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MINIREVIEW

This article is dedicated to Professor Vratislav Schreiber, the founder of Czechoslovak experimental endocrinology, on the occasion of his 75th birthday

The Regulation of Adenohypophyseal Prolactin Secretion: Effect of Triiodothyronine and Methylene Blue on Estrogenized Rat Adenohypophysis

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Summary

Estrogens and thyroid hormones contribute importantly to cell proliferation and tumor transformation in the pituitary gland. We found that methylene blue antagonized estrogen-promoted adenohypophyseal enlargement and the enhancement of prolactin secretion. The purpose of the present article is to provide a review about neurotransmitters and their receptors involved in estrogen-induced anterior pituitary growth and in the antagonistic effects of triiodothyronine (T3) and methylene blue (MB). Central dopaminergic and noradrenergic systems are the most important factors regulating pituitary growth and function. Recently nitric oxide (NO) was added to the list of the neurotransmitters and neuropeptides involved in the control of the anterior pituitary secretion. Our data suggest that estrogen-induced anterior pituitary growth is associated with decreased synthesis and metabolism of central catecholamines, reduction of adenohypophyseal β-adrenergic receptors and increase of dopamine DA-2 receptors. We found that the treatment with T3 or MB prevented both estrogen-induced catecholaminergic inhibition and dopamine DA-2 receptor increment in the anterior pituitary. In contrast to T3, MB given alone also slightly decreased the anterior pituitary weight. Serum levels and anterior pituitary content of prolactin were increased after treatment with estradiol benzoate (EB), whereas T3 or MB partially attenuated prolactin hypersecretion after estrogen administration. This is in accord with the attenuation of EB-induced inhibition of dopaminergic system by T3 and MB. MB given in combination with EB also partially attenuated EB-promoted rise of adenohypohyseal NO synthase activity which plays an important role in the regulation of prolactin secretion. Further studies on central catecholaminergic systems, pituitary receptors, the nitrergic system and mechanisms of intracellular signal transduction are necessary for better understanding of pituitary tumor transformation and possibly for the discovery of new approaches towards treating patients with these diseases.

Key words

Estrogen • Thyroid hormone • Methylene blue • Catecholamines • Dopamine receptors • NO • Prolactin

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Introduction

The brain is one of the specific target tissues for sex steroid hormones. The purpose of the present article is to provide a review about neurotransmitters that are involved in estrogen-induced anterior pituitary growth and prolactin secretion, and about substances which attenuate these estrogenic effects. We studied the influence of two of them: hormone triiodothyronine (T3) and the synthetic molecule, methylene blue (MB).

Estrogens

Estrogens are able to induce several effects in particular areas of the central nervous system through binding to specific receptors. These specific receptors for gonadal steroids have been identified, among others, in the pituitary gland. Central dopaminergic and noradrenergic systems including their receptors are thought to be the most important systems in regulation of pituitary growth and function. These systems appear to participate in the interactions between thyroid hormones and estrogens in regulating anterior pituitary hyperplasia and hyperprolactinemia. Dopamine (DA) is the key transmitter in the inhibition of adenohypophyseal prolactin secretion. Abnormalities of dopaminergic neurons that release DA, a potent physiological inhibitor of prolactin secretion, cell division and tumor transformation, can accompany the development of pituitary tumors. The direct effects of inhibitory and stimulatory hypothalamic factors on the lactotrophs are modified by „peripheral" hormones. These include estrogens and thyroid hormones which have an important

