CHAPTER 7

Modulation of Learning and Memory by Adrenal and Ovarian Hormones

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I. INTRODUCTION

Hormones have a host of effects on physiological functions, many of which include behavioral actions. Stress hormones not only shift glucose utilization from smooth to striate muscle but also dispose an organism toward classic fight-or-flight responses. Reproductive hormones not only prepare sex organs for reproduction but also dispose an organism toward mating behaviors. Gut hormones not only regulate digestive processes but also dispose an organism toward or away from feeding behaviors. With hormonal regulation of multiple behaviors, it is perhaps not surprising to note that hormones also have effects on learning and memory. Interestingly, the classes of learning and memory effects influenced by a particular hormone include cognitive actions associated with other behavioral functions of the hormone, e.g., stress, reproduction, and digestion from the foregoing list, but also include a wide range of less intuitive effects. For example, stress hormones such as epinephrine and corticosterone influence learning and memory for avoidance tasks, well within the genre of stress, but these hormones also have important effects on learning and memory in appetitive and other nonstressful tasks (for reviews see de Kloet, 2000;
Roozendaal, 2002; Gold and McCarty, 1995). Reproductive hormones such as estrogen also have potent influences on learning in avoidance and appetitive tasks that, on their face, have little direct role in reproduction (Korol, 2004; Dohanich, 2002).

This chapter focuses on the effects on learning and memory of the stress-related adrenal hormones, epinephrine and corticosterone, and the reproduction-related ovarian hormones, estrogen and progesterone. There is much known about each of these hormones in terms of their actions on and via different memory systems in the brain and also in terms of the neurobiological mechanisms by which the hormones influence learning, memory, and neural plasticity.

Before describing experimental findings linking the actions of these hormones to memory, we present some general ideas that guide the later sections of this chapter. Hormones can have both organizational and activational influences on the brain. Generally, organizational effects occur early and act on neural development, leaving lasting changes in brain structure and function and behavior that alter subsequent responses to stimuli, including the hormones themselves that produce the change. In contrast, activational effects of hormones refer mainly to action resulting from the presence of the hormone. In classical terms, organizational effects occur during developmental stages and activational effects occur during adulthood. However, current findings that exposure to hormones in adults can alter neuronal morphology (for review: McEwen, 2001, 2002), among other effects, certainly obscure this distinction between organizational and activational effects.

Thus, while organizational influences on the brain are traditionally studied in the context of development, there are now many demonstrations of hormonal organizational effects, i.e., long-lasting changes in brain structure and function, in adult organisms. Findings that hormones can have both short- and long-lasting effects on learning and memory fit two different views of what the role of hormones is in regulating these processes. One interpretation of demonstrations that hormones administered near the time of learning can enhance later memory for the experience is that the hormones modulate memory formation (Gold and McGaugh, 1975; McGaugh et al., 2002; Gold, 1995, 2005). Modulation of memory involves processes acting on the mechanisms of memory formation or consolidation to enhance or to impair those mechanisms. Results like this suggest that hormonal modulation of memory augments neural plasticity to enhance memory formation.

While both corticosterone and estrogen modulate memory in this sense, these steroids also have additional slower effects on memory that are somewhat different. These hormones can apparently bias the use of one strategy over another to solve a task, e.g., under one condition favoring the use of place strategies sensitive to hippocampal disruption, and under another condition favoring the use of response strategies sensitive to striatal disruption (Kim
et al., 2001; Korol and Kolo, 2002; Chapa et al., 2005). These changes in strategy are reflected in differences in the specific responses expressed during tests of learning. Hormonal control over strategy selection can be viewed as a form of metamodulation, in which modulation of neural plasticity can be differentially up- and down-regulated in different neural systems, thereby changing the cognitive structure of what is learned (Korol, 2004).

These general comments are illustrated within the discussion of the stress-related hormones, epinephrine and corticosterone, and the sex-related hormones, estrogen and progesterone, considered in this chapter.

II. STRESS HORMONES AND MEMORY

A. Epinephrine

Epinephrine is perhaps the hormone best studied as a modulator of memory. Epinephrine is released from the adrenal medulla into blood in response to stress (cf. Wortsman, 2002; Wurtman, 2002) and, importantly, is also released in rats in response to handling or exposure to a novel compartment. The hormone is released into blood in a graded manner, from low levels in response to the mild arousal of gentle handling, to placement in a novel environment, to foot shock increasing in a monotonic manner by shock intensity, to the extremely high levels released during immersion in water, as in the swim task (cf. Mabry et al., 1995).

