Life Sciences, Vol. 37, pp. 893-906 Pergamon Press
Printed in the U.S.A.

MINIREVIEW

ROLE OF FEMALE GONADAL HORMONES IN THE CNS: CLINICAL AND EXPERIMENTAL ASPECTS

Adriana Maggi and Jorge Perez

Milano Molecular Pharmacology Laboratory
Institute of Pharmacology and Pharmacognosy, University of Milan
P.za Durante 11 - 20131 Milan, Italy

Introduction

Various lines of evidence have clearly demonstrated that female steroid hormones can act in the Central Nervous System (CNS), principally in the thalamic and hypothalamic areas, to regulate endocrine functions and sex related behavior. In the past few years, clinical observations have been accumulated suggesting that estrogens and progesterone may be involved also in the modulation of functions not strictly related to endocrine control. In fact, these hormones seem to partecipate in the control of motor areas (as demonstrated by their effects on clinical or experimental tardive dyskinesia, chorea, epilepsy) and limbic areas (since they are reported to influence psychiatric disorders like depression and schizophrenia). However, it is still controversial whether these effects are secondary to the hormone action in the well known brain target areas (thus resulting in altered levels of gonadotropins, etc.) or are due to a direct action of the sex steroids in the motor and limbic areas. The finding that receptors for progesterone and estrogens are present in numerous extrahypothalamic brain regions has given a new impulse to studies aimed at understanding whether these hormones are implicated also in the regulation of brain functions not related to endocrine control or sexual behavior.

The goal of this report is to review the clinical and experimental data supporting a widespread effect of estrogens and progesterone in the C.N.S. of mammals.

Areas target for sex hormones in the CNS of mammals

In most of the mammalian species studied the major number of binding sites specific for estrogens can be found in the following regions of the CNS: 1) preoptic area (nuclei preopticus-medialis and interstitialis, striae terminalis); 2) hypothalamic area (nuclei infundibularis, ventro-medialis, premammilaris-ventralis); and 3) amygdaloid area (nuclei medialis, corticalis and basalis) (1).

Outside these three major areas other regions display estrogen binding activity: ^{3}H-estradiol visibly accumulates in the septal nuclei and hippocampus

0024-3205/85 $3.00 + .00

of rat (but not of monkey), in the midbrain (inferior colliculus), in the dorsal region of the pons (nucleus parabrachialis, locus ceruleus and central gray), in the cerebellar cortex (Golgi-type II cells) and in the spinal cord (2). Therefore, the neuronal regions displaying the highest estrogen receptors concentration are primarily located in the phylogenetically older regions of the brain. In contrast, progesterone receptors seem to be spread throughout the brain: proteins specifically binding this hormone may be detected in the cortex, habenula, area postrema, hypothalamus, lamina terminalis, olfactory bulb, hippocampus, caudate and cerebellum (3,4,5).

Pharmacological and physiological studies have demonstrated that the receptors for sex hormones present in the brain are indistinguishable from those in the periphery (4,5). Furthermore, in accord to the model of steroid action (135,136) the central receptors may be found in the nuclei of target cells within two hours after hormone administration, bind chromatin "in vitro" (7) and elicit the synthesis of specific proteins (4,5) and mRNAs (8).

Clinical evidence of estrogen and progestin involvement in the regulation of extrapyramidal functions

a) Steroid hormones and chorea

Many lines of evidence suggest cause-and-effect relationship between high levels of steroid hormones and chorea:

1) For a long time it has been known that reversible chorea may be observed during pregnancy ("chorea gravidarum") (9,10).

2) In 1966 Fernando (11) reported a case of a 22-year-old woman who developed typical chorea while taking contraceptive drugs, since then, many other reports have signaled similar findings (12,13,14,15,16).

3) Further evidence of an association between high levels of steroid hormones and chorea is provided by the observation that Sydenham chorea, which has an identical incidence in males and females below the age of 10, in adults is prevalent in females and is usually associated with pregnancy (17,18,19).

b) Steroid hormones and tardive dyskinesia

For many years it has been disputed whether tardive dyskinesia, could appear with prevalence in elderly women (20,21) indicating a hormonal influence on the expression of the disease. Few clinical reports support this theory. The first report by Gratton et al. (22) indicated that estrogens accelerate the onset and increase the intensity of drug-induced parkinsonism in both man and women. Subsequently, Bedard (23) reported two cases of patients where dyskinesias caused by two different mechanisms (levodopa-triggered and neuroleptic-induced) were of lower intensity in periods corresponding to raised circulating estrogen activity. Bedard et al. (23) indicated that the dyskinesias improved upon administration of a progestin with antiestrogenic activity or after the decrease in circulating estrogens during menstruation while Koller et al. published that estrogens have limited efficacy in the treatment of dyskinetic disorders (47).

Comment: The studies reported clearly demonstrate that sex hormones may influence the functionality of the extrapyramidal system. However, the occurrence of extrapyramidal malfunction induced by changes of the plasma level of estrogens and progestins represents a very rare event. Therefore, it has been hypothesized that the change in hormonal status could merely highlight a subclinical damage already present in the basal ganglia. In fact, Riddoch et al. (14) report that a past history of rheumatism can be found in most patients with chorea gravidarum. Similarly, most of the cases exhibiting oral-contraceptive chorea frequently had a prior history of similar movements disorders due to various etiological factors. If this were the case, sex hormones could simply have an extramodulatory action in the regulation of neuronal circuitry preceding movements and their action would become evident only in the absence of other primary circuitry.

