Progress in Neuroendocrinology

Neuroendocrinology 35: 139–147 (1982)

Neurotransmitter Control of Thyrotropin Secretion

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Key Words. TSH · TRH · Somatostatin · Dopamine · *l*-Dopa · Bromocryptine · Norepinephrine · Serotonin · Acetylcholine · GABA · Opioids

Abstract. The central dopaminergic system seems to have an inhibitory influence on the secretion of thyrotropin (TSH) both in humans and rats. This is documented by observations that in humans, especially in subjects with primary hypothyroidism, the dopamine precursor *l*-Dopa, dopamine receptor agonist bromocryptine, and dopamine itself decrease plasma levels of TSH and in some instances inhibit TSH secretory response to thyrotropin-releasing hormone (TRH). Conversely blockade of dopamine receptors leads to an elevation of circulating TSH. It is probable the dopaminergic drugs act on the pituitary thyrotrops rather than on the release of hypothalamic TRH. Analogous results were obtained in rats. In contrast, the noradrenergic system, studied mainly in rats, has a stimulatory influence on the secretion of TSH. This view is mainly supported by findings that acute interruption of noradrenergic neurotransmission causes a decrease of serum TSH levels and blocks the cold-induced stimulation of TSH secretion. The role of the central serotonergic system remains undecided because some experimental findings indicate that it has an inhibitory influence but others indicate an opposite function. The remaining transmitter systems have not been studied extensively enough to allow definite conclusions about their roles in the regulation of TSH secretion.

The role of the central neurotransmitters in the regulation of thyrotropin (TSH) secretion has been studied less extensively than for instance the neurotransmitter control of the secretion of prolactin. Many aspects are therefore poorly understood and the whole area is replete with controversial or outrightly contradictory findings. Part of the problem might be in the relatively high degree of complexity of the mechanisms regulating secretion of TSH from the pituitary. The system consists of a stimulatory input represented by the hypothalamic thyrotropin-releasing hormone (TRH) and probably three inhibitory inputs represented in turn by the feedback effect of thyroid hormones and by the inhibiting effects of hypothalamic somatostatin and dopamine, the release of the latter two being also under neurotransmitter control [for review see 66, 106]. The current information about involvement of neurotransmitters in the individual inputs is quite uneven and it seems therefore more feasible to arrange the present review according to the individual transmitter systems rather than according to the individual inputs.

Received: December 18, 1981
Accepted after revision: February 19, 1982

Dopamine

The most numerous studies have been oriented towards the dopaminergic system both in humans and experimental animals (rats) and it seems that the dopaminergic system exerts an inhibitory influence on secretion of TSH in both species.

In humans this possibility was first suggested by *Spaulding* et al. [123] who found that the TSH response to administration of TRH was virtually abolished in Parkinsonians treated with the precursor of dopamine, *l*-Dopa. Spaulding's finding was later confirmed by several authors [12, 59, 103] but it turned out that only chronic administration of the drug had this effect, whereas a single dose in euthyroid subjects did not affect either basal or TRH-stimulated secretion of TSH [25, 40, 78, 89, 98, 120, 121]. In hypothyroid pa-

tients, however, a single dose of *l*-Dopa lowered the elevated TSH levels without modifying the response to TRH [30, 62, 64, 79, 97, 98].

Comparable results were obtained when 2-Br-α-ergocryptine (bromocryptine), a potent agonist of dopamine receptors, or dopamine itself was used instead of *l*-Dopa. Bromocryptine blunted the effect of TRH in euthyroid subjects according to some authors [92, 140] whereas the majority of investigators [22, 31, 45, 55, 117] did not notice any influence. In hypothyroid subjects bromocryptine decreased basal levels and inhibited the TSH response to TRH [31, 64, 80]. Infusion of dopamine, with the exception of *Leblanc's* [60] negative results, was reported to lower basal levels and decrease the response to TRH [8, 11, 18, 52, 61, 69] regardless of the thyroid status of the subject. The effect of dopamine could be abolished by administration of the dopamine receptor antagonist domperidone [19].

