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HORMONES, BRAIN DIFFERENTIATION AND FUNDAMENTAL PROCESSES OF LIFE

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SUMMARY

Fundamental processes of life, such as reproduction, metabolism and information processing, are controlled by neuroendocrine feedback systems. From extensive animal experiments and clinical studies the following ontogenetic differentiation rules were deduced for these systems: 1. During critical periods of brain differentiation, open-loop regulatory systems are transformed into feedback control systems (*transformation rule*). 2. During brain differentiation, the quantity of hormones (systemic hormones or neurotransmitters) determines the quality, i.e. the responsiveness (set point) of the central nervous controllers and hence the functional and tolerance ranges of the neuroendocrine feedback control systems throughout the life (*determination rule*).

Systemic hormones and neurotransmitters, if occurring in nonphysiological concentrations during brain differentiation, can act as teratogens leading to relevant functional disturbances of reproduction, metabolism or information processing. Experimental and clinical findings suggest that numerous malfunctions of fundamental processes of life, called 'idiopathic, primary, essential, endogenous or genuine' so far, can be based on such environment-dependent teratogenetic effects. Therefore, important malfunctions of reproduction, metabolism and information processing may be prevented, at least in part, by optimizing the external and/or internal environment during critical periods of brain differentiation.

INTRODUCTION

Hormones may be defined as intercellularly active chemical messengers that are produced in specifically differentiated cells and exert biological effects on other cells of the same organism by acting locally (as local hormones) or at distant target cells (as systemic hormones). They affect reversibly (during functional periods) or irreversibly (during differentiation periods) cell activities, especially enzyme activities, by intracellular receptors or by cell membrane receptors, cyclases and intracellular messengers, such as cyclic AMP or GMP. Thus, hormones can be classified according to their chemical structure, their site of production, their site of action, their biological action and/or their mechanism of action.

In view of this definition, neurotransmitters may be regarded as local hormones of the nervous system, and a strict differentiation between neurohumors or neurotransmitters, i.e. local neurohormones, on the one hand, and systemic neurohormones, on the other, appears to be no longer justified. Therefore, all local and/or systemic hormones produced by neurones may be defined as neurohormones and classified in the same way as the non-neurohormones (according to their chemical structure, site of production, site of action, biological action and/or mechanism of action).

Consequently, the brain can be regarded as a neuroendocrine organ and the complete neuroendocrine system may be divided into the neural endocrine system, i.e. the CNS, and the non-neural endocrine system controlled by the brain. Therefore, neuroendocrinology has to investigate the neuroendocrine processes within the CNS, i.e. local interactions between neurones and hormones as well as the interactions between the brain and other endocrine organs.

Fundamental processes of life, such as reproduction, metabolism and information processing, are then recognized to be controlled in highly developed organisms by neuroendocrine feedback control systems: reproduction by the central nervous–hypophysial–gonadal system, metabolism by several neuroendocrine systems and information processing by neuroendocrine behavioural systems.

The set point of controllers of neuroendocrine systems is primarily determined by the genetic material. However, this phylogenetical determination of neuroendocrine systems is re-established ontogenetically by hormones; i.e. the transcriptibility and/or translatability of the genetic material in central nervous neurones is irreversibly determined by hormones during critical periods of brain differentiation [1–3].

Numerous malfunctions of fundamental processes of life, which are controlled by neuroendocrine systems, are based upon differentiation disturbances of the brain, either caused by genetic defects or by teratogenetic defects acquired during critical differentiation periods in pre- and/or early postnatal life. It may be emphasized that hormones, including neurotransmitters, can act as teratogens, if present in nonphysiological concentrations during critical organization periods of neuroendocrine systems. Thus, structural teratology, i.e. teratomorphology, should be com-

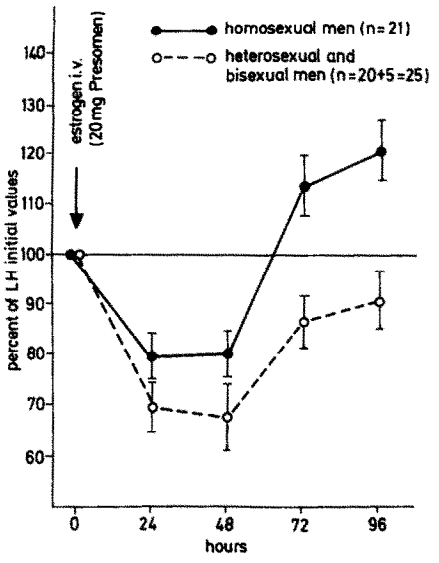

Fig. 1. Serum LH response to an intravenous oestrogen injection expressed as per cent of the mean initial LH values in homosexual and hetero- or bisexual men (Means ± S.E.M.).

pleted by functional teratology, i.e. teratophysiology and teratopsychology [1–3].

