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NEUROLEPTICS AND NEUROENDOCRINE FUNCTION

Joseph W. Gunnet and Kenneth E. Moore

Department of Pharmacology and Toxicology, Michigan State University, East Lansing, Michigan 48824

INTRODUCTION

Antipsychotics, or neuroleptics, are drugs used to treat severe psychiatric illnesses, including schizophrenia and a variety of other psychotic disorders. There are several chemical classes of neuroleptics including phenothiazines, thioxanthines, and butyrophenones, which have in common the ability to ameliorate a number of psychotic symptoms such as delusions, hallucinations, and thought disorders. These drugs have a wide spectrum of biological effects resulting from their ability to produce a variety of actions at the cellular-molecular level. Nevertheless, the antipsychotic potency of these compounds appears to be best correlated with their ability to block central dopamine (DA) receptors. In addition, their ability to block these receptors is responsible for their clinical efficacy in preventing nausea and vomiting, induced by DA agonists, and for many of their adverse effects such as extrapyramidal disorders and endocrine effects. This review focuses on the latter effects and how the DA antagonistic properties of neuroleptics alter the secretion of prolactin, growth hormone (GH), and thyrotropin (thyroid-stimulating hormone; TSH) from the anterior pituitary.

NEUROLEPTICS AS DOPAMINE RECEPTOR ANTAGONISTS

Throughout the brain, DA receptors exhibit different characteristics and have been categorized into various subtypes based on these characteristics. A number of reviews describe these subtypes and their characteristics (see 1–7). The most accepted classification differentiates between DA receptor subtypes

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based on their association with adenylate cyclase and their affinity for DA agonists and antagonists. Four receptor subtypes have been proposed (3) but only two, the D-1 and D-2 subtypes, have been well-characterized (Table 1). Although neuroleptics can bind to all subtypes of DA receptors, these drugs bind with the greatest affinity to D-2 receptors (2, 3).

In vivo and in vitro receptor-binding studies have identified D-2 receptors within a number of brain regions including the striatum, various limbic regions, the substantia nigra, and the hypothalamus (2, 8–11). Within the striatum, D-1 receptors are located postsynaptic to DA terminals while D-2 receptors are found both pre- and postsynaptically (2, 10). Presynaptic DA receptors serve as autoreceptors that modulate the synthesis and release of DA (12). Results of in vivo and in vitro binding studies have also revealed D-2 receptors on endocrine cells within the anterior, intermediate, and neural lobes of the pituitary (3, 13–15). The DA receptors in the anterior and intermediate pituitary have been described as the prototype for D-2 receptors (2).

Neuroleptics acting as selective D-2 and nonselective D-1/D-2 antagonists have antipsychotic activity. The antipsychotic potency of neuroleptic drugs and their affinity for D-2 receptors show a positive linear relationship (16, 17), suggesting that the antipsychotic effects of the neuroleptics are primarily due to blockade of D-2 receptors. The role of D-1 receptors in the antipsychotic action of neuroleptics has until recently been unexplored because of the lack of selective D-1 antagonists. A specific D-1 receptor antagonist, SCH 23390, has recently been developed (18, 19) and found to exert "antipsychotic effects" in several animal models (20). D-1 and D-2 receptors may function in a synergistic manner. The production of classical DA-related behaviors (i.e. stereotypy) requires activation of both D-1 and D-2 receptors. Selective D-1

Table 1 Characteristics of D-1 and D-2 dopamine receptors

	D-1 receptor	D-2 receptor
Selective antagonists	SCH 23390	Sulpiride
Location in pituitary	None	Anterior, intermediate, and neural lobes
Location on striatal neurons	Postsynaptic	Pre- and postsynaptic
In vitro binding affinity		
DA agonist IC_{50}	Micromolar	Micromolar
DA antagonist IC_{50}	Micromolar	Nanomolar
Effects of receptor activation:		
Adenylate cyclase activity	Stimulatory	None or inhibitory
Pituitary hormone secretion	None	Inhibitory

Modified from References 1 and 2.

or D-2 agonists do not induce stereotypic behavior in rats unless administered together (21). Similar conclusions have been drawn from the results of electrophysiological studies where only with D-1 agonist administration could the D-2 agonist quinpirole alter electrical activity in the globus pallidus and nucleus accumbens (21, 22).

