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## The Development of Male-Oriented Behavior in Rams

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### Abstract

The sheep offers a unique mammalian model in which to study paradoxical same-sex sexual partner preferences. Variations in sexual partner preferences occur spontaneously with as many as 8% of rams in a population exhibiting a sexual preference for other rams (male-oriented). The current review presents an overview and update of the male-oriented ram model and discusses several theories that have been invoked to explain same sex preferences in this species. Although our understanding of the biological determinants and underlying neural substrates of sexual attraction and mate selection are far from complete, compelling evidence is discussed that supports the idea that neural substrates regulating sexual partner preferences are organized during prenatal development. The challenge for future research will be to construct an integrated picture of how hormones, genes, and experience shape sexual partner preference.

### Keywords

sheep; rams; sexual partner preferences; sexual orientation; aromatase; sexually dimorphic area; medial preoptic area; gonadal steroids; sexual differentiation

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## The Biology of Sexual Partner Preference

Sexual partner preference refers to an animal's courtship and mating preferences for partners of the same or opposite sex when given a choice [1]. These are enduring and highly sexually dimorphic behaviors. Across species males typically court, mount, and mate with females while females solicit and mate with males. The determinants of this sexually dimorphic sexual attraction result from a complex interplay of anatomical, endocrine and genetic factors throughout the development and lifetime of the animal [2].

For the past 50 years, the organizational hypothesis of sexual differentiation has provided a key framework for understanding the development of these and other sexual dimorphic behaviors [46]. According to this hypothesis, a critical period exists in early perinatal life during which circulating testosterone produced from the fetal testis masculinizes and defeminizes both the neuroendocrine and behavioral potential of the brain. In the absence of testosterone the brain is feminized and can support cyclic gonadotropin-releasing hormone secretion required for ovulation and the expression of feminine sexual behaviors. The sex-typical programs established early in life can be disrupted or reprogrammed by experimental

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changes in the hormonal environment during perinatal development [16]. Several animal models (e.g. mice, rats, ferrets, zebra finches) have been used to study the impact of perinatal hormone manipulation on sexual partner preferences [3;7;8]. While this approach provides important information about the processes involved in brain differentiation, they are, with the exception of the zebra finch, complicated by uncontrolled effects on genital morphology.

In accordance with the organizational hypothesis, animals that exhibit same-sex mate preferences are predicted to have experienced perinatal hormonal environments that are more typical of the opposite sex [3]. Thus, males that prefer same-sex sexual partners will have experienced a subthreshold exposure or response to testosterone that is more typical of females. In turn, this leads to incomplete masculinization and/or defeminization during development. The ability to identify and study a small proportion of rams that exhibit exclusive same sex preference has provided us with a unique opportunity to test the organizational hypothesis in unmanipulated animals by examining correlations between endocrine responses, brain morphology, and sexual preferences. The current review will provide a synthesis of recent research on this novel and important animal model.

## Sheep as a Model System

Same-sex sexual behavior in sheep was first described by Giest in his field studies of Rocky Mountain Bighorn Sheep (*Ovis canadensis*) [20]. Bighorn sheep are polygynous and physically sexually dimorphic, with mature rams weighing about 75% more than adult ewes. In the wild, adult rams tend to be solitary or segregate into all male groups, except during the breeding season known as the rut, when rams join flocks of females in search of ewes in estrus. Social rank is established in all male groups just before the rut. Social rank correlates with age and individual mass, and is the major determinant of reproductive success. Within the male group, dominant rams occasionally mount subordinate rams in a show of social rank. In a report by Pelletier and Festa-Bianchet [40], mounting constituted only 4% of the interactions in male groups.

Domestic rams are kept in all-male groups between weaning and their first mating experience at about 18 months of age. Observations of domestic rams from diverse geographic areas have reported that as many as one third of all healthy rams in a population fail to mate estrous ewes. These rams have been labeled asexual [49], non-workers [33], sexually inhibited [24] or low-response rams [75] to distinguish them from the more typical ram that exhibits vigorous sexual performance with ewes. Zenchak and Anderson [75] suspected that all-male rearing contributed to low sexual performance in rams. This hypothesis was tested by comparing a group of rams reared in all male groups where contact was permitted with a second group of rams reared under conditions that prevented physical contact with other rams (although visual, olfactory and auditory communication was possible). They found that all of the non-performers came from the all-male group that were permitted to physically interact with other rams and concluded that the occurrence of low-response sexual behavior in rams is related to experiential factors such as rearing conditions. Zenchak et al. [76] next observed that when non-responding rams were given a choice between two estrous ewes and two sexually active ram, some of rams that failed to mate females instead exhibited a same-sex mate preference [76]. Subsequent studies by Price and colleagues [49;52] demonstrated that early exposure of rams to females will increase the probability of rams becoming sexually active, but will not prevent some rams from being male-oriented or low sexual performers. Social rank does not explain same-sex partner preferences in rams because no correlations are found between dominance behaviors or social rank and the expression of male-oriented preference [61;76]. Taken together, these

observations make *Ovis aries* the only mammal, apart from humans, in which some individuals are known to display exclusive same-sex mating preferences.

