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The Immunobiology of Sexual Behavior: Gender Differences in the Suppression of Sexual Activity During Illness

RONIT AVITSUR AND RAZ YIRMIYA

Department of Psychology, The Hebrew University of Jerusalem, Jerusalem 91905, Israel

AVITSUR, R. AND R. YIRMIYA. *The immunobiology of sexual behavior: Gender differences in the suppression of sexual activity during illness.* PHARMACOL BIOCHEM BEHAV **64**(4) 787–796, 1999.—Following infection or injury, sick individuals experience profound psychological and behavioral changes, such as anorexia, depressed activity, and reduced self-care behavior. In the present review, we present evidence for a gender-difference in the behavioral response to sickness. Specifically, following immune activation, sexual activity is suppressed in female, but not in male rats. This gender difference is specific to sexually related responses, because other behaviors, such as locomotion, are equally affected by immune challenges in males and estrous females. The suppression of female sexual behavior, induced by either endotoxin (lipopolysaccharide), or the cytokine interleukin-1 (IL-1), are mediated by central mechanisms that are independent of alterations in ovarian hormone secretion. Furthermore, synergistic effects of the cytokines IL-1 and tumor necrosis factor α (TNFα) are involved in modulating sexual behavior in sick females, and prostaglandins synthesis is required for the effects of IL-1 on female sexual behavior. The gender difference in the behavioral response to immune activation may be related to the findings that at the same doses and timing in which IL-1 suppressed sexual activity in female but not in male rats, females produced more prostaglandin E_2 (PGE_2) in the brain, and less corticosterone than males. Finally, we are suggesting that the suppressive effect of cytokines on female reproductive behavior may serve as a mechanism to reduce conception during infection, which exposes the mother and the fetus to dangers such as spontaneous abortions, preterm labor and maternal mortality. © 1999 Elsevier Science Inc.

Sickness behavior Sexual behavior Cytokines Interleukine-1 Tumor necrosis factor-α Lipopolysaccharide Brain Rats

SICKNESS BEHAVIOR

Following infection or injury, the immune system is activated. Many immune factors are released, and participate in attempts to remove the invading pathogens. In addition to the local actions of these immune factors in recognizing and destroying foreign substances, they also orchestrate a complex set of widespread changes throughout the entire organism, which assist in combating infection and injury. This defensive response, often called the "acute phase response", consists of physiological, hormonal, and behavioral processes (32,43, 60,108). Physiological changes include fever, increased slow-wave sleep, alterations in plasma ions, and increased number of circulating white blood cells (43). The hormonal changes that are associated with sickness are a rapid and sustained activation of the hypothalamic–pituitary–adrenal axis along with a marked inhibition of the hypothalamic–pituitary–gonadal axis (14). In addition, a variety of behavioral, affective, and cognitive phenomena are initiated by events in the immune system. Sick individuals experience weakness, malaise, listlessness, and inability to concentrate. They become depressed and lethargic, show little interest in their surroundings, and stop eating and drinking (32,43,60,108).

These behavioral changes, which are collectively termed "sickness behavior" (49) are not specific to humans, and may also be observed in a variety of animal species, following systemic diseases or some more localized infections. It has been argued that sickness behavior is not merely a secondary consequence of the disease process, but rather a part of an organized defense response to the immune challenge (43). Accordingly, the behavioral changes associated with being sick can be viewed as part of the organism's effort to recruit all of its resources for fighting against the invading pathogen and

Requests for reprints should be addressed to Raz Yirmiya, Ph.D., Dept. of Psychology, The Hebrew University of Jerusalem, Mount Scopus, Jerusalem 91905, Israel.

overcoming the disease. Sickness behavior centers around the fever response that accompanies infection with most pathogens. Fever improves the organism's ability to cope with infectious agents by potentiating immunological responses, such as lymphocyte proliferation and antibody synthesis, and by suppressing the growth of some temperature-sensitive pathogens (43,53). Raising and maintaining a higher body temperature can be achieved by physiological mechanisms (e.g., increased metabolism), or by behavioral alterations, such as preventing the expression of activities that are associated with heat loss (e.g., locomotion), and favoring the expression of activities that increase heat production and preservation (e.g., shivering and assuming a curled up posture) (43).

The mechanisms that are involved in the modulation of behavior during sickness have been studied using various models of disease, in which pathogens or pathogen particles are administered to human subjects or to laboratory animals. For instance, in humans, experimentally induced colds reduced psychomotor performance (87), influenza was found to be associated with psychiatric disorders (65), and immunization with live-attenuated rubella virus vaccine was shown to produce affective and behavioral problems in vulnerable individuals (68). Similarly, infection of laboratory mice with influenza virus resulted in body weight loss as well as a reduction in food and milk intake (90). We have recently reported that intracerebral administration of heat-inactivated *Mycoplasma fermentans* (MF), a small micro-organism that has been found in the brain of some AIDS patients, induced fever and body weight loss, reduced locomotor, exploratory, and social activity, and suppressed the consumption of food and saccharin solution in rats (110,112). Additionally, ample research on the behavioral effects of lipopolysaccharide (LPS), a complex glycolipid found in the outer membrane of all Gram-negative bacteria, has been reported. LPS administration to laboratory animals induces several sickness-like behavioral symptoms, including fever, anorexia, body weight loss, reduced locomotion, social exploration, and maternal behavior (2,32,37,56,107,108,111).

