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NEUROENDOCRINE PHARMACOLOGY OF SEROTONERGIC (5-HT) NEURONS

Louis D. Van de Kar

Loyola University Chicago, Stritch School of Medicine, Department of Pharmacology, 2160 South First Avenue, Maywood, Illinois 60153

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INTRODUCTION

Serotonergic neurons are believed to play a role in depression, anxiety, and aggression (for review see 1). There is evidence that serotonergic neurons send collaterals to limbic and neuroendocrine control areas in the brain (2–3). Consequently, hormones that are released by serotonergic neurons might serve as diagnostic tools to evaluate the serotonergic involvement in emotional disorders. This review is a survey of the evidence for serotonergic regulation of ACTH, β-endorphin, prolactin, renin, oxytocin, vasopressin, growth hormone (GH), and luteinizing hormone (LH) secretion. The anatomy of the serotonergic pathways is discussed briefly, followed by a concise overview of the pharmacology of serotonergic neurotransmission. The evidence for a role of serotonergic neurons in the regulation of each individual hormone is divided into three sections: (*a*) the anatomical organization; (*b*) the physiological function; and (*c*) the 5-HT receptor subtypes involved in the regulation of each hormone.

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NEUROANATOMY OF BRAIN SEROTONERGIC NEURONS

Serotonergic cell bodies, designated B1-B8 cell groups, are found in the midline areas of the brainstem in close association with the raphe nuclei (4). The exception is the serotonergic cell group in the ventrolateral midbrain, the B9 cell group (4). The pontine (B5-B6) and mesencephalic (B7-B9) cell groups primarily innervate various areas in the forebrain. The cells in the dorsal raphe nucleus (B7) innervate the caudate-putamen, whereas the cells in the median raphe nucleus (B8) project to the hippocampus (5–9). The serotonergic neurons involved in the regulation of hormone secretion are located in the midbrain and pons. The ascending 5-HT fibers to the hypothalamus originate in the dorsal and median raphe nuclei in the midbrain (8, 10–12). The few 5-HT immunoreactive fibers that innervate the paraventricular nucleus (PVN) are concentrated in the parvocellular division and arise from the dorsal raphe, median raphe, and the lateral (B9) cell group in the midbrain (8). This is important because neurons containing corticotropin releasing factor (CRF) in the PVN receive direct serotonergic synaptic input (13). Furthermore, neurons in the PVN are involved in the regulation of prolactin (14–16) and renin secretion (1, 17–19).

PHARMACOLOGY OF 5-HT

The synthesis of 5-HT begins with the enzymatic hydroxylation of the amino acid l-tryptophan to 5-hydroxytryptophan (5-HTP), followed by decarboxylation to 5-hydroxytryptamine (5-HT). 5-HT synthesis inhibitors can reduce the endogenous stores of 5-HT in nerve terminals. The most frequently used 5-HT synthesis inhibiting drug is p-chlorophenylalanine (PCPA). PCPA inhibits tryptophan hydroxylase, the rate-limiting enzyme in the synthesis of 5-HT (20). The activity of tryptophan hydroxylase is increased when serotonergic neurons are stimulated (21). 5-HT is metabolized by oxidation to 5-hydroxyindole acetic acid (5-HIAA). Monoamine oxidase inhibitors (MAOI) increase the concentration of 5-HT in nerve terminals (22). Administration of l-tryptophan and 5-HTP increases the concentration of 5-HT in the brain, but does not necessarily increase the release of 5-HT into the synaptic gap (22).

Upon release into the synaptic gap, 5-HT is taken back up into the nerve terminal by an active mechanism. 5-HT uptake inhibitors prevent this passage, thus leading to enhanced concentration of 5-HT in the synaptic gap (23). The 5-HT uptake inhibitors fluoxetine, citalopram, and zimelidine are used as antidepressants (24, 25). Drugs that release 5-HT from nerve terminals

activate 5-HT receptors through endogenous 5-HT and require intact serotonergic neurons to be effective. 5-HT releasing drugs such as the amphetamine analogues p-chloroamphetamine (26), fenfluramine, and norfenfluramine (27) can be considered indirect 5-HT agonists. They are taken up into the 5-HT nerve terminals by the active uptake mechanism leading to the release of 5-HT into the synaptic gap. Inhibition of the 5-HT uptake mechanism prevents the entry of the 5-HT releasers into the nerve terminals and thus the release of 5-HT (28, 29). The d-isomer of fenfluramine is a more selective 5-HT releaser than the l-isomer (27). Since the endocrine effect of 5-HT releasers depends on the integrity of 5-HT neurons, these drugs can be used to locate the 5-HT neurons that increase the secretion of a hormone. This identification can be accomplished by a combination of lesion followed by injection of the 5-HT releaser.

Neurotoxins can destroy 5-HT neurons. The most commonly used neurotoxin is 5,7-dihydroxytryptamine (5, 7-DHT), which is structurally similar to 5-HT and can be taken up into nerve terminals by the 5-HT uptake mechanism. Inside, 5,7-DHT causes degeneration of the 5-HT nerve terminal. 5,7-DHT also can be taken up by noradrenergic and, to a lesser extent, by dopaminergic nerve terminals. This effect can be avoided by treating the experimental animals with a norepinephrine uptake-inhibiting drug such as desipramine (30, 31) or the dopamine/norepinephrine uptake-inhibiting drug nomifensine (32). Since 5,7-DHT does not cross the blood-brain barrier readily, it must be injected intracerebroventricularly (i.c.v.) or into the brain parenchyma (12). Several amphetamine analogues are toxic to serotonergic neurons. These include the hallucinogenic drugs (±)-3,4-methylenedioxyamphetamine (MDA), and methylenedioxymethamphetamine (MDMA), and 5-HT releasers p-chloroamphetamine and fenfluramine (33, 34, 68).

Table 1 illustrates how 5-HT receptors are divided into four major groups, 5-HT_1, 5-HT_2, 5-HT_3 and 5-HT_4. The 5-HT_1 receptor group is further subdivided into 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, and 5-HT_{1D} receptor subtypes (35–38). The initial information leading to the designation of 5-HT receptor subtypes was based on ligand binding studies. More recently, the DNA sequences of several 5-HT receptor subtypes have been identified (Table 1). These indicate that 5-HT_{1C} receptors are more closely related to 5-HT_2 receptors than to the 5-HT_1 receptor family (39, 40). Both activate the phosphoinositide second messenger system (39, 40). In contrast, the 5-HT_1 receptors inhibit adenylyl cyclase (38). 5-HT_3 receptors are found in various brain areas (41) and form part of membrane-traversing cation channels (42–44). A 5-HT_3 antagonist, odansetron (GR38032F), has been proposed as a potential antipsychotic drug devoid of dopamine-related side effects (45) and as a potential anxiolytic drug (46, 47). The 5-HT_4 receptor stimulates adenylyl cyclase (48, 49).