Four behavioral phenotypes have been described in domestic rams raised in all-male groups: female-oriented, male-oriented, bisexual, and asexual. To make behavioral assignments, rams are first given sexual performance tests, also known as serving capacity tests, to determine whether or not they are attracted to females and to get a measure of their sexual performance [36;44]. These tests are quite extensive involving a 30 min test during which the ram is presented with two to three estrous ewes. The test is repeated 9 to 18 times during a 2 month period of time. Following the last performance test, select rams that showed high sexual performance or no interest in ewes are given sexual partner choice test [41;54]. In the choice tests, rams are simultaneously exposed to two unfamiliar sexually active rams and two estrous ewes. The four stimulus animals are restrained in order to prevent aggression [77]. The test ram is free to interact and mate with each of the stimulus animals or remain in a neutral part of the testing arena. The frequencies of precopulatory (i.e., anogenital sniffs, foreleg kicks, flehmen or lip curls, licks, and vocalizations) and copulatory (i.e., mounts and ejaculations) behaviors are recorded as well as the sex of the animals to which they are directed. Rams that exclusively mount ewes in this test are classified as female-oriented, whereas rams that exclusively mount other rams are classified as male-oriented. A fuller discussion of partner preference testing in rams can be found in several earlier reviews [45;50;56]. In our studies since 2004 [60], sexual partner choice tests were administered at least twice when the rams are 18 mo. old and then twice again one year later to assure that the trait was stable. Overall, exclusively male-oriented rams account for ~8% of all rams in the populations studied [43;53;61].

## Biology and Male-Oriented Sexual Preferences in Rams

Several hypotheses have been proposed to explain the development of same-sex sexual preferences in rams. These include the effect of same-sex rearing, genes, olfactory responsiveness, and brain differences. None of these mechanisms are mutually exclusive and none have been demonstrated conclusively to play a causal role.

### Same-sex rearing

As previously mentioned, domesticated rams are commonly reared in all male groups, which raises the question of whether this environment leads to sexual preferences for other males later in life in a manner perhaps analogous to “sexual imprinting” [30]. Katz et al. [27] tested the hypothesis that exclusive exposure to males after rearing and lack of social experiences with females could lead to male-oriented preferences in rams. These investigators compared a group of rams that had been weaned and then raised in a mixed sex group that included estrous ewes with a group of rams that had only been exposed to other rams after weaning. The rams reared with females mounted more and achieved more ejaculations with estrous ewes than those reared with males only, suggesting that postnatal learning contributes to the development of sexual behavior. However, the majority of rams in both groups later developed a female-oriented mate preference. The exceptions were 2 out of 25 rams reared in the mixed sex group and 1 out of 23 rams reared with males only. Price et al. [51;52] also found that early experience with estrous ewes either direct or through fence line contact enhances sexual performance scores later in life, but does not prevent male-oriented behavior in rams. These results indicate that early social experience and learning increase the likelihood that rams will become sexually active at an early age, but do not prevent or promote same-sex preferences in rams.

## Genetic Determinants

Another possible explanation for same sex preferences in rams is that this behavioral phenotype is influenced by genotype. There are reports that male behavior is heritable in species as diverse as fruit flies and humans [55;61]. In rams, sexual motivation and mating performance is moderately heritable. The proportion of population variance for these traits that is attributable to genetic factors was estimated to be 0.22 in Western ram breeds. Although no long-term selection experiment for male sexual performance in sheep has been conducted, Bench et al. [10] reported that selection for high and low sexual performance in rams resulted in a significant response in offspring after a single generation. Sons of high libido rams showed significantly more mounts and ejaculations than sons of low libido rams. Daughters of high libido rams reached their first behavioral estrus significantly earlier than daughters of low libido rams.