All treatment of genetic disorders is purely symptomatic so far, whereas a genuine (causal) preventive therapy seems to be possible in structural and/or functional disturbances based on teratogenetic defects. This principle has been used most successfully as far as congenital malformations are concerned caused by infections, radiation, immunological conflicts, oxygen deficiency or drugs acting during critical periods of pre- and/or early postnatal life. On the other hand, it has not been realized sufficiently in order to prevent malfunctions, especially of neuroendocrine systems.

HORMONE-DEPENDENT BRAIN DIFFERENTIATION AND REPRODUCTION

Clear-cut correlations were found between temporary 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 [2, 3]:

1. In genetic males, androgen deficiency during a critical differentiation phase of the CNS results in a more or less female organization of the brain; i.e. a neuroendocrine predisposition for male hypo, bi- or even homosexuality and a strong evocability of a positive oestrogen feedback action. Limbic and hypothalamic structures of these feminized males are more comparable to those of normal females.

In this context, it may be mentioned that a positive oestrogen feedback on LH secretion could be evoked in intact homosexual men in contrast to intact heterosexual men, suggesting the development of a predominantly female-differentiated brain in male homosexuals (Fig. 1).

2. In genetic females, on the other hand, an androgen overdosage during the differentiation phase leads to a more or less male organization of the brain, i.e. acyclic gonadotrophin secretion associated with anovulatory sterility and/or a neuroendocrine predisposition for female hypo-, bi- or homosexuality. Specific brain structures of these masculinized females are more comparable to those of normal males.

3. Very high androgen and/or oestrogen levels during the critical differentiation phase give rise to permanent hypogonadotrophic hypogonadism in both sexes.

In view of these findings, important disturbances of reproduction appear to develop from discrepancies between the genetic sex and the sex hormone level during a critical period of brain differentiation. There-

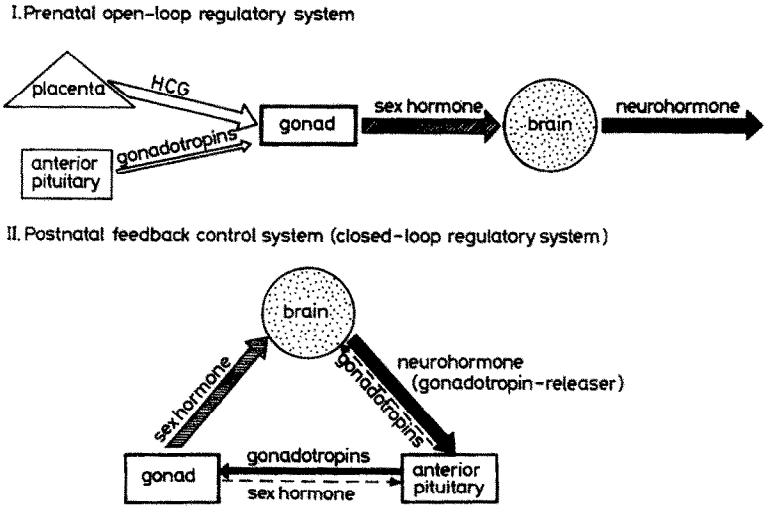

Fig. 2. Ontogenesis of the feedback control system for reproduction.

fore, a genuine (causal) prophylaxis may thus become possible in the future by preventing such discrepancies during the period of sex-specific brain organization.

Three preconditions towards this aim have already 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 hypothalamic differentiation period may be timed in the human between the 4th and 7th month of fetal life [4].

2. A simple and reliable method for the prenatal diagnosis of genetic sex was developed using fluorescence microscopy of amniotic fluid cells [3, 5].