Table 1 Summary of serotonin (5-HT) receptor subtypes

Site	Coupling	2nd Messenger	Cloned	Agonist	Antagonist
5-HT_{1A}	G-protein	K^+ Ch/AC(−)	Y	8-OH-DPAT	NAN 190
5-HT_{1B}	G-protein	AC(−)	N	RU 24969	cyanopindolol
5-HT_{1D}	G-protein	AC(−)	N	sumatriptan	methiothepin
5-HT_2	G-protein	IP3	Y	DOI	ketanserin/spiperone
5-HT_{1C}	G-protein	IP3	Y	DOI	mesulergine
5-HT_3	Ion channel	(Na^+/K^+)	N	2-Me-5-HT	odansetron
5-HT_4	G-protein	AC(+)	N	5-Meo-Tryp	renzapride

Abbreviations: AC, adenylyl cyclase; IP3, phosphoinositide second messenger; K^+ Ch, K^+ channel

The classification of 5-HT receptors has led to the development of new and more selective 5-HT agonists and antagonists. Furthermore, an understanding of the 5-HT receptor subtypes has led to a reevaluation of old data on the neuroendocrine effects of 5-HT agonists and antagonists. Table 2 lists drugs that influence serotonergic transmission and their receptor specificity. Many of these drugs have been used to study the serotonergic control of hormone release. For example, MK-212, a 5-HT agonist (50), is both a 5-HT_1 (51) and a 5-HT_2 agonist (52). The most recently described 5-HT_2 agonists are DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane) and DOB (4-bromo-2,5-dimethoxyphenylisopropylamine), respectively (54, 55). However, DOI has a comparable affinity for 5-HT_{1C} receptors (39, 40). RU 24969 (5-methoxy-3-(1,2,3,4-tetrahydro-4-pyridinyl)-1H-indole) is a $5\text{-HT}_{1A}/5\text{-HT}_{1B}$ agonist (36), which also has a high affinity to ^{3}H-DOB binding sites, suggesting that it too is a 5-HT_2 agonist (53). 5-HT antagonists such as ritanserin and LY53857 bind with high affinity to 5-HT_2 and 5-HT_{1C} binding sites (56, 57). Spiperone binds with high affinity to 5-HT_{1A} and to 5-HT_2 sites but binds with a lower affinity to 5-HT_{1C} sites (40). The prototype of 5-HT_2 antagonists, ketanserin (58, 59), is also an α_1 adrenoceptor antagonist (60). Many drugs in Table 2 are discussed in subsequent sections with respect to their effect on hormone secretion.

SEROTONERGIC REGULATION OF ACTH/CORTICOSTERONE SECRETION

Corticotropin releasing factor-41 (CRF-41) is the predominant peptide-stimulating ACTH secretion from the anterior lobe of the pituitary gland (82, 83). Vasopressin only potentiates the effect of CRF on ACTH secretion (84). The hypothalamic CRF-neurons in the PVN release CRF from their nerve terminals into hypophysial portal vessels that transport it to the pituitary gland to stimulate ACTH secretion (82). Many 5-HT agonists stimulate ACTH,

Table 2 Drugs which affect serotonergic function

Drug	Specificity	References
	Agonists	
8-OH-DPAT	5-HT_{1A}	61
Buspirone	5-HT_{1A} part agonist/	62
	D_2 antagonist	64
Gepirone	5-HT_{1A}	62
Ipsapirone	5-HT_{1A}	62
5-MeODMT	5-HT_{1A}/(5-HT_2)	36
SM-3997	5-HT_{1A}	64
m-CPP	5-HT_{1B}/5-HT_{1C}	65
TFMPP	5-HT_{1B}/5-HT_2	53
RU 24969	5-HT_{1A}/5-HT_{1B}/5-HT_2	36, 53, 66
MK-212	5-HT_1/5-HT_2	50–52
Quipazine	5-HT_{1B}/5-HT_2	65
	(also 5-HT_3 ligand)	67
DOB	5-HT_2	55
DOI	5-HT_2/5-HT_{1C}	54, 68
MDMA	5-HT_{1A}/5-HT_2	68
Ly 165163	5-HT_{1A}	106
	Other	
P-chloroamphetamine	5-HT releaser	26
Fenfluramine	5-HT releaser	27
Norfenfluramine	5-HT releaser	69
Fluoxetine	5-HT uptake inhibitor	70
Citalopram	5-HT uptake inhibitor	71
Indalpine	5-HT uptake inhibitor	72
Zimelidine	5-HT uptake inhibitor	73
Clorgyline	MAO-A inhibitor	74
	Antagonists	
Xylamidine	5-HT may not cross BBB	75
Cyproheptadine	5-HT/Histl (nonselective)	76
Mianserin	5-HT (nonselective)	77
Methysergide	5-HT (nonselective)	78
Metergoline	5-HT (nonselective)	79
NAN 190	5-HT_{1A}	142
BMY 7378	5-HT_{1A}	143
Methiothepin	5-HT_1	38
Ketanserin	5-HT_2/5-HT_{1C}/α_1-adrenergic	57, 58, 60
Ritanserin	5-HT_2/5-HT_{1C}	40, 57
LY53857	5-HT_2/5-HT_{1C}	40, 56
LY281067	5-HT_2	80
Spiperone	5-HT_2/5-HT_{1A}/dopamine D_2	40
Odansetron	5-HT_3	45
ICS 205-930	5-HT_3/5-HT_4	48
MDL 72222	5-HT_3	43
Granisetron	5-HT_3	81
	Neurotoxins/depletors	
5,7-DHT	5-HT neurotoxin	30
MDA	5-HT neurotoxin	34
MDMA	5-HT neurotoxin	34, 68
P-chloroamphetamine	5-HT neurotoxin	33
PCPA	5-HT synthesis inhibitor	21

