Ann. Rev. Pharmacol. Toxicol. 1982. 22:555–98

GONADAL STEROID ACTION ON THE BRAIN: NEUROCHEMISTRY AND NEUROPHARMACOLOGY

Bruce S. McEwen and Bruce Parsons

The Rockefeller University, New York, New York 10021

INTRODUCTION

Steroid hormones of the gonads and adrenals influence the brain and alter the affective state as well as overt behavior and neuroendocrine function. These actions are manifested in various ways and at various levels of observation and experimentation. For example, in female vertebrates of many species, estrogens prime the brain and pituitary gland and make possible the occurrence of ovulation and sexual receptivity. Androgens, on the other hand, facilitate male reproductive behavior including vocalizations (e.g. song in passerine birds, mate-calling in frogs), defense of territory and related aggressive displays, and copulatory behavior. At another level of analysis, estrogen treatment counteracts tardive diskinesia and L-DOPA-induced diskinesia (1) and has antidepressant effects in women resistant to other kinds of antidepressant drug therapy (2). Moreover, changes in estrogen and progestin levels are often linked to the emotional lability associated with the premenstrual and postpartum periods (3, 4).

Studies of the action of steroid hormones on the brain have progressed to a point where specific mechanisms and brain sites of action are now recognized. Especially important to the neuropharmacologist are those aspects of mechanism which have begun to deal with hormonal modification of properties and functions of synapses. Synaptic function and neurotransmission are indeed the common currency for the analysis of neuroendocrine events and hormone-regulated behaviors, as well as other aspects of brain function; and the study of drugs which modify neurotransmission through blockade of synthesis, degradation, reuptake, and recep-

0362-1642/82/0415-0555$02.00

tors has produced a substantial literature implicating certain neurotransmitter candidates in those neuroendocrine and behavioral events. This article will summarize both hormone (especially gonadal steroid) action on synaptic properties and functions and the neuropharmacology of two well-studied hormone-regulated events, the control of feminine sexual behavior and ovulation in rodents. Out of this summary will emerge, we hope, some generalizations which will help to guide future research.

MECHANISMS OF STEROID ACTION ON NERVE CELLS

Steroid hormones can alter nerve cell activity by direct actions on membrane as well as by indirect actions at the genomic level which are mediated by intracellular receptors (Figure 1). Direct effects are typically of short latency and brief duration. For example, 17β estradiol hemisuccinate inhibits cell firing within milliseconds when applied iontophoretically in the preoptic area and hypothalamus (4a). This effect is not produced by the 17 α epimer. Indirect effects, in contrast, are of longer latency and duration. For example, activation of sexual receptivity in female rats by estradiol, which has an 18- to 24-hour onset latency (5, 6) and which outlasts the removal of the estrogen stimulus by 24 to 36 hours (6), is blocked reversibly by inhibitors of RNA and protein synthesis (see 7–9). Furthermore, estradiol treatment has been shown to stimulate RNA polymerase II activity in the rat hypothalamus for a number of hours (10).

There are steroid effects that fall between these two extremes in terms of latency and duration. Such is the case for the facilitation of sexual receptivity and proceptivity in estrogen primed rats by progesterone, which may occur within 30–60 min after administration, and which persists for only a few hours after plasma clearance (11–13). Nevertheless, rapid progesterone effects on the facilitation of feminine reproductive behavior can be blocked reversibly by a protein synthesis inhibitor, anisomycin (8).

Another question pertaining to the mechanism of steroid effects is whether they are primary or secondary. Primary effects are those caused by an interaction of hormone with the responding cells. Secondary effects are those mediated by another hormone. For example, prolactin, which is secreted as a result of stimulation by estradiol, is implicated as mediator of a number of estrogen effects on neurotransmitter turnover in the brain (14, 15). Similarly increased noradrenergic neural activity and release of noradrenaline from nerve endings appears to be responsible for increased accumulation of cyclic adenosine 5'-monophosphate in estrogen-treated neural tissue (16, 17).

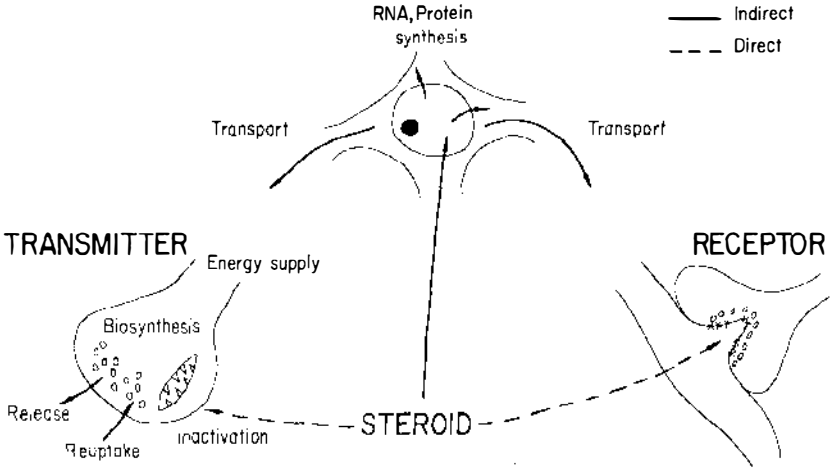

Figure 1 Genomic and nongenomic effects of steroid hormones on pre- and postsynaptic events. Nongenomic effects (dashed line) may involve the action of the hormone on the pre- or postsynaptic membrane to alter permeability to neurotransmission or their precursors and/or functioning of neurotransmitter receptors. Genomic action of the steroid (unbroken line) leads to altered synthesis of proteins, which, after axonal or dendritic transport, may participate in pre- or postsynaptic events. Reprinted from McEwen et al (68) by permission of Raven Press.

Whether direct or indirect, primary or secondary, steroid effects on neural tissue must be regarded also in terms of their relation to neuronal electrical activity and synaptic transmission, which constitute the common currency by which the mechanisms of brain function and behavior are analyzed. Categories of demonstrated steroid effects on cell functions related to neurosecretion and synaptic transmission include release of neurosecretory products, uptake, capacity for enzymatic inactivation, biosynthetic capacity, and receptor sensitivity to neurosecretion. As will become evident in the next section, work on this topic has brought to light examples of each category. Therefore, we know in principle that these various aspects of neuronal function can be regulated by steroids.

STEROID EFFECTS ON VARIOUS ASPECTS OF NERVE CELL STRUCTURE AND FUNCTION

Steroid hormones have been shown to influence various aspects of nerve cell structure and function. Certain hormones promote neuronal growth at certain stages of development and regulate synaptic properties which are related to neural transmission. In this section, various influences of steroid

hormones will be described according to six categories. At the end of each category there will be a brief discussion of likely or possible mechanisms of the steroid effects.

Effects of Gonadal Steroids on Neuronal Growth and Morphology

Gonadal steroids influence the growth of neuronal processes during brain development and after brain damage in the adult. In explants of hypothalamus and preoptic area from newborn mice, both testosterone and estradiol stimulate outgrowth of neurites (18–20). In the arcuate nucleus region of rat hypothalamus, estrogen treatment prior to puberty increases the number of axodendritic synapses (21). Moreover, an enhancing effect of estradiol on synapse formation in the arcuate nucleus is seen as a result of hypothalamic deafferentation of adult rats. New synapses are found to occupy sites vacated by degenerating afferents cut by the surgery (21).

Although the adult brain is not believed to grow markedly, if at all, there is one reported instance of changes in neuronal size in hormone-sensitive cells of undamaged adult brains. In the canary, the size of neurons in several androgen-sensitive song control areas decreases markedly after castration (22). The adult brain also may be damaged irreversibly by excess steroids: i.e. there is a report that injection of 2 mg estradiol valerate into young cycling female rats induces delayed and prolonged degenerative changes in the arcuate nucleus and leads to disrupted gonadal cyclicity (23).

COMMENT ON MECHANISM In the case of testosterone and estrogen effects on neurite outgrowth, such outgrowth has been seen in two cases to emanate from cell groupings which contain intracellular estrogen receptors (20). This implies that outgrowth is a primary effect of the steroid, although it is also possible that the steroid action is permissive and allows other growth-promoting agents to produce their effects. Such outgrowth and other morphological consequences of gonadal hormone action in early development are regarded as having an important role in brain sexual differentiation (24). None of the other effects described above has so far been analyzed with regard to mechanism.

Neuronal Electrical Activity

Neuronal firing rates and responses to electrical stimulation are different in gonadectomized (GDX) rats receiving hormone replacement therapy than in GDX controls (25–28). Such effects are found in the preoptic area (POA) and hypothalamus (Hyp) and consist of increased as well as decreased basal firing rates, changes in the absolute refractory period, alterations in magnitude and even direction of the electrical response to sensory stimulation,

and decreases in the threshold for activation of specific neural pathways (e.g. from POA to Hyp). Single systemic injections of gonadal steroids also may lead to altered neuronal firing, with onset latencies on the order of minutes (29–31). These effects are also found in the POA and Hyp and consist of both transient increases and decreases in neural activity as well as prolonged decreases in firing rates. Local application of gonadal steroids by cannula and by iontophoresis produces changes in neuronal firing with onset latencies on the order of milliseconds to seconds (4, 25, 32, 33). Such direct hormone effects may be both hormone- and sex-specific: e.g. estradiol decreases firing in POA and Hyp of OVX female rats but has no effect when applied to male rats; testosterone increases unit activity in POA and Hyp of intact male rats, in which estradiol is ineffective (32, 33). Estrogen effects can be stereospecific: the natural 17β epimer is effective, whereas the estradiol 17α is not (4a). Although responsive neurons are found primarily in the POA and Hyp (4a), some responsive neurons can also be detected in cortical regions such as hippocampus (34), where sex-specific effects may also be apparent (35). E_2 at 0.1 nM increases the excitability of hippocampal pyramidal cells in slices from male, but not from female, rats (35). Estradiol (E_2) application at 1 nM to prolactin-secreting pituitary cells in culture is also reported to induce action potentials within 1 min (36).

COMMENT ON MECHANISM Extremely rapid effects of estradiol on cell firing are not likely to occur through the genome but rather at the cell surface. Some direct actions of estrogens are considered in detail below under the section on neurotransmitter receptors. Among the mechanisms under consideration are possible steroid effects on the fluidity of the cell membrane (37), which may have far-reaching consequences for many aspects of cell membrane function. More delayed changes in cell firing resulting over minutes to hours after estradiol administration may have as their basis the genomically-mediated changes on the levels of neuronal constituents which are involved in neurotransmission.

Turnover of Monoamines

The turnover of monoaminergic neurotransmitters is an index of neuronal electrical activity in certain neurons. Turnover is estimated by radioisotopic labeling as well as by depletion of levels after synthesis blockade.

Estrogen treatment reportedly increases DA turnover in median eminence (38–42). Another report failed to demonstrate increases in DA turnover in median eminence after estrogen treatment, but did demonstrate estrogen-induced reductions in DA turnover in two basal forebrain nuclei (43). Crowley et al (43) found that progesterone treatment reversed the effects of estradiol. In the striatum, an important DA projection area, DA

turnover is decreased by castration of males (44). In females, estrogen treatment is reported to increase striatal DA turnover (45) or to have no effect (42). It is important to note that some estrogen actions on DA turnover may be mediated by pituitary prolactin (see below).

There is widespread agreement that gonadal secretions decrease the turnover of cerebral norepinephrine (NE), which is increased following castration (43, 46–49). These changes are parallel to changes in gonadotropin secretion and it has been suggested that they may even be mediated by gonadotropin (47). The decreases in turnover produced by estrogen therapy are evidently reversed in a number of hypothalamic areas by progesterone (43, 49, 50). It should be noted that among hypothalamic nuclei, the responses to estrogen and progesterone are heterogenous: increases in NE turnover produced by estradiol and reversal by progesterone in some nuclei; decreases in turnover produced by estradiol and reversal by progesterone in other nuclei (43). The response of the entire hypothalamic block must therefore reflect the net balance of these changes. The relationship of changes in NE turnover in individual brain nuclei to the preovulatory LH surge has been examined in a series of recent papers (51–53). Estrogen-induced LH surges were accompanied by increased NE turnover in median eminence (ME), arcuate nucleus, medial preoptic nucleus, and suprachiasmatic nucleus (SCN). Progesterone treatment on the morning of the surge advanced and enhanced the surge, and with this advancement occurred an advancement of increases in NE turnover in SCN and ME (52). One day after progesterone treatment, LH surges are temporarily extinguished, and this event is accompanied by a loss on that day of increased NE turnover in SCN and ME: instead, turnover of dopamine in several hypothalamic nuclei is increased (53). Thus, increased NE turnover in at least two brain nuclei is tightly linked to the LH surge. That inhibitors of NE synthesis and adrenergic receptor blockers prevent the LH surge (54–60) argues for a key role of NE neurotransmission in the surge mechanism. This topic is discussed again below.

Serotonin (5HT) levels and $5HT_1$ receptor levels change during the estrous cycle in rats and mice (61–64). Attempts to alter serotonin turnover with estradiol and progesterone administration have not produced a clear picture (Table 1). If these steroids indeed alter turnover, they may do so differently depending on the time of day, as suggested by the work of Everitt et al (65) (see Table 1).

COMMENT ON MECHANISM The changes in turnover, like the steroid effects on electrical activity, may be the result either of some direct membrane action or of indirect, genomically mediated effects. In addition, the possible mediation by other hormones like FSH and prolactin has also

Table 1 Effects of gonadal steroids on the synthesis, concentration, and turnover of serotonin in the central nervous system

Steroid	Time of application prior to sacrifice	Structures	Steroid effects	Additional manipulations	References
E_2 + P	E_2: –48 h; P: –8 h	Whole brain	No effect on 5HT turnover	pCPA or α-propyldopacetamid[a] administered 3 h prior to sacrifice	226
E_2 + P	E_2: –54 h; P: –6 h	Anterior and posterior hypothalamus	No effect on 5HT synthesis	^{3}H-tryptophan administered 2 h prior to sacrifice	48
P	P : –3 h	Midbrain and hindbrain	Increase in 5HT levels	None	62
P	P: –96, –72, –48, and –24 h	Septum, raphe and hypothalamus	Increase in 5HT turnover	Pargyline[b] administered ½–1 h prior to sacrifice	239
E_2 + P	E_2: –48 and –24 h P: –5 h	Whole brain	E_2 increased turnover when given at the beginning of dark period; P prevented the E_2-stimulated increase	α-Propyldopacetamid[a] administered 2–4 h prior to sacrifice	65
E_2 + P	E_2: –48 and –24 h P: –5 h	Whole brain	E_2 decreased 5HT turnover when given at the beginning of light period; P prevented the decrease	α-Propyldopacetamid[a] administered 2–4 h prior to sacrifice	65
Ethinyl-E_2	Not specified	Midbrain and pons/medulla	Decrease in reuptake of 5HT	4-Methyl-α-ethyl-*m* tryramine (H75/12) administered prior to sacrifice	244
Ethinyl-E_2	Not specified	Midbrain and pons/medulla	Increase in 5HT synthesis	Phenelzine[b] administered 4 h prior to sacrifice	244
TP	TP: –120, –72, and –24 h	Hypothalamus	Reversed increase in 5HT levels observed following castration	None	216

[a] Inhibitors of tryptophan hydroxylase
[b] Inhibitor of monoamine oxidase

been considered. These actions can be teased apart experimentally by determining latency and duration of effects and thus distinguishing rapid direct from slower indirect actions; and also by hypophysectomy and pituitary hormone administration to establish secondary steroid effects, mediated by pituitary secretion. Clearly, changes in turnover, like changes in electrical activity, reflect the net result of many events within neurons. We shall now consider some of these individual cellular events and processes.

Enzyme Regulation

Gonadal steroid treatment results in the alteration of a number of neural enzyme activities. It is noteworthy that these effects have been found in brain regions which contain intracellular steroid receptors; they may, therefore, reflect the inductive effects of the steroids acting at the level of the cell nucleus [see below and (66, 67) for discussion]. It is also important to note that some of the reported effects represent an increase in enzyme activity while others consist of a decrease. The increase of one enzyme, choline acetyltransferase (CAT), has been analyzed by immunotitration and has been shown to involve an increase in the number of immunoreactive enzyme molecules (68). The estrogen-dependent decrease of Type A monoamine oxidase (MAO) was analyzed in terms of synthesis vs degradation and was shown to be due to an increased rate of degradation rather than decreased rate of synthesis (69).