The design and results of an early experiment illustrate modulation of memory by epinephrine (Gold and van Buskirk, 1975). The task used was a one-trial inhibitory (passive) avoidance task in which rats were trained to avoid crossing from a well-lit start compartment into the end of a dark compartment where shock was previously administered. In this type of task, it is not surprising that a mild shock results in smaller increases in latency on the test trial than does a more intense shock. An increase in the intensity of the shock results in better memory, certainly in part because of the increased aversiveness. The key question regarding hormonal modulation of memory is whether the increase in epinephrine release that accompanies increased shock intensity can enhance memory processing by mechanisms separate from changes in aversiveness of the shock. To address this question, rats were trained with a mild shock and were then removed from the training apparatus and given an injection of epinephrine, at one of several doses and times after training. Memory was tested 24 hr later, well after circulating epinephrine levels had returned to baseline. A single injection of intermediate doses of epinephrine administered immediately after training enhanced 24-hr memory (Fig. 7-1, left panel).

As seen for many hormonal and drug treatments that enhance memory (Koob, 1991; Gold, 2006), the dose–response curve had an inverted-U shape
in which low and high doses did not enhance memory; in other experiments, high doses of epinephrine impair memory, i.e., produce retrograde amnesia. One implication of the inverted-U dose–response curve is that the same dose of epinephrine might enhance memory for training under low-foot-shock conditions but impair memory under high-foot-shock conditions. This pattern of results is evident for epinephrine and many other treatments that modulate the formation of new memories (Gold, 2006). Also, the epinephrine doses that enhance memory result in elevations in circulating epinephrine levels that match quite well those seen after training with a higher-intensity foot shock (McCarty and Gold, 1996). The effects of epinephrine on later memory are time dependent, diminishing as a function of time after training (Fig. 7-1, right panel), suggesting that the enhancement of memory reflects actions on the processes of memory formation.

Epinephrine enhances learning and memory in a wide range of tasks, including avoidance, extinction of avoidance, and spatial memory tasks (Gold, 1995). Considerable effort has gone into understanding the mechanisms by which the pervasive effects of epinephrine on memory are manifested. Because of an effective blood–brain barrier mechanism, circulating epinephrine does not appear to have significant direct access to the brain (Axelrod et al., 1959). Therefore, the initial epinephrine signal transduction mechanism relevant to enhancement of memory is likely to be outside the brain.

Two main lines of research have explored peripheral mechanisms that mediate epinephrine effects on memory formation. One has examined the role
of vagal afferents to the brain as a mediator of these effects of epinephrine. The vagus nerve contains β-adrenergic receptors, opening the possibility that the nerve conveys to the brain information that circulating epinephrine levels are high. Consistent with this view, drugs that block or activate the brain region that receives vagal input, the nucleus tractus solitarius, block or mimic epinephrine effects on memory and on release of norepinephrine in the amygdala (Williams et al., 1998; Miyashita and Williams, 2004). Vagotomy blocks the effects on memory of some treatments, including cholecystokinin-A (Lemaire et al., 1994; Flood et al., 1987), substance P (Tomaz and Nogueira, 1997), and bombesin and gastrin-related peptide (Flood and Morley, 1988), though to our knowledge there are no direct tests of vagotomy effects on epinephrine enhancement of memory. The potential to do so is suggested, however, by findings that vagotomy blocks epinephrine suppression of brain seizures (Krahl et al., 2000).

A second set of experiments has demonstrated that epinephrine effects on memory are mediated, at least in part, by increases in blood glucose levels subsequent to epinephrine release or administration (for reviews see: McNay and Gold, 2002; Messier, 2004; Gold, 2005). A classic physiological response to increases in circulating epinephrine levels is the liberation of glucose from hepatic stores, resulting in increases in blood glucose levels. Like epinephrine, systemic administration of glucose enhances memory in rodents for a wide range of tasks. The dose–response function has an inverted-W shape, with one peak of memory enhancement seen at 100–300 mg/kg and another at 1–3 g/kg. The underlying biology appears to be different for the two peaks. The higher peak dose is not effective in vagotomized rats (Fig. 7-2;
Talley et al., 2002) or in rats after coeliac ganglion removal (White, 1991). However, the lower peak dose remains effective in vagotomized rats (Talley et al., 2002); efficacy of the lower dose after coeliac ganglion removal has not been tested. Of interest, slowly metabolized fructose and nonmetabolized sugars, e.g., 2-deoxyglucose, 3-O-methylglucose, and L-glucose, can also enhance memory (cf. Messier, 2004). The enhancement of memory by one of these sugars, L-glucose, appears at high (3 g/kg) but not low (300 mg/kg) doses, and the efficacy of L-glucose in enhancing memory at high doses is blocked in vagotomized rats (Talley et al., 2002).