Stellflug and Berardinelli [69] conducted an experiment to determine whether long-term selection of ewes for high or low fertility (number of lambs born) would affect sexual behavior and orientation in male offspring and found no difference between groups in the percentage of sexually active rams or their sexual performance scores. Only one male-oriented ram out of a total 48 rams tested from the high and low fertility lines was identified as male-oriented and he was from the high fertility line. Thus, these investigators concluded that selection for reproduction rate in ewes does not affect the sexual behavior or sexual orientation of male offspring. Although not explicitly stated by these investigators, this study seems to refute the idea that male-oriented behavior (or the genes controlling it) persists in rams because it promotes reproductive success in ewes.

## Sensory Processing

A third possibility for why male- and female-oriented rams differ in their sexual mating preferences may be because they differ in their ability to process sensory cues and/or formulate appropriate physiological and behavioral responses. Numerous studies have shown that rams rely predominantly on olfaction to sense volatile signals that in turn stimulate copulatory behavior. In particular, during courtship rams determine estrus by investigation of the anogenital region or the urine of ewes, by sniffing, licking, or performing Flehmen or lip curls to present low-volatile compounds to the vomeronasal organ. Lindsay first demonstrated that rams made anosmic by olfactory ablation are unable to distinguish between estrous and non-estrous ewes [32]. Blisset et al. showed that rams discriminate between sexually receptive and nonreceptive ewes on the basis of urine odor [11] and that this requires the main olfactory system not the vomeronasal organ [12]. Several lines of evidence reviewed by Baum [9], point to a sexual dimorphism in scent detection as well as central processing of pheromonal cues by the main olfactory system that likely play a role in mate recognition in several mammalian species. Peripheral anosmia in mice and ferrets blocks the preference of both male and female subjects to approach and interact with opposite-sex conspecifics in partner preference tests [28;29]. There is accumulating evidence that both the main and accessory olfactory systems have the ability to sex-specifically process partly overlapping pheromonal chemosignals and that both systems converge at a downstream level of pheromonal processing [13;35;74]. As a consequence, both systems have the ability to support complimentary aspects in mate discrimination and sexual behavior [67].

The question of whether olfactory sensory processing differs between male- and female-oriented rams has not been studied extensively but there is some intriguing evidence that it may. Perkins et al. [41;43] found that exposure of adult female-oriented rams to estrous ewes provokes an increase in LH and testosterone secretion (i.e. ewe effect) [14;21;22]; whereas male-oriented rams did not show this hormonal response to ewes. However, male-

oriented rams did exhibit an elevation in testosterone concentrations unaccompanied by changes in LH secretion when they were exposed to other rams. The hormone response in male-oriented rams, although paradoxical, suggests that they respond differently from female-oriented rams when presented with the same sensory cues. Alexander et al. [6] demonstrated that sexual contact is not necessary to evoke a neuroendocrine response in female-oriented rams. Concentrations of LH increase after high libido female-oriented rams are given fence line exposure to estrous ewes, but not to other rams. Concentrations of LH are unchanged in low libido and male-oriented rams regardless of the sex of the stimulus animal. Interestingly, high libido rams exhibit more investigatory olfactory behaviors toward stimulus animals than low libido or male-oriented rams, suggesting that the ability to discriminate between sexual partners relies on adequate sensory input. In a subsequent study, Alexander et al. [5] reported that more neurons stained positively for fos-related antigen in the medial preoptic area of female-oriented than of male-oriented rams after exposure to stimulus ewes and rams. As will be discussed later, the medial preoptic area in sheep contains a dense cluster of neurons that correlates volumetrically with sexual preference. Thus, the different behavioral and endocrine responses that female- and male-oriented rams exhibit to sexual stimuli may be related not only to differences in olfactory sensitivity or detection, but also to differences in neural processing.

### Brain Differences

Several studies have attempted to relate same-sex preferences in rams with altered or incomplete sexual differentiation of the brain by examining the expression of sexually dimorphic brain function and structure in male- and female-oriented rams. Perkins et al. [42] were the first to examine this possibility by testing the effect of estradiol on gonadotropin secretion. Gonadotropin secretion is sexually dimorphic in sheep [26]. Treatment of intact, ovariectomized, or anestrous ewes with estradiol initially decreases serum LH (negative feedback), but is followed by an LH surge within ~18 h (positive feedback). In rams and prenatally androgenized ewes, estradiol administration exerts negative feedback, but fails to evoke positive feedback. Both male- and female-oriented rams exhibit male-typical LH responses to estrogen indicating that their GnRH control mechanisms have been masculinized/defeminized [42;70].