3. Significantly higher testosterone concentrations were found in amniotic fluids of male fetuses than in those of female fetuses [3, 6, 7].

The following ontogenetic organization (differentiation) rules [2, 3] were deduced from our animal experiments and clinical studies (Fig. 2):

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). The regulating variable (sex hormone) and the regulated element (fetal brain) of the primary open-loop regulatory system are then transformed into the controlled condition (homeostatic variable) and the central nervous controller of the secondary feedback control system (*transformation rule*).

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 the life (e.g. a normo- or hypogonadotrophic range; cyclic or acyclic gonadotrophin secretion; hypo-, bi- or homosexual behaviour). Several findings indicate that neurotransmitters are involved in the sex-specific differentiation and maturation of the brain:

Ladosky and Gaziri[8] have found a significant elevation of monoamine oxidase activity in the brain of 12-day-old male rats associated with a diminution of serotonin content as compared to female rats of the same age. Androgen deficiency produced by castration in newborn genetic males gave rise to decreased monoamine oxidase activity and increased serotonin content [9].

We have observed [10] that inhibition of the monoamine oxidase activity by pargyline in newborn males, which apparently also resulted in an increase of serotonin content in the brain, led to delayed onset and permanent decrease of male sexual behaviour (Fig. 3). In contrast, pargyline treatment of newborn females during the first two weeks of life gave rise to precocious puberty [11]. Thus, serotonin appears to inhibit a male differentiation and maturation, but to facilitate a female differentation and maturation of the brain.

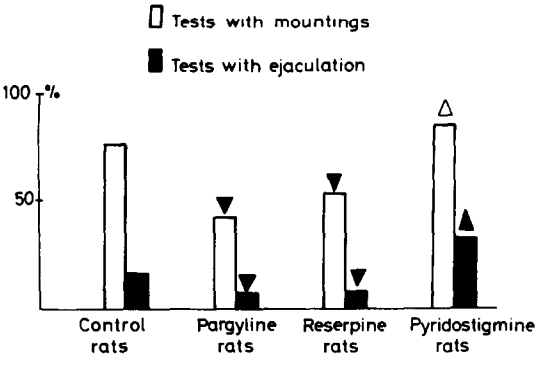

Fig. 3. Male sexual behaviour in juvenile and adult male rats following the treatment with pargyline, reserpine or pyridostigmine during the first two weeks of life [10]. Male sexuality was expressed in % of positive tests with mounting and ejaculation when exposed to castrated and oestrogen-treated female rats; ▼ significantly decreased and ▲ significantly increased as compared to the controls (▼ and ▲ $P < 0.001$, △ $P < 0.05$).

Ward[12] exposed pregnant rats to stress during the last few days of pregnancy and found that their male offspring exhibited hypo-, bi- or even homosexual behaviour in adulthood. In this context, it should be mentioned that increased glucocorticoid levels can be assumed to exist in fetuses of stress-exposed pregnant rats. Glucocorticoids, on the other hand, are also able to increase the serotonin content in the brain, at least in adult rats [13].

Finally, we have found that inhibition of acetylcholine esterase in newborn rats produced by pyridostigmine treatment during the first two weeks of life gave rise to precocious puberty, especially in males, and a permanent increase in male sexual behaviour in both sexes [10, 11].

HORMONE-DEPENDENT BRAIN DIFFERENTIATION AND METABOLISM

Several data were obtained suggesting that the ontogenetic organization rules deduced for the central nervous–hypophysial–gonadal system are also valid for other neuroendocrine systems controlling metabolism and information processing [3]. Iodine and thyroid hormone deficiency, if present during brain differentiation, gives rise to cretinism, which can be prevented by iodine or thyroid hormones if administered during this period. On the other hand, thyroid hormone overdosage produced in animal experiments during brain differentiation results in permanent hypothyreotrophic hypothyroidism [14]. With respect to adrenal function, we have found that high doses of progestagens with glucocorticoid-like activities, if injected during brain differentiation, give rise to permanent adrenal atrophy [15].

