The Differentiation of the Neuroendocrine System and Fundamental Processes of Life

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In my opinion, the neuroendocrine system may be regarded as the complex unity of the nervous system and the endocrine system, which are closely interconnected by neurotransmitters and systemic hormones. It is responsible for the control of fundamental processes of life, such as reproduction, metabolism and information processing.

Hormones may be defined today as chemical messengers that are produced in specialized cells and exert biological effects on other cells of the same organism by acting either locally (as local hormones) or on distant target cell (as systemic, blood-borne or classical hormones). In view of this definition, neurotransmitters may be regarded as local hormones of the neuroendocrine system, and two different hormonal actions can be distinguished for neurotransmitters as well as for systemic hormones: (1) transient i.e. reversible activational or inactivational effects of hormones on gene expression and/or enzyme activities in adult life and (2) persistent, i.e. more or less irreversible differentiational effects on gene expressibility, if the hormones act during critical developmental periods, especially of the brain.

Several findings were obtained in our laboratory which suggest that neurotransmitters, which are influenced by the external and internal environment, may even be regarded as direct organizers of the brain. If occurring in unphysiological concentrations during brain development they may act as teratogens, giving rise to permanent structural and biochemical changes in the brain associated with permanent dysfunctions of fundamental processes of life. Consequently, many disorders and diseases of the neuroendocrine system called endogenous, idiopathic, genuine, primary, essential or cryptogenic thus far can be based on teratogenic defects acquired during critical developmental periods in pre- and/or early postnatal life.

1. Hormone-Dependent Brain Development and Reproduction

Significant correlations have been found between transient changes of sex hormone levels during critical periods of brain differentiation and permanent functional as well as structural alterations of the central nervous-hypophysial-gonadal system. In view of these findings, important disturbances of reproduction can develop from discrepancies between the genetic sex and the sex hormone level during a critical period of brain differentiation.

As early as in 1936, Pfeiffer observed that in rats, independent of the genetic sex, the lack of testes during a critical neonatal differentiation phase resulted in cyclic hypo-
physseal gonadotropin release, whereas the presence of testes during this critical phase gave rise to tonic hypophysseal gonadotropin secretion in later life.

Grady and Phoenix and Harris reported that male rats orchidectomized shortly after birth showed especially strong female sexual behavior when treated with estrogen in adulthood. Similar findings were obtained in adult male rats which had been treated with anti-androgen during perinatal life. All these observations pointed to the significance of the sex hormone level during a critical differentiation phase for the development of sexual behavior.

During the last decade, the following findings were obtained in our laboratories on sexual differentiation of the brain:

1. Male rats castrated on the day of birth showed predominantly heterotypical behavior, i.e., a significant preference of sexual responsiveness to male partners, following androgen substitution in adulthood.

2. The higher the androgen level during the differentiation phase, the stronger was the male and the weaker the female sexual behavior during the postpubertal functional phase, irrespective of the genetic sex. Even a complete inversion of sexual behavior was observed in male and female rats following androgen deficiency in males and androgen excess in females during the critical differentiation period of the brain. According to these findings, a neuroendocrine predisposition for primary hypo-, bi- and homo-sexuality may be based on different degrees of androgen deficiency in males and androgen excess in females during sex-specific brain differentiation.

3. The permanent changes of sexual behavior were associated with permanent structural and/or chemical changes in discrete brain regions controlling sexual behavior and/or gonadotropin secretion (sexual dimorphism of the brain).

4. In male rats castrated on the day of birth, a strong positive estrogen feedback effect on LH secretion could be induced in a similar way as in normal females, but not in neonatally androgenized females. In view of these findings a strong positive estrogen feedback effect appears to be only evocable in adulthood if there existed a low androgen level during brain differentiation.

5. A positive estrogen feedback effect on LH release could also be elicited in homosexual men, in contrast to heterosexual and bisexual men. These findings suggest that homosexual men may possess, at least in part, a predominantly female-differentiated brain due to androgen deficiency during brain differentiation. In addition, significantly lower plasma free testosterone levels and higher basal FSH and LH levels were found in homosexual males, but only in effeminate homosexual males, than in heterosexual males.

In view of our experimental and clinical data, the following hypothesis was deduced: An androgen deficiency occurring in genetic males during a critical period of brain organization gives rise to predominantly female differentiation of the brain. The predominantly female-differentiated brain is then activated postpubertally by an approximately normal androgen level leading to homosexual behavior.

In genetic females, the results of animal experiments obtained in various species were
supported by some clinical findings which suggest that an androgen excess occurring during a critical period of brain differentiation can predispose to the development of hypo-, bi- or even homosexual behavior in adult life.

In transsexual women with homosexual behavior, we could only evoke a weak or at best moderate positive estrogen feedback action on LH release as compared to the evocability of a strong estrogen feedback action found in normal heterosexual women. Seyler et al. reported that the LH response to LRH could not be clearly enhanced by estrogen-priming in transsexual and homosexual females, in contrast to heterosexual females.

