Published in final edited form as:

Behav Brain Res. 2015 November 1; 294: 50–61. doi:10.1016/j.bbr.2015.07.057.

Progestogens' effects and mechanisms for object recognition memory across the lifespan

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Abstract

This review explores the effects of female reproductive hormones, estrogens and progestogens, with a focus on progesterone and allopregnanolone, on object memory. Progesterone and its metabolites, in particular allopregnanolone, exert various effects on both cognitive and non-mnemonic functions in females. The well-known object recognition task is a valuable experimental paradigm that can be used to determine the effects and mechanisms of progestogens for mnemonic effects across the lifespan, which will be discussed herein. In this task there is little test-decay when different objects are used as targets and baseline valence for objects is controlled. This allows repeated testing, within-subjects designs, and longitudinal assessments, which aid understanding of changes in hormonal milieu. Objects are not aversive or food-based, which are hormone-sensitive factors. This review focuses on published data from our laboratory, and others,

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Conflict of Interest: All authors report that they have no conflicts of interest (financial or otherwise) that would bias them to the outcome of these experiments.

Author Contributions

All authors on this paper contributed to the composition of this manuscript. AAW was involved in: the conception and study design of experiments described; collection, analyses, and interpretation of data represented in the paper; updating the tables and figures; performing literature searches; drafting, editing, and revising all sections of each version of the paper. CJK was involved in data collection, entry, and analyses; drafting the tables and figures, performing literature searches; drafting sections of the paper; reviewing and editing versions of the manuscript. CAF was involved in: the conception and study design of experiments described; resource management for studies described; collection, analyses, and interpretation of data; drafting, reviewing, editing, and revising all versions of the work.

using the object recognition task in rodents to assess the role and mechanisms of progestogens throughout the lifespan. Improvements in object recognition performance of rodents are often associated with higher hormone levels in the hippocampus and prefrontal cortex during natural cycles, with hormone replacement following ovariectomy in young animals, or with aging. The capacity for reversal of age- and reproductive senescence-related decline in cognitive performance, and changes in neural plasticity that may be dissociated from peripheral effects with such decline, are discussed. The focus here will be on the effects of brain-derived factors, such as the neurosteroid, allopregnanolone, and other hormones, for enhancing object recognition across the lifespan.

Keywords

hormones; progesterone; allopregnanolone; neurosteroid; aging; hippocampus

1. Introduction

Steroid hormones have profound effects on the Central Nervous System, and influence a broad spectrum of activities involved in growth and plasticity. One such class of steroid hormones are the progestogens, which include progesterone and its neuroactive metabolites that can also be formed in the brain (“neurosteroids”), such as 5 α -pregnan-3 α -ol-20-one (3 α ,5 α -THP, aka allopregnanolone). Not surprisingly, as the name of this class implies, a traditional focus on the effects of these progestogens were on the maintenance of pregnancy (“pro-gestational”). However, in recent decades, it has become clearer that progestogens have robust actions in the brain underlying stress responding, mood, neuroprotection, and cognition; we will focus on the effects on learning and memory herein, with an emphasis on progestogens’ effects on object memory. Of interest is the extent to which there may be commensurate mechanisms for growth enhancing effects (e.g. those necessary for maintenance of pregnancy) with effects on brain plasticity that would support progestogens’ role for learning and memory. Thus, we focus our discussion on published data on the actions of progestogens in the object recognition task, with suggestions of novel mechanisms and consideration of the context of trophic processes in the body from pilot data in support.

2. Utility of object recognition task to investigate progestogens’ role for behavioral plasticity

This review focuses on key findings, using the object recognition task in rodents, to assess actions and mechanisms of progestogens. In behavioral endocrinology, to understand mechanisms and brain targets of a particular hormone’s effects on a specific behavior involves considering effects of: natural variations (e.g. estrous cycle, pregnancy, aging) in the hormone; removal of the gland that produces the hormone (i.e. following extirpation of the ovaries); and replacement of the hormone among those with low levels. Endogenous increases in progestogens over the estrous cycle or with pregnancy, support beneficial cognitive effects of progestogens in many spatial, emotional, and object memory tasks [1], [2], [3], [4], [5], [6], and [7]. Ovariectomy of rodents produces performance deficits in

memory tasks, including object recognition; which can be abrogated by progesterone or allopregnanolone administration [1], [6], [8], [9], and [10]. Beneficial effects of progestogens in rodents are not uniformly observed, which may be due to experiential factors and tasks (see [11] and [12] and later sections herein).

2.1. Utility of the object recognition task

The object recognition task is now a widely used animal model of cognition (non-spatial working, declarative memory). This task, developed for use in rats over 25 years ago, has since been modified for use in mice [13], [14], [15], and [16]. Key brain regions involved in performance of this task are the frontal cortex and hippocampus, (see [17] and [18] and others in the object recognition special issue [9], [20], [21], [22], and [23]); albeit, the literature in this area is somewhat controversial and beyond the scope of this review [24]. This task limits confounding variables because it does not rely on aversive stimuli or food rewards, which progestogens influence [25], [26], [27], [28], and [29]). Object recognition is not considered a task that typically promotes high levels of hypothalamic pituitary adrenal stress axis activation [14], which progestogens and other gonadal hormones can alter [30], [31] and [32]. However, different objects may influence baseline levels of exploration, perhaps due to factors such as the size of the object and the animal [7]. In our laboratory, potential objects to be utilized in this task are screened to determine their valence; as such, confounding of results by a natural preference for one object over the other used in the task is mitigated. The object recognition task, exploits the natural affinity of rodents for novelty. Using objects of different shapes and complexity limits test decay and enables repeated within-subject testing which can be advantageous to understanding lifespan effects of progestogens [33], described in the sections that follow.