Experimental models supporting the hypothesis of estrogen modulation of extrapyramidal functions

One of the earliest reports suggesting the involvement of estrogens in the control of motor activities is due to Young and Fish (24) who observed that the "spontaneous running activity" of female rats is higher during oestrus. More recently, many other animal studies have been carried out to test the effect of estrogens on extrapyramidal functions. In view of the well known role of dopamine (DA) transmission in the activity of the basal ganglia, most of the studies have been aimed at determining whether sex hormones could in any way control DA neurons functionality. Estrogens have been reported to both antagonize and potentiate the activity of the DA system:

1) Behaviorally it has been shown that estrogens:

   a) increase the stereotyped behavior produced by the administration of dopamine (DA) agonists in the rat (25,26,27,28,29).
   b) increase the rotational behavior in response to amphetamine and apomorphine in rat with unilateral nigro-striatal lesions of the DA tract (30).

   These data suggest that estrogens potentiate DA activity. Other behavioral studies, on the other hand, demonstrate the opposite effect; estrogens in fact have also been reported to:

   a) increase apomorphine-induced circling in rats with unilateral forebrain depletion of DA (31).
   b) decrease apomorphine-induced circling in rats with unilateral lesion of the entopeduncular nucleus (32).
   c) diminish the stereotypic response to apomorphine and amphetamine (27,28).
   d) intensify the cataleptic response to DA antagonist (33,34,35,36).
   e) antagonize apomorphine-induced yawning in rats (37).

2) Biochemically it has been shown that estrogens:

   a) increase the number of DA receptors in striatum (30,32,35,38).
   b) antagonize the increase in ^{3}H-spiroperidol binding sites induced by haloperidol (39).
   c) interfere with catechol-O-methyltransferases (COMT) activity (40).

d) increase DA synthesis and turnover (41).
e) potentiate DA release stimulated by amphetamine or K^+ in striatum (44).

However they are reported also to:

a) reduce striatal DA concentration (42,43).
b) reduce the response of intrastriatal cholinergic neurons to DM (44).
c) reduce the neuroleptic-induced supersensitivity (45,46).

3) Electrophysiologically it has been observed that neurons in the substantia nigra that respond to DA have a higher resting firing rate in animals treated with estrogens (48) while in similar animals a reduced sensitivity to iontophoretically applied DA was shown (49).
Very limited are the studies concerning the control of sex hormones on other neurotransmitter systems in extrapyramidal areas. In the striatum estrogens and progesterone have been described to increase the number of GABA receptors (50) and to have no effect on cholinergic binding sites (51,52).
In the cortex both hormones augment the number of $5\text{-}HT_1$ receptors (53).

Comment: it appears evident that the data available are too fragmentary and incomplete to allow an understanding of the biochemical mechanisms of the action of sex hormones on extrapyramidal activity. The data on the dopaminergic system indicate the possibility of a dual role of estradiol, at least in the striatum. In fact, as pointed out by Gordon (26) and Joyce et al. (54) short term exposure to estrogens seem to desensitize DA transmission (23,26,27,31) while prolonged treatment results in the opposite effect (27,28,30,33). However, even for this system we are far from understanding the mechanisms underlaying the observed changes.

Much more work needs to be done in order to understand the details of the control of motor activities by sex hormones. To elucidate the effect of progesterone on the extrapyramidal system the studies should be focused principally on the cortex and striatum where receptors for this hormone have been described (3,4,5), while for estrogens, the extrapyramidal areas richest of specific receptors are the brain stem and pons (1,2).

Besides, more studies should be conducted "in vitro" on isolated organs in order to discriminate between direct and indirect effect of sex hormones. In fact it has been demonstrated that pituitary hormones (e.g. prolactin, which is under estrogenic control) may influence the nervous transmission of striatum (55).

Clinical evidence of estrogens and progesterone involvement in the manifestation of epilepsy

The existence of a relationship between ovarian function and seizure susceptibility has been postulated a long time ago. Evidence supporting this hypothesis is as follows:

1) Gowers (56) first indicated a prevalence of females among patients who have onset of seizure disorders between 10 and 20 years of age, and later on other authors (57) have published similar results in a study on patients subject to "petit mal".

2) Light evoked electroencephalographic abnormalities are observed with a higher incidence in females during the years of active ovarian function (58,59).

3) In many patients affected by epilepsy it has been shown that the frequency and the intensity of seizures were increased in well defined periods of the menstrual cycle (60,61,62). Particularly, these studies demonstrated that fits are less severe and less frequent during the luteal phase (low estrogen/progesterone ratio) than in the follicular phase (high estrogen/progesterone ratio).

4) In agreement with these studies Zimmerman et al. (63) reported that a change in the ratio estrogen/progesterone achieved by administration of progestational agents may be effective in the treatment of seizures associated with menstruation and refractory to other pharmacological treatments.