A counterpart to studies with dopaminergic agonists is a series of reports based on the use of blockers of the dopamine receptors. *Sowers* et al. [122] were probably the first to describe a slight elevation of serum TSH levels in euthyroid men following administration of metoclopramide. Their results were subsequently confirmed and expanded by other workers using metoclopramide [41, 109, 110], the related drug sulpiride [68, 143] or the novel blocker, domperidone [20, 67, 94]. It soon became evident that the magnitude of the rise in the TSH levels is determined by several factors. One of them is sex of the subjects. Women in general show a larger response than men, who on occasion do not react at all [6, 51, 68, 109]. Another factor is the thyroid status. Patients with primary hypothyroidism display a larger increase than euthyroid controls [68, 110]. Within the hypothyroid group the TSH response is inversely related to the severity of the condition [31, 105, 110]. Another determinant is possibly time of the day, because, according to *Scanlon* et al. [108], the TSH release is more pronounced at the acrophase (around 23.00 h) of the human TSH daily rhythm than at its nadir (around 11.30 h). Finally, a greater reaction was observed in patients with hyperprolactinemia [69, 95] which may reflect changes in metabolism of dopamine due to sustained elevation of prolactin levels.

It has been shown recently that the effect of DA receptor blockade does not apply to TSH alone but affects also the α and β subunits [105] and that blockade of synthesis of dopamine with monoidotyrosine is as effective in elevating TSH levels as blockade of dopamine receptors [107]. It should be noted that the elevation of serum TSH levels following blockade of DA receptors is quite small and in normal subjects usually does not exceed 1.0 μU/ml. This together with a relatively large interindividual variability may perhaps explain several negative results [43, 50, 91, 124]. Hard to fit into this general framework is the report of *Collu* et al. [17] that pimozide, another DA receptor blocker caused a marked decrease of TSH levels in euthyroid subjects. *Collu's* results were, however, not corroborated by a recent study [19] showing that the classical dopamine receptor blockers pimozide or haloperidol are as effective as the substituted benzamides metoclopramide or sulpiride in stimulating TSH secretion in humans.

On the basis of all these reports it seems that in humans the dopaminergic system has some tonic inhibitory influence on the secretion of TSH which possibly modulates the effects of the stronger negative feedback regulation. The DA system may be perhaps instrumental in setting of the diurnal rhythm. Since neither dopamine nor domperidone penetrates into the brain, the natural dopaminergic influence is probably represented by dopamine released into the portal vessels from endings of the tuberoinfundibular DA neurons and acting directly on the pituitary thyrotrophs. This conclusion is also supported by the fact that *l*-Dopa, bromocryptine or dopamine decrease the TSH releasing effect of TRH.

Results obtained in rats are in general agreement with clinical observations and also indicate an inhibitory influence of the DA system. Rats, unlike humans, react to sudden exposure to cold with a secretory TSH surge and this experimental design has often been used to test inhibitory effect of various treatments.

According to several reports [56, 83, 146] administration of *l*-Dopa lowered basal TSH levels, but according to other investigators it had no effect on basal levels [14, 129] but inhibited the cold-induced release of TSH [90, 129, 146]. Similarly, dopamine receptor agonists apomorphine, piribedil or bromocryptine in large doses depressed TSH levels and/or prevented the cold-stimulated secretion [56, 74, 85, 96]. A TSH-inhibiting effect was also seen following systemic administration of a large dose of dopamine or intraventricular injection of microgram quantities of the transmitter [133]. However, none of these results went unchallenged and negative results were reported for apomorphine, bromocryptine and intraventricular administration of dopamine [3, 113, 146], respectively. Difference in dosage of some of the drugs [96, 113], administration of dopamine into the lateral ventricle [3] instead into the 3rd ventricle [133] and other differences in the respective experimental protocols may explain some of the discrepancies.