Experimental and clinical findings suggest that changes of the insulin level and/or glucose utilization during brain differentiation, produced for example by overnutrition, represent important risk factors for the

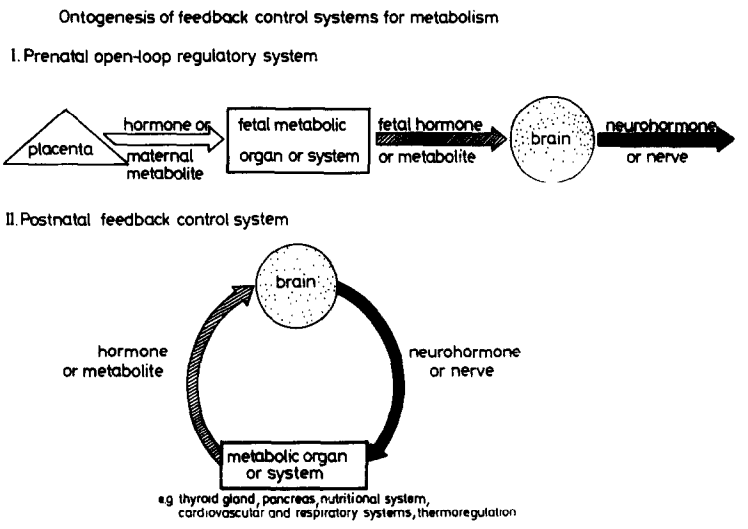

Fig. 4. Ontogenesis of feedback control systems for information processing.

development of obesity, diabetes mellitus and hyperlipoproteinaemia leading to arteriosclerosis and its complications [3]:

1. In female rats an alloxan diabetes was induced before or during pregnancy. These diabetic females then gave birth to animals which developed spontaneous diabetes in juvenile and/or adult life [16].

2. Women with glucosuria and decreased glucose tolerance or overt diabetes during pregnancy were also often observed to give birth to children who developed glucosuria, altered insulin secretion or even overt diabetes [17, 18].

3. Recently, we have found that the adult-onset diabetes is transmitted significantly more often on the maternal side than on the paternal side [19]. This phenomenon can be hardly explained by genetic defects alone, but rather by teratogenetic defects acquired during critical developmental periods of the fetus or newborn.

4. Human subjects born in war and post-war periods with shortage of food supply had a significantly decreased frequency of obesity, diabetes and hyperlipoproteinaemia in adulthood as compared to subjects of similar age, but born in periods with high food supply [20].

5. Significant positive correlations were found between the weight gain of human newborns during the first trimenon of postnatal life and their body weight per body length in adulthood [21].

These findings indicate that overnutrition during the early postnatal life represents an important risk factor for the development of obesity and hence of diabetes mellitus, hyperlipoproteinaemia and arteriosclerosis in adult life. It may be assumed that overnutrition during a critical period of brain differentiation can permanently alter, mediated by hormones (e.g. insulin and/or neurotransmitters), the set point of central nervous controllers regulating food intake and metabolism. In view of these data a genuine prophylaxis of obesity, diabetes mellitus, hyperlipoproteinaemia and arteriosclerosis appears to be possible by preventing overnutrition during the early postnatal life.

HORMONE-DEPENDENT BRAIN DIFFERENTIATION AND INFORMATION PROCESSING

Regarding the ontogenesis of neuroendocrine systems controlling information processing (Fig. 4), a primary open-loop regulatory system (environmental signals—sensory receptors—afferent nerves—brain) is transformed again into a secondary feedback control system (environmental signals—sensory receptors—afferent nerves—brain—efferent nerves—target organs—behaviour—environment). In this case environmental signals stimulate, mediated by sensory receptors and afferent nerves, the production of specific neurotransmitters in the brain. These neurotransmitters which can be regarded as local hormones of the brain appear to represent not only temporary activators or inhibitors, but also organizers of the brain, as it was previously demonstrated for systemic hormones.

Most recently, we have obtained experimental data suggesting that the quantity of neurotransmitter concentrations and/or turnover rates during brain differentiation is able to determine the quality, i.e. the reactivity and adaptability of central nervous controllers for information processing throughout the life.

