Mechanism of Toxic Action on Some Target Organs
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Neuroendocrine Effects of Neuropsychotropic Drugs and Their Possible Influence on Toxic Reactions in Animals and Man – The Role of the Dopamine-Prolactin System

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Abstract. As an example for the importance of the neuroendocrine system in the toxicological evaluation of neuropsychotropic drugs, the influence of functional dopaminergic agonists and antagonists on the secretion of prolactin is studied. In rats, all functional dopamine antagonists (reserpine alone or combined with α-methyl-p-tyrosine or benserazide, haloperidol, spiroperidol, sulpiride) increased serum PRL levels. Dopaminergic agonists (apomorphine, piribedil, d-amphetamine, L-DOPA, and the ergot derivatives bromocriptine and lisuride) all caused a decrease of serum prolactin levels. The same effect could be observed also after treatment with other ergot derivatives such as d-LSD, methergoline, methysergide and ergotamine. Also in this case, the prolactin-lowering effect seems to be related to dopaminergic activity. This was suggested by the inhibitory effect of pretreatment with the dopamine antagonist spiroperidol or with sulpiride on the prolactin-lowering effect of lisuride. In dogs, thyrotropin releasing hormone (TRH) increased and lisuride decreased serum prolactin levels determined with a new radioimmunoassay. As an example for the situation in humans, the effects of the dopamine antagonist sulpiride and of the dopamine agonist bromocriptine were described. The prolactin levels were higher in the presence of estrogens. The relevance of these neuroendocrine effects of neuropsychotropic drugs on physiological systems in animals and man is discussed.

Key words: Dopamine agonists – Dopamine antagonists – Prolactin – Prolactin-dependent function.

Introduction

Many advances in the development of neuropsychotropic drugs are closely connected with increasing knowledge on the morphology and function of monoaminergic systems in the brain, and many neuropsychotropic drugs are known to produce their effects by influencing these systems. Comparable monoaminergic systems play

an important role in the regulation of anterior pituitary function. For this reason it is easily understood that neuropsychotropic drugs also can influence the neuroendocrine system and thereby produce desired or undesired effects. This will be demonstrated in the case of the dopaminergic (DA) system involved in many brain functions (for review see Ungerstedt, 1978), whose predominant role in the regulation of prolactin (PRL) secretion is now well established. The effects of both functional DA antagonists and agonists (for their mechanism of action see Carlsson, 1972) on the PRL system and their consequences on organ function will be discussed in the following text.

Methods

If not stated otherwise, drugs were injected intraperitoneally (DA agonists subcutaneously) into Wistar rats (Dr. Schwarz, Schering AG) maintained with standard food (Altromin®) and water ad libitum in climatized rooms with constant day-night rhythm (6.00 on, 18.00 h off). Blood was obtained by decapitation, allowed to clot at 4° C and serum was frozen until assayed. In the experiment shown in Figure 1, rats were pretreated with 2 mg/kg reserpine hydrochloride intraperitoneally 22 hours before subcutaneous injection of the different ergot derivatives dissolved in saline (lisuride, d-LSD), a 10% (v/v) solution of Cremofor EL (polyethoxylated castor oil, BASF, Ludwigshafen) in saline (methysergide, methergoline, ergotamine), or in a small volume of ethanol which was then diluted with saline (bromocriptine). 2 hours after this treatment, animals were killed by decapitation.

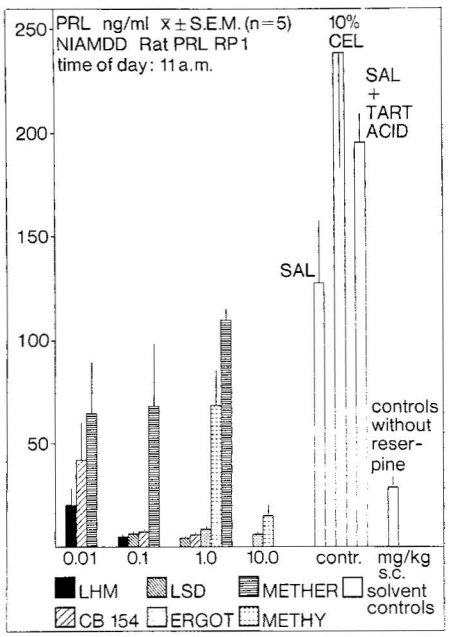

Fig. 1. Influence of ergot derivatives on serum PRL concentrations in reserpine-pretreated female rats 2 hours after s.c. injection. Ergot derivatives were injected at 9 a.m. (22 hours after reserpine injection) and serum PRL was determined at 11 a.m. LHM = lisuride hydrogen maleate, CB 154 = Bromocriptine, METHER = methergoline, ERGOT = Ergotamine tartrate, METHY = Methysergide, SAL = 0.9% saline, 10% CEL = 10% solution of Cremophor EL, SAL + TART ACID = 0.9% saline with a few drops of tartaric acid