The site of action of dopamine or the dopaminergic drugs in the rat is uncertain. Apomorphine or *l*-Dopa did not change the TSH response to TRH [56, 96, 128], which suggests a central effect on the release of TRH. However, the TSH lowering effect of dopamine indicates a peripheral site of action. This view also is supported by a recent finding that dopamine or bromocryptine inhibits TSH release from dispersed, cultured pituitary cells in vitro [35] and also by a report that blockade of dopamine receptors elevates serum TSH levels [29]. The physiological role of the dopaminergic influence on TSH secretion in the rat is not known.

Norepinephrine

In contrast to the dopaminergic system the role of the noradrenergic mechanism(s) has been studied more frequently in rats than in humans and according to the prevailing opinion norepinephrine has a stimulatory influence.

This view is mainly supported by findings that acute impairment of noradrenergic neurotransmission by specific blockade of norepinephrine synthesis with disulfiram, diethyldithiocarbamate or fusaric acid lowered resting levels of TSH and blocked cold-stimulated secretion [56, 73–75, 81, 90]. Similarly, effective was blockade of α-adrenergic receptors with phentolamine or phenoxybenzamine [54, 56, 81, 129, 130].

However, blockade of synthesis of all catecholamines with α-methyl-*p*-tyrosine (αMT) produced inconsistent results ranging from elevation of TSH levels [129] to no effect [2] to a decrease [56, 75]. A similar confusion also exists with respect to the effect of cold on TSH levels in animals treated with αMT [75, 81, 130]. Some of these discrepancies may result from the fact that α-methyl-*p*-tyrosine affects neurotransmission in the dopaminergic system earlier than in the noradrenergic system and the timing of the experiments may therefore influence the results. This possibility seems to be supported by observation that the maximum inhibition of the cold-stimulated TSH secretion occurred 4 h after administration of the blocker [73]. Chronic depletion of brain norepinephrine by intraventricular administration of 6-hydroxydopamine had no lasting effect on basal TSH levels, and according to *Scapagnini* et al. [112] no effect on cold-stimulated TSH release. However, *Schettini* et al. [115] using a larger dose of 6-hydroxydopamine than *Scapagnini* saw a lasting loss of the reaction to cold.

Even more confusing are results obtained with adrenergic agonists. Intraventricular injection of norepinephrine elevated basal TSH levels [46, 133] or had no effect [73] while infusion of the transmitter into the anterior or mediobasal hypothalamus actually decreased TSH concentration [73, 126]. Intraventricular administration of the α adrenergic agonist clonidine-stimulated TSH secretion [111] whereas systemic administration produced varied result from stimulation to inhibition [58, 74, 111, 146]. Differences in dosage or route of administration may perhaps explain some of the inconsistencies. It seems, however, that clonidine augments the TSH reaction to cold in intact rats [81, 146] or restores the TSH response to cold in animals treated with α-MT or 6-hydroxydopamine [2, 111, 115].

Very little is known about the noradrenergic system and secretion of TSH in humans. According to several authors [9, 28, 101, 138] administration of adrenergic blockers or agonists had no effect on TRH-induced activation of TSH. However, *Yoshimura* et al. [141] described a decrease of TSH levels in hypothyroid patients treated with fusaric acid, a blocker of norepinephrine synthesis, and *Zgliczyński and Kaniewsky* [145] observed a decrease of TSH levels following infusion of α blocker phentolamine, which implies existence of a positive noradrenergic drive also in man. These authors as well as *Nilsson* et al. [89] also observed a blunting of the secretory response to TRH during infusion of phentolamine, indicating existence of a component operating at the level of the pituitary thyrotrophs.