The anterior pituitary contains D-2 but not D-1 receptors (1, 14, 23). Receptors for DA are located on lactotrophs, somatotrophs, and thyrotrophs within the anterior lobe (24–27). The secretion of prolactin, GH, and TSH is influenced by stimulation or blockade of these pituitary DA receptors (see Table 2). The affinity of neuroleptics for DA receptors in the anterior pituitary is directly related to the ability of these neuroleptics to increase the secretion of prolactin (3, 28).

The release of prolactin from pituitary fragments or dispersed pituitary cells in vitro is inhibited by DA, and this inhibition is reversed by nanomolar concentrations of neuroleptics (29, 30). Higher concentrations of neuroleptics in the micromolar range also reduce the release of prolactin from the anterior pituitary cells in vitro, but this effect is not via a DA receptor-mediated mechanism. For example, high concentrations of DA antagonists inhibit the spontaneous release of prolactin from cultured GH_3 cells, a prolactin-secreting cell line that lacks DA receptors (31). Only those endocrine actions involving DA receptors are considered in the remainder of this review.

Table 2 Actions of dopamine agonists and antagonists on anterior pituitary cells[a]

Action	DA or DA agonist	DA antagonist[b]	References
Adenylate cyclase activity	(−)	(+)	14, 86
Spontaneous electrical activity	(−)	(+)	87–89
Lysosomal enzyme activity	(+)	(−)	162, 163
Phosphatidylinositol turnover	(−)	(+)	91
Prolactin			
gene transcription	(−)	—	164
synthesis	(−)	(+)	124, 164
secretion	(−)	(+)	27, 34
intracellular degradation	(+)	-	165
Growth hormone			
secretion	(−)	(+)	26, 84
synthesis	--	(−)	124
TSH			
secretion	(−)	(+)	24

[a] Abbreviations: (+) = increase; (−) = decrease; — = no data.
[b] Blockade or reversal of DA/DA agonist effects.

EFFECTS OF NEUROLEPTICS ON REGULATION OF PROLACTIN SECRETION

Prolactin secretion from the anterior pituitary is regulated by releasing and inhibiting factors originating from the hypothalamus. Neurosecretory factors released from neuronal terminals within the median eminence are carried to pituitary lactotrophs by the hypophysial portal blood. Severing this vascular link or grafting the pituitary to a site distant from the medial basal hypothalamus results in high circulating levels of prolactin, which suggests that the predominant hypothalamic influence over prolactin secretion is inhibitory. As detailed in numerous reviews, the primary hypothalamic prolactin inhibiting factor is DA (27, 32–34).

Regulation of Prolactin Secretion by Dopamine

DA destined for the anterior pituitary is released from terminals of the tuberoinfundibular dopaminergic (TIDA) neurons (27, 35). Short axons of these neurons project from perikarya in the arcuate nucleus and terminate in the external layer of the median eminence. Treatments that alter the activity of these neurons affect prolactin secretion. Direct activation of TIDA neurons by electrical stimulation of their perikarya within the arcuate nucleus reduces serum prolactin levels (36). Administration of gamma-butyrolactone, an anesthetic that blocks impulse flow in DA neurons (37), reduces TIDA neuronal activity and increases prolactin secretion (36, 38). Stimuli that increase circulating levels of prolactin, such as suckling or stress, produce concurrent decreases in TIDA neuronal activity as estimated from measurements of the rates of synthesis and turnover of DA in the median eminence (39–41).