Finally, it is important to note that the alterations in enzyme activity may change as a function of the time after or duration of estrogen treatment. For example, a single injection of estradiol benzoate (EB) into OVX rats causes a transient increase of tyrosine hydroxylase activity in medial basal hypothalamus (MBH) (70), whereas repeated injections of EB for 1 week lead to decreased MBH tyrosine hydroxylase (TOH) (71). In related studies, castration was found to increase TOH activity in MBH, even in animals in which lesions had destroyed a major portion of noradrenergic innervation of the MBH from the brainstem (72). This strongly suggests that the main effects are in the tuberoinfundibular dopamine neurons.

COMMENT ON MECHANISM For the most part, estrogen effects on brain enzyme activities appear to reflect changes in amount of the catalytic unit rather than direct steroid effects on catalytic properties. However, it is unclear in most instances whether the hormone effects are primary or secondary. The estrogen-induced change in choline acetyltransferase activity in preoptic area is most likely a primary action, since it has been shown to occur in hypophysectomized rats (73). In contrast, estrogen-induced changes in Type A monoamine oxidase activity in hypothalamus were eliminated by hypophysectomy (73). Primary estrogen effects on catechola-

mine-producing neurons are consistent with autoradiographic observations of accumulation of ^3H estradiol over catecholamine fluorescing neuron soma in the arcuate nucleus-median eminence (74) and brainstem (75, 76).

Neurosecretion

The release of neurosecretory products is susceptible to steroid influences in certain instances. For example, glucocorticoids acting in vivo are known to increase efflux of serotonin from hypothalamic synaptosomes (77) and are capable of inhibiting CRF release from hypothalamic fragments in vitro (78). Estrogen treatment of OVX rats reduces serum LHRH as well as LH and FSH and it increases tissue levels of LHRH in MBH; MBH tissue levels of LHRH decrease after gonadectomy (79–81). There is no indication that changes in LHRH synthesis accompany gonadal steroid-induced changes in LH serum levels (82), although this particular study failed to demonstrate changes in serum LHRH levels accompanying short-term gonadectomy and steroid replacement.

High concentrations of estradiol 17β, 100 to 20,000 nM, increase efflux of DA and NE from short-term organ cultures of intact hypothalamus; estradiol 17α is inactive (17). This estrogen-induced efflux of catecholamines may explain the estrogen stimulation of cyclic AMP accumulation in incubated rat hypothalamic tissue which has been reported by several laboratories (16, 83) and which is blocked by both adrenergic and dopaminergic blocking drugs. It is important for subsequent discussion to note that this estrogen effect is attenuated by an anti-estrogenic drug, clomiphene (16, 83). The high concentrations of estrogens which are required for these effects raise doubts as to their physiological importance at circulating estrogen concentrations which are in the subnanomolar range (84).

The effects of gonadal steroid treatment on neurosecretory processes may be permissive as well as causal. In studies of Rotsztejn and coworkers on DA-induced release of LHRH from MBH tissue in vitro, it was found that tissue had to be obtained from gonadally-intact rats, implying a priming action of, or at least a requirement for, the presence of gonadal hormones (85, 86).

COMMENT ON MECHANISM The direct action of steroids on membrane properties, resulting in altered membrane fluidity or other changes, could affect the release of neurosecretory products. Secondary actions, such as those mediated by prolactin or DA release (87, 88), must also be considered. Primary, genomically-mediated action of steroids leading to increased or decreased amounts of membrane constituents (e.g. ion channels) is a potential mechanism for the permissive effects of gonadal steroids on LHRH release (see above).

Uptake of Neurosecretion

Re-uptake mechanisms for neurosecretion are an important means of removing neurotransmitters from the vicinity of postsynaptic and presynaptic receptors and thereby terminating their membrane actions (89). High concentrations of steroids in the micromolar range are able to block the catecholamine uptake in isolated rat heart known as $Uptake_2$ (90). Such inhibition, together with estrogen inhibition of the enzymatic inactivation of catecholamines by COMT, appear to be responsible for enhanced responses of end organs such as the heart and vascular smooth muscle to catecholamines after steroid treatment (90, 91).

Both estradiol and progesterone applied to hypothalamic slices in vitro reportedly inhibit uptake not only of DA but also of NE and 5HT (92). Yet in vivo estrogen treatment of OVX rats for 3 days with 1 μg estradiol increases in vitro NE uptake by hypothalamic slices; administration of estradiol together with 4 mg progesterone per day leads to a decrease of DA uptake in vitro in such slices. Another study demonstrated that in vivo estradiol followed by progesterone treatment increases DA uptake in vitro in POA-septum tissue from OVX rats (93); in this study no effects of hormone treatment were found in hypothalamus. A third study found that estrogen-dependent increases in monoamine uptake in hypothalamus were detectable only at certain times of day and only in certain subregions of hypothalamus (94). Although Cardinali & Gomez (94) did not report studies of progestin action, their results with estradiol are sufficient to suggest the complexity of the steroid effects on uptake and the importance of both time of day and neuroanatomical subdivisions as variables which were not adequately investigated in the other two cited studies. None of the studies of monoamine uptake cited above have dealt adequately with another potentially important issue, namely, that since steroids may influence efflux of amines from nerve endings (see above), changes in uptake of labeled amines produced by steroids may be due, at least in part, to altered rates of efflux of the labeled amines. Such a possibility requires that careful measurements of uptake are made to obtain only the initial rate of influx.

COMMENT ON MECHANISM Direct steroid effects on membrane transport were reported by Iversen & Salt (90) at micromolar estradiol concentrations. It is unknown whether they occur at lower concentration, although it has recently been reported for pituitary that physiological concentrations of estradiol block the internalization of dopamine by pituitary cells, presumably lactrotrophs (95). Presumably this is a direct membrane action of estradiol. It is also possible that indirect genomically-mediated steroid effects may result in changes in the amount of particular membrane carriers used in transport.

Neurotransmitter Receptors

Steroid hormones regulate the sensitivity of cell membranes to a variety of hormones: ACTH, in fat cells, by glucocorticoids (96); oxytocin, alpha adrenergic, and angiotensin II receptors, in uterus, by estradiol (97–98a); and alpha adrenergic receptors, in platelets, by estradiol (99). Estrogen treatment sensitizes the pituitary gland to TRH and to LHRH (100, 101) and antagonizes the dopamine inhibition of prolactin release (102, 103). Estrogen treatment also desensitizes the rat pineal gland to the adrenergic stimulation of adenylate cyclase activity (104).

It is therefore not so surprising that steroid hormones also influence the neurotransmitter receptor systems of the brain. Estrogen treatment of ovariectomized rats increases the level of putative beta adrenergic, muscarinic, cholinergic, and serotonergic ($5HT_1$) receptors in hypothalamus but not in other brain regions which lack estrogen receptors (Table 2). In cases where the effects have been localized within hypothalamus, they appear to occur in known estrogen-concentrating cell groupings: ventromedial, anterior hypothalamic, medial preoptic, and bed nucleus for muscarinic receptors (105, 106); and arcuate nucleus, lateral preoptic area near bed nucleus of stria terminalis, and ventrolateral septum for $5HT_1$ receptors (107, 107a).

Various direct actions of estradiol or a metabolite, 2-hydroxyestradiol, also occur on putative neurotransmitter receptor systems (Table 3). The estrogens are competitive inhibitors of binding of ^3H ligands to α_1 adrenergic and dopaminergic receptors but are without effect on β or α_2 adrenergic binding. The effective steroid competitor range is 10–100 μM, which is extremely high and unphysiological. Estradiol and 2-hydroxyestradiol are also able to affect in vitro binding to $5HT_1$ receptors. However, these effects reduce the number of available receptors, rather than altering apparent affinity via competitive effects. Moreover, they occur at steroid concentra-

Table 2 Estrogen effects in vivo on putative neurotransmitter receptors

Receptor, ^3H ligand, and tissue	Estrogen treatment	Effect	Reference
Muscarinic; ^3H QNB; H, POA	Acute, 72 h	Increase	105, 106
Serotonin; ^3H 5HT; H, POA, A	Acute, 72 h	Increase	107
Beta-adrenergic; ^3H DHA; H	Acute, 72 h	Increase	240, 241
Histamine-stimulated adenylate cyclase	Chronic, 7 days	Decrease	242
Dopamine; ^3H spiperone, striatum	Chronic, 7 days	Increase	125
Beta-adrenergic; ^3H DHA; cortex	Chronic, 14 days	Decrease	243

Abbreviations: H, hypothalamus; POA, preoptic area; A, amygdala; QNB, quinuclidinyl benzilate; DHA, dihydroalprenalol; 5HT, serotonin.

tion as low as 1 nM in vitro when membranes are preincubated with steroid, and they can be demonstrated in brain areas like cortex and striatum, as well as hypothalamus, after in vivo administration of a few micrograms of estradiol or estradiol benzoate (108). Such direct estrogen effects on brain membranes may be responsible for acute reduction in $5HT_1$ receptor availability on proestrus, whereas the indirect effects cited above may give rise to elevated $5HT_1$ receptors in estrogen-sensitive cell groupings several days later, on diestrus.

Another receptor phenomenon in which gonadal steroids are involved is the imipramine-induced decrease in $5HT_2$ receptors in cerebral cortex. This decrease does not occur in ovariectomized rats and it is reinstated by replacement therapy with either estradiol or progesterone (109).

COMMENT ON MECHANISM Besides the permissive effects of ovarian steroids on $5HT_2$ receptors just cited, there appear to be at least four mechanisms by which steroid hormones, especially estrogens, can alter neurotransmitter receptors. One is by direct competition, but these effects occur at such high steroid concentrations as to virtually preclude their participation in events occuring in vivo. The second is by influencing membrane properties, possibly fluidity (37), so as to alter the availability of receptor to ligands [e.g. $5HT_1$ (108)] or coupling of receptor to adenylate cyclase (110). In the case of $5HT_1$ receptor effects noted above, there is good reason to believe that they may participate in normal physiology (64, 108). A third mechanism appears to be the induction of receptor formation via a genomic action. This is, of course, an inference based upon the occurrence of increased receptor binding in estrogen-concentrating brain regions and cell groupings as a result of in vivo estrogen treatment. Further analysis of this possibility must include the use of inhibitors of protein and RNA synthesis, and also must consider how such increases in receptor number as are produced by in vivo steroid treatment could come about by steroid-

Table 3 Effects of 2-hydroxyestradiol 17β or estradiol 17β in vitro on neurotransmitter receptor binding

Competitive interaction with	Noncompetitive interaction with	No effect
α_1 = Adrenergic (^{3}H WB4101, prazosin)[a]	$5HT_1$ (^{3}H serotonin)[b]	α_2 = Adrenergic (^{3}H clonidine, ^{3}H yohimbine)[a]
Dopaminergic (^{3}H spiperone, ^{3}H ADTN)[a]		β = Adrenergic (^{3}H dihydroalprenalol)[a]
		Muscarinic (^{3}H quinuclidinyl benzilate)[a]

[a] Based on B. S. McEwen, C. Paden, and L. Snyder, unpublished.
[b] Based on Biegon & McEwen (108).

influenced alteration in electrical activity and attendant changes in receptor number through desensitization or supersensitization. If, for example, an increase in receptor number is correlated with a decrease in transmitter turnover in that brain region, or a decreased receptor number with increased turnover, then supersensitivity or desensitization are good possibilities. We have argued previously (106) that the muscarinic cholinergic receptor is the best example of those noted in Table 3 of steroid-regulated receptor formation, because supersensitivity of muscarinic receptors, related to the absence of synaptic activity, is not reported to occur, e.g. after denervation (111, 112).

ESTROGEN AND DOPAMINE

Estrogens influence the dopaminergic system of the corpus striatum and median eminence and the dopamine response system of the pituitary, and there are so far many mechanisms proposed to account for these effects. The problems and mechanistic possibilities encountered in studies of dopamine are illustrative of much of what is discussed in the preceding two sections. This work, therefore, deserves special emphasis in this review.

Pituitary

The pituitary is the best studied system. Estradiol benzoate treatment (20 μg/day for 7 days) markedly attenuates inhibition by exogenous DA of morphine-stimulated prolactin secretion in rats while at the same time enhancing the prolactin response to morphine (103). Primary cultures of rat pituitary exposed to 1 nM estradiol 17 β for 120 hours display a similar attenuation of the inhibitory action of dopamine agonists (102, 113). The estrogen effect is not manifested at the level of pituitary dopamine receptors (114). Rather, it is manifested as an estrogen-induced reduction of the ability of pituitary lactotrophs to incorporate DA into prolactin secretory granules (95) and as an estrogen-induced inhibition of the capacity of dopamine to stimulate lysosomal enzyme activity in the anterior pituitary gland (115, 116). Estradiol action on pituitary cells is also manifested as a blockade of the ability of DA to decrease membrane resistance prior to inhibiting the generation of action potentials (36).

Median Eminence

Estrogen treatment increases the concentration of DA in hypophysial portal blood (95). This may be the result of increased prolactin secretion, since estrogen treatment increases circulatory prolactin and prolactin stimulates DA release into hypophysial portal blood (117, 118) and from isolated hypothalamic nerve endings (88).

Three daily injections of estradiol benzoate increase the accumulation of DOPA elicited by a DOPA decarboxylase inhibitor, suggesting that increased DA turnover results from estrogen treatment (119). This effect is prevented by hypophysectomy, which implies that prolactin secretion is again involved (42, 119). This estrogen effect was not found in striatum (42, 119), in spite of the fact that estrogens are believed to affect aspects of striatal dopamine neurotransmission (see below).

Long-term ovariectomy leads to increased DA levels in median eminence; elevated DA levels fall during estrogen replacement therapy (14). Prolonged estrogen treatment also leads to decreased tyrosine hydroxylase activity in medial basal hypothalamus (71). It is not known whether these estrogen effects are also mediated by the pituitary. Neurons of the tuberoinfundibular DA system do appear to contain intracellular estrogen receptors (74–76), indicating that primary effects of estradiol may take place as well as pituitary-mediated effects.

Striatum

The most complicated and controversial effects of estrogens on the dopaminergic system are those which are presumed to occur in the corpus striatum. At issue are the direction of the estrogen effect and whether pituitary hormones, especially prolactin, may mediate them. The discussion of the data will be divided into three sections: the effects of endocrine ablation; the effects of estrogen administration; and a summary of explanatory hypotheses.

ENDOCRINE ABLATION Endocrine ablation is frequently the most useful manipulation for ascertaining a physiological influence of endogenous hormones on a system such as the nigrostriatal DA neurons. Ovariectomy (OVX) leads over 4–6 weeks to a decrease of dopamine and apomorphine-stimulated adenylate cyclase in rat striatum and nucleus accumbens; at shorter times after OVX, DA sensitivity of adenylate cyclase may be enhanced (120). OVX also leads to a reduction in the ability of amphetamine to stimulate DA and noradrenaline release from rat striatal tissue (121), as well as a decrease in amphetamine stimulation of activity in a shuttle box (122). On the other hand, 2–3 weeks after ovariectomy, stereotyped behavior elicited by apomorphine is increased (123).

Hypophysectomy, unlike ovariectomy, does not change DA-stimulated adenylate cyclase activity in striatum and accumbens (120). Moreover, hypophysectomy tends to reduce or abolish certain estrogen effects, leading to the presumption that they normally may be mediated by elevated prolactin pituitary hormone (e.g. prolactin) secretion. This is the case for the effect of a synthetic estrogen to attenuate an apomorphine-induced increase of

striatal acetylcholine levels (15). It was subsequently found that prolactin-producing pituitary grafts under the kidney capsule in the absence of estrogen reinstate the same effect as was obtained by giving the synthetic estrogens: i.e. apomorphine-induced elevation of ACh is reduced, suggesting that a pituitary factor (possibly prolactin) inhibits response of dopaminergic receptors (124). Another estrogen effect, namely, to elevate binding of ^{3}H spiperone, is reportedly abolished by hypophysectomy (125) and mimicked by prolactin administration (126). It is also claimed that hypophysectomy abolishes the development of DA receptor supersensitivity produced by chronic haloperidol treatment (127). Thus, according to these results, the effect of estrogen treatment is similar to that of haloperidol, and both effects may be mediated by elevated prolactin secretion.

