Actions of Steroid Hormones in the Brain

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Some actions of steroid hormones in brain - 1

Estradiol – neuroendocrine regulation and sexual behavior; attention, mood, memory; induction of synaptic connections in hippocampus, cortex and hypothalamus; neuroprotection from stroke, Parkinson's, Alzheimer's disease

Testosterone – neuroendocrine regulation; sexual and aggressive behavior; synapses in hippocampus, gap junctions in spinal cord motor neurons
Leranth, C., Pelletier, D., and MacLusky, N. J., Gonadal hormones affect spine synaptic density in the CA1 hippocampal subfield of male rats, J. Neurosci., 2003, 23: 1588-1592

Progesterone – neuroendocrine regulation and sexual behavior; neuroprotection; mood regulation
Some actions of steroid hormones in brain - 2

Glucocorticoids – neuroendocrine regulation; acute enhancement of memory; mediate chronic stress effects on neuronal remodeling

Mineralocorticoids – regulate salt appetite; mineralocorticoid receptors play a key role in excitability

Vitamin D – increases expression of NGF and p75, influences mood; developmental deficiency may increase risk for schizophrenia, multiple sclerosis
McGrath J. et al., Trends in Neuroscience 24: 570-571, 2001

Steroid receptors in the brain

<table>
<thead>
<tr>
<th>Receptor type</th>
<th>Methods used to detect them</th>
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<td>Estrogen</td>
<td>Steroid autoradiography</td>
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<td>Androgen</td>
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<td>Progestin</td>
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<td>Glucocorticoid</td>
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<td>Mineralocorticoid</td>
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<tr>
<td>Vitamin D</td>
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Adrenal steroid receptors in hippocampus
Estrogen receptors in hypothalamus, amygdala

Pfaff and Kever, 1973

Immunocytochemistry

Vitamin D receptors in forebrain

Fig. 7. Schematic provide outline maps of the forebrain of the Siberian hamster. Medial septal nucleus, nucleus of the diagonal band of Broca and the central amygdaloid group. The latter has been defined as consisting of the central nucleus of the amygdala, its extension into the sublenticular part of the substantia innominata of Reichert, and the lateral division of the bed nucleus of the stria terminalis. All these structures have been reported to be involved in memory and other cognitive processes, and to be affected by age-dependent neurodegenerative disorders such as Alzheimer's disease.

Corresponding localization of vitamin D receptor sites in these select basal forebrain nuclei of the Siberian hamster may implicate vitamin D (soltriol), the steroid hormone of sunlight, in memory processing.

Lordosis behavior

- Steroid hormones coordinate brain function with rest of body to ensure reproduction appropriate to environment.
- The lordosis response is triggered by touch on the back. It is primed by the actions of estradiol and progesterone acting sequentially on neurons in the ventromedial hypothalamus.
- The surge of progesterone at the time of ovulation not only primes lordosis but also the hopping, darting and ear wiggling of the female known as “proceptivity.”

Pfaff, “Drive”, MIT Press, 1999
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Neural circuit for lordosis behavior; From Estrogens & Brain Function (Pfaff, Springer-Verlag, 1980)

Estrogen regulation of female sexual behavior in the rat: genomic actions via ERE

The ventromedial nuclei of hypothalamus (VMN) are the sites of E regulation of female sexual behavior

E-inducible progesterone receptors in VMN

Cell nuclear ER alpha in ventromedial nuclei of rat hypothalamus (VMN)

Regulation of lordosis involves actions of ER alpha via the ERE

Estrogen induction of oxytocin receptors

Silencing of estrogen receptor α in the ventromedial nucleus of hypothalamus leads to metabolic syndrome

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Morris water maze - finding hidden platform

Rat/mouse learns by finding shortest path to platform using either global spatial cues or local contextual clues

Glucocorticoid receptors (GR) facilitate Morris water maze learning; Defective GR prevent the beneficial action

Point mutation in the mouse glucocorticoid receptor preventing DNA binding impairs spatial memory

Key transformations of steroids in the nervous system

Schumacher M et al., Steroid hormones and reversible, normal and pathological aging of the nervous system, Progress in Neurobiology 79: 3-29, 2003

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Limited capacity for steroid hormone synthesis

Cholesterol to pregnenolone and pregnenolone sulfate
Actions: regulation of NMDA, GABA receptors


Limited capacity for steroid hormone synthesis

Cholesterol to progesterone
Actions: neuroprotection; myelin formation


Schumacher M. et al., Steroid hormones and neurosteroids in normal and pathological aging of the nervous system, Progress in Neurobiology, 71: 3-29, 2003