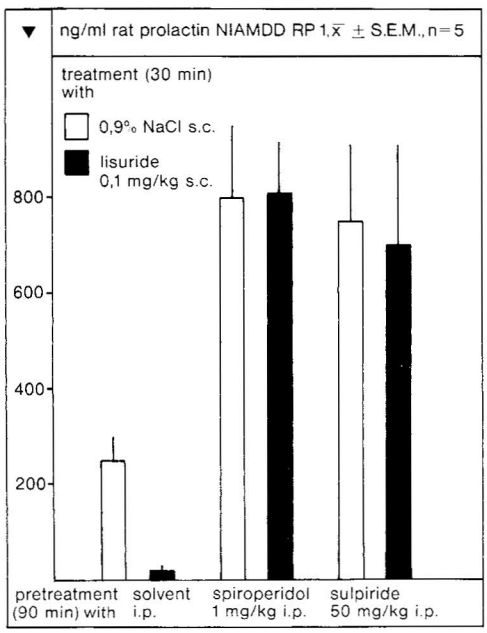

Fig. 2. Influence of pretreatment with spiroperidol or sulpiride on the prolactin-lowering effect of lisuride in female rats pretreated with reserpine (2 mg/kg i.p.). Spiroperidol, sulpiride or solvent (10% CEL) were injected 1 hour before injection of lisuride or 0.9% saline (21 hours after reserpine injection) and serum for PRL determination was obtained 30 min after lisuride respect. saline

In the experiment shown in Figure 2, reserpine-pretreated rats (as above) received 30 mins before lisuride or saline injection either spiroperidol (1 mg/kg) or sulpiride (50 mg/kg) or solvent (Cremofor EL) as an i.p. injection.

In the experiment with dogs, 2 female Beagle dogs weighing 10 kg received an s.c. injection of 0.01 mg/kg lisuride or saline followed 1 hour later by an i.v. injection of 100 μg TRH (Relefact®, Hoechst)/dog. Serum was obtained by venipuncture. In the human experiment, 10 healthy female volunteers, from whom written informed consent had been obtained, received after an overnight fast 2.5 mg bromocriptine (Pravidel®, Sandoz) or identical placebo in capsules with standardized breakfast. 50 mg sulpiride (Dogmatil®, Schürholz) was injected intramuscularly 2 hours later, and blood was obtained by venipuncture from −15′ (15 mins before bromocriptine respectively placebo ingestion) until 6 hours.

Rat serum PRL levels were estimated using the NIAMDD Radioimmunoassay (RIA) kit RP1. In the dog experiment, PRL was estimated using a newly developed RIA for canine PRL (Gräf et al., 1977). Human PRL was measured using the NIAMDD RIA kit VLS-3. All determinations were made in duplicate, and results were expressed as mean ± standard error of the mean.

Results and Discussion

As can be seen from Table 1, all functional DA agonists lowered and all functional DA antagonists increased serum PRL levels in rats, when tested under our experimental conditions (Horowski and Gräf, 1976). All these drugs of different structure

Table 1. Influence of drugs interacting with DA systems on serum PRL levels in rats (from Horowski and Gräf, 1976)