On the other hand, another laboratory has reported that hypophysectomy does not abolish response to estrogen treatment or to chronic haloperidol administration (128, 129). Whereas these results of haloperidol treatment in hypophysectomized rats appear to be in direct conflict with those of Ludmer & Hruska (127) cited in the previous paragraph, the results of estrogen treatment are not necessarily in conflict, owing to differences in estrogen treatment regimes used by the two laboratories. One group used a single massive injection of estradiol valerate 5–8 days before killing and observed increased ^{3}H spiperone binding; this effect is abolished by hypophysectomy (125, 126). The other laboratory used repeated estradiol benzoate injections during the withdrawal period from haloperidol and observed an attenuation of the haloperidol-induced increase of ^{3}H spiperone binding; this effect occurs in hypophysectomized rats (128, 129). In attempting to reconcile these reports, it is attractive to postulate that, besides the prolactin-elevating effects of estrogen treatment, which is one of the factors contributing to the increase of ^{3} spiperone binding, there are also primary effects of estradiol on the striatum which lead, among other possible effects, to the inhibition of the changes induced by withdrawal from haloperidol. One possibility to be discussed below is that estradiol is itself acting as a neuroleptic.

ESTROGEN TREATMENT Just as is the case for the effects of hypophysectomy, discussed above, there are also inconsistencies and even contradictions in the reported effects of estrogen treatment on dopaminergic functions linked to the striatum. On the one hand, estrogen treatment has been reported to be facilitative: e.g. estrogen replacement elevates DA-dependent adenylate cyclase activity (120); it potentiates stereotyped behavior elicited by dopamine agonists (130–133); and it prolongs the duration of ipsilateral rotation elicited by amphetamine in rats with unilateral 6-hydroxydopamine lesions of nigrostriatal projections (126, 131). On the

other hand, estrogen treatment can also apparently antagonize dopaminergic function: e.g. estrogen treatment potentiates catalepsy resulting from spiperone administration (134); it reduces the increase in striatal acetylcholine levels elicited by dopamine agonists (15); it reduces the amount of apomorphine-induced rotation in unilaterally-lesioned rats (124, 135); it attenuates phenylethylamine and amphetamine-induced stereotypy in mice (136); it reduces the magnitude of apomorphine-elicited stereotyped behavior in female rats chronically pretreated with haloperidol (137); and it has a biphasic effect on apomorphine-induced stereotypy in rats not treated with haloperidol (123).

POSSIBLE EXPLANATIONS Thus the effects of estrogens on dopaminergic functions in the nigrostriatal system are complex, since they appear to be biphasic and since they may involve primary effects of the hormone as well as secondary actions mediated by increased pituitary prolactin secretion. As to the biphasic nature of estrogen effects, suppression of sensitivity to apomorphine appears to be the major estrogen effect both in intact female rats with endogenous hormone and during and up to 24 hours after estradiol benzoate injection in OVX rats, whereas enhanced sensitivity to apomorphine is seen 48 hours or more after castration of estrogen replacement (123, 138). Such biphasic effects may ultimately help to resolve the apparent contradictions in the literature cited in the previous paragraph (138).

The increased behavioral sensitivity to apomorphine after withdrawal of estrogen replacement (123, 137, 138) is reminiscent of the supersensitivity following cessation of chronic haloperidol treatment. One view of this similarity is that estradiol can act like a dopamine receptor blocker. Indeed, 2-hydroxyestradiol, which can be formed from estradiol by enzymes present in neural tissue (139), binds to the dopamine receptor in pituitary (140) and striatum and has at least one property in common with dopamine antagonists, namely, the failure of GTP to shift the displacement curve for ^{3}H spiperone binding (B. S. McEwen, C. Paden, and L. Snyder, unpublished). However, these interactions occur in vitro only at estrogen concentrations above 1 μM, concentrations which appear unlikely to occur in vivo. Moreover, insofar as enhanced behavioral sensitivity to apomorphine is a reflection of higher DA receptor levels in striatum, it has been claimed that the pituitary mediates the increase in striatal DA receptors (125, 126), although, as noted above, there is disagreement on this point (129).

It is therefore difficult at this stage to provide a working model to account for both a pituitary prolactin involvement and separate, primary (and possibly biphasic) estradiol influences on striatal DA receptors. Another factor which may play a role in the complexity of the phenomena is the apparent functional heterogeneity of the DA receptors of the striatum. In recent

studies which attempted to isolate effects of apomorphine on striatal DA autoreceptors, it was found that 48 hours after a low dose of estradiol benzoate both apomorphine action on locomotor behavior and apomorphine inhibition of electrical activity in "Type B" DA neurons were markedly attenuated (141). Under these conditions, "Type A" neurons were not affected by estrogen treatment (141). In a related recording study of caudate neuronal electrical activity, Arnauld et al (142) reported that 20 μg of estradiol benzoate caused the number of neurons inhibited by (iontophoresed) DA to fall and the number excited by DA to increase, while at the same time spontaneously active cells increased by a factor of fourfold. These effects occurred within 4–6 hours of EB administration in OVX rats and were not observed in hypophysectomized animals. A final factor to be considered in estrogen action on the dopaminergic system is the possible mediation by serotonergic neurons. This suggestion is made for two reasons: First, 5HT neuronal function is implicated in dopamine-dependent stereotyped behaviors (143) and in the action of morphine on striatal, as well as tuberoinfundibular, dopaminergic neurons (144);secondly, estradiol acutely suppresses serotonergic sensitivity via $5HT_1$ receptors in striatum as well as in the rest of the rat brain (108).

Conclusion

Estradiol effects on the dopaminergic system of the rat brain and pituitary may be both primary and secondary, as well as membrane-mediated and intracellularly-mediated. Possible primary actions of estradiol include that which affects apparent internalization of dopamine by pituitary membranes and the interaction of high concentration of catecholestrogen with striatal and pituitary dopamine receptors. Secondary actions include the apparent mediation of certain estrogen effects by pituitary prolactin and the suggested role of serotonergic neurotransmission in estrogen effects on the dopaminergic system. For the most part, membrane effects of estrogens may account for the primary action of estrogens on their target cells which alter dopaminergic function. However, a role for intracellular estrogen receptors which are essential for other estrogen actions on the brain, such as ovulation and sexual behavior, is not totally excluded in the nigrostriatal system.

NEUROPHARMACOLOGY OF FEMININE SEXUAL BEHAVIOR AND OVULATION

Understanding the mechanism of the feedback of hormones to influence behavior and neuroendocrine function requires that we know not only the brain sites and cellular effects of hormones on neuronal structure and function but also the putative neurotransmitter systems which are involved.

This section attempts to summarize the neuropharmacology related to two well-studied hormone-regulated events in rodents, feminine sexual behavior and ovulation, which are dependent on the sequential action of estradiol followed by progesterone.

Before addressing the specific contribution of each of four neurotransmitter systems to the expression of feminine reproductive behavior and gonadotropin secretion, it first is necessary to describe the induction of these neuroendocrine events by estradiol and progesterone.

During the rat estrous cycle, estradiol (E_2) and progesterone (P) act in concert to activate and terminate sexual receptivity and to induce ovulation. A 36–48 hour rise in plasma E_2 levels is followed by a surge in both plasma P and LH (84) which occurs several hours prior to the appearance of reproductive behavior on the evening of proestrus. During the initial phase of P action, P activates proceptive behaviors, such as soliciting and ear-wiggling, and facilitates sexual receptivity, as measured by the frequency and quality of the lordosis posture (145–149). Ovulation occurs during the early morning hours of estrus, and reproductive behavior disappears several hours later.

Treatment of ovariectomized rodents with E_2 and/or P has allowed a more precise characterization of the E_2-P synergism which underlies the induction of feminine reproductive behavior in the rat. Feminine sexual behavior is first observed 18–24 hours after initiation of E_2 treatment (5, 6), although E_2 treatment need not be continuous during this 24 hour period (9). If E_2 is administered in physiological concentrations (using 5 mm Silastic capsules containing 10% E_2), little receptivity and no proceptivity is observed unless P is also administered (150). However, teatment of ovariectomized rats with P only is without behavioral effect. In contrast to the long latency (18–24 hours) between E_2 administration and the activation of reproductive behavior, is the shorter latency (½–1 hour) between P administration and the facilitation of mating (11, 13). The activation of mating behavior by E_2 and P appears to involve a stimulation of protein synthesis [for review, see (7); for recent work, see (8, 9)]. For example, estrogen has been shown to induce specifically cytosol progestin receptors in those areas of the brain implicated in the control of ovulation and reproductive behavior, the medial basal hypothalamus-preoptic area (151, 152), and this induction is temporally correlated with the appearance of receptivity following P administration (6).

The termination of feminine reproductive behavior is poorly understood. On the one hand, feminine sexual behavior could disappear by a simple decay of E_2-P stimulation. However, recent evidence suggests that the termination of mating may depend partially on protein synthesis after P administration (153).

Treatment of ovariectomized animals with E_2 and/or P has also facilitated our understanding of ovulation. Preovulatory LH secretion is first observed 16–30 hours after the initiation of E_2 treatment (154, 155), although E_2 treatment need not be continuous during this period (155). If E_2 is administered in physiological concentrations (using Silastic capsules), a daily LH surge results, and P advances and amplifies these surges on the day that it is administered (52, 156). However, treatment of ovariectomized rats with P only is without effect on LH release. In contrast to the long latency (16–30 hours) between E_2 administration and the induction of gonadotropin secretion is the shorter latency (2–5 hours) between P administration and the facilitation of LH release (52, 155). The stimulation of gonadotropin secretion by estradiol has been shown by Jackson (154, 157) to involve stimulation of protein and RNA synthesis.

Thus in all the actions of estradiol and progesterone on ovulation and sexual behavior in female rats there is a lag period between hormone administration and the neuroendocrine or behavioral event, during which essential RNA and protein synthesis is believed to occur. One of the goals of research on the mechanism of hormone action on such neurally-mediated events is to identify essential rate-limiting cellular events regulated by hormones which influence synaptic function. It is therefore essential to understand the neuropharmacology and neurochemical anatomy of the relevant neural circuits. In this light, the present section attempts to summarize the neuropharmacology of four putative neurotransmitter systems with regard to the control of ovulation and feminine sexual behavior. We have not attempted to provide an exhaustive list of neurotransmitters implicated in these processes, but rather we have chosen to focus on those for which sufficient information has been gathered: dopamine, norepinephrine, acetylcholine, and serotonin. For the most part, the discussion will be limited to data obtained using the rat.

Dopamine: Ovulation and Feminine Sexual Behavior

Although there have been many reports which suggest that central dopaminergic systems are involved in the regulation of feminine sexual receptivity and gonadotropin secretion in the rodent, no consistent view of the facilitative or inhibitory nature of these systems has emerged thus far. In interpreting the often contradictory literature pertaining to contribution of dopaminergic systems to neuroendocrine function, several points should be borne in mind. First, there are multiple central dopaminergic pathways, such as the tuberoinfundibular, mesolimbic, and incentohypothalamic, and these may contribute differentially to the control of sexual receptivity and gonadotropin release. Thus, information derived from pharmacological manipulation, particularly systemic drug administration, may reflect the sum

of actions at multiple sites of control. Second, effects of drug or ovarian steroid treatment on components of central dopaminergic activity—such as turnover—may be mediated indirectly by feedback effects of anterior pituitary hormones, such as prolactin. In such instances, the interpretation of experimental findings may be obscured (see below). Third, there are data which suggest that the actions of some of the dopaminergic agonists, such as apomorphine, on gonadotropin secretion and feminine reproductive behavior, are biphasic with respect to dose (see below) (158–161). Fourth, preliminary evidence from this laboratory indicates that the action of the dopamine antagonist, spiroperidol, on sexual receptivity in the rat is biphasic with respect to time of administration (B. Parsons and B. S. McEwen, unpublished results).

With these reservations, one may approach gingerly the literature on the dopaminergic control of gonadotropin secretion. Because this topic has been reviewed so well by Weiner & Ganong (162), we will attempt to highlight only a few studies.

Conflicting or incongruous experimental data obscure the contribution, if any, of central dopaminergic pathways to gonadotropin secretion in the cycling animal. For example, Rubinstein & Sawyer (163) reported that intraventricular application of dopamine (DA) stimulated LH release in rats on proestrus. However, Schneider & McCann (164) found that blockade of the preovulatory LH surge by pentobarbital could not be overridden by intraventricular administration of DA. Ahren and colleagues (165) and Löfström (166) reported that in rats pretreated with α-methyl-*p*-tyrosine dopamine turnover decreased on proestrus in tuberoinfundibular neurons, suggesting that these neurons inhibit preovulatory LH release. In contrast, Lichtensteiger (167) found increased turnover of dopamine in the tuberoinfundibular system of untreated rats on proestrus, and postulated that the tuberoinfundibular neurons facilitate the preovulatory surge.

It is unclear whether dopaminergic systems are implicated in the control of episodic LH release in ovariectomized rats. Intraventricular administration of DA or apomorphine is without effect on pulsatile LH secretion in ovariectomized rats (161, 164). Although dopamine agonists such as apomorphine stimulate pulsatile LH release, and although these effects of agonists may be blocked by antagonists such as pimozide (168, 169), the contribution of dopaminergic systems to the regulation of episodic LH is questionable because the administration of antagonists alone elicits no response in the ovariectomized animal (168, 169).

The majority of experimental findings suggest that (the summed effects of) central dopaminergic systems facilitate gonadotropin secretion in ovariectomized rats treated with ovarian steroids. For example, ovariectomized rats pretreated with estradiol (E_2) and progesterone (P) showed increased

LH release after intraventricular administration of dopamine or apomorphine (191). However, Ojeda and coworkers (170) found that these treatments did not alter LH secretion in rats primed only with E_2. Kawakami and coworkers (171) reported that implantation of DA into the medial preoptic area facilitated LH release in ovariectomized rats pretreated with estrogen. More recently, Rotsztejn and coworkers (85, 86, 172–174) found that in vitro incubation of medial basal hypothalamus fragments with dopamine resulted in LHRH release, if (and only if) the animals had received estrogen prior to sacrifice.

In summary, conclusive evidence implicating dopaminergic systems in the regulation of pulsatile LH release in ovariectomized animals is lacking. Experiments performed on cycling animals likewise offer no clear indication of the role of DA in the regulation of the preovulatory LH surge. Although it appears as if DA can stimulate LH secretion in ovariectomized animals treated with estrogen and/or progesterone, the neuroendocrine events which underlie E_2- and/or P-stimulated changes in central dopaminergic systems are unknown. Such events could be the result of direct actions of ovarian steroids on dopaminergic neurons, or indirect actions mediated by anterior pituitary hormones, or other consequences of steroid hormone action. That catecholamine-containing neurons in the arcuate-median eminence (74) and brainstem (76) can concentrate ^3H-E_2 suggests that at least some steroid actions on dopaminergic pathways may be primary.

The literature pertaining to the dopaminergic control of feminine reproductive behavior must be approached with the same reservations as those applied to the control of LH release by DA (see first paragraph of this section). Very few experimental data have been gathered in cycling rodents; the experiments described below were performed in ovariectomized animals which received estrogen or estrogen plus progesterone replacement therapy.

The balance of experimental findings supports the notion that central dopaminergic pathways (collectively) inhibit steroid-dependent sexual receptivity in the female rat, although this conclusion is preliminary. Ahlenius and coworkers (175, 176) reported that administration of α-methyl-p-tyrosine facilitated lordosis in estrogen-primed rats. Pretreatment with the dopamine precursor, l-dihydroxyphenylalanine, abolished this facilitation and restored central DA levels to control levels. Everitt and colleagues (65, 177) observed that systemic administration of the dopamine receptor blockers, pimozide or spiroperidol, increased sexual receptivity in rats pretreated with estrogen. Similarly, systemic injections of the dopamine agonists, ET-495 or apomorphine, have been found to decrease receptivity in female rats primed with E_2, or with E_2 + P (65, 177). However, systemic administration of low doses of apomorphine (178, 179), and stereotaxic application of apomorphine into the medial preoptic area or arcuate-ven-

tromedial nucleus (160), paradoxically have been reported to increase sexual receptivity in E_2-primed rats.