Several lines of evidence indicate that sickness behavior is mediated by immune-derived cytokines, rather than being produced by the pathogen itself. Cytokines are proteins that are synthesized and released by activated immune cells both in the periphery and in the brain, and are involved in facilitating the development of an inflammatory reaction (83). Many studies have shown that exogenous administration of proinflammatory cytokines produces sickness behavior, and cytokine antagonists or cytokine synthesis blockers attenuate the behavioral effects of pathogens (32,60,108). Studies on the behavioral effects of proinflammatory cytokines have focused mainly on interleukin-1 (IL-1)-α and -β, tumor necrosis factor (TNF)-α, interleukin-6 (IL-6), and interferons, which are released by activated monocytes and macrophages during the course of an infection. For example, administration of IL-1 induces anorexia (73), suppresses general activity and social exploration (32), and alters pain sensitivity (99); TNFα administration also produces a reduction in social exploration and suppresses food and water consumption (18–20).

SEXUAL BEHAVIOR DURING SICKNESS

A variety of medical conditions are associated with sexual dysfunction. According to the "Diagnostic and Statistical Manual of Mental Disorders" (35), "general medical conditions" such as neurological, endocrine, vascular, and infectious diseases can cause disturbances in sexual function. Because immune activation during sickness suppresses various reproductive functions and induces sickness behavior, we hypothesized that immune challenges would also be accompanied by a reduction in sexual activity. Thus, we conducted a series of experiments to examine the effects of immune activation on sexual motivation and performance in male and female rats.

Sexual behavior was examined in the present study using several paradigms that represent distinct and relatively independent behavioral processes (13). Sexual motivation, i.e., the eagerness to seek sexual contact, was examined using the partner preference (PP) test (67). In this paradigm, the subject is placed in a U-shaped apparatus. Each side of the apparatus contains a tethered stimulus partner, one sexually active, and the other sexually indifferent. In tests of female sexual behavior, partners are a sexually experienced and a castrated male, and in tests of male sexual behavior, partners are an estrous and a nonestrous female. The time subjects spend with the sexually active and the sexually indifferent partner was recorded, and served as an index of the preference for the sexually active over the indifferent partner. Additionally, the consummatory aspects of the sexual behavior were examined by observing the motor patterns that were displayed in connection with the copulatory act, including mount, intromission, and ejaculation in males, and the lordosis reflex, as well as several soliciting (proceptive) gestures, in females [for a detailed description see (9)].

Immune Activation Reduces Sexual Behavior in Female But Not Male Rats

The effects of immune activation on sexual behavior of male and female rats were examined using various immune challenges. In the first experiment, estrous females and males were injected with either saline or LPS (50 or 250 μg/kg, IP, (*E. coli* 055, Difco Laboratories, Detroit, MI) and sexual behavior was measured 2, 4, and 6 h later (5). The results of this experiment showed that LPS inhibited sexual behavior in females, up to 6 h after administration. Specifically, following LPS administration females exhibited less proceptive gestures compared to controls, indicating that these females were less likely to initiate a sexual interaction. In addition, LPS-injected females spent less time with the sexually active but not with the indifferent male, reflecting reduced motivation for sexual activity. Furthermore, following LPS administration females were less responsive to males' courting, exhibiting suppressed lordosis response to males' sexual mounts. In contrast, sexual behavior of males was not altered by an identical dose of LPS. Specifically, neither their sexual performance nor the preference for an estrous over a nonestrous female partner were altered by LPS (5). These findings indicate that the effects of LPS on sexual behavior are gender dependent. A similar gender difference was found following administration of recombinant human (rh)IL-1β (2 or 10 μg/kg): IL-1β significantly reduced all aspects of sexual behavior in estrous females, but not in males (109), indicating that the effects of IL-1 on sexual behavior are also gender dependent.

Changes in the levels of sexual activity may have further implications for reproduction. Beach (13) suggested that by remaining in the vicinity of a sexually active and attractive male, and by performing the species-specific proceptive behaviors the female rat arouses the sexual interest of a potential mate. Thus, during sickness, the capability of a female to attract a potential mate, or her "sexual attractivity value" (13), may be significantly reduced. Males' attractivity value in

the eyes of their female mates may be less affected by illness because their behavior is less altered by immune activation. This hypothesis was examined in the following studies (3).