2.2. Methods

Implementation of the object recognition task, vary in their methodological and theoretical parameters [7], [19], [20], [21], [22], [23], and [34]. In our laboratory, rodents are habituated to an empty open field (dimensions for rats $45 \times 24 \times 21$ cm; for mice $39 \times 39 \times 30$ cm) to reduce neophobia and increase attentiveness to objects during training. Immediately after habituation for five minutes, rodents are trained in a single trial, with two identical objects. Objects are placed furthest from where the rodent is introduced at the beginning of the three-minute training trial. The duration that rodents spend exploring the objects is recorded. The operational definition of exploration is the rodent directing its nose and whiskers at the object at a distance of no greater than 1 cm and/or licking, touching, or climbing on, the object. An inclusion criterion for valid analyses of performance in this task is that during training rodents must explore both objects for similar durations. Minimally, rats have to reach the criteria of exploring each object for at least 1 second during training for valid comparisons of their data during the testing phase. In our laboratory, we utilize objects of approximately the same size but different shapes (e.g. toy apple, boat, blocks, etc.) [6] and [7]. These objects that are chosen to be utilized in training and testing trials are ones that were validated to be uniformly explored by rats in the laboratory. Notably, by having a large number of validated objects, it is possible to re-test the same subjects in within-subjects and longitudinal designs.

There is a retention interval between the training and testing trials of four hours. Rodents' performance in the task is better with shorter retention intervals [17], [35], [36], and [37], but with intervals shorter than 3 hours, there may be difficulty interpreting the results solely as related to memory processing, rather than performance [38] and [39]. When assessing the role of hormones in this task, which have circadian and estrous cycles to consider, a four hour interval ensures rodents are in similar hormonal states during training and testing of short-term memory in this task [6], [40], and [41]. Another aim of using this protocol is that short-term memory is being assessed during the process of memory consolidation, which occurs in several waves for at least six hours (for a review, please see [42]). Given that short-term memory traces are more unstable and vulnerable to disruption than long-term memory traces, we have utilized this similar duration of the interval between training and testing for this task for assessing short-term hormonal effects. Indeed, if progestogens are administered even 1 to 1.5 hours post-training to rodents with low circulating progestogens, then performance is not enhanced when subjects are tested at this test 4 hours after the training phase [6] and [43]. Although it is beyond the scope of this review, it is worth noting that progestogens can produce a similar pattern of effects in this type of object recognition protocol as in tasks assessing declarative long-term memory [44] and [45].

Rodents' performance is assessed by recording the time spent investigating the familiar object used during training and a novel object. Performance is calculated as the percentage of time spent exploring the novel object to the total time spent exploring both the familiar and novel objects. Chance levels of performance would be when 50% of the time spent exploring the novel objects occurs during testing. As such, when rodents spend more than 50% of the total investigation time in investigating the novel object, the interpretation is that rodents are demonstrating object recognition. A secondary analysis in these types of studies then becomes whether rodents in different conditions are showing this object recognition for the novel object beyond these chance levels of object exploration.

Object placement, a related, but spatial cognition task, relying on the hippocampus, involves use of the same objects during training and testing; however, during testing one object is moved from the location it was in during training. Comparing results in from object recognition and placement tasks has clear implications for the interpretation of steroid effects on non-spatial and spatial cognition, respectively. As well, the roles of specific brain regions in each type of memory can be elucidated given that object recognition and placement may disproportionately rely upon the prefrontal cortex and hippocampus, correspondingly. Thus, a discussion of data regarding the role and mechanisms of progestogens and, to a lesser extent estrogens, for object memory in rodents follows.

3. Natural variations in progestogens of rodents for object recognition memory

3.1. Object recognition memory - pregnancy and post-partum

Female rodents spend most of their reproductive life under the influence of estradiol and progestogens (progesterone and its neuroactive metabolites), and fluctuations in these steroids may positively influence cognitive performance in an ecologically relevant way (e.g.

enhancing abilities for finding and recognizing mates, pups, food, etc.). Natural variations in progesterones and estradiol, which occur during pregnancy and post-partum, influence performance in the object recognition task (as well as other cognitive tasks). In support, there are effects of fluctuations in these steroids in different states of pregnancy and over the estrous cycle for object recognition ([5], summarized in **Figure 1, left**). In rats, the length of gestation and lactation are each three weeks long. A comparison between rats in early (first week of) pregnancy, and those in late pregnancy (third week of), two days post-partum, and lactating/nursing for two weeks (postpartum day 14) revealed that rats in early pregnancy performed at chance levels in the object recognition task; the other groups spent considerably more time investigating the novel object coincident with, or following, robust increases in estradiol and progesterones (**Figure 1, left**). A similar pattern occurs in the object placement task with pregnant rats outperforming non-pregnant rats [46]. Thus, performance in object memory tasks improve for rats that recently experienced high physiological levels of estradiol and progesterones.