Functional DA agonists lowering serum PRL levels		Functional DA antagonists increasing serum PRL levels	
compound:	mechanism of action on DA systems:	compound:	mechanism of action on DA systems:
apomorphine	stimulation of DA receptors	haloperidol	blockade of DA receptors
piribedil	stimulation of DA receptors	sulpiride	blockade of some DA receptors
d-amphetamine	release of endogenous DA	reserpine	depletion of DA within storage granules
L-DOPA (alone or combined with low doses of benserazide)	precursor of DA	α-methyl-p-tyrosine (combined with reserpine)	depletion of DA by inhibition of tyrosine hydroxylase
bromocriptine	stimulation of DA receptors	benserazide (combined with reserpine)	depletion of DA by inhibition of aromatic amnioacid decarboxylase
lisuride	stimulation of DA receptors		

and different mechanism of action changed serum PRL levels in a way which could be predicted from their influence on DA systems, a result which demonstrates the predominant role of DA in the regulation of PRL secretion from the anterior pituitary. In order to investigate the importance of the serotoninergic system, we have previously tested the effect of four different ergot derivatives (Horowski et al., 1976), namely lisuride (LHM), bromocriptine (CB 154), methysergide (METHY) and d-LSD. As inhibitors of peripheral serotonin effects, the following order of potency had been reported:

METHY > LSD = LHM > CB 154.

In contrast, the PRL-lowering effect of these drugs was as follows:

LHM = CB 154 > LSD > METHY.

It can be concluded from these results that the peripheral antiserotonin effect of ergot derivates is not correlated with the PRL-lowering effect of these drugs, but that there is good agreement with the DA agonistic effect of these drugs. In the meantime, we have extended these experiments, and have included into these studies methergoline (METHER), another antiserotoninergic drug, as well as the vasoconstrictive ergotamine (ERGOT). All these ergot derivatives were able to lower serum PRL levels under different experimental conditions (as an example, see Fig. 1). Their PRL-lowering activity was as follows:

LHM $\geqslant$ CB 154 > d-LSD > METHER > METHY = ERGOT.

These results clearly demonstrate that in the case of these different ergot derivatives, used for quite different clinical purposes, depending on the dose, a PRL-lowering effect has to be considered in the evaluation of effects and side effects. That these effects are related to DA agonist activity is shown in the case of the PRL-lowering effect of lisuride in reserpinized female rats which is completely inhibited by pretreatment with the DA antagonist spiroperidol or sulpiride (Fig. 2). It can also be seen from this figure that even in rats where DA neurotransmission is already impaired by pretreatment with reserpine, DA receptor blocking drugs can cause an additional increase in serum PRL levels.

As has been described earlier (Gräf et al., 1976a), the PRL-increasing effect of DA antagonists like reserpine is enhanced in the presence of exogenous or endogenous estrogens. In addition, one single injection of exogenous estradiol benzoate has been found to induce marked circadian PRL increases with a maximum at 5 p.m. in ovariectomized rats (Gräf et al., 1976b). For this reason, the endocrine situation in animals treated with DA antagonists or agonists has to be taken into consideration in the planning and evaluation of toxicological studies.

Studies in different species indicate that the physiological role of PRL may differ, but that the central regulation of PRL secretion seems to be essentially the same. Preliminary observations in dogs using a newly developed radioimmunoassay seem to confirm this view, as can be seen from Figure 3. As in other species, TRH injection leads to an increase in serum PRL levels which can be fully inhibited by pretreatment with a very low dose of the DA agonist lisuride.

A similiar effect of DA antagonists and DA agonists on PRL levels as described in the rat studies, can also be demonstrated in humans. This can be seen from our

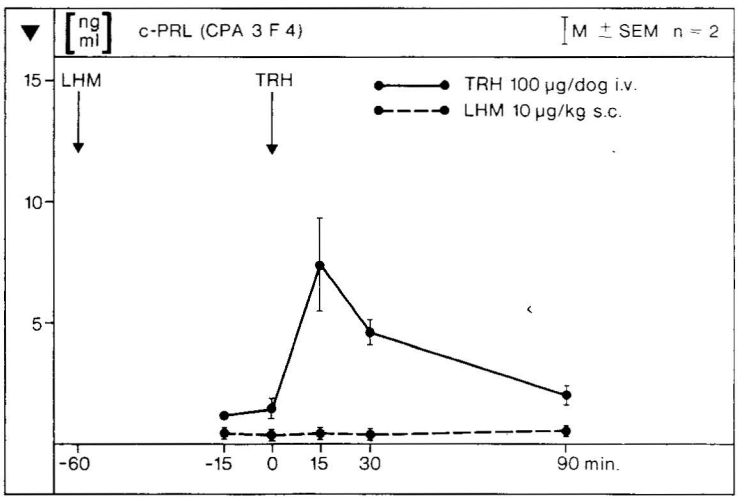

Fig. 3. Influence of lisuride on the TRH-induced PRL increase in female Beagle dogs. Lisuride respect. 0.9% saline was injected 1 hour before TRH

results obtained in a study with 10 healthy female volunteers (Fig. 4). An intramuscular injection of 50 mg sulpiride increased serum PRL levels up to 100 ng/ml, an effect which could be reduced by pretreatment with bromocriptine. In the group of 5 women taking estrogen-containing oral contraceptives, serum PRL levels were significantly higher both in the placebo- and in the bromocriptine-group ($p \leqslant 0.05$, comparison of squares followed by Tukey-test).