One of the most interesting results to emerge from the pharmacological manipulation of central dopaminergic systems is the possible differential contribution of these systems to feminine receptivity and proceptivity. Caggiula and colleagues (180, 181) found that intraventricular administration of 6-hydroxydopamine (6-OHDA) to rats primed with estrogen increased sexual receptivity, as measured by the lordosis quotient score, but not soliciting behavior. In animals made receptive with $E_2 + P$, intraventricular 6-OHDA produced an increase in receptivity, as measured by duration of the lordosis picture, but a decrease in the number of solicitations. Although these effects could have been produced by differential damage to DA- and NE-containing neurons by 6-OHDA, they were mimicked only by systemic administration of the dopamine antagonist, spiroperidol, but not α- or β-adrenergic receptor blockers, in rats pretreated with estrogen and progesterone. Thus, Caggiula and coworkers postulated that central dopaminergic pathways differentially affect the passive (lordosis) and active (soliciting) motor components of feminine reproductive behavior, inhibiting the former and facilitating the latter.

In conclusion, the experimental evidence which implicates dopaminergic systems in the control of feminine reproductive behavior in rats is stronger than that which suggests that DA contributes to the regulation of gonadotropin secretion. The balance of evidence obtained from pharmacological manipulation of animals primed with steroids indicates that dopaminergic systems collectively can inhibit at least the passive components (lordosis) of feminine reproductive behavior. What is lacking at present is a description of the direct and indirect actions of ovarian steroids on individual dopaminergic pathways in the central nervous system, and an evaluation of the import of these effects to the induction of sexual receptivity by estrogen and progesterone.

Norepinephrine and Ovulation

Between 1947 and 1955, Sawyer and coworkers published a series of papers which implicated central noradrenergic fibers in the control of LH secretion. Sawyer and colleagues first reported that injection of dibenanine, an α-adrenergic antagonist, into the third ventricle inhibited ovulation in estrous rabbits. Sawyer (182) later demonstrated that ovulation could be triggered in estrous rabbits by intraventricular application of norepinephrine (NE). Similarly, Prezkop and coworkers (183) found that ovulation and LH secretion could be stimulated in anestrus ewes by stereotaxic application of NE into the third ventricle.

Since the seminal work of Sawyer, a number of experimental observations have supported the hypothesis that there is a central noradrenergic system(s) which facilitates steroid-dependent LH secretion in several reflex and spontaneously-ovulating species. First, noradrenergic activity in the hypothalamus has been shown to change during the estrous cycle. NE synthesis (184), concentration (185), and turnover (186) increase in rat hypothalamus on the day of proestrus. Such quantitative changes are particularly striking in discrete hypothalamic nuclei obtained by microdissection; for example, NE content in the suprachiasmatic nucleus increases threefold between 1000 and 1700 hours on proestrus (187). Similarly, NE turnover is increased one- to threefold in the rat median eminence (166) and medial preoptic nucleus (162) on proestrus. That these changes in NE activity on proestrus are accompanied by parallel increases in LHRH content in the medial preoptic nucleus, suprachiasmatic nucleus, arcuate nucleus, and median eminence suggests that perhaps these discreet limbic nuclei function as an integrated unit under (at least partial) noradrenergic control, whose function is to direct the ultimate release of LHRH from the median eminence (51).

In the experimentally-manipulated rodent, noradrenergic pathways appear to play a key role in the facilitation of LH release. In rats made anovulatory by electrolytic lesions in the anterior hypothalamus (188) or by neonatal administration of testosterone (189), ovulation can be stimulated by intraventricular application of NE. In the ovariectomized rat treated with estrogen (E_2) and/or progesterone (P), stereotaxic application of NE into the third ventricle stimulates LH release in a dose-dependent manner (190, 191). That the administration of P to ovariectomized rats treated with E_2 increases LHRH content (57) as well as NE turnover (52) in the median eminence suggests that the effect of progesterone on the timing and magnitude of the LH surge may involve a hypothalamic noradrenergic mechanism (52).

Several studies have shown that inhibition of NE synthesis by the dopamine-β-hydroxylase inhibitors sodium diethyldithiocarbamate (DDC), 1-phenyl-3-(2-thiazolyl)-2-thiourea (4–14, 624) or bis(4-methyl-1-homopiperanzinyl-thiocarbonyl) disulfide (FLA-63) disrupts the preovulatory (54, 192), as well as the episodic (168) release of LH. Additionally, the blockade of the progesterone-induced preovulatory LH surge by DBH inhibitors in the E_2-primed rat can be overridden by prior treatment with the NE precursor, DL-threo-dihydroxyphenylserine (DOPS) (54). Furthermore, Martinovic & McCann (193) reported that lesions in the ventral noradrenergic tract produced by microinjection of 6-hydroxydopamine on proestrus resulted in an inhibition of the progesterone-induced preovulatory LH surge in the E_2-primed rat.

Several reports collectively suggest that the facilitation of both preovulatory and episodic LH release is mediated by α-adrenergic receptors. As noted previously, Sawyer and coworkers found that the injection of dibenanine, an α-adrenergic antagonist, into the third ventricle blocked ovulation in estrous rabbits (194). The administration of phenoxybenzamine, an α-adrenergic receptor blocker, inhibited the P-induced preovulatory LH surge in the E_2-treated rat, while propranolol, a β-adrenergic receptor blocker, was without effect (192). Phenoxybenzamine was found also to inhibit LH release in ovariectomized rats (195, 196) and ewes (197). More recently, Kinoshita and colleagues (198) found that clonidine, an α-adrenergic agonist, restored pulsatile LH release in ovariectomized rats treated with reserpine, whereas apomorphine, a dopamine agonist, was without effect. Such experiments clearly implicate central α-adrenergic pathways in the facilitation of both preovulatory and pulsatile LH release. It should be emphasized, however, that although NE may be involved in the normal preovulatory surge mechanism in rats, it also may be dispensable. This is the conclusion of Clifton and Sawyer (59), based upon experiments in which they could demonstrate preovulatory surges not blocked by phenoxybenzamine in rats with chronic depletion of hypothalamic noradrenaline.

Norepinephrine and Feminine Sexual Behavior

Relatively few experiments have been performed in order to elucidate the role of norepinephrine (NE) in the regulation of feminine reproductive behavior. It appears that a central noradrenergic system facilitates sexual receptivity in the female guinea pig, although this conclusion remains preliminary. Crowley and coworkers (199) reported that the administration of clonidine, an α_2-noradrenergic agonist, to E_2-treated female guinea pigs facilitated lordosis. Nock & Feder (200) observed that pretreatment of E_2-treated female guinea pigs with the α-adrenergic antagonist, phenoxybenzamine, blocked the facilitated lordosis by clonidine. In addition, Nock & Feder (200) found that the administration of the dopamine-β-hydroxylase inhibitor, U14-624, to guinea pigs blocked the induction of lordosis by E_2 + P. Clonidine was effective in restoring the lordosis reflex in these animals, whereas the dopamine receptor blocker, pimozide, and the serotonin receptor blocker, methysergide, were without effect (200).

In the rat, the contribution of noradrenergic neurotransmission to the induction of feminine reproductive behavior by ovarian hormones is unknown. The relatively few reports which are currently available offer contradictory experimental findings and divergent theoretical interpretations of data. For example, Ward and coworkers (201) found that stereotaxic application of the β-adrenergic receptor blocker, LB-46, into the anterior or posterior hypothalamus, facilitated lordosis in female rats primed with

E_2. Everitt and coworkers (65) have advocated that β-adrenergic receptors, if occupied by epinephrine, may facilitate the lordosis reflex in the female rats. These investigators observed that systemic administration of low doses of piperoxane facilitated lordosis in E_2-treated rats, and preferentially blocked adrenaline receptors (202). However, it should be noted that the behavioral effects of piperoxane in these studies may be attributed to partial blockade of α-adrenergic receptors. Furthermore, Foreman & Moss (203) reported that infusion of the β-adrenergic receptor blocker, propranolol, into the medial preoptic area or the arcuate region-ventromedial nucleus (VMN), decreased the lordosis quotients of female rats primed with estrone.

Everitt and coworkers (65) observed that amphetamine facilitated sexual receptivity in E_2-primed rats treated with pimozide. They reasoned that although amphetamine enhanced release of dopamine (DA) and NE, the increased receptivity in these animals was produced by increased NE activity, because DA receptors were rendered insensitive by pimozide blockade (65). In contrast, Ahlenius and colleagues (176) postulated that decreased NE neurotransmission facilitates feminine reproductive behavior in the rat. These investigators found that administration of the dopamine β-hydroxylase inhibitor, FLA-63, to E_2-treated female rats facilitated the lordosis reflex. Davis & Kohl (205) have suggested that at least some of the conflicting interpretations of experimental data noted above may be resolved by considering the possibility that there are two types of α-adrenergic receptors in rats (α_1 and α_2) which are implicated in the regulation of feminine reproductive behavior by NE.

In summary, the role of NE neurotransmission in the induction of sexual receptivity in rodents by estradiol and progesterone is poorly understood. Limited experimental data suggest that NE neurotransmission mediated by α-receptors can facilitate lordosis in the steroid-treated female guinea pig. The role of NE in the regulation of sexual receptivity in the rat does not appear to be analogous to that in the guinea pig, and is even less well characterized.

Acetylcholine: Ovulation and Feminine Sexual Behavior

In contrast to the numerous studies which have detailed the relationship between catecholamines and the neural control of ovulation, few have focused on the contribution of a central cholinergic system(s) to the regulation of gonadotropin release. Limited evidence suggests that a cholinergic system(s) may facilitate preovulatory gonadotropin secretion in the female rat. Everett et al (58) found that administration of atropine sulfate before 2 P.M. on proestrus blocked ovulation in cycling rats. Libertun & McCann (206) reported that intraventricular infusion of atropine on proestrus blocked the preovulatory LH and FSH surge. Vijayan & McCann (161)

observed that infusion of ACh into the third ventricle stimulated LH and FSH secretion in long-term ovariectomized rats. Because pretreatment of females with either atropine or the dopamine receptor blocker, pimozide, abolished the facilitative effect of ACh on gonadotropin release, the authors postulated that ACh may stimulate dopaminergic neurons in the median eminence to release LHRH.

Few investigators have studied the role of ACh in the control of feminine reproductive behavior by ovarian hormones. It appears that central cholinergic system(s) may influence sexual receptivity in the female rat, although this conclusion is, at present, preliminary. On the one hand, Fuxe and coworkers (206a) reported that systemic administration of nicotine facilitated lordosis in female rats primed with E_2. The facilitative effect of nicotine was blocked by pretreatment with the nicotinic antagonist, mecamylamine, but not by the dopamine antagonist, pimozide. Thus, nicotinic cholinergic neurotransmission may facilitate sexual behavior. On the other hand, Clemens & Dohanich (207) observed that stereotaxic application of the muscarinic agonist, bethanechol (carbamyl-β-methyl-choline) into the medial preoptic region facilitated lordosis in female rats treated with estrogen. The facilitative effect of bethanechol was blocked by pretreatment of females with the muscarinic antagonist, atropine sulfate. Clemens and colleagues (208) also reported that females made receptive by $E_2 + P$ treatment displayed lower levels of sexual receptivity after application of atropine sulfate or hemicholinium-3, a compound which inhibits high-affinity uptake of choline and retards ACh synthesis, into the medial preoptic region. The inhibitory effect of hemicholinium-3 was blocked by simultaneous infusion of choline chloride, which prevents depletion of ACh.

Two experimental findings from our laboratory have underscored the likelihood that a central cholinergic system(s) may contribute to the control of gonadotropin secretion and/or sexual receptivity in the female rat. The first is the observation that estrogen treatment increases the activity of choline acetyltransferase (CAT), an enzyme which regulates ACh synthesis, in the preoptic area (73). This increase represents a change in CAT content, and can be observed within 24 hours of E_2 treatment (68). It should be noted that other workers have shown that estrogen implants in the preoptic area (but not into the medial basal hypothalamus) can promote preovulatory LH release within 30 hours (204).

The second observation is the report that estrogen treatment elevates muscarinic cholinergic receptors labeled by ^{3}H-QNB within 72 hours of administration (105). This elevation in ^{3}H-QNB binding in the hypothalamus after E_2 is a change in receptor number rather than affinity (Kd). Furthermore, this increase in muscarinic receptors occurs specifically in

discrete brain regions involved in the control of ovulation and reproductive behavior: the bed nucleus of the stria terminalis, the medial preoptic area, the ventromedial nucleus, and the anterior hypothalamic nucleus. In short, while such increases in muscarinic receptor number or in CAT content have not been shown to be related causally to the induction of sexual receptivity and/or gonadotropin release in the rat, they are nevertheless discrete neurochemical consequences of E_2 action, and are possible candidates for the (partial) regulation of neuroendocrine function by ovarian hormones.

Serotonin and Ovulation

Serotonergic mechanisms are implicated in the control of luteinizing hormone (LH) release, although both facilitative and inhibitory influences have been found. Kordon and coworkers (209) found that injections of the monoamine oxidase inhibitor, nialamide, into the median eminence blocked gonadotropin-induced ovulation in the rat 2 hours later. Prior blockade of serotonin synthesis by pCPA antagonized the effect of nialamide, whereas blockade of catecholamine synthesis by α-methyl-*p*-tyrosine was without effect (209). Labhsetwar (210) reported that the administration of the MAO inhibitor, mebanazine, in combination with 5-hydroxytryptophan (5HTP) but not dihydroxyphenylalanine (L-DOPA), blocked spontaneous ovulation in 4-day cycling rats. Additionally, systemic or intraventricular injection of 5HT or 5HTP has been shown to decrease follicle-stimulating hormone (FSH) and LH levels and to inhibit ovulation in cycling female rats within a few hours of administration (164, 209, 211, 212). Infusions of 5HT into the mediobasal hypothalamus of the ewe (213) and rabbit (183) has also been shown to block the preovulatory surge of LH and delay ovulation in these species. Kamberi (212) has postulated that the serotonergic blockade of gonadotropin release and ovulation is a result of the suppression of LHRH discharge from the median eminence. In this regard, it is important to note that the inhibition of preovulatory LH surges by serotonin is possible only when experimental treatment is applied within a few hours of the "critical period" of ovulatory control (209, 214).

More recently, several studies have suggested that 5HT may also have a facilitative effect upon preovulatory LH release as well as on the circadian diurnal release of luteinizing hormone. Using ovariectomized rats outfitted with Silastic capsules containing estradiol, Hery and coworkers (215) observed that pCPA treatment would block the normal circadian increase in LH 24–48 hours later. Furthermore, intraperitoneal or intraventricular administration of 5HTP to animals which had received pCPA previously resulted in the reappearance of the circadian LH rhythm the following day. The administration of methiothepin, a 5HT receptor blocker, 9 or more hours prior to the expected increase in circadian LH, also disrupted the

cycle, whereas the administration of a dopamine receptor blocker was without effect (215). Thus, it appears that serotonergic pathways implicated in the control of circadian LH release exert an early, facilitative effect on (or within) the hypothalamus. Consistent with this notion is the finding that lesions or pharmacological destruction of the dorsal raphe, which sends 5HT fibers to the mediobasal hypothalamus and medial preoptic area, strongly reduce the circadian release of LH in the rat (216.)

Experimental evidence also suggests that central, serotonergic pathways mediate a facilitative effect on the preovulatory LH surge. For example, Meyer (217) reported that injections of the serotonin neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) into the raphe nuclei or third ventricle produced a decrease in the incidence of ovulation in young female rats. Marko & Flükiger (218, 219) screened a number of tricyclic compounds and ergot derivations, and found that the more potent 5HT antagonists were also the more potent inhibitors of ovulation in the rat, when administered on proestrus. Using pCPA during diestrus, Gonzales-Baron and coworkers (220) demonstrated that adequate levels of brain 5HT are necessary for normal ovulation.