5) Activation of seizures, EEG abnormalities and induction of "grand mal" (60) have been reported following intravenous administration of 20-40 mg of conjugated estrogenic substances (Premarin). However Marcus et al. (64) did not find either significant EEG change or seizure exacerbation in six seizure patients following administration of 20 to 60 mg of this agent.

Animals models for the study of the influence of sex hormones on epilepsy

Many studies indicate that both estrogens and progesterone may alter the seizure threshold in various experimental conditions: 1) It is known that sexually mature female rats demonstrate grater convulsive reactivity than prepuberally ovariectomized animals or than sexually mature males of the same age (65), 2) the changes in seizure threshold show a continuing rhythmicity paralleling the hormonal cyclicity of the gonads (66,67), 3) estradiol even in small doses increases convulsability in mice (68) rats (69,70) rabbits (71,73) and cats (72), 4) the threshold and pattern of electroshock seizures in rats varies during the estral cycle (74), the threshold for minimal seizures being highest during diestrus, lower during proestrus and lowest during estrus while the duration of tonic flexion during maximal seizures is longest during diestrus and shortest during estrus (65), 5) progesterone alone has some anticonvulsant effect on rats subjected to electroshock (75,69,70), on rats which are audiogenic seizure-resistant (76), and markedly inhibits kindling in immature animals (77); finally, 6) 0.1 - 1% conjugated estrogenic substances applied directly to acute and chronic epileptogenic foci in rabbit cerebral cortex have a pronounced epileptogenic effect (60,71).

The mechanisms through which sex hormones modulate the convulsive activity are unknown. Many reports indicate that these hormones alter the electrical activity of the brain: 1) estrogens have been reported to increase the mean spontaneous firing rate and to reduce the strength of post-stimulus inhibition in various areas like the hippocampus, amygdala (74) and nucleus reticularis lateralis (78,79), 2) to be capable of inducing epileptiform electrical activity when applied directly to the intact cerebral cortex (80,72), to various regions of the thalamus, or to chronically isolated cortical stabs (81). Conversely, progesterone has been described to first decrease and then increase the cortical arousal threshold for electrical

stimulation of the reticular activating system (82) and to suppress neuronal activity in the hippocampus and amygdala (74). Which can be the chemical mediators of these effects is just a matter of speculation.

In order to alter brain electrical activities steroid hormones may act in two different ways:

1) specifically, by binding their nuclear receptors, hereby inducing the synthesis of specific proteins (neurotransmitters, receptors, etc).
2) non specifically, by having a generalized effect on the neuronal membrane resulting in a disorganization of their electrical activity.

Many studies have indeed proven that estrogens and progesterone alter the uptake and release of neurotransmitter (83,84) the turnover of various neurotransmitters (85,86,87,88,89,90,91,92,93), the activity of their metabolizing enzymes (94,95,96,97,98,99) and the levels of their receptors (100,101,102,103). However, since most of these quantitative determinations have been conducted "in vivo" after 1 or more days of hormonal stimulation, it is impossible to distinguish between primary or compensatory effects and to pinpoint a neurotransmitter system target for the hormonal action. The time course of the effect of estradiol on electrical brain activities has been studied more closely from the electrophysiological point of view. Marcus et al. (59) demonstrated that a topical application of high concentrations (0.25%) of conjugated estrogenic substances to intact rabbit cerebral cortex produced an electrical spike within 5 minutes. The spike was localized, its amplitude dependent from hormonal dosage and was primarily a surface negative discharge often preceded or followed by lower amplitude surface positive components. The fact that γ-aminobutyric acid could eliminate the surface negative component and accentuate the positive component of the effect would argue against a generalized effect of the steroids on the membrane.

On the other hand, would 5 minutes be sufficient for the hormone to enter the cell, bind first its receptor then specific sequences of the DNA, increase mRNA and protein synthesis and for the newly synthesized proteins to migrate to the specific cellular region where they will act?

Other means to elucidate the details of sex hormone involvement in the expression of epileptic behaviour could be the study of the effect of antiepileptic drugs on estrogen-induced EEG spike wave discharges. Along this line of thought Julien et al. (80), provided a further piece of evidence against a non-specific effect of estrogen on brain electric activity. Their study demonstrates that the only drugs effective in reducing estrogen-induced spike wave discharges were acetazolamide, ethosuximide, trimethadione and diazepam (clinically all four agents are effective in the treatment of "petit mal") (104). Diphenylhydantoin together with imipramine were generally ineffective and actually intensified the epileptiform activity; even the local anestethic lidocaine was only slightly active in reducing either the amplitude or the occurrence of estrogen-induced spike wave episodes. Taken all together the studies seem to indicate that estrogens and progesterone may have a specific action on neurotransmission, but we are still far from understanding at which level of neurotransmission steroids act and which are the target systems.

Evidence of estrogens and progesterone involvement in the manifestation of affective disorders

It is widely accepted that the incidence of affective disorders is more frequent in women than in men (105). This phenomenon could be explained in part by the hypothesis that sex steroid hormones are involved in the etiology of some type of depression. A large body of evidence demonstrates that variation of sex hormone secretion are often associated with behavioral changes. First, we will discuss the behavioral consequences of physiological changes of gonad secretion like those observed during the menstrual cycle, parturition and menopause.