It is obvious that it is not easy to draw any definite conclusions concerning the role of the noradrenergic system in the regulation of TSH secretion. It seems safe to assume that an unimpaired function of the system is required for the cold-stimulated secretion of TSH in rats, but it is less certain whether it is necessary for maintenance of normal resting levels. It also is assumed that the noradrenergic system acts, in contrast to the dopaminergic system by modulation of the release of hypothalamic TRH. The role of the noradrenergic system in humans is unknown.

The complexity of the situation is documented by our recent work [57], in which we showed that activation of adrenergic receptors can induce either stimulation or inhibition of TSH secretion depending on the type of α-adrenergic receptors which are involved. Activation of the α_1 type conveys an inhibitory influence whereas activation of the α_2 type has a stimulatory effect. Clonidine in low doses stimulates α_2-receptors whereas in large doses it activates also α_1-receptors and may induce a transient inhibition.

Serotonin

The possible role of the serotonergic (5HT) system is the most confusing of all and both a stimulatory and an inhibitory influence has been attributed to it.

Mess and Péter [77] concluded from indirect indices that intrahypothalamic implants or intraventricular injection of 5HT inhibit TRH-TSH secretion. Serotonin was reported by *Grimm and Reichlin* [39] to inhibit synthesis of TRH in hypothalamic tissue in vitro and *Krulich* et al. [58] reported inhibitory effect of intraventricular administration of 5HT and intraventricular or systemic injection of the serotonin receptor agonist quipazine. Quipazine or the serotonin releaser *d*-fenfluramine also had an inhibitory action according to *DiRenzo* et al. [23, 24].

However, *Jordan* et al. [49] in experiments almost identical with Krulich's described an elevation of TSH levels following injection of 5HT into the third ventricle. A similar claim ws also made by *Holak* et al. [46], whereas *Wystrichowski* et al. [139] saw an activation following a large dose of the transmitter and an inhibition following a smaller dose.

Contradictory results were also reported when the serotonin precursor 5-hydroxytryptophan was tested. *Chen and Meites* [14] as well as *Sakoda* et al. [104] found an activation of TSH secretion, whereas *Mueller* et al. [86] saw no effect.

According to *Tuomisto* et al. [129] and *Onaya and Hashizume* [90], 5HTP had no effect on basal TSH levels but inhibited the cold-induced activation. In contrast, tryptophan, another precursor of 5HT, was reported to have inhibitory influence on TSH secretion by several authors [71, 83, 86]. Results obtained with the blocker of serotonin synthesis, *p*-chlorophenylalanine are also difficult to fit into any consistent pattern. Some investigators [129] did not see any effect of the drug on serum TSH levels, others reported an inhibition [14, 118], while *Ruzsaz* et al. [102] found an activation. *Jordan* et al. [48] and *Fukuda* et al. [36] claim that depletion of brain serotonin eliminates the daily peak of TSH occurring around noon but has no effect on TSH levels at other times of the day. The complexity of the serotonergic regulation of TSH secretion is well documented by a recent paper by *Mattila and Männistö* [71] as well as by *Morley* et al. [84].

There are only a handful of clinical studies of serotonin in relation to TSH secretion. 5HTP inconsistently decreased TSH levels in patients with primary hypothyroidism [26, 142], whereas tryptophan had no effect [137]. Serotonin receptor blocker metergoline did not influence either basal or TRH stimulated TSH levels, but cyproheptadine, another receptor antagonist blunted TSH response to TRH [26, 33, 42]. These results were, however, not confirmed by another group of investigators [37].

Other Transmitters

The remaining neurotransmitter systems have received only scattered attention. As far as the cholinergic system is concerned, administration of pilocarpine into the third ventricle [46] or physostigmine systemically [129] had no effect, whereas nicotine lowered basal TSH levels [1]. Not much more is known about the histaminergic system. In humans, cimetidine, the blocker of the H_2 histaminic receptors had no effect on either basal or stimulated TSH levels when given acutely [21, 53, 132], while chronic treatment seemed to increase the response to TRH [72]. Feeding histidine deficient diets to rats to decrease histamine concentration and thus the histaminergic neurotransmission in the brain did not alter TSH levels [47]. In contrast the GABA-ergic system may be involved. *Vijayan and McCann* [134] reported that intraventricular administration of GABA lowered basal TSH levels possibly via activation of the dopaminergic system because the effect could be abolished by pretreatment of the rats with a dopamine receptor blocker [134]. *Mattila and Männistö* [70] also concluded that activation of the GABA-ergic system is inhibitory to the secretion of TSH.