Table 3 5-HT Agonists which increase ACTH/corticoid secretion

Agonist	Reference
8-OH-DPAT	94, 96, 104, 105, 136
Ipsapirone	95, 96, 104, 135**
Buspirone	63, 95, 100, 104
LY 165163	106
Gepirone	95, 104
RU 24969	32
Quipazine	92, 103, 107
TFMPP	92
m-CPP	87, 99, 108*, 109**, 110**
5-MeODMT	92
MK-212	94, 96, 111**
DOI	112, 113
MDMA	114
P-chloroamphetamine	29, 97, 103
Fenfluramine	29, 93, 98, 102, 115**, 116, 117**, 118**
Norfenfluramine	119

Unless otherwise specified, all studies were performed in rats.
*Study performed in rhesus monkeys. **Study was performed in humans.

corticosterone, or cortisol secretion in experimental animals and in humans (85–103). An exception is fenfluramine, which increases corticosterone secretion by a nonserotonergic mechanism (102). Table 3 lists the 5-HT agonists capable of increasing plasma ACTH or corticosterone/cortisol concentrations in laboratory animals and in humans.

ANATOMICAL ORGANIZATION The origin of the serotonergic neurons that stimulate ACTH secretion has not been established. Lesions in the dorsal and median raphe nuclei do not inhibit the effect of p-chloroamphetamine on plasma corticosterone concentration (120). However, the lateral serotonergic neurons in the ventral midbrain (the B9 cell group) were spared in the study above (120), and could be the origin of the 5-HT fibers that stimulate CRF secretion. Mechanical lesions in the mediobasal hypothalamus and electrolytic lesions in the PVN block the effect of p-chloroamphetamine on plasma ACTH or corticosterone concentration (17, 101). Destruction of serotonergic nerve terminals in the PVN, by direct injection of 5,7-DHT, prevents the increase in plasma corticosterone in response to several stimuli (89). Serotonergic nerve terminals innervate CRF-immunoreactive cells in the PVN (13). Thus, the accumulated data indicate that 5-HT nerve terminals in the PVN stimulate CRF secretion by direct synaptic activation.

PHYSIOLOGICAL FUNCTION Serotonergic neurons could mediate the effect of insulin hypoglycemia on ACTH secretion (121). Insulin-induced hypogly-

cemia can be considered a stressor. Other stressors that increase ACTH secretion through a serotonergic mechanism are exposure to ether vapors (122) and immobilization (123). The anxiolytic 5-HT_{1A} agonists buspirone and ipsapirone inhibit the effect of conditioned fear (100, 124) and of immobilization (125) on corticosterone secretion. Both buspirone and ipsapirone decrease the firing rate of serotonergic neurons in the dorsal raphe nucleus (126, 127). Electrolytic lesions in the dorsal raphe nucleus inhibit the conditioned fear-induced increase in plasma corticosterone concentrations (128). The data so far suggest that 5-HT neurons are involved in the stress-induced increase in ACTH secretion.

Another possible physiological role for serotonergic neurons could be in the feedback loop by which glucocorticoids control ACTH secretion. Adrenalectomy changes 5-HT metabolism (129) and chronic administration of corticosterone also diminishes 5-HT-mediated behaviors in rats (130, 131). Glucocorticoid receptors are found in 5-HT cell bodies in the raphe region (132). Adrenalectomy increases 5-HT_1-binding density in the dorsal raphe nucleus, in the hypothalamus, and in the hippocampal formation (133, 134). The 5-HT_1-binding density returns to normal after injection of corticosterone (133). The data suggest that 5-HT neurons in the dorsal raphe nucleus and/or their nerve terminals in the hippocampus or hypothalamus participate in the feedback inhibition of ACTH secretion.

5-HT RECEPTOR SUBTYPE The 5-HT_{1A} agonists 8-OH-DPAT, ipsapirone, buspirone, and LY 165163 increase plasma corticosterone concentration in rats (94–96, 100, 104–106) and in humans (135). Pretreatment with 5-HT antagonists that have a high affinity for 5-HT_{1A} sites, such as spiperone, propranolol or pindolol, inhibits the effect of 8-OH-DPAT in rats (94, 136) and of ipsapirone in humans (135), Ketanserin, ritanserin, and altanserin did not prevent the effect of 8-OH-DPAT (94). These data suggest a role for 5-HT_{1A} receptors in regulating corticosterone secretion. However, some evidence supports a role of additional 5-HT receptors in stimulating ACTH secretion. For example, spiperone (which also is a 5-HT_{1A} antagonist) does not prevent the increase in plasma corticosterone concentration after injection of quipazine (94), whereas relatively high doses of LY53857 inhibit the effect of quipazine (92). Lower doses of LY53857 do not inhibit the elevation in plasma corticosterone concentration after injection of MK-212, but inhibit the effect of MK-212 on other hormones (renin and vasopressin; 96, 137). King et al (141) suggested that the MK-212-induced increase in ACTH is mediated by activation of 5-HT_{1C} receptors because mesulergine and metergoline inhibit the MK-212-induced increase in ACTH, whereas ketanserin, spiperone and pindolol are ineffective. Since ketanserin has approximately equal affinity for the 5-HT_2 and 5-HT_{1C} receptors (40), these data are not

sufficient to conclude that activation of 5-HT_{1C} receptors increases ACTH secretion. On the other hand, since spiperone has a higher affinity for 5-HT_2 than for 5-HT_{1C} sites, a role for 5-HT_{1C} receptors cannot be excluded. MDMA, a 5-HT_2 agonist, increases corticosterone secretion and this effect is inhibited by high doses of ketanserin but not by metergoline or (−)-pindolol, suggesting that 5-HT_2 receptors mediate the effect of this hallucinogenic drug (114). Similarly, DOI increases CRF secretion in vitro (113) and in vivo (112, 138). The effect of DOI in vivo is not inhibited by ritanserin (138), only partly inhibited by xylamidine (112, 138) and only minimally inhibited by a low dose (0.1 mg/kg, sc) of spiperone (138). In human male volunteers, the 5-HT_2 antagonist ketanserin did not prevent the cortisol-elevating effect of insulin-induced hypoglycemia (139). Similarly, ritanserin did not inhibit the 5-HTP-induced increase in plasma β-endorphin, β-LPH, and cortisol in male volunteers (140). Collectively, the data suggest that activation of 5-HT_{1A}, 5-HT_{1C} and/or 5-HT_2 receptors stimulates ACTH secretion.