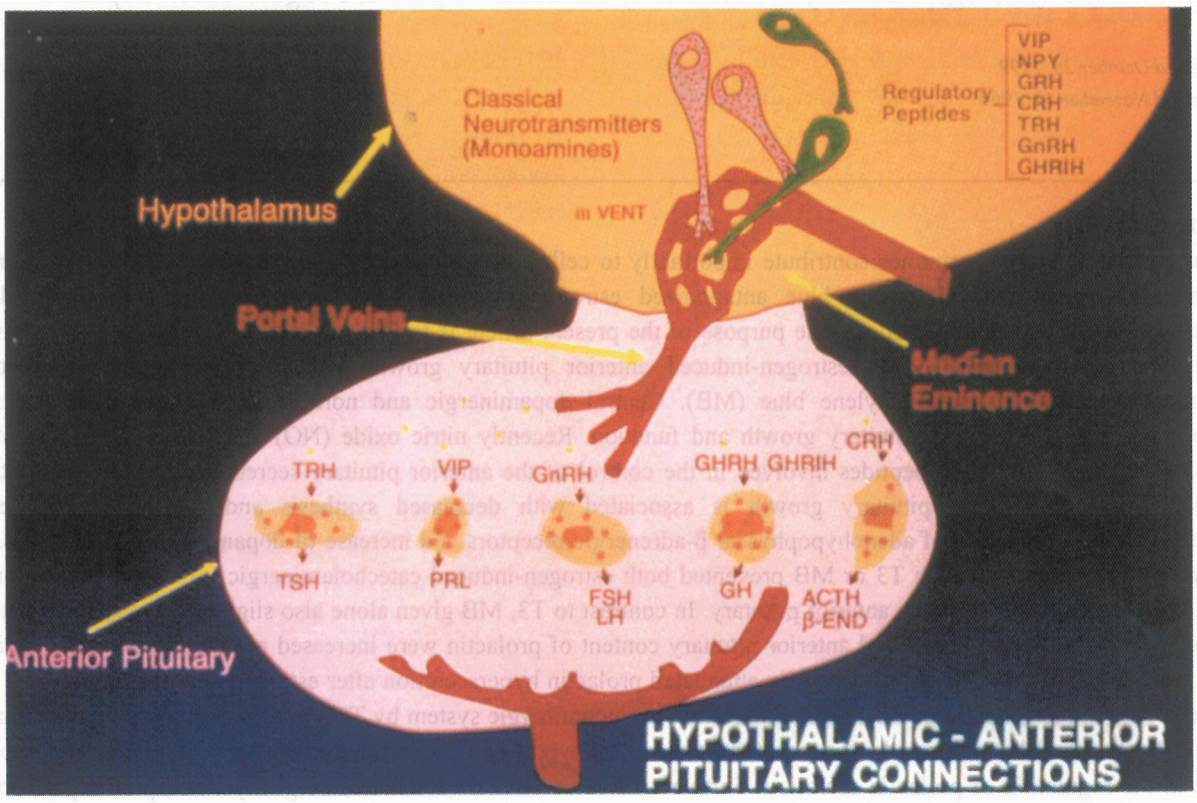

Fig. 1. *The entry of hypothalamic monoamines and regulatory peptides via the portal system into anterior pituitary cells, where they modulate the secretion of anterior pituitary hormones. VIP – vasoactive intestinal peptide, NPY – neuropeptide Y, GRH – growth releasing hormone, CRH – corticotropin releasing hormone, TRH – thyreotropin releasing hormone, GnRH – gonadotropin releasing hormone, GHRIH – growth hormone release inhibiting hormone, TSH – thyreotropin, PRL – prolactin, FSH – follicle stimulating hormone, LH – luteinizing hormone, GH – growth hormone, ACTH – adrenocorticotropin, β-END – β-endorphin.*

influence on cell division of anterior pituitary cells, particularly lactotrophs (Schreiber *et al.* 1970, Schreiber 1979, Dušková and Schreiber 1989). Experimental hypertrophy of rat anterior pituitary cells after

administration of estrogens was first described by Selye *et al.* (1935). Dušková and Schreiber (1989) and Hána *et al.* (1998) showed that this growth reaction is potentiated by dopaminergic antagonists and inhibited by dopaminergic agonists and thyroid hormones. Velardo *et al.* (1994) confirmed that thyroxine treatment of hypothyroid patients depressed the augmented plasma levels of prolactin and modified the enhanced response to TRH.