TIDA neuronal activity can also be estimated by measuring DA concentrations in hypophysial portal plasma. DA concentrations in hypophysial portal blood are sufficient to inhibit prolactin release (42, 43). Plasma prolactin levels during the estrous cycle are inversely related to portal plasma DA concentrations (42). DA levels in portal plasma decline during times of prolactin surges whether the surges are induced by gonadal steroids or uterine cervical stimulation as occurs during mating (42, 44, 45). Progressive changes in TIDA neurons in aging rats have been correlated with reduced portal plasma DA concentrations and increased serum prolactin levels (46, 47). The relationship between prolactin secretion and portal DA concentrations also holds true with pharmacological manipulations. For example, administration of morphine decreases portal blood DA concentrations (48) and increases plasma prolactin levels (49).

Prolactin Release After Dopamine Receptor Activation or Blockade

Much of what is known of the DA regulation of prolactin secretion has been learned through the use of DA receptor agonists and antagonists. In vivo and in vitro studies have consistently found that DA and DA agonists inhibit the release of prolactin, and that this inhibition is reversed by DA receptor blockade with neuroleptics (27, 32, 34). DA has multiple actions on the anterior pituitary (see Table 2). Some of the alterations in anterior pituitary function following DA administration (i.e. changes in intracellular cyclic AMP levels or lysosomal enzyme activity) cannot be definitively attributed to the lactotroph because of the mixed population of DA-responsive cells in the pituitary. The use of clonal pituitary cell lines has reduced this problem, but many tumor cell lines secrete a second hormone, in addition to prolactin. The reverse hemolytic plaque assay offers a more direct approach to correlating cellular events with secretion of individual hormones. This assay permits the detection and quantification of hormone released from individual pituitary cells in vitro (50). With this technique it should be possible to gain a detailed understanding of the cellular events regulating the secretion of specific pituitary hormones.

DA agonists inhibit prolactin secretion and are commonly used in the clinical treatment of hyperprolactinemia. Administration of DA agonists (e.g. bromocriptine, lisuride, pergolide) to hyperprolactinemic patients lowers circulating prolactin levels and can reduce the size and growth of pituitary adenomas, which are generally prolactin-secreting cells (51). The DA agonists act directly on these cells by replacing or supplementing DA released from TIDA neurons.

Neuroleptics, by blocking DA receptors on lactotrophs, produce hyperprolactinemia, thus indicating that the release of this hormone is under the tonic inhibitory control of DA released from TIDA neurons. Therapeutic doses of neuroleptics increase serum prolactin in psychotic patients (52–56). The effects of neuroleptic drugs on prolactin secretion occur at lower doses and after shorter latent periods than do the antipsychotic effects of these drugs. Prolactin elevations occur upon absorption of the neuroleptic, whereas the antipsychotic effects require days or weeks to become fully manifest (57, 58). Furthermore, serum prolactin levels decline to normal values within 2–4 days after oral neuroleptic treatment stops, whereas relapse of the mental state of psychotic patients may be delayed for weeks (59–61). The lack of a close temporal relationship between elevations of serum prolactin levels, reflecting the DA receptor blocking action of the neuroleptics, and the antipsychotic effect of the drugs (52, 54, 62–64), suggests that this latter effect is indirect and secondary to DA receptor blockade.

In animals, chronic neuroleptic treatment can increase D-2 receptor density within the striatum and induce behavioral or motor hyper-responsiveness to DA agonists (3, 65, 66). On the other hand, DA receptor density in the anterior pituitary does not increase with chronic neuroleptic treatment (67), and this is reflected in a low degree of tolerance to the hyperprolactinemia produced in rats by chronic neuroleptic treatment (68–70). The degree of tolerance to the neuroleptic-induced hyperprolactinemia and the consequent prolactin-induced activation of TIDA neurons in rodents (70) is much less than the tolerance observed in the nigrostriatal and mesolimbic dopaminergic neuronal systems. Marked tolerance to the electrophysiological (71, 72), behavioral (73, 74), and neurochemical (75–77) effects of neuroleptics on these major ascending DA neuronal systems develops with chronic administration of these drugs.