Thus, there appear to be two mechanisms that might contribute to the enhancement of memory by sugars, a high-dose range, at which several sugars are effective and for which memory enhancement is blocked by vagotomy, and a low-dose range, at which glucose and not nonmetabolized sugar is effective and for which enhancement of memory processing is not susceptible to vagotomy. When the evidence linking epinephrine release to increases in blood glucose levels is viewed in terms of the underlying biology and in terms of the blood glucose levels optimal for epinephrine enhancement of memory, it appears that the lower peak glucose dose, and not the higher dose, contributes importantly to epinephrine enhancement of memory processes. As has been done in studies of glucose effects on memory, it will be important to assess systematically the effects of vagotomy on memory-enhancing actions of epinephrine.

Thus, glucose may serve as an intermediate step between the release of epinephrine, excluded from the brain, and enhancement of memory. In contrast to epinephrine, glucose is actively transported into the brain from blood. Although the mechanism may be indirect, glucose augments the release of acetylcholine in the hippocampus, while rats perform spatial memory tasks and may interact with potassium-ATP channels to regulate release of other neurotransmitters and modulators (cf. McNay and Gold, 2002; Gold, 2004).

The results of a series of experiments indicate that microinjections of glucose into specific brain regions can modulate memory processes, findings consistent with the view that glucose increases in blood after epinephrine injection or release can act directly on neural systems to promote memory functions. For example, glucose injections into the hippocampus, striatum, amygdala, and medial septum enhance learning and memory, generally on tasks for which learning would be impaired by damage to these brain regions (Canal et al., 2005; Erickson et al., 2006; Schroeder and Packard, 2003; cf. Gold, 2003). Interestingly, up-regulation of learning and memory processing in the striatum by injections of glucose interferes with acquisition of a spatial task sensitive to hippocampal lesions (Pych et al., 2006), suggesting that augmented striatal functions may impair spatial learning by competition across memory systems (White and McDonald, 2002; Gold, 2004).

Glucose is also a potent enhancer of memory in humans, with demonstrations that glucose can enhance memory in healthy young adult and aged...
individuals as well as in people with Alzheimer's disease (see Korol, 2002; Messier, 2004). Epinephrine has similarly been reported to enhance memory in young adults (Cahill and Alkire, 2003).

The differing findings regarding the mechanisms mediating epinephrine effects on brain functions, i.e., via increases in blood and brain glucose levels or via vagal afferents, may reflect multiple neurobiological actions acting in concert to enhance memory. As reviewed elsewhere (McIntyre et al., 2003; McGaugh et al., 2002), considerable evidence suggests that the convergence of these factors underlying modulation of memory may include actions at the amygdala. Epinephrine may act through vagal afferents to influence modulation of memory by the amygdala and, in parallel, increase blood glucose levels to act directly on the amygdala and other neural systems to enhance memory formation. Controls of brain neurotransmitter release, particularly acetylcholine and norepinephrine, appear to contribute to epinephrine regulation of memory processing (McIntyre et al., 2002; Gold, 2003).

B. Corticosterone

Some of the earliest research examining hormones and memory included demonstrations that ACTH could modulate learning and memory (for review, see de Wied, 1990). Among the findings were results indicating that ACTH fragments, including some that did not release adrenal steroids, influenced memory when administered either systemically or directly into specific brain areas (e.g., van Rijzingen et al., 1996).

Although ACTH therefore appears to have effects on learning and memory independent of adrenal steroids, a significant body of recent work indicates that adrenal steroids, particularly corticosterone, have potent effects on learning and memory (Roozendaal, 2002; McEwen, 2001; Sandi, 2004; Wolf, 2003; Luine, 2002). Like injections of epinephrine, injections of corticosterone enhance memory for a wide range of tasks, e.g., inhibitory avoidance, fear conditioning, and object recognition (Okuda et al., 2004; see left panel, Fig. 7-3). As in Figure 7-3, the dose–response curve for the effects of corticosterone on memory follows an inverted-U dose–response function (e.g., Okuda et al., 2004), as noted earlier for both epinephrine and glucose. These results are consistent with findings that circulating corticosterone levels have an inverted-U relationship with the hippocampal primed-burst form of long-term potentiation (Diamond et al., 1992). Another feature of corticosterone enhancement of memory shared with epinephrine is that the effects of posttraining injections of corticosterone on memory are time dependent: Posttraining injections enhance memory at short but not long intervals between training and corticosterone treatment (Flood et al., 1978; Sandi and Rose, 1994). Thus, the effects of corticosterone on memory likely reflect actions on memory processes.
Not surprisingly, as with epinephrine and glucose, the dose–response curve for corticosterone effects on memory interacts with stress at the time of training. For example, corticosterone enhances memory for the spatial version of the swim task when rats are trained in relatively warm but not cold water (Akirav et al., 2004; Sandi et al., 1997). To enhance object-recognition memory, prior habituation of rats to an experimental context, i.e., a novel environment, blocked enhancement of memory by corticosterone, showing that at least modest training-related arousal is important for demonstrations of corticosterone-induced enhancement of memory (Okuda et al., 2004; see Fig. 7-3, right panel).