Acute or chronic estrogen treatment decreases tyrosine hydroxylase activity and gene expression in tuberoinfundibular dopaminergic neurons and decreases DA concentrations in the arcuate nucleus, decreases basal and stimulated DA release from median eminence and inhibits dihydroxyphenylanin (DOPA) accumulation after 3-hydroxybenzylhydrazine dihydrochloride (NSD-1015), an irreversible inhibitor of L-aromatic acid decarboxylase.

It is now clear that the anterior pituitary gland is under the influence of hypothalamic and extrahypothalamic structures. The functional activity of hypothalamic neurosecretory neurons, which produce and deliver specific hypophysiotropic regulatory peptides into the portal system, is in turn under the control of numerous neurotransmitters and neuropeptides (Fig. 1). Central dopaminergic and probably noradrenergic systems (dopamine, norepinephrine, epinephrine, and others such as serotonin or histamine) are considered to regulate pituitary growth and secretion. We have therefore studied the effects of triiodothyronine and methylene blue on estrogenized anterior pituitary, its growth and prolactin secretion in relation to the dopaminergic, β-adrenergic and nitrergic systems.

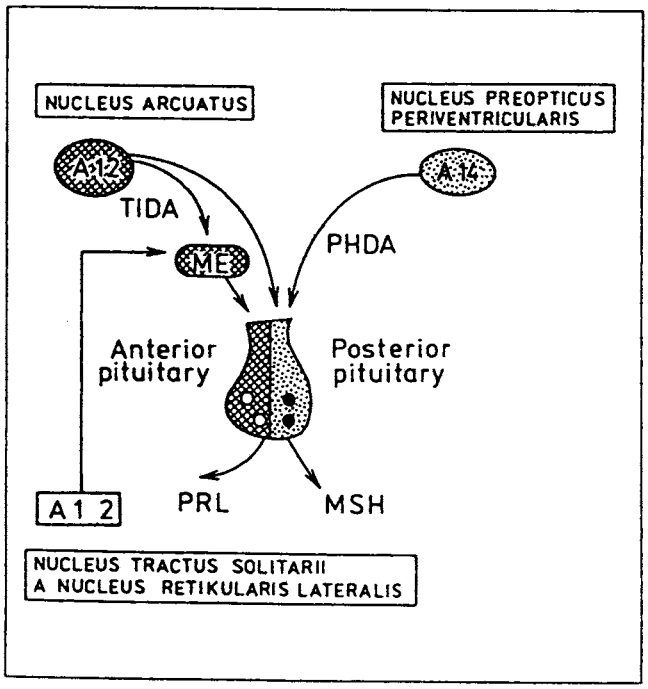

Fig. 2. *Central dopaminergic and noradrenergic systems are considered to be the most important systems in regulation of pituitary growth and function. The source of dopamine is the tuberoinfundibular system (TIDA) (area A 12) and tuberohypophyseal system (PHDA) (area A 14). TIDA neurons project from the arcuate nucleus to the median eminence. DA is released directly into the hypophyseal portal vessels and from the portal system DA is transported to anterior pituitary cells. In contrast to TIDA, the PHDA system influences anterior pituitary secretion directly. Noradrenergic neurons are in the ventrolateral area – A 1 (nucleus reticularis lateralis) and A 2 (nucleus tractus solitarii). PRL – prolactin, MSH – melanocytes stimulating hormone.*

Dopaminergic regulation of pituitary prolactin secretion

There is evidence regarding dopamine as a major prolactin-inhibiting factor. It was demonstrated that α_2-adrenergic receptors stimulate dopamine release in the hypothalamus (Hosny and Jennes 1998). The tuberoinfundibular dopamine (TIDA) pathway is of particular relevance for neuroendocrine control, since it projects from the arcuate nucleus to the median eminence and releases dopamine directly into the hypophyseal portal vessels (Fig. 2). Several lines of evidence have suggest that one of the basic functions of TIDA neurons is to form a link in the feedback loop which guarantees stable low basal prolactin levels (Muller *et al.* 1983). DOPA, the precursor of all endogenous catecholamines, is the product of tyrosine hydroxylation, the rate-limiting enzymatic step in catecholamine biosynthesis. Since interruption of the blood supply to the pituitary prevents the increase in anterior pituitary DOPA levels produced