SEROTONERGIC REGULATION OF β-ENDORPHIN SECRETION

Pharmacological studies indicate that serotonergic mechanisms stimulate β-endorphin secretion in rats (144, 145), and humans (146). The serotonergic stimulation of β-endorphin secretion can be inhibited by pretreatment with the synthetic corticosteroid dexamethasone.

ANATOMICAL ORGANIZATION Electrical stimulation of the median raphe nucleus increases plasma β-endorphin concentration, suggesting that the median raphe plays a role in β-endorphin release (144).

PHYSIOLOGICAL FUNCTION Destruction of serotonergic neurons by i.c.v. injections of 5,7-DHT inhibits the effect of immobilization on β-endorphin secretion, suggesting that stress utilizes 5-HT neurons to increase β-endorphin secretion (147).

5-HT RECEPTOR SUBTYPE The 5-HT receptor subtypes that stimulate β-endorphin secretion are similar to those that stimulate ACTH secretion, i.e. 5-HT_{1A} and 5-HT_2 receptors (94). Table 4 shows the 5-HT agonists, precursors, and releasers that stimulate β-endorphin secretion.

In summary, serotonergic neurons may regulate β-endorphin secretion by the same mechanisms that regulate the secretion of ACTH, namely by activating 5-HT_{1A} receptors (and possibly also 5-HT_2 receptors) on CRF neurons in the PVN.

Table 4 5-HT Agonists which increase β-endorphin secretion

Agonist	Reference
8-OH-DPAT	94
Quipazine	145, 147, 230
MK-212	94
L-tryptophan	145
Fenfluramine	118
Fluoxetine	146, 230
5-HTP	145, 146

SEROTONERGIC REGULATION OF PROLACTIN SECRETION

Prolactin is secreted by cells in the anterior lobe of the pituitary gland. The regulation of prolactin secretion is contolled by two hypothalamic factors: A tonic inhibitory input of dopamine, originating in the hypothalamic arcuate nucleus, and a putative prolactin releasing factor or hormone (PRF). PRF is released from an as yet unidentified site in the hypothalamus (148). Studies in rats and monkeys, and pharmacologically confirmed in humans, indicate that serotonergic neurons stimulate the secretion of prolactin. 5-HT precursors, agonists, and releasers increase prolactin secretion when they are injected systemically or i.c.v. (32, 101, 102, 109, 149–156).

ANATOMICAL ORGANIZATION Most studies have indicated that 5-HT-containing neurons in the dorsal raphe nucleus stimulate prolactin secretion (157–159). One study suggests that both dorsal and median raphe nuclei are involved in the serotonergic stimulation of prolactin secretion (160). However, the authors did not present histological or biochemical evidence of selective destruction of the dorsal and/or median raphe nuclei. The serotonergic nerve terminals that stimulate prolactin secretion are located in the hypothalamus (101). Electrolytic lesions in the PVN inhibit the effects, on prolactin concentration, of 5-HTP or of restraint and ether stress (16). Because 5-HTP can enter nonserotonergic nerve terminals, this study does not provide conclusive evidence for a role of 5-HT nerve terminals in the PVN in the regulation of prolactin secretion. However, this study does suggest a role for either cells or nerve terminals in the PVN in the physiological regulation of prolactin secretion. Injection of 5,7-DHT into the anterior hypothalamus of female rats inhibits the suckling-induced increase in prolactin secretion (161). In this study, the authors determined the placement of the injection by histology (Nissl stain), but did not analyze the tissue biochemically or im-

munocytochemically to determine the diffusion and thus chemical destruction pattern of the neurotoxin. Therefore, caution is needed in accepting the conclusion that the anterior hypothalamus is the only target of 5-HT nerve terminals that increase prolactin secretion. To summarize, cells in either the PVN, the anterior hypothalamus, or both, play a role in the regulation of prolactin secretion.

Other hypothalamic sites may also play a role in the regulation of prolactin secretion. There is evidence that the serotonergic stimulation of prolactin secretion is not mediated by inhibition of the dopaminergic tuberoinfundibular neurons but that 5-HT stimulates the release of PRF from neurons in the hypothalamus (150, 162). Several studies provided evidence that release of vasoactive intestinal polypeptide (VIP) into the portal vessels mediates the serotonergic stimulation of prolactin secretion. The VIP neurons in the suprachiasmatic nucleus are innervated by serotonergic nerve terminals (163, 164) and release their content into the pituitary portal vessels, to reach the pituitary lactotrophes and increase prolactin secretion (165–167). Suckling induces a significant increase in plasma VIP and prolactin concentration in nursing women (168). These data suggest that VIP could be an important, though not necessarily an exclusive, mediator of the serotonergic stimulation of the prolactin secretion, especially as administration of VIP antisera inhibits, but does not completely block the effect of 5-HTP on prolactin secretion (165, 167).

PHYSIOLOGICAL ROLE Suckling-induced prolactin secretion in women is disrupted by 5-HT antagonists (169). Similar effects were observed in rats. Depletion of 5-HT stores with PCPA inhibits suckling-induced prolactin secretion (170). Lesions in serotonergic neurons in the dorsal raphe nucleus block suckling-induced prolactin secretion in female rats (157). Injection of 5,7-DHT into the anterior hypothalamus blocks suckling-induced prolactin secretion (161). Since suckling induces a significant increase in plasma VIP concentration with a concomitant increase in plasma prolactin concentration (168), 5-HT neurons could mediate suckling-induced prolactin secretion through the release of VIP in both humans and laboratory rats (see above). Another physiological condition that uses 5-HT neurons in the dorsal raphe nucleus to increase prolactin secretion in female rats is the estrogen-induced prolactin surge (158). Finally, 5-HT neurons might mediate the diurnal but not the nocturnal prolactin surge in female rats between days 7 and 9 of their pregnancy (171).