Limited capacity for steroid hormone synthesis

Cholesterol to dehydroepiandrosterone
Actions: precursor of androgens, estrogens and other potentially neuroactive steroids

Schumacher M. et al., Steroid hormones and neurosteroids in normal and pathological aging of the nervous system, Progress in Neurobiology, 71: 3-29, 2003
Limited capacity for steroid hormone synthesis

Cholesterol to estradiol

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The Journal of Neuroscience, September 24, 2003, 23(25): 8701-8705

Important transformations of steroid hormones in the nervous system

11 hydroxysteroid dehydrogenase 2
Action: inactivation of active glucocorticoid

11 hydroxysteroid dehydrogenase 1
Action: reactivation of active glucocorticoid


Important transformations of steroid hormones in the nervous system

Aromatase and 5 alpha reductase

Androgen receptor

ER alpha
ER beta

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Important transformations of steroid hormones in the nervous system


Limitation of steroid access: e.g., synthetic glucocorticoids

Meijer OC et al., Penetration of dexamethasone into brain glucocorticoid targets is enhanced in mdr1a P-glycoprotein knockout mice. Endocrinology 1998, 139:1789-1793

Figure 1. Representative autoradiograms of 10 µm coronal sections of the brain of wild type and mdr1a (E/E) mice; Autoradiograms show labeling with [3H]dexamethasone of the following groups; a, Wild type treated with [3H]dexamethasone, hippocampus level; The dark spots represent transversal section of the cerebroventricular space and adjacent ventricular walls; b, Mutant treated with [3H]dexamethasone, hippocampus level; c, Mutant treated with [3H]dexamethasone, PVN level, note the pituitary mounted on top of the brain; d, Mutant treated with [3H]ecorticosterone, hippocampus level; Note the pituitary mounted on top of the brain

Rapid non-genomic actions of steroids in brain

Glucocorticoid action on mating via G protein coupled receptors in Taricha granulosa

Rapid, sex and subtype selective effects of androgens, estrogens and glucocorticoids in electric fish

Signaling via second messenger pathways
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**Rapid non-genomic actions of steroids in brain**

*Taricha granulosa*

**Fig. 2.** Distribution of putative, membrane-bound \[^3\]H\textsubscript{CORT} binding sites in the POA; Section (left) showing darkly stained perikarya of POA neurons; Autoradiogram of identical section (right) shows localization of \[^3\]H\textsubscript{CORT} specific binding sites in the oculopil surrounding perikarya of POA neurons


**Rapid non-genomic actions of steroids in brain**

*Communication in teleost fish*

Plasticity in Brain Sexuality Is Revealed by the Rapid Actions of Steroid Hormones

Julie Hormes Easteal and Andrew R. Bass

Department of Psychology and Biology, Cornell University, Ithaca, New York, USA, 1997

Different neuroendocrine profiles can shape the development of male versus female neural phenotypes, but little is known about how these differences in the adult brain, neuroendocrinological patterns of behavior in animals, and how these differences in the adult brain, in turn, affect neuroendocrinological patterns of behavior in animals. We now show that steroid hormones can modulate the expression of sex-specific genes in the brain, likely non-genomically. However, our current understanding of the mechanisms underlying these observations is still limited. This study uses a combination of pharmacological, behavioral, and neuroendocrinological approaches to investigate the role of steroid hormones in the brain. Our results suggest that steroid hormones can modulate the expression of sex-specific genes in the brain, likely by modulating the activity of specific transcription factors, which in turn can alter the expression of downstream genes. This study provides a new understanding of the mechanisms underlying sex-specific gene expression in the brain, and opens new avenues for future research in this area.

*The Journal of Neuroscience*, January 31, 2007, [27]: 1114-1122
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Steroid regulation of signaling pathways

- Estradiol and CREB phosphorylation

- Estradiol and MAPK activation

- Estradiol and AKT phosphorylation

- Progesterone and adenylate cyclase

See also:

Steroid hormones have widespread effects on brain structure and function

- Estradiol works in many brain areas via non-genomic as well as genomic receptors
  - e.g., regulation of spine synapse formation by estradiol

- Chronic stress affects brain structure and glucocorticoids play a role along with excitatory amino acids
  - e.g., regulation of neurogenesis, dendritic branching and spine density by chronic stress