by NSD-1015, it appears that the anterior pituitary lacks tyrosine hydroxylase and that all DOPA in rat anterior pituitary is derived from hypophyseal portal blood. Among neurotransmitters, dopamine, which is a metabolite of DOPA, plays a prominent role in the neuroendocrine regulation. It has been documented that there are at least five types and subtypes of DA receptors (Flores *et al.* 1999). Dopamine in the hypophyseal portal capillaries may act at the level of pituitary DA receptors to control anterior pituitary function, namely prolactin secretion (Lamberts and MacLeod 1990). Furthemore, peripheral signals may modulate a particular neurotransmitter pathway *via* different mechanisms. For example, estrogens stimulate DA turnover in TIDA neurons and may competitively inhibit both tyrosine hydroxylase and catechol-O-methyltransferase, and induce hyperplasia of the anterior pituitary (Pacák *et al.*, unpublished data).

A further system participating in the synthesis of DA is the tuberohypophyseal system which originates in the nucleus preopticus periventricularis and in the rostral part of nucleus arcuatus. In contrast to the TIDA system, it is not associated with the portal system, but directly innervates the anterior pituitary (Fig. 2). Dopamine may also be synthesized directly in the anterior pituitary (Schussler *et al.* 1992).

Effect of T3 on the dopaminergic system, estradiol benzoate-induced hyperplasia of anterior pituitary and prolactin secretion

It was demonstrated in our experiments that chronic treatment with estradiol benzoate (EB) inhibited the synthesis and release of dopamine from the tuberoinfundibular dopaminergic system, reduced the content of catecholamines and their metabolites in the anterior pituitary and increased the number of anterior pituitary DA-2 receptors. The supraphysiological concentrations of T3, resulting in a thyrotoxic state, attenuated these changes without altering DA-2 receptor affinity (Nedvídková *et al.* 1996). Moreover, T3 inhibited EB-induced anterior pituitary hyperplasia and EB-induced increases in plasma and anterior pituitary prolactin levels. It is evident that i) DA-2 receptors in the anterior pituitary play a role in EB-induced hyperplasia and tumor transformation, ii) T3 inhibits the EB-induced increase in the number of DA-2 receptors and EB-induced anterior pituitary hyperplasia, and iii) EB induces the depletion of tissue DA in the anterior pituitary. We therefore assume that these results help to explain why the administration of DA-2 agonists can prevent pituitary tumor transformation and hyperprolactinemia. The findings that i) EB treatment increased the number of DA-2 receptors, ii) T3 alone altered neither the number nor the affinity of DA-2 receptors, and iii) EB+T3 administration attenuated the EB-induced increase of DA-2 receptors, could reflect compensatory rather than primary changes in the DA-2 receptor number. This could be explained by our recent findings that estrogens inhibit the synthesis and release of DA from the TIDA system and reduce the catecholamine content in the anterior pituitary, whereas T3 prevents these effects. EB also elicits hyperprolactinemia, while T3 administration attenuates this effect. Our present and previous findings that estrogens increase cAMP and prolactin levels in the anterior pituitary and decrease DA levels in the anterior pituitary would be in accordance with the cAMP-induced stimulation of the prolactin gene or DA-induced inhibition of prolactin secretion.

The DA-2 receptor changes in response to EB, T3 and their combination could be explained by the fact that EB inhibits DA receptor occupation in the anterior pituitary and that T3 prevents this inhibition. Thus, EB would cause the upregulation of local DA-2 receptors and T3 could prevent this upregulation. This explanation leads to the prediction that administration of a DA-2 agonist should prevent EB-induced tumorigenesis. The finding of bromocryptine-induced inhibition of pituitary tumor formation in estrogen-treated animals is in accordance with this prediction.