Greater effort has been spent on studies concerning the role of the opioid system. There are several reports that in rats, morphine [10, 63, 76, 87, 116] or metenkephalin [10] lowered basal serum TSH levels or inhibited activation of TSH secretion by cold or thyroidectomy [87, 116]. Morphine did not, however, inhibit the TRH-stimulated TSH surge and according to one group of investigators [87] it actually potentiated the effect of TRH. Naloxone, the blocker of opioid receptors abolished all effects of morphine but it did not induce any changes of the basal or activated levels of TSH. It did, however, prevent decrease of TSH in animals exposed to heat [116], which may be taken as evidence for a physiological role of the endogenous opioid peptides in the regulation of TSH secretion. Morphine [127] or an enkephalin analogue [125] had no effect on serum TSH levels in humans. Naloxone had no effect either according to one report [82]; however, according to *Zanoboni* et al. [14] it augmented the TSH response to exogenous TRH. The reason for these discordant results is not apparent.

Effect of Transmitters on Release of TRH in vitro

Since hypothalamic TRH is the only stimulatory input to the pituitary thyrotrophs, one might assume that additional information about the role of neurotransmitters in the regulation of TSH might be obtained from studies of the effects of the transmitters directly on TRH release. This approach is not feasible in vivo conditions because the concentration of TRH in systemic blood is to low to be measured with any accuracy and instead results obtained in vitro might be used. The most common finding in this respect was stimulation of TRH release from hypothalamic tissue or from synaptosomes prepared from the hypothalamus by dopamine [7, 65, 114]. Other investigators, however, reported stimulating effect of norepinephrine [39, 44] stimulating [15] but also inhibiting [7, 39] effect of serotonin and finally also stimulating effect of histamine acting through the H_2 type of histamine receptors [13]. The reason for this variety of results is not clear. A stimulating effect of norepinephrine and to a certain degree also of serotonin would agree with the effects of these transmitters on TSH secretion in vivo. In contrast, the TRH releasing effect of dopamine is difficult to understand and one might speculate that in vivo the TRH releasing action of dopamine is overridden by its inhibiting effect on TSH secretion from pituitary thyrotrophs.

Role of Somatostatin

It has been established that somatostatin inhibits secretion of TSH in rats and humans [119, 131]. For a physiological role of somatostatin in the regulation of TSH secretion speak observations that administration of antiserum to somatostatin induced in rats an increase of basal serum TSH levels and augmented responsiveness to exogenous TRH or to exposure to cold [5, 32, 34, 38]. As with TRH one might expect that further ideas about the possible role of somatos-

tatin in the regulation of TSH secretion might be obtained from studies of neurotransmitter regulation of somatostatin secretion. Activation of somatostatin release from the hypothalamus by dopamine was described both in vitro [65, 88, 136] and in vivo [16]. It is possible to speculate that release of somatostatin might be a part of the dopaminergic inhibition of TSH secretion. A direct inhibitory effect on TRH release has to be also taken into account [44]. However, under similar experimental conditions release of somatostatin was also activated by norepinephrine [16, 27, 88] which is difficult to bring together with the alleged TSH stimulating role of norepinephrine. Studies of the effects of other transmitters produced varied results, which are difficult to relate to regulation of TSH secretion: acetylcholine has been reported to stimulate [16] but also to inhibit [99] somatostatin release while serotonin had no effect [16] or according to another report [100] had an inhibitory effect. For further information see *Arimura and Fishback* [4].

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