In conclusion, it appears that central serotonergic pathways may facilitate, as well as inhibit, the preovulatory surge of LH, and may facilitate the episodic release of LH. The inhibition of preovulatory LH by serotonergic pathways only can be demonstrated by experimental manipulation a few hours before the "critical period" for ovulation, and may be the result of the suppression of LHRH discharge from the median eminence. By contrast, the facilitation of preovulatory and episodic LH by serotonergic pathways can be demonstrated by experimental manipulation as much as 48 hours in advance of the biological response. The anatomical elucidation of the precise serotonergic pathways which facilitate and/or inhibit LH release, as well as the manner in which the activities of these pathways are temporally integrated to determine whether LH release occurs, is a promising area for future investigation.

Serotonin and Feminine Sexual Behavior

Serotonin has been found to be inhibitory towards feminine sexual behavior in a number of mammalian species, including rats. Between 1964 and 1968, Meyerson published a series of papers which demonstrated that the activation of feminine reproductive behavior in the rat could be inhibited by the administration of drugs which increase central monoaminergic activity (221–225). Specifically, Meyerson observed that different monoamine oxidase inhibitors, as well as amphetamines and imipramine and related antidepressants (iminodibenzyl and dibenzocycloheptane derivates) decreased the lordosis quotient scores of ovariectomized female rats treated with

estrogen plus progesterone. Furthermore, Meyerson noted that animals which had an inhibitor of monoamine oxidase, pargyline, in addition to the serotonin precursor, 5-hydroxytryptophan (5HTP), showed a particularly striking reduction in sexual receptivity, as well as a twofold increase in brain serotonin levels (221). On the basis of these experiments, Meyerson postulated that there are specific serotoninergic neurons or pathways in the central nervous system which "mediate heat inhibition" (221).

Since this pioneering work, a number of experimental observations have supported the notion that there is a serotoninergic system(s) in the brain which tonically inhibits steroid dependent reproductive behavior. These findings will be reviewed first for ovariectomized animals which have received estrogen, and second for females treated with estrogen plus progesterone.

The systemic administration of 5-hydroxytryptamine (5HT) inhibitors, such as para-chlorophenylalanine (pCPA) or α-propyldopacetamid (H22/54), produces an increase in the lordosis quotients of ovariectomized estrogen-primed rats (65, 176, 226, 227) and mice (228) within 2–4 hours of administration. pCPA has also been shown to facilitate sexual receptivity acutely in the estrogen-treated female rhesus monkey (229). Although pCPA depletes brain catecholamines (CA) as well as 5HT within 2–4 hours of administration (175), two observations implicate specifically a serotoninergic system in the facilitation of sexual receptivity by pCPA: (*a*) pCPA continues to facilitate lordosis in rats 26 and 50 hours after administration; at these times, brain CA have returned to control levels, while 5HT is still depleted (65), and, (*b*) the facilitation of receptivity by pCPA in the rhesus monkey is prevented by administration of the serotonin precursor, 5-hydroxy-tryptophan.

Blockade of 5HT receptors by the systemic administration of methysergide maleate or cinanserin hydrochloride increases the frequency (LQ) and quality (LS) of lordoses in estrogen-treated ovariectomized rats (65, 175, 201, 226, 227). Furthermore, stereotaxic application of methysergide or cinanserin to the medial preoptic area-anterior hypothalamus or ventromedial nucleus-arcuate region increases sexual receptivity in rats primed with estrogen, while application of these 5HT receptor blockers to the caudate putamen is without effect (201, 227, 230). Thus, blockade of 5HT receptors in those areas of the brain known to mediate feminine reproductive behavior, the mediobasal hypothalamus and preoptic area (MBH-POA), is sufficient to increase sexual receptivity in the estrogen-primed female rat. Interestingly, the stereotaxic application of cinanserin and methysergide to areas within the MBH-POA does not increase proceptivity (soliciting and hop-darting) in estrogen-primed female rats (201, 227), suggesting that these behaviors are mediated by systems that are, at least

partially, anatomically or neurochemically distinct from those which mediate the lordosis reflex.

Ovariectomized rats treated with estrogen plus progesterone display decreased levels of sexual receptivity 5–8 hours after the systemic administration of the monoamine oxidase inhibitors, pargyline, nialamide, or pheniprazine (221, 231, 232). Two findings implicate specifically a serotoningic system in the inhibition of sexual receptivity by pargyline: (*a*) following the administration of monoamine oxidase inhibitors, behavioral deficits are related to increases in hypothalamic 5HT levels in a graded manner (231), and (*b*) the inhibition of sexual receptivity by pargyline can be augmented by administration of a serotonin precursor (5HTP), but not by a catecholamine precursor alpha-methyl-para-tyrosine (AMPT) (223).

Two different 5HT receptor agonists, α-methyltryptamine (AMT) and lysergic acid diethylamide (LSD), have been shown to decrease sexual receptivity activated by estradiol plus progesterone, but to have no effect on sexual behavior activated by estradiol alone (232, 233). Unfortunately, neither of these studies measured the effects of these 5HT receptor agonists on the expression of proceptive behaviors, which are more specific indicators of progesterone action than is the lordosis reflex (8, 234). Nevertheless, the selective inhibition of estrogen plus progesterone dependent receptivity by AMT and LSD suggests that at least some of the neurochemical consequences of estrogen action in the central nervous system are different from those of progesterone.

NEUROCHEMISTRY AND NEUROPHARMACOLOGY OF GONADAL STEROID ACTION: FUTURE RESEARCH OPPORTUNITIES AND DIRECTIONS

In concluding this review we shall suggest ways of refining research strategies directed at elucidating mechanisms of gonadal steroid action on the brain. The point of view and suggestions which we shall offer grow out of our own experience in studying estradiol and progesterone facilitation of feminine sexual behavior (summarized earlier). We feel that much of this experience may be applicable to further study of the neural control of ovulation, as well as other hormone effects upon brain function.

One of the most important points to emerge regarding estradiol and progesterone action is that each hormone contributes differently to the facilitation of mating behavior and gonadotropin secretion. This is most clearly illustrated for feminine sexual behavior in rats, for which separate periods of protein synthesis stimulated by each hormone have been identi-

fied (8, 9). Of course, progesterone does not by itself induce ovulation or mating behavior, and estradiol treatment in doses which are minimally effective in doing so requires the sequential application of progesterone to see the full neuroendocrine and behavioral effect. In future studies, it should nevertheless be possible to differentiate the neurochemical features of estradiol action from those of progesterone action in estrogen-primed rats. In this regard, the analysis of the neuropharmacology and neurochemistry of feminine sexual behavior is facilitated by the finding that the proceptive components (hopping, darting, ear-wiggling) are more specific indicators of progesterone action than the lordosis reflex itself (8, 234) and can be selectively elminated, e.g. by protein synthesis inhibition (8). It is therefore imperative that future investigations record not only receptive (lordosis) behavior but also proceptivity.

A major advantage of using steroid hormones as tools for probing brain function is the opportunity they afford for localizing sites of hormone action within the brain. Estradiol action on feminine sexual behavior involves an important contribution from the ventrolateral portion of the ventromedial nuclei of the hypothalamus (235–237). The same region of the hypothalamus is implicated in progesterone action in estrogen-primed rats (B. Rubin and R. Barfield, unpublished). Estradiol action on preovulatory LH release appears to involve an important contribution of neural targets within the preoptic area (204). In fact, localization of such sites is the most important step in meaningful studies of mechanism, for it permits focal neurochemical studies as well as localized drug application.

Let us now consider some of the problems raised by systemic drug administration and by nonlocalized or semilocalized neurochemical measurements, and some of the preferred alternative research strategies.

Over the past two decades, most of the experiments which have focused upon the relationship between neurotransmitter systems and specific neuroendocrine endpoints such as feminine sexual behavior and ovulation were based on correlations between systemic drug administration and neurochemical changes in large, grossly-dissected brain regions. Systemic drug administration is problematic in that a change in a neuroendocrine or behavioral parameter may be the result of drug action anywhere in the body. At best, the results may provide support for, but never proof of, a facilitative or inhibitory role of a neurotransmitter system in a particular brain region. At worst, systemic drug action may evoke changes in antagonistic systems, which cancel each other out and provide no information at all. Studies of drug action or hormone effects in grossly-dissected brain regions are fraught with analogous problems, in that neighboring brain nuclei may change in opposite directions to a stimulus. This has in fact been

reported for norepinephrine turnover in hypothalamic nuclei after estradiol administration (43).

Our further understanding of the contribution of neurochemical changes such as altered catecholamine turnover to the induction of ovulation and sexual behavior depends upon our ability to measure these changes in discrete brain nuclei, especially in neural pathways known to be important in the neural events under study. Furthermore, studies which utilize pharmacological manipulations should, if possible, use localized drug application as well as evaluation of the consequences of drug application on regional neurochemistry.

Additional requirements must be placed upon the design of future neuropharmacological and neurochemical investigations of steroid hormone action, if these are to yield critical and pertinent data. This is particularly true of the choice of the dose and time of hormone treatment. For example, many investigators have reported changes in hypothalamic biosynthetic activity after estradiol treatment [e.g. see Table 7 of reference (7)], and yet have chosen doses and treatment times which are supraphysiological. Thus the relevance of the changes to events such as activation of sexual behavior and ovulation remains obscure.

In future studies it would be of great value to characterize the neurochemical consequences of estradiol and progesterone stimuli which in dose and time are just sufficient (e.g. 9) to induce behavioral or neuroendocrine changes in relevant brain nuclei of ovariectomized animals. As an illustration of this approach, we have determined that two 1-hour exposures to estradiol are sufficient to activate feminine sexual behavior and to increase significantly the level of progestin receptors in cytosol of medial basal hypothalamus and preoptic area (9). Ongoing studies are directed at determining the magnitude of this progestin receptor induction in individual diencephalic nuclei, such as the ventromedial nucleus. Although these experiments will not constitute strict proof of the hypothesis that one of the neurochemical events involved in sexual behavior is progestin receptor induction, they will provide the best example of this correlative approach, one in which both the hormone treatment conditions and the brain regions are chosen so as to optimize the relevance of the findings to the brain function under study. We believe that this approach can be used to characterize potentially relevant changes in neurotransmission, such as the induction of muscarinic cholinergic receptors in the ventromedial hypothalamus (105), which may contribute to the activation of feminine sexual behavior by estradiol.

Given the requirements of studying relevant brain regions and using minimally sufficient hormonal stimuli to evoke neurochemical changes in those regions, it remains to be seen which parameters of synaptic function

summarized in an earlier section of this article are most critical for the hormonal control of behavior and neuroendocrine function. Present indications are that estradiol may change several parameters even in one discrete brain region such as the ventromedial nucleus: e.g. progestin receptors (B. Parsons, T. C. Rainbow, and B. S. McEwen, unpublished); muscarinic receptors (105), Type A monoamine oxidase (V. N. Luine, unpublished); and glutamic acid decarboxylase (238). It also remains to be established whether direct actions of estradiol and progesterone make a significant contribution to the regulation of feminine sexual behavior and ovulation. Such a role has been suggested for direct estrogen effects on $5HT_1$ receptor levels (108), based on observations of decreased $5HT_1$ binding at the time of elevated estradiol secretion (65). At the same time, it is apparent that indirect, genomically-mediated actions of estradiol and progesterone are primarily responsible for the appearance of sexual behavior and ovulation at precise times during the estrus cycle (106).

ACKNOWLEDGMENTS

Research in the authors' laboratory is funded by USPHS grant NS07080 and by an institutional grant RF70095 from the Rockefeller Foundation for research in reproductive biology. Bruce Parsons received support from Research Service Award 7524 from the National Institute of General Medical Sciences. We wish to thank Mrs. Oksana Wengerchuk for editorial assistance and typing of the manuscript.

Literature Cited

1. Bedard, P., Langelier, P., Villeneuve, A. 1977. Estrogens and extrapyramodal system. *Lancet* pp. 1367–68
2. Klaiber, E. L., Broverman, D. M., Vogel, W., Kobayashi, Y. 1979. Estrogen therapy for severe persistent depression in women. *Arch. Gen. Psychiatry* 36: 550–54
3. Dalton, K. 1964. *The Premenstrual Syndrome.* London: Heineman Med. Books
4. Dalton, K. 1971. Prospective study into puerperal depression. *Br. J. Psychiatry* 118:689–92

4a. Kelly, M. J., Moss, R. L., Dudley, C. A. 1977. The effects of microelectrophoretically applied estrogen, cortisol and acetylcholine on medial preoptic-septal unit activity through the estrous cycle of the female rat. *Exp. Brain Res.* 30:53–64

5. Green, R., Luttge, W. G., Whalen, R. E. 1970. Induction of receptivity in ovariectomized female rats by a single intravenous injection of estradiol 17β. *Physiol. Behav.* 5:137–41
6. Parsons, B., MacLusky, N. J., Krey, L. C., Pfaff, D. W., McEwen, B. S. 1980. The temporal relationship between estrogen-inducible progestin receptors in the female rat brain and the time course of estrogen activation of mating behavior. *Endocrinology* 107:774–79
7. McEwen, B. S., Davis, P. G., Parsons, B., Pfaff, D. W. 1979. The brain as a target for steroid hormone action. *Ann. Rev. Neurosci.* 2:65–112
8. Rainbow, T. C., Davis, P. G., McEwen, B. S. 1980. Anisomycin inhibits the activation of sexual behavior by estradiol and progesterone. *Brain Res.* 194: 548–55
9. Parsons, B., Rainbow, T. C., Pfaff, D. W., McEwen, B. S. 1981. Oestradiol, sexual receptivity and cytosol progestin receptors in rat hypothalamus. *Nature* 292:58–59

10. Kelner, K. L., Miller, A. L., Peck, E. J. Jr. 1980. Estrogens and the hypothalamus: nuclear receptors and RNA polymerase activation. *J. Receptor Res.* 1:215–37
11. Meyerson, B. 1972. Latency between intravenous injection of progestins and the appearance of estrous behavior in estrogen-treated ovariectomized rats. *Horm. Behav.* 3:1–10
12. Fadem, B. H., Barfield, R. J., Whalen, R. E. 1979. Dose-response and time-response relationships between progesterone and the display of patterns of receptive and proceptive behavior in the female rat. *Horm. Behav.* 13:40–48
13. McGinnis, M. Y., Parsons, B., Rainbow, T. C., Krey, L. C., McEwen, B. S. 1981. Temporal relationship between cell nuclear progestin receptor levels and sexual receptivity following intravenous progesterone administration. *Brain Res.* 218:365–71
14. Gudelsky, G. A., Simpkins, J., Mueller, G. P., Meites, J., Moore, K. E. 1976. Selective actions of prolactin on catecholamine turnover in the hypothalamus and on serum LH and FSH. *Neuroendocrinology* 22:206–15
15. Euvrard, C., Labrie, F., Boissier, J. R. 1979. Effect of estrogen on changes in the activity of striatal cholinergic neurons induced by DA drugs. *Brain Res.* 169:215–20
16. Gunaga, K. P., Kawano, A., Menon, K. M. J. 1974. *In vivo* effect of estradiol benzoate on the accumulation of adenosine 3',5'-cyclic monophosphate in the rat hypothalamus. *Neuroendocrinology* 16:273–81
17. Paul, S. M., Axelrod, J., Saavedra, J. M., Skolnick, P. 1979. Estrogen-induced efflux of endogenous catecholamines from the hypothalamus in vitro. *Brain Res.* 178:499–505
18. Toran-Allerand, C. D. 1976. Sex steroids and the development of the newborn mouse hypothalamus and preoptic area in vitro: implications for sexual differentiation. *Brain Res.* 106:407–12
19. Toran-Allerand, C. D. 1978. Gonadal hormones and brain development: cellular aspects of sexual differentiation. *Am. Zool.* 18:553–65
20. Toran-Allerand, C. D. 1980. Sex steroids and the development of the newborn mouse hypothalamus and preoptic area in vitro. II. Morphological correlates and hormonal specificity. *Brain Res.* 189:413–27
21. Arai, Y., Matsumoto, A., Nishizuka, M. 1978. Synaptogenic action of estrogen on the hypothalamic arcuate nucleus (ARCN) of the developing brain and of the deafferented adult brain in female rats. In *Hormones and Brain Development,* ed. G. Dörner, M. Kawakami, pp. 43–48. New York: Elsevier/North Holland. 473 pp.
22. Nottebohm, F. 1980. Testosterone triggers growth of brain vocal control nuclei in adult female cannaries. *Brain Res.* 189:429–36
23. Brawer, J. R., Naftolin, F., Martin, J., Sonnenschein, C. 1978. Effects of a single injection of estradiol valerate on the hypothalamic arcuate nucleus and on reproductive function in the female rat. *Endocrinology* 103:501–11
24. Goy, R. W., McEwen, B. S. 1980. *Sexual Differentiation of the Brain.* Based on a work session of the Neurosciences Research Program. Cambridge: MIT Press. 211 pp.
25. Pfaff, D. W., Pfaffman, C. 1969. Olfactory and hormonal influences on the basal forebrain of the male rat. *Brain Res.* 15:137–56
26. Kubo, K., Gorski, R. A., Kawakami, M. 1975. Effects of estrogen on neuronal excitability in the hippocampal-septal-hypothalamic system. *Neuroendocrinology* 18:176–91
27. Bueno, J., Pfaff, D. W. 1976. Single unit recording in hypothalamus and preoptic area of estrogen-treated and untreated ovariectomized female rats. *Brain Res.* 101:67–78
28. Kendrick, K. M., Drewett, R. F. 1979. Testosterone reduced refractory period of stria terminalis neurons in the rat brain. *Science* 204:877–79
29. Yagi, K. 1973. Changes in firing rates of single preoptic and hypothalamic units following an intravenous administration of estrogen in the castrated female rat. *Brain Res.* 53:343–52
30. Whitehead, S. A., Ruf, K. B. 1974. Responses of antidromically identified preoptic neurons in the rat to neurotransmitters and to estrogen. *Brain Res.* 79:185–98
31. Dufy, B., Partouche, C., Poulain, D., Dufy-Barbe, L., Vincent, J-D. 1976. Effects of estrogen on the electrical activity of identified and unidentified hypothalamic units. *Neuroendocrinology* 22:38–47
32. Yamada, Y., Nishida, E. 1978. Effects of estrogen and adrenal androgen on unit activity of the rat brain. *Brain Res.* 142:187–90
33. Yamada, Y. 1979. Effects of testoster-

