SEXUAL MEDICINE REVIEWS

The Present and Future of Human Sexuality: Impact of Faulty Perinatal Hormonal Imprinting

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ABSTRACT

Introduction: Hormonal imprinting occurs perinatally, when the developing hormone receptors connect to their target hormones. This is required for the normal development of the receptor-hormone connection. At this time, the selectivity of receptors is weak and can be misdirected to related endogenous or exogenous molecules, such as other members of the same hormone family, synthetic hormones, drugs, hormone-like environmental pollutants, and endocrine disruptors. In this situation, faulty hormonal imprinting develops with lifelong consequences, which are manifested by altered receptor binding capacity, hormone production, changed bone formation, and brain neurotransmitter content. The effect of faulty imprinting is epigenetically inherited and manifested in progeny.

Aim: To evaluate the effects of hormonal imprinting on sexuality based on published results.

Methods: Review of perinatal (mainly single) treatment of experimental animals with hormones or hormone-like materials and the study of their effects in adulthood and in progeny.

Main Outcome Measure: Consistency of experimental results with the previous information and expectations.

Results: In each published experiment, perinatal treatments with hormones acting on members of a steroid receptor superfamily or endocrine disruptors (eg, bisphenol A, vinclozolin, benzpyrene or soybean genistein) caused faulty imprinting with altered sexual hormone receptor binding and sexual function. Indices of sexual activity showed the strong influence of these treatments.

Conclusion: Sexuality is influenced by perinatal faulty hormonal imprinting at the receptor and behavioral levels. Because faulty imprinting is an epigenetic process, it is transmitted to the members of cell line and to progeny. In the modern age, the amount of artificial (industrial, communal, and medical) imprinters and their effects on the human organism are increasing enormously. This is likely to change human sexuality now and in the future.

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Key Words: Hormonal Imprinting; Perinatal Actions; Hormones; Endocrine Disruptors; Sexual Development; Environmental Pollution

INTRODUCTION

Birth is a milestone in a person's life. Before birth, the mother's body protects the fetus, and the mother's hormones, which pass through the placenta, influence the fetal endocrine system. After birth, the infant starts its life and the brain-controlled endocrine system chemically directs the actions of the organism. This requires the setting of the relation between the receptor and the hormone system. Part of this process is perinatal hormonal imprinting, the first encounter between the hormone receptors and the body's hormones. Imprinting is needed for normal maturation of the receptor-hormone complex, and in normal cases this process results in a well-balanced endocrine system.[1] However, some problems can occur if related molecules disturb this first encounter or the amount of physiologic hormones is more or less than normal.

The discriminating capacity of the developing receptors is weak. This means that molecules similar (but not identical) to the target hormone also can bind to the receptor, resulting in faulty imprinting.[2] The problem is that the effect of imprinting is lifelong. Faulty imprinting results in the altered binding capacity of receptors, which causes functional changes of the cells affected. Several biochemical processes, such as hormone, cytokine, or neurotransmitter synthesis and secretion, enzyme synthesis, bone formation, behavior, or pain sensitivity, can be susceptible to faulty imprinting and malignancies are not excluded.[3] Hormonal imprinting is an epigenetic process that is inherited from cell to cell without change in the basis sequence of genetic material

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(mutation).[4] The phenomenon of transgenerational hormonal imprinting has been demonstrated up to the third generation.[5] Receptors, which are members of hormone families (eg, pituitary hormones, steroid hormones), are especially sensitive to such related hormones or synthetic hormones, because the cells of one organ and the cells of multiple organs are influenced by the same faulty imprinting at the same time.

Sexuality is based on a very complex endocrine interrelation. It is influenced by many hormones that are the polypeptide type (eg, pituitary tropic hormones) or the steroid type (eg, gonadal hormones). They act under the control of the central nervous system. Therefore, failure of physiologic hormonal imprinting can influence the entire system. In the modern age, many synthetic hormone-like molecules are entering organisms during the perinatal period, and these can influence lifelong sexuality by faulty hormonal imprinting. The introduction of these effects and the demonstration of the problems caused by these effects are the subject of this review.