With regard to humans, however, there are conflicting reports of tolerance to the hyperprolactinemia caused by long-term neuroleptic use. Numerous studies indicate that circulating levels of prolactin are not markedly elevated in patients treated chronically with neuroleptics (e.g. 62–64, 78, 79), whereas others have found that hyperprolactinemia is maintained during neuroleptic therapy (52, 80, 81). The different responses may depend on the duration of neuroleptic treatment and on the frequency and dose of neuroleptic being administered (see 64, 82). For example, patients may receive relatively high doses of neuroleptics in order to control psychotic symptoms, and these doses may be supramaximal with regard to blockade of DA receptors on lactotrophs. In such patients, tolerance to the elevation of prolactin levels may be masked. Persons maintained on neuroleptic therapy who have circulating prolactin levels within the normal range, may still exhibit a decrease in plasma levels of this hormone when neuroleptic treatment stops (61, 83). This response indicates that in these individuals, even though the prolactin levels are not markedly elevated, the neuroleptic is still producing some blockade of the DA inhibition of prolactin secretion.

Sites of Neuroleptic Action on Prolactin Secretion

The primary site of neuroleptic action for stimulation of prolactin secretion is the anterior pituitary. Neuroleptic drugs block the DA-induced inhibition of prolactin secretion from normal and tumor pituitary cells in vitro (84). The DA receptor affinity of neuroleptics can be correlated with the ability of these drugs to reverse DA-induced inhibition of prolactin release from rat anterior pituitary cells in vitro (28). DA antagonists that do not readily cross the blood-brain barrier, such as domperidone, stimulate prolactin secretion in vivo (85). Neuroleptics increase prolactin secretion in vivo by blocking D-2 type receptors on the lactotroph (3). D-1 type receptors have not been found in

the anterior pituitary, and D-1 antagonists cannot reverse the inhibition of prolactin secretion produced by DA agonist administration (23).

DA and DA antagonists affect several intracellular mechanisms involved in prolactin secretion (32). DA inhibits adenylate cyclase activity in human prolactinomas and normal rat anterior pituitaries (86). Neuroleptics antagonize this effect of DA. Normal and adenomatous prolactin-secreting cells exhibit electrical activity that can be inhibited by DA and reinstated with D-2 receptor antagonists (87, 88). This electrical activity is calcium dependent [i.e. voltage-dependent calcium channels are involved (89)]. Calcium and its binding protein, calmodulin, are important factors for stimulus-secretion coupling in the release of prolactin (30). Calmodulin blockers inhibit prolactin secretion, and DA is reported to inhibit calcium influx into pituitary cells (90). Phospholipid metabolism also participates in the secretion of pituitary hormones. Phospholipid turnover is inhibited in the pituitary by DA, and DA antagonists reverse this effect (91).

The hypothalamus may also play a role in mediating the prolactin stimulatory effects of neuroleptics. The hypothalamus contains D-1 and D-2 receptors (8, 92). DA can alter the release of peptidergic inhibiting- and releasing-factors from neurons within the hypothalamus. Somatostatin can inhibit secretion of prolactin from the pituitary (84, 93). Results of in vitro studies have shown that DA stimulates the release of somatostatin from the hypothalamus and that neuroleptics block this effect (94, 95).

Effects of Hyperprolactinemia

Prolactin has been proposed as a modulator of DA receptor density in the striatum. Chronic treatment with haloperidol has been reported to increase both striatal DA receptor density and serum prolactin levels in intact but not hypophysectomized rats (96). Administration of prolactin alone is reported to increase the number of DA receptors in the striatum of both intact and hypophysectomized rats (97, 98). On the other hand, several investigators have failed to find an effect of prolactin on nigrostriatal DA neurons. Long-term treatment with neuroleptics has been found to be equally effective in elevating striatal DA receptor density in both sham-operated and hypophysectomized male rats (99, 100). Chronic treatment with DA antagonists (domperidone, sulpiride) that increase plasma concentrations of prolactin but do not penetrate the blood-brain barrier, failed to alter cerebral DA function (101, 102), and manipulations that cause marked increases in circulating levels of prolactin [implantation of prolactin-tumors (103); depot injections of prolactin (104)] failed to alter the characteristics of DA receptors in the striatum.

Some side effects of neuroleptics may be due to hyperprolactinemia.