3.2. Object recognition memory - parity

What is the role of parity, or experiences with pregnancy and caring for offspring (lactation), for these effects? An influential paper published over 15 years ago demonstrated that spatial memory was enhanced in a radial arm maze and dry-land version of the Morris water maze among rats that were dams compared to those that had not had this experience of pregnancy and lactation [47]. This linked behavioral plasticity involved in care for the offspring known to occur in the first-time dam to behavioral and neural plasticity beyond reproductive function *per se* to spatial learning and hippocampal plasticity, which have been corroborated in several other studies (reviewed in: [2] and [48]. As an example of hippocampal plasticity, late pregnant and lactating rats have more dendritic spines in the hippocampus than do cycling nulliparous rats [49] and [50]. Adult neurogenesis in the hippocampus occurs post-parturition in rats [51]. Indeed, several other studies have complemented and extended this initial report to support the notion that pregnancy and lactation have robust effects in performance in other tasks, including object recognition, as well as several measures of neural plasticity in corticolimbic regions beyond the hippocampus (Readers are directed to excellent reviews of these data that are more thorough than can be accommodated herein: [2], [4], [52], [53], and [54].). As one example, female rats that were multiparous (pregnant and lactating over multiple occasions) and tested in different stages of the estrous cycle or pregnancy had better performance in both the object placement and object recognition task when compared to nulliparous (virgin) rats across these endogenous states [5]. Interestingly, parity can also be associated with greater perseverative behavior, and, thereby, worse performance in a strategy set-shifting task among female rats [55]. This is important to note because many of these tasks designed to test for spatial and object recognition memory, as well as this strategy set shifting task, use visual cues in training and testing and are considered to involve prefrontal cortical input. As well, when interpreting object recognition in rodents, it is important to consider that exploration of objects is not limited to visual processing and involves rich somatosensory cues, with information coming from the whiskers, paws, and tongue, and, thus, other cortical areas mediating this somatosensory information. The differences in performance with parity begin to suggest specificity in brain

circuitry and mechanisms involved, in cortical function, which need to be investigated further.

Another consideration is how long these improvements last and whether effects are due to pregnancy-related or lactation-related factors, or both. Spatial working and reference memory of rats that had experienced one pregnancy and lactation (primiparous) had the best performance when tested 55 days post-parturition, compared to multiparous and nulliparous rats [56]. Additionally, rats that had experienced pregnancy, but not lactation, learned this task in fewer trials than did primiparous, multiparous, or nulliparous rats [56]. Cost and colleagues found that primiparous females displayed better object-in-place memory than nulliparous females during lactation and up to 42 days after giving birth [57]. Thus, effects of parity are long-lasting.

Using object recognition, a longitudinal design can examine performance within and between subjects. Pregnant primiparous or multiparous rats were assessed each day in the object recognition or object placement tasks. Multiparous, but not primiparous, rats in Gestational Days 6-12, had improved object placement performance coincident with levels of corticosterone and estradiol, which were low and high, respectively [5]. Primiparous rats in Gestational Day 13 to parturition had improved object placement performance coincident with higher circulating levels of allopregnanolone [5]. Another longitudinal study assessing performance every 4 months in a dry land maze in rats during young adulthood (5 months) to advanced age (22 months) demonstrated that rats that had become pregnant had better performance at 5, 9 and 13 months of age than did their nulliparous counterparts; all groups showed aged-related decline at 17 and 22 months of age [58]. Thus, experiential factors (number of pregnancies and bouts of lactation and offspring care), age, as well as current hormonal milieu may influence cognitive performance.

3.3. Object recognition memory - estrous cycle

A question is the extent to which there are differences in performance associated with fluctuations in estrogens and progestogens across a timeframe shorter than pregnancy and/or lactation. Levels of progesterone and allopregnanolone are high during proestrus; however, the peak circulating concentrations of estradiol and progestogens during pregnancy are far greater and persist for a much longer than during the estrous cycle. Rats in proestrus (aka behavioral estrus, the estrous state coinciding with ovulation when female rats will mate with a male) or estrus outperform females in diestrus ([48] and summarized in **Figure 1, left**). These findings corroborate previously published findings that included measurement of estradiol, progesterone, and allopregnanolone across the cycle (i.e. higher levels of all three steroids in proestrous compared to diestrous) and behavioral assessment [6]. Levels of estradiol, progesterone, and allopregnanolone were measured in rodents following testing to confirm estrous cycle state and investigate variability in performance associated with specific hormone levels in hippocampus and prefrontal cortex. Regression analyses revealed that there was a significant positive relationship between estradiol levels in the hippocampus, but not the prefrontal cortex, for performance in this task. Moreover, there was a positive correlation between allopregnanolone levels in the hippocampus and cortex and object recognition task performance [6]. These data provide initial insights that there may be

dissociable actions of these steroids, which co-vary over natural cycles, in brain targets important for object recognition. Ultimately, we hope to explain the relationships between steroid levels in the hippocampus, prefrontal cortex, and other brain regions and performance on the object recognition task based upon the roles of various brain regions in this particular cognitive task. Further investigation is necessary to achieve this goal.

3.4. Object recognition memory- aging

The published data described above focused on the role of natural variations in progestogens for object recognition and performance in other cognitive tasks and concluding with describing interactions between experiential factors, age, and current hormone state of laboratory rodents. Given the clear clinical relevance for the aging population of women, and backlash against hormone-replacement therapies (discussed in more detail at the end), further discussion of the role of aging for progestogens' actions for object recognition is warranted. What follows is discussion of the reported effects of aging, hormone status, and neurodegeneration among laboratory rodents.

There is age-related decline in performance in the object recognition task, as well as other cognitive tasks, described as follows, of female rodents; a question is whether breeding history alters this age-related loss. For example, aged Fisher 344 rats (21 months old) had worse performance than younger strain-matched rats (4 months old) as well as significantly reduced dendritic spine densities in the prefrontal cortex [59]. A speculation is that ovarian steroids, such as those associated with parity, may be protective against age-related cognitive decline observed in female rodents. In support, in the Morris Water Maze spatial memory task, late middle-aged (18 months old) primiparous rats outperformed age-matched nulliparous rats [60]. A similar long-lasting effect of parity across even later ages (24 months) was observed in a dry land modification of the Morris Water Maze as well as reduced expression of a brain plaque-associated factor, amyloid precursor protein, in the hippocampus [61]. Further support is that a protective effect of multiparity among middle-aged (12 months old) has also been described for object recognition memory of rats, as well as object placement spatial task, and these improvements over nulliparous rats were associated with increased brain derived neurotrophic factor (BDNF) levels in the hippocampus [62]. An important question that needs to be further addressed is whether such protective effects would be similarly observed with long-term treatment with progestogens among rodents. Some notions to consider further are related to experience- and age-related changes in progestogens.