A sexually experienced male was placed with two female partners, one of which had been injected with saline and the other with rhIL-1β (2μg/kg), and the quality of his sexual behavior with each of his partners was compared. Males exhibited a clear preference for the "healthy" partner over the "sick" one: they performed significantly fewer mounts and intromissions and spent less time with the IL-1-injected partner compared to the saline-injected female. Females, on the other hand, did not differentiate between saline and rhIL-1β (5 μg/kg)-injected male partners. They performed similar levels of proceptive behavior, and spent the same amount of time with the "sick" and the "healthy" partner (3). These findings indicate that the effects of IL-1 on sexual attractivity are also gender dependent: IL-1 reduced the attractivity value of female, but not male rats.

However, males were able to "cheat" their female partners only when injected with doses of IL-1 that had no effect on their sexual behavior. When injected with an extremely high dose of rhIL-1 (20 μg/kg), a dose that markedly affected both the appearance and behavior of the male rat, females were capable of differentiating between saline- and IL-1–injected males, and exhibited a preference toward the "healthy" one (3). These findings suggest that sexual behavior functions as a communication mechanism, signaling one's health state and sexual desire to the potential mate.

Gender Differences in Sickness Behavior: Is It Specific to Sexual Behavior?

Gender differences in immune activity and resistance to infections have been previously reported. For instance, higher prevalence and intensity of infections was found in males compared to females (88,117), and females were found to be more immunoreactive than males, exhibiting greater antibody formation, cell-mediated immunity, and predisposition for autoimmune disorders and allergies (42,64,101). Additionally, females also exhibit higher levels of IL-1 during chronic inflammation compared to males (34). Thus, it may be argued that the gender difference in the effects of immune activation on sexual behavior (3,5,109), resulted from the increased general reactivity of the immune system in females compared to males. However, in the studies mentioned above, increased behavioral response to an immune challenge was found in females only in sexually related behaviors, whereas other behavioral responses were equally altered by immune activation in estrous females and males. For instance, we examined the effects of LPS administration on locomotor and exploratory activity in the open-field test, and found a comparable reduction in males and estrous females (5). Similarly, administration of rhIL-1 reduced open-field activity in males and estrous females to a similar degree (4,109). Thus, it may be suggested that the gender difference in the behavioral response to immune activation is specific to sexual behavior.

It should be noted that because in female rats sexual behavior occurs only during the estrous phase of the cycle, the above-mentioned studies compared the behavior (both sexual and locomotion) of males to that of estrous females, and the behavior of females in other phases of the estrous cycle was not measured. Thus, in another study we compared the effects of rhIL-1β on locomotor activity of males and females in different stages of the estrous cycle, and found that open-field activity of males and estrous females was indeed equally affected by IL-1, but females that were not in the estrous phase of the cycle were less responsive to the effects of IL-1 on this behavior (4). The reduced sensitivity of nonestrous females to the behavior effects of IL-1 may be related to the lack of progesterone in these animals, because exogenous administration of progesterone significantly increased the responsiveness of ovariectomised females to the behavioral effects of rhIL-1β (4). Thus, it may be concluded that the behavioral response to immune challenges is affected by gender and by the changes in hormonal secretions during the female estrous cycle.

MECHANISMS INVOLVED IN THE MODULATION OF FEMALE SEXUAL BEHAVIOR DURING SICKNESS

The following studies examined several possible mechanisms that may play a role in mediating the effects of immune challenges on sexual behavior of female rats.

The Central Nervous System Is Involved in Mediating the Effects of Immune Challenges on Female Sexual Behavior

Ample evidence indicates that the central nervous system is involved in mediating the effects of cytokines on behavior. This has been demonstrated in several studies in which low doses of cytokines administered into the cerebral ventricles or to discrete locations in the brain induced sickness behavior [e.g., (6,50,58)]. Additionally, receptors for several cytokines, including IL-1, TNFα, and IL-6, have been localized in a number of brain regions, both on glia and neurons (10,31,84). Furthermore, some of the effects of immune activators such as endotoxins, were prevented by blocking these receptors (82).

According to our findings, the reduction in sexual behavior in estrous females during immune activation is also mediated by central mechanisms. First, central administration of low doses of either LPS (200 ng/rat) or rhIL-1β (10 ng/rat) suppressed female sexual behavior (5,109). These doses are one to two orders of magnitude lower than the minimal doses required to produce these effects in the periphery, suggesting that both LPS and IL-1 can act via central mechanisms. Moreover, central administration of IL-1 receptor antagonist (IL-1ra) completely prevented the effects of centrally administered IL-1 on female sexual behavior, indicating that these effects of IL-1 are mediated by IL-1 receptors within the brain (5).