Long-term hyperprolactinemia reduces sexual behavior in humans and rodents of both sexes (105–110). Hyperprolactinemia also inhibits estrous cyclicity in rats (110a) and can cause amenorrhea in women (110). One way in which elevated levels of prolactin produce anovulation is by disrupting the pulsatile release of the pituitary gonadotrophins (111, 112). Reducing circulating prolactin concentrations with the DA agonist bromocriptine can restore normal gonadotrophin release and ovulation in hyperprolactinemic women (11).

Continued elevation of serum prolactin levels induced by chronic neuroleptic therapy has caused some concern about increased risk of breast cancer in female patients. In the rat, long-term neuroleptic treatment increases the incidence of mammary tumors, but there is no evidence that chronic use of neuroleptics in humans alters the risk of breast cancer (113).

EFFECTS OF NEUROLEPTICS ON REGULATION OF GROWTH HORMONE SECRETION

The secretion of GH is primarily under the control of two hypothalamic neuropeptides released into the hypophysial portal system. Somatostatin inhibits, and GH-releasing factor (GRF) stimulates GH release from somatotrophs in the anterior pituitary (114). Under normal conditions, the secretion of GH occurs at a low basal rate with pulses of release every 3–4 hr. The episodic nature of GH secretion is believed to be due to variations in the hypothalamic release of both GRF and somatostatin (115–118). Other factors, such as DA, have a secondary role in GH regulation.

Regulation of Growth Hormone Secretion by Dopamine

Peripheral administration of DA or DA agonists increases circulating levels of GH in humans and rats (119–122). Neuroleptics can block the effects of DA agonists and reduce basal or stimulated GH secretion (122, 123). GH synthesis within the anterior pituitary, as measured by ^{3}H-leucine incorporation, is inhibited in rats by injection of pimozide (124). In contrast to the stimulatory effects of DA and DA agonists in vivo, basal GH release from dispersed pituitary cells in vitro is inhibited by DA and DA agonists (26, 84, 125). GRF-stimulated GH secretion is also reduced by DA in vitro (126). Somatotrophs contain DA receptors (25) and can internalize and sequester ^{3}H-DA (127).

The actions of DA on somatotrophs have not been as thoroughly studied as the actions of DA on lactotrophs, but there may be some similarities in the actions of DA on these two cell types. Lactotrophs and somatotrophs have a number of common cytological properties and respond to many of the same regulatory factors (34, 128). In addition, a large percentage of cells within the

normal anterior pituitary secrete both prolactin and GH (129). The potency of DA on hormone release differs between the two cell types; DA inhibits prolactin secretion at concentrations lower than those needed for inhibition of GH secretion (26, 84). It has been proposed that DA inhibition of adenylate cyclase occurs only in lactotrophs and not in somatotrophs (86). Adenylate cyclase does, however, have a stimulatory role in the secretion of GH from somatotrophs and does respond to GRF and somatostatin (130).

In addition to acting at the pituitary, DA can influence GH secretion indirectly by acting within the hypothalamus to modulate the neurosecretion of somatostatin and GRF. Somatostatin concentrations in hypophysial portal blood have been reported to increase following the intraventricular injection of DA (131). The release of somatostatin from hypothalamic or median eminence fragments in vitro is also stimulated by DA or DA agonists (94, 95, 132). These effects of DA are blocked with D-2 but not D-1 receptor antagonists (95). The stimulatory effect of DA on somatostatin release is difficult to reconcile with the stimulatory effects DA and DA agonists have on GH secretion in vivo. The effects of DA-induced somatostatin release may be countered by DA stimulation of GRF release. L-dopa administration to humans increases GH and GRF concentrations in peripheral plasma (133). However, L-dopa is a precursor for both DA and norepinephrine, and so the effects of L-dopa administration may be due to nonadrenergic receptor activation, a known stimulus for GH secretion (34). The same argument holds true when DA is administered as an experimental manipulation. Without confirmation by use of specific agonists or blockade with specific antagonists, one should not assume that the effects of DA administration are mediated solely by DA receptors. The issue of GRF regulation by DA is further complicated by the recent demonstration that virtually all neurons containing immunoreactive GRF within the arcuate nucleus also contain immunoreactive tyrosine hydroxylase and are probably dopaminergic (134). Obviously, the relationship between DA and GRF within the hypothalamus is not a simple one. In vitro studies relating hypothalamic GRF release to DA agonist and antagonist administration might clarify this issue.