1) Mood changes can be observed during a particular period of the menstrual cycle as demonstrated by the following findings:
   a) Some women may experience a depressive syndrome during the premenstrual period severe enough to seek treatment for the condition (106,107).
   b) Suicide attempts and admission to psychiatric hospitals for depressive episodes are often associated with premenstrual period (108,109).
   c) In patients with depressive disorders, premenstrual exacerbations of depressive symptoms can be observed (110).

2) Another interesting period, from the endocrinological point of view, is the post-partum period, when the levels of sex hormones, very high in pregnancy, drop precipitously. It has been reported that up to 1/3 of women can encounter severe depression which lasts for about 3 months after delivery (111,112,113,114).

3) The last physiological event which leads to a change of the hormonal status is the menopause: traditionallly this has been considered a time when the incidence of depressive illness is unusually high (115). However, recently Winokur and Cadoret (116) conclude that data do not support this notion since there is no discernible peak in either depressive illness or suicide in the decade 45-54, the age in which cessation of menses occirs most frequently.

Mood changes have also been reported as a consequence of oral contraceptive use (117). However, it is very difficult to review the effect of these drugs because of their various composition and style of administration. Kane et al. (118,119) reported that 10 to 40 per cent of oral contraceptive users may suffer mild to moderate depression syndromes. Grant and Psyse-Davies (120) indicate that high risk of depression exists when the level of estrogen in the pill is low and the level of progestin is high; while in pills where both levels of estrogens and progesterone are high, the high levels of estrogen seemed to offset the adverse mental changes associated with the progestins. However, several studies failed to find a correlation between the incidence of affective disorders and oral contraceptive therapy (121,122).

Finally, Sachar (123) and Halbreich (124) have described the presence of abnormalities in hormone secretion and activities in depressed patients.

All the studies reported indicate a possible role of sex hormones in the modulation of depression. If sex hormones were indeed the cause of depression

it would be conceivable that the same hormones could be employed as a therapeutic agent in the treatment of this disease. In fact, it has been reported that a significant number of patients who failed to respond to antidepressant drugs were treated successfully with estrogen therapy (125) or estrogens in combination with antidepressants (115,126,127,128).

Comment: While most of the studies reported seem to favor the theory of a role of sex hormones in the pathogenesis of depression, it is worthy to state that many authors disagree with this view.

A possible explanation for this disagreement could be due to the fact that the depressive features of women with premenstrual, menopause or post partum depression are not those of the "classic" endogenous depression: e.g. guilt, early morning wakening, lack of reactivity of mood, loss of appetite. Many women manifest their depression with "atypical" features as hypersomnia, overeating and reactive mood, whereas in others it is characterized by anxiety and agitation or hostility and anger. The presence of these atypical characteristics has generated many difficulties in the correct scoring of depressed patients.

Experimental evidence of sex hormones involvement in the manifestation of affective disorders

The classical hypothesis for the manifestation of affective disorders (129,130,131) implies that depression involves an impairment of central adrenergic and serotoninergic transmission. As previously mentioned, estrogens and progestins may alter catecholamine transmission by altering the levels of NA and 5-HT receptors, the release of the neurotransmitters or their rate of synthesis or catabolism.

In addition, various authors have described the presence in the brain of enzymes which transform estrogens in catechol estrogens. These compounds may competitively inhibit the enzymatic methylation and biological inactivation of NA by catechol-O-methyltransferases (COMT) (132,133,134).

Recently, Kendall et al. (102) have demonstrated that sex steroids may play an important role in the neurochemical response to a classical antidepressant: imipramine. The data suggest that estrogens and progesterone are important for imipramine to cause down regulation of $5HT_2$ receptor in cerebral cortex, but are not implicated in the effect of this drug on the ß-adrenergic receptor.

Summary and conclusions

The large body of evidence presented indicates that in the brain the action of sex hormones cannot be thought as restricted to the regulation of endocrine functions and mating behavior. Estrogens and progestone seem to act in numerous regions of the CNS to regulate motor as well as limbic functions. Furthermore, the data reviewed indicate that these hormones may modulate neuronal activity through a wide variety of mechanisms. More studies should focus on such mechanisms in order to better understand the role of sex hormones in the CNS and to devise ways of limiting their effects on depression, epilepsy etc.

It is known that in peripheral target organs these hormones modulate cell activities by binding to specific receptors which can recognize the DNA sequence and activate the trascription of selected genes (135,136). There is evidence supporting the hypothesis that this mechanism of action has been conserved also in the brain. First, the brain receptors for progesterone and estrogens are functionally and biochemically indistinguishable from those in the periphery (4,5): they may be concentrated in neuronal nuclei and bind chromatin "in vitro" (7). Second, a temporal relationship has been observed between administration of steroids and the increase of polymerase II activity (137) and protein synthesis (4,5). Third, various hormone-induced behaviors may be blocked by inhibitors of the protein synthesis (138,139,140,141).