Reproductive behaviors including sexual attraction in sheep are strongly influenced by gonadal hormones and are also sexually dimorphic [17]. Pickard et al [47] demonstrated that mounting behavior declined after castration of both male- and female-oriented rams and that this decline was not reversed by estrogen treatments. Stormshak et al. [70] demonstrated that despite their female-typical sexual preference, male-oriented rams do not display proceptive and receptive behaviors when castrated and treated with estradiol. These data suggest that the neural mechanisms controlling the LH surges and receptive sexual behaviors are defeminized in male-oriented rams, but that sexual preferences are not. Dissociation of individual components of the masculinizing program for brain sexual differentiation is theoretically possible if there is more than a single critical period of androgen sensitivity. Emerging evidence suggests that in long gestation animals, such as sheep each sexually dimorphic trait may have unique requirements with regard to the timing, duration, and amount or type of steroid (androgen versus estrogen) [19]. Moreover, other complex developmental relationships may exist, such as requirements for sequential hormone exposures or paracrine actions [66;71].

### Sexually Dimorphic Brain Structures

The medial preoptic area has long been recognized as essential for male sexual behavior in many species of animals [25], and for this reason was one of the first brain areas systematically studied for the presence of a morphological sex difference. Gorski et al. [23]

discovered a nucleus within the medial preoptic area that was 3 to 7 times larger in males than in females and called it the sexually dimorphic nucleus (SDN) of the preoptic area. Consistent with the organizational hypothesis, the size of the SDN is controlled by the amount of androgen present during perinatal development. The critical period for SDN development in rats begins on the eighteenth day of gestation and ends during the first week of postnatal life [57;58].

The SDN lies at the center of a forebrain circuit that relays sensory information from the periphery and integrates it with information about hormone status to regulate male sexual behaviors [68]. Lesions limited to the rat SDN produce little or no decrement in male sexual behavior, but have been found to disrupt sexual partner preferences in male rats [39]. In male ferrets, the medial preoptic area contains a cluster of neurons that was named the male nucleus (MN) because it is not seen in females [72]. Destruction of the MN in male ferrets caused them to prefer to approach and interact sexually with another male, as opposed to a female [9]. Humans have a sexually dimorphic nucleus in the hypothalamus called the third interstitial nucleus of the anterior hypothalamus (INAH3) that is larger in heterosexual men than in women, and of intermediate size in homosexual men [31]. However, no information is available on the development of INAH3 and whether it is regulated by prenatal androgen exposures.

These reports provide some of the strongest evidence to date that sexual partner preferences and sexual orientation are regulated at the level of the hypothalamus- preoptic area and are affected by the same organizational actions of androgens that modify brain structure. With this as prologue, we asked whether structural differences existed in the preoptic area that correlate with sexual partner preferences of sheep. We found that sheep also have a sexually dimorphic cluster of neurons in the preoptic area that express high levels of aromatase mRNA. This cluster is named the ovine SDN (oSDN) because of its similarity to the SDN in rats [60]. The oSDN is larger in female-oriented rams than in male-oriented rams and ewes in the luteal phase. Differences in the size of the oSDN among female-oriented rams, male-oriented rams, and ewes are not due to differences in adult serum levels of testosterone because these differences persist even after adult sheep are gonadectomized and treated with physiological doses of testosterone [59].

The observation that male-oriented rams have a smaller oSDN than female-oriented rams does not establish whether the size of the oSDN is the cause or consequence of mate preference. Ideally, the volume of the oSDN should be measured over time as the animal gains sexual experience so that it would be possible to determine whether size differences emerge before sexual preferences are expressed. This would not only establish whether oSDN predisposes an animal to behavior in a predictable manner, but would also make it possible to assess whether sexual experiences contribute to or alter oSDN size. In lieu of this approach, which is not technically feasible, it is plausible to ask whether the oSDN develops early in life before animals engage in social or sexual behaviors. Masculinization and defeminization of sexual behavior in sheep begins shortly after sexual differentiation of the testes on gestational day (GD) 30 and persists until approximately GD 90 (term pregnancy in sheep is approximately 150 days) [18]. A cluster of centrally located neurons that express aromatase are present within the medial preoptic area as early as GD 60 and probably constitute a nascent oSDN at this time. Later in gestation at ~GD 135, the oSDN is clearly present and twice as large in males as in females [63]. Thus, development of this dimorphism occurs independently from sexual experience, although these results do not address the question of whether experience also plays a role.

To address the question of whether testosterone is responsible for the emergence of the sex difference, lamb fetuses were exposed to elevated levels of exogenous testosterone during

the critical period of sexual differentiation. Exposure to testosterone significantly enlarged the oSDN in females, but had no effect in males [63]. Thus, prenatal testosterone exposure defeminizes and masculinizes the oSDN, suggesting it is possible that variations in prenatal testosterone can account for the size of oSDN in male-oriented rams compared to female-oriented rams. It is not yet known whether such masculinized females show male-typical sexual partner preferences, although this treatment regimen has been shown previously to masculinize copulatory behaviors and defeminize receptive behaviors in sheep [17].