Effects of methylene blue on the dopaminergic system, estradiol benzoate-induced hyperplasia and prolactin secretion

Methylene blue (MB) represents a new class of antioxidant drugs that competitively inhibit the reduction of molecular oxygen to superoxide by acting as an alternative electron acceptor for tissue oxidases and one of the substances that selectively inhibit the soluble guanylate cyclase activity (Salaris *et al.* 1991). We have recently found that MB influenced the hypothalamo-hypophyseal-thyroid axis (Nedvídková *et al.* 1995), attenuated the development of streptozotocin-induced diabetes in rats (Haluzík *et al.* 1998), prevented the increase of ascorbic acid concentration in anterior pituitary of EB-treated rats (Haluzík *et al.* 1995), and partially inhibited anterior pituitary growth after chronic estrogen administration (Nedvídková *et al.* 1999). On the basis of these results, we studied the role of dopaminergic

system which contributes importantly to the regulation of growth and function of the anterior pituitary. Methylene blue alone significantly reduced the anterior pituitary weight and the number of DA-2 receptors, whereas the affinity of DA-2 receptors was increased when compared to the controls. Methylene blue given in a combination with EB attenuated EB effects on the anterior pituitary weight, catecholamine content and the number of DA-2 receptors. It is evident from our results that both MB and T3 inhibit EB-induced anterior pituitary hyperplasia and growth. One possible explanation is that MB would prevent the upregulation of DA-2 receptors after EB by increasing dopamine content in the anterior pituitary.