Extra-hypothalamic brain systems affected by estrogens

- Basal forebrain cholinergic
- Mesolimbic dopamine
- Nigrostriatal dopamine
- Brain stem noradrenergic
- Midbrain serotonin
- Cerebellum
- Hippocampus
- Cerebral cortex
- Spinal cord

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**Dendritic spine density in stratum radiatum of CA1 fluctuates over the estrus cycle**

- ERα in interneuron cell nuclei
- Estrogen induction of spine synapses takes several days; Progesterone causes rapid down-regulation within 12h; NMDA receptor blockade prevents synapse formation; Estradiol treatment enhances hippocampal-dependent memory in rodents and humans

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**Non-nuclear ER alpha in dendritic spines**

- By EM, ERα is detected in dendritic spines in the CA1 region of the hippocampus (Teri Milner, Weill College of Medicine, Cornell)

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**NG-108-15 cells as a model system**

- Estradiol
- LY294002
- Rapamycin
- 4E-BP1
- PSD-95 protein translation


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Estradiol acts via GABA neurons and cholinergic mechanisms to up-regulate NMDA receptors. Estradiol inhibits GAD expression transiently and reduces inhibition on CA1 neuron. Estradiol up-regulates NMDA receptors via a mechanism involving cholinergic activity which is regulated by estrogens.

Gonadal Hormones Affect Spine Synaptic Density in the CA1 Hippocampal Subfield of Male Rats

Figure 2. Bar graph shows the result of the unbiased stereological calculation of spine synapse density in the stratum radiatum of the CA1 subfield of control, gonadectomized (GDX), gonadectomized plus testosterone-treated (GDX-T), gonadectomized plus dihydrotestosterone-treated (GDX-DHT), and gonadectomized plus estrogen-treated (GDX+E2) rats. There is no significant difference between the density values of spine synapses between the Control, GDX-T and GDX-DHT animals. However, the spine synapse density of the GDX and GDX+E2 rats is significantly (p < 0.001) lower (48%) than that of control animals.

Hippocampal formation: plasticity and vulnerability

Repeated stress causes CA3 pyramidal cells to show reversible dendritic shrinkage

Mimicked by chronic glucocorticoid treatment
Increased extracellular glutamate after stress
Prevented by:
1. Blocking glucocorticoid synthesis
2. Blocking NMDA receptors
3. Lithium
4. Dilantin
5. Antidepressants
6. Benzodiazepine

Testosterone levels in human and rat male: a comparison

Note: X and Y linked genes are expressed in many tissues and contribute to sex differences

Sexual differentiation and sex differences

Summary - 1
Every class of steroid hormones affects the nervous system
Cell nuclear as well as non-nuclear receptors mediate these effects
Some, but not all, of the non-nuclear receptors appear to be products of the same genes that produce the nuclear receptors
The nervous system has a limited capacity for de novo steroid hormone synthesis, e.g., pregnenolone, DHEA, progesterone and estradiol
The nervous system transforms steroids, e.g., aromatization, 5alpha reductase, A-ring reduction to steroids active on the GABAa receptor, reactivation of cortisone to cortisol
The nervous system also excludes some synthetic steroids, e.g., dexamethasone, via the multiple drug resistance p glycoprotein

Summary - 2
Genomic actions of steroids on the brain include the regulation of female sexual behavior in the hypothalamus and the modulation of spatial memory in the hippocampus
Non-genomic actions of steroids on the brain include G-protein coupled receptors for glucocorticoids, and rapid effects of estrogens, androgens and glucocorticoids in mating behavior in fish
A number of second messenger systems are activated by estrogens in brain and some of these systems play a role in neuroprotection and in structural plasticity, i.e., synapse formation induced by estradiol
Glucocorticoids participate in stress-induced remodeling of dendrites, synapses and the regulation of neurogenesis in the hippocampus; they do so by acting in concert with excitatory amino acids and NMDA receptors and other neurotransmitters
Summary - 3

Estrogen actions on synapse formation in the hippocampus involve a collaboration between genomic and non-genomic actions in a number of cell types: cholinergic neurons, inhibitory neurons producing GABA, excitatory neurons producing glutamate, glial cells; NMDA receptors play a key role.

Estrogens have widespread influences on many non-reproductive functions throughout the nervous system, along with their effects on reproductive processes; (The same is true for androgens).

Developmentally programmed sex differences exist throughout the nervous system and affect non-reproductive as well as reproductive processes; Some, but not all, of the sex differences are produced in mammals by androgens acting on the developing brain either as androgens or after aromatization to estrogens; Genes of the X and Y chromosomes are also involved.