The amygdala, in particular the basolateral nucleus, appears to play an important role in mediating the effects of corticosterone on memory, as was discussed earlier for epinephrine. Lesions of the amygdala or the stria terminalis or injections of β-adrenergic antagonists into the amygdala block the effects of corticosteroids on memory (Roozendaal, 2002).

Findings also suggest that corticosteroids injected at the time of memory testing impair retrieval of memory (Roozendaal, 2003). These effects do not appear to be the result of direct action of glucocorticoids on the amygdala, since direct injections into the basolateral nucleus of the amygdala do not impair memory retrieval for a swim task. However, lesions of the basolateral nucleus or injections of β-adrenergic antagonists into the amygdala block the effects of intrahippocampal injections of glucocorticoid agonists (Roozendaal et al., 2004). Thus, the basolateral amygdala does not appear to be the primary target of glucocorticoid regulation of retrieval processes but instead is permissive of such effects.
III. GONADAL STEROIDS AND COGNITION

A. Estrogen

Estrogen has potent effects on the structure and function of the adult brain (Brinton, 2001; McEwen, 2002) that, in addition to involvement in reproductive behaviors, may modulate cognition. The direction of estrogen action on learning and memory depends on several variables, including stress levels, type and duration of hormone regimen, and specific task and memory demands (for reviews: Dohanich, 2002; Korol, 2004). Emerging from a growing literature is the idea that estradiol, perhaps the most potent naturally found estrogen in mammals, modulates memory formation and maintenance and biases the learning strategy used to solve a task by altering the relative participation of different neural systems during task performance.

There are numerous reports supporting the finding that specific regimens of estrogen enhance working memory in a variety of tasks (cf. Dohanich, 2002; Korol, 2004), including delayed T-maze, radial maze, and spatial swim tasks. The greatest enhancements on working memory are observed when task difficulty is increased by extending the intertrial interval. Importantly, in some tasks that dissociate types of memory, reference memory, thought to be insensitive to hippocampal manipulations, appears to remain unaffected by estrogen treatment (Dohanich, 2002; Korol, 2004; but also see Heikkinen et al., 2002). It is possible that reference memory components in past studies have not been sufficiently difficult to observe estrogen effects, though assessments of task-difficulty-dependent effects of estrogen on reference memory have not yet been made.

Direct tests of estrogen modulation of memory formation come from studies in which animals are given posttraining treatments and tested for later retention. Systemic treatments of a rapidly metabolized estrogen, estradiol-hydroxypropyl β-cyclodextrin inclusion complex, to ovariectomized rats given immediately but not two hours after training in the swim task enhanced savings during a test 24 hours later (Fig. 7-4; Packard and Teather, 1997b). In addition, memory for inhibitory avoidance training was facilitated by posttraining estrogen injections (Rhodes and Frye, 2006). Object- and place-recognition memory tested with a 4-hr retention interval were enhanced by both natural and synthetic estrogenic compounds that have varying affinities for the two classical estrogen receptor (ER) subtypes, ERα and ERβ (see later; Luine et al., 2003). Again, memory facilitation was seen only with immediate posttraining treatments and not with delayed injections, pointing to actions of estrogen on memory processes per se. Posttraining intrahippocampal infusions of estrogen also enhanced memory in spatial-swim (Packard and Teather, 1997a) and active-avoidance (Farr et al., 2000) paradigms, suggesting that estrogen may engage neurobiological mechanisms involved in different types
of memory formation and that certain neural systems may mediate the modulating effects of estrogen.

1. **Estrogen and Learning Strategy**

One property of estrogen's effects on cognition is that tasks that tap hippocampus function appear to be sensitive to modulation by estrogen, a quality that is not surprising, given the robust effects of estrogen on hippocampus structure and function (for review: McEwen, 2002). Estrogen promotes good performance in hippocampus-sensitive tasks, such as acquisition of a standard eight-arm radial maze test (Daniel et al., 1997) and, as mentioned earlier, tests of working memory in various land- and water-based working memory tasks (Korol, 2004).