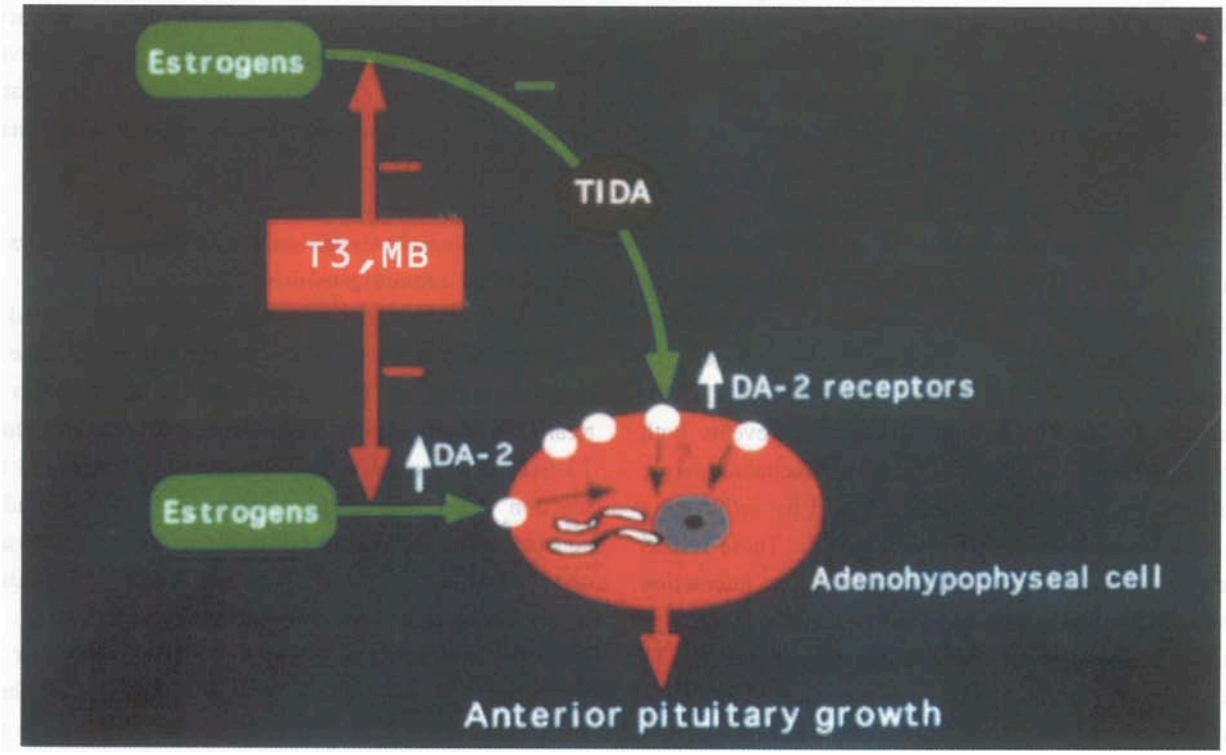

Fig. 3. *The influence of estrogens on the tuberoinfundibular system (TIDA) and dopamine D-2 receptors of the anterior pituitary: the antagonizing effects of T3 and MB.*

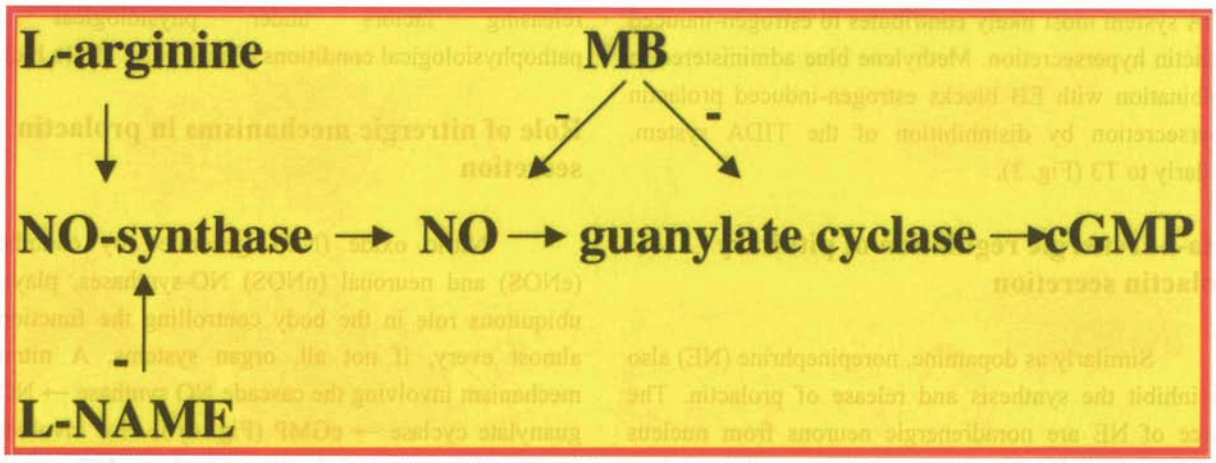

Fig. 4. *Nitrergic mechanism involving the cascade NO synthase – NO – guanylate cyclase – cGMP. The substrate for NO synthase is L-arginine. cGMP – cyclic guanylate monophosphate. MB – methylene blue, which inhibits the production of NO and inhibits guanylate cyclase producing cGMP.*

DOPA is a product of tyrosine hydroxylation, the rate-limiting enzymatic step in catecholamine biosynthesis. It appears that all DOPA in the rat anterior pituitary is derived from hypophyseal portal blood. Methylene blue alone does not attenuate DOPA accumulation in the anterior pituitary, whereas EB inhibits DOPA accumulation in the anterior pituitary after administration of NSD-1015. These findings suggest that EB, but not MB, inhibits DA synthesis in the tuberoinfundibular dopaminergic system. This is consistent with findings that acute or chronic estrogen treatment decrease tyrosine hydroxylase activity and gene expression in tuberoinfundibular dopaminergic neurons and decrease DA concentration in the nucleus arcuatus (Schussler *et al.* 1992).