Rats were treated with pargyline, reserpine or pyridostigmine during the first two weeks of life. These animals showed significant, permanent changes not only of sexual behaviour, but also of conditioned learning behaviour and emotional reactivity in juvenile and/or adult life [10, 22]. Male sexual activity (Fig. 3) as well as learning and/or memory capacity (Fig. 5) were permanently decreased in neonatally pargyline- or reserpine-treated animals, but permanently increased in neonatally pyridostigmine-

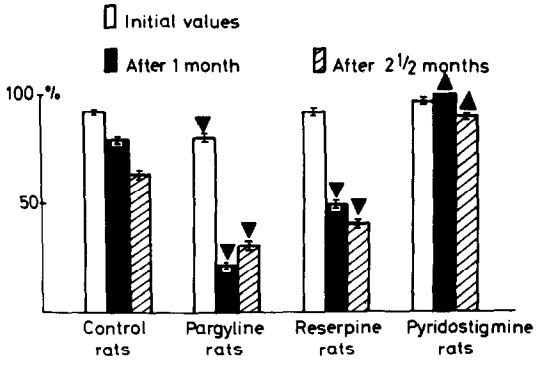

Fig. 5. Extinction tests of conditioned avoidance behaviour in adult male rats following the treatment with pargyline, reserpine or pyridostigmine during the first two weeks of life [10]. Means of success rates and variance of relative frequency; $n = 100$, i.e. 100 conditioned stimuli per day in 5 rats per group: significantly decreased and significantly increased as compared to the controls ($P < 0.001$).

treated rats [10]. In addition, emotional reactivity was decreased in adult rats treated neonatally with pargyline or reserpine [22]. Thus, it was demonstrated that nonphysiological concentrations and/or turnover rates of neurotransmitters during brain differentiation can act as teratogens leading to lifelong-effective behavioural changes.

Furthermore, these findings indicate that the environment-dependent brain differentiation may be mediated by neurotransmitters; the more so as changes of the external environment during brain differentiation can permanently affect the responsiveness and adaptability of the brain in a similar way [23, 24]. Therefore, the reactivity and adaptability of the central nervous system may be decisively improved throughout the life by optimizing the environment and hence the neurotransmitter concentrations and/or turnover rates during brain differentiation.

In view of these findings, numerous relevant disturbances of reproduction, metabolism and information processing called 'idiopathic, primary, endogeneous, genuine or essential' so far can be based on environment-dependent pre- and/or early postnatally acquired differentiation disturbances and are accessible, at least in part, to a genuine preventive therapy.