The differential involvement of multiple neural systems in memory can be dissociated based on task attributes (White and McDonald, 2002; White, 2004; Kesner and Rogers, 2004). When estrogen effects on memory are taken together and placed within a memory system framework, the findings suggest that estrogen promotes the use of hippocampus-sensitive solutions and may prohibit or impair the use of other, nonhippocampal strategies. Direct tests of this theory show that acute (Fig. 7-5; Korol and Kolo, 2002) and chronic
(Davis et al., 2005) estradiol treatments to ovariectomized female rats enhance place learning (hippocampus sensitive) but impair response learning (striatum sensitive) in food-motivated tasks. Conversely, estradiol deprivation promotes response learning but impairs place learning (Fig. 7-5). These results are supported by work using a dual-solution version of the swim task in which chronic estradiol exposure impaired performance in the cued, nonspatial, version, while hormone deprivation impaired performance in a spatial probe.
test with no cue (Daniel and Lee, 2004). Strategy choice in a land-based dual-solution task in the T-maze, in which either place or response strategies are effective (Tolman et al., 1947; Restle, 1957), was biased toward place learning in cycling rats with endogenously high profiles of estrogen and toward response learning in rats with endogenously low profiles of estrogen (Korol et al., 2004; McElroy and Korol, 2005). Thus, it is becoming clear that estrogen changes not only how much is learned but also what is learned.

Relative to our knowledge of epinephrine and corticosterone dose–response functions (described earlier), very little is known about effective dose–response functions for estradiol and cognition. Similar to that shown for stress hormones, Packard and colleagues demonstrated a robust inverted-U dose–response function for systemic posttraining estradiol injections on retention in the spatial swim task (Fig. 7-4; Packard and Teather, 1997b). Furthermore, in a series of experiments, different doses of estradiol produced varying effects on cognition, depending on the attributes required — and perhaps the memory systems engaged — by the task of interest. Specifically, in a working-memory task that is thought to depend on an intact prefrontal cortex, low doses of estrogen tended to enhance performance (decrease errors) under low-working-memory load, whereas higher doses impaired memory under higher memory loads (Wide et al., 2004). However, in radial maze working-memory tasks that may tap hippocampal function, physiologically low doses of estradiol enhanced while higher doses impaired working memory (Holmes et al., 2002). In contrast, supraphysiological but not lower doses of estradiol enhanced acquisition of a conditioned response in a trace conditioning eye-blink paradigm (Leuner et al., 2004), also a task thought to require hippocampal function. Undoubtedly, to reconcile these differences, more systematic examinations of dose-dependent effects of estrogen across various tasks are needed.

2. Estrogen Modulates Distinct Neural Systems

Framed by the idea of multiple memory systems, the effects of estrogen on cognition can be dissociated by the neural system engaged during learning. To produce such opposing effects on cognition, it is possible that estrogen up-regulates hippocampal involvement and down-regulates striatal involvement during cognition and thus modulates the relative contribution of different neural systems to learning. If so, direct application of estrogen to specific brain areas would mimic the effects of systemic elevations in estrogen for the cognate task. Hippocampal actions of estrogen on spatial learning have been implicated by studies showing that central treatments enhance spatial memory (Packard and Teather, 1997a) and systemic treatments can reverse spatial deficits resulting from hippocampal cholinergic blockade (Packard and Teather, 1997b; Fader et al., 1998; Gibbs, 1999). While these data address the possibility that estrogen acts at the hippocampus, they fail to address whether actions are site and task
specific. Recent findings show that direct infusions of estradiol into the hippocampus enhance place learning specifically, whereas infusions into the dorsolateral striatum selectively impair response learning (Zurkovsky et al., 2007). Furthermore, intrahippocampal blockade of estrogen receptors attenuates facilitation of place learning by systemic estrogen (Zurkovsky et al., 2004), and intrastriatal blockade of estrogen receptors prevents impairment by systemic estradiol (Kent et al., 2005). Thus, estrogen likely modulates learning through activation of estrogen receptors in specific neural systems.

How estrogen acts to alter the balance of different neural systems during learning is largely unknown. However, there is a growing literature reporting that estrogen influences the neurobiology of the hippocampus and striatum (Davis et al., 2005; for review: Korol, 2004) as well as other brain areas, such as the prefrontal cortex and the amygdala (Kritzer and Kohama, 1999; J. Wang et al., 2004; Tinkler et al., 2004; Womble et al., 2002). Naturally occurring fluctuations and treatments of estrogen produce dramatic changes in dendritic and spine morphology, in the synthesis, release, and kinetics of neurotransmitter systems such as acetylcholine, GABA, glutamate, and dopamine, and in neural transmission and synaptic plasticity (for reviews: Becker, 1999; Cyr et al., 2001; Dohanich, 2002; Korol, 2004; McEwen, 2002; Woolley, 1998). While many neuronal cell types in hippocampus contain identified estrogen receptors, until recently, when estrogen receptors were localized to the striatum (C. Wang et al., 2005), it was thought that estrogen acts in the striatum through novel membrane sites only.

