Available online at www.sciencedirect.com
SCIENCE DIRECT
Brain Research 1038 (2005) 59–68
BRAIN RESEARCH
www.elsevier.com/locate/brainres

Research report

Progesterone's 5α-reduced metabolite, 3α,5α-THP, mediates lateral displacement of hamsters

Cheryl A. Frye[a,b,c,*], Madeline E. Rhodes[a]

[a]Department of Psychology, The University at Albany-SUNY, Albany, NY, USA
[b]Biological Sciences, The University at Albany-SUNY, Albany, NY, USA
[c]The Center for Neuroscience Research, The University at Albany-SUNY, Albany, NY, USA

Accepted 2 January 2005

Abstract

5α-pregnan-3α-ol-20-one (3α,5α-THP), progesterone (P_4)'s 5α-reduced, 3α-hydroxysteroid oxidoreduced product, facilitates lordosis of rodents in part via agonist-like actions at $GABA_A$/benzodiazepine receptor complexes in the ventral tegmental area (VTA). Whether 3α,5α-THP influences another reproductively-relevant behavior, lateral displacement, of hamsters was investigated. Lateral displacement is the movement that female hamsters make with their perineum towards male-like tactile stimulation. This behavior facilitates, and is essential for, successful mating. Hamsters in behavioral estrus had greater lateral displacement responses when endogenous progestin levels were elevated compared to when progestin levels were lower. Administration of P_4, a prohormone for 3α,5α-THP, dose-dependently (500 > 200 > 100, 50, or 0 μg) enhanced lateral displacement of ovariectomized hamsters that had been primed with SC estradiol benzoate (5 or 10 μg). Inhibiting P_4's metabolism to 3α,5α-THP by co-administering finasteride, a 5α-reductase inhibitor, or indomethacin, a 3α-hydroxysteroid oxidoreductase inhibitor, either systemically or to the VTA, significantly decreased lateral displacement and midbrain progestin levels of naturally receptive or hormone-primed hamsters compared to controls. These data suggest that lateral displacement is progestin-sensitive and requires the formation of 3α,5α-THP in the midbrain VTA.

Theme: Neural basis of behavior
Topic: Hormonal control of reproductive behavior

Keywords: Neurosteroids; Lordosis; Sexual function; Non-genomic; $GABA_A$ receptors

1. Introduction

Progestins mediate the onset and duration of sexual receptivity in rodents in part through actions at intracellular progestin receptors (PRs) in the ventromedial hypothalamus (VMH) and at $GABA_A$/benzodiazepine receptor complexes (GBRs) in the ventral tegmental area (VTA) [11]. In the VMH, there are many estrogen (E_2)-induced PRs that are up-regulated concomitant with sexual responsiveness. Activating PRs enhances, and blocking PRs disrupts, initiation of lordosis, the stereotypic posture female rodents assume to enable mating to occur [4,6,7,9,10,39,42,43]. In the VTA, there are few non-E_2-induced PRs and antagonizing them does not disrupt lordosis [12,30,45]. Rather, progestins that are devoid of activity at PRs, but enhance GBR function, facilitate lordosis when applied to the VTA [22]. Infusions of GBR agonists and antagonists to the VTA, respectively, facilitate and inhibit progestin-mediated lordosis [11–13,15,28]. Thus, progestins' actions at PRs in the VMH and at GBRs in the VTA can mediate lordosis.

In the VTA, progestins' actions to facilitate lordosis may involve progesterone (P_4) serving as a prohormone for 5α-pregnan-3α-ol-20-one (3α,5α-THP), which has potent, agonist-like actions at GBRs. P_4 produced peripherally by

* Corresponding author. Social Science 369, The University at Albany-SUNY, Albany, NY 12222, USA. Fax: +1 518 442 4867.
E-mail address: cafrye@albany.edu (C.A. Frye).

0006-8993/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2005.01.014

the ovaries or adrenals, or centrally by glia, is readily metabolized to 3α,5α-THP in the VTA. The enzymes necessary for P_4 biosynthesis (P450 side chain cleavage, 3β-hydroxysteroid dehydrogenase), and to convert P_4 to 3α,5α-THP (5α-reductase, 3α-oxidoreductase), have been localized to the VTA [11,40]. Interfering with biosynthesis of P_4, or P_4's metabolism to 3α,5α-THP in the VTA, attenuates lordosis of rodents [13,18,24,25,35]. Increasing levels of 3α,5α-THP in the VTA by stimulating de novo synthesis in glial cells enhances lordosis [19,20]. Not only is lordosis enhanced by 3α,5α-THP administration to the VTA, but mating also increases de novo production of 3α,5α-THP in the midbrain [11,12]. Although these data indicate that 3α,5α-THP in the VTA has an important role in mediating lordosis (the posture that female rodents exhibit in response to male-typical stimuli), 3α,5α-THP's influence on other behaviors related to mating has not been extensively investigated. Indeed, lordosis primarily reflects the consummatory component of mating, and thus does not take into account appetitive aspects of female sexual function.