Do age- and experience-related changes in performance in object recognition occur concomitant with decline in progestogens? By using a longitudinal approach and assessing middle-aged rats' performance in the object recognition task, we have found that multiparous rats show less age-related decline in object recognition performance than nulliparous rats [5]. A key observation relating to progestogens' role in object recognition among aged individuals is that multiparous middle-aged rats with declining reproductive status, compared to those that had reproductive function intact (i.e. normal estrous cycles, fertility and litter size), had worse performance in the object recognition task [63]. Notably, these performance deficits occurred coincident with a lowered capacity to metabolize

progesterone to allopregnanolone in the prefrontal cortex [63]. A similar pattern of effects among these comparison groups was not observed for circulating levels of estradiol or corticosterone. These data show that there may be interactive effects of reproductive experience, status, age and progestogens for object recognition performance. Another important point to address regarding age-related decline in object recognition is whether older subjects can respond to hormone replacement. We have observed that mid-aged and aged rats do not typically perform as well as their younger counterparts in the object recognition task (**Figure 1, right**). Administration of estradiol and progesterone immediately after training improves object recognition performance (**Figure 1, right**). A similar pattern has been reported among aged female mice; progesterone administration immediately after training in the object recognition task improved performance [43]. Notably, these beneficial effects of progesterone were not observed in performance of mice in every task assessed, suggesting specificity of the observed effects. Another important aspect to note is that by using object recognition, as well as other tasks that have greater (e.g. water maze) or fewer (e.g. conditioned fear) movement requirements, we can consider the role of locomotion for behavior; this may be particularly important during pregnancy and with aging.

Reproductive status may modify the response to hormone replacement. In comparing age-matched middle-aged rats that were maintaining reproductive function (“maintaining” normal cycles, fertility, fecundity), had evidence of decline in at least one of these measures of reproductive function (“declining”), or were no longer cycling or fertile (“diminished”), there was decline in object recognition performance among the diminished group [63]. Thus, further consideration of how individual responses of mid-aged rats to progesterone, and other hormone therapies, post-training in the object recognition task may be related to extent of reproductive decline is warranted.

3.5. Progesterone replacement in animal models of neurodegeneration

An additional approach to assess the role of progestogens for object recognition performance is to determine the effects of progesterone replacement in an animal model of neurodegeneration. In support, chronic progesterone treatment (for 3-6 months) improved object recognition performance in a mouse model of Alzheimer's Disease (mice co-overexpressing a mutant form of amyloid precursor protein and a deletion in presenilin 1), similar to wildtype controls, compared to vehicle treatment [64]. Both wildtype and mutant mice had higher levels of progestogens in the prefrontal cortex, but there were deficits in allopregnanolone formation in the hippocampus and spatial memory deficits in the mouse model of Alzheimer's Disease [64]. Conversely, an acceleration in brain pathology and performance deficits has been observed with chronic high dosing of allopregnanolone in mouse models of Alzheimer's Disease that overexpress amyloid precursor protein and a deletion in presenilin 1 [65] and [66]; yet, benefits have also been observed with different dosing of allopregnanolone, models of Alzheimer's Disease, and individual characteristics of subjects (age, timing/duration of treatment, etc.) [67], [68], [69], and [70]. Together, these data suggest that there may be differences in response to progesterone replacement in older rodents, which depends upon task as well as current hormone/reproductive state and disease-related neurodegeneration.

3.6. Synthetic hormone replacement

An important consideration is the strength of the response to synthetic hormone replacement therapies that are clinically used in human subjects for object recognition among rats. The types of hormone replacement therapy that have been utilized the most often among menopausal women are not estradiol or progesterone, but rather synthetic hormone therapies, such as CEE and MPA. There is a paucity of research in animal models using CEE and/or MPA for behavior, but these types of studies would enable more direct manipulations and measurements of these effects than can be completed in human subjects. For example, administration of CEE to mid-aged (10-14 months) female rats enhances object recognition performance [71]. A pilot study in our laboratory demonstrated a similar pattern of effects when comparing whether aged rats (15-18 months) had greater object recognition performance following post-training CEE or placebo (**Figure 1, right**). Although CEE can improve object recognition performance in older rodents, MPA is generally associated with poorer cognitive performance in other tasks than that observed following vehicle administration to older female rodents [72] and [73]. MPA does not seem to increase BDNF in brain areas assessed, as CEE has been shown to [74], [75], [76], [77], [78], and [79]. Thus, commonly-used synthetic hormone treatments, CEE and MPA, may have opposing effects for cognitive performance of rodents.

A question is the extent to which differences in response to synthetic hormones may be related to progestogen synthesis. As far as we know, effects of MPA have not been systematically assessed in aged rats for object recognition performance. We have observed that middle-aged rats respond poorly to MPA for anxiety behavior in the elevated plus maze [75] and that young, ovariectomized mice respond poorly to MPA for object recognition performance [74] and [80]. In both of these studies, MPA administration was not associated with enhancement in allopregnanolone levels (as was CEE or progesterone replacement) [74], [75], and [80]. Moreover, among young, ovariectomized mice, MPA administration reduced BDNF levels in the hippocampus and the prefrontal cortex [74]. On the other hand, CEE can increase allopregnanolone levels of middle-aged rats [75] and [76] in addition to improving object recognition performance of middle-aged female rats, compared to vehicle [71]. Thus, these data suggest that aged female rodents, and/or those with decline in object recognition performance, may benefit from hormone replacement if progestogen and/or growth factor levels are enhanced; further investigation on this hypothesis is warranted.