3. Short-Term Versus Durable Changes: Requirements for Cognition?

It is now known that estrogen has both rapid and slow effects at target tissues, including the brain (McEwen, 2002; Moss et al., 1997; Toran-Allerand et al., 2004). These different actions have been defined as nongenomic and genomic events, respectively, with the slow (>1–2 hr), or “genomic,” actions of estrogen thought to be mediated by intranuclear receptor-induced changes in gene expression and the rapid (<1 hr), “nongenomic,” actions through several different intracellular signaling cascades (Belchner and Zsarnovsky, 2001; Barnea and Gorski, 1970; Kelly and Wagner, 1999). However, recent data suggest that even rapid effects may act through classical receptors (e.g., ERβ; Abraham et al., 2004) and that nongenomic events, while rapid in onset and reversible, produce long-lasting changes through cell signaling pathways (Orchinik and McEwen, 1993), blurring the distinction of genomic and nongenomic actions, but again emphasizing important cellular differences based on duration and timing of estrogen exposure.

Numerous reports document rapid effects of estrogen in the hippocampus that may or may not require the presence of estrogen receptors. Estrogen consistently increases excitability of hippocampal neurons, perhaps leading to
increased likelihood of synaptic plasticity (cf. Woolley, 1998), a more durable change. An exciting new finding that 30 min of systemic treatment with estradiol produced robust increases in spine synapse densities in CA1 pyramidal neurons (MacLusky et al., 2005) suggests that some aspects of estrogen-induced restructuring may not require long exposures. Rapid estrogen effects have been well-documented in the striatum (Becker, 1999; Dluzen and Horstink, 2003). For example, estradiol decreases Ca\(^{2+}\) currents through membrane-related events within seconds of treatment to dissociated striatal cells (Mermelstein et al., 1996). Activation of c-jun can be measured in striatum as early as 15 min following estrogen administration (Zhou and Dorsa, 1994). Interestingly, estradiol may rapidly modulate dopaminergic G-protein-coupled receptors, the direction of which has been shown in other brain regions to vary by estrogen receptor subtype (Kelly et al., 2003), pointing to the role of estrogen as a metamodulator.

In concert with these processes, estradiol can trigger within seconds to minutes dramatic intraneuronal changes in levels and activity of adenylate cyclase, PKA, PKC, and MAPK pathways (Bi et al., 2000; Singh et al., 2000; Driggers and Segars, 2002). One downstream consequence of PKA activity is phosphorylation of CREB, enhancement of which is observed within 15 min of estrogen treatment in hypothalamus (Abraham et al., 2004) and hippocampus (McEwen et al., 2001). Importantly, estradiol effects on CREB induction are duration sensitive and differ by brain region (Carlstrom et al., 2001).

Consistent with these neurobiological effects, rapid actions of estrogen on cognition have been reported. Estrogen injections given 30 minutes prior to training enhanced recognition memory for objects and place (Luine et al., 2003). Similarly, findings from studies using immediate posttraining injections of estrogen (e.g., Luine et al., 2003; Packard and Teather, 1997b) suggest rapid modulation of cognition by estrogen, because delayed injections are ineffective.

4. Distribution of Estrogen Receptor Subtypes in the Brain

The estrogen receptor belongs to a superfamily of nuclear receptors that regulate gene transcriptional activity. Advances have led to the discovery of at least two different estrogen receptor subtypes, ER\(\alpha\) and ER\(\beta\) (and even more isoforms of ER\(\beta\); Kuiper et al., 1996). When activated, the different receptors show unique profiles of gene expression in estrogen-responsive tissues (Pettersson and Gustafsson, 2001) that may translate into different functional outcomes. Both receptor subtypes bind estradiol with high affinity, have a nearly identical DNA-binding domain, and activate transcription through binding to the same estrogen receptor response elements (Cowley et al., 1997).

In brain tissue, the two estrogen receptor subtypes are differentially distributed across anatomically and neurochemically distinct neural systems (Shughrue
Within a given brain area, cells may express one receptor subtype (ERα or ERβ), both subtypes, or neither subtype (Shughrue et al., 1998). Initial studies demonstrating differential distribution of ERα and ERβ together with the behavioral results of studies using ERα and ERβ knockout mice (ERαKOs and ERβKOs) suggested that ERα is involved primarily in reproductive behaviors, whereas ERβ is involved in nonreproductive functions, such as memory and mood (Osterlund et al., 2000; Shughrue and Merchenthaler, 2001; but see Fugger et al., 2000). However, more recently, regions involved in cognition, including the hippocampus, have been found to contain ERα. Interestingly, extranuclear ERα receptors are found both pre- and postsynaptically in the hippocampus, suggesting that estrogen may regulate neurotransmitter release or sensitivity (Mitra et al., 2003). Until recently, it has been thought that the striatum lacks both estrogen receptor subtypes (Shughrue et al., 1997), but new findings highlight the presence of extranuclear ERα in striatal neurons (C. Wang et al., 2005). Thus, the robust effects of estradiol on striatal function and striatum-sensitive learning (Korol, 2004) may act through these receptors, through a novel, uncharacterized cytosolic receptor or through membrane receptor-mediated actions (Kelly and Wagner, 1999; Mermelstein et al., 1996; Toran-Allerand, 2004).