In conclusion, we have shown that many different DA antagonists can increase serum PRL levels in different experimental conditions. Conversely, DA agonists apparently can inhibit PRL secretion from the anterior pituitary. Both effects can be observed at quite low dose levels of these neuropsychotropic drugs which indicates that the dopaminergic regulation of PRL secretion is a very sensitive index for altered dopaminergic function.

What are now the endocrine consequences of the changes in PRL levels induced by dopaminergic antagonists and agonists? PRL has been reported to have an effect on many organs, including mammary gland, ovary, testes and prostate, adrenals, kidney and liver. At least in some organs, these effects may be mediated by specific PRL receptors, but PRL may also affect the number and activity of gonadotropin and steroid receptors as well as of enzymes involved in organ function. It is therefore not surprising that some effects of DA agonists and antagonists on different organs can be attributed to their influence on the PRL system. The following observations refer, if not stated otherwise, to the situation in rodents. We will restrict our discussion to the effects of these drugs on the anterior pituitary, mammary gland, ovary as well as to the situation in pregnancy (see Table 2).

At the level of the pituitary DA agonists inhibiting the activity of PRL-producing cells may lead to a reduction of pituitary tumour growth as reported in the case of ergot derivatives (Mac Leod and Lehmeyer, 1973). It is not clear whether an

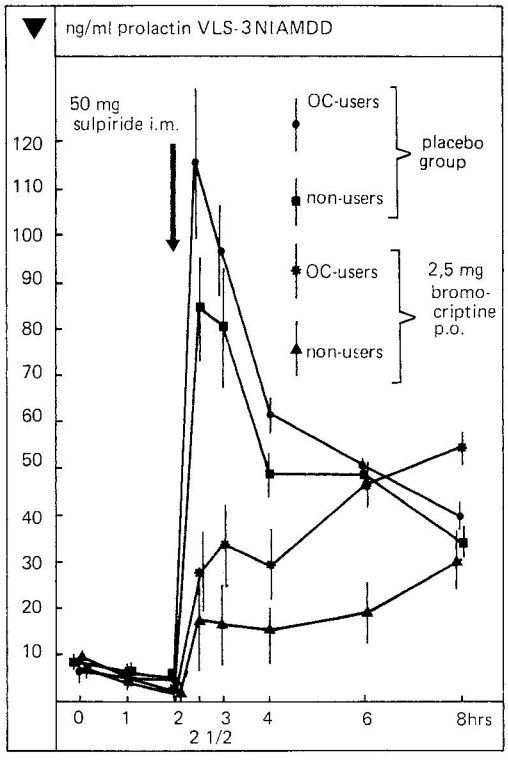

Fig. 4. Influence of bromocriptine on the sulpiride-induced PRL increase in women taking oral contraceptives ('OC-users') and other women ('non-users'). Bromocriptine respect. placebo was injected at 8 a.m. (time 0), and sulpiride (50 mg/kg i.m.) was injected 2 hours later. Women treated with bromocriptine had lower PRL levels before and after sulpiride injection, and women taking oral contraceptives had higher PRL levels after sulpiride injection both in the placebo and bromocriptine group

Table 2. Some possible consequences of the neuroendocrine effects of DA agonists and DA antagonists in rodents

DA agonists	DA antagonists
(especially of the ergot type)	
Anterior pituitary	
decrease in PRL secretion	increase in PRL secretion
Mammary gland	
inhibition of lobulo-alveolar growth; inhibition of lactation	stimulation of lobulo-alveolar growth; induction of lactation
Ovary	
inhibition of ovulation? inhibition of luteolysis and accumulation of corpora lutea; inhibition of deciduoma reaction in the uterus of pseudopregnant rats	delay or inhibition of ovulation; prolonged diestrous; induction of pseudopregnancy
Pregnancy	
inhibition of implantation; termination of early gestation or pseudopregnancy; weight reduction in offspring	decreased conception rate due to prolonged diestrous and delayed implantation

increase of PRL secretion induced by neuroleptics or reserpine results in hypertrophy of this organ.