4. Extirpation and replacement of progestogens for object recognition performance

Although the sections prior discussed the role of progestogens across the lifespan for object recognition performance, progestogens rarely fluctuate independent of estradiol, or many other steroids, in these natural reproductive cycles, or with aging. As such, another approach is needed to understand the role of progestogens for object recognition. Our laboratory, and others, have utilized extirpation of the peripheral sources of these hormones, the ovaries, and comparisons of the effects of replacement back with progestogens alone, or with estradiol, for object recognition performance. This approach of somatic manipulation, enables causation to be addressed that correlative studies discussed heretofore cannot address

sufficiently. Rats were ovariectomized for a similar duration before being treated with hormones or placebo condition within each experiment; it is generally the case that rats recover from ovariectomy for 10-14 days. Additional findings from investigation of the effects and brain targets of progestogens for object recognition, using extirpation and replacement, follow.

4.1. Object recognition memory- ovariectomy and replacement

A first step for understanding the role of reproductive hormones for object recognition performance is to remove the major peripheral gland that produces progestogens and estrogen, the ovaries, and assess performance. If object recognition performance is poorer following ovariectomy than that observed among cycling rats, an interpretation can be that progestogens may be involved in the improved object recognition performance observed. Rats that are tested following ovariectomy perform closer to chance levels in the object recognition task, unlike young female rodents in proestrus, which perform better than chance and demonstrate object recognition [6] and (Figure 1, middle). Thus, ovariectomy is associated with poor object recognition performance that can be reversed with dosing of estradiol and progesterone that produces circulating hormone levels akin to proestrus.

The majority of investigations into the effects and mechanisms of progesterone for cognitive performance have assessed these effects of progesterone in ovariectomized rodents following estradiol priming. This is substantiated because, naturally, progesterone very rarely acts independent of estradiol over endogenous cycles. Additionally, there is a long history of focusing on the effects of estradiol in investigations of the capacity for ovarian hormones to influence behavioral and neural plasticity [81]. Early investigations of the role of hormones in the object recognition task demonstrated that estrogens, such as 17 α - and 17 β -estradiol, have robust effects to improve object recognition memory *per se* (and not other performance factors as supported by no effects when estrogens were administered 2 hours after training) [82]. A similar pattern was observed when other synthetic estrogens (selective estrogen receptor modulators) were administered immediately post-training to ovariectomized rats [6] and [83]. Estrogens can improve object recognition memory and can promote progestogen formation. To ascertain their relative roles, we have investigated effects and mechanisms of each steroid alone and in conjunction with each other.

4.2. Object recognition memory- progestogen replacement and capacity for progestogen production

Up until more recently, very little was known about progestogens' mnemonic effects, independent of estradiol. There is even evidence of disorganizing effects of progestogens on cognitive performance, particularly when levels are high or sustained, or in specific memory tasks (reviewed in: [30]). For example, progesterone administration to female rats impaired object placement performance, but not object recognition performance [84]. Progesterone alone, without the influence of estradiol, can enhance object recognition memory when administered to ovariectomized rodents. The percentage of time that rats spent investigating the novel object during the testing trial was increased among ovariectomized rats administered progesterone immediately post-training, and not after a 1 or 1.5 hour delay, and associated with increased progestogen levels in corticolimbic structures [6] and [44]. Among

mice, improved performance following progesterone post-training was observed in the object recognition task, but not in the object placement task [43]. Similarly, even with retention trials of over 2 hours, object recognition memory is enhanced by post-training systemic or intra-hippocampal administration of progesterone [85] and [86]. At this point, we have compared effects of immediate or delayed post-training administration of progestogens for object recognition during a testing trial four hours later. Of future interest is further investigation of whether effects and mechanisms can be dissociated for object recognition memory acquisition, consolidation, and recall.

Although there are data to support the notion that progesterone may have beneficial effects in rats and mice, independent of estradiol, for object recognition memory, these effects may depend upon task and dosing. An additional important consideration is how progestogens' known anxiolytic effects may influence performance in the object recognition task; the reader is referred to [30] and [87] for review of progestogens' effects for affective tasks. We have attempted to begin to address the potential for anxiolytic effects of progestogens' altering object recognition by conducting studies with different timing of progestogen administration as described above. It is of interest for future studies to continue to investigate this consideration more directly as well as ascertain how stress responding (e.g. corticosterone levels) before or after training may influence object recognition.

Progesterone's enhancing effects in object recognition are observed among mice, irrespective of progesterone binding to its cognate progesterin receptor. This pattern of results suggests potential non-traditional mechanisms of progestogens [45]. A recent study investigating such non-steroid receptor effects among mice for object recognition memory demonstrated that extracellular signal-regulated kinase (ERK) and/or the mammalian target of rapamycin (mTOR) pathways in the hippocampus may be involved [88]. A question of particular interest is whether these non-progesterin receptor mediated actions involve progesterone's metabolites. The role of progesterone's metabolite, allopregnanolone, which also co-varies with estradiol and progesterone over endogenous cycles, and does not bind progesterin receptors, when in physiological concentrations, is an important consideration.