Synergistic Effects of TNFα and IL-1 in Modulating Female Sexual Behavior

Immune-derived cytokines are known to interact and alter each other's effects. Thus, the net effect of several cytokines that participate in the response to a pathogen is usually different from the cumulated effect of each of these cytokines by itself. TNFα and IL-1 act synergistically to produce many of their effects [for reviewed see (29)], including sickness behavior (17,19,89,105). Thus, we sought to examine the effects of simultaneous administration of TNFα and IL-1β on female sexual behavior. First, we examined the behavioral effects of recombinant rat (rr)TNFα administration, and found that a dose of 7.5 μg/rat (icv) suppressed sexual behavior in estrous female rats, whereas a lower dose (3μg/rat) had no effect on this behavior. Subsequently, we administered subthreshold doses of both rrTNFα and rrIL-1β simultaneously, and found that this treatment significantly reduced all aspects of female sexual behavior (8). These findings suggest that both TNFα and IL-1 are involved in the modulation of sexual behavior in

estrous females during illness, and that these cytokines may act synergistically to suppress female sexual behavior during illness.

Because LPS triggers the synthesis and secretion of both IL-1 and TNFα, which in turn, are involved in mediating many of the effects of LPS, we sought to examine the role of IL-1 and TNFα in mediating the effects of LPS on sexual behavior of estrous female rats. First, the involvement of IL-1 in mediating the effects of LPS on female sexual behavior was studied, using IL-1ra. Administration of IL-1ra to LPS-treated estrous female rats did not prevent the effects of LPS on their sexual behavior, neither following IP nor ICV administration of the drug. However, identical doses of IL-1ra completely prevented the effects of rhIL-1 on female sexual behavior (5). This finding indicates that IL-1 is not required for the effects of LPS on this behavior.

The involvement of TNFα in mediating the effects of LPS on female sexual behavior was studied using the TNFα synthesis inhibitor pentoxifylline. Pretreatment with pentoxifylline (IP) completely prevented the suppression of the lordosis reflex in response to LPS (IP) administration, but it did not alter the effects of LPS on proceptive behavior and the preference for the sexually active over the indifferent partner (8). These findings indicate that TNFα is essential for the effect of LPS on the lordosis response, but not on the motivational components of this behavior.

Because IL-1 and TNFα interact to affect female sexual behavior, we sought to examine the possible synergistic effects of these cytokines in mediating the effects of LPS on sexual behavior of estrous female rats. Estrous females were pretreated (IP) with pentoxifylline and IL-1ra simultaneously, followed by LPS, and their sexual activity was measured. The effects of LPS on all aspects of female sexual behavior were completely prevented by the combined treatment with IL-1ra and pentoxifylline (8). These findings indicate that the effects of LPS on female sexual behavior are mediated by interactions between IL-1 and TNFα. However, the mechanisms that are involved in mediating the lordosis response are different from those of proceptivity and partner preference, because the effects of LPS on lordosis were prevented by pentoxifylline, whereas its effects on proceptivity and partner preference were altered only by the combined administration of pentoxifylline and IL-1ra.

The Effects of IL-1 on Female Sexual Behavior Are Mediated by Prostaglandin Synthesis

Prostaglandins (PGs) are synthesized and released following IL-1 administration (55,98), and are involved in mediating some of the effects of IL-1. Blocking PG synthesis, using various cyclooxygenase inhibitors, prevents many of the physiological and neuroendocrine effects of IL-1, including fever (69), corticotropin-releasing hormone, adrenocorticotropic hormone, and corticosterone release (38,71,78,97). Sickness behavior induced by IL-1 was also prevented by cyclooxygenase inhibitors: anorexia and gastric emptying were significantly improved by ibuprofen (63,86) and indomethacin (93), and the reduction in drinking behavior was reversed by piroxicam and ibuprofen (72,86). In addition, IL-1–induced reduction in social exploration and operant responding was completely reversed by both indomethacin and piroxicam (30).

Because PGs were found to play an important role in mediating various effects of IL-1, we hypothesized that PG synthesis may also be involved in mediating the effects of IL-1 on female sexual behavior. This hypothesis was studied in a subsequent study, using two cyclo-oxygenase inhibitors: indomethacin and ibuprofen. Pretreatment with either inhibitor (IP) completely prevented the effects of rhIL-1β on female sexual activity, including proceptive behavior, the lordosis reflex, and the preference for a sexually active male (7). These findings indicate that the effects of IL-1 on sexual behavior of females are mediated by prostaglandin synthesis.

ROLE OF GONADAL HORMONES IN MEDIATING FEMALE REPRODUCTIVE BEHAVIOR DURING SICKNESS

Immune Activation Suppresses the Reproductive System

In addition to the above-mentioned behavioral consequences of immune activation, infection or injury also suppresses various reproductive functions, such as sex hormone secretion and ovulation. For example, clinical evidence indicate that acute severe illness, such as traumatic brain injury, myocardial infarctions or surgery, resulted in reduced testosterone levels in men and decreased estradiol levels in women (102). In addition, under these conditions a significant decrease in luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels were found in both men and women (102). Similarly, testosterone levels were reduced in men hospitalized for treatment of burns (96) and in patient with T-cell leukemia (94).