Growth Hormone Release After Dopamine Receptor Blockade

GH secretion following neuroleptic administration has been measured in a large number of studies with inconsistent results (135). While it may be difficult to observe reductions in GH secretion because of low basal GH concentrations in plasma, it has been reported that acute neuroleptic administration inhibits the spontaneous release of GH in humans and rodents (122, 123, 136). Neuroleptics can also blunt the stimulatory GH responses to exercise, insulin-induced hypoglycemia, and the administration of arginine or apomorphine (57, 137, 138). The inability of low doses of domperidone to

alter basal or GRF-stimulated serum GH levels in humans (121) suggests that neuroleptics exert their inhibitory effects at some site protected by the blood-brain barrier. Neuroleptics may influence GRF release from the hypothalamus. In rats passively immunized against somatostatin, chlorpromazine is still able to suppress the episodic pulses of GH secretion (136), which suggests that DA stimulates the release of GRF.

Neuroleptics are not used clinically to treat dysfunctions in GH regulation. The inhibitory effects of neuroleptics on GH secretion might suggest the use of neuroleptics to treat acromegaly, but such treatment has not been successful (139). The normal DA regulatory mechanisms controlling GH secretion are altered in acromegaly. DA agonists increase GH secretion in normal subjects (135) but decrease GH secretion in acromegalic patients (140). This paradoxical effect of DA agonists is thought to be due to the direct action of these drugs on the pituitary tumor (140). The hypersecretion of GH in patients with acromegaly can be controlled with administration of the DA agonist bromocriptine (141).

EFFECTS OF NEUROLEPTICS ON REGULATION OF THYROTROPIN SECRETION

TSH is the primary stimulus for secretion of thyroid hormones from the thyroid gland. The secretion of TSH from pituitary thyrotrophs is controlled by tonic negative feedback provided by the thyroid hormones and by both stimulatory and inhibitory factors provided by the hypothalamus. Of the several neuropeptides demonstrated to influence TSH release (142), thyrotropin-releasing hormone (TRH) is the major stimulatory factor. Other hypothalamic factors, such as DA, have lesser, albeit physiological, roles in controlling TSH secretion.

Regulation of Thyrotropin Hormone Secretion by Dopamine

The general consensus is that DA inhibits the secretion of TSH (34, 142, 143). Administration of DA or DA agonists lowers circulating TSH levels (120, 122, 144, 145) and blunts the positive TSH response to cold stress (144, 146). Serum TSH levels are inhibited by DA infusion and remain suppressed during prolonged infusion (147). It should be noted, however, that some investigators have generated contradictory results and concluded that DA has no role in TSH regulation (148–150).

The primary site of action for DA inhibition of TSH release is the anterior pituitary. DA agonists inhibit the secretion of TSH from dispersed anterior pituitary cells in vitro (24). DA agonists and antagonists display the same rank order of potency for affecting TSH and prolactin secretion in vitro, suggesting

that TSH secretion is regulated by DA receptors similar to those DA receptors on lactotrophs (24). When dispersed anterior pituitary cells were cultured in a perfusion system, as opposed to a static system, DA did not inhibit basal or TRH-stimulated TSH secretion (151). The low concentration of TSH in the perfusion media may be responsible for this lack of responsiveness to DA. Pituitary cells display DA inhibition of TSH secretion in vitro only in the presence of TSH in the culture media (152). DA inhibition of prolactin secretion is unaffected by the presence or absence of TSH. It is hypothesized that TSH regulates DA receptor binding on thyrotrophs; the addition of fresh, non-TSH-containing, culture media to pituitary cells in vitro reduces DA receptor binding (152).