one on unit activity in rat hypothalamus and septum. *Brain Res.* 172:165–68
34. Innes, D. L., Michael, E. K. 1970. Effects of progesterone and estrogen on the electrical activity of the limbic system. *J. Exp. Zool.* 175:487–92
35. Teyler, T. J., Vardaris, R. M., Lewis, D., Rawitch, A. B. 1980. Gonadal steroids: effect on excitability of hippocampal pyramidal cells. *Science* 209: 1017–19
36. Dufy, B., Vincent, J-D., Fleury, H., DuPasqier, P., Gourdji, D., Tixier-Vidal, A. 1979. Dopamine inhibition of action potentials in a prolactin secreting cell line is modulated by oestrogen. *Nature* 282:855–57
37. Heron, D. S., Shinitzky, M., Hershkowitz, M., Samuel, D. 1980. Lipid fluidity markedly modulates the binding of serotonin to mouse brain membranes. *Proc. Natl. Acad. Sci. USA* 77:7463–67
38. Fuxe, K., Hökfelt, T., Nilsson, O. 1969. Castration, sex hormones, and tuberoinfundibular dopamine neurons. *Neuroendocrinology* 5:107–20
39. Fuxe, K., Löfström, A., Eneroth, P., Gustafsson, J-A., Skett, P., Hökfelt, T., Wiesel, F-A., Agnati, L. 1977. Involvement of central catecholamines in the feedback actions of 17 β-estradiolbenzoate on luteinizing hormone secretions in the ovariectomized female rat. *Psychoneuroendocrinology* 2:203–25
40. Lichtensteiger, W., Keller, P. J. 1974. Tubero-infundibular dopamine neurons and the secretion of luteinizing hormone and prolactin: extrahypothalamic influences, interaction with cholinergic systems and the effect of urethane anesthesia. *Brain Res.* 74:279–303
41. Löfström, A., Eneroth, P., Gustafsson, J-A., Skett, P. 1977. Effects of estradiol benzoate on catecholamine levels and turnover in discrete areas of the median eminence and the limbic forebrain, and on serum luteinizing hormone, follicle stimulating hormone and prolactin concentrations in the ovariectomized female rat. *Endocrinology* 101:1559–69
42. Eikenburg, D. C., Ravitz, A. J., Gudelsky, G. A., Moore, K. E. 1977. Effects of estrogen on prolactin and tuberoinfundibular dopaminergic neurons. *J. Neural Transm.* 40:235–44
43. Crowley, W. R., O'Donohue, T. L., Wachslicht, H., Jacobowitz, D. M. 1978. Effects of estrogen and progesterone on plasma gonadotropins and on catecholamine levels and turnover in discrete brain regions of ovariectomized rats. *Brain Res.* 154:345–57
44. Alderson, L. M., Baum, M. J. 1981. Differential effects of gonadal steroids on dopamine metabolism in mesolimbic and nigrostriated pathways of male rat brain. *Brain Res.* 218:189–206
45. Algeri, S., Ponzio, F., Dolfini, E., Jori, A. 1976. Biochemical effects of treatment with oral contraceptive steroids on the dopaminergic system of the rat. *Neuroendocrinology* 22:343–51
46. Coppola, J. A. 1969. Turnover of hypothalamic catecholamines during various states of gonadotropin secretion. *Neuroendocrinology* 5:75–80
47. Anton-Tay, F., Anton, S. M., Wurtman, R. J. 1970. Mechanism of changes in brain norepinephrine metabolism after ovariectomy. *Neuroendocrinology* 6:265–73
48. Bapna, J., Neff, N. H., Costa, E. 1971. A method for studying norepinephrine and serotonin metabolism in small regions of rat brain: effect of ovariectomy on amine metabolism in anterior and posterior hypothalamus. *Endocrinology* 89:1345–50
49. Munaro, N. I. 1977. The effect of ovarian steroids on hypothalamic norepinephrine neuronal activity. *Acta Endocrinol.* 86:235–42
50. Simpkins, J. W., Huang, H. H., Advis, J.P., Meites, J. 1979. Changes in hypothalamic NE and DA turnover resulting from steroid-induced LH and prolactin surges in ovariectomized rats. *Biol. Reprod.* 20:625–32
51. Wise, P. M., Rance, N., Selmanoff, M., Barraclough, C. A. 1981. Changes in radioimmunoassayable luteinizing hormone-releasing hormone in discrete brain areas of the rat at various times on proestrus, diestrous day 1, and after phenobarbital administration. *Endocrinology* 108:2179–85
52. Wise, P. M., Rance, N., Barraclough, C. A. 1981. Effects of estradiol and progesterone on catecholamine turnover rates in discrete hypothalamic regions in ovariectomized rats. *Endocrinology* 108:2186–93
53. Rance, N., Wise, P. M., Barraclough, C. A. 1981. Negative feedback effects of progesterone correlated with changes in hypothalamic norepinephrine and dopamine turnover rates, median eminence luteinizing hormone-releasing hormone, and peripheral plasma gonadotropins. *Endocrinology* 108:2194–99
54. Kalra, S. P., McCann, S. M. 1974. Effects of drugs modifying catecholamine synthesis on plasma LH and ovu-

lation in the rat. *Neuroendocrinology* 15:79–91
55. Terasawa, E., Bridson, W. E., Davenport, J. W., Goy, R. W. 1975. Role of brain monoamines in release of gonadotropin before proestrus in the cyclic rat. *Neuroendocrinology* 18:345–58
56. Simpkins, J. W., Advis, J. P., Hodson, C. A., Meites, J. 1979. Blockade of steroid-induced luteinizing hormone release by selective depletion of anterior hypothalamic norepinephrine activity. *Endocrinology* 104:506–9
57. Simpkins, J. W., Kalra, P. S., Kalra, S. P. 1980. Temporal alterations in luteinizing hormone-releasing hormone concentrations in several discrete brain regions: effects of estrogen-progesterone and norepinephrine synthesis inhibition. *Endocrinology* 107:573–77
58. Everett, J. W., Sawyer, C. H., Markee, J. E. 1949. A neurogenic timing factor in control of the ovulatory discharge of luteinizing hormone in the cyclic rat. *Endocrinology* 44:234–50
59. Clifton, D. K., Sawyer, C. H. 1980. Positive and negative feedback effects of ovarian steroids on luteinizing hormone release in ovariectomized rats following chronic depletion of hypothalamic norepinephrine. *Endocrinology* 106: 1099–1102
60. Sarkar, D. K., Fink, G. 1981. Gonadotropin-releasing hormone surge: possible modulation through postsynaptic α-adrenoreceptors and two pharmacologically distinct dopamine receptors. *Endocrinology* 108:862–67
61. Greengrass, P. M., Tonge, S. R. 1971. Changes in brain monoamine concentrations during the oestrous cycle in the mouse: possible pharmacological implications. *J. Pharm. Pharmacol.* 23: 897–98
62. Tonge, S. R., Greengrass, P. M. 1971. The acute effects of estrogen and progesterone on the monoamine levels of the brain of ovariectomized rats. *Psychopharmacologia* 21:374–81
63. Kueng, W., Wirz-Justice, A., Menzi, R., Chappuis-Arndt, E. 1976. Regional brain variations of tryptophan, monoamines, monoamine oxidase activity, plasma free and total tryptophan during the estrous cycle of the rat. *Neuroendocrinology* 21:289–96
64. Biegon, A., Bercovitz, H., Samuel, D. 1980. Serotonin receptor concentration during the estrous cycle of the rat. *Brain Res.* 187:221–25
65. Everitt, B. J., Fuxe, K., Hökfelt, T., Jonsson, G. 1975. Role of monoamines in the control of hormones of sexual receptivity in the female rat. *J. Comp. Physiol. Psychol.* 89:556–72
66. McEwen, B. S., Luine, V. N. 1978. Specificity, mechanisms and functional significance of steroid-receptor interactions in the brain and pituitary. In *Biologie Cellulaire des Processus Neurosecretoires Hypothalamique,* Colloq. Int. C.N.R.S. NO. 280, ed. J-D. Vincent, C. Kordon, pp. 239–76. Paris: CNRS. 823 pp.
67. McEwen, B. S., Krey, L. C., Luine, V. N. 1978. Steroid hormone action in the neuroendocrine system: when is the genome involved? In *The Hypothalamus,* ed. S. Reichlin, R. J. Baldessarini, J. B. Martin, pp. 255–68. New York: Raven. 490 pp.
68. Luine, V. N., Park, D., Joh, T., Reis, D., McEwen, B. S. 1980. Immunochemical demonstration of increased choline acetyltransferase concentration in rat preoptic area after estradiol administration.
69. Luine, V. N., McEwen, B. S. 1977. Effect of oestradiol on turnover of Type A monoamine oxidase in brain. *J. Neurochem.* 28:1221–27
70. Tobias, H., Carr, L., Voogt, J. 1979. Effects of estradiol on catecholamine synthesizing enzymes, luteinizing hormone (LH) and prolactin in the ovariectomized rat. *Soc. Neurosci.* 5:461 (Abstr.)
71. Luine, V. N., McEwen, B. S., Black, I. B. 1977. Effect of 17 β-estradiol on hypothalamic tyrosine hydroxylase activity. *Brain Res.* 120:188–92
72. Kizer, J. S., Palkovits, M., Zivin, J., Brownstein, M., Saavedra, J. M., Kopin, I. J. 1974. The effect of endocrinological manipulations on tyrosine hydroxylase and dopamine-β-hydroxylase activities in individual hypothalamic nuclei of the adult male rat. *Endocrinology* 95:799–812
73. Luine, V. N., Khylchevskaya, R. I., McEwen, B. S. 1975. Effect of gonadal steroids on activities of monoamine oxidase and choline acetylase in rat brain. *Brain Res.* 86:293–306
74. Grant, L. D., Stumpf, W. E. 1973. Localization of ^{3}H-estradiol and catecholamines in identical neurons in the hypothalamus. *J. Histochem. Cytochem.* 21:404
75. Heritage, A., Stumpf, W. E., Sar, M., Grant, L. D. 1980. Brainstem catecholamine neurons are target sites for sex steroid hormones. *Science* 207: 1377–79

76. Sar, M., Stumpf, W. E. 1981. Central noradrenergic neurones concentrate ^{3}H-oestradiol. *Nature* 289:500–2
77. Vermes, I., Smelik, P. G., Mulder, A. H. 1976. Effects of hypophysectomy, adrenalectomy and corticosterone treatment of uptake and release of putative central neurotransmitters by rat hypothalamic tissue in vitro. *Life Sci.* 19:1719–26
78. Jones, M. T., Hillhouse, E. W., Burden, J. L. 1977. Dynamics and mechanics of corticosteroid feedback at the hypothalamus and anterior pituitary gland. *J. Endocrinol.* 73:405–17
79. Moguilevsky, J. A., Scacchi, P., Debeljuk, L., Faigon, M. R. 1975. Effect of castration upon hypothalamic luteinizing hormone releasing factor (LH-RF). *Neuroendocrinology* 17:189–92
80. Kalra, S. P. 1976. Tissue levels of luteinizing hormone-releasing hormone in the preoptic area and hypothalamus, and serum concentrations of gonadotropins following anterior hypothalamic deafferentation and estrogen treatment of the female rat. *Endocrinology* 99:101–7
81. Kobayashi, R. M., Lu, K. H., Moore, R. Y., Yen, S. S. C. 1978. Regional distribution of hypothalamic luteinizing hormone-releasing hormone in proestrous rats: effects of ovariectomy and estrogen replacement. *Endocrinology* 102:98–105
82. Hall, R. W., Steinberg, E. 1977. Synthesis of LHRH by rat hypothalamic tissue *in vitro*. II. Effect of short-term orchiectomy and estradiol benzoate therapy. *Neuroendocrinology* 24:325–32
83. Weissman, B. A., Skolnick, P. 1975. Stimulation of adenosine 3',5'-monophosphate formation in incubated rat hypothalamus by estrogenic compounds: relationship to biologic potency and blockade by antiestrogen. *Neuroendocrinology* 18:27–34
84. Smith, M. S., Freeman, M. E., Neill, J. D. 1975. The control of progesterone secretion during the estrus cycle and early pseudopregnancy in the rat: prolactin, gonadotropin and steroid levels associated with the resue of the corpus luteum of pseudopregnancy. *Endocrinology* 96:219–26
85. Rotsztejn, W. H., Charli, J. L., Pattou, E., Epelbaum, J., Kordon, C. 1976. In vitro release of luteinizing hormone-releasing hormone (LHRH) from rat mediobasal hypothalamus: effects of potassium, calcium and dopamine. *Endocrinology* 99:1663–66
86. Rotsztejn, W. H., Charli, J. L., Pattou, E., Kordon, C. 1977. Stimulation by dopamine of luteinizing hormone-releasing hormone (LHRH) release from the mediobasal hypothalamus in male rats. *Endocrinology* 101:1475–83
87. Perkins, N. A., Westfall, T. C. 1978. The effect of prolactin on dopamine release from rat striatum and medial basal hypothalamus. *Neuroscience* 3:59–63
88. Foreman, M. M., Porter, J. C. 1981. Prolactin augmentation of dopamine and norepinephrine release from superfused medial basal hypothalamic fragments. *Endocrinology* 108:800–4
89. Iversen, L. L. 1971. Role of transmitter uptake mechanisms in synaptic neurotransmission. *Br. J. Pharmacol.* 41: 571–91
90. Iversen, L. L., Salt, P. J. 1970. Inhibition of catecholamine uptake$_2$ by steroids in the isolated rat heart. *Br. J. Pharmacol.* 40:528–30
91. Kalsner, S. 1969. Mechanism of hydrocortisone potentiation of res onses to epinephrine and norepinephrine in rabbit aorta. *Circ. Res.* 24:383–95
92. Endersby, C. A., Wilson, C. A. 1974. The effect of ovarian steroids on the accumulation of ^{3}H-labelled monoamines by hypothalamic tissue *in vitro*. *Brain Res.* 73:321–31
93. Wirz-Justice, A., Hackman, E., Lichtsteiner, M. 1974. The effect of oestradiol diproprionate and progesterone on monoamine uptake in rat brain. *J. Neurochem.* 22:187–89
94. Cardinali, D. P., Gomez, E. 1977. Changes in hypothalamic noradrenaline, dopamine and serotonin uptake after oestradiol administration to rats. *J. Endocrinol.* 73:181–82
95. Gudelsky, G. A., Nansel, D. D., Porter, J. C. 1981. Role of estrogen in the dopaminergic control of prolactin secretion. *Endocrinology* 108:440–44
96. Braun, T., Hechter, O. 1970. Glucocorticoid regulation of ACTH sensitivity of adenyl cyclase in rat fat cell membranes. *Proc. Natl. Acad. Sci. USA* 66:995–1001
97. Soloff, M. S. 1975. Uterine receptor for oxytocin: effects of estrogen. *Biochem. Biophys. Res. Commun.* 65:205–12
98. Roberts, J. M., Insel, P. A., Goldfien, R. D., Goldfien, A. 1977. α-adrenoreceptors but not β-adrenoreceptors increase in rabbit uterus with oestrogen. *Nature* 270:624–25