4.3. Role of allopregnanolone synthesis

The capacity to produce allopregnanolone may underlie the beneficial effects of progesterone for object recognition. In comparing effects in the object recognition task of post-training progesterone or allopregnanolone, in dosages that produce proestrous-like levels of progesterone and allopregnanolone in the prefrontal cortex and hippocampus of ovariectomized rats, data suggest that there are similar improvements with either progestogen treatment [6]. Additional support about the role of allopregnanolone is that, among ovariectomized mice, only progestogen treatments that enhanced allopregnanolone in the prefrontal cortex and/or hippocampus were associated with better object memory [80]. These treatments included post-training progesterone, allopregnanolone or allopregnanolone co-administered with MPA; MPA alone or co-administered with progesterone was ineffective [80]. Moreover, the importance of production of allopregnanolone for object recognition memory of mice has been corroborated by using a pharmacogenetic approach. In this study, mice that were knockouts of the 5 α -reductase gene (and thereby have deficits in

converting progesterone to allopregnanolone) had poorer object recognition memory than did wildtype mice following post-training progesterone administration [74]. Both wildtype and 5 α -reductase knockout mice administered allopregnanolone, but not MPA, had improved object recognition memory compared to vehicle-administered controls, demonstrating that the mutant mice were able to respond to allopregnanolone. Another intriguing finding from this study was that levels of BDNF in the prefrontal cortex and hippocampus were lowest among mice administered MPA, suggesting a downstream role of this growth factor. We have demonstrated in young, cycling rats that manipulation of allopregnanolone synthesis in the midbrain alters expression of BDNF in the hippocampus [89], and others have noted that allopregnanolone alters BDNF expression in other limbic structures, such as the amygdala and hypothalamus, in addition to the hippocampus [90]. Although these data suggest an intriguing role of BDNF, it is likely not the only causative factor involved and substantiates further investigation of the molecular mechanisms of progestogens for object recognition. There are several other expert reviews on the effects and mechanisms of hormones, and brain targets, for object recognition among rodents that the reader is referred to [19], [20], [21], [22], and [23]. Together, these studies point to the notion that production of allopregnanolone in the hippocampus and prefrontal cortex may be required for progestogens' mnemonic effects in the object recognition task.

Although these data suggest that progesterone or allopregnanolone can benefit object recognition memory of rats and mice, another consideration is that some of estrogens' effects for object recognition involve downstream changes in capacity to produce allopregnanolone. We have been investigating the complementary effects of estrogen receptor β and allopregnanolone actions for object recognition performance. Selective estrogen receptor modulators that act at estrogen receptor α or β can improve performance in the object recognition task; yet, estrogens do not improve performance of mice that have had estrogen receptor β knocked out [82], [83], [91], and [92]. Notably, these mice with estrogen receptor knocked out have lower levels of allopregnanolone in corticolimbic structures than do their wildtype counterparts, when in proestrus, or following ovariectomy and estradiol or selective estrogen receptor modulator administration [91] and [92]. Similarly, ovariectomized rats that are administered estrogen receptor β ligands, versus estrogen receptor α ligands, have a greater capacity to produce allopregnanolone [93]. We have compared responses of gonadally-intact, female wildtype and estrogen receptor β knockout mice with progesterone and its metabolites administered post-training in the object recognition task. Wildtype, but not estrogen receptor β knockout mice, respond to progesterone with enhanced memory in this task, compared to vehicle; both strains respond to allopregnanolone and its prohormone, dihydroprogesterone, which is produced following 5 α -reduction of progesterone, with improved memory for the novel object compared to that observed in the vehicle control group (**Figure 2**). Importantly, these data suggest in a knockout mouse model that deficits in capacity to produce, but not respond to, allopregnanolone may be associated with poorer object recognition. Thus, a non-traditional target of progestogens for object recognition performance to consider further are the estrogen receptors, namely estrogen receptor β ; actions at which may be important for allopregnanolone production, and thereby, object recognition memory.

5. What about males?

An overarching focus in the previous sections is that there are many contexts to consider for interpreting hormones' effects for object recognition (e.g. age, experience, etc.) Another context to consider is organizational effects of hormones. In support, there are sex/gender effects in learning and memory (reviewed in: [94]), with some of the most robust findings across species being differences in spatial performance (which males typically outperform females). Conversely, females seem to have the advantage for object recognition performance, as well as object placement memory, when estradiol and progestogens are high [84], [95], [96], [97], and [98]. Manipulations of allopregnanolone during in utero development (last week of pregnancy), produces impairments in object recognition memory of male and female rats when they are assessed as juveniles coincident with reductions in allopregnanolone in the hippocampus and increased corticosterone among females, but not males, compared to controls [99]. A question that needs to be addressed further is the extent to which adult males may benefit from progestogens for object recognition. In support, in comparing male mice administered progesterone or vehicle, an improvement in object recognition and increased levels of progesterone in the hippocampus was observed [100]. As observed in aged female mice previously [45], this effect of progesterone was independent of whether mice expressed progestin receptors, suggesting potential non-traditional actions to consider in future studies. Thus, a context to consider in future studies beyond current hormonal milieu and experience with states, such as pregnancy and lactation, are sex/gender differences and the role and mechanisms of progestogens for object recognition.

6. Considering the context further- the body

Hormone replacement can produce a cognitive benefit in the object recognition task among mid-aged and older rodents. Neurosteroids and growth factors, such as BDNF, may underlie these effects, and there may be dissociable actions of these factors and hormones, which co-vary over natural cycles and aging, in brain targets important for object recognition. A consideration of the extent to which there are coincident trophic effects in the body is warranted.

A major criticism of hormone-replacement therapies among menopausal women, or hormone-based therapies among younger women, is their potential to increase risk for reproductive cancers, stroke, and other negative cardiovascular outcomes. To address relative benefits of progestogens, and other steroids, for object recognition performance, we also examine their trophic actions in the body of the same subjects. For example, uterine growth and carcinogen-induced mammary tumor proliferation among young, ovariectomized rats is increased by estradiol or ER α , but not ER β , ligand administration; conversely, estradiol or ER β ligands enhance hippocampally-mediated behaviors (e.g. elevated plus maze as an anxiety measure as well as cognitive measures) [101] and [102]. Thus, it is possible to dissociate steroids divergent trophic actions in the brain from those in the body.