However, sex hormones must be capable to regulate neuronal functions by mechanisms other then genomic. In fact, the topical application of estrogen or progesterone on nervous tissue results in a rapid change of membrane potential (60,71). Such a rapid effect is not likely to be the consequence of nuclear action, but rather must be related to events occurring on the cell surface. It has been hypotized that sex steroids affect the fluidity of the cell membrane, therefore modifying the ion transport or neurotransmitter receptor activity (142). It this were the case we would expect to observe a similar effect after application of any steroid. Experimental evidence demonstrates that not all the steroids affect the nervous membrane potential. Moreover, two steroids, estradiol and progesterone, have been described to modulate membrane potential in an opposite way (66,67,69,75).

At the moment, there is no evidence for the presence of steroid receptors on neuronal membranes which could mediate the described phenomena. However, at least estrogens may interfere with catecholaminergic transmission by means of its 2,4-hydroxylated catabolites. These metabolites, denominated catecholestrogens because of their chemical structure, may interact with catecholamine receptors (143) and inhibit catecholaminergic enzymes (COMT etc.) (132,133,134) still, the electrophysiological action of estrogens cannot be explained by a membrane effect of catecholestrogens because the hydroxylation should not occur at the fast rate required (milliseconds).

Finally, it is worth reminding that sex hormones may modulate the activity of extrahypothalamic areas via a third mechanism which is secondary to the effects elicited by these hormones in the hypothalamus. In fact, at the hypothalamic level these steroids induce the synthesis of proteins and peptides (e.g. gonadotropin releasing factors, prolactin, etc.) which can then reach also other regions of the CNS and exert their regulatory effect (55). Through these proteins then, sex hormones may regulate the activity of areas where their receptor are not present. Studies should be devised in order to discriminate between primary and secondary effects of these steroids.

While it is now evident that sex hormones have a widespread influence on brain activities, still the evolutionary process and the teleological meaning that brought these hormones to acquire such a role in the C.N.S. of mammals remain an open question.

Acknowledgements

We are grateful to Dr. S. Cantaluppi, Ms S. Dallerba and Ms M. Zamati for restyling and typing our manuscript.

References

1. D.A. KEEFER and W.E. STUMPF, Anatomical Neuroendocrinology, Karger, Basel, pp. 153-173 (1975).
2. W.E. STUMPF and M. SAR, J. Steroid. Biochem. 11, 801-807 (1979).
3. B. UMBERKOMAN-WIITA and T.C. ANAND KUMAR, J. Steroid Biochem. 11, 809-818 (1979).
4. N.J. MacLUSKY and B. McEWEN, Endocrinology, 106, 192-202 (1980).
5. M. MOGUILEWSKY and J.P. RAYNAUD, Brain Res. 164, 165-175 (1979).
6. I. LIEBERBURG, N. MacLUSKY and B.S. McEWEN, Brain Res., 193, 487-503 (1980).
7. R.E. WHALEN and K.L. OLSEN, Brain Res. 152, 121-131 (1978).
8. A. MAGGI and I. ZUCCHI, in preparation.
9. P.A. NAUSIEDA, W.C. KOLLER, W.J. WEINER and N.L. KLAWANS, Neurology 29 1605-1609 (1979).
10. J.O. DONALDSON, Neurology of Pregnancy, p. 74, W.B. Saunders Co., Philadelphia (1978).
11. S.J.M. FERNANDO, Practitioner 197 210-212 (1966).
12. P.H. LEWIS and M.J. HARRISON, Br. Med. J. 4 404-408 (1969).
13. E.T. GAMBOA, G. ISAACS and D.H. HARTER, Arch. Neurol. 25 112-114 (1971).
14. D. RIDDOCH, M. JEFFERSON and E.R. BICKERSTAFF, Br. Med. J. 4 217-218 (1971).
15. A.D. MALCOM, Br. Med. J. 4 491-498 (1971).
16. P.V. BARBER, A.G. ARNOLD and G. EVANS, Clin. Endocrinol. 5 291-293 (1976).
17. P. WILLSON and A.A. PREECE, Archives of Internal Medicine 49 471-671 (1932).
18. O.D. BERESFORD and A.M. GRAHAM, Journal of Obstetrics and Gynaecology of the British Empire 57 616-618 (1950).
19. W.C. KOLLER, W.J. WEINER, H.L. KLAWANS et al., 31st Annual Meeting of the American Academy of Neurology, Chicago, April (1979).
20. P.T. DOULON and R.L. STENSON, Dis. Nerv. Syst. 37 629-634 (1976).
21. J.M. SMITH, W.T. OSWALD, L.T. KUCHINSKY and L.J. WATERMAN, Psychopharmacologia 58 207-209 (1978).
22. L. GRATTON, Union Med. Can. 89 681-694 (1960).
23. P. BEDARD, P. LANGELIER, A. VILLENEUVE, Lancet 2 1367-1368 (1977).
24. W. YOUNG and W. FISH, Endocrinology 36 181-184 (1945).
25. S. LAL and T.L. SOURKES, Arch. Int. Pharmacodyn. 199 289-301 (1972).
26. J.H. GORDON, Brain Res. Bull. 5 679-682 (1980).
27. J.H. GORDON, R.L. BORISON and B.I. DIAMOND, Biol. Psychiat. 15 389-391 (1980).
28. R.E. HRUSKA and E.K. SILBERGELD, Eur. J. Pharmacol. 61 397-402 (1980).
29. A. CHIODO, A.R. CAGGIULA and C.F. SALLER, Life Sci. 28 827-831 (1981).
30. R.E. HRUSKA and E.K. SILBERGELD, Science 208 1466-1469 (1980).
31. C. EUVRARD, C. OBERLANDER and J.R. BOISSIER, J. Pharmacol. Exp. Ther. 214 179-186 (1980).
32. P. BEDARD, J. DANKOVA, R. BOUCHER and P. LANGELIER, Can. J. Physiol. Pharmacol. 56 538-541 (1978).
33. L.A. CHIODO, A.R. CAGGIULA and C.F. SALLER, Brain Res. 172 360-365 (1979).
34. M. DE RYCK, R.E. HRUSKA and E.K. SILBERGELD, Soc. Neurosci. Abst. 7 217