At the mammary gland, DA agonists like bromocriptine and lisuride clearly reduce the organ weight due to an inhibition of lobuloalveolar growth (Gräf et al., 1977) and lactation is inhibited. The incidence of spontaneous mammary tumours was reduced after long-term treatment with bromocriptine in rats (Griffith, 1977), and in mice (Welsch, 1976). The growth of dimethyl-benzanthracene (DMBA)-induced mammary tumours in rats (Heuson et al., 1970) and estrogen-induced mammary tumours in mice (Welsch et al., 1977) was reduced as well by treatment with bromocriptine. In the case of DMBA-induced mammary tumours, the same effect could be obtained with lisuride (Horowski, unpublished results). In contrast, marked stimulation of mammary glands of both rats and dogs including galactogenesis in some cases has been described as a result of chronic toxicity studies with DA antagonists used as neuroleptics. Finally, it has been reported by Welsch and Meites (1970) that reserpine increases the growth of DMBA-induced mammary tumours in rats.

While the mammary gland and their biological function are by definition the classical target organ of PRL, a more complex picture emerges from studying the effects of increased and reduced PRL levels on the gonads. What is quite clear now is that both reduced and increased PRL levels have a negative effect on normal ovarian function. DA agonists of the ergot type have been reported to inhibit ovulation on rodents. It has, however, been demostrated by Flückiger's group that this activity of ergot drugs is not correlated with their PRL-suppressing effect, but that in addition to the dopaminergic action of these compounds, an interference with central noradrenergic or, more likely, serotoninergic systems may be involved (Flückiger and del Pozo, 1978).

The luteolytic effect of PRL in rats explains why treatment with dopaminergic ergot derivatives like bromocriptine and lergotril in these animals can led to the persistence of corpora lutea in nonpregnant rats. In connection with this, increases in ovarian weight (Heuson et al., 1970) and, in the case of lergotril, even the occurrence of some ovarian tumours has been reported (Kleinberg et al., 1977). In dogs, bromocriptine has produced cystic corpora lutea (Griffith et al., 1978).

PRL, however, has not only a luteolytic function in rats, but seems also to produce the critical luteotropic stimulus for progesterone secretion during the first days of pregnancy and pseudopregnancy. For this reason, inhibition of deciduoma formation in the uterus of pseudopregnant rats as well as inhibition of implantation have been used for a long time as biological tests for PRL-lowering drugs in rodents. In studying reproduction toxicology of DA agonists it is therefore important to know that PRL-lowering agents can terminate early pregnancy, an effect which can be inhibited by administration of exogenous PRL or progesterone (for review see Flückiger and del Pozo, 1978). The duration of the PRL-lowering effect produced by DA agonists seems to be of particular importance for these biological effects as has been demonstrated by Wuttke and Döhler (1973). Finally, treatment with PRL-lowering DA agonists at the end of pregnancy or during the early postpartum period will result, of course, in reduced weight gain or even death of the offspring due to inhibition of lactation (Flückiger and del Pozo, 1978).

For DA antagonists like neuroleptics of the phenothiazine- and butyrophenone-type, which increase PRL levels, disturbances of the estrus cycle with delay or inhibition of ovulation have been described. Under some conditions, rats have been in a state of constant diestrus (Tuchmann-Duplessis et al., 1968) whilst from other studies, e.g. with neuroleptic spirilene, it was reported that pseudopregnancies occured with a duration of about 2 weeks (de C. Baker and Tucker, 1968). This was followed by ovulation, and then by another 2 weeks of pseudopregnancy. At post-mortem, the ovaries of treated rats contained more and larger corpora lutea than the controls, an effect which has also been reported by Janssen in his review of the toxicology of DA antagonists of the butyrophenone type (Janssen, 1968).

It remains to be investigated by which mechanisms ovulation is inhibited in these animals. An indication for an important role of PRL in this respect is the recent observation by Lotz and Krause (1978), that the cycle disturbances in rats induced by different neuroleptics including sulpiride are closely correlated to their mammotropic and PRL increasing effects. In addition, it has been demonstrated that these disturbances are counteracted by dopaminergic agonists like bromocriptine (Flückiger et al., 1972). In view of the influence of elevated PRL levels on the gonads, it is not surprising that treatment of both female and male rats with, e.g., a dose of 10 mg/kg chlorpromazine p.o. has led to a clearly reduced number of pregnancies (Julou et al., 1968).