EXPERIMENTS DEMONSTRATING FAULTY PERINATAL HORMONAL IMPRINTING

Impact of Perinatal Natural or Synthetic Hormone Treatments at the Receptor Level

Hormones are recognized by receptors and receptors transmit information (command) for the cells. Therefore, the binding capacity and affinity of receptors are decisive factors in the development of the response.

A single neonatal treatment with 17β-estradiol significantly decreased the binding capacity of uterine estrogen receptors.[6] Estradiol-benzoate given at the third day postnatally decreased the specific 8S receptor before puberty.[7] Diethylstilbestrol or allyl-estrenol exposure produced similar effects.[8] However, receptor affinity remained at the control level. Treatment of 3-day-old animals was neutral. Neonatal treatment with testosterone or estradiol decreased the concentration of estrogen receptors in adolescent rats.[7] Perinatal allyl-estrenol treatment decreased uterine estrogen receptor density in adult rats.[9] Triiodothyronine (T3) treatment, which increased the binding capacity of thymus glucocorticoid receptors, was indifferent to uterine estrogen receptors.[10] However, neonatal hypothyroidism decreased the number of estrogen binding sites in rats when applied from day 7 to day 28, similar to the response to TSH and contrary to receptor amplification in chickens.[11–13]

These experiments show that perinatal hormone treatments influence the binding capacity of receptors without influencing their affinity.

Effect of Perinatal Hormone Treatments on Sexual Behavior

Perinatal hormone treatments are manifested in the change of sexual behavior in adulthood and these changes can be studied quantitatively.

Pre- and postnatal treatment with testosterone completely masculinized the sex-specific aromatization capacity of adult female rats.[14] This treatment also increased the receptivity of female rats.[15] Postnatal testosterone treatment inhibited lordosis in female prairie voles and allo-parental behavior was inhibited in male voles.[16,17] Pre- and postnatal exposure to testosterone caused anovulation and decreased the weight of the sexually dimorphic nucleus.[18] Perinatal progesterone and estradiol exposures caused feminization of sexual behavior in the opossum.[19] A single perinatal (at day 21 of pregnancy, at the day of birth, or at day 5 postpartum) administration of estradiol completely abolished the estrogen-induced luteinizing hormone surge in adult female rats without inhibiting lordosis.[20] Perinatal estradiol treatment disrupted normal sexual behavior and receptivity in female rats.[21] A single neonatal diethylstilbestrol or allyl-estrenol exposure decreased the sexual activity of adult male rats, and the female rat's sexual activity was decreased only by diethylstilbestrol.[22] Neonatal tamoxifen or mifepristone exposure decreased the binding capacity of uterine estrogen receptors[23] and completely abolished male and female rats' sexual activity.[24] Postnatal corticosterone exposure inhibited allo-parental behavior in female prairie voles.[16] Partner preference also was influenced by perinatal steroid hormone treatment.[25] A single neonatal serotonin treatment decreased the serotonin content of the brain of adult male rats and increased their sexual activity.[26] After a single neonatal β-endorphin treatment, adult (5-month-old) female rats' sexual activity decreased and male rats became more aggressive. The brain serotonin level was decreased.[27] Single neonatal treatment with T3 increased mounting activity and decreased the number of intromissions by male rats.[28]

Vitamins A and D are steroid hormones that are recognized and bound by receptors of the steroid receptor superfamily. A single neonatal vitamin A (retinol) exposure dramatically decreased the sexual activity of male rats and significantly decreased the Meyerson index of female rats.[29] Neonatal treatment with vitamin D_3 completely inhibited the ejaculation of adult male rats without influencing sexual desire[30] and a larger dose abolished desire and ejaculation. A single vitamin E perinatal exposure significantly decreased the sexual activity of adult female and male rats and vitamin K caused only a slight effect.[31]

The results show that perinatal treatments with hormones strongly influence the sexual behavior of experimental adult animals.

Effect of Endocrine Disruptors on Sexuality

Endocrine disruptors are natural or synthetic molecules that, after entering mammalian organisms, can bind to (mainly steroid) hormone receptors and thus influence the endocrine system in adulthood. Therefore, a similar or stronger imprinting effect is expected by perinatal treatments.

The polycyclic hydrocarbon benzpyrene administered postnatally significantly decreased the binding capacity of estrogen receptors[32] and caused a dramatic decrease in the sexual activity