The effects of immune activation on various reproductive functions have also been studied in the laboratory, both in vivo and in vitro. Most studies have shown that immune activation induces a rapid and sustained suppression of the hypothalamus–pituitary–gonadal (HPG) axis in both males and females.

Studies in Females

Immune activation suppresses gonadotropin-releasing hormone secretion. Immune activation following LPS administration reduced the percentage of gonadotropin-releasing hormone (GnRH)-immunoreactive neurons in intact cycling female rats during proestrus, and induced a profound down-regulation of GnRH-receptor gene expression in the anterior pituitary throughout the entire estrus cycle (70). LPS also reduced GnRH pulsatile release into the hypophyseal portal blood in ovariectomized ewes (11). Similarly, in intact cycling female rats, central administration of IL-1 reduced GnRH levels in the median eminence (77) and in vitro stimulation with IL-1 significantly suppressed GnRH release from the medial basal hypothalamus–preoptic area of ovariectomized rats treated with estrogen and progesterone (48,75).

Immune activation suppresses gonadotropin secretion. Increasing evidence indicate that immune challenges also inhibit gonadotropin secretion: LPS significantly reduced LH concentrations and LH pulse amplitude in OVX rats or ewes (11,113). In addition, central administration of IL-1 decreased LH and FSH levels in the plasma of intact cycling rats (80,76,77) and reduced basal LH secretion (75,77) and progesterone-induced LH surge (48) in OVX rats.

Different findings were reported regarding the effects of IL-1 in female rhesus monkeys. Central administration of IL-1α inhibited the pulsatile LH and FSH secretion in OVX females, in which gonadotropins levels are very high (40). However, following hormonal replacement with estrogen and progesterone, IL-1α administration resulted in a progressive release of LH (103). Similarly, in intact cycling females IL-1 significantly increased LH release in monkeys during the mid-

follicular phase (104). The authors suggested that the increased LH release is the result of IL-1–induced release of small amounts of progesterone from the adrenals of the OVX monkeys, which induces positive feedback on LH secretion. In rodents, IL-1 inhibits LH secretion because in these species higher levels of progesterone are secreted from the adrenal relative to primates, and high levels of progesterone induce a negative feedback on LH secretion (104).

Immune activation suppresses ovarian hormone secretion and ovulation. Ovarian activity was also found to be suppressed by immune challenges: ovulation was inhibited by central, but not by peripheral administration of LPS (80). Moreover, chronic administration of IL-1 into the brain ventricles induced constant diestrus (76), and acute administration to females during the proestrus stage prevented ovulation (80). Similarly, in vitro stimulation with IL-1 reduced progesterone synthesis in luteinized granulosa cells, obtained from rats (54), swines (106), or women during in vitro fertilization (15). Interestingly, peripheral administration of IL-1 had no effect on either the LH surge and ovulation in intact cycling female rats (80), or on LH secretion in OVX, hormonally treated rats (92). These findings suggest that IL-1 exerts its effects on the HPG axis via a direct effect on the CNS.

Studies in Males

Sex hormones were also found to be suppressed by immune activation in males. For example, GnRH release was suppressed following in vitro exposure of medial basal hypothalamus of male rats to LPS (39), and ICV administration of IL-1 (20,77,79,80) or TNFα (80) reduced LH and FSH levels in castrated males. In addition, testosterone levels were suppressed by peripheral injections of LPS (21) or central infusion of IL-1 in intact males (92). In vitro incubation of Leydig cells from rat or porcine testes with IL-1 (α or β) significantly reduced testosterone synthesis (24,57,61). Similarly, IFN-γ and IL-2 reduced testosterone levels in isolated Leydig cells from mice (66), and TNFα reduced testosterone conversion to estrogen in porcine sertoli cells (62).

Local Effects of IL-1 During Ovulation

In addition to the above-mentioned suppressive effects of cytokines on reproductive function, increasing evidence suggest that proinflammatory cytokines, especially IL-1, are also involved in ovarian physiology as autocrine or paracrine factors. The presence of a complete intraovarian IL-1 system (including ligand, receptor and receptor antagonist) has been demonstrated (44), and its source was suggested to be either ovarian macrophages (1) or granulosa cells that contain mRNA for IL-1α and β [44]. A role of IL-1 during ovulation was indicated by the findings of preovulatory increase in IL-1 in the mouse uterus (33) and elevation in IL-1 levels following ovulation in women (25,74). A more direct evidence for the role of IL-1 during ovulation is provided by studies that demonstrated IL-1–induced ovulation, and secretion of progesterone and prostaglandins in rat ovaries in culture (23). A similar ovulatory effect was reported in the perfused rabbit ovary, and inseminated oocytes from IL-1–treated ovaries were found to have higher fertilization rates than controls (91). The precise role of IL-1 in inducing ovulation is not clear yet; however, it may be suggested that IL-1 is a mediator of the inflammatory-like cascade of events during ovulation. The role of IL-1 in the ovary may be similar to its stimulatory role during the inflammatory reaction, where it induces the production of mediators such as eicosanoids and collagenase, and enhances vascular permeability, which are also essential in ovulation (22).