REFERENCES

1. Dörner G.: Problems and terminology of functional teratology. *Acta biol. med. germ.* **34** (1975) 1093–1095.
2. Dörner G.: Sexualhormonabhängige Gehirndifferenzierung und Sexualität. Fischer, Jena und Springer, Wien/New York (1972).
3. Dörner G.: *Hormones and Brain Differentiation.* Elsevier, Amsterdam (1976).
4. Dörner G. and Standt J.: Vergleichende morphologische Untersuchungen der Hypothalamusdifferenzierung bei Ratte und Mensch. *Endokrinologie* **59** (1972) 152–155.
5. Dörner G., Rohde W. and Baumgarten G.: Bestimmung des genetischen Geschlechts des Foeten durch fluoreszenzmikroskopischen Nachweis des *Y*-Chromosoms in Fruchtwasserzellen. *Acta biol. med. germ.* **26** (1971) 1095–1098.
6. Dörner G., Stahl F. and Baumgarten G.: Signifikante Unterschiede im Testosteron- und 11-OHCS-Gehalt des Fruchtwassers zwischen männlichen und weiblichen Foeten. *Endokrinologie* **60** (1972) 285–288.
7. Giles H. R., Lox C. D., Heine M. W. and Christian C. D.: Intrauterine fetal sex determination by radioimmunoassay of amniotic fluid testosterone. *Gynec. Invest.* (Basel) **5** (1974) 317–323.
8. Ladosky W. and Gaziri L. C. J.: Brain serotonin and sexual differentiation of the nervous system. *Neuroendocrinology* **6** (1970) 168–174.
9. Ladosky W. and Campos D. G. J.: Influence of biogenic amines on hypothalamic metabolism during the period of sexual differentiation. In *Endocrinology of Sex* (Edited by G. Dörner). Barth, Leipzig (1974) pp. 133–139.
10. Dörner G., Hecht K. and Hinz G.: Teratopsychogenic effects apparently produced by nonphysiological neurotransmitter concentrations during brain differentiation. *Endokrinologie* **68** (1976) 1–5.
11. Dörner G., Döcke F., Tönjes R. and Hinz G.: Effects of neurodrugs administered during brain differentiation on puberty and sexual behaviour of female rats. *Endokrinologie* (1977) (in preparation).
12. Ward I. L.: Sexual behaviour differentiation: prenatal hormonal and environmental control. In *Sex Differences in Behavior* (Edited by R. C. Friedman, R. M. Richart and R. L. Vande Wiele). Wiley (1974) pp. 3–17.
13. Telegdy G. and Vermes I.: Effect of adrenocortical hormones on activity of the serotoninergic system in limbic structures in rats. *Neuroendocrinology* **18** (1975) 16–26.
14. Bakke J. L., Lawrence N. and Wilber J. F.: The late effects of neonatal hyperthyroidism upon the hypothalamic–pituitary–thyroid axis in the rat. *Endocrinology* **95** (1974) 406–411.
15. Dörner G., Phuong N. T. and Hinz G.: Einfluß von Chlormadinonazetat auf die Hypothalamusdifferenzierung männlicher Ratten. *Acta biol. med. germ.* **26** (1971) 105–114.
16. Okamoto K.: Induction of diabetic disposition and of spontaneous diabetes in the descendants of diabetic animals. *Proc. 2nd. Int. Congr. Endocrinology*, London 1974, *Excerpta Medica*, Amsterdam (1965) p. 1018.
17. Dörner G., Mohnike A., Honigmann G., Singer P. and Padelt H.: Zur möglichen Bedeutung eines pränatalen Hyperinsulinismus für die postnatale Entwicklung eines Diabetes mellitus. *Endokrinologie* **61** (1973) 430–432.
18. Amendt P., Michaelis D. and Hildmann W.: Clinical and metabolic studies in children of diabetic mothers. *Endokrinologie* **67** (1976) 351–361.
19. Dörner G. and Mohnike A.: Further evidence for a predominantly maternal transmission of maturity-onset type diabetes. *Endokrinologie* **68** (1976) 121–124.
20. Dörner G.: *Zur Bedeutung der hormonabhängigen Gehirndifferenzierung für die Regelung elementarer Lebensfunktionen. Deutsches Ges.-wesen* (1977) (in press).
21. Dörner G., Hagen N. and Witthuhn W.: Die frühpostnatale Überernährung als ätiopathogenetischer Faktor der Erwachsenenfettsucht. *Acta biol. med. germ.* **35** (1976) 799–803.
22. Dörner G.: Further evidence of permanent behavioural changes in rats treated neonatally with neurodrugs. *Endokrinologie* **69** (1977) (in press).
23. Denenberg V. H.: Critical periods, stimulus input, and emotional reactivity: a theory of infantile stimulation. *Psychol. Rev.* **71** (1964) 335–351.
24. Rosenzweig M. R.: Effects of environment on development of brain and behaviour. In *The Biopsychology of Development* (Edited by E. Tobach, L. Aronson and E. Shaw). Academic Press. New York (1971) p. 303.

DISCUSSION

Kalra. I have a question for Dr. Dorner. Dr. Dorner, you mentioned that there is an open feedback loop during fetal life and that the gonadal steroids act on the hypothalamus to modify the secretion of neurohormones. Do you think that the gonadal steroids during this period also regulate the development of the neurosecretory neurones in the hypothalamus?

Dörner. I do not think that gonadal steroids are involved in the proliferation but only in the differentiation of neurons; i.e. the structures and function of specific neurons are permanently influenced. We do not know, however, whether this differentiation effect of sex hormones is a direct or more indirect one mediated by neurotransmitters. Since similar effects could be achieved by changing the neurotransmitter metabolism during brain differentiation by means of psychotrophic drugs it is conceivable that changes of sex hormone levels primarily result in changes of neurotransmitter concentrations and/or turnover rates of specific receptor neurons, which may influence in turn the diffferentiation of specific effector neurons.

We have not found any significant changes of the gonads and accessory sex organs immediately after perinatal administration of psychotropic drugs. Nevertheless, we have found long-term behavioural effects in these cases. Thus, we think that changes of neurotransmitter concentrations and/or turnover rates during brain differentiation may be capable in fact of affecting directly and permanently the responsiveness of central nervous neurons.