It is clear that an understanding of the estrogen receptor subtype that mediates estrogen's effects on cognition in hippocampus and striatum will direct future work on the cellular mechanisms underlying these effects. In addition, some of the different cellular responses to ERα and ERβ are likely to map against fast and slow effects of estrogen, such that the rapid versus slow effects of estrogen may dissociate by estrogen receptor subtype or brain region. In certain murine brain areas, estrogen-induced CREB phosphorylation required the presence of either ERα or ERβ; which receptor subtype depended on the type of receptor normally expressed in the respective brain area (Abraham et al., 2004). Particularly striking was a lack of rapid estrogen induction of CREB phosphorylation in the striatum. Thus, rapid effects of estradiol can be mediated by both ERs, with specificity of effects likely to be defined by the particular brain area and effector pathway.

Cognitive effects may also be based on receptor subtype, though very few studies have examined receptor specificity in mediating the effects of estrogen on learning and memory. One recent study found that an ERα-selective agonist was ineffective compared to estradiol in enhancing place memory but was effective in enhancing object-recognition memory (Luine et al., 2003). Estrogen receptors are differentially distributed across brain areas, which, in turn, may be differentially engaged in tasks with specific attributes. Thus, these findings suggest again that actions of estrogen at its receptors may underlie different memory effects across structures. The independent effects of ERα and ERβ on cognition have also been demonstrated in a pioneering set of studies by Rissman and colleagues using ERα and ERβ knockout mice.
In the spatial version of the swim task, estradiol treatment to ovariectomized ERαKO mice failed to produce impairing effects seen in wild-type mice. In ERβKOs, however, estradiol effectively impaired performance, pointing to a key role of ERα in estrogen-induced spatial learning deficits reported previously (Rissman et al., 2002). Interestingly, in a different task, i.e., inhibitory avoidance, estradiol acts through an ERα-independent mechanism to enhance memory (Fugger et al., 2000). Recent findings using selective estrogen receptor modulators, termed SERMS, demonstrated that postraining administration of ERβ-selective compounds tended to enhance spatial-escape memory in the swim task, whereas compounds acting at both ERα and ERβ sites were most effective at enhancing memory for inhibitory avoidance tasks (Rhodes and Frye, 2006). Together, these findings suggest that estrogen may have opposing actions on different forms of memory and that the actions may be through different estrogen receptor subtypes or brain structures.

B. Progesterone

A review of ovarian hormone actions on cognition would be incomplete without a discussion of the effects of progesterone on learning and memory. Progesterone is an ovarian steroid produced by the corpus luteum that, among other things, can act as an anticonvulsant, prohypnotic, and anxiolytic agent (for review: Reddy, 2003; Zinder and Dar, 1999). Examinations of the effects of progesterone on learning and memory are complicated by the fact that progesterone metabolism produces many neuroactive metabolites that may have diverse neurobiological actions. Despite this complexity, there are consistent findings showing that progesterone has dramatic effects on brain function and behavior, particularly related to anxiety and fear.

Endogenous or exogenous elevations in circulating progesterone decrease anxiety on a variety of tasks including the elevated plus maze and open field behavior (Frye and Walf, 2002, 2004; for review: Dubrovsky, 2005). The anxiolytic actions of progesterone on plus-maze and open-field behaviors can be observed with direct amygdala infusions as well (Frye and Walf, 2004). However, progesterone may actually facilitate certain fear responses, e.g., startle (Hiroi and Neumaier, 2006), thereby producing mixed or null effects in tasks that are aversive or stressful by nature.