Immune Activation Suppresses the Reproductive System: Possible Role in Mediating Sickness Behavior in Females

Because immune activation inhibits both sex hormone secretion and sexual behavior, and sex hormones are necessary for the expression of female sexual behavior in rodents (26), we hypothesized that the reduction in female sexual behavior in response to immune activation may be the result of IL-1- or LPS-induced suppression of ovarian hormone secretion. However, both rhIL-1 and LPS reduced sexual behavior in OVX, hormonally treated rats (5,109), indicating that changes in ovarian hormones secretion are not involved in mediating these effects. Therefore, when an estrous female is infected, proinflammatory cytokines are released and mediate the suppression of sexual behavior via hormonally independent mechanisms, presumably involving a direct effect on the central nervous system.

Hormonally independent mechanisms for the effects of immune challenges on behavior is in accordance with current knowledge on the mechanisms that are involved in the induction of sexual behavior in female rats. Behavioral estrus critically depends on the release of estrogen about 40 h before ovulation. This estrogen priming induces the expression of progesterone receptors, which subsequently bind to the progesterone that is released a few hours before ovulation and behavioral estrus (26). Thus, female sexual behavior is the result of the long-lasting biological action of hormones that were released hours or even days before the actual expression of behavior. Therefore, when a female is already in estrus, a reduction in hormonal secretion is unlikely to affect the level of her behavior.

However, it may be suggested that during chronic disease conditions, alterations in sex hormones do play an important role in modulating female sexual behavior. As was described previously, chronic activation of the immune system may disturb the normal events of the estrus cycle, resulting in a constant diestrus and prevention of ovulation [e.g., (76)]. The same physiological and endocrine events that prevent ovulation may consequently interfere with the behavior that is associated with ovulation. In summary, we suggest that there are two complementary mechanisms for the reduction in female sexual behavior during sickness. During chronic illness the reduction in sexual behavior may be a part of the overall reduction in reproductive activity, and thus reflects the effects of an hormonally dependent mechanism. In addition, a hormonally independent mechanism that involves a direct effect of proinflammatory cytokines on the brain may affect female sexual behavior when infection occurs during estrus. This mechanism may be regarded as a "backup" mechanism, which may be activated during the estrous phase, when the overall suppression of reproductive function is unlikely to affect behavior. The existence of such a backup mechanism may emphasize the importance of this behavioral change for the female's survival, recovery, and reproductive success.

Putative Hormonal Mechanisms Affecting Male Sexual Behavior During Infection

The above-mentioned findings indicate that activation of the immune system in males suppresses sex hormone secre-

tion, but not sexual behavior. In males, testicular hormones are necessary for the expression of sexual behavior (12); therefore, it is puzzling that sick animals with reduced levels of testicular hormones maintained normal levels of sexual behavior. The physiological mechanisms that enable maintained sexual behavior with reduced testosterone levels may be related to the mechanisms that enable sexual behavior following castration. In primates and humans, males usually experience a graduated decline of sexual activity following castration, but some continue to show sexual behavior for years after castration (27). Similarly, in rodents, sexual activity following castration gradually declines until a complete cessation occurs (12). The duration between castration and a complete cessation of sexual behavior is variable, and depends mainly on precastration levels of testicular hormones and previous experience in sexual behavior (12). In all vertebrates, therefore, sexual activity does not disappear immediately following castration, suggesting that the biological activity of testicular hormones on behavior is long lasting. According to these findings, it may be concluded that, because changes in sex hormones levels are not immediately followed by changes in sexual behavior, IL-1- or LPS-induced reduction in testosterone levels would not be accompanied by an immediate reduction in male sexual performance. Additionally, it may be hypothesized that during chronic infection or inflammation the constant reduction in sex hormone levels may eventually induce a suppression of sexual performance. Indeed, several autoimmune diseases, such as multiple sclerosis and diabetes mellitus, were found to be associated with sexual dysfunction in men, but these symptoms were usually considered to be due to neurological factors or vascular insufficiency (16,85,95). Thus, to our knowledge, the role of inflammation-induced androgen suppression in mediating sexual activity has never been demonstrated.

This putative reduction in male sexual behavior resulting from chronic infection may correspond to the proposed hormone-mediated mechanism for the effects of immune activation on female sexual behavior. However, in contrast to females, there is no hormonally independent mechanism for the effects of immune challenges on behavior in males and, therefore, acute illness does not affect male sexual behavior.