(1981).
35. T. DI PAOLO, P. POYET and F. LABRIE, Eur. J. Pharmacol. 73 105-106 (1981).
36. F. NICOLETTI, N. FERRARA, F. PATTI, M. VIGLIANES et al., Brain Res. 279 352-358 (1983).
37. G. SERRA, M. COLLU, A. SERRA and G.L. GESSA, Europ. J. Pharmacol. 104, 383-386 (1984).
38. K. FUXE, K. ANDERSSON, R. SCHWARCZ, L.F. AGNATI, PEREZ DE LA MORA, T. HOKFELT, M. GOLDSTEIN, L. FERLAND, L. POSSAM and R. TAPIA, In Advances in Neurology, vol. 24 (Pitier L.J., Sourkes T.L. and Bedard P.J. eds.), pp. 199-215, Raven Press, New York (1979).
39. J.Z. FIELDS, M.F. CALLAHAN and J.H. GORDON, Abst. Soc. Neurosci. 6 255 (1980).
40. P. BALL, R. KNUPPEN, M. HAUPT and H. BREUR, J. Clin. Endocrinol. Metab. 34 736-739 (1972).
41. J.B. BECKER, M.E. BEER and T.E. ROBISON, Brain Res. 311, 157-160 (1984).
42. A. DUPONT, T. DI PAOLO, B. GAGNE, N. BARDEN, Neurosci. Lett. 22 69-74 (1981).
43. M.M. FOREMAN and J.C. PORTER, J. Neurochem. 34 1175-1178 (1980).
44. C. EUVRARD, F. LABRIE and J. BOISSIER, Brain Res. 169 215-220 (1979).
45. J.H. GORDON and B.I. DIAMOND, Biol. Psychiatry 16 365-371 (1981).
46. W.C. KOLLER, W.J. WEINER and H.L. KLAWANS, Neuropharmacology 19 387-391 (1980).
47. W.C. KOLLER, A. BARR and N. BIARY, Neurology 32 547-549 (1982).
48. L.A. CHIODO, A.R. CAGGIULA, Eur. J. Pharmacol. 67 165-166 (1980).
49. E. ARNAUD, B. DUFY, M. PESTRE, J.D. VINCENT, Neurosci. Lett. 21 325-331 (1981).
50. A. MAGGI and J. PEREZ, Europ. J. Pharmacol. 103, 165-168 (1984).
51. G.P. DOHANICH, J.A. WITCHER, D.R. WEAVER, L.G. CLEMENS, Brain Res. 241, 347-350 (1982).
52. T.C. RAINBOW, V. DEGROFF, V.N. LUINE and B.S. McEWEN, Brain Res. 198, 239-243 (1980).
53. A. BIEGON, A. RECHES, L. SNYDER and B.S. McEWEN, Life Sciences 32, 2015-2020 (1983).
54. J.N. JOYCE, R.L. SMITH, C. VAN HARTESVELDT, Eur. J. Pharm. 81 117-122 (1982).
55. R.E. HRUSKA, L. LUDMER, E.K. SILBERGELD, Neuropharmacology 19, 923-926 (1980).
56. W.R. GOWERS, Epilepsy and other chronic diseases, their causes, symptomes and treatment, New York, William Wood, p. 10-16 (1885).
57. W.G. LENNOX and M.A. LENNOX, Epilepsy and related disorders, Boston, Little Brown and Co., vol. 1, pp. 170-172 (1960).
58. E.M. MARCUS, C.W. WATSON and R. BOWKER, Proceedings of the American Academy Neurology, 12th Annual Meeting, p. 28 (1960).
59. E.M. MARCUS, C.W. WATSON, P.L. GOLDMAN, Arch. Neurol. 15 521-532 (1966).
60. J. LOGOTHETIS, R. HARNER, F. MORREL and F. TORRES, Neurology 9 352-360 (1959).
61. T. BACKSTROM, Experientia 32 248-249 (1976).
62. J. LAIDLOW, Lancet 2 1235-1236 (1956).
63. A.W. ZIMMERMAN, K.R. HOLDEN, E.O. REITER and A.S. DEKABAN, J. Pediatr. 83