In view of the described data, sexual deviations in the human may be based, at least in part, on discrepancies between the genetic sex and a sex-specific sex hormone level during brain differentiation. Therefore, a genuine prophylaxis may become possible in the future by preventing such discrepancies during the period of sexual differentiation of the brain.

Three preconditions towards this aim have been achieved:

1. Our comparative studies of hypothalamic biomorphosis in 84 human fetuses and hundreds of rats have led to the conclusion that the critical period of sex-specific brain differentiation occurs in the human between the 4th and 7th month of fetal life. Furthermore, we have found that the plasma level of biologically active free testosterone is even higher in male fetuses of mid-pregnancy than in adult men.

2. A simple and reliable method for the prenatal diagnosis of genetic sex was developed using fluorescence microscopy of amniotic fluid cells.

3. Testosterone levels were found to be significantly increased and FSH levels significantly decreased in amniotic fluids of male fetuses as compared to those of female fetuses.

Therefore, the examination of amniotic fluids for genetic defects should be supplemented in the future by determination of hormone levels in order to find out and possibly correct abnormalities that might lead to maldifferentiations, especially of the brain.

In recent years, it was demonstrated that neurotransmitters are also responsible for the control of sexual behavior. Interestingly enough, such neurotransmitters — like sex hormones — appear to represent not only transient activators but even organizers of the brain.

Rats were treated with the monoamine oxidase inhibitor pargyline or the acetylcholine esterase inhibitor pyridostigmine during the first two weeks of life.

Male sexual activity was permanently decreased in neonatally pargylinized, but permanently increased in neonatally pyridostiginized rats. These permanent behavioral changes that were produced by psychotrophic drugs administered during brain differentiation were associated with permanent structural and biochemical changes in discrete regions of the brain.

Similar teratogenic effects may be induced by unphysiologic neurotransmitter concentrations produced by abnormal levels of sex hormones as well as by abnormal psychosocial influences, since both were found to affect neurotransmitter metabolism during brain
Prenatal psychosocial influences should be regarded as possible aetiogenetic factors in the development of sexual deviations. Thus Ingeborg Ward reported that prenatal stress in male rats demasculinized and feminized sexual behavior potentials in adult life. In our experiments, the testosterone level was found to be significantly decreased in prenatally stressed males during prenatal and early postnatal life as compared to non-stressed control males.

The norepinephrine content in the hypothalamus of these prenatally stressed animals was also significantly decreased on the day of birth. These findings suggest that following stress during pregnancy increased concentrations of adrenal hormones may pass from the mother via placenta to the foetus giving rise to irreversible changes of neurotransmitter metabolism in the brain and sexual behavior in later life. Such permanent effects on the brain may be induced, at least in part, by decreased testicular secretion of testosterone in male fetuses caused by the increased glucocorticoids from mother animals. Following stress in pregnant rats we have found a significant increase of the plasma corticosterone level in the mother animals associated with a significant decrease of the adrenal and testes weights and decreased testosterone levels in the male fetuses. Following glucocorticoid administration to pregnant women, we have also found low testosterone levels in the amniotic fluids of male fetuses.

In view of these data, a pilot study was carried out to answer the question whether stressful maternal life during pregnancy may have irreversibly affected sexual differentiation of the brain in men who were born in Germany during or shortly after the stressful period of the Second World War. 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 war. These findings indicate that stressful maternal life events, if occurring during pregnancy can represent, in fact, an aetiogenetic factor for the development of sexual deviations in the male offspring.

Two organization (differentiation) rules for neuroendocrine systems were deduced from our animal experiments and clinical studies on sexual differentiation of the brain.

1. During a critical period of brain differentiation, an open-loop regulatory system (e.g. placenta – fetal gonad – fetal brain) is converted into a feedback control system (central nervous-hypophysial-gonadal system).

2. During brain differentiation, the quantity of the regulating variable (e.g. sex hormone) determines the quality, i.e., the responsiveness (set point), of the central nervous controller and hence the functional and tolerance ranges of the neuroendocrine feedback control system throughout life (e.g. cyclic or acyclic gonadotropin secretion; hetero-, bi- of homosexual behavior).
trolling metabolism.

Iodine and thyroid hormone deficiencies, if present during brain differentiation, give rise to cretinism which can be prevented by iodine or thyroid hormone if administered during this period. On the other hand, thyroid hormone excess produced in animal experiments during brain differentiation results in permanent hypothyrotropic hypothyroidism.

High doses of glucocorticoids, if injected during brain differentiation, give rise – as we have found – to permanent adrenal atrophy.

Finally, we have obtained several experimental and clinical findings which indicate that overnutrition during pre- and/or early postnatal life represents an important risk factor for the development of obesity and hence of diabetes mellitus, hyperlipoproteinemia and arteriosclerosis in adult life.

Regarding diabetes mellitus, teratogenetic mechanisms may also play a role in the case of maternal diabetes transmission:

1. Newborns of diabetic mothers were found to be characterized by significantly increased insulin levels.

2. The incidence of overt diabetes was found to be about 20 times higher in 2000 children of diabetic mothers than in the total population.