98a. Schirar, A., Capponi, A., Catt, K. J. 1980. Regulation of uterine angiotensin

II receptors by estrogen and progesterone. *Endocrinology* 106:5–12
99. Roberts, J. M., Goldfien, R. D., Tsuchiya, A. M., Goldfien, A., Insel, P. A. 1979. Estrogen treatment decreases α-adrenergic binding sites on rabbit platelets. *Endocrinology* 104:722–28
100. DeLean, A., Ferland, L., Drouin, J., Kelly, P. A., LaBrie, F. 1977. Modulation of pituitary thyrotropin releasing hormone receptor levels by estrogens and thyroid hormones. *Endocrinology* 100:1496–1504
101. Vilchez-Martinez, J. A., Arimura, A., Debuljuk, L., Schally, A. V. 1974. Biphasic effect of estradiol benzoate on the pituitary responsiveness to LHRH. *Endocrinology* 94:1300–3
102. Raymond, V., Beaulieu, M., Labrie, F., Boissier, J. 1978. Potent antidopaminergic activity of estradiol at the pituitary level on prolactin release. *Science* 200:1173–75
103. Ferland, L., Labrie, F., Euvrard, C., Raynaud, J-P. 1979. Antidopaminergic activity of estrogens on prolactin release at the pituitary level *in vivo*. *Mol. Cell. Encocrinol.* 14:199-204
104. Weiss, B., Crayton, J. 1970. Gonadal hormones as regulators of pineal adenyl cyclase activity. *Endocrinology* 87: 527–33
105. Rainbow, T. C., DeGroff, V., Luine, V. N., McEwen, B. S. 1980. Estradiol-17b increases the number of muscarinic receptors in hypothalamic nuclei. *Brain Res.* 198:239–43
106. McEwen, B. S., Biegon, A., Rainbow, T. C., Paden, C., Snyder, L., DeGroff, V. 1981. The interaction of estrogens with intracellular receptors and with putative neurotransmitter receptors: implications for the mechanism of activation of sexual behavior and ovulation. In *Steroid Hormone Regulation of the Brain,* ed. K. Fuxe, pp. 15–30. London: Pergamon. 406 pp.
107. Biegon, A., Rainbow, T. C., McEwen, B. S. 1981. Serotonin receptor localization by autoradiography: quantitative analysis and the effect of steroid hormones. *Soc. Neurosci.* 7:9 (abstr.)
107a. Fischette, C. T., Biegon, A., McEwen, B. S. 1981. Serotonin receptors in estrogen concentrating brain nuclei and their modulation by estradiol. *Soc. Neurosci.* 7:9 (Abstr.)
108. Bigeon, A., McEwen, B. S. 1982. Modulation of estradiol of serotonin receptors in brain. *J. Neurosci.* In press
109. Kenda l, D. A., Stancel, G. M., Enna, S. J. 1981. Imipramine: effect of ovarian steroids on modifications in serotonin receptor binding. *Science* 211:1182–84
110. Finidori-Lepicard, J., Schorderet-Slatkine, S., Hanoune, J., Baulieu, E-E. 1981. Steroid hormone as regulatory agent of adenylate cyclase. Inhibition by progesterone of the membrane bound enzyme in *Xenopus laevis* oocytes. *Nature.* 292:255–57
111. Yamamura, H. I., Kuhar, M. J., Snyder, S. H. 1974. *In vivo* identification of muscarinic cholinergic receptor binding in the rat brain. *Brain Res.* 80:170–76
112. Rotter, A., Birdsall, N. J. M., Burgen, A. S. V., Field, P. M., Smolen, A., Raisman, G. 1979. Muscarinic receptors in the central nervous system of the rat. IV. A comparison of the effects of axotomy and deafferentation on the binding of the ^{3}H-propylbenilylcholine mustard and associated synaptic changes in the hypoglossal and pontine nuclei. *Brain Res. Rev.* 1:207–24
113. West, B. L., Dannies, P. S. 1980. Estradiol pretreatment of male rat pituitary cells cultured in a defined medium decreases the sensitivity to dopaminergic inhibition of prolactin production. *Endocrine Soc.* p. 265 (Abstr.)
114. DiPaolo, T., Labrie, F., Dupont, A., Barden, N., Langelier, P. 1979. Effects of estrogen treatment on normal and sensitized rat striatal dopamine (DA) receptors and DA-sensitive adenylyl cyclase. *Soc. Neurosci.* 5:443 (Abstr.)
115. Nansel, D. D., Gudelsky, G. A., Reymond, M. J., Porter, J. C. 1981. Estrogen alters the responsiveness of the anterior pituitary gland to the actions of dopamine on lysosomal enzyme activity and prolactin release. *Endocrinology* 108:903–7
116. Nansel, D. D., Gudelsky, G. A., Reymond, M. J., Neaves, W. B., Porter, J. C. 1981. A possible role for lysosomes in the inhibitory action of dopamine on prolactin release. *Endocrinology* 108: 896–902
117. Gudelsky, G. A., Porter, J. C. 1980. Release of dopamine from tuberinfundibular neurons into pituitary stalk blood following prolactin or haloperidol administration. *Endocrinology* 106: 526–29
118. Cramer, O. M., Parker, C. R. Jr., Porter, J. C. 1979. Estrogen inhibition of dopamine release into hypophysial portal blood. *Endocrinology* 104:419–21
119. Demarest, K. T., Moore, K. E. 1980. Accumulation of L-dopa in the median eminence: an index of tuberoinfundibu-

lar dopaminergic nerve activity. *Endocrinology* 104:463–68
120. Kumakura, K., Hoffman, M., Cocchi, D., Trabucchi, M., Spano, P. F., Müller, E. E. 1979. Long-term effect of ovariectomy on dopamine-stimulated adenylate cyclase in rat striatum and nucleus accumbens. *Psychopharmacology* 61:13–16
121. Becker, J. B., Ramirez, V. D. 1981. Sex differences in the amphetamine stimulated release of catecholamines from rat striatal tissue *in vitro*. *Brain Res.* 204:361–72
122. Savageau, M. M., Beatty, W. W. 1981. Gonadectomy and sex differences in the behavioral responses to amphetamine and apomorphine of rats. *Pharmacol. Biochem. Behav.* 14:17–21
123. Gordon, J. H., Gorski, R. A., Borison, R. L., Diamond, B. I. 1980. postsynaptic efficacy of dopamine: possible suppression by estrogen. *Pharmacol. Biochem. Behav.* 12:515–18
124. Euvrard, C., Oberlander, C., Boissier, J. R. 1980. Antidopaminergic effect of estrogens at the striatal level. *J. Pharmacol. Exp. Ther.* 214:179–85
125. Hruska, R. E., Silbergeld, E. K. 1980. Increased dopamine receptor sensitivity after estrogen treatment using the rat rotation model. *Science* 208:1466–68
126. Hruska, R. E., Ludmer, L. M., Silbergeld, E. K. 1980. The striatal dopamine receptor supersensitivity produced by estrogen may be mediated through prolactin. *Soc. Neurosci.* 2:441 (Abstr.)
127. Ludmer, L. M., Hruska, R. E. 1980. Hypophysectomy prevents the striatal dopamine receptor supersensitivity produced by chronic haloperidol treatment. *Soc. Neurosci.* 1:441 (Abstr.)
128. Fields, J. Z., Callahan, M. F., Gordon, J. H. 1980. Effects of estrogen on the development and expression of dopamine receptor supersensitivity. *Soc. Neurosci.* 6:790 (Abstr.)
129. Perry, K. O., Diamond, B. I., Gordon, J. H. 1980. Hypophysectomy induced hypersensitivity to apomorphine. *Soc. Neurosci.* 6:759 (Abstr.)
130. Chiodo, L. A., Caggiula, A. R., Saller, C. F. 1981. Estrogen potentiates the stereotype induced by dopamine agonists in the rat. *Life Sci.* 28:827–35
131. Hruska, R. E., Silbergeld, E. K. 1979. Increased dopamine receptor sensitivity after estrogen treatment. *Soc. Neurosci.* 236:73 (Abstr.)
132. Nausieda, P. A., Koller, W. C., Weiner, W. J., Klawans, H. L. 1979. Modification of postsynaptic dopaminergic sensitivity by female sex hormones. *Life Sci.* 25:521–26
133. Koller, W. C., Weiner, W. J., Klawans, H. L., Nausieda, P. A. 1980. Influence of female sex hormones on neuroleptic-induced behavioral supersensitivity. *Neuropharmacology* 19:387–91
134. Chiodo, L. A., Caggiula, A. R., Saller, C. F. 1979. Estrogen increases both spiperone-induced catelepsy and brain levels of (^{3}H) spiperone in the rat. *Brain Res.* 172:360–66
135. Bedard, P., Dankova, J., Boucher, R., Langelier, P. 1978. Effect of estrogens on apomorphine-induced circuling behavior in the rat. *Can. J. Physiol. Pharmacol.* 56:538–41
136. Naik, S. R., Kelkar, M. R., Sheth, U. K. 1978. Attenuation of stereotyped behaviour by sex steroids. *Psychopharmacology* 57:11–214
137. Gordon, J. H., Borison, R. L., Diamond, B. I. 1980. The effects of estrogen on an experimental model of tardive dyskinesia. *Neurology* 30:551–54
138. Gordon, J. H. 1980. Modulation of apomorphine-induced stereotypy by estrogen: time course and dose response. *Brain Res. Bull.* 5:679–82
139. Fishman, J. 1976. The catechol estrogens. *Neuroendocrinology* 22:363–74
140. Schaeffer, J. M., Hsueh, A. J. 1979. 2-hydroxyestradiol interaction with dopamine receptor binding in rat anterior pituitary. *J. Biol. Chem.* 254:5606–8
141. Chiodo, L. A., Caggiula, A. R. 1980. Alterations in basal firing rate and autoreceptor sensitivity of dopamine neurons in the substantia nigra following acute and extended exposure to estrogen. *Eur. J. Pharmacol.* 67:165–66
142. Arnauld, E., Dufy, B., Pestre, M., Vincent, J. D. 1981. Effects of estrogens on the responses of caudate neurons to microiontophoretically applied dopamine. *Neurosci. Lett.* 21:325–31
143. Carter, C. J., Pycock, C. J. 1981. The role of 5-hydroxytryptamine in dopamine-dependent stereotyped behaviour. *Neuropharmacology* 20:261–65
144. Demarest, K. T., Moore, K. E. 1981. Disruption of 5-hydroxytryptaminergic neuronal function blocks the action of morphine on tuberoinfundibular dopaminergic neurons. *Life Sci.* 28: 1345–51
145. Ball, J. 1937. A test for measuring sexual excitability in the female rat. *Comp. Psychol. Mon.* 14:1–37
146. Kuehn, R. F., Beach, F. A. 1963. Quantitative measurement of sexual recep-

tivity in female rats. *Behavior* 21:282–99
147. Hardy, D. F., deBold, J. F. 1971. The relationship between levels of exogenous hormones and the display of lordosis by the female rat. *Horm. Behav.* 2:287–97
148. Hardy, D. F. 1972. Sexual behavior in continuously cycling rats. *Behavior* 41:288–97
149. Beach, F. A. 1976. Sexual attractivity, proceptivity and receptivity in female animals. *Horm. Behav.* 7:105–38
150. Parsons, B., McGinnis, M. Y., McEwen, B. S. 1981. Sequential inhibition by progesterone: effects on sexual receptivity and associated changes in brain cytosol progestin binding in the female rat. *Brain Res.* 221:149–60
151. MacLusky, N. J., McEwen, B. S. 1978. Oestrogen modulates progestin receptor concentrations in some rat brain regions but not in others. *Nature* 274: 276–77
152. MacLusky, N. J., McEwen, B. S. 1980. Progestin receptors in rat brain: distribution and properties of cytoplasmic progestin binding sites. *Endocrinology* 106:192–202
153. Parsons, B., McEwen, B. S. 1981. Sequential inhibition by progesterone is prevented by a protein synthesis inhibitor and is not causally related to decreased levels of hypothalamic progestin receptors in the female rat. *J. Neurosci.* 1:527–531
154. Jackson, G. L. 1973. Time interval between injection of estradiol benzoate and LH release in the rat and effect of actinomycin D or cycloheximide. *Endocrinology* 93:887–891
155. Krey, L. C., Parsons, B. 1982. Characterization of the estrogen stimulus sufficient to restore cyclic luteinizing hormone release in recently ovariectomized rats. *Neuroendocrinology.* In press
156. DePaolo, L. V., Barraclough, C. A. 1979. Interactions of estradiol and progesterone on pituitary gonadotropin secretion: possible sites and mechanisms of action. *Biol. Reprod.* 20: 1173–85
157. Jackson, G. L. 1972. Effect of actinomycin D on estrogen-induced release of luteinizing hormone in ovariectomized rats. *Endocrinology* 91:1284–87
158. Hamburger-Bar, R., Rigter, H. 1975. Facilitation of sexual behavior in female rats. *Eur. J. Pharmacol.* 32:357–60
159. Fuxe, K., Hökfelt, T., Agnati, L., Löfström, A., Everitt, B. J., Johansson, O., Jonsson, G., Wuttke, W., Goldstein, M. 1976. Role of monoamines in the control of gonadotropin secretion. In *Neuroendocrine Regulation of Fertility,* ed. A. Kumar, pp. 124–60. Basel: Karger
160. Foreman, M. M., Moss, R. L. 1979. Role of hypothalamic dopaminergic receptors in the control of lordosis behavior in the female rat. *Physiol. Behav.* 22:283–89
161. Vijayan, E., McCann, S. M. 1980. Effect of blockade of dopaminergic receptors on acetylcholine (Ach)-induced alterations of plasma gonadotropin and prolactin (Prl) in conscious ovariectomized rats. *Brain Res. Bull.* 5:23–29
162. Weiner, R. I., Ganong, W. F. 1978. Role of brain monoamines and histamine in regulation of anterior pituitary secretion. *Physiol. Rev.* 58:905–76
163. Rubenstein, L., Sawyer, C. H. 1970. Role of catecholamines in stimulating the release of pituitary ovulating hormone(s) in rats. *Endocrinology* 86: 988–95
164. Schneider, H. P. G., McCann, S. M. 1970. Monoamines and indolamines and control of LH secretion. *Endocrinology* 86:1127–33
165. Ahren, K., Fuxe, K., Hamberger, L., Hökfelt, T. 1971. Turnover changes in the tuberoinfundibular neurons during the ovarian cycle of the rat. *Endocrinology* 88:1415–24
166. Löfström, A. 1977. Catecholamine turnover alterations in discrete areas of the median eminence of 4 and 5 day cyclic rat. *Brain Res.* 120:113–31
167. Lichtensteiger, W. 1969. Cyclic variations of catecholamine content in hypothalamic nerve cells during the estrous cycle of the rat, with a concomitant study of the substantia nigra. *J. Pharmacol. Exp. Ther.* 165:204–15
168. Drouva, S. V., Gallo, R. V. 1976. Catecholamine involvement in episodic luteinizing hormone release in adult ovariectomized rats. *Endocrinology* 99:651–58
169. Drouva, S. V., Gallo, R. V. 1977. Further evidence for inhibition of episodic luteinizing hormone release in ovariectomized rats by stimulation of dopamine receptors. *Endocrinology* 100:792–98
170. Ojeda, S. R., Harms, P. G., McCann, S. M. 1974. Effect of blockade of dopaminergic receptors on prolactin and LH release: median eminence and pituitary sites of action. *Endocrinology* 94:1650–57