In this case, also the inhibitory effect of elevated PRL levels on androgen-dependent organs in the male may be involved since, for example, a reduction in the weight of the prostate has been reported from toxicological studies using high doses of neuroleptics (Janssen, 1968).

What is now the relevance of these animal results for the situation in humans? This, of course, depends on the physiological role of PRL in man as compared with rodents.

Table 3. Clinical effects of elevated prolactin levels

Females
premenstrual symptomatology?
inhibition of ovulation
short luteal phase
amenorrhoea
galactorrhoea
low basal estrogen levels elevated androgenic steroids?
Males
signs of androgen failure
loss of sexual potency
oligo-aspermia
galactorrhoea
low androgen production

From the study of the consequences of pituitary adenomas or microadenomas producing large quantities of PRL, and also from the long use of DA antagonists as neuroleptics, much more is known of the effects of high PRL levels (see Table 3). It must be stressed that some of these consequences like amenorrhoea and galactorrhoea are rather infrequent as clinical side effects of neuroleptics, since very high PRL levels as well as other hormonal changes are necessary for the induction of these effects. Less is known of the neuroendocrine consequences of treatment with DA agonists lowering PRL levels. These drugs, of course, are potent inhibitors of lactation in post-partum women or in secondary galactorrhoa. In the case of the ovary, it is now highly probable that PRL is necessary for corpus luteum function in humans, and that both decreased and increased PRL levels can disturb menstrual cycles. Luteal insufficiency is a wellknown consequence of hyperprolactinemia due to DA antagonists like sulpiride. On the other hand, treatment with high doses of the DA agonist bromocriptine can produce signs of luteal insufficiency in women with normal cycles (Schulz et al., 1977). In both cases progesterone plasma levels are considerably lowered.

These effects of DA antagonists and agonists in humans are in good agreement with the effects observed in animal studies. This stresses the importance of the neuroendocrine effects of these drugs for the prediction of effect and side effects in humans. There are other effects, however, which, due to the different physiological role of PRL in rodents and in humans, should be interpreted with caution. This applies, for example, to the inhibition of implantation caused by DA ergot derivatives. In contrast to the situation in rats, PRL apparently has no important function in maintaining corpora lutea during early pregnancy in humans. This is clearly demonstrated by the clinical use of bromocriptine in treating hyperprolactinemic conditions in women, in whom pregnancy and normal delivery is obtained quite easily. Another example for species-specific effects may be the influence of PRL-lowering DA agonists on the incidence of tumours of the ovary and endometrium in rodents. This applies to the ovarian tumours reported for lergotril, which seem to be related to the inhibition of luteolysis, and also to the endometrial tumours observed in a 2-year's study with bromocriptine. In this study, a decreased mortality, decreased chronic nephropathy and a decrease in adrenal tumours in male and mammary tumours in female animals has been observed (Griffith, 1977). At least this last effect is obviously caused by the inhibition of mammary growth due to PRL inhibition. The increase in uterine tumours has been interpreted by Griffith as being due to a particular role of PRL in old rats, which is quite different from the situation in humans. In old female rats, bromocriptine prevents the occurence of pseudopregnancy periods often observed in these animals, and correspondingly increases the incidence of the alternative situation, persistent vaginal cornification. The rise in progesterone levels seen during pseudopregnancy apparently is prevented by bromocriptine treatment. This results in a continuous action of unopposed estrogens on the endometrium. Since in humans, neither an increase of PRL with age, nor a luteolytic effect of PRL is known, the relevance of these tumours observed in rodents is rather doubtful.

We have discussed the influence of DA agonists and antagonists on the PRL system and the consequences of this on some organs. It must be stressed that in a similar way, other anterior pituitary hormones like GH, LH, FSH, TSH and ACTH

are regulated by monoamines, and therefore, also their function can be influenced by neuropsychotropic drugs. It is obvious from this as well as from the examples mentioned that especially in the case of drugs interferring with monoamine neurotransmission, effects on the neuroendocrine system can be of great importance in toxicology. Therefore, much more has to be learned about the neuroendocrine system and possible species-differences in its regulation and function.

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