959-963 (1979).
64. E.M. MARCUS, C.W. WATSON, A.M. DE LUCA, Electroenceph. Clin. Neurophysiol. 15 150-151 (1963).
65. D.E. WOOLEY and P.S. TIMIRAS, Am. J. Physiol. 202 379-382 (1962).
66. B.K. Mc GOWAN-SASS and P.S. TIMIRAS, The hippocampus, vol. 1, edited by R.L. Isaacson and K.H. Pribram, pp. 355-374, Plenum Press, New York (1975).
67. P.S. TIMIRAS, In Basic Mechanism of the Epilepsies, ed. by H.H. Jasper, A.A. Ward Jr. and A. Pope, pp. 727-736, Little Brown & Compay, Boston (1969).
68. A. BLACKHAN and P.S.J. SPENCER, J. Pharm. Pharmacol. 22, 304-305 (1970).
69. S.L. STITT and W.J. KINNARD, Neurology 18, 213-216 (1968).
70. D.E. WOLLEY and P.S. TIMIRAS, Endocrinology 70, 196-209 (1962).
71. J. LOGOTHETIS and R. HARNER, Arch. Neurol. 3 290-297 (1960).
72. E.M. MARCUS, C.W. WATSON and P.L. GOLDMAN, Arch. Neurol. 15, 521-532 (1966).
73. D.E. WOOLEY, P.S. TIMIRAS, M. ROSENZWEIG, D. KRECH and E. BENNET, Nature 190 515-516 (1961).
74. M. KAWAKAMI, E. TERASAWA and T. IBUKI, Neuroendocrinology 6 30-48 (1970).
75. E. SPIEGEL and H. WYCIS, J. Lab. Clin. Med. 30, 947-957 (1954).
76. J. WERBOFF, L. HEDLUND, J. HAULENA, Gen. Comp. Endocr. 3, 389-397 (1963).
77. G.L. HOLMES and D.A. WEBER, Develop. Brain Res. 16, 45-53 (1984).
78. H. KABA, H. SAITO, K. SETO and M. KAWAKAMI, Brain Res. 234 149-154 (1982).
79. H. KABA, H. SAITO, K. OTSUKA, K. SETO and M. KAWAKAMI, Brain Res. 274 156-159 (1983).
80. R.M. JULIEN, G.W. FOWLER and M.G. DANIELSON, J. Pharmacol. Exp. Ther. 193 647-656 (1975).
81. S.C. LANGE and R.M. JULIEN, Electroencephalogr. Clin. Neurophysiol. 44 94-103 (1977).
82. M. KAWAKAMI and C.H. SAWYER, Endocrinology 65 652-668 (1959).
83. E. HACKMANN, A. WIRZ-JUSTICE and M. LICHSTEINER, Psychopharmacologia 32 183-191 (1973).
84. S.A. VOGEL, D.S. JANOWSKY and J.M. DAVIS, Res. Commun. Chem. Path. Pharm. 1 451-459 (1970).
85. W.R. CROWLEY, T.L. O'DONOHUE, T.H. WACHSLICH and D.M. JACOBOWITZ, Brain Res. 154 345-357 (1978).
86. W.R. CROWLEY, Neuroendocrinology 34 381-386 (1982).
87. A. LOFSTROM, P. ENEROTH, J.A. GUSTAFSSON and P. SKETT, Endocrinology 101 1559-1569 (1974).
88. K. HONMA and W. WUTTKE, Endocrinology 106 1848-1853 (1980).
89. P.M. WISE, N. RANCE and C.A. BARRACLOUGH, Endocrinology 108 2186-2193 (1981).
90. R.I. CONE, G.A. DAVIS and R.W. GOY, Brain Res. Bull. 7 639-644 (1981).
91. W.R. CROWLEY, T.L. O'DONOHUE, E.A. MUTH and D.M. JACOBOWITZ, Brain Res. Bull. 4 571-574 (1979).
92. W. LADISH, Advanc. Biochem. Psychopharmacol. 10 273-277 (1974).
93. S. BERNASCONI, S. GARATTINI and R. SAMANIN, Arch. Int. Pharmacodyn. 222 272-274 (1966).
94. C.W. BEATTIE, C.H. RODGERS and L.F. SOYKA, Endocrinology 91 276-279 (1972).