5-HT RECEPTOR SUBTYPE The stimulation of prolactin secretion is mediated by several 5-HT receptor subtypes. These include 5-HT_{1B} receptors, 5-HT_2 receptors, and/or an as yet unidentified 5-HT receptor subtype. This

conclusion is based on several observations. The 5-HT_{1A} agonists ipsapirone and 8-OH-DPAT do not consistently elevate plasma prolactin concentration (172–173). The inability of ipsapirone to increase plasma prolactin concentration could be due to its dopamine D_2 agonist properties (174). However, the inability of 8-OH-DPAT to consistently increase prolactin secretion remains to be explained. Buspirone increases plasma prolactin concentration (63, 100) due to the blockade of D_2 receptors in the pituitary (63). These studies do not support, but cannot exclude, a possible involvement of the 5-HT_{1A} receptor in stimulating prolactin secretion. The possible involvement of 5-HT_2 receptors in stimulating prolactin secretion is less well understood. LY53857 does not prevent an increase of plasma prolactin after the release of endogenous 5-HT by fenfluramine (173) or after injection of RU 24969 (32). Ketanserin does not block the increase in plasma prolactin after injection of 5-methoxy-N,N-dimethyltryptamine (5-MeODMT), quipazine and 5-HTP (155). Ritanserin also fails to block the increase in plasma prolactin after administration of l-tryptophan to male human volunteers (175), or after intravenous injection of a high dose of 8-OH-DPAT to rats (86). Metergoline binds to both 5-HT_1 and to 5-HT_2 receptors, and also inhibits the effect of m-CPP (a putative 5-HT_{1B} agonist) on plasma prolactin concentration in human volunteers (110). The effect of 8-OH-DPAT is not inhibited by pindolol, but is attenuated by pretreatment with metergoline (86). Moreover, metergoline, but not ketanserin, inhibits the increase in plasma prolactin concentration after injection of 5-HT into the mediobasal hypothalamus (176). However, metergoline has dopamine agonist activity and can inhibit the effect of 5-HT agonists by inhibiting prolactin secretion via direct activation of D_2 receptors in the pituitary (107). This result could also occur with LY53857, an ergot derivative. The data, so far, do not support a prominent role for 5-HT_2 receptors in the regulation of prolactin secretion.

Recently, we tested DOI (a 5-HT_{1C} and 5-HT_2 agonist) and found that it increases plasma prolactin levels (138). This effect was inhibited by ritanserin, suggesting that activation of 5-HT_2 or 5-HT_{1C} receptors can increase prolactin secretion (138). It is presently unclear whether DOI can produce this effect in humans as well. Quipazine raises prolactin concentration in rats (159, 178) but not in human volunteers (179). In contrast, m-CPP increases plasma prolactin both in rats (87, 177) and in humans (109). It is interesting to note that human brains apparently lack 5-HT_{1B} recognition sites (180). Consequently, it is unclear which 5-HT receptors stimulate prolactin secretion in humans. Table 5 summarizes 5-HT agonists and releasers that stimulate prolactin secretion.

According to some evidence, the 5-HT receptors that increase prolactin secretion are sensitive to changes in serotonergic neurotransmission. Destruction of 5-HT nerve terminals, by i.c.v. injection of 5,7-DHT, results in a shift

Table 5A 5-HT agonists that increase prolactin secretion

Agonist	Reference[1]
TFMPP	150
m-CPP	87, 99**, 108*, 109**, 110**, 150, 177
RU 24969	32, 66, 173
Quipazine	107, 159, 178, 231
5-MeODMT	155, 231
MK-212	111**, 173
Buspirone	63**, 100
8-OH-DPAT (in female rats)	172
DOI	138
P-chloroamphetamine	159, 232, 233
Fenfluramine	93, 115**, 118**, 156**, 225, 231, 233, 234**, 235**
Norfenfluramine	69, 119

[1]Unless specified as otherwise, all other studies were performed in rats.
*Study performed in rhesus monkeys. **Study performed in humans.

Table 5B 5-HT agonists that do not increase prolactin secretion

Agonist	Reference
Ipsapirone (male rats)	173
8-OH-DPAT (male rats)	173

to the left of the dose-response effect of m-CPP (177) and RU 24969 on prolactin levels in rats (32). These results suggest that postsynaptic 5-HT_{1B} receptors (or other 5-HT receptor subtypes that are activated by m-CPP and RU 24969) have become supersensitive.

The combined data suggest that serotonergic neurons in the dorsal raphe nucleus project to hypothalamic sites to stimulate prolactin secretion by activating 5-HT_{1B} and/or 5-HT_2 receptors or as yet unclassified 5-HT receptors located on putative PRF neurons. The PRF could be the VIP neurons in the hypothalamus.

SEROTONERGIC REGULATION OF RENIN SECRETION

Renin is the rate-limiting enzyme in the formation of angiotensin II. Renin is synthesized, stored in, and released from juxtaglomerular cells in the afferent arterioles of the kidney (181, 182). Angiotensin II is a peptide with profound regulatory influence on blood volume, blood pressure, and sodium balance. Renin secretion is regulated by renal mechanisms such as sodium concentration in the distal tubules, renal perfusion pressure, and sympathetic nervous activity (181). Early evidence suggesting a role of 5-HT in the regulation of

renin release was obtained when cyproheptadine inhibited the increase in plasma renin activity in humans after injection of the diuretic drug furosemide (183). Administration of l-tryptophan to humans increases renin release. This increase was prevented by cyproheptadine (184). Infusion of 5-HTP and l-tryptophan to pentobarbital-anesthetized dogs increases plasma renin activity (185). Release of endogenous 5-HT increases renin release since p-chloroamphetamine and fenfluramine increase plasma renin activity in conscious rats in a dose-dependent manner (103, 186). The effect of both drugs is blocked by pretreatment with PCPA (103, 186). Furthermore, the effect of fenfluramine is prevented by pretreatment with 5-HT uptake inhibitors but is enhanced after 5-HT stores are enlarged by injection of l-tryptophan (186). Table 6 shows that other 5-HT agonists increase plasma renin activity. Among them are DOI, MK-212, quipazine, RU 24969, m-CPP, and TFMPP (32, 96, 138, 187–189). Recent studies (188, 190) suggest that DOI and quipazine increase renin release by activating peripheral 5-HT_2 receptors, which increase arterial pressure and decrease renal blood flow, thereby activating the renal baroreceptor reflex. This conclusion is based on the observation that the peripheral 5-HT antagonist xylamidine inhibits the effect of DOI (186) and the lack of effect of i.c.v. injection of quipazine on plasma renin activity (190). However, i.c.v. injection of DOI at doses (100–200 μg/kg) lower than the peripherally effective minimal dose (500 μg/kg, i.p.) increases renin release (194). Consequently, DOI could act both at peripheral and central sites to increase renin release. Several 5-HT agonists increase blood pressure, including m-CPP (191) and quipazine (190) but not MK-212 (192). These data ought to encourage investigators to consider the hemodynamic effects of direct and indirect 5-HT agonists before concluding that a brain site is involved. RU 24969 increases renin release when injected directly into the PVN at a dose (10 μg/kg) 50-fold lower than the minimally effective intraperitoneal dose (189). Fenfluramine also increases renin release without affecting blood pressure or heart rate (186). In short, not all 5-HT agonists increase renin secretion because of peripheral cardiovascular effects.