GENDER DIFFERENCES IN SICKNESS BEHAVIOR: NEUROENDOCRINE MECHANISMS

The gender difference in the effects of immune challenges on sexual behavior may result from gender differences in other components of the response to immune activation. We have recently examined various aspects of the responses of males and females to IL-1 to elucidate the mechanisms that are involved in producing the gender difference in the behavioral response to this cytokine.

Because the effects of IL-1 on female sexual behavior were found to be mediated by PGs synthesis, and IL-1 induces the synthesis and secretion of prostaglandins, we hypothesized that gender difference in IL-1–induced PGs synthesis may account for the gender differences in the behavioral response to IL-1. Indeed, we found that doses of rhIL-1β, which reduced sexual behavior in estrous females but not in males, elevated prostaglandins synthesis in the hypothalamus of estrous females, but not in males (7).

Interestingly, in the same study we also found that rhIL-1β induced an elevation in serum corticosterone (CS) levels in males but not in estrous females (7). This finding is in agreement with previous studies, which demonstrated that CS is involved in preventing profound disturbances in response to minor immune challenges. For example, it was demonstrated that adrenalectomy enhanced the effects of LPS or IL-1 on social exploration, and CS treatment prevented these effects (41,46). Similarly, CS blocked the pyrogenic effect of IL-1 (28). To sum up, we are suggesting that the lack of the protective effects exerted by CS during immune activation may be related to the increased behavioral response to IL-1 in estrous females. Furthermore, because glucocorticoids were found to reduce LPS-induced PGs synthesis in the brain (100), it may be suggested that the blunted CS response to IL-1 in the estrous females resulted in enhanced PGs release, which in turn, enhanced the PGs-dependent behavioral response to IL-1.

GENDER DIFFERENCES IN SICKNESS: A SOCIOBIOLOGICAL PERSPECTIVE

Sickness-Induced Suppression of Reproductive Behavior: A Female Strategy to Reduce the Chances of Conception

As mentioned earlier, sickness behavior can be viewed as a part of an organized defensive response to the immune challenge, recruiting all of the organism's resources for fighting against the invading pathogen. Sickness behavior may contribute to recovery by preventing the expression of activities that are costly or hazardous at the time of illness (43). According to this theory, the increased behavioral responsiveness to immune activation, observed in estrous females may be related to the risks of pregnancy during sickness. Several studies have shown that infection during pregnancy increases the risk of spontaneous abortions, preterm labor, and stillbirth (45,81). Although infectious agents are not usually transferred from the maternal to the fetal circulation, some maternal infections do lead to prenatal infection (45). In fact, in utero infections account for 5–10% of fetal death cases each year (36). Some infectious agents were found to be associated with in utero mortality, growth retardation, mental retardation, and mental illness (36,52,59). According to these findings, a female engaging in sexual activity while sick impairs her own chances of recovery and the viability of her offspring. In view of these dangers, it is likely that mechanisms have evolved that reduce the chance of conception during an infection. LPS or IL–induced suppression of female sexual behavior may serve such a mechanism.

To examine the effects of immune activation at the time of mating on the quality of the sexual interaction, and on the probability of successful pregnancy we performed several experiments. In the first experiment, an estrous female, injected with either rhIL-1β (2 or 10 μg/kg, IP) or saline was placed with a male rat, and the sexual performance of the male was measured. Administration of rhIL-1β to female rats resulted in a less efficient mating performance by their male partners; males had to work harder and longer to impregnate an IL-1–treated female (3). It is suggested that this reduction in the quality of the mating also reduced the probability of conception by reducing sexual behavior of the female.

A second experiment was designed to examine the effects of immune activation at the time of conception on reproductive success of females. In this experiment, 16 female and 8 male rats were group housed in four "colonies"; each colony contained two males and four females. For 5 consecutive days, two out of the four females in each of these colonies were injected IP with increasing doses of LPS (100, 200, 400, 600, and 800 μg/kg on the first to the fifth day, respectively), while the other two females were injected with saline. On the sixth day,

females and males were separated. The results of this experiment show that 87.5% of the saline-injected females gave birth, whereas none of the LPS-injected females did. These finding demonstrated that immune activation during the time of conception may reduce the female's chances to deliver a healthy litter.

Several explanations may be suggested for these findings. As mentioned above, LPS suppresses sexual activity in females, thus reducing their attractivity value in the eyes of their male partners. Consequently, males may have preferred to mate with the "healthy" partners, and the LPS-injected females were, therefore, not impregnated. According to this explanation, the behavioral effects of LPS are the cause for the prevention of conception during sickness. Alternatively, the reduction in pregnancy rate in the LPS-injected group may have been due to a direct interference with either the conception process or induction of fetal resorption following conception. Previous studies have demonstrated that LPS administration at later stages of pregnancy (from day 12) induces preterm parturition [e.g., (47)]. But to our knowledge, there is no evidence that LPS interferes with conception or induces fetal resorption in earlier stages of pregnancy. To sum up, the present data indicate that LPS reduces reproductive success when administered during the time of conception, but the relative contribution of the behavioral vs. physiological processes triggered by LPS to the alterations in pregnancy rate remains to be determined.