The abundance of aromatase mRNA within oSDN neurons raises the question of whether local conversion of testosterone to estradiol is required for organization of this nucleus and for masculinization of sexual partner preference. This seems especially plausible since aromatization and estrogen receptor activation has been implicated in the perinatal organization of sexual partner preferences in several other species including rats, mice and pigs [73]. However, transplacental administration of the aromatase inhibitor 1,4, 6-androstatrien-3,17-dione (ATD) to male lamb fetuses failed to alter adult sexual partner preference and oSDN volume, and had only a minimal effect on copulatory behavior [62;64]. There are several possible explanations for why ATD was ineffective. First, the dose or extent of treatment may not have been optimal. This seems unlikely since this treatment inhibited aromatase activity >90% in the fetal preoptic area. Furthermore, subsequent experimental increases in dosage treatment time still had no effects on sexual partner preferences [64]. Second, estrogen and androgen may act together to organize the male brain, thus an androgen mediated mechanisms may compensate for loss of estrogen signaling. Third, masculinization of mate preferences in the ram may be controlled entirely through an androgen receptor mechanism in the ram similar to what has been demonstrated for play behavior in sheep [38] and coital behaviors in guinea pigs and primates [15]. Finally, in the pig, rat, and ferret, elevated levels of testosterone or estrogenic metabolites during early gestation may sensitize the male to the masculinizing/defeminizing actions later in gestation or during early postnatal life, even as late as puberty in a way reminiscent of androgen effects on the genitalia [34;65]. Supporting this idea, one study suggested that masculinization in sheep is not complete until the second month after birth [37] and in pigs male-typical organization of sexual partner preferences occurs as late as three months postnatally [4]. Clearly more research is needed to understand the complexities involved in the organization of male-typical sexual partner preferences in sheep and the role that the oSDN plays in this behavior.

## Conclusions

Our understanding of the proximate causes of same-sex preferences in rams is far from complete. Although the evidence to date indirectly supports the organizational hypothesis, many questions remain unanswered. First is the question of structure and function. How does the smaller structure of the oSDN in male-oriented rams and ewes dictate a preference for male sex partners? For answers, we will need to understand the connections and functions of the components that make up the oSDN. A first step towards understanding this neural circuitry would be to lesion the oSDN and assay for reversal or loss of male-typical sexual partner preference. A more thorough description of the functional circuitry of oSDN can be established using retrograde and anterograde tracers. Connectivity with anatomical structures of known functions will help to integrate the oSDN, as well as partner preference, into the complex picture of how variations arise in the development and expression reproductive behaviors.

Following from the broader issues of circuit formation, is the question of how male-oriented rams come to have an oSDN that is intermediate in size between that of female-oriented rams and ewes. On first approximation, the larger size of the oSDN in males appears to be

the result of fetal androgen exposure because females exposed to testosterone during midgestation have an enlarged oSDN. However, initial attempts to interfere with the development of the oSDN by inhibiting aromatase, which is abundantly expressed in oSDN neurons, were unsuccessful. As enumerated above there are additional theoretical and technical options and approaches that can and should be explored, all grounded in the organizational hypothesis. If the smaller oSDN in male-oriented rams is the result of interference with the androgenization program during development, we will need to understand how and when this occurs naturally. The limited information available suggests that there are few behavioral or neuroendocrine consequences when aromatase is inhibited for two months of critical brain development. Will androgen receptor antagonism prenatally be more effective, or is this paradigm too simplistic given the failsafe biological redundancies that exist at all levels of the reproductive system?

Finally, a more complete understanding is needed to explain how the organizational hypothesis can account for the fact that male-oriented rams exhibited masculinized neuroendocrine responses and copulatory behaviors, but female-typical sexual partner preferences. As discussed, the critical period is probably not a single entity and distinct windows or hormone requirements could exist for different dimorphic traits. For instance, recent unpublished data from our laboratory demonstrates that the critical period for masculinization of oSDN occurs after the period for masculinization and defeminization of the external genitalia and estradiol-induced surge mechanism. Another possibility recently proposed by Poiani [48] is that the difference between male- and female-oriented rams could occur in the olfactory system, which in turn might affect the organization of the oSDN and alter sexual partner preferences. The answers to these questions will help us gain further insight into the biological mechanisms of same-sex attraction and provide deeper insights into how sexuality is encoded in the mammalian brain.

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