Hamsters are an excellent species in which to examine the functional role of 3α,5α-THP. Hamsters, compared to other rodents, are particularly sensitive to progestins [7] and social experience [33,41,54]. Lateral displacement, female hamsters' movement of their perineum in response to stimulus behavior by males, is a reproductively-relevant behavior that may encompass both appetitive and consummatory aspects of sexual responsiveness. Solicitation behaviors (i.e., hopping, darting, pacing), that female rats exhibit toward males to increase the probability of successful mating, are progestin-dependent and require P_4's metabolism to 3α,5α-THP in the VTA [29]. Although these proceptive behaviors are indices of sexual responsiveness, their utility as measures of appetitive behavior is limited. Typically, proceptive behaviors are not qualitative (they are either present or absent), they require gross motor function (which may result in non-specific disruption by drugs), and the behaviors are not an explicit component of sexual responses (as such appetitive aspects are inferred). In contrast, lateral displacement of hamsters is both qualitative and quantitative, does not require gross motor movement, and is a necessary component of successful mating. Female hamsters, like various other species, make pelvic adjustments prior to mating, in response to stimulus behavior by males that facilitate insertion by the male and enable successful mating [8,34,37,46–48,50,51]. Unlike other rodents, female hamsters that have adequate hormonal (estrogen and progestins) and sensory stimuli (flank stimuli and/or the presence of a male) assume the lordosis posture for minutes at a time. Because tonic immobility characterizes lordosis of female hamsters, the lateral displacement responses of hamsters are a particularly important appetitive component of hamsters' sexual function. If male-typical stimuli are applied to the perineum of hamsters in lordosis, robust lateral displacement responses are readily observable and quantifiable [46–48]. Further, lateral displacement precedes mating, which may minimize any effects of mating-induced 3α,5α-THP production to obscure our investigation of 3α,5α-THP's role in other reproductively-relevant behaviors. Thus, lateral displacement was used to discern whether 3α,5α-THP's influence on lordosis extends to another behavioral component that precedes mating.

The purpose of the present experiments was to test the hypothesis that if 3α,5α-THP in the VTA influences lateral displacement, then lateral displacement should be: greater when endogenous midbrain 3α,5α-THP levels are higher, increased with progestin administration, and reduced by attenuating formation of 3α,5α-THP in the VTA.

2. Materials and methods

These methods were pre-approved by the Institutional Animal Care and Use Committee at SUNY-Albany.

2.1. Animals and housing

Four hundred and forty five sexually-naïve female hamsters (*Mesocricetus auratus*) were obtained from Charles River Laboratories (Kingston, NY), at ~60 days of age or 100–125 g of body weight, or were bred in our laboratory from stock obtained from this vendor.

All hamsters were initially group housed in solid bottom, plastic cages (38 × 33 × 17 cm) in the temperature (22 °C) and humidity (60%) controlled hamster *vivarium* at SUNY-Albany. Hamsters that received guide cannulae were individually housed following surgery. Hamsters were on a reversed light dark cycle (light/dark 14:10, lights off at 08:00). Chow and water were available ad libitum in the home cages.

2.2. Surgery

Some hamsters were ovariectomized (OVX) under sodium pentobarbital anesthesia (75 mg/kg IP or to effect). Concurrent with OVX, some hamsters were also stereotaxically implanted with bilateral guide cannulae aimed over the VTA (coordinates from bregma AP = −2.8, ML = ±0.3, DV = −7.8 (ventral extent of the cannula) [44]. Cannulae consisted of 23-gauge thin wall guide tubing and 30-gauge removable inserts, made to extend 3 mm beyond the end of the guide cannulae. After surgery, hamsters were monitored daily for weight loss, loss of righting response, failure to respond to a flank stimulus, or deficiencies in hindlimb withdrawal; there were no hamsters that exhibited any loss of aforementioned functions.

2.3. Hormonal status

Intact hamsters were screened daily between 0630 and 0700 to ascertain those that were receptive. Only hamster demonstrating consistent 4-day cycles were used as expe-