Gender Differences in Sickness: Male's Strategy to Increase Reproductive Success

Males and females differ from each other in many aspects that are important for their resistance to pathogens. It may be suggested that the gender differences in the behavioral patterns that are associated with reproduction may contribute to the gender differences in immunity and parasite infestation discussed above.

In species in which females choose their mates, male reproductive success, i.e., the number of offspring that survive and reproduce, is limited by the number of matings the male can obtain. During breeding, males of these species tend to compete fiercely for access to mates; males of many species establish and defend a territory, and have agonistic encounters with other males (115). Evolutionary biologists have suggested that the higher tendency for aggressive competitions and other risk-taking behavior associated with breeding may be a masculine strategy to increase reproductive success. Zahavi (114) was the first to claim that in species in which the female chooses her mate, males develop traits that are costly and potentially risky to show potential mates their ability to survive despite this "handicap." Specifically, according to Zahavi's "handicap theory" secondary sexual characters, such as the peacock's tail or the deer's antlers, are metabolically expensive to produce, and once developed, may be detrimental to the viability of their bearer by reducing agility or increasing conspicuousness to predators. The reason males developed these costly traits may be that they indicate to the female that the male can "afford" this excessive burden. Thus, these masculine traits reveal the health status and resistance to parasites of the males, and females choosing mates according to these traits may be gaining heritable benefits of disease resistance for their offspring. This theory was further developed by Zuk (115–117), who argued that the risk-taking behavioral patterns that are associated with reproduction, such as competing and fighting over a potential female mate, are a possible cause for serious injury or even death. These behavioral patterns are chosen by the males because they may increase their chances to mate. Therefore, masculine reproductive strategies may account for the higher incidence of several kinds of diseases and lower life expectancy documented in males of various species (115).

In the present set of studies, we found that males seem to conceal their sickness when presented with an estrous female (5,109). Doses of LPS or IL-1 that produced fever and marked reduction of food consumption and body weight, and suppressed locomotor, exploratory, and social activity (50,51,107, 111), had no effect on male's sexual behavior. Moreover, whereas in their home cage or in the open field LPS- and IL-1–injected males usually appeared sick (e.g., had slow and sluggish movements), it was almost impossible to "clinically" identify sickness in males in the presence of a receptive female. Concealing sickness during copulation, demonstrated by males (5,109), may also be viewed as a risk-taking behavior, which is aimed to increase reproductive success. As was mentioned earlier, sickness behavior is not merely a secondary by-product of the immune response, but rather a part of an organized defense response to combat infection and to promote recovery (43). Sexual behavior is metabolically expensive, and therefore, may be maladaptive at times when resources are needed to defend the individual from an infectious agent attack. Thus, the male's attempts to exhibit normal "healthy" behavior in the presence of a potential female partner may be risky, in that it reduces his chances for complete recovery. But "cheating" the female may increase the male's chances to be chosen for mating, and therefore, it may also increase his reproductive success. According to this theme, males try to cheat their potential female mates by maintaining normal levels of sexual performance during illness to elevate their mating chances.

SUMMARY AND CONCLUSIONS

Immune activation induces various behavioral alterations including reduction of goal-directed behavior and anhedonia. In the present study, we demonstrated that following immune challenge, using either LPS or IL-1, sexual behavior is suppressed in female, but not in male rats. In addition, several mechanisms that are involved in mediating the effects of immune challenges on female sexual behavior were demonstrated.

Pathogens, such as LPS, induce the secretion of cytokines, which in turn, affect behavior. We have demonstrated that the effects of LPS on sexual behavior of estrous females are mediated by the synergistic effects of TNFα and IL-1. The effects of IL-1, in turn, are mediated by prostaglandin secretion. Furthermore, prostaglandins may also be involved in producing the gender differences in the behavioral response to immune challenges because higher levels of prostaglandins were found following IL-1 administration in the hypothalamus of estrous females compared to males. In addition, IL-1–induced CS secretion in males, but not in estrous females. This lack of CS response in estrous females may account for the increased responsiveness to the behavioral effects of IL-1, because CS exerts a protective effect against excessive immune responses. Finally, we are suggesting that the reduction in female sexual behavior during sickness may serve as a mechanism to reduce conception during infection, which exposes the mother and the fetus to dangers such as spontaneous abortions, preterm labor, and maternal mortality.

The present study focused on the behavior of rats, and its

results may not be directly applicable for humans. In humans, studies on the effects of illness on sexual behavior have focused on diseases that may directly impair sexual performance, such as diabetes. However, these cases are usually accompanied by normal levels of motivation to engage in sexual activity. To our knowledge, possible changes in sexual motivation and performance that are a part of the nonspecific symptoms of illness have not yet been examined in humans, and thus remain to be determined.

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