171. Kawakami, M., Kimura, F., Manaka, M., Kawagoe, S. 1975. LH discharge induced by medial preoptic implantation of estrone or dopamine in the ovariectomized estradiol primed rat. *Endocrinol. Jpn.* 22:549–54
172. Charli, J. L., Rotsztejn, W. H., Pattou, E., Kordon, C. 1978. Effect of neurotransmitters on *in vitro* release of luteinizing-hormone-releasing hormone from the mediobasal hypothalamus of male rats. *Neurosci. Lett.* 10:159–63
173. Rotsztejn, W. H., Drouva, S. V., Pattou, E., Kordon, C. 1978. Effect of morphine on the basal and the dopamine-induced release of LHRH from mediobasal hypothalamic fragments in vitro. *Eur. J. Pharmacol.* 50:285–86
174. Rotsztejn, W. H., Drouva, S. V., Pattou, E., Kordon, C. 1978. Met-enkephalin inhibits in vitro dopamine induced LHRH release from mediobasal hypothalamus of male rats. *Nature* 274: 281–82
175. Ahlenius, S., Engel, J., Eriksson, H., Modigh, K., Södersten, P. 1972. Importance of central catecholamines in the mediation of lordosis behavior in ovariectomized rats treated with estrogen and inhibitors of monoamine synthesis. *J. Neural Transm.* 33:247–55
176. Ahlenius, S., Engel, J., Eriksson, H., Modigh, K., Södersten, P. 1975. Involvement of monoamines in the mediation of lordosis behavior. In *Sexual Behavior: Pharmacology and Biochemistry.* ed. M. Sandler. G. L. Gessa, pp. 137–45. New York: Raven. 354 pp.
177. Everitt, B. J., Fuxe, K., Hökfelt, T. 1974. Inhibitory role of dopamine and 5-hydroxytryptamine in the sexual behavior of female rats. *Eur. J. Pharmacol.* 29:187–91
178. Rodriquez-Sierra, J. F., Naggar, A. N., Komisaruk, B. R. 1976. Monoaminergic mediation of masculine and feminine copulatory behavior in female rats. *Pharmacol. Biochem. Behav.* 5: 457–63
179. Everitt, B. J., Fuxe, K. 1977. Dopamine and sexual behavior in female rats. Effects of dopamine receptor agonists and sulpiride. *Neurosci. Lett.* 4:209–13
180. Caggiula, A. R., Herndon, J. G., Scanlon, R., Greenstone, D., Bradshaw, W., Sharp, D. 1979. Dissociation of active from immobility components of sexual behavior in female rats by central 6-hydroxydopamine: implications for CA involvement in sexual behavior and sensorimotor responsiveness. *Brain Res.* 172:505–20
181. Caggiula, A. R., Antelman, S. M., Chiodo, L. A., Lineberry, C. G. 1979. Brain DA and sexual behavior: psychopharmacological and electrophysiological evidence for an antagonism between active and passive components. In *Catecholamines: Basic and Clinical Frontiers,* ed. E. Usdin, I. J. Kopin, J. Barchas. New York: Pergamon
182. Sawyer, C. H. 1955. Stimulation of ovulation in the rabbit by the intraventricular injection of epinephrine or norepinephrine. *Anat. Rec.* 112:385
183. Przekop, F., Skubiszewski, B., Wolinska, E., Domanski, E. 1975. The role of catecholamines in stimulating the release of pituitary hormones in sheep. *Acta Physiol. Pol.* 26:433–37
184. Zschaeck, L. L., Wurtman, R. J. 1973. Brain ^{3}H-catechol synthesis and the vaginal estrous cycle. *Neuroendocrinology* 11:144–49
185. Stefano, F. J. E., Donoso, A. O. 1967. Norepinephrine levels in the rat hypothalamus during the estrous cycle. *Endocrinology* 81:1405–6
186. Donoso, A. O., Moyano, M. B. 1970. Adrenergic activity in hypothalamus and ovulation. *Proc. Soc. Exp. Biol. Med.* 135:633–35
187. Selmanoff, M. K., Pramik-Holdaway, M. J., Weiner, R. I. 1976. Concentration of dopamine and norepinephrine in discrete hypothalamic nuclei during the rat estrous cycle. *Endocrinology* 99:326–29
188. Tima, L., Flerko, B. 1974. Ovulation induced by norepinephrine in rats made anovulatory by various experimental procedures. *Neuroendocrinology* 15: 346–54
189. Tima, L., Flerko, B. 1974. Ovulation induced by the intraventricular infusion of norepinephrine in rats made anovulatory by neonatal administration of various doses of testosterone. *Endocrinology* 66:218–20
190. Krieg, R. J., Sawyer, C. H. 1976. Effects of intraventricular catecholamines on luteinizing hormone release in ovariectomized-Steroid-primed rats. *Endocrinology* 99:411–19
191. Vijayan, E., McCann, S. M. 1978. Reevaluation of the role of catecholamines in control of gonadotropin and prolactin release. *Neuroendocrinology* 25: 150–65
192. Kalra, P. S., Kalra, S. P., Krulich, L., Fawcett, C. P., McCann, S. M. 1972. Involvement of norepinephrine in transmission of the stimulatory influence of

progesterone on gonadotropin release. *Endocrinology* 90:1168–76
193. Martinovic, J. V., McCann, S. M. 1977. Effect of lesions in the ventral noradrenergic tract produced by microinjection of 6-hydroxydopamine on gonadotropin release in the rat. *Endocrinology* 100:1206–13
194. Sawyer, C. H., Markee, J. E., Hollinshead, W. H. 1947. Inhibition of ovulation in the rabbit by the adrenergic-blocking agent dibenamine. *Endocrinology* 41:395–402
195. Gnodde, H. P., Schuiling, G. A. 1976. Involvement of catecholaminergic and cholinergic mechanisms in the pulsatile release of LH in the long-term ovariectomized rat. *Neuroendocrinology* 20:213–23
196. Weick, R. F. 1978. Acute effects of adrenergic receptor blocking agents and neuroleptic agents on pulsatile discharges of luteinizing hormone in the ovariectomized rat. *Neuroendocrinology* 26:108–17
197. Jackson, G. L. 1973. Effect of adrenergic blocking drugs on secretion of luteinizing hormone in the ovariectomized ewe. *Biol. Reprod.* 16:543–48
198. Kinoshita, F., Nakai, Y., Katakami, H., Kato, Y., Imura, H. 1981. Role of α-adrenergic mechanism in regulating tonic luteinizing hormone release in conscious ovariectomized rats. *Endocrinology* 108:1271–75
199. Crowley, W. R., Nock, B. L., Feder, H. H. 1977. Facilitation of lordosis behavior by clonidine in female guinea pigs. *Pharmacol. Biochem. Behav.* 8:207–9
200. Nock, B., Feder, H. H. 1979. Noradrenergic transmission and female sexual behavior of guinea pigs. *Brain Res.* 166:369–80
201. Ward, I. L., Crowley, W. R., Zemlan, F. P., Margules, D. L. 1975. Monoaminergic mediation of female sexual behavior. *J. Comp. Physiol. Psychol.* 88:53–61
202. Bolme, P., Corrodi, H., Fuxe, K., Hökfelt, T., Lidbrink, P., Goldstein, M. 1974. Possible involvement of central adrenaline neurons in vasomotor and respiratory control. Studies with clonidine and its interactions with piperoxane and yohimbine. *Eur. J. Pharmacol.* 28:89–94
203. Foreman, M. M., Moss, R. L. 1978. Role of hypothalamic alpha and beta adrenergic receptors in the control of lordotic behavior in the ovariectomized estrogen-primed rat. *Pharmacol. Biochem. Behav.* 9:235–41
204. Goodman, R. L. 1978. A quantitative analysis of the physiological role of estradiol and progesterone in the control of tonic and surge secretion of luteinizing hormone in the rat. *Endocrinology* 102:142–50
205. Davis, G. A., Kohl, R. 1977. The influence of α-receptors on lordosis in the female rat. *Pharmacol. Biochem. Behav.* 6:47–53
206. Libertun, C., McCann, S. M. 1973. Blockade of the release of gonadotropins and prolactin by subcutaneous or intraventricular injection of atropine in male and female rats. *Endocrinology* 92:1714–24
206a. Fuxe, K., Everitt, B. J., Hökfelt, T. 1977a. Enhancement of sexual behavior in the female rat by nicotine. *Pharmacol. Biochem. Behav.* 7:147–51
207. Clemens, L. G., Dohanich, G. P. 1980. Inhibition of lordotic behavior in female rats following intracerebral infusion of anti-cholinergic agents. *Pharmacol. Biochem. Behav.* 13:89–95
208. Clemens, L. G., Humphrys, R. R., Dohanich, G. P. 1980. Cholinergic brain mechanisms and the hormonal regulation of female sexual behavior in the rat. *Pharmacol. Biochem. Behav.* 13:81–88
209. Kordon, C., Javoy, F., Vassent, G., Glowinski, J. 1968. Blockade of superovulation in the immature rat by increased brain serotonin. *Eur. J. Pharmacol.* 4:169–74
210. Labhsetwar, A. P. 1972. Role of monoamines in ovulation: evidence for a serotonergic pathway for inhibition of spontaneous ovulation. *J. Endocrinol.* 54:269–75
211. O'Steen, W. K. 1965. Suppression of ovarian activity in immature rats by serotonin. *Endocrinology* 77:937–39
212. Kamberi, I. A. 1973. The role of brain monoamine and pineal indolamines in the secretion of gonadotropins and gonadotropin-releasing factors. *Prog. Brain Res.* 39:261–79
213. Domanski, E., Przekop, F., Skubiszewski, B., Wolinska, E. 1975. The effect and site of action of indoleamines on the hypothalamic centers involved in the control of LH release and ovulation in sheep. *Neuroendocrinology* 17:265–73
214. Hery, M., Laplante, E., Pattou, E., Kordon, C. 1975. Interaction de la serotonine cerebrate avec la liberation cyclique de LH chez la ratte. *Ann. Endocrinol.* 36:123–20
215. Hery, M., Laplante, E., Kordon, C. 1976. Participation of serotonin in the

phasic release of LH. Evidence from pharmacological experiments. *Endocrinology* 99:496–503
216. vandeKar, L. D., Lorens, S. A., Vodraska, A., Allers, G., Green, M., Van Orden, D. E., Van Orden, L. S. 1980. Effect of selective midbrain and diencephalic 5,7-dihydroxytryptamine lesions on serotonin content in individual preopticohypothalamic nuclei and on serum luteinizing hormone level. *Neuroendocrinology* 31:309–15
217. Meyer, D. C. 1978. Hypothalamic and raphe serotonergic systems in ovulation control. *Endocrinology* 103:1067–74
218. Marko, M., Flückiger, E. 1976. Inhibition of ovulation in rats by antagonists to serotonin and by a new tricyclic compound. *Experientia* 32:491–92
219. Marko, M., Flückiger, E. 1980. Role of serotonin in the regulation of ovulation. *Neuroendocrinology* 30:228–31
220. Gonzalez-Baron, S., Jimenez-Vargas, J., Marco, T. 1975. Effecto de la *p*-chlorofenialanina sobre la reproduccion en la rata. *Revista Esp. Fisiol.* 31:63–68
221. Meyerson, B. J. 1964. Central nervous monoamines and hormone-induced estrus behaviour in the spayed rat. *Acta Physiol. Scand.* 63: Suppl. 241, pp. 1-32
222. Meyerson, B. J. 1964. Estrous behaviour in spayed rats after estrogen or progesterone treatment in combination with reserpine or tetrabenazine. *Psychopharmacologia* 6:210–18
223. Meyerson, B. J. 1964. The effect of neuropharmacological agents on hormone-activated estrus behavior in ovariectomized rats. *Arch. Int. Pharmacodyn.* 150:4–33
224. Meyerson, B. J. 1966. The effect of imipramine and related antidepressive drugs on estrus behavior in ovariectomized rats activated by progesterone, reserpine or tetrabenazine in combination with estrogen. *Acta Physiol. Scand.* 65:411–22
225. Meyerson, B. J. 1968. Amphetamine and 5-HT inhibition of copulatory behavior in the female rat. *Ann. Med. Exp. Biol. Fenn.* 46:394–98
226. Meyerson, B. J., Lewander, T. 1970. Serotonin synthesis inhibition and estrous behavior in female rats. *Life Sci.* 9:661–71
227. Zemlan, F. P., Ward, I. L., Crowley, W. R., Margules, D. L. 1973. Activation of lordotic responding in female rats by suppression of serotonergic activity. *Science* 179:1010–12
228. Hansult, C. D., Uphouse, L. L., Schlesinger, K., Wilson, J. R. 1972. Induction of estrus in mice: hypophyseal-adrenal effects. *Horm. Behav.* 3:113–21
229. Gradwell, P. B., Everitt, B. J., Herbert, E. J. 1975. 5-hydroxytryptamine in the central nervous system and sexual receptivity of female rhesus monkeys. *Brain Res.* 88:281–93
230. Foreman, M. M., Moss, R. L. 1978. Role of hypothalamic serotonergic receptors in the control of lordosis behavior in the female rat. *Horm. Behav.* 10:97–106
231. Luine, V. N., Paden, C. M. 1982. Effects of monoamine oxidase on female sexual behavior, serotonin level and Type A and B monoamine oxidase activity. *Neuroendocrinology.* In press
232. Espino, C., Sano, M., Wade, G. N. 1975. Alpha-methyltryptamine blocks facilitation of lordosis by progesterone in spayed estrogen-primed rats. *Pharmacol. Biochem. Behav.* 3:557–59
233. Sietnieks, A., Meyerson, B. J. 1980. Enhancement by progesterone of lysergic acid diethylamide inhibition of the copulatory response in the female rat. *Eur. J. Pharmacol.* 63:57–64
234. Tennent, B. J., Smith, E. R., Davidson, J. M. 1980. The effects of estrogen and progesterone of female rat proceptive behavior. *Horm. Behav.* 14:65–75
235. Barfield, R. J., Chen, J. J. 1977. Activation of estrous behavior in ovariectomized rats by intracerebral implants of estradiol benzoate. *Endocrinology* 101: 1716–25
236. Davis, P. G., McEwen, B. S., Pfaff, D. W. 1979. Localized behavioral effects of tritiated estradiol implants in the ventromedial hypothalamus of female rats. *Endocrinology* 104:898–903
237. Rubin, B. S., Barfield, R. J. 1980. Priming of estrous responsiveness by implants of 17-β-estradiol in the ventromedial hypothalamic nucleus of female rats. *Endocrinology* 106:504–9
238. Wallis, C. J., Luttge, W. G. 1980. Influence of estrogen and progesterone on glutamic acid decarboxylase activity in discrete regions of rat brain. *J. Neurochem.* 34:609–13
239. Ladisch, W. 1974. Effect of progesterone on regional 5-hydroxytryptamine metabolism in the rat brain. *Neuropharmacology* 13:877–83
240. Vacas, M. I., Cardinali, D. P. 1980. Effect of estradiol on α- and β-adrenoceptor density in medial basal hypothalamus, cerebral cortex and pi-

neal gland of ovariectomized rats. *Neurosci. Lett.* 17:73–77

241. Wilkinson, M., Herdon, H., Pearce, M., Wilson, C. 1979. Radioligand binding studies on hypothalamic noradrenergic receptors during the estrous cycle or after steroid injection in ovariectomized rats. *Brain Res.* 168:652–55
242. Portaleone, P., Genazzani, E., Pagnini, G., Crispino, A., DiCarlo, F. 1980. Interaction of estradiol and 2-hydroxyestradiol with histamine receptors at the hypothalamic level. *Brain Res.* 187: 216–20
243. Wagner, H. R., Crutcher, K. A., Davis, J. N. 1979. Chronic estrogen treatment decreases β-adrenergic responses in rat cerebral cortex. *Brain Res.* 171: 147–51
244. Kendall, D. A., Tonge, S. R. 1977. Effects of testosterone and ethinyloestradiol on the synthesis and uptake of noradrenaline and 5-hydroxytryptamine in rat hindbrain: evidence for a presynaptic regulation of monoamine synthesis? *Br. J. Pharmacol.* 60:309p–10p