Our results suggest that estrogen-induced anterior pituitary growth is associated with decreased synthesis, metabolism and turnover of catecholamines in the TIDA system, i.e. with the reduced release of catecholamines into the portal circulation of anterior pituitary. The treatment with MB or T3 prevents both estrogen-induced growth and catecholaminergic inhibition in the anterior pituitary gland by influencing the catecholamine metabolism or turnover. These results therefore support a mutually antagonistic interaction between MB or T3 and estrogens on catecholaminergic function influencing anterior pituitary growth. While T3 attenuates the EB-induced increase of DA-2 receptors through a rather compensatory mechanism, because T_3 treatment does not influence dopaminergic system. In the case of MB we assume the primary changes of DA-2 receptors, because MB given alone affects the content of dopamine and its receptors in the anterior pituitary.

Estradiol benzoate-induced inhibition of the TIDA system most likely contributes to estrogen-induced prolactin hypersecretion. Methylene blue administered in combination with EB blocks estrogen-induced prolactin hypersecretion by disinhibition of the TIDA system, similarly to T3 (Fig. 3).

Beta-adrenergic regulation of pituitary prolactin secretion

Similarly as dopamine, norepinephrine (NE) also can inhibit the synthesis and release of prolactin. The source of NE are noradrenergic neurons from nucleus reticularis lateralis (area A1) and from nucleus tractus solitarii (area A2) terminated in medulla oblongata. Norepinephrine is then transported *via* the portal system into anterior pituitary cells (Fig. 2).

Adrenergic receptors for NE are involved in a variety of physiological processes (heart rate, blood pressure, thermoregulation, food intake etc.) including the control of hormone secretion. These membrane receptors are linked with adenylate cyclase *via* guanine nucleotide regulatory proteins. The role of α-adrenergic receptors in regulation of prolactin release was studied *in vivo* in rats. Yohimbine administration elevated plasma prolactin levels, while clonidine suppressed basal prolactin levels (Lien *et al.* 1986). The β_2-agonist zinterol stimulated prolactin release from superfused rat anterior pituitary cell aggregates (Baes and Denef 1984).

Effect of triiodothyronine on β-adrenergic receptors of estrogenized adenohypophysis

The administration of EB for 20 days elicited an increase of anterior pituitary weight and a decrease in specific binding for ^{3}H-dihydroalprenolol compared to T3 treatment which increased the number of these receptors. T3 treatment decreased both the growth reaction and the reaction of β-adrenergic receptors after estradiol benzoate. Both the affinity of β-adrenergic receptors and cAMP levels before and after isoprenaline stimulation were unchanged. We found increased levels of norepinephrine (without changes of epinephrine) after T3 treatment, whereas there were no changes of these neurotransmitters after EB treatment as compared to the control group. Besides the direct effect of T3 on β-adrenergic receptor biosynthesis, it is also possible to assume its indirect effect *via* catecholamines leading to receptor downregulation. These receptor feedback regulations might influence the release of hypothalamic releasing factors under physiological and pathophysiological conditions (Pacák *et al.* 1991a,b,c).

Role of nitrergic mechanisms in prolactin secretion

Nitric oxide (NO), generated by endothelial (eNOS) and neuronal (nNOS) NO-synthases, plays an ubiquitous role in the body controlling the function of almost every, if not all, organ systems. A nitrergic mechanism involving the cascade NO synthase → NO → guanylate cyclase → cGMP (Fig. 4) is also involved in anterior pituitary prolactin secretion. NO synthase inhibitor, N^{ω}-nitro-L-arginine methyl ester (L-NAME),

blocks the diurnal changes of TIDA neuronal activity and prolactin secretion in rats (Yen and Pan 1999).