3. Most of all, in about 4000 diabetics, a significant predominance of diabetes transmission was observed on the maternal side. The ratio of familial diabetes aggregation between the maternal and paternal side was 2.54:1.0. In my opinion, this phenomenon cannot be explained by genetic but rather by teratogenetic mechanisms.

4. Human subjects born in period with high food supply displayed a significantly increased incidence of diabetes mellitus in later life as compared to those born in postwar periods with shortage of food supply.

In view of these data, a genuine prophylaxis of diabetes appears to be possible by preventing hyperglycemia in pregnant diabetic mothers and hence hyperinsulinaemia in fetuses and newborns as well as by preventing overnutrition during perinatal life.

Regarding the cardiovascular system, we have found hypertension in adult rats treated with angiotensin during neonatal life. In addition, Grollman and Grollman (1962) have observed hypertension in adult rats when their mother animals had been treated with aldosterone or deoxycorticosterone during pregnancy. These findings suggest that unphysiological levels of angiotensin or mineralocorticoids, when occurring during critical developmental periods, can exert teratogenic effects on neuroendocrine controllers of blood pressure. Such teratogenetic mechanisms may also be important in the aetiopathogenesis of essential hypertension in the human.

All these data indicate that unphysiological concentrations of hormones and metabolic variables, if occurring in critical developmental periods, may be able to exert teratogenic effects on neurons.

3. Environment-Dependent Brain Differentiation and Information Processing

In the ontogenesis of information processing, open-loop regulatory systems are con-
Verted again into feedback control systems. In this case, external signals can stimulate sensory receptor cells of the central nervous system, inducing the production of specific neurotransmitters in these receptor neurons. These neurotransmitters may act as organizers during the critical period of brain differentiation, affecting the quality, i.e., the responsiveness (functioned and tolerance ranges), of central nervous controllers throughout life.

We have observed that school children who were reared by their mothers during the first 2 to 3 years of life showed significantly increased learning capacity associated with increased social adaptability in comparison with children lacking maternal care during the critical period of early postnatal life.

Behavioral teratogenetic defects were also observed in adult animals after prenatal administration of psychotropic drugs. More recently, we have found that changes of neurotransmitter concentrations and/or turnover rates produced by psychotropic drugs during early postnatal brain differentiation can give rise to permanent alterations not only of sexual behavior but also of avoidance behavior, emotional reactivity, exploratory activity and memory capacity.

Data obtained from various authors indicate that nutritional factors, environmental stress and systemic hormones can affect neurotransmitter concentrations and/or turnover rates in a similar way as psychotropic substances. Thus malnutrition, abnormal psychotropic stimuli and unphysiological concentrations of systemic hormones may also cause unphysiological concentrations and/or turnover rates of neurotransmitters which can result in teratogenetic defects, if occurring during brain differentiation.

Psychosomatic interrelationships are mediated by neurotransmitters in the brain. Thus, psychosocial influences as well as systemic hormones and metabolic variables can affect neurotransmitter metabolism in the brain, resulting in alterations in information processing, reproduction and/or metabolism. Hence, fundamental processes of life are controlled by closed-loop neuroendocrine subsystems that are combined with each other by neurotransmitter metabolism in the brain. Thus, it is also conceivable that changes in the external environment — particularly in psychosocial conditions — as well as changes in the internal environment — that is, in systemic hormones and metabolic variables — can produce alterations in neurotransmitter metabolism of the brain and hence in information processing, reproduction and metabolism as well.

Thus relevant disorders and diseases of information processing, reproduction and metabolism called endogenous, idiopathic, genuine, primary, essential or cryptogenic thus far can be based on abnormalities in the external, particularly psychosocial environment, and/or the internal environment, if occurring during critical developmental periods of the brain.

Hence, irreversible differentiation disturbances of the neuroendocrine system produced by teratogenic effects of the external environment may be prevented not only by improving this external environment, but also by correcting abnormalities of the internal environment.
(1) Delayed puberty induced by neonatal deprivation, i.e. by partial maternal and littermate deprivation, could be completely prevented by administration of the monoamine oxidase inhibitor pargyline.

(2) Permanent disorders of emotionality, learning capability and memory capacity produced by neonatal maternal and littermate deprivation could be prevented by simultaneous administration of the acetylcholinesterase inhibitor pyridostigmine.

(3) Permanent teratogenic effects induced by prenatal maternal stress occurring during critical developmental periods of the brain may also be prevented by drugs, e.g. by administration of testosterone or psychotrophic drugs.

Finally, teratogenic defects produced by abnormalities of hormones or metabolic variables can be based not only on environment-dependent disturbances but also on primary genetic defects (e.g. in congenital adrenal hyperplasia or in Fölling's disease). However, such teratogenic defects can also be prevented by correcting the abnormalities of hormones or metabolites during critical developmental periods, without correcting the primary genetic defects.

Thus, teratomorphology — which was founded during the last century — should be supplemented now by teratophysiology, teratopsychology and even teratoimmunology three most promising cornerstones of preventive medicine.

References

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