ANATOMICAL CONSIDERATIONS The evidence suggests that 5-HT neurons in the dorsal raphe and their nerve terminals in the hypothalamus increase renin release (17, 120). Lesions in the mediobasal hypothalamus (193) or posterolateral knife cuts that destroy fibers ascending into the hypothalamus, block the increase in plasma renin activity produced by p-chloroamphetamine. Anterolateral deafferentation through the retrochiasmatic area is ineffective (193), suggesting that an ascending serotonergic pathway stimulates renin release by stimulating sites within the mediobasal hypothalamus. The PVN could be the site containing the neurons mediating the serotonergic stimulation of renin release. Electrical stimulation of neurons

Table 6A 5-HT agonists that increase renin secretion

Agonist	Reference
DOI	138, 186
m-CPP	213
MK-212	96
5-MeODMT	Van de Kar (unpublished observations)
Quipazine	103, 187
RU 24969	32
TFMPP	199
Fenfluramine	186
P-chloroamphetamine	103, 120, 195, 196, 198
5-HTP	185

Table 6B 5-HT agonists that do not increase renin secretion

Agonist	Reference
Buspirone	201
8-OH-DPAT	96
Ipsapirone (low doses)	124

in the PVN increases plasma renin activity (18). Electrolytic lesions in either the hypothalamic PVN or the ventromedial nucleus (VMN) prevent the p-chloroamphetamine-induced increase in plasma renin activity (17). Finally, as mentioned above, injection of RU 24969 into the PVN increases plasma renin activity (189). The data suggest that 5-HT receptors in the PVN stimulate renin secretion from the kidneys. A possible role of the VNM in renin release warrants investigation.

How do the serotonergic receptors in the brain send the stimulus to the kidneys to release renin? One study suggested that the sympathetic nervous system mediates this message from the brain to the kidneys, because β-adrenoceptor antagonists inhibit the p-chloroamphetamine-induced increase in plasma renin activity (195). This seems unlikely because adrenal medullectomy combined with chemical sympathectomy (using 6-hydroxydopamine) failed to inhibit the effect of p-chloroamphetamine or of fenfluramine on plasma renin activity (196). Likewise, spinal transection proximal to the exit of the adrenal and renal nerves, between the first and second thoracic vertebrae (T1-T2), failed to inhibit the effect of p-chloroamphetamine on plasma renin activity (196). An alternative theory suggests a hormonal mediation of the stimulation of renin release. A bloodborne renin releasing factor (RRF) was found to transmit the serotonergic stimulus from the brain to the kidneys (198, 199). The RRF is a peptide found in high concentration both in rat and bovine hypothalamus (199). P-chloroamphetamine, MK-212, and TFMPP

increase both plasma RRF and renin activity, suggesting that activation of 5-HT receptors increases the release of RRF into the circulation, leading to stimulation of renin release (189, 199). A second mediator could be induction of sodium loss, triggering the macula densa mechanism in the distal tubules of the kidney. I.c.v. injections of either p-chloroamphetamine or 5-HT produce natriuresis in rats (197). P-chloroamphetamine-induced natriuresis is prevented by depletioin of 5-HT stores or when the rats were pretreated with a 5-HT uptake inhibitor. RRF might mediate this effect but no data support this hypothesis.

PHYSIOLOGICAL ROLE Renin is the only endocrine factor known to be sensitive both to inhibition and to stimulation of serotonergic neurotransmission. Unlike ACTH and prolactin, which are not decreased in plasma of rats whose brain 5-HT neurons were destroyed, plasma renin activity is decreased by destruction of brain serotonergic neurons (103, 120). The decrease in plasma renin activity after depletion of hypothalamic 5-HT stores with PCPA is reversed by a subsequent replenishment of hypothalamic 5-HT stores by injection of 5-HTP (103). These studies suggest that serotonergic neurons maintain plasma renin activity at a homeostatic balance. Injection of PCPA also inhibits the increase in plasma renin activity after adrenalectomy, suggesting that serotonergic mechanisms play a role in the homeostatic mechanisms that interrelate electrolyte balance (aldosterone) to renin release (200).

Stress is another physiological condition that might utilize 5-HT neurons to increase renin secretion. The anxiolytic 5-HT_{1A} agonists buspirone and ipsapirone inhibit the increase in renin release after exposure of rats to conditioned fear (124, 201) or immobilization (125). As described above, these anxiolytic drugs inhibit the firing of dorsal raphe neurons (126, 127). Since electrolytic lesions in the dorsal raphe block the stress-induced increase in renin release (202), 5-HT neurons could be involved in mediating the stress-induced stimulation of renin release. However, a 5-HT_2 antagonist does not prevent stress-induced increase in renin release (128) but it does prevent the pharmacological stimulation of renin release (96). These observations suggest that 5-HT_{1A} receptors could be involved in the "anxiety" phenomenon (203) but not necessarily in direct mediation of stress-induced renin release.

Sleep is a third physiological condition that could use 5-HT neurons to control renin secretion. Serotonergic neurons have been proposed to play a prominent role in the induction and maintenance of sleep, particularly in the mechanisms that reduce vigilance before the onset of sleep (204, 205). Brandenberger et al (206–208) described a rhythmic cycle of plasma renin activity in humans associated with their sleep stages. Plasma renin activity increases during non-REM sleep and decreases during REM sleep. Serotonergic neurons could play a role in this phenomenon.