Comparisons of behavior and neuroendocrine effects on cardiovascular function and metabolism are of interest. In a pilot study, CEE to aged rats, compared to placebo vehicle, increased cholesterol (**Table 1**) and reduced fasting glucose (CEE 157 ± 4 vs. placebo 125

± 2). Selective estrogen receptor modulators and CEE benefit glucose levels in mice [103]. Administration of estradiol and progesterone enhanced object recognition performance to ovariectomized or mid-aged rats increased cholesterol compared to that observed in placebo control groups (Table 1). Cardiovascular function immediately after testing was assessed using a non-invasive tail cuff measure (CODA monitor, Kent Scientific, Torrington, CT). Among the aged rats, CEE modestly increased heart rate compared to vehicle, but did not alter systolic or diastolic blood pressure (Table 1). Administration of estradiol and progesterone enhanced object recognition performance uniformly reduced heart rate and blood pressure among ovariectomized and mid-aged rats compared to placebo vehicle administration (Table 1). These data are important to mention because they speak to potential confounding factors in interpretation of the behavioral data. These patterns among animal subjects are akin to those reported in the clinical literature of some benefit of hormones on the cardiovascular system [104], [105], [106], [107], [108], and [109]. Thus, by using this approach, we have been able to pilot out an approach to begin to differentiate the enhancing effects of hormone therapies on neuroendocrine function and measures of brain plasticity (e.g. memory, BDNF) in the context of cardiovascular and metabolic function.

7. Effects of progestogens for cognitive performance among women

7.1. Effects among young, cycling women

Despite the data from animal models that support beneficial effects of progestogens from early until later life, which was described in detail in the previous sections, there is great variability in the patterns of response to progestogens among women for memory processes. Many of the cognitive effects of progestogens occur in conjunction with estrogen. Separating the effects of progestogens from estrogens on any function is inherently problematic because these steroids often are both present and fluctuate in tandem, thereby affecting biological outcomes in complex ways. Thus, first we discuss effects during pregnancy, when progestogen levels are higher than at any other point in the lifespan.

Pregnancy was considered a clear example of how progestogens, when in high concentrations for a prolonged period of time, can have disorganizing effects among women (reviewed in [110]). However, this has been contested with findings from a large study employing a baseline and later assessments during pregnancy or after pregnancy that did not find evidence for performance deficits in immediate or working memory, or delayed recall tasks [111]. Among young women, there are variations in cognitive performance across the menstrual cycle, and with administration of synthetic progesterone. During the luteal (high progestogen) phase, performance on verbal and visual memory and attention tasks is enhanced and positively correlated with circulating progesterone levels [112] and [113]. As well, the number of spontaneous intrusive recollections after watching emotional films is increased during the luteal phase and correlated with salivary progesterone levels [114] and [115]. Administration of progesterone to young, cycling women can impair performance in negative image recall and verbal memory [116] and [117], but can enhance performance in tasks of attention, response speed, and visuomotor coordination [118]. However, when young, healthy cycling women were acutely administered a gonadotropin releasing hormone inhibitor, which reduces ovarian secretion of estradiol and progesterone, robust changes in

cognition were not observed and estradiol and progesterone add-back did not significantly alter performance on tasks of memory or attention [119]. Thus, responses to progestogens for cognitive function among young, pre-menopausal women may depend upon task assessed.

7.2. Effects across the menopause transition

Another approach to elucidate the role of progestogens for cognition in women is to assess function in older women across the menopausal transition. Menopause is clinically defined by loss of menstrual cyclicity for one year, and through this transition (perimenopause to postmenopause), women experience robust fluctuations in circulating ovarian steroids followed by a sharp decline [120], [121], and [122]. Of interest is the extent to which there is cognitive decline in this period that may be associated with steroid decline, and not only aging *per se*, and if there is a critical window for beneficial effects of hormone-replacement [123], [124], and [125]. Aging and neurodegeneration influence many cognitive abilities, including object recognition (see [126], [127], [128], and [129]).

Understanding specificity of age-related cognitive decline among women is important. Individuals with probable Alzheimer's Disease or dementia have 33% lower circulating levels of allopregnanolone than do age-, gender-, and hormone therapy-matched controls [130]. Age, health, timing, and tasks may influence hormones' effects [122], [123], [131], and [132]). Circulating progesterone, verbal memory and global cognition positively correlate among women postmenopause for less than 6, but not more than 10, years [133]. Micronized progesterone (which does convert to allopregnanolone), compared to medroxyprogesterone acetate (MPA, a synthetic progestin, which does not convert to allopregnanolone), is associated with better verbal memory performance (reviewed in: [134] and [135]). Indeed, conjugated equine estrogen (CEE) plus MPA) increased risk of dementia and reduced verbal memory task performance, a predictor of later dementia risk [136] and [137]. Indeed, large clinical trials were truncated due to increased cancer and cardiovascular risks; yet, duration of menopause, predispositions to stroke or reproductive cancers, and/or hormone-replacement therapy were not always considered [138], [139], and [140].