The effects of progesterone on cognition are mixed and likely depend on factors such as the timing of treatments and testing paradigms. Progesterone treatment was shown to be ineffective in enhancing spatial memory when given prior to training in a radial maze task (Tanabe et al., 2004; Sato et al., 2004) or when given postraining to rats tested in an inhibitory avoidance task (Rhodes and Frye, 2004), though in these same examples estrogen treatments...
facilitated memory. In addition, when examined across the menstrual cycle in young adult women (Maki et al., 2002) or rhesus monkeys (Lacreuse et al., 2001), circulating levels of progesterone did not correlate with performance on a subset of cognitive tests, while estradiol levels did. Interestingly, when given to estrogen-primed rats, progesterone can oppose the cognitive actions of estrogen or progesterone alone (Diaz Veliz et al., 1994; Chesler and Juraska, 2000; Sandstrom and Williams, 2001). Interestingly, progesterone administered to old ovariectomized rats reversed the enhancing effects of the ovariectomy on delay-based spatial-memory tasks, suggesting that the higher levels of progesterone in old rats may contribute to some of the age-related memory deficits (Bimonte-Nelson et al., 2004). In contrast, however, impairing effects of progesterone in old rats were not found when weekly treatments were given to estrogen-primed ovariectomized rats and initiated within 3 months of ovariectomy (Gibbs, 2000). Thus, the effects of estrogen and progesterone appear to have complexly interacting characteristics based on such variables as hormone timing, age, and dose.

Actions of progesterone may be mediated by its actions on gene transcription via binding of intracellular progesterone receptors or through modulation of neurotransmitter function, particularly by progesterone metabolites that are produced in the periphery (corpus luteum, adrenal cortex) and the central nervous system (for review: Reddy, 2003). Progesterone’s neuroactive 5-alpha reduced metabolite, allopregnanolone (3α5α-THP), is a potent positive allosteric GABA<sub>A</sub> receptor modulator that produces dramatic and rapid suppression of neural excitability via increases in the frequency or duration of opening of chloride channels (Rupprecht and Holsboer, 1999). It is thought that 3α5α-THP acts through distinct, neuroactive steroid-binding sites on the GABA<sub>A</sub> receptor. However, like benzodiazepines, which also modulate GABA<sub>A</sub> receptor function, acute increases in 3α5α-THP through treatment or across the reproductive cycle are anxiolytic (for review: Reddy, 2003), decreasing anxiety, measured as increased entries into open arms of the plus maze and time spent toward the center of an open-field arena, suggesting that progesterone’s antianxiety properties emerge from GABA<sub>A</sub> receptor-, and not progesterone receptor-, mediated events (Reddy et al., 2005). Not all treatments of progesterone produce positive regulation of GABA<sub>A</sub> receptor; the direction of GABA receptor modulation depends on the duration and timing of progesterone exposure, in addition to the metabolite through which progesterone acts. For example, longer treatments of progesterone and its metabolite 3α5α-THP (48 hr) have been shown to be anxiogenic, perhaps through alterations in specific GABA<sub>A</sub> receptor subunits (Gulinello and Smith, 2003).

Transiently elevated levels of 3α5α-THP not only influence anxiety but also impair learning and memory in a variety of tasks. Systemic and direct brain injections of 3α5α-THP impaired learning and memory in the spatial
version of the swim task (Johansson et al., 2002; Matthews et al., 2002; Turkmen et al., 2006) but not on a nonspatial, cued task (Matthews et al., 2002). Progesterone and its metabolites undoubtedly produce cognitive effects that depend on the duration and timing of exposure to these neuroactive steroids.

IV. MAJOR POINTS

This chapter has described evidence that both stress hormones and reproductive hormones have robust and reliable effects on learning and memory. There are several features of these findings that are evident across different hormones and experiments.

• Broad cognitive effects. Particularly in tests of peripheral hormone fluctuations and manipulations, the hormones modulate learning and memory for wide ranges of tasks, beyond the domain, e.g., stress or reproduction, traditionally associated with each hormone.

• Timing matters. Both pre- and posttraining injections of most hormones influence memory. These effects appear to reflect many actions: on both memory formation processing and on learning strategy selection. The steroids, corticosterone, estrogen, and progesterone, have both rapid and slow effects that may participate differently in learning and memory processes.

• Peripheral and central effects. Steroidal effects on learning and memory may reflect direct actions on the brain. In contrast, the effects of epinephrine appear to be mediated peripherally by increases in circulating glucose levels and by actions on vagal afferents to the brain. The brain actions are mediated, in part, by local changes in glucose availability and by release of neurotransmitters, such as norepinephrine and acetylcholine, which modulate memory formation.

• Molecular and cellular bases. The neural bases of hormone action include genomic effects through classical intracellular receptors and through initiation of signal transduction mechanisms (corticosterone, estrogen, progesterone) and also include secondary effects (metamodulation) (epinephrine, corticosterone, estrogen, progesterone) through modulation of neurotransmitter systems.

ACKNOWLEDGMENTS

Supported by research grants from NSF (IOB 0520876) (DLK) and from NIA (AG 07648), and NIDA (DA 016951) (PEG), and by the University of Illinois Initiative on Aging and the Office of the Vice-Chancellor for Research (DLK, PEG).
REFERENCES


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