5-HT RECEPTOR SUBTYPE Ample evidence suggests that 5-HT_2 receptors stimulate renin secretion. For example, low doses of LY53857 prevent the increase in plasma renin activity produced by fenfluramine and by MK-212 (96). The effect of R U 24969 and DOI on renin relase is blocked by low doses of LY53857 and ritanserin, suggesting that the effect of RU 24969 is mediated through activation of 5-HT_2 or 5-HT_{1C} receptors (188, 194). DOI has similar affinity for 5-HT_2 and 5-HT_{1C} receptors, but spiperone has a higher affinity for 5-HT_2 than for 5-HT_{1C} receptors. We used spiperone to determine whether 5-HT_2 or 5-HT_{1C} receptors mediate the renin-elevating effect of DOI. Injection of low doses of spiperone (0.01 or 0.1 mg/kg, s.c.) inhibited the effect of DOI on plasma renin activity (138), suggesting that DOI increases renin release by activating 5-HT_2 receptors. There is little evidence for an involvement of 5-HT_{1A} receptors in renin release. 8-OH-DPAT (96) and buspirone (201) *decrease* plasma renin activity while ipsapirone increases plasma renin activity only at high doses (96). These findings suggest that stimulation of 5-HT_2 receptors enhances renin release whereas stimulation of 5-HT_{1A} receptors either decreases or is without a significant role in the control of renin release. The 5-HT receptors that stimulate renin release are sensitive to changes in the integrity of the nerve terminals. Destruction of brain 5-HT neurons, by i.c.v. injection of 5,7-DHT, produces a leftward shift of the dose-response effect of RU 24969 on plasma renin activity (32), suggesting supersensitivity of brain 5-HT_2 receptors that stimulate renin release (32). The role of 5-HT_{1B} or 5-HT_3 receptors in the regulation of renin release has not been investigated.

The data collectively indicate that serotonergic neurons that originate in the dorsal raphe nucleus and terminate in the hypothalamic PVN or VMN stimulate renin secretion by activating 5-HT_2 receptors.

SEROTONERGIC REGULATION OF VASOPRESSIN SECRETION

Neurons in the PVN and supraoptic nucleus (SON) release vasopressin into the circulation through their nerve terminals in thc neural lobe of the pituitary gland. Early evidence for a role in vasopressin secretion included the ability of several agonists to increase plasma vasopressin concentration. These included TFMPP (209), fluoxetine (210), quipazine, and fenfluramine (211). The effect of fenfluramine was blocked in rats pretreated with PCPA (211).

ANATOMICAL CONSIDERATIONS Electrical stimulation of the dorsal raphe nucleus decreases urine output, suggesting that 5-HT neurons in the dorsal raphe stimulate vasopressin secretion (229). P-chloroamphetamine increases plasma vasopressin concentration and this effect was blocked by a postero-

lateral deafferentation of the hypothalamus (137). Immunocytochemical staining (9) showed few serotonergic nerve fibers in the magnocellular subdivisions of the SON and PVN. Therefore, it is unlikely that serotonergic nerve terminals directly stimulate the vasopressinergic cells in the SON or PVN. However, it is possible that an interneuron mediates the serotonergic stimulation of vasopressin secretion. The serotonergic stimulation of vasopressin secretion is not mediated by increased plasma angiotensin II concentrations (212).

PHYSIOLOGICAL ROLE Water deprivation increases vasopressin secretion by activating 5-HT neurons. PCPA and i.c.v. injection of 5,7-DHT decreased forebrain 5-HT concentration and prevented the increase in plasma vasopressin concentration after water deprivation (211). Water deprivation can increase vasopressin secretion by increasing osmotic pressure and decreasing blood volume. The 5-HT neurons regulating vasopressin secretion mediate the osmotic but not hypovolemic stimulation of vasopressin secretion (215) because destruction of 5-HT neurons, by i.c.v. injection of 5,7-DHT, abolished the osmotic stimulation of vasopressin secretion by hypertonic saline (215). Hypovolemia-induced increase in vasopressin secretion is not inhibited by destruction of 5-HT neurons (215). Injection of PCPA blocks the osmotically induced increase in hypothalamic concentration of vasopressin and oxytocin mRNA, supporting the conclusion that 5-HT neurons mediate the osmotic stimulation of vasopressin release (216).

5-HT RECEPTOR SUBTYPES The studies so far (137, 213, 214) suggest that either 5-HT_2 or 5-HT_{1C} receptors stimulate vasopressin secretion. MK-212 produces a dose-dependent increase in plasma vasopressin concentration that can be blocked by low dose (0.1 mg/kg, i.p.) of LY53857 and inhibited by a high dose of ritanserin (2.5 mg/kg). Many 5-HT agonists are ineffective in increasing plasma vasopressin concentration. Among them are 8-OH-DPAT, ipsapirone, RU 24969 (137), m-CPP, and DOI (213, 214). The lack of stimulation of vasopressin secretion by DOI is puzzling since the effect of MK-212 on vasopressin secretion was totally blocked by low doses of LY53857. MK-212 is a less selective 5-HT agonist than DOI. For example, MK-212 increases homovanilic acid concentration in the striatum and MOPEG concentrations in rat brains (50). It also increases the accumulation of DOPA after decarboxylase inhibition, suggesting stimulation of dopaminergic neurotransmission (50). The data are currently insufficient to conclude whether the serotonergic regulation of vasopressin secretion is mediated by one receptor subtype or whether a more complex relationship among multiple neurotransmitter neurons results in increased vasopressin secretion after injection of MK-212. Table 7 lists the 5-HT agonists that

Table 7A 5-HT agonists that increase vasopressin secretion

Agonist	Reference
Quipazine	211
MK-212	137
TFMPP	209
Fenfluramine	211
P-chloroamphetamine	137
Fluoxetine	210

Table 7B 5-HT agonists that do not increase vasopressin secretion

Agonist	Reference
RU 24969	137
DOI	214
m-CPP	213
8-OH-DPAT	137
Ipsapirone	137

increase plasma vasopressin concentration. Serotonergic neurons may not directly stimulate vasopressin secretion, since several 5-HT agonists failed to increase plasma vasopressin concentrations. Instead, they could modify the excitability of vasopressinergic neurons to other neurons (or osmotic stimuli) to increase vasopressin secretion.