Although the anterior pituitary is believed to be the primary locus at which DA regulates TSH release, the secretion of this hormone may also be regulated by an action of DA within the brain. Injection of the DA agonist piribedil into the third ventricle decreases plasma TSH levels (120). The inhibitory effect of apomorphine on the TSH response to cold stress is blocked by the DA antagonists metoclopramide and haloperidol but not by domperidone, presumably because the latter DA antagonist does not easily cross the blood-brain barrier (144). The median eminence is a likely site for the DA regulation of TSH secretion. DA turnover within the median eminence is reduced by thyroidectomy, a procedure that increases TSH secretion (153). Administration of thyroid hormones to thyroidectomized rats increases the rate of DA turnover in the median eminence to levels measured in intact rats. These results indicate that thyroid hormone feedback may operate not only through the pituitary but also through the TIDA neurons of the hypothalamus. A second explanation for these results, however, is that the changes in TIDA neuronal activity are due to changes in circulating prolactin levels. TIDA neurons are regulated by a positive prolactin feedback mechanism (35). The lack of thyroid hormones following thyroidectomy reduces prolactin synthesis and release from the anterior pituitary (153, 154), and this would be expected to lower the rate of DA turnover in TIDA neurons. Thyroid hormone replacement in thyroidectomized rats would be expected to increase prolactin secretion and TIDA neuronal activity within the median eminence.

Some investigators have studied the possibility of a DA-TRH interaction within the hypothalamus. TRH release from hypothalamic fragments in vitro is stimulated by DA or bromocriptine, and this effect is blocked by haloperidol (132). The release of TRH from hypothalamic synaptosomes is also increased by DA (155), and DA antagonists block this effect. Anatomical evidence for such interactions has not been found. Immunocytochemical studies have not located synaptic contacts between DA neurons and TRH-containing neurons within the hypothalamus (156).

Thyrotropin Hormone Release After Dopamine Receptor Blockade

If DA inhibits TSH secretion, then neuroleptics might be expected to stimulate the secretion of this hormone. A number of clinical studies show that acute administration of neuroleptics increases both basal circulating levels of TSH and the TSH response to a TRH challenge (58, 121, 157–159). The thyroid status of the subjects affects the magnitude of the TSH response to neuroleptic treatment. The metoclopramide-induced increase in serum TSH levels is greater in patients with subclinical hypothyroidism than in those patients with overt hypothyroidism (160). The TSH response to neuroleptic administration also tends to be greater in women than in men (157, 158). There are conflicting reports on the effects of chronic neuroleptic treatment on TSH secretion. The majority of studies find either no change or only a small increase in TSH secretion following long-term neuroleptic use (64, 157, 161). Given the minor role of DA in the regulation of TSH secretion, the lack of marked alterations in the release of this hormone during neuroleptic administration is not surprising.

SUMMARY

Neuroleptics have been developed primarily to treat psychoses, but they have become invaluable research tools. Because of their selective action on DA receptors, neuroleptics are commonly employed to study the function and regulation of DA neurotransmission. The relationship between the antipsychotic efficacy and the DA receptor affinity of the various neuroleptic drugs has lead to the development of new DA antagonists in hopes of discovering novel antipsychotic agents. This approach has produced interesting new compounds selective for the DA receptor subtypes. The use of DA receptor antagonism as a measure of the potential antipsychotic efficacy of a compound will undoubtedly change as the mechanisms behind the antipsychotic actions of neuroleptics become better understood.

Although endocrine side effects of neuroleptic administration are undesired in the clinic, they have provided insight into the neuroendocrine regulation of pituitary hormones. Through the use of neuroleptics, DA neurons in the hypothalamus have been shown to play a role in the regulation of prolactin, GH, and TSH secretion. The ability of DA to act at the pituitary and thereby inhibit the secretion of these three hormones suggests that other regulatory factors must provide the specificity needed for the differential secretion of the individual hormones during varying physiological states. Future research will certainly explore the interactions of DA and these regulatory factors at the pituitary. The role of DA in neuroendocrine regulation is not limited to the

pituitary. The presence of DA neurons within the hypothalamus offers the possibility of DA regulation of hypothalamic neurosecretory activity.

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