Effect of estradiol benzoate and methylene blue on NO-synthase

Estradiol benzoate significantly increased cAMP and cGMP levels in the anterior pituitary (Nedvídková and Schreiber 1992, Schreiber *et al.* 1993) and MB partially attenuated this effect. Besides the dopaminergic system, NOS may also be involved in the anterior pituitary response to EB and MB (Fig. 4). It is known that NO generated from the nitrates increases the cGMP content in many tissues and that MB has frequently been used as an inhibitor of soluble guanylate cyclase. Recent evidence suggests that NO plays an important role in the regulation of LH and prolactin secretion (Gonzalez *et al.* 1998) and that estrogens may modulate this effect through cGMP. We also recently studied the regulation of the anterior pituitary cGMP content after the administration of L-NAME, an inhibitor of NO-synthase. We consider that EB increases the anterior pituitary content of NO and cGMP (and consequently also prolactin) due to stimulation of hypophyseal NO-synthase. We observed that MB decreased the content of NO in the anterior pituitary when given alone or in combination with estardiol benzoate (Nedvídková *et al.* 1999) and we therefore assumed that MB influences not only guanylate cyclase, but also affects NO-synthase.

Other systems

Others neuropeptides, affecting growth and prolactin secretion of the anterior pituitary either directly or indirectly, are synthesized in the hypothalamus or in the anterior pituitary as galanin, vasoactive intestinal peptide (Hammond *et al.* 1997), endothelins (Kanyicska *et al.* 1995, 1998), γ-aminobutyric acid (GABA) (Gonzalez *et al.* 1999) and excitatory amino acid glutamate system (Gonzalez *et al.* 1999).

Gonzalez *et al.* (1999) found that different subtypes of glutamate receptors are involved in the control of anterior pituitary secretion through the dopamine system. The effects of alpha-amino-3-hydroxy-5-methylizoxazole-4-propionic acid (AMPA) appeared to be modulated by ovarian secretion, as the inhibition of prolactin secretion was partially suppressed after administration of AMPA to ovariectomized animals. These authors have suggested that this action of AMPA is probably mediated by enhanced DA activity. Furthermore, cannabinoids, for example hasis and marihuana (Murphy *et al.* 1998, Wenger *et al.* 1999), glucocorticoids (Piroli *et al.* 1993, Lindley *et al.* 1999), and the pituitary transcripting factor Pit-1, are also involved in the regulation of growth and secretion of the anterior pituitary.

The acute effects of cannabinoids on the endocrine system are consistent with their action on brain neurotransmitter systems involved in the regulation of neuropeptides that modulate anterior pituitary hormone secretion. The treatment with estrogens blocked the effect of cannabinoids on the central dopamine system. Although cannabinoid receptors appear to play a major role in the ability of cannabinoids to influence hormone release, much remains to be learned concerning their function in the neuroendocrine regulation of hormone secretion. De Miguel *et al.* (1998) proposed that changes in hypothalamic GABA inputs are involved in the effects of cannabinoids.

Ying *et al.* (1999) found that the estrogen responsiveness of rat prolactin gene expression requires the presence of both the estrogen receptor (ER) and the tissue-specific transcription factor, the Pit-1 protein. These authors suggest that an estrogen-dependent physical interaction between ER and the Pit-1 protein exists *in vivo*, and that this interaction might play an important role in the regulation of prolactin gene expression.

Piroli *et al.* (1993) demonstrated that there exists a negative correlation between the number of glucocorticoid receptors in the anterior pituitary and serum levels of prolactin. Treatment with estrogens, but also with other steroids, can modify the number of anterior pituitary glucocorticoid receptors. Lindley *et al.* (1999) observed that peripheral corticosterone affects dopaminergic terminal regions, i.e. that it slightly diminishes dihydroxyphenylacetic acid to dopamine ratio in the striatum.

Conclusions

Our results suggest that the mechanism by which triiodothyronine and methylene blue inhibit estradiol benzoate-induced anterior pituitary hyperplasia involve changes in the number of anterior pituitary DA-2 receptors due to altered anterior pituitary dopamine concentrations. Furthermore, other factors such as the β-adrenergic system, cyclic nucleotide system or NO system can be involved in MB inhibition of EB-induced anterior pituitary growth. The use of substances which do not belong to those naturally occurring in the organism, as for example methylene blue, which interacts with some natural regulators, might serve as an approach for the

study of some regulatory mechanisms, which are involved in the control of hormone secretion or growth activity of the anterior pituitary.

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Reprint requests

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