95. C. CHEVILLARD, N. BARDEN and J.M. SAAVEDRA, Brain Res. 222 177-181 (1981).
96. V.N. LUINE and B.S. Mc EWEN, J. Neurochem. 28 1221-1227 (1977).
97. V.N. LUINE, B.S. Mc EWEN and I.B. BLACK, Brain Res. 120 188-192 (1977).
98. V.N. LUINE and J.C. RHODES, Neuroendocrinology 36 235-241 (1983).
99. S.R. TONGE and P.M. GREENGRASS, Psychopharmacologia 21 374-381 (1971).
100. A. BIEGON, H. BERCOVITZ and D. SAMUEL, Brain Res. 187 221-225 (1980).
101. A. BIEGON, A. RECHES, SNYDER L. and B.S. Mc EWEN, Life Sci. 32 2015-2021 (1983).
102. D.A. KENDALL, G.M. STANCEL and S.J. ENNA, Science 211 1183-1185 (1981).
103. D.A. KENDALL, G.M. STANCEL and S.J. ENNA, J. Neurosci. 2 354-360 (1982).
104. T.W. RALL and L.S. SCHLEIFER, The pharmacological basis of therapeutics, A.G. Gilman, L.S. Goodman, A. Gilman, pp. 448-471, MacMillan Publishing Company, New York (1980).
105. C.SILVERMAN, The epidemiology of depression, The John Hopkins Press, Baltimore, MD (1968).
106. T. JACOBS, E. CHARLES, Am. J. Psychiatry 126 10-12 (1970).
107. K. DALTON, The premenstrual syndrome, Springfield Ill., Charles & Thomas Publisher 1964.
108. D. JANOWSKY, R. GORNEY, P. TEDESCO et al., Am. J. Obstet. Gynecol. 103 189-191 (1965).
109. R.D. WETZEL and J.N. Mc CLURE Jr., A review Compr. Psychiatry 13 369-374 (1972).
110. D.J. PALLIS, T.A. HOLDING, J. Biosoc. Sci. 8 27-33 (1976).
111. D.A. HAMBURG, R.H. MOSS and I.D. YALOM, Endocrinology and human behavior, Oxford Univ. Press London (1968).
112. S. GOLUB, Psychosom Med. 38 4-6 (1976).
113. C.K. SMITH, J. BARISH, J. CORREA, R.H. WILLIAMS, Psychosom. Med. 34 69 (1972).
114. D.S. JANOWSKY, R. GORNEY, A.J. MANDELL, Arch. Gen. Psychiatry 17 459-461 (1967).
115. A.J. PRANGE, J. Am. Med. Assoc. 219, 143-144 (1972).
116. G. WINOKUR and R. CADORET, Topics in Psychoendocrinology, pp. 59-66, Grune & Stratton, New York (1975).
117. A.J. PRANGE, M.A. LIPTON, C.B. NEMEROFF and I.C. WILSON, Life Sciences 20 1305-1318 (1977).
118. F.J. KANE, C.R. TREADWAY and J.A. EWING, Comprehen. Psychiatry 10 16-30 (1969).
119. F.J. KANE, Am. J. Obstet. Gynecol. 126 968-972 (1976).
120. E.C. GRANT and J. PSYSE-DAVIES, Brit. Med. J. 3 777-780 (1968).
121. G. PINCUS, Science 153 493-500 (1966).
122. A. NILSSON, L. JACOBSON and C.A. INGEMANSON, Acta Obstet. Gynecol. Scand. 46 537-540 (1976).
123. E.J. SACHAR, Hormones, Behavior and Psychopharmacology, Raven Press, New York (1975).
124. U. HALBREICH, J. ENDICOTT and J. NEE, Arch. Gen. Psychiatry 40 (1983).
125. E.L. KLAIBER, D.M. BROVERMAN, W. VOGEL and T. KOBAYASHI, Arch. Gen. Psychiat. 36 550-554 (1979).
126. G. OPPENHEIM, Am. J. Psychiat. 139 939-941 (1982).
127. G. OPPENHEIM, Biol. Psych. 18 721-725 (1983).

128. L.C. GERDES, E.W. SONNENDECKER and E.S. POLAKOW, Am. J. Obstet. Gynecol 142 98-104 (1982).
129. R.J. BALDESSARINI, Arch. Gen. Psychiatry 32, 1087-1089 (1975).
130. J.J. SCHILDKRAUT, Am. J. Psychiat. 122 509-522 (1967).
131. F. SULSER, Psychopharmacological treatment. Theory and practice, H.C.B. Denber Ed., pp. 97-120, New York, Marcel Dekker (1975).
132. T. LLOID and J. WEISZ, J. Biol. Chem. 253, 4841-4843 (1978).
133. H. BREURER and G. KOSTER, J. STEROID BIOCHEM. 5, 961-967 (1974).
134. G.R. MERRIAM, N.J. MacLUSKY, L.A. JOHNSON and F. NAFTOLIN, Steroids 36, 13-20 (1980).
135. E.V. JENSEN and H.I. JACOBSEN, Recent Prog. Horm. Res. 18, 387-414 (1972).
136. B.W. O'MALLEY, W.V. WEDECKIS, M. BIRNBAUMAER and W.T. SCHRADER, Molecular Endocrinology, McIntyre and Szelke eds. pp. 135-150, Elsevier, Amsterdam (1977).
137. E.J. PECK, Ontogeny of receptors and molecular mechanisms of reproductive hormone action, T. Hamilton Ed. New York, Raven Press (1978).
138. R.L. MEISEL and D.W. PFAFF, Brain Res. Bull. 12, 187-193 (1984).
139. J.H. GLASER and R.J. BARFIELD, Neuroendocrinol. 38, 337-343 (1984).
140. J.D. BLAUSTEIN and H.H. FEDER, Brain Res. 169, 481-497 (1979).
141. J.D. BLAUSTEIN and H.H. FEDER, Endocrinology 106, 1064-1069 (1980).
142. D.S. HERON, M. SHINITZKY, M. HERSHKOWITZ and D. SAMUEL, Proc. Natl. Acad. Sci. USA 77, 7463-7467 (1980).
143. C.M. PADEN, B.S. MCEWEN, J. FISHMAN, L. SNYDER and V. DEGROFF, J. Neurochem. 39, 512-520 (1982).