29, 30]. Therefore, possible effects of lisuride on sexual orientation in the human remain to be elucidated.

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