Progestogens have actions for plasticity in the body and brain but most studies focus on effects and mechanisms in brain *or* reproductive tissue. The interplay between systems affected by steroids is typically ignored by most investigators and represents a serious gap in the current literature. For instance, the effects of progestogens and estrogens on cardiovascular systems or on metabolic activities could have important implications for brain function. Hormone replacement use has declined precipitously in the past decade since early clinical trials showed mixed effects for cancer and/or cardiovascular risks [138], [139], and [140]. However, for breast cancer treatment, hormone receptor expression and single nucleotide polymorphisms are critical prognostic factors [141], [142], [143], [144], and [145]. Thus, differential effects and mechanisms of progestogens in the brain vis-à-vis the body need to be better understood.

8. Conclusions

Progesterone influences object recognition and may and do so in part through actions of its metabolite, allopregnanolone in the hippocampus and prefrontal cortex. These effects were considered in different hormone contexts, such as across the lifespan. A generality noted across many studies using object recognition and the similar object placement task as well as many other rodent cognitive tasks is that there may different responses based upon brain age or health. To summarize, object recognition and placement show a similar pattern of effects following progestogen manipulations among young, healthy rodents. Interestingly, these effects seem to diverge for object recognition and placement with aging or neurodegeneration. Lastly, these studies provide proof-of-concept that benefits of progestogens for cognitive performance (namely, object recognition), and mechanisms for such benefit (e.g. BDNF), may diverge from those on the periphery (e.g. cardiovascular and metabolic function).

Acknowledgements

Assistance on the studies described herein provided by members of the laboratory, past and present, is greatly appreciated.

Role of the funding source

Research herein was supported in part by grants National Institute of Mental Health (MH-06769801, RMH067698B) and the National Institute of General Medical Sciences of the National Institutes of Health (P20GM103395). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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HIGHLIGHTS

The object recognition task is well-suited for studying hormones and aging.

Hormones modulate behavioral and neural plasticity across the lifespan.

Object recognition task has been used to investigate progestogens and estrogen.

Progestogens' memory effects may be due allopregnanolone.

Figure 1.

Mean % of time spent with the novel object ($\pm$ SEM) as a function of the total time spent investigating objects during the testing phase. The portion of bars showing performance above chance are in white and below chance are in gray. Data depicted on the left side are from rats with typical ovarian function across the estrous cycle (diestrous, proestrous, and estrous phases), and during early (week 1) and late (week 3) pregnancy, and two days (PPD2) and 14 days (PPD14) postpartum. Data depicted in the middle are from young adult rats that had typical ovarian function before they were ovariectomized (OVX, surgical ovarian decline) and replaced back with oil vehicle placebo or estradiol (E₂; 0.9 mg/kg, which produces proestrous-like levels of circulating E₂) and progesterone (P₄; 4 mg/kg, which produces proestrous-like levels of circulating P₄). Data depicted on the right side are from rats with decline in ovarian function with aging: mid-aged (12-14 months old) administered placebo vehicle, E₂, P₄, or E₂+P₄ immediately after training and aged (15-18 month old) rats administered placebo vehicle or conjugated equine estrogens (CEE; 0.625 mg/kg). All placebo or hormone treatments were administered via subcutaneous injections immediately after the training phase. All rats were tested four hours after training. There were 8-12 rats per experimental group.

Figure 2.

Mean % of time spent with novel object ($\pm$ SEM) of wild type mice and estrogen receptor β knockout (β ERKO) mice administered placebo vehicle, progesterone (P₄; 4 mg/kg), dihydroprogesterone (DHP; 4 mg/kg), or allopregnanolone (3 α ,5 α -THP; THP; 4 mg/kg). There were 8-13 mice per group. All injections were subcutaneous and administered immediately after the training trial. * over line indicates significant effect of genotype revealed by Analyses of Variance ($F_{1,82} = 5.18$) and Fisher's LSD post hoc testing for group differences ($p = 0.02$). * over individual bars indicates significant effect of hormone condition revealed by analyses of variance ($F_{3,82} = 2.60$) and Fisher's LSD post hoc testing for group differences ($p = 0.05$).

Table 1

Depicts the mean $\pm$ standard error of the mean (SEM) of circulating levels of cholesterol (as measured with the Cardio Check device by Test Medical Symptoms), and systolic and diastolic blood pressure and heart rate as measured non-invasively with the Coda Monitor (Kent Scientific). Samples are from rats that have behavioral data depicted in Figure 1. Samples were collected from young adult diestrous rats, young adult ovariectomized (OVX) and replaced back with oil vehicle placebo or estradiol (E₂; 0.9 mg/kg) and progesterone (P₄; 4 mg/kg; E₂+P₄), mid-aged (12-14 months old) rats administered placebo or E₂+P₄, or aged rats (15-18 months old) that were administered placebo or conjugated equine estrogens (CEE; 0.625 mg/kg).

Measures of hormone's effects in the body of rats following Object Recognition testing				
	Cholesterol (mg/dl)	Systolic (mmHG)	Diastolic (mmHG)	Heart Rate (beats/minute)
Diestrous	119 $\pm$ 9	145 $\pm$ 4	114 $\pm$ 3	462 $\pm$ 9
OVX, placebo	100 $\pm$ 10	106 $\pm$ 18	81 $\pm$ 14	428 $\pm$ 16
OVX, E₂+P₄	133 $\pm$ 18	74 $\pm$ 32	51 $\pm$ 23	382 $\pm$ 31
Mid-aged, placebo	111 $\pm$ 11	142 $\pm$ 11	83 $\pm$ 17	442 $\pm$ 49
Mid-aged, E₂+P₄	157 $\pm$ 54	108 $\pm$ 20	78 $\pm$ 16	402 $\pm$ 49
Aged, placebo	122 $\pm$ 22	106 $\pm$ 12	65 $\pm$ 10	408 $\pm$ 26
Aged, CEE	144 $\pm$ 36	117 $\pm$ 7	79 $\pm$ 7	449 $\pm$ 10