SEROTONERGIC REGULATION OF OXYTOCIN SECRETION

Oxytocinergic neurons in the PVN and SON release oxytocin into the circulation via their nerve terminals in the posterior lobe of the pituitary gland. Until recently, very little was known about the regulation of oxytocin secretion by serotonergic neurons. An early observation was that injection of PCPA 8 hours before suckling inhibited the milk ejection reflex (217). A subsequent injection of 5-HTP to the PCPA-treated rats reversed the effect of PCPA, suggesting that intact serotonergic neurotransmission is needed to induce the secretion of oxytocin during suckling (217). The 5-HT releasers p-chloroamphetamine and fenfluramine increase plasma oxytocin concentrations (214). D-fenfluramine is effective at a lower dose (5 mg/kg, i.p.) than the l-isomer of fenfluramine (20 mg/kg, i.p.). Since d-fenfluramine is considered the more selective 5-HT releaser (27), these results suggest that the effect of fenfluramine on oxytocin release are mediated though the release

Table 8A 5-HT agonists that increase oxytocin secretion

Agonist	Reference
MK-212	214
D-fenfluramine	214
L-fenfluramine (less potent)	214
P-chloroamphetamine	214
DOI	214
m-CPP	214

Table 8B 5-HT agonists that do not increase oxytocin secretion

Agonist	Reference
RU 24969	214

of endogenous 5-HT. Table 8 lists 5-HT agonists that increase oxytocin secretion.

ANATOMICAL ORGANIZATION Immunocytochemical staining (9) showed few serotonergic nerve fibers in the magnocellular subdivisions of the SON and PVN. Therefore, it is unlikely that serotonergic nerve terminals directly stimulate the oxytocin-containing cells in the SON or PVN.

PHYSIOLOGICAL ROLE Serotonergic neurons might mediate the osmotic stimulation of oxytocin in a manner similar to their effect on the osmotic stimulation of vasopressin secretion. As was stated above, PCPA blocked the osmotically induced increase in hypothalamic concentration of vasopressin and oxytocin mRNAs (216). Suckling-induced oxytocin secretion is also mediated by serotonergic neurons (217).

5-HT RECEPTOR SUBTYPES The limited data suggest an involvement of 5-HT_2 and 5-HT_{1C} receptors. MK-212 increased plasma oxytocin concentrations and this effect was partly inhibited by a high dose (2.5 mg/kg, i.p.) of ritanserin. This dose of ritanserin more effectively inhibited the effect of MK-212 on plasma vasopressin concentrations (see above). Thus, these data suggest that 5-HT_2 receptors only partly mediate the serotonergic stimulation of oxytocin secretion. RU 24969 was ineffective in increasing plasma oxytocin concentration. Other 5-HT agonists that effectively increase plasma oxytocin concentrations include DOI and m-CPP (214). The DOI-induced increase in plasma oxytocin concentration was inhibited by ritanserin

(0.01 and 0.1 mg/kg, i.p.) and by spiperone (0.01 and 0.1 mg/kg, s.c.), suggesting that 5-HT_2 rather than 5-HT_{1C} receptors mediate this effect (214). Finally, i.c.v. injection of DOI at a dose (200 μg/kg) lower that the peripherally effective dose (500 μg/kg) increased plasma oxytocin concentration (214).

The combined data suggest that serotonergic neurons increase oxytocin secretion and could mediate the osmotic stimulation and suckling-induced stimulation of oxytocin secretion. The receptor subtypes include 5-HT_2 and possibly other 5-HT receptors.

5-HT AND GROWTH HORMONE SECRETION

Growth hormone (GH) secretion is inhibited by somatostatin and stimulated by a releasing factor (GH-RH), both of which are released from neurons in the hypothalamus. The role of serotonergic neurons in the regulation of growth hormone (GH) secretion is controversial. Several studies indicate that 5-HT agonists increase plasma GH concentration (108, 109, 218–220), while others found that 5-HT agonists are ineffective or even lower plasma GH concentration (87, 111, 115, 221). On the other hand, there is evidence that the elevation in plasma GH after injection of the α_2 agonist clonidine is mediated through a serotonergic mechanism (222).

ANATOMICAL ORGANIZATION Serotonergic nerve terminals make synaptic connections with somatostatin-immunoreactive cell bodies in the hypothalamic periventricular nucleus (223). Anti-somatostatin serum reversed the metergoline-induced decrease in GH secretion, suggesting that the serotonergic regulation of GH secretion could be mediated by inhibition of somatostatin release into the pituitary portal vessels (224). This disinhibitory effect of 5-HT on GH secretion could account for the confusing data obtained after administration of various 5-HT agonists. Contrasting with this conclusion is the observation that intravenous injection of anti-GRF serum almost completely blocked the increase in plasma GH after i.c.v. injection of 5-HT (219). Hence, there could be both a serotonergic stimulation of GRF and a serotonergic inhibition of somatostatin. It is not clear why several investigators cannot find an increase in plasma GH after injection of 5-HT agonists.

5-HT AND LUTEINIZING HORMONE (LH)

Evidence for a role of 5-HT in LH secretion is neither abundant nor conclusive (225–228). Destruction of serotonergic perikarya in the midbrain and 5-HT nerve terminals in the hypothalamus decreased plasma LH concentration in male rats and decreased and preovulatory LH surge (12, 31, 225).

Some 5-HT agonists increase LH concentration in female rats if they are administered at a critical time before the preovulatory LH peak occurs (228). In contrast, 5-HT agonists do not elevate LH concentration, especially in males (154). The lack of direct stimulation of LH secretion by 5-HT agonists, especially in male rats, suggests that the serotonergic regulation of LH secretion may involve disinhibition rather than a direct stimulation of LH-RH release by serotonergic nerve terminals in the hypothalamus.

CONCLUSIONS

The available evidence strongly supports a stimulatory role for serotonergic neurons in the regulation of ACTH, β-endorphin, prolactin, renin, oxytocin, and vasopressin secretion. I have discussed the physiological importance, the serotonergic pathways and the 5-HT receptor subtypes that are involved. The evidence is weaker for an involvement of serotonergic neurons in LH and GH secretion. With respect to specific receptors, the data suggest that 5-HT_{1A} and 5-HT_2 receptor activation increases ACTH and β-endorphin secretion, whereas activation of 5-HT_2 receptors (but not 5-HT_1 receptors) increases renin and possibly also oxytocin and vasopressin secretion. The stimulation of prolactin secretion might be mediated, at least in rats, by activation of 5-HT_{1B} receptors. Selective 5-HT_{1A} and 5-HT_{1B} antagonists are needed to clear the ambiguity concerning the role of the 5-HT_1 receptor family in the regulation of neuroendocrine function. Finally, little is known about the involvement of 5-HT_3 receptors in hormone secretion, a subject that can now be studied using